**PRIMARY RESEARCH**

# Serious physical assault and subsequent risk for rehospitalization in individuals with severe mental illness: a nationwide, register-based retrospective cohort study

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## Abstract

**Background:** Victimization is associated with worse social and clinical outcomes of individuals with severe mental illness (SMI). A relapse of SMI may be one of the clinical consequences of assaultive trauma. As far as we know, there is no published study that analyzes nationwide health registers to assess the risk of SMI rehospitalization following assault.

**Aim:** We aimed to assess whether exposure to assault is associated with an increased risk of psychiatric hospitalization in those with SMI.

**Methods:** We utilized data from the Czech nationwide registers of all-cause hospitalizations and all-cause deaths. We defined exposed individuals as those discharged from a hospitalization for SMI between 2002 and 2007, and hospitalized for serious injuries sustained in an assault in the subsequent 7 years. For each assaulted individual, we randomly selected five counterparts, matched on SMI diagnosis, age and sex, who were not assaulted in the examined time period. We used mixed effect logistic regression to assess the effect of assault on the risk of SMI rehospitalization within the following 6 months. We fitted unadjusted models and models adjusted for the number of previous SMI hospitalizations and drug use disorders.

**Results:** The sample consisted of 248 exposed and 1 240 unexposed individuals. In the unadjusted model, assaulted individuals were almost four times more likely to be rehospitalized than their non-assaulted counterparts (odds ratio (OR) = 3.96; 95% CI 2.75; 5.71). After adjusting for all covariates, the OR remained threefold higher (OR = 3.07; 95% CI 2.10; 4.49).

**Conclusion:** People with a history of SMI hospitalization were approximately three times more likely to be rehospitalized for SMI within 6 months after an assault than their non-assaulted SMI counterparts. Soon after a person with SMI is physically assaulted, there should be a psychiatric evaluation and a close follow-up.

**Keywords:** Victimization, Assault, Severe mental illness, Hospitalization, Violence, Aggression

## Introduction

### Severe mental illness and relapse

Severe mental illness (SMI) is defined as schizophrenia, schizoaffective disorder, bipolar disorder, or major depressive disorder. It leads to a substantive reduction of quality of life, affecting both individuals and their

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caregivers [1, 2], and is associated with a large societal cost. [3, 4] Recurrent SMI hospitalizations drive up the cost of psychiatric care, and can further impair quality of life [5]. Relapses in individuals with SMI are associated with an increased risk of long-term disability and suicide attempts [6].

### SMI and risk of victimization

As confirmed by an influential meta-analysis, individuals with SMI experience victimization disproportionally more often than the general population [7]. Victimization may take various non-violent or violent forms [1]. Specific risk factors for victimization in adults diagnosed with psychotic disorders include drug or alcohol abuse, a high overall psychotic symptom score, homelessness, perpetration of a crime, and negative life experiences, such as previous adult victimization or child maltreatment [7, 8].

### Victimization and risk of impaired course of SMI

We have seen that SMI can affect the risk of victimization. However, the relationship between SMI and victimization may also work in the opposite direction: victimization may affect the time course of SMI. Preliminary evidence from several sources based largely on convenience samples of patients suggests that victimization may make the SMI worse. The likelihood of remission was found to be decreased in people with bipolar disorder who suffered assaultive trauma [9]. In men with schizophrenia, victimization was associated with a general impairment of functioning [10], while victimization of people with mental disorders was followed by an increased incidence of depression, anxiety and panic attacks when compared to the control group [11]. Recent violent victimization can also independently increase the risk of violence in individuals with schizophrenia [12]. In addition, women with schizophrenia victimized by sexual assault demonstrated an elevated risk for annual rehospitalization following the assault when the assault was preceded or accompanied by drug use [13]. However, to our knowledge, there is no published assessment of risk for psychiatric rehospitalization after victimization in individuals with SMI based on epidemiological data from nationwide health registers. Such data could be useful for prevention or reduction of relapse risk in future victimized patients with SMI.

### The hypothesis

To formally test a relationship between physical victimization and relapse, we hypothesized that during 6 months after an assault, the risk for a psychiatric hospitalization of people with SMI living in the community would be greater than that of their non-assaulted counterparts.

The aim of the present study was to examine this hypothesis using data from Czech nationwide health registers.

## Methods

### Data

We used data from two nationwide health registers, maintained by the Czech Institute of Health Information and Statistics: 1. the register of all-cause hospitalizations; and 2. the register of all-cause deaths. Both registers are described in-depth elsewhere [14]. Briefly, data from the register of all-cause hospitalizations are available from 1994, with approximately 2.3 million hospital records per year, of which around 2.5% are related to mental disorders. It contains diagnoses coded as per the International Statistical Classification of Diseases and Related Health Problems (ICD-10), information regarding admission and discharge and basic socio-demographic information. The coding procedure is briefly described in the Additional file 3. The register of all-cause deaths also goes back to 1994 and consists of basic socio-demographic information and primary cause of death according to the ICD-10. In the present study, we used data covering the time period from January 1st, 1995 to December 31st, 2017. The approval for this study was obtained from the ethics committee of the National Institute of Mental Health, Czech Republic (number 105/18). Individual informed consent was not obtainable, since this is an observational study using anonymized data from nationwide health registers.

### Sample

The construction of the sample is illustrated in Fig. 1. We identified individuals hospitalized for SMI (ICD codes F20, F25, F31, F32, F33; details in Additional file 2) and discharged between 2002 and 2007 from the register of all-cause hospitalizations ($n = 40,500$). Identical or similar definitions of SMI have been used by other investigators [15–17]. Then, we assessed whether individuals were admitted due to injury sustained in an assault in 7 years after SMI hospitalization (ICD codes X93–95, X99, Y00–Y05). Using this procedure, we obtained 254 individuals with a history of hospitalization for SMI who were assaulted. One of these individuals had no valid information on age and five individuals were discharged from SMI hospitalization the same day the assault occurred, thus, we excluded them from further analysis. The final sample consisted of 248 individuals, and throughout the text we refer to them as exposed individuals.

To minimize the differences between those exposed and those not exposed to assault, we performed a matching on age (with the possibility of non-exact match, up to a difference of $+—3$ years), gender, and the SMI diagnosis on the exposed individual's last SMI hospitalization

**Fig. 1** Flowchart of sample creation
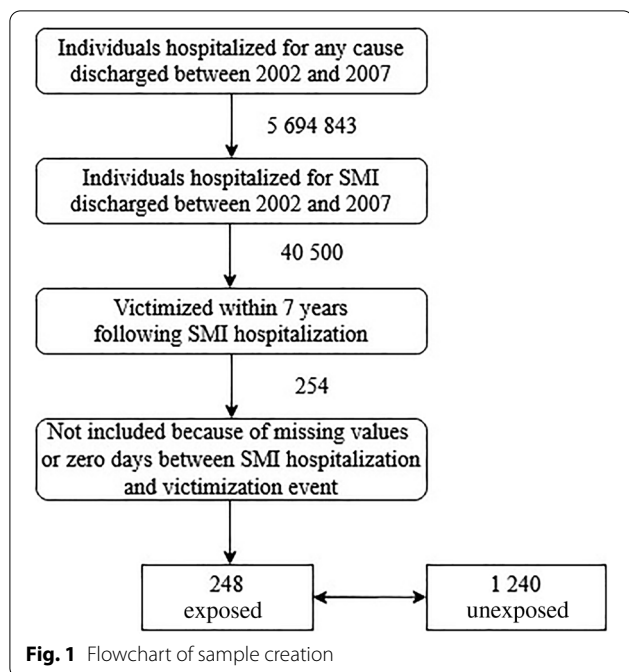
before exposure to assault. We matched these characteristics in particular as they are understood to be the key sociodemographic and clinical characteristics. In addition, for each exposed individual, we calculated the time difference (in days) between the discharge date from the last SMI hospitalization and the admission date of the assault-related hospitalization, and excluded the matching counterparts who experienced hospitalization for

SMI in the equivalent of this time period (Fig. 2). Then, using data from the register of all-cause deaths, we included only those individuals who did not die before the end of study period. We randomly selected 5 unexposed individuals for each exposed one, ending up with 1 240 unexposed individuals. We used a 5:1 ratio given the large number of potential matching candidates, while also reflecting that the use of a higher ratio would likely translate to only a marginal gain in efficiency [18].

## Outcomes
### Rehospitalization
We used rehospitalization as the main outcome as it is widely used as a proxy to define relapse in people with SMI [6]. In assaulted individuals, SMI rehospitalizations were assessed in a time window of 6 months after the assault-related hospitalization. As per the definition of the cohorts, the unexposed individuals did not experience an assault-related hospitalization; thus, for them, we established a 6-month follow-up window which emulated the one used for the exposed individuals. First, for each exposed individual, we calculated the time difference between the discharge date from the last SMI hospitalization preceding the assault and the discharge date of the assault-related hospital stay. Second, we added this time difference (expressed in days) to the unexposed counterpart's discharge date on the matching SMI hospitalization. Finally, we assessed the presence of any SMI rehospitalization in 6 months following the obtained timepoint.



**Fig. 2** Matching procedure

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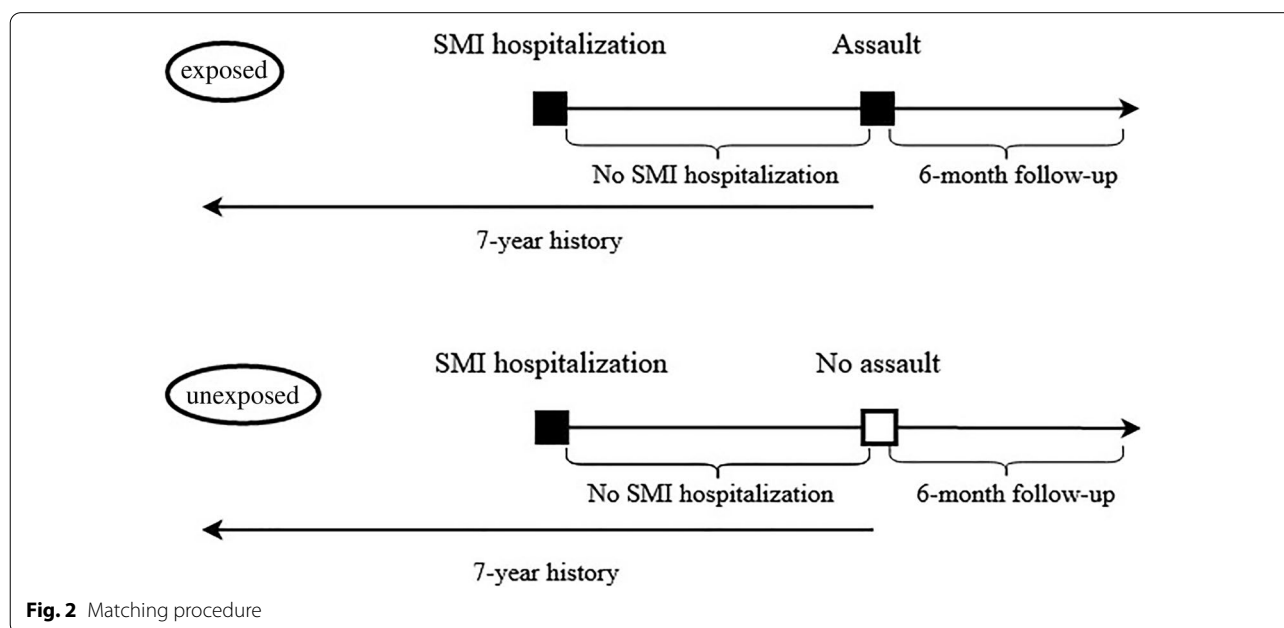
## Covariates

### Hospitalization for drug use disorder in 7 years prior to the start of the follow-up

Drug use is associated with increased risk for assault in people with mental disorders [7], thus, we considered the history of drug use disorders (DUD) as a potential confounder. In assaulted individuals, we assessed hospitalizations for DUD (ICD codes F11, F13, F14, F15 and F16) in 7 years before the assault-related hospitalization. In unexposed individuals, we computed the matching assaulted individual's number of days from the end date of the last SMI hospitalization to the admission date of the assault-related hospitalization. We added this time difference to the unexposed individual's discharge date, and assessed the presence of DUD in 7 years preceding this timepoint. We created a binary coded variable, with no DUD hospitalization being the reference category.

### Number of SMI hospitalizations in 7 years prior to the start of the follow-up

To control for potentially differing histories of SMI hospitalizations between assaulted and non-assaulted cohorts, we computed a variable denoting the individuals' history of SMI hospitalizations. We established the number of SMI hospitalizations (any of ICD codes F20, F25, F31, F32 and F33) for assaulted individuals as the sum of SMI hospitalizations in the 7-year period prior to the date of admission to assault-related hospitalization. For non-assaulted individuals, we established the history of SMI hospitalizations using the same

procedure as described above for the history of DUD hospitalization.

## Statistical methods

We computed descriptive statistics of the sample, expressed as counts (n) with proportions (%) for categorical variables, means (M) with standard deviations (SD) for normally distributed variables, and medians with interquartile range (IQR) for non-normally distributed variables. We used Chi-square test (for comorbid DUD) and the Mann–Whitney $U$ test (for the number of previous SMI hospitalizations) to assess the differences between cohorts. To assess the association between assault-related hospitalization and subsequent psychiatric hospitalization, we employed mixed effects logistic regression, with exposed individuals being set as random intercepts. We computed three models, overall: (1) the crude model containing only a variable referring to assault, (2) a model adjusted for the number of SMI hospitalizations in 7 years prior to the start of the follow-up, and 3. a model adjusted for the number of SMI hospitalizations and comorbid DUD in 7 years prior to the start of the follow-up. We considered associations with $p < 0.05$ as statistically significant. We performed the data analysis using Microsoft Access 2013 and R statistical programming language (version 3.6.0). We followed the STROBE guidelines (see Additional file 1).

## Results

### Description of the sample

The detailed description of the sample is provided in Table 1. The final dataset consisted of 248 assaulted and 1240 non-assaulted individuals (mean age 36 years, 63%

**Table 1** Characteristics of the sample

|  | Exposed | Unexposed |
|---|---|---|
| Age on last SMI hospitalization, mean (SD) [a] | 36.34 (12.33) | 36.34 (12.31) |
| Males, % (*n*) [a] | 62.90 (156) | 62.90 (780) |
| Last SMI diagnosis before the start of follow-up, % (*n*) [a] |  |  |
| Schizophrenia F20.0–F20.9 | 36.69 (91) | 36.69 (455) |
| Schizoaffective disorder F25.0–F25.9 | 15.73 (39) | 15.73 (195) |
| Bipolar disorder F31.0–F31.9 | 7.66 (19) | 7.66 (95) |
| Major depressive disorder, single episode F32.0–F32.9 | 27.82 (69) | 27.82 (345) |
| Major depressive disorder, recurrent episode F33.0–F33.9 | 12.10 (30) | 12.10 (150) |
| Comorbid DUD in the last 7 years before victimization, % (*n*) [b] ** | 5.65 (14) | 1.94 (24) |
| Number of SMI hospitalizations in the last 7 years before victimization, median (IQR) [b] ** | 2 (2) | 1 (1) |

[a] The unexposed individuals were matched with exposed on gender, age and last SMI diagnosis; therefore, the distribution on these variables is identical

For the comparison on comorbid DUD, a Chi-square test was used. For the comparison on number of SMI rehospitalizations, a Mann–Whitney $U$ test was used

[b] The unexposed individuals did not experience an actual victimization-related hospitalization. Thus, the presence of DUD and the number of SMI hospitalizations in unexposed individuals was assessed using a generated time windows copying the time windows of the exposed individuals with which they were matched

** $p$ value of the test was lower than 0.01

males for both cohorts). The vast majority of exposed individuals (201; 81%) experienced an assault by bodily force (ICD code Y04) and 50% of exposed ($n = 125$) suffered intracranial injury (ICD code S06). The largest proportion of individuals had schizophrenia as their diagnosis on their last SMI hospitalization (37%), followed by major depressive disorder (28%), schizoaffective disorder (16%), recurrent depressive disorder (12%) and bipolar disorder (8%). Approximately 6% of assaulted individuals were hospitalized for DUD in the past, whereas in non-assaulted it was 2%. This difference was statistically significant ($p$ value < 0.01). In addition, we observed a statistically significant higher number of previous SMI hospitalizations in assaulted individuals (median = 2, IQR = 2 and median = 1, IQR = 1, $p$ value < 0.001), when compared to non-assaulted ones.

### Mixed effects logistic regression
Detailed results are provided in Table 2. The results of the crude model indicate that experiencing assault was associated with increased odds for subsequent SMI rehospitalization (OR 3.96; 95% CI 2.75; 5.71). When adjusting for the number of previous SMI hospitalizations, the effect size was slightly mitigated, nevertheless the trend remained unchanged (OR = 3.10; 95% CI 2.13; 4.53). Similar results were obtained after the inclusion of previous DUD-related hospitalizations, with the effect size of assault on subsequent psychiatric hospitalization being further attenuated (OR = 3.07; 95% CI 2.10; 4.49).

## Discussion
### What is new
In this register-based retrospective cohort study, we found that individuals with SMI who experienced an assault-related hospitalization had an approximately three times higher risk to be hospitalized for SMI within the subsequent 6 months than their non-assaulted counterparts. In general, the risk of SMI relapse and rehospitalization is increased by comorbid DUD, [7, 13, 19] and comorbid DUD was detected significantly more

frequently in assaulted individuals than in non-assaulted ones. Nevertheless, our analysis has demonstrated that our principal finding was not due to potential confounding effects of DUD. Likewise, the number of previous SMI hospitalizations was greater in assaulted individuals, and the inclusion of this variable in the logistic regression model further reduced the effect of assault.

### Comparison with existing literature
Our observation of a relative increase of hospitalization risk after assault is comparable with a number of studies, all of which used designs that differed from ours. A principal difference between our study and other published investigations on this topic is the sample selection. We have included only assaults that were severe enough to require hospitalization. Comparable studies used less stringent definitions of violent victimization [20, 21].

Rabinovitz et al. reported a statistically significant contribution of comorbid DUD to the elevation of the rehospitalization risk after assault of people with schizophrenia [13]. We did not find that in our study, however, these differences might be at least partially due to methodological differences, since Rabinovitz et al. had access to information contemporaneous with the assault, while our information was historical and register-based. Our findings are consistent with those published by Neria et al. [9], who assessed trauma histories in a cohort of people with first episode of bipolar disorder, and found that trauma affected the course of illness: exposed individuals were more symptomatic than unexposed, and were less likely to remit than the unexposed. The principal contribution of our new findings to the existing literature consists in the quantitative estimate of the risk of SMI relapse following victimization of SMI patients.

### Theoretical aspects and interpretation
The causal mechanisms of the difference in hospitalization risks in assaulted and non-assaulted individuals are not clear yet. Some assaults might have been provoked by an individual's behavior influenced by psychotic

**Table 2** Mixed effects logistic regression with odds ratios of being rehospitalized in the 6 months following assault

|  | Model 1 OR (95% CI) | Model 2 OR (95% CI) | Model 3 OR (95% CI) |
|---|---|---|---|
| Experienced assault | 3.96 (2.75; 5.71) *** | 3.10 (2.13; 4.53) *** | 3.07 (2.10; 4.49) *** |
| Number of SMI hospitalizations in the last 7 years before assault[a] | – | 1.27 (1.20; 1.35) *** | 1.27 (1.20; 1.35) *** |
| Comorbid DUD in the last 7 years before assault[a] | – | – | 1.31 (0.52; 3.33) |

[a] The unexposed individuals did not experience an actual assault-related hospitalization. Thus, the presence of DUD and the number of SMI hospitalizations in unexposed individuals was assessed using a generated time windows copying the time windows of the exposed individuals to which they were matched

*** $p$ value of the test was lower than 0.001

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symptoms heralding an incipient relapse and hospitalization. Unintentional major trauma (as opposed to assault, which is intentional by definition) was associated with a significant increase of hospital admission for new or pre-existing mental health diagnoses in a population-based cohort study [22]. Thus, it is possible that factors other than SMI, for example the stress of physical trauma, were at least partly responsible for the difference in the hospitalization risks we observed. Mueser hypothesized that traumatic experiences of people with SMI might elicit posttraumatic stress disorder (PTSD) which in turn worsen the course of SMI by direct and indirect effects [23]. A direct effect would be PTSD symptoms acting as stressors on vulnerable people with SMI, leading to more SMI symptoms and relapse. An indirect effect would be associated with the use of alcohol or drugs to cope with PTSD symptoms, resulting in relapse and rehospitalization. PTSD-related personal problems would be another example of indirect effect of PTSD on functioning.

### Practical implications

Our results have both clinical and public health implications. To mitigate or prevent the effects of a physical assault on the mental health of individuals with SMI, and in particular to prevent a relapse, the victim should be evaluated by a mental health professional. As victimized people with SMI are at elevated risk for relapse, the mental health professional should provide support and schedule a follow-up. Antipsychotic medication may need adjustment, and adherence should be stressed. The circumstances of the assault should be explored, and strategies for avoiding repeated assault should be discussed. The evaluation should include inquiry about the person's own violent behavior, since victimization and perpetration of violence increase each other's risk [8, 20, 24]. If the person with SMI is also a perpetrator of violence, appropriate treatments using cognitive behavioral approach and conflict resolution strategies should be added [25]. In all cases of victimization, the psychiatrist should inquire about substance use and address it in the treatment plan if necessary. From a public health perspective, studies looking at cost-effectiveness of enhanced psychiatric care for victimized people with SMI are encouraged. Compared to in-patient care, care in the community has been found to be notably more cost-effective in the Czech Republic as well as in other countries [26, 27]. Interventions that could reduce rehospitalizations would help to use scarce resources more effectively. At the very least, a history of victimization has important risk implications regarding the prognosis of individuals with SMI and efforts are needed to ensure that this information is collected routinely when assessing persons with major mental disorders.

### Strengths of the study

This study benefited from the use of data from nationwide registers, consisting of essentially all hospitalizations in a period of more than 20 years, effectively eliminating the selection biases inherent in prospective cohort studies. Second, we randomly matched the assaulted individuals with unexposed individuals on several socio-demographic and clinical characteristics, assuring they had approximately the same profile. This procedure increased the likelihood that the differences between assaulted and non-assaulted individuals were not because of the matching procedure itself, but because of real differences between the cohorts. Third, the definition of assault was clear and objective by requiring injury severe enough to lead to hospitalization. There were no false positives. Finally, our study has external validation as evidenced by the observation of the victimization effect on the time course of bipolar disorder [9], and in a report on mental health outcome of major traumatic injury [22].

### Limitations of the study and scope for future studies

Although this study had several strengths, its limitations also need to be addressed. First, the definition of assault used in this study did not include victimization incidents that were less serious and did not require hospitalization. Because of this, the results may not be generalizable to less severe incidents. To an extent, our report shares this limitation with a recent major study that also focused only on assault resulting in injuries requiring medical care [21]. Second, the health registers contain information on psychiatric diagnoses, but no information on individuals' psychiatric symptoms, duration of the illness, treatment, or treatment adherence is contained in the registers. In addition, we lack information on the individuals' outpatient care. Third, we have no information on the individuals' socioeconomic status, living conditions and families. Fourth, for legal/ethical reasons, we were unable to access the individuals' records of arrests, convictions and incarcerations. Fifth, victimization is associated with an increased risk of subsequent violent crime [8, 21]. Incarceration may be an alternative outcome to hospitalization, reducing the number of observed hospitalizations. Sixth, our analyses have not accounted for potential effects of alcohol use disorders. Since there is a 93% treatment gap for alcohol use disorders in the Czech Republic [28], most of the individuals with these disorders are not recorded in health registers. Thus, using register records of alcohol use disorders as a covariate would be inappropriate. These lacking data represent factors that may have affected our results, and thus must be considered unmeasured confounders.

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Our results need to be replicated, preferably using longitudinal prospective design or utilizing health registers containing information from both in-patient and out-patient care.

## Conclusions

In this study, we showed that individuals with a history of SMI hospitalization were approximately three times more likely to be rehospitalized for SMI within a 6-month post-assault period than their non-assaulted counterparts. A history of comorbid DUD and the number of previous SMI hospitalizations slightly reduced the observed effects. Soon after a person with SMI is physically assaulted, there should be an evaluation by a mental health professional and close follow-up. Medical and psychological support should be provided as needed. After the patient is victimized, care givers should be particularly vigilant regarding the potential for drug and alcohol abuse. This approach could potentially improve the quality of life of individuals with SMI as well as reduce societal and rehospitalization costs, particularly in the 6-month period following an assault.

## Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12991-021-00358-y.

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**Additional file 1.** STROBE checklist

**Additional file 2.** ICD codes for severe mental illnesses, drug use disorders and assaults

**Additional file 3.** Coding procedure

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## Declarations

**Ethics approval and consent to participate**
Not applicable.

**Consent for publication**
Not applicable.

**Competing interests**
Authors declare that they have no potential competing interests.

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# Deaths with COVID-19 and from All-causes following First-ever SARS-CoV-2 Infection in Individuals with Pre-existing Mental Disorders: A National Cohort Study from Czechia

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## Abstract

### Background

Evidence suggests reduced survival rates following SARS-CoV-2 infection in people with pre-existing mental disorders, especially psychotic disorders, before the broad introduction of vaccines. It remains unknown whether this elevated mortality risk persisted at later phases of the pandemic and when accounting for the confounding effect of vaccination uptake and clinically-recorded physical comorbidities.

### Methods and Findings

We used data from Czech national health registers to identify first-ever serologically-confirmed SARS-CoV-2 infections in five epochs related to different phases of the pandemic: 1st March 2020-30th September 2020, 1st October 2020-26th December 2020, 27th December 2020-31st March 2021, 1st April 2021-31st October 2021, and 1st November 2021-29th February 2022. In these people, we ascertained cases of mental disorders using two approaches: (1) per the International Classification of Diseases 10th Revision (ICD-10) diagnostic codes for substance use, psychotic, affective, and anxiety disorders and (2) per ICD-10 diagnostic codes for the above mental disorders coupled with a prescription for anxiolytics/hypnotics/sedatives, antidepressants, antipsychotics or stimulants per the Anatomical Therapeutic Chemical (ATC) classification codes. We matched individuals with pre-existing mental disorders with counterparts who had no recorded mental disorders on age, sex, month and year of infection, vaccination status, and the Charlson Comorbidity Index. We assessed deaths with COVID-19 and from all-causes in the time period of 28 and 60 days following the infection using stratified Cox proportional hazards models, adjusting for matching variables and additional confounders. The number of individuals in matched-cohorts ranged from 1,328 in epoch 1 to 854,079 in epoch 5. The proportion of females ranged from 34.98% in people diagnosed with substance use disorders in epoch 3 to 71.16% in individuals diagnosed and treated with anxiety disorders in epoch 5. The mean age ranged from 40.97 years (standard deviation [SD] = 15.69 years) in individuals with substance use disorders in epoch 5 to 56.04 years (SD = 18.37 years) in people with psychotic disorders in epoch 2. People diagnosed with or diagnosed and treated for psychotic disorders had a consistently elevated risk of dying with COVID-19 in epochs 2, 3, 4, and 5, with adjusted hazard ratios (aHR) ranging from 1.46 [95% confidence intervals (CIs), 1.18, 1.79] to 1.93 [95% CIs, 1.12, 3.32]. This patient group demonstrated also a consistently elevated risk of all-cause mortality in epochs 2, 3, 4, and 5 (aHR from 1.43 [95% CIs, 1.23, 1.66] to 1.99 [95% CIs, 1.25, 3.16]). The models could not be reliably fit for psychotic disorders in epoch 1. People diagnosed with substance use disorders had an increased risk of all-cause mortality 28 days post-infection in epoch 3, 4, and 5 (aHR from 1.30 [95% CIs, 1.14, 1.47] to 1.59 [95% CIs, 1.19, 2.12]) and 60 days post-infection in epoch 2, 3, 4, and 5 (aHR from 1.22 [95% CIs, 1.08, 1.38] to 1.52 [95% CIs, 1.16, 1.98]). Cases ascertained based on diagnosis of substance use disorders and treatment had increased risk of all-cause mortality in epoch 2, 3, 4, and 5 (aHR from 1.22 [95% CIs, 1.03, 1.43] to 1.91 [95% CIs, 1.25, 2.91]). The models could not be reliably fit for substance use disorders in epoch 1. In contrast to these, people diagnosed with anxiety disorders had a decreased risk of death with COVID-19 in epoch 2, 3, and 5 (aHR from 0.78 [95% CIs, 0.69, 0.88] to 0.89 [95% CIs, 0.81, 0.98]) and all-cause mortality in epoch 2, 3, 4, and 5 (aHR from 0.83 [95% CIs, 0.77, 0.90] to 0.88 [95% CIs, 0.83, 0.93]). People diagnosed and treated for affective disorders had a decreased risk of both death with COVID-19 and from all-causes in epoch 3 (aHR from 0.87 [95% CIs, 0.79, 0.96] to 0.90 [95% CIs, 0.83, 0.99]), but demonstrated broadly null effects in other epochs. Given the unavailability of data on a number of potentially influential confounders, particularly body

92 mass index, tobacco smoking status, and socioeconomic status, part of the detected associations
93 might be due to residual confounding.
94

95 Conclusions
96 People with pre-existing psychotic, and, less robustly, substance use disorders demonstrated a
97 persistently elevated risk of death following SARS-CoV-2 infection throughout the pandemic.
98 While it cannot be ruled out that part of the detected associations is due to residual confounding,
99 this excess mortality cannot be fully explained by lower vaccination uptake and more
100 clinically-recorded physical comorbidities in these patient groups.

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# Author Summary

## Why Was This Study Done?

- Existing research has demonstrated consistently elevated risk of death with COVID-19 or all-cause mortality in people with pre-existing psychotic and substance use disorders following a SARS-CoV-2 infection.
- The evidence on people with pre-existing affective and anxiety disorders is broadly consistent with increased mortality risk; however, multiple studies demonstrated null effects.
- No study has used national data covering almost all inpatient and outpatient settings, including primary care, and laboratory-confirmed SARS-CoV-2 infections to investigate whether this elevated mortality risk was present throughout the pandemic, including its later phases, and when robustly accounting for the confounding effect of vaccination uptake and clinically-recorded physical comorbidities.

## What Did the Researchers Do and Find?

- Using Czech national, whole population, all healthcare encompassing register-based data, individuals with pre-existing psychotic and, less consistently, substance use disorders had increased risk of death with COVID-19 and all-cause mortality, including at the later phases of the pandemic.
- People with pre-existing anxiety disorders had decreased risk of death with COVID-19 and all-cause mortality in multiple epochs, whereas people with pre-existing affective disorders demonstrated broadly null effects throughout the pandemic.
- These associations could not be fully explained by differences in vaccination uptake or clinically-recorded physical comorbidities.

## What Do These Findings Mean?

- The consistently lower survival in people with pre-existing psychotic and substance use disorders aligns with existing evidence on fatal health inequalities in these patient groups.
- Systemic efforts are needed to fully reverse the risk attributable to long-term, structural processes affecting health of people with psychotic and substance use disorders.
- The main limitation of the present study was its inability to fully control for a number of characteristics, particularly body mass index, tobacco smoking status, and socioeconomic status, that might confound the associations between mental disorders and mortality: future studies should explore these associations while accounting for these confounders.

## Introduction

Evidence before the outbreak of the COVID-19 pandemic showed that people with mental disorders have a higher risk of developing a wide range of physical health conditions relative to their counterparts without these disorders [1-3] as well as higher mortality rates and shorter life expectancies than the general population [2, 4-7]. Worse general health, often associated with lower socioeconomic status and lifestyle risk factors (e.g., smoking) could contribute to an increased risk of SARS-CoV-2 infection and potentially lower survival following the infection in these people.

Previous research has demonstrated that individuals with a diagnosis of a mental disorder had an increased risk for SARS-CoV-2 infection [8] as well as for breakthrough infection after vaccination [9]. Existing evidence on mortality post-infection, then, showed consistently increased risk in people with psychotic [10-17] and substance use disorders [18-21], elevated risk [11, 13, 16, 22] or null effects [15, 18] in people with anxiety disorders, and elevated risk [11, 14, 16, 23] or null effects [15] in people with affective disorders.

While this evidence suggests lower survival following SARS-CoV-2 infection in people with pre-existing mental disorders, to the best of our knowledge, no study has used national data covering almost all inpatient and outpatient settings, including primary care, and laboratory-confirmed SARS-CoV-2 infections to investigate whether this elevated mortality risk persisted at later phases of the pandemic and when robustly accounting for the confounding effect of vaccination uptake and clinically-recorded physical comorbidities.

In the present study, we used national, whole population, all healthcare encompassing register-based data to investigate the risk of death with COVID-19 and from all-causes following first-ever laboratory-confirmed infection with SARS-CoV-2 in individuals with pre-existing mental disorders compared with matched counterparts without mental disorders at five distinct pandemic phases. By performing matching on vaccination status and clinically-recorded physical comorbidities, we explored associations that were not confounded by differences between people with and without pre-existing mental disorders on these characteristics.

## Methods

The research questions and the analytical plan were pre-registered at Open Science Framework before data analyses started [24]: any deviations from the plan are described in Supplementary Methods. This study was reported as per the Reporting of studies Conducted using Observational Routinely-collected health Data (RECORD) Statement (see Supplementary Checklist).

### Setting

Mental health care in Central and Eastern European region relies on large psychiatric hospitals [25-27]. Considering Czechia in particular, more than 50% of its mental health budget is allocated to inpatient services [28], with the majority of inpatient care provided in outdated psychiatric hospitals [29]. However, Czechia has launched its mental health reform in 2013, with its initial main goals focusing on deinstitutionalization. This entails the expansion of community-based services, alongside a reduction in long-term inpatient beds and complemented by educational, destigmatization and other implementation programs aimed at improving the quality of care and overall quality of life of people with psychiatric conditions [27, 30].

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The first wave of the pandemic in Czechia lasted roughly from 1st March 2020 to 30th September 2020, with a State of Emergency being in place from 12th March 2020 to 17th May 2020. The first wave resulted in 70,968 incident infections [31]. The second wave of the pandemic lasted approximately from 1st October 2020 to 31th March 2020, with a State of Emergency imposed from 5th October 2020 to 11th April 2021. The second wave led to 1,486,198 incident infections [31]. The Czech National Vaccination Strategy was launched in December 2020, with pre-existing mental disorders not considered as reason for priority inoculation [32]. The period of post-second wave lasted roughly from 1st April 2021 to 31st October 2021, resulting in 231,286 incident infections [31]. Then, the 2021-2022 winter wave lasted from approximately 1st November 2021 to 28th February 2022, with a State of Emergency imposed from 26th November to 25th December, and led to 2,017,028 incident infections [31].

Ethics Statement

This study was approved by the Ethics Committee of the National Institute of Mental Health (approval number 176/21).

Data

We used data from the National Registry of Reimbursed Health Services (NRRHS), part of the National Health Information System (NHIS), covering inpatient and outpatient services, including primary care, as well as prescription medications. The register covers nearly the entire Czech population (approximately 10.7 million inhabitants). The records are created by health professionals who complete information on diagnosis (primary and secondary diagnoses) as per the International Classification of Diseases 10th Revision (ICD-10), date (for inpatient settings, admission and discharge date), Anatomical Therapeutic Chemical (ATC) classification codes for prescription medications (with the exception of common medications administered in inpatient settings), and basic sociodemographic information such as age, sex and region of permanent residency. Additionally, we used data from the Information System of Infectious Diseases (ISID) covering nationwide testing for SARS-CoV-2 and COVID-19 vaccination status. Furthermore, we used data from the register of all-cause mortality, containing information on the date of death, the ICD-10 cause, and, if applicable, the external cause of death. All three registers can be interlinked using a common unique identifier and are maintained by the state-funded Institute of Health Information and Statistics of Czechia (IHIS). Data in the NHIS are collected in accordance with Act No. 372/2011 Coll., on Health Services and Conditions of Their Provision, while ISID data are collected in accordance with Act No. 258/2000 Coll., on Public Health Protection. Due to this legal mandate, the retrospective analyses of data in these registries did not require informed consents from participants.

We retrieved all individuals aged 10 or above – the earliest plausible onset age of the studied mental disorders [33] – with first-ever laboratory-confirmed SARS-CoV-2 infection occurring in five epochs:

(1) 1st March 2020-30th September 2020, the first wave of the pandemic.
(2) 1st October 2020-26th December 2020, the second wave of the pandemic before the initiation of the national vaccination programme.
(3) 27th December 2020-31st March 2021, the beginning of the national vaccination programme to the end of the second wave of the pandemic.
(4) 1st April 2021-31st October 2021, the post-second wave period.
(5) 1st November 2021-28th February 2022, the 2021-2022 winter wave.

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## Exposure

In individuals with first-ever laboratory-confirmed SARS-CoV-2 infection, we used two approaches to ascertain cases. The first approach relied on identifying the occurrence of diagnosis per ICD-10 codes for (1) substance use disorders (F1), (2) psychotic disorders (F2), (3) affective disorders (F3), and (4) anxiety disorders (F4) in the period of five years prior to the date of infection (see details in Supplementary Methods). We considered the occurrence of at least one of the above codes as any mental disorder. We established the occurrence of each of the mental disorders separately. We considered an individual to have a diagnosis when the given ICD-10 code was listed on a record in either inpatient (primary diagnosis, considered from discharge date) or any outpatient setting. Conversely, the unexposed cohort included individuals who had no such occurrence in the period of five years before the date of their SARS-CoV-2 infection.

The second approach entailed establishing whether an individual was prescribed psychopharmaceuticals at least once in the period of five years prior to the date of SARS-CoV-2 infection, in addition to occurrence of diagnosis (inpatient or any outpatient setting) for a given ICD-10 code. We considered the prescription per ATC codes of any anxiolytics/hypnotics/sedatives (N05B, N05C), antidepressants (N06A), antipsychotics (N05A) or stimulants (N06B). Conversely, the unexposed cohort included individuals who had no diagnosis of a mental disorder and no prescription of any psychopharmaceutical in the period of five years before the date of their infection.

We used the two ascertainment approaches to investigate the consistency of estimates across different exposure definitions: broadly consistent results between these would increase the confidence in the robustness of inferences.

## Control of Confounding

In our identification and selection of potential confounders, we followed the "disjunctive cause criterion", in which one controls for covariates that are causes of the exposure *or* causes of the outcome *or* causes of both [34, 35].

## Matching

In the first two epochs, we matched on age, sex, month and year of infection as well as the Charlson Comorbidity Index (CCI) [36]. In the three subsequent epochs, we matched on age, sex, month and year of infection, vaccination status, and the CCI. Since vaccination does not confer an immediate protection, we did not consider vaccinations that were administered 14 or less days before the infection. For instance, when an individual received the first dose of a two-dose regimen more than 14 days before the infection, and the second dose 14 or less days before the infection, we considered them as having received the first dose at the time of the infection. The CCI referred to the period of five years before the date of the SARS-CoV-2 infection, and was coded as 0, 1, 2, 3, and 4 or more comorbidities. Each exposed individual was matched with up to five unique unexposed counterparts. Some people with pre-existing mental disorders had no matching counterparts (in each cohort <10%, see details in Supplementary Table 1-5); we excluded these unmatched individuals from the respective analyses.

## Additional Confounders

To further reduce the level of unaccounted for confounding, we adjusted for region of permanent residency, overall number of contacts with inpatient services and overall number of contacts with outpatient services (disregarding contacts related to the exposure), and

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prescription medications (see the detailed list with ATC codes in Supplementary Methods). We considered prescription of each of the medications or treatment administration in the period of one year prior to the SARS-CoV-2 infection, separately. The number of contacts with the healthcare system referred to the period of five years before the date of the SARS-CoV-2 infection. For details, see the proposed directed acyclic graph in Supplementary Figure 1.

## Outcome

We considered (1) deaths with COVID-19 (ICD-10 codes U071 and U072 listed as a cause of death on the death certificate) and (2) all-cause mortality occurring in the period of (1) 28 days and (2) 60 days after a positive test for SARS-CoV-2. These cut-offs are based on Public Health England's analysis that showed that 88% and 96% of deaths occurred within 28 and 60 days of a positive test, respectively [37].

## Statistical Analysis

Following descriptive analysis, we used stratified Cox proportional hazards models to assess the risks of deaths with COVID-19 and from all-causes in individuals with pre-existing mental disorders compared with matched counterparts without such disorders, separately for each studied mental disorder and epoch. Each stratum consisted of one person with pre-existing mental disorder and up to five matched counterparts. Time-to-event was expressed in days. In models investigating the risk of death with COVID-19, we considered death due to any other cause as competing risk, and the affected individuals were censored. We fitted models adjusting for confounders, with the CCI used as a continuous measure. The results were expressed as hazards ratios (HRs) with 95% confidence intervals (95% CIs). We tested the proportionality assumption using Schoenfeld residuals; in some instances the assumption was violated, we therefore interpreted the HRs as weighted averages of the time-varying HRs over the entire follow-up period [38]. In line with the statement from the American Statistical Association on $p$-values [39], we present effect sizes with 95% CIs throughout the manuscript. However, we provide $p$-values as complementary information in Supplementary Results. All analyses were conducted in R statistical programming language (version 4.2.2) [40], using the libraries *survival* (version 3.5-5) and *EValue* (version 4.1.3) [41].

## Sensitivity Analyses

Having a history of a mental disorder might influence the risk of being tested for SARS-CoV-2 infection; thus, restricting the analysis to individuals who had a positive test might lead to collider bias [42]. To examine potential presence of collider bias, we conducted negative control exposure analyses by assessing the associations between the characteristics that are expected to be unrelated to the outcome and the outcome itself within the chosen cohorts [42]. To do so, we considered the occurrence of (1) migraine (ICD-10 code G43), (2) fracture of forearm (ICD-10 code S52), (3) acne (ICD-10 code L70), (4) mild allergies (ICD-10 codes J301, L500 and L23), and (5) transport accidents (ICD-10 codes V01-V99) in the time period of five years prior to the positive SARS-CoV-2 test. We assessed the occurrence of each of these separately. Then, we fitted stratified Cox proportional hazards models with the above characteristics being the exposures, while using the confounders and outcomes from the main analysis. We reported the total number and proportion of non-null tests, with the theoretical maximum being 40 (or 100%) per one epoch-mental disorder combination (i.e., two case ascertainment definitions X five negative control exposures X four outcomes). Since some of our cohorts were considerably large (i.e., anxiety disorders in epochs 2 to 5), it would be possible to have non-null results even if the effect sizes were negligible [43]. Thus, we complementarily provided averaged HRs across the 40 tests per one epoch-mental disorder

359  combination. Proportion of non-null tests closer to 0% and/or averaged HRs closer to 1 would
360  suggest the absence of collider bias.
361
362  To assess the level of potential unmeasured confounding, we calculated E-values for each of
363  our regression model where the results were not consistent with a null effect. The E-value
364  indicate the strength of association – here expressed in hazards ratio – an unmeasured
365  confounder, or set of confounders, would need to have with both the exposure and the outcome
366  to nullify the association between the exposure and the outcome observed in the model [44].
367  Smaller E-values indicate lower confidence in the results not being due to residual confounding
368  [44].

# Results

370  The number of individuals in matched-cohorts ranged from 1,328 in epoch 1 (247 diagnosed
371  and treated with psychotic disorders and 1,081 counterparts) to 854,079 in epoch 5 (150,211
372  diagnosed with anxiety disorders and 703,868 counterparts). The proportion of females ranged
373  from 34.98% in people diagnosed with substance use disorders in epoch 3 to 71.16% in
374  individuals diagnosed and treated with anxiety disorders in epoch 5. The mean age ranged from
375  40.97 years (standard deviation [SD] = 15.69 years) in individuals with substance use disorders
376  in epoch 5 to 56.04 years (SD = 18.37 years) in people with psychotic disorders in epoch 2.
377  The detailed descriptive statistics are provided in Table 1-2 and those with additional
378  confounders in Supplementary Table 6-7.
379

## Risk of Death with COVID-19 in People with Pre-existing Mental Disorders

381  In the models adjusting for all considered confounders, including vaccination uptake and
382  clinically-recorded physical comorbidities, people diagnosed with or diagnosed and treated for
383  psychotic disorders had an elevated risk of death with COVID-19 in epochs 2, 3, 4, and 5, both
384  28 and 60 following SARS-CoV-2 infection. The models could not be reliably fit for psychotic
385  disorders in epoch 1. Those diagnosed with substance use disorders had an increased risk of
386  death with COVID-19 28 days post-infection in epoch 3 and 4 and 60 days post-infection in
387  epoch 3. Cases ascertained based on diagnosis of substance use disorders and treatment by
388  psychopharmaceuticals had an elevated risk of death with COVID-19 in epoch 3, both 28 and
389  60 days following infection. The models could not be reliably fit for substance use disorders in
390  epoch 1, and the remaining ones were consistent with a null effect.
391

392  In contrast, people diagnosed with or diagnosed and treated for anxiety disorders had a
393  decreased risk of death with COVID-19 in epoch 2, 3, and 5, both 28 and 60 days post-
394  infection. The remaining models for anxiety disorders were consistent with a null effect.
395  Additionally, people diagnosed and treated for affective disorders had a decreased risk of death
396  with COVID-19 in epoch 3, both 28 and 60 days post-infection, but all other models involving
397  affective disorders were broadly consistent with a null effect. The results for any studied mental
398  disorder were – regardless of case ascertainment definition – consistent with a null effect in all
399  epochs. For detailed results see Figure 1, Supplementary Table 8-10, and Supplementary Figure
400  2-101.
401

## Risk of All-Cause Mortality in People with Pre-existing Mental Disorders

403  In the models adjusting for all considered confounders, including vaccination uptake and
404  clinically-recorded physical comorbidities, people diagnosed with or diagnosed and treated for
405  psychotic disorders were more likely to die in epochs 2, 3, 4, and 5, both 28 and 60 days post-
406  infection. The models could not be reliably fit for psychotic disorders in epoch 1. In those

407  diagnosed with substance use disorders, there was an elevated risk of all-cause mortality 28
408  days post-infection in epoch 3, 4, and 5 and 60 days post-infection in epoch 2, 3, 4, and 5.
409  Cases ascertained based on diagnosis of substance use disorders and treatment had increased
410  risk of all-cause mortality in epoch 2, 3, 4, and 5, both 28 and 60 days post-infection. The
411  models could not be reliably fit for substance use disorders in epoch 1, and the remaining ones
412  were consistent with a null effect.
413
414  Conversely, people diagnosed with anxiety disorders had a decreased risk of all-cause mortality
415  in epoch 2, 3, 4, and 5, both 28 and 60 days post-infection. Cases ascertained based on diagnosis
416  of anxiety disorders and treatment by psychopharmaceuticals demonstrated broadly consistent
417  results, with decreased risks of all-cause mortality in epoch 2, 3, and 5, both 28 and 60 days
418  post-infection. The remaining models for anxiety disorders were consistent with a null effect.
419  In addition, people diagnosed and treated for affective disorders had a decreased risk of all-
420  cause death in epoch 3, both 28 and 60 following SARS-CoV-2 infection, but all other models
421  involving affective disorders were broadly consistent with a null effect. The results for any
422  studied mental disorder were – regardless of case ascertainment definition – consistent with a
423  null effect in all epochs. For detailed results see Figure 2, Supplementary Table 11-13, and
424  Supplementary Figure 102-201.
425

426  ## Sensitivity Analyses
427  In negative control exposure analyses, the proportion of non-null tests did not exceed 15% for
428  substance use disorders, 15% for psychotic disorders, 20% for affective disorders, 40% for
429  anxiety disorders, and 45% for any of the studied mental disorders. Proportion of non-null tests
430  closer to 0% increases the confidence in the lack of collider bias. See details, including
431  averaged HRs, in Supplementary Table 14.
432
433  For models not consistent with a null-effect, the E-values ranged from 1.71 to 3.22 for
434  substance use disorders, from 2.21 to 3.39 for psychotic disorders, from 1.50 to 1.88 for anxiety
435  disorders, and from 1.45 to 1.55 for affective disorders. Higher E-values increase the
436  confidence that the detected associations are not due to unaccounted for confounding. See
437  details in Supplementary Table 15-16.

438  # Discussion
439  Using Czech national health register data we demonstrated that people with pre-existing
440  psychotic disorders were more likely to die with COVID-19 or due to any cause following
441  SARS-CoV-2 infection throughout the pandemic. We demonstrated less robust associations
442  for deaths with COVID-19 in people with substance use disorders but they had a consistent and
443  sustained elevated risk of all-cause mortality following SARS-CoV-2 infection. The two
444  exposure definitions produced broadly consistent results across each epoch-mental disorder
445  combination. This detected excess mortality is not fully explicable by differences in
446  vaccination uptake or clinically-recorded physical comorbidities between people with and
447  without pre-existing substance use and psychotic disorders. Separately, people with anxiety
448  disorders demonstrated decreased risk of death with COVID-19 and from all-causes in multiple
449  epochs, whereas the risk in people with affective disorders was broadly consistent with a null
450  effect throughout the pandemic.
451
452  Our findings are in line with existing evidence showing elevated mortality risk in people with
453  psychotic [10-17] and substance use disorders [18-21]; however, we demonstrated that these
454  health disparities were consistent throughout the pandemic and persisted at its later phases too.

455 Robust control for vaccination uptake or clinically-recorded somatic comorbidity in our study
456 did not reverse the increased risk of death.
457
458 These results, broadly consistent with a citywide study from the United Kingdom [45],
459 demonstrate vulnerability in these patient groups that cannot be fully explained by differences
460 in vaccination uptake or clinically-recorded physical comorbidities. This suggest that other
461 individual and structural factors might be responsible for the detected outcomes. Inequalities
462 in access to healthcare and differences in the quality of care received, cannot be discounted as
463 contributing to the excess mortality. Previous studies showed that these patient groups may
464 face delayed diagnosis [46, 47] if physical health conditions are recognized at all [48]; such
465 sub-optimal episodes of care may be related to, among other things, incorrectly attributing the
466 symptoms of somatic conditions to mental disorders [49]. Thus, people with psychotic and
467 substance use disorders potentially have more severe and insufficiently addressed or clinically
468 unrecognized physical comorbidities that contributed to lower survival.
469
470 People with lower socioeconomic status were less likely to be tested for SARS-CoV-2 infection
471 [50-52], but more likely to experience delayed test results [53]. Both substance use and
472 psychotic disorders are negatively associated with socioeconomic status [54-57]. It is plausible
473 that SARS-CoV-2 infection in these people was recognized comparatively late, and that this
474 potentially adversely influenced the therapeutic response.
475
476 Further, negative health behaviours such as smoking tobacco and suboptimal nutrition and
477 physical activity are common in these patient groups [58, 59] and may have contributed to
478 worse prognosis. Pharmacological treatments for psychotic disorders are known to contribute
479 to metabolic disturbances [60], interact with or limit the use of treatment for somatic
480 conditions, thus potentially contributing to lower survival also post-SARS-CoV-2 infection.
481 However, pre-pandemic research has demonstrated that the use of antipsychotics is associated
482 with decreased risk of all-cause mortality in people with schizophrenia [61], with no
483 differences between concomitant use of several ones compared with monotherapy [62].
484 Alternatively, lower adherence to prescription medications [63] that would contribute to
485 worsened overall health at the baseline, cannot be ruled out.
486
487 Overall, the existing evidence and our results suggest the presence of fatal but largely tractable
488 health inequalities in these patient groups. Wholesale system approaches, predicated on
489 evidence-based policy changes and, ideally, combined with evaluation, are required to address
490 the multi-layered factors behind these fatal health inequalities. In a future pandemic or other
491 health emergency, substance use and psychotic disorders need to be considered as a specific
492 vulnerability factor beyond liability to the health threat, itself.
493
494 Regarding other psychiatric conditions, our study further showed decreased mortality risk in
495 people with anxiety disorders in multiple epochs, contrasting findings of existing studies that
496 demonstrated elevated risks [11, 13, 16, 22] or null effects [15, 18]. Multiple factors might be
497 responsible for these differences, including the scope of data, definition of cases and the
498 comparison group, as well as analytical approaches. In two French studies, for instance, anxiety
499 disorders were identified through a hospital register [18, 22], while our study included cases in
500 all healthcare settings, likely capturing less severe cases with better outcomes. In a UK Biobank
501 study, narrower definitions of anxiety and stress-related disorders were used [13], focusing on
502 more severe conditions. The study also did not use a matched-cohort design [13], making it
503 difficult to rule out that adjusting for clinical, sociodemographic, and behavioural confounders
504 in regression models still led to residual confounding due to covariate imbalance. Similarly, in

505    a QResearch database study, the authors did not implement a matched-cohort design and also
506    did not condition on positive test for a SARS-CoV-2 infection, hence, comparisons involved
507    different populations [16].

509    Evidence shows that anxiety symptoms may have been linked to higher endorsement of
510    preventive measures by heightened contamination fear [64, 65]. Together with our findings of
511    decreased mortality risk, this may suggest that excessive preoccupation with COVID-19-
512    related events may have facilitated early detection and improved the health outcomes in some
513    people with anxiety disorders.

515    The broadly null effect we detected for mortality in people with affective disorders was
516    reported before also elsewhere [15]; however, other studies demonstrated an elevated risk [11,
517    14, 16, 23]. As with anxiety disorders, the factors responsible for these diverging results are
518    most likely multiple and include breadth of data (all healthcare settings vs. specific settings),
519    case definitions (all affective disorders diagnostic codes vs. specific diagnoses of affective
520    disorders), and analytical choices (matched-cohorts vs. unmatched-cohorts, conditioning on
521    positive SARS-CoV-2 infection tests vs. not conditioning on these).

523    Strengths included the use of national, whole population, fully standardized data on
524    SARS-CoV-2 infection status, healthcare utilization, and mortality. Next, we investigated the
525    robustness of our results through using multiple definitions of the exposure and the outcome.
526    Then, we used negative control exposures to explore the potential presence of collider bias and
527    E-values to establish what level of unaccounted for confounding would explain away the
528    observed associations.

530    This study has also some limitations. First, we used broad diagnostic categories of mental
531    disorders; thus disregarding the diagnostic heterogeneity in these, including the differing levels
532    of severity (e.g., bipolar disorder in affective disorders). Second, we matched on key
533    sociodemographic and clinical covariates and subsequently adjusted for a wide range of
534    additional health-related confounders; however, we did not control for a number of previously
535    identified influential clinical, sociodemographic, and behavioural confounders [66]. In
536    particular, we had no information on body mass index, smoking status, and socioeconomic
537    status *per se*; however, these are likely to influence an individual's overall health [67-72],
538    which we considered by controlling for a comorbidity index, overall number of contacts with
539    inpatient and outpatient services, and prescription medications, including antihypertensives
540    and statins that would be administered for conditions commonly present in people who smoke
541    or who are obese [73-76]. These steps likely reduced the level of confounding due to these
542    covariates; however, we cannot rule out that part of the detected associations is still due to
543    residual confounding, both related to these known and directly unmeasured and potential
544    unknown confounders, with the most plausible direction of bias being the overestimation of
545    true effects. Third, we were able to match the vast majority of people with mental disorders
546    with counterparts without mental disorders; however, "bias due to incomplete matching"
547    cannot be ruled out [77]. In particular, the unmatched individuals with mental disorders tended
548    to be, on average, older and have a higher number of comorbidities. Since these individuals
549    can be expected to have the worse outcomes post-infection, the most plausible direction of bias
550    seems to be the underestimation of true effects. Fourth, while clinically-recorded physical
551    comorbidities are among the factors most strongly associated with worse prognosis following
552    a SARS-CoV-2 infection [78], we cannot rule out that in some individuals with mental
553    disorders, they would act as a mediator instead of an confounder, thus raising the possibility of
554    overadjustment bias [79]. Fifth, both the curator of the data, IHIS, and the insurance companies

who use them to reimburse service providers employ mechanisms to ensure the validity of data; however, all diagnoses used in this study have not been fully validated yet. Thus, under-registration and/or errors in diagnoses coding cannot be ruled out. Sixth, some of our analyses included considerably few individuals, leading to profound uncertainty in our estimates. Seventh, we did not investigate survival following SARS-CoV-2 re-infections in people with pre-existing disorders. Eighth, we did not investigate the responses to medications and/or other treatment modalities following the infection itself in people with pre-existing mental disorders. Ninth, we did not consider the outcomes of people with multiple psychiatric conditions. Last, the follow-up period following infection was short; however, we had no information on emigration status, and we cannot rule out that some individuals were lost to follow-up.

People with pre-existing psychotic, and, less robustly, substance use disorders demonstrated persistently lower survival following SARS-CoV-2 infection throughout the pandemic. While we cannot rule out that part of the detected associations is due to residual confounding, the consistently increased vulnerability beyond vaccination uptake and clinically-recorded physical comorbidity aligns with existing evidence on fatal health inequalities in these patient groups and underlines the importance of implementing systemic efforts to fully reverse these. To at least reduce these disparities, it must be assured that these patient groups are included in future vaccination campaigns.

## Data Availability Statement

Due to legal regulations, individual-level patient data cannot be publicly deposited. For sharing the data, access must be granted by IHIS, the curator of Czech national health registers. Access to data can be requested through the procedure described at the web page of IHIS: https://www.uzis.cz/index-en.php?pg=contact--provision-of-information. The full analytical code is available at a dedicated GitHub repository: https://github.com/libpot/COVID_Mortality_Preexisting_Mental_Disorders. HM and JJ had full access to all registers and take responsibility for the integrity of the data export. TF, LP, HM, KM, and JJ had full access to all exported data. TF and LP responsibility for the accuracy of the data analysis.

## Authors Contributions

TF initiated and designed the study, contributed to the statistical analysis, performed the code review, and led the writing of the manuscript. LP contributed to designing the study, performed the statistical analysis, contributed to interpretation of results, and provided critical revisions to the manuscript. KW contributed to designing the study and interpretation of results, performed the literature review, and provided critical revisions to the manuscript. HM contributed to designing the study, performed the data export, and provided critical revisions to the manuscript. KM contributed to designing the study and interpretation of results, and provided critical revisions to the manuscript. AW contributed to designing the study and interpretation of results, and provided critical revisions to the manuscript. DCH contributed to designing the study and interpretation of results, and provided critical revisions to the manuscript. PM contributed to designing the study and interpretation of results, and provided critical revisions to the manuscript. PW contributed to designing the study and interpretation of results, and provided critical revisions to the manuscript. PBJ contributed to designing the study and interpretation of results, and provided supervision and critical revisions to the manuscript. JJ contributed to designing the study and to the data export, and provided critical revisions to the manuscript. All authors approved the decision to submit for publication.

## Conflict of Interest Statement

The authors have nothing to disclose.

## Financial Disclosure Statement

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898

Table 1 Descriptive statistics per matching variables, cases ascertained by diagnosis per the International Classification of Diseases 10$^{th}$ Revision (ICD-10) diagnostic codes

| Epoch | Characteristic | Any mental disorder | | Substance use disorders | | Psychotic disorders | | Affective disorders | | Anxiety disorders | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | unexposed | exposed | unexposed | exposed | unexposed | exposed | unexposed | exposed | unexposed | exposed |
| 1 | Total, n | 29549 | 7274 | 3670 | 789 | 1275 | 271 | 7601 | 1647 | 24925 | 5797 |
| | Age, mean (SD) | 42.45 (17.38) | 44.36 (17.95) | 41.12 (17.62) | 42.25 (18.27) | 49.44 (19.81) | 50.39 (20.20) | 47.32 (17.06) | 48.17 (17.42) | 42.12 (17.10) | 43.43 (17.54) |
| | Sex, n (%) | | | | | | | | | | |
| | Females | 18028 (61.01) | 4684 (64.39) | 1476 (40.22) | 317 (40.18) | 738 (57.88) | 156 (57.56) | 5026 (66.12) | 1092 (66.30) | 16134 (64.73) | 3892 (67.14) |
| | Infection month, median (IQR) | 9 (1) | 9 (1) | 9 (2) | 9 (2) | 9 (1) | 9 (1) | 9 (1) | 9 (1) | 9 (1) | 9 (1) |
| | Infection year, median (IQR) | 2020 (0) | 2020 (0) | 2020 (0) | 2020 (0) | 2020 (0) | 2020 (0) | 2020 (0) | 2020 (0) | 2020 (0) | 2020 (0) |
| | Charlson Comorbidity Index, mean (SD) | 0.92 (1.55) | 1.2 (1.78) | 1.17 (1.8) | 1.33 (1.98) | 1.44 (2.04) | 1.58 (2.11) | 1.32 (1.82) | 1.47 (1.93) | 0.93 (1.53) | 1.14 (1.71) |
| 2 | Total, n | 322884 | 72815 | 40742 | 8160 | 21480 | 4300 | 86932 | 17396 | 266089 | 55758 |
| | Age, mean (SD) | 48.73 (18.28) | 49.48 (18.20) | 48.28 (17.79) | 48.27 (17.80) | 56.06 (18.36) | 56.04 (18.37) | 53.50 (17.48) | 53.50 (17.50) | 47.91 (18.04) | 47.86 (17.86) |
| | Sex, n (%) | | | | | | | | | | |
| | Females | 205759 (63.73) | 48654 (66.82) | 15549 (38.16) | 3111 (38.12) | 12336 (57.43) | 2468 (57.40) | 61675 (70.95) | 12341 (70.94) | 183790 (69.07) | 39126 (70.17) |
| | Infection month, median (IQR) | 11 (1) | 11 (1) | 11 (2) | 11 (2) | 11 (1) | 11 (1) | 11 (1) | 11 (1) | 11 (1) | 11 (1) |
| | Infection year, median (IQR) | 2020 (0) | 2020 (0) | 2020 (0) | 2020 (0) | 2020 (0) | 2020 (0) | 2020 (0) | 2020 (0) | 2020 (0) | 2020 (0) |
| | Charlson Comorbidity Index, mean (SD) | 1.32 (1.85) | 1.55 (2.03) | 1.75 (2.1) | 1.79 (2.17) | 1.98 (2.25) | 1.99 (2.26) | 1.78 (2.12) | 1.82 (2.2) | 1.33 (1.85) | 1.43 (1.93) |
| 3 | Total, n | 443728 | 99307 | 63623 | 12768 | 26859 | 5405 | 113967 | 22900 | 362380 | 76462 |
| | Age, mean (SD) | 47.35 (17.46) | 47.82 (17.23) | 44.97 (16.25) | 44.98 (16.26) | 50.51 (17.04) | 50.58 (17.04) | 51.80 (16.51) | 51.81 (16.53) | 46.72 (17.21) | 46.79 (17.04) |
| | Sex, n (%) | | | | | | | | | | |
| | Females | 273385 (61.61) | 64115 (64.56) | 22267 (35.00) | 4466 (34.98) | 13875 (51.66) | 2792 (51.66) | 79484 (69.74) | 15971 (69.74) | 243249 (67.13) | 52333 (68.44) |
| | Vaccination status, n (%) | | | | | | | | | | |

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| | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | Not vaccinated | 440565 (99.29) | 98185 (98.87) | 63295 (99.48) | 12673 (99.26) | 26394 (98.27) | 5281 (97.71) | 112701 (98.89) | 22576 (98.59) | 359796 (99.29) | 75648 (98.94) |
| | First dose | 2906 (0.65) | 993 (1.00) | 296 (0.47) | 80 (0.63) | 441 (1.64) | 117 (2.16) | 1164 (1.02) | 285 (1.24) | 2372 (0.65) | 713 (0.93) |
| | Full vaccination | 257 (0.06) | 129 (0.13) | 32 (0.05) | 15 (0.12) | 24 (0.09) | 7 (0.13) | 102 (0.09) | 39 (0.17) | 212 (0.06) | 101 (0.13) |
| | Booster | 0 (0.00) | 0 (0.00) | 0 (0.00) | 0 (0.00) | 0 (0.00) | 0 (0.00) | 0 (0.00) | 0 (0.00) | 0 (0.00) | 0 (0.00) |
| | Infection month, median (IQR) | 2 (2) | 2 (2) | 2 (2) | 2 (2) | 2 (2) | 2 (2) | 2 (2) | 2 (2) | 2 (2) | 2 (2) |
| | Infection year, median (IQR) | 2021 (0) | 2021 (0) | 2021 (0) | 2021 (0) | 2021 (0) | 2021 (0) | 2021 (0) | 2021 (0) | 2021 (0) | 2021 (0) |
| | Charlson Comorbidity Index, mean (SD) | 1.22 (1.74) | 1.43 (1.89) | 1.49 (1.89) | 1.54 (2.02) | 1.59 (2.02) | 1.62 (2.07) | 1.65 (1.97) | 1.68 (2.06) | 1.24 (1.73) | 1.36 (1.82) |
| 4 | Total, n | 95357 | 22638 | 14480 | 3016 | 5334 | 1108 | 24092 | 5079 | 78317 | 17643 |
| | Age, mean (SD) | 43.01 (17.46) | 44.12 (17.48) | 41.84 (16.16) | 42.05 (16.23) | 47.55 (16.73) | 47.80 (16.87) | 48.79 (16.27) | 49.20 (16.42) | 42.41 (17.29) | 43.03 (17.30) |
| | Sex, n (%) | | | | | | | | | | |
| | Females | 58648 (61.50) | 14589 (64.44) | 5443 (37.59) | 1131 (37.50) | 2658 (49.83) | 551 (49.73) | 16499 (68.48) | 3500 (68.91) | 52168 (66.61) | 12104 (68.61) |
| | Vaccination status, n (%) | | | | | | | | | | |
| | Not vaccinated | 81471 (85.44) | 18897 (83.47) | 12942 (89.38) | 2660 (88.20) | 4557 (85.43) | 934 (84.30) | 19835 (82.33) | 4105 (80.82) | 66661 (85.12) | 14707 (83.36) |
| | First dose | 2266 (2.38) | 727 (3.21) | 215 (1.48) | 65 (2.16) | 159 (2.98) | 42 (3.79) | 696 (2.89) | 188 (3.70) | 1866 (2.38) | 566 (3.21) |
| | Full vaccination | 11620 (12.19) | 3014 (13.31) | 1323 (9.14) | 291 (9.65) | 618 (11.59) | 132 (11.91) | 3561 (14.78) | 786 (15.48) | 9790 (12.50) | 2370 (13.43) |
| | Booster | 0 (0.00) | 0 (0.00) | 0 (0.00) | 0 (0.00) | 0 (0.00) | 0 (0.00) | 0 (0.00) | 0 (0.00) | 0 (0.00) | 0 (0.00) |
| | Infection month, median (IQR) | 5 (6) | 5 (6) | 4 (5) | 4 (5) | 4 (6) | 5 (6) | 5 (6) | 5 (6) | 5 (6) | 5 (6) |
| | Infection year, median (IQR) | 2021 (0) | 2021 (0) | 2021 (0) | 2021 (0) | 2021 (0) | 2021 (0) | 2021 (0) | 2021 (0) | 2021 (0) | 2021 (0) |
| | Charlson Comorbidity Index, mean (SD) | 0.95 (1.5) | 1.19 (1.72) | 1.19 (1.66) | 1.3 (1.82) | 1.27 (1.77) | 1.35 (1.85) | 1.35 (1.77) | 1.46 (1.9) | 0.96 (1.48) | 1.14 (1.66) |
| 5 | Total, n | 832235 | 187321 | 110334 | 22205 | 37958 | 7626 | 198047 | 39860 | 703868 | 150211 |
| | Age, mean (SD) | 41.32 (16.82) | 42.22 (16.79) | 40.92 (15.65) | 40.97 (15.69) | 46.25 (16.76) | 46.30 (16.80) | 46.51 (16.03) | 46.58 (16.09) | 40.89 (16.65) | 41.30 (16.59) |
| | Sex, n (%) | | | | | | | | | | |
| | Females | 526059 (63.21) | 123962 (66.18) | 44774 (40.58) | 8989 (40.48) | 20539 (54.11) | 4126 (54.10) | 139277 (70.33) | 28043 (70.35) | 477405 (67.83) | 104241 (69.40) |

| | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| Vaccination status, n (%) | | | | | | | | | | |
| Not vaccinated | 334155 (40.15) | 74090 (39.55) | 49970 (45.29) | 10021 (45.13) | 14797 (38.98) | 2962 (38.84) | 68819 (34.75) | 13809 (34.64) | 281216 (39.95) | 59521 (39.62) |
| First dose | 9740 (1.17) | 2791 (1.49) | 1990 (1.80) | 475 (2.14) | 609 (1.60) | 143 (1.88) | 2187 (1.10) | 538 (1.35) | 8316 (1.18) | 2224 (1.48) |
| Full vaccination | 372694 (44.78) | 83372 (44.51) | 46014 (41.70) | 9214 (41.50) | 17050 (44.92) | 3413 (44.75) | 92887 (46.90) | 18612 (46.69) | 316251 (44.93) | 67149 (44.70) |
| Booster | 115646 (13.90) | 27068 (14.45) | 12360 (11.20) | 2495 (11.24) | 5502 (14.49) | 1108 (14.53) | 34154 (17.25) | 6901 (17.31) | 98085 (13.94) | 21317 (14.19) |
| Infection month, median (IQR) | 2 (10) | 2 (10) | 2 (10) | 2 (10) | 2 (9) | 2 (9) | 2 (10) | 2 (10) | 2 (10) | 2 (10) |
| Infection year, median (IQR) | 2022 (1) | 2022 (1) | 2022 (1) | 2022 (1) | 2022 (1) | 2022 (1) | 2022 (1) | 2022 (1) | 2022 (1) | 2022 (1) |
| Charlson Comorbidity Index, mean (SD) | 0.91 (1.43) | 1.12 (1.62) | 1.17 (1.63) | 1.21 (1.73) | 1.28 (1.74) | 1.29 (1.78) | 1.32 (1.73) | 1.34 (1.78) | 0.95 (1.43) | 1.07 (1.56) |

The results are presented as absolute numbers (n) with proportions (%), means with standard deviations (SD), and medians with interquartile ranges (IQR). The time frames for epochs were: (1) 1st March 2020-30th September 2020 for epoch 1, (2) 1st October 2020-26th December 2020 for epoch 2, (3) 27th December 2020-31st March 2021 for epoch 3, (4) 1st April 2021-31st October 2021 for epoch 4, and (5) 1st November 2021-29th February 2022 for epoch 5. "Exposed" and "unexposed" refer to people with the respective mental disorder and their matched counterparts without that mental disorder, respectively. The International Classification of Diseases 10th Revision (ICD-10) diagnostic codes were (1) F10-F19, F20-F29, F30-F39, F40-F48 for any mental disorder, (2) F10-F19 for substance use disorders, (3) F20-F29 for psychotic disorders, (4) F30-F39 for affective disorders, and (5) F40-F48 for anxiety disorders.

Table 2 Descriptive statistics per matching variables, cases ascertained by diagnosis per the International Classification of Diseases 10th Revision (ICD-10) diagnostic codes coupled with prescription for psychopharmaceuticals per the Anatomical Therapeutic Chemical (ATC) classification codes

| Epoch | Characteristic | Any mental disorder | | Substance use disorders | | Psychotic disorders | | Affective disorders | | Anxiety disorders | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | unexposed | exposed | unexposed | exposed | unexposed | exposed | unexposed | exposed | unexposed | exposed |
| 1 | Total, n | 18842 | 5121 | 1870 | 434 | 1081 | 247 | 6254 | 1470 | 15963 | 4127 |
| | Age, mean (SD) | 43.02 (15.68) | 46.58 (16.83) | 42.97 (16.04) | 45.54 (17.50) | 47.16 (17.70) | 49.55 (18.88) | 46.26 (15.84) | 48.53 (16.96) | 42.81 (15.54) | 45.75 (16.59) |
| | Sex, n (%) | | | | | | | | | | |
| | Females | 11483 (60.94) | 3390 (66.20) | 822 (43.96) | 193 (44.47) | 621 (57.45) | 144 (58.30) | 4027 (64.39) | 970 (65.99) | 10227 (64.07) | 2826 (68.48) |
| | Infection month, median (IQR) | 9 (1) | 9 (1) | 9 (1) | 9 (2) | 9 (1) | 9 (1) | 9 (0) | 9 (1) | 9 (1) | 9 (1) |
| | Infection year, median (IQR) | 2020 (0) | 2020 (0) | 2020 (0) | 2020 (0) | 2020 (0) | 2020 (0) | 2020 (0) | 2020 (0) | 2020 (0) | 2020 (0) |
| | Charlson Comorbidity Index, mean (SD) | 0.82 (1.34) | 1.26 (1.76) | 1.16 (1.64) | 1.58 (2.16) | 1.19 (1.78) | 1.48 (1.98) | 1.08 (1.54) | 1.44 (1.9) | 0.83 (1.33) | 1.22 (1.72) |
| 2 | Total, n | 213314 | 57301 | 27022 | 5441 | 19500 | 3914 | 76430 | 16200 | 180941 | 44226 |
| | Age, mean (SD) | 48.03 (16.56) | 51.68 (17.59) | 50.83 (17.40) | 50.81 (17.41) | 55.94 (18.31) | 55.97 (18.39) | 53.00 (16.80) | 54.15 (17.36) | 47.70 (16.57) | 50.16 (17.39) |
| | Sex, n (%) | | | | | | | | | | |
| | Females | 131715 (61.75) | 39534 (68.99) | 11562 (42.79) | 2319 (42.62) | 11318 (58.04) | 2273 (58.07) | 53282 (69.71) | 11555 (71.33) | 120407 (66.54) | 31760 (71.81) |
| | Infection month, median (IQR) | 11 (1) | 11 (1) | 11 (2) | 11 (2) | 11 (1) | 11 (1) | 11 (1) | 11 (1) | 11 (1) | 11 (1) |
| | Infection year, median (IQR) | 2020 (0) | 2020 (0) | 2020 (0) | 2020 (0) | 2020 (0) | 2020 (0) | 2020 (0) | 2020 (0) | 2020 (0) | 2020 (0) |
| | Charlson Comorbidity Index, mean (SD) | 1.1 (1.59) | 1.68 (2.09) | 1.99 (2.12) | 2.1 (2.32) | 1.97 (2.16) | 2.03 (2.27) | 1.62 (1.91) | 1.87 (2.22) | 1.14 (1.61) | 1.57 (2.02) |
| 3 | Total, n | 300335 | 76731 | 39933 | 8048 | 24564 | 4968 | 101592 | 21165 | 252244 | 59918 |
| | Age, mean (SD) | 47.58 (16.41) | 50.01 (16.68) | 46.65 (15.95) | 46.66 (15.97) | 50.39 (16.96) | 50.54 (17.03) | 52.01 (16.29) | 52.41 (16.39) | 47.32 (16.33) | 48.95 (16.48) |
| | Sex, n (%) | | | | | | | | | | |
| | Females | 181621 (60.47) | 51538 (67.17) | 15807 (39.58) | 3178 (39.49) | 12961 (52.76) | 2627 (52.88) | 70433 (69.33) | 14888 (70.34) | 164964 (65.40) | 41981 (70.06) |
| | Vaccination status, n (%) | | | | | | | | | | |
| | Not vaccinated | 298691 (99.45) | 75921 (98.94) | 39746 (99.53) | 7986 (99.23) | 24274 (98.82) | 4865 (97.93) | 100860 (99.28) | 20903 (98.76) | 250901 (99.47) | 59323 (99.01) |

| | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | First dose | 1521 (0.51) | 732 (0.95) | 177 (0.44) | 54 (0.67) | 280 (1.14) | 96 (1.93) | 680 (0.67) | 235 (1.11) | 1242 (0.49) | 535 (0.89) |
| | Full vaccination | 123 (0.04) | 78 (0.10) | 10 (0.03) | 8 (0.10) | 10 (0.04) | 7 (0.14) | 52 (0.05) | 27 (0.13) | 101 (0.04) | 60 (0.10) |
| | Booster | 0 (0.00) | 0 (0.00) | 0 (0.00) | 0 (0.00) | 0 (0.00) | 0 (0.00) | 0 (0.00) | 0 (0.00) | 0 (0.00) | 0 (0.00) |
| | Infection month, median (IQR) | 2 (2) | 2 (2) | 2 (2) | 2 (2) | 2 (2) | 2 (2) | 2 (2) | 2 (2) | 2 (2) | 2 (2) |
| | Infection year, median (IQR) | 2021 (0) | 2021 (0) | 2021 (0) | 2021 (0) | 2021 (0) | 2021 (0) | 2021 (0) | 2021 (0) | 2021 (0) | 2021 (0) |
| | Charlson Comorbidity Index, mean (SD) | 1.1 (1.58) | 1.56 (1.97) | 1.7 (1.93) | 1.81 (2.17) | 1.56 (1.92) | 1.63 (2.06) | 1.58 (1.87) | 1.74 (2.08) | 1.13 (1.58) | 1.49 (1.89) |
| 4 | Total, n | 61983 | 16322 | 8311 | 1795 | 4723 | 1006 | 20439 | 4555 | 51628 | 12870 |
| | Age, mean (SD) | 44.20 (16.12) | 46.75 (16.60) | 44.08 (15.48) | 44.55 (15.81) | 47.03 (16.33) | 47.48 (16.55) | 48.59 (15.72) | 49.68 (16.04) | 43.75 (16.05) | 45.69 (16.42) |
| | Sex, n (%) | | | | | | | | | | |
| | Females | 38225 (61.67) | 10925 (66.93) | 3494 (42.04) | 763 (42.51) | 2374 (50.26) | 513 (50.99) | 13863 (67.83) | 3158 (69.33) | 34093 (66.04) | 9026 (70.13) |
| | Vaccination status, n (%) | | | | | | | | | | |
| | Not vaccinated | 52930 (85.39) | 13489 (82.64) | 7465 (89.82) | 1583 (88.19) | 4143 (87.72) | 862 (85.69) | 17007 (83.21) | 3695 (81.12) | 43931 (85.09) | 10620 (82.52) |
| | First dose | 1371 (2.21) | 524 (3.21) | 91 (1.09) | 34 (1.89) | 106 (2.24) | 33 (3.28) | 501 (2.45) | 160 (3.51) | 1129 (2.19) | 407 (3.16) |
| | Full vaccination | 7682 (12.39) | 2309 (14.15) | 755 (9.08) | 178 (9.92) | 474 (10.04) | 111 (11.03) | 2931 (14.34) | 700 (15.37) | 6568 (12.72) | 1843 (14.32) |
| | Booster | 0 (0.00) | 0 (0.00) | 0 (0.00) | 0 (0.00) | 0 (0.00) | 0 (0.00) | 0 (0.00) | 0 (0.00) | 0 (0.00) | 0 (0.00) |
| | Infection month, median (IQR) | 5 (6) | 5 (6) | 4 (5) | 4 (5) | 4 (6) | 4 (6) | 5 (6) | 5 (6) | 5 (6) | 5 (6) |
| | Infection year, median (IQR) | 2021 (0) | 2021 (0) | 2021 (0) | 2021 (0) | 2021 (0) | 2021 (0) | 2021 (0) | 2021 (0) | 2021 (0) | 2021 (0) |
| | Charlson Comorbidity Index, mean (SD) | 0.89 (1.38) | 1.29 (1.76) | 1.31 (1.63) | 1.52 (1.91) | 1.17 (1.63) | 1.31 (1.81) | 1.23 (1.63) | 1.46 (1.89) | 0.9 (1.37) | 1.25 (1.73) |
| 5 | Total, n | 544077 | 135003 | 65572 | 13286 | 34590 | 6981 | 173299 | 36134 | 467140 | 109359 |
| | Age, mean (SD) | 42.51 (15.60) | 44.98 (16.12) | 43.18 (15.32) | 43.28 (15.40) | 46.08 (16.45) | 46.19 (16.55) | 46.74 (15.68) | 47.30 (15.88) | 42.32 (15.55) | 44.11 (15.92) |
| | Sex, n (%) | | | | | | | | | | |
| | Females | 345333 (63.47) | 92640 (68.62) | 29877 (45.56) | 6038 (45.45) | 18999 (54.93) | 3843 (55.05) | 121041 (69.85) | 25577 (70.78) | 314398 (67.30) | 77820 (71.16) |
| | Vaccination status, n (%) | | | | | | | | | | |
| | Not vaccinated | 207757 (38.19) | 49441 (36.62) | 27772 (42.35) | 5623 (42.32) | 13325 (38.52) | 2675 (38.32) | 59141 (34.13) | 12226 (33.84) | 177201 (37.93) | 40260 (36.81) |

| | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | First dose | 6037 (1.11) | 1777 (1.32) | 1032 (1.57) | 257 (1.93) | 484 (1.40) | 122 (1.75) | 1601 (0.92) | 429 (1.19) | 5213 (1.12) | 1463 (1.34) |
| | Full vaccination | 250276 (46.00) | 61676 (45.68) | 28349 (43.23) | 5696 (42.87) | 15708 (45.41) | 3152 (45.15) | 82241 (47.46) | 16992 (47.02) | 215799 (46.20) | 50102 (45.81) |
| | Booster | 80007 (14.71) | 22109 (16.38) | 8419 (12.84) | 1710 (12.87) | 5073 (14.67) | 1032 (14.78) | 30316 (17.49) | 6487 (17.95) | 68927 (14.76) | 17534 (16.03) |
| Infection month, median (IQR) | | 2 (10) | 2 (10) | 2 (10) | 2 (10) | 2 (9) | 2 (9) | 2 (10) | 2 (10) | 2 (10) | 2 (10) |
| Infection year, median (IQR) | | 2022 (1) | 2022 (1) | 2022 (1) | 2022 (1) | 2022 (1) | 2022 (1) | 2022 (1) | 2022 (1) | 2022 (1) | 2022 (1) |
| Charlson Comorbidity Index, mean (SD) | | 0.87 (1.32) | 1.26 (1.7) | 1.38 (1.72) | 1.46 (1.88) | 1.27 (1.71) | 1.3 (1.79) | 1.25 (1.62) | 1.39 (1.8) | 0.9 (1.34) | 1.21 (1.65) |

The results are presented as absolute numbers (n) with proportions (%), means with standard deviations (SD), and medians with interquartile ranges (IQR). The time frames for epochs were: (1) 1st March 2020-30th September 2020 for epoch 1, (2) 1st October 2020-26th December 2020 for epoch 2, (3) 27th December 2020-31st March 2021 for epoch 3, (4) 1st April 2021-31st October 2021 for epoch 4, and (5) 1st November 2021-29th February 2022 for epoch 5. "Exposed" and "unexposed" refer to people with the respective mental disorder and their matched counterparts without that mental disorder, respectively. The International Classification of Diseases 10th Revision (ICD-10) diagnostic codes were (1) F10-F19, F20-F29, F30-F39, F40-F48 for any mental disorder, (2) F10-F19 for substance use disorders, (3) F20-F29 for psychotic disorders, (4) F30-F39 for affective disorders, and (5) F40-F48 for anxiety disorders. The considered psychopharmaceuticals per the Anatomical Therapeutic Chemical (ATC) classification codes were (1) anxiolytics/hypnotics/sedatives (N05B, N05C), (2) antidepressants (N06A), (3) antipsychotics (N05A), and (4) stimulants (N06B).

Figure 1 Relative risk of death with COVID-19 following SARS-CoV-2 infection in people with pre-existing mental disorders



Relative risk of death with COVID-19 following SARS-CoV-2 infection in people with pre-existing mental disorders

All results are expressed as hazard ratios with 95% confidence intervals. The models were adjusted for matching variables and all additional confounders. The time frames for epochs were: (1) 1$^{st}$ March 2020-30$^{th}$ September 2020 for epoch 1, (2) 1$^{st}$ October 2020-26$^{th}$ December 2020 for epoch 2, (3) 27$^{th}$ December 2020-31$^{st}$ March 2021 for epoch 3, (4) 1$^{st}$ April 2021-31$^{st}$ October 2021 for epoch 4, and (5) 1$^{st}$ November 2021-29$^{th}$ February 2022 for epoch 5. "Diagnosed" refers to cases ascertained by diagnosis per the International Classification of Diseases 10$^{th}$ Revision (ICD-10) diagnostic codes: (1) F10-F19, F20-F29, F30-F39, F40-F48 for any mental disorder, (2) F10-F19 for substance use disorders, (3) F20-F29 for psychotic disorders, (4) F30-F39 for affective disorders, and (5) F40-F48 for anxiety disorders. "Diagnosed and treated" refers to cases ascertained by diagnosis per the above ICD-10 codes coupled with prescription for anxiolytics/hypnotics/sedatives (N05B, N05C), (2) antidepressants (N06A), (3) antipsychotics (N05A) or (4) stimulants (N06B) per the Anatomical Therapeutic Chemical (ATC) classification codes. The models could not be reliably fit for substance use and psychotic disorders in epoch 1.

Figure 2 Relative risk of all-cause mortality following SARS-CoV-2 infection in people with pre-existing mental disorders



**Relative risk of all-cause mortality following SARS-CoV-2 infection in people with pre-existing mental disorders**

All results are expressed as hazard ratios with 95% confidence intervals. The models were adjusted for matching variables and all additional confounders. The time frames for epochs were: (1) 1st March 2020-30th September 2020 for epoch 1, (2) 1st October 2020-26th December 2020 for epoch 2, (3) 27th December 2020-31st March 2021 for epoch 3, (4) 1st April 2021-31st October 2021 for epoch 4, and (5) 1st November 2021-29th February 2022 for epoch 5. "Diagnosed" refers to cases ascertained by diagnosis per the International Classification of Diseases 10th Revision (ICD-10) diagnostic codes: (1) F10-F19, F20-F29, F30-F39, F40-F48 for any mental disorder, (2) F10-F19 for substance use disorders, (3) F20-F29 for psychotic disorders, (4) F30-F39 for affective disorders, and (5) F40-F48 for anxiety disorders. "Diagnosed and treated" refers to cases ascertained by diagnosis per the above ICD-10 codes coupled with prescription for anxiolytics/hypnotics/sedatives (N05B, N05C), (2) antidepressants (N06A), (3) antipsychotics (N05A) or (4) stimulants (N06B) per the Anatomical Therapeutic Chemical (ATC) classification codes. The models could not be reliably fit for substance use and psychotic disorders in epoch 1.

# Severe mental illness contributing to fatally deleterious effects of physical disorders: A national cohort study

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# Abstract

## Background

It remains unknown whether severe mental illness contributes to fatally deleterious effects of physical illness.

## Aims

To investigate the risk of all-cause death and loss of life-years following the onset of a wide range of physical health conditions in people with severe mental illness compared with matched counterparts who had only these physical health conditions, and to assess whether these associations can be fully explained by this patient group having more clinically-recorded physical illness.

## Methods

Using Czech national inpatient register data, we identified individuals with 28 physical health conditions recorded between 1999 and 2017, separately for each condition. In these people, we identified individuals who had severe mental illness recorded before the physical health condition, and exactly-matched them with up to five counterparts who had no recorded prior severe mental illness. We estimated the risk of all-cause death and lost life-years following each of the physical health conditions in people with pre-existing severe mental illness compared with matched counterparts without severe mental illness.

## Results

People with severe mental illness had an elevated risk of all-cause death following the onset of seven out of nine broadly defined and 14 out of 19 specific physical health conditions, respectively. People with severe mental illness lost additional life-years following the onset of eight out nine broadly defined and 13 out of 19 specific physical health conditions, respectively. The vast majority of associations results remained robust after considering the potentially confounding role of somatic multimorbidity and other clinical and socio-demographic factors.

## Conclusions

A wide range of physical illnesses are more likely to result in all-cause death in people with pre-existing severe mental illness. This premature mortality cannot be fully explained by having more clinically-recorded physical illness, suggesting that physical disorders are more likely to be fatally deleterious in this patient group.

## Introduction

Comorbidity of mental and physical health conditions is referred to as "a key problem for medicine in the 21st century" (1). Studies using nationwide health registers show that people with severe mental illness have an elevated risk of developing a large number of physical health conditions compared with people without severe mental illness (2-4). This patient group is also more likely to die prematurely (3, 5-8), with deaths from comorbid physical health conditions far outweighing the impact of suicides and accidents (5).

However, it is uncertain as to whether people with severe mental illness experience premature mortality solely because they are more likely to develop a larger number of physical illnesses, or whether those illnesses are also more likely to result in death due to biological, behavioral, socio-demographic, and structural factors that are related to this patient group. Substance use disorders seem to increase the fatally deleterious effect of subsequent physical health conditions (9), but no national study of people with severe mental illness has considered the temporal order of the mental and physical health conditions and the contribution of severe mental illness to fatally deleterious effects of physical illness.

Thus, the aim of the current study was to investigate the risk of all-cause death and loss of life-years in people with physical health conditions who had a pre-existing severe mental illness compared with matched counterparts who had the same physical health condition but did not have a severe mental illness. In sensitivity analyses, we considered the potentially confounding role of somatic multimorbidity as well as disorders due to psychoactive substance use, the number of past hospitalizations, and socio-demographic factors. We hypothesized that people with pre-existing severe mental illness would have a consistently increased risk of all-cause death as well as larger losses of life-years following the onset of physical health conditions than their matched counterparts.

## Methods

We performed a cohort study based on routinely collected Czech national health data, investigating all-cause mortality in individuals with pre-existing severe mental illness compared with matched counterparts without pre-existing severe mental illness. The research questions and the analytical plan were pre-registered at Open Science Framework before data analyses started (10). Any deviations from the analytical plan are described in Supplementary Methods.

### Data

We used individual-level, de-identified data from the Czech nationwide registers of all-cause hospitalizations and all-cause deaths, encompassing the time-period from 1st January 1994 to 31st December 2017. Linkage of registers is possible by means of a unique identifier assigned at birth. The registers are maintained by the state-funded Czech Institute of Health Information and Statistics (IHIS), which granted access to complete data to the Czech National Institute of Mental Health (NIMH). The main purpose of the registers is the monitoring of public health, however, importantly, they also serve as a claims database used by Czech insurance companies. This study was approved by the Ethics Committee of the NIMH (105/23).

The register of all-cause hospitalizations comprises of records created from information routinely collected by health professionals using a standard form, following each discharge from virtually all Czech inpatient health-care settings, and includes day cases. The English translation of the form and detailed description of registers is provided elsewhere (11). Clinical

128    and socio-demographic characteristics collected include the dates of admission and discharge,
129    the primary and secondary diagnoses coded according to the International Classification of
130    Diseases 10th Revision (ICD-10), age, sex, marital status, occupation, and region of residence.
131    However, the provision of information on marital status, occupation, and region of residence
132    is not mandatory. The register of all-cause deaths consists of information based on death
133    certificates that are routinely completed by physicians for all deaths occurring in Czechia. The
134    provided information included the date of death, age at death, sex, the ICD-10 cause of death,
135    and, if applicable, the external cause of death.
136
137    We excluded (1) records with missing information on key variables (sex, age, admission and
138    discharge date, region of residence, primary diagnosis) or incorrect (i.e., non-existent) dates,
139    (2) all records of individuals who have more than one date of death available or have
140    hospitalizations following the date of death, and (3) all records where a hospitalization began
141    before the end of a previous one (i.e., overlapping hospitalizations). We used the first two
142    criteria to remove records affected by administrative and/or technical errors (0.06% of all
143    records), while the third criterion was to limit the risk of severe identification problems
144    (negative time-to-events). For details see the flowchart in Figure 1.
145

146    ## Cohorts of people with physical health conditions
147    We identified all people hospitalized (i.e., primary diagnosis) with one or more of 9 broadly
148    defined and 19 specific physical health conditions between 1st January 1999 until 31st
149    December 2017, separately for each health condition (Supplementary Table 1). For each health
150    condition, we considered the first occurrence as the index record (i.e., study baseline). To
151    include incident cases of physical health conditions, we removed individuals who had a
152    diagnosis of the specific physical health condition in the time-period between 1st January 1994
153    and the index record (i.e., wash-out period of five or more years) from the respective analysis.
154    When an individual had records related to multiple physical health conditions, we included
155    them in cohorts representing each of these physical health conditions separately (i.e., any
156    individual could contribute more than once). We did not consider combinations of multiple
157    different physical health conditions (e.g., cancers and diseases of the neurological system).
158
159    Then, to avoid loss to follow-up due to emigration, we excluded individuals with region of
160    residence outside of Czechia listed on the index record.
161

162    ## Exposure
163    We defined severe mental illnesses as comprising of hospital records listing (1) psychoses
164    (ICD-10 codes F20-F29), (2) bipolar disorder (ICD-10 code F31) or (3) severe depression
165    (episode or recurrent; ICD-10 codes F322-F323 and F332-F333) as the primary diagnosis. We
166    considered the occurrence of any of the above codes before the studied physical health
167    conditions (assessed from 1st January 1999) to be indicative of having a pre-existing severe
168    mental illness. The comparison cohort consisted of individuals without a severe mental illness
169    between 1st January 1999 and the onset of the studied physical health conditions (see
170    Supplementary Figure 1 for an example of one condition).
171

172    ## Matching
173    We exact matched each individual with severe mental illness with counterparts without severe
174    mental illness on the first record related to a given physical health condition on sex, age (± 3
175    years), and discharge year listed on the record. We used matching on sex and age because we
176    considered them as important confounders, and matching on discharge year to ensure that the

177  individuals would have a comparable follow-up period and to control for possible calendar and
178  cohort effects. By matching on age ± 3 years, we aimed to maximize the number of matched
179  individuals while simultaneously minimizing confounding due to age. We were able to match
180  every individual with severe mental illness with up to five unique counterparts across all
181  studied physical health conditions, with the exception of Parkinson's disease (2.5% unmatched
182  individuals).
183

184  Outcome
185  We investigated (1) the risk of all-cause death and (2) life-years lost following the onset of
186  each of the 9 broadly defined and 19 specific physical health conditions.
187

188  Statistical analysis
189  Following descriptive analysis of the cohorts, we used stratified Cox proportional hazards
190  models to assess the risk of all-cause death in people with pre-existing severe mental illness
191  following the development of physical health conditions, when compared with counterparts
192  without a history of severe mental illness. Each stratum consisted of one individual with severe
193  mental illness and up to five individually-matched, unexposed counterparts. We considered the
194  outcome as all-cause mortality between the first record related to a given physical health
195  condition and 31st December 2017: individuals who did not experience the outcome during the
196  follow-up period were censored at that point. We adjusted for confounders used for matching,
197  with age included as a continuous measure to further reduce the potential residual confounding.
198  The results are expressed as hazard ratios (HRs) with 95% confidence intervals (CIs),
199  indicating the risk of all-cause death in people with pre-existing severe mental illness compared
200  with unexposed counterparts. We examined whether the proportionality assumption was
201  fulfilled using Schoenfeld residuals. In some cases, this assumption was violated; thus, HRs
202  must be interpreted as weighted averages of the time-varying HRs over the entire follow-up
203  period (12). We created a Kaplan-Meier plot on all-cause death following the onset of each of
204  the studied physical health conditions, separately.
205

206  Then, we calculated differences in loss of life-years between individuals with severe mental
207  illness and people without severe mental illness. We defined life-years lost as differences in
208  remaining life-expectancy (13) after the onset of each physical health condition, and before
209  reaching the age of 81 years. We used a method that took into consideration the ages at which
210  the physical health conditions occurred (13), and used 10 000 bootstrap iterations to establish
211  the 95% CIs.
212

213  Sensitivity analysis
214  First, to account for potentially different distributions of physical health conditions in people
215  with severe mental illness and their counterparts that could influence the outcomes, we adjusted
216  for the presence of other physical health conditions occurring in the period of five-years prior
217  to the index hospitalization for a given physical health condition in stratified Cox proportional
218  hazard models, in addition to matching variables. In each broadly defined physical health
219  condition, we adjusted for each of the 8 remaining broadly defined physical health conditions,
220  while in each specific physical health condition, we adjusted for each of the remaining 18
221  physical health conditions.
222

223  Second, individuals with serious mental illnesses might have a worsened overall health state
224  relative to their counterparts, thus potentially contributing to worsened outcomes in these
225  individuals after the onset of a given physical health condition. To partially address this, we

226  controlled for the number of hospitalizations occurring in the period of five-years prior to the
227  index hospitalization for a given physical health condition in stratified Cox proportional hazard
228  models, in addition to matching variables. Since the number of past hospitalizations can include
229  hospitalizations for severe mental illness, and thus be part of the exposure, we also calculated
230  this number not considering hospitalizations for severe mental illness.
231
232  Third, we adjusted in stratified Cox proportional hazard models for history of disorders due to
233  psychoactive substance use (defined as ICD-10 code F1 on primary diagnosis) in the period of
234  five-years prior to the index hospitalization, in addition to matching variables. Serious mental
235  illnesses and disorders due to psychoactive substance use have a complex relationship, and we
236  cannot rule out that for some individuals disorders due to psychoactive substance use would
237  act as mediators, thus leading to overadjustment bias (14). However, we conceptually
238  considered history of disorders due to psychoactive substance use as a confounder.
239
240  Fourth, in addition to the matching variables, we controlled for work status and marital status
241  in the stratified Cox proportional hazard models since these could be important confounders
242  per se, or proxies for socioeconomic status and social functioning.
243
244  Fifth, to rule out the possibility that the results might be driven by unnatural causes of death
245  (defined as ICD-10 codes V01-Y98), we performed the analysis with considering only natural
246  causes of death as event, with unnatural causes of death being a competing risk.
247
248  Last, to quantify what level of confounding would be necessary to nullify the associations we
249  observed, we computed E-values for each of our regression models where the 95% CIs did not
250  include a null effect (15). Higher E-values increase the confidence that the results are not due
251  to residual confounding (15).
252
253  Throughout the study, we followed the statement from the American Statistical Association on
254  p-values; thus, we refrained from performing null-hypothesis significance testing (16). All
255  analysis were performed in R (version 4.2.2), using libraries *survival* (version 3.5-5), *llilies*
256  (version 0.2.129) (13), and *EValue* (version 4.1.3) (17).

## Results

258  The number of individuals in disease-specific cohorts ranged from 600 (100 with and 500
259  without severe mental illness) for tuberculosis to 37 962 (6 327 with and 31 635 without severe
260  mental illness) for diseases of the circulatory system, with a median of 4 593 individuals. The
261  mean age at onset varied from around 34 years for chronic viral hepatitis to around 68 years
262  for peripheral artery occlusive disease. The proportion of females ranged from around 28% for
263  tuberculosis to approximately 87% for thyroid disorder (excluding prostate disorders, in which
264  there were only males). For detailed descriptive statistics see Table 1.
265

### Risk of all-cause death

267  We detected an elevated risk of all-cause death in people with severe mental illness following
268  the onset of seven out of nine studied broadly defined physical health conditions, when
269  compared with matched counterparts. The hazard ratios for these conditions ranged from 1.20
270  (1.09 to 1.32) for diseases of the neurological system to 1.91 (1.83 to 2.00) for diseases of the
271  circulatory system. For connective tissue disorders and infectious and parasitic diseases, the
272  results were consistent with a null effect.
273

Considering specific physical health conditions, we detected an increased risk of all-cause death in people with severe mental illness following the onset of 14 out of 19. The hazard ratios ranged from 1.24 (1.06 to 1.46) for chronic kidney disease to 3.01 (2.30 to 3.93) for thyroid disorder. The results for chronic liver disease, epilepsy, Parkinson's disease, tuberculosis, and chronic viral hepatitis were consistent with a null effect. For detailed information see Figure 2 and Supplementary Table 2.

### Differences in losses of life-years

We detected that people with severe mental illness had shorter life expectancy after the onset of a physical health condition than people without severe mental illness for eight out of nine broadly defined physical health conditions. The additional losses of life-years ranged from 1.73 (0.88 to 2.57) for diseases of the neurological system to 4.38 (1.45 to 7.27) for connective tissue disorders. For infectious and parasitic diseases, the results were consistent with no differences in life-years lost.

Considering specific physical health conditions, people with severe mental illness lost more life-years following the onset of 13 out of 19 specific physical health conditions. The additional losses of life-years ranged from 1.40 (1.05 to 1.74) for heart failure to 8.94 (5.08 to 12.66) for inflammatory bowel disease. The results for tuberculosis, chronic viral hepatitis, Parkinson's disease, multiple sclerosis, epilepsy, and chronic liver disease were consistent with no differences in life-years lost. For detailed information see Figure 3 and Supplementary Table 3.

### Sensitivity analysis

For five out of seven broadly defined physical health conditions for which we found elevated risks in the main analysis, the results remained robust following adjustment for other physical health conditions, number of past hospitalizations, history of disorders due to psychoactive substance use and additional socio-demographic characteristics. For diseases of the urogenital system and diseases of the neurological system, the results of at least one sensitivity analysis were consistent with a null effect. Considering specific physical health conditions, we found results consistent with the main analysis for 13 out of 14 conditions. For chronic kidney disease, the results of at least one sensitivity analysis were consistent with a null effect. See details in Table 2.

The E-values for conditions that were inconsistent with a null effect in both the main and the sensitivity analysis ranged from 1.67 for diabetes mellitus to 3.67 for thyroid disorder. See details in Supplementary Table 4.

# Discussion

### Principal findings

Using data from the Czech national register of inpatient care, we demonstrated that people with severe mental illness were more likely to die than people without severe mental illness following the development of seven out of nine broadly defined, and 14 out of 19 specific physical health conditions. For most associations, particularly those related to cardiovascular diseases and cancers, the results remained robust after considering the potentially confounding role of somatic multimorbidity as well as disorders due to psychoactive substance use, the number of past hospitalizations, and socio-demographic factors. Compared with people without severe mental illness, people with pre-existing severe mental illness showed marked additional losses of life-years in most of the studied physical health conditions. These results

322   suggest that a wide range of physical health conditions are more likely to result in all-cause
323   death when they occur in people with pre-existing severe mental illness, and these associations
324   cannot be entirely explained by this patient group having more physical illness that is clinically
325   recorded.
326
327   ## Comparison with other studies
328   To the best of our knowledge, this is the first national study to systematically investigate
329   mortality and loss of life-years in people with severe mental illness who subsequently develop
330   physical health conditions. A Danish nationwide study, while not taking into consideration the
331   temporal order of mental illness and physical health conditions, compared individuals with
332   schizophrenia who also had physical health conditions with individuals who only had the
333   physical health conditions, and found increased mortality and excess life-years lost in nine out
334   of nine broadly defined physical health conditions (18). The magnitude of the associations we
335   detected in our study was, on average, smaller. This might be related to differences in case mix,
336   methodology, with our study focusing on the importance of the temporal order of severe mental
337   illness and physical health conditions, and in the underlying populations and healthcare
338   systems. Another Danish study based on national register data demonstrated higher risk of all-
339   cause death in 18 out of 19 physical health conditions in individuals with pre-existing
340   depression (19). The strength of the associations is broadly in line with those detected in our
341   study, however, the authors considered many physical health conditions that we did not
342   consider (19). Further contributing to limited comparability, the authors considered all
343   occurrences of depression, including those of mild and moderate severity, and did not consider
344   the outcomes in individuals with pre-existing depression compared with matched counterparts
345   without pre-existing depression (19). When compared with our own previous study that
346   investigated the risk of all-cause death and loss of life-years following the development of
347   physical health conditions in people with substance use disorders, we found that, for most
348   conditions, people with substance use disorders displayed even higher risks of all-cause death
349   and larger losses of life-years than people with severe mental illness (9).
350
351   Multiple factors might be responsible for the worsened outcomes of physical health conditions
352   arising in people with pre-existing severe mental illness. Sub-optimal nutrition, exercise and
353   lifestyle factors such as smoking tobacco are prevalent in this patient group (20-22).
354   Antipsychotics use is associated with decreased risk of all-cause mortality in people with
355   psychotic disorders (23); however, it can lead to metabolic side-effects of varying degree (24).
356   There may be reluctance or difficulties, importantly, due to socioeconomic factors (25-28), in
357   people with severe mental illness accessing or engaging with screening programs (29, 30),
358   dental (31, 32) and surgical health services (33), and difficulties with adherence to treatments,
359   including those for physical health conditions (34). People with severe mental illness may
360   experience delayed diagnosis (35, 36) or complete unrecognition of physical health conditions
361   (37), potentially due misattribution of physical symptoms to mental disorders by medical
362   professionals (i.e., diagnostic overshadowing) (38). The widespread stigma (39), including
363   among medical professionals (40), and discrimination (41) towards people with severe mental
364   illness may contribute to lower service utilization in these people (42, 43), and consequently
365   decrease the attention paid to their physical health. Finally, the healthcare system is fragmented
366   beyond primary care, with separation between outpatient and inpatient services and between
367   physical and mental health services (44), creating obstacles for people with severe mental
368   illness to get their health conditions addressed in an integrated manner and militates against
369   holistic awareness and training of clinical staff who see themselves as either managing physical
370   or mental disorders.

## Clinical implications

The World Health Organization emphasizes the need for better physical health in people with mental disorders and calls for an integrated approach to care (45). Several countries have policies and national guidelines in place to improve the physical health of people with severe mental illness. For instance, the UK National Institute of Care Excellence includes physical health management in its guidance on the treatment of first-episode psychotic disorders and schizophrenia (46), considering that secondary mental health services should lead physical health management, certainly during the initial phase of the mental disorder. The Czech Psychiatric Association has recently issued recommendations on monitoring and addressing physical health in people with severe mental illness. These contain, among others, the regular monitoring of biomarkers such as high-density lipoprotein, low-density lipoprotein and triglycerides (47). However, the existing national recommendations do not acknowledge the notion of physical disorders being more likely to be fatally deleterious in this patient group. These findings clearly demonstrate that people with severe mental illnesses are particularly vulnerable and should be a high priority not only within psychiatric but also within broader health services. Ensuring the provision of holistic care for severe mental illnesses and physical health conditions can be considered as a minimally adequate first step, and requires a health system-wide, collaborative change. However, to fully reverse the adverse outcomes experienced by people with severe mental illness, systemic efforts, encompassing changes to public perception, policy, public health and clinical practice, are required.

## Methodological considerations

Strengths include nationwide, routinely collected, standardised health and mortality data. This supported the analysis of usefully precise matched cohorts of people with and without severe mental illness who developed a range of common physical health conditions. Our design lends confidence that the associations regarding increased mortality would be driven by pre-existing severe mental illness and its consequences rather than physical illnesses leading to severe mental illness as well as to death.

Our study has some limitations. First, the cohorts consisted of individuals treated in inpatient settings. However, a large proportion of the physical health conditions will be diagnosed and managed in community settings; thus, it could be argued that diagnoses reached following inpatient admission might be more severe and demonstrate specificity over sensitivity. This would not contribute to selection bias since all inpatient settings were considered, but it would potentially limit the generalisability of results beyond inpatient care. Second, we aimed to include only incident cases of physical health conditions, but we cannot rule out that some individuals already had these before the onset of severe mental illness. Third, our data did not include information on several biological, behavioral, and socio-demographic confounders, most notably body mass index, prescription medication use, smoking status, and income; thus, part of our results could be due to residual confounding. Fourth, some cohorts were considerably small, leading to excessive uncertainty in estimates. Relatedly, the size of cohorts precluded of us from investigating the outcomes of people with specific severe mental illnesses. Last, while the number of individuals emigrating from Czechia is low (9), we did not have information on emigration status, so it is possible that some individuals were lost to follow-up.

## Conclusions

Almost all categories of physical illness are more likely to result in all-cause death in people with pre-existing severe mental illness. This premature mortality cannot be fully explained by having more clinically-recorded physical illness, suggesting that the physical disorders are also more likely to be fatally deleterious in this patient group. Implementing holistic care for people

421  with severe mental illness and physical health conditions is the necessary first step; however,
422  coordinated changes to policy, public health and clinical practice are imperative to fully reverse
423  the adverse outcomes experienced by this patient group.

## Data availability

425  Due to its sensitive nature, the observational data cannot be published or shared with external
426  subjects without permission from the Czech Institute of Health Information and Statistics. The
427  full  analytical  code  of  the  study  is  available  at  a  dedicated  GitHub  repository:
428  https://github.com/tmfmnk/Severe-mental-illness-contributing-to-mortality-following-
429  physical-disorders. TF and KM had full access to all data in the study and take responsibility
430  for the integrity of the data and the accuracy of the data analysis.

## Authors contributions

432  TF initiated and designed the study, performed the statistical analysis and led the writing of the
433  manuscript. DK contributed to designing the study and interpretation of results and provided
434  critical revisions to the manuscript. BIP contributed to designing the study and interpretation
435  of results and provided critical revisions to the manuscript. KM contributed to the statistical
436  analysis and interpretation of results, performed the code review and provided critical revisions
437  to the manuscript. EFO contributed to designing the study and interpretation of results and
438  provided  critical  revisions  to  the  manuscript.  JM  contributed  to  designing  the  study  and
439  interpretation of results and provided critical revisions to the manuscript. PBJ contributed to
440  designing the study and interpretation of results, provided supervision and wrote a substantial
441  part of the manuscript. OP-R contributed to designing the study, the statistical analysis, the
442  code review and interpretation of results and provided critical revisions to the manuscript. All
443  authors approved the decision to submit for publication.

## Conflict of interest statement

445  The authors have nothing to disclose.

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461  other funders.

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607  Table 1 Descriptive statistics of cohorts
608

| Cohort | Total, n | | Age, mean (SD) | | Females, n (%) | | Discharge year, median (IQR) | |
|---|---|---|---|---|---|---|---|---|
| | People without severe mental illness | People with severe mental illness | People without severe mental illness | People with severe mental illness | People without severe mental illness | People with severe mental illness | People without severe mental illness | People with severe mental illness |
| Diseases of the circulatory system | 31 635 | 6 327 | 63.34 (12.53) | 63.22 (12.58) | 18 885 (59.70) | 3 777 (59.70) | 2010 (2006-2014) | 2010 (2006-2014) |
| Hypertension | 7 290 | 1 458 | 62.39 (13.37) | 62.27 (13.42) | 5 115 (70.16) | 1 023 (70.16) | 2010 (2006-2014) | 2010 (2006-2014) |
| Ischemic heart disease | 11 000 | 2 200 | 63.92 (12.03) | 63.76 (12.12) | 5 850 (53.18) | 1 170 (53.18) | 2009 (2005-2013) | 2009 (2005-2013) |
| Atrial fibrillation | 3 810 | 762 | 67.51 (11.20) | 67.40 (11.26) | 2 360 (61.94) | 472 (61.94) | 2012 (2007-2015) | 2012 (2007-2015) |
| Heart failure | 8 015 | 1 603 | 67.57 (11.76) | 67.29 (11.83) | 5 135 (64.07) | 1 027 (64.07) | 2012 (2008-2015) | 2012 (2008-2015) |
| Peripheral artery occlusive disease | 6 395 | 1 279 | 68.14 (12.23) | 67.96 (12.30) | 3 835 (59.97) | 767 (59.97) | 2009 (2005-2013) | 2009 (2005-2013) |
| Stroke | 11 575 | 2 315 | 65.73 (12.33) | 65.54 (12.36) | 7 000 (60.48) | 1 400 (60.48) | 2011 (2006-2014) | 2011 (2006-2014) |
| Diseases of the endocrine system | 11 115 | 2 223 | 56.90 (13.69) | 56.81 (13.67) | 7 315 (65.81) | 1 463 (65.81) | 2010 (2006-2014) | 2010 (2006-2014) |
| Diabetes mellitus | 8 735 | 1 747 | 58.04 (13.56) | 57.84 (13.56) | 5 245 (60.05) | 1 049 (60.05) | 2010 (2006-2014) | 2010 (2006-2014) |
| Thyroid disorder | 2 620 | 524 | 53.67 (13.32) | 53.62 (13.46) | 2 290 (87.40) | 458 (87.40) | 2010 (2006-2014) | 2010 (2006-2014) |
| Chronic pulmonary diseases | 6 735 | 1 347 | 59.82 (14.19) | 59.70 (14.17) | 3 985 (59.17) | 797 (59.17) | 2011 (2006-2014) | 2011 (2006-2014) |
| Diseases of the gastrointestinal system | 8 080 | 1 616 | 54.13 (16.34) | 54.03 (16.31) | 3 945 (48.82) | 789 (48.82) | 2010 (2006-2014) | 2010 (2006-2014) |
| Ulcer or chronic gastritis | 3 515 | 703 | 58.35 (14.75) | 58.25 (14.74) | 1 790 (50.92) | 358 (50.92) | 2010 (2006-2014) | 2010 (2006-2014) |
| Chronic liver disease | 2 540 | 508 | 45.10 (14.56) | 44.99 (14.60) | 895 (35.24) | 179 (35.24) | 2009 (2005-2014) | 2009 (2005-2014) |
| Inflammatory bowel disease | 760 | 152 | 46.06 (17.16) | 46.07 (17.05) | 380 (50.00) | 76 (50.00) | 2010 (2005-2014) | 2010 (2005-2014) |
| Diverticular disease of intestine | 1 710 | 342 | 63.27 (12.28) | 63.12 (12.33) | 1 115 (65.20) | 223 (65.20) | 2011 (2007-2014) | 2011 (2007-2014) |
| Diseases of the urogenital system | 3 845 | 769 | 63.57 (11.25) | 63.31 (11.34) | 1 165 (30.30) | 233 (30.30) | 2011 (2007-2014) | 2011 (2007-2014) |
| Chronic kidney disease | 1 805 | 361 | 63.80 (13.86) | 63.61 (13.89) | 1 165 (64.54) | 233 (64.54) | 2011 (2007-2015) | 2011 (2007-2015) |
| Prostate disorders | 2 109 | 422 | 63.39 (8.43) | 63.16 (8.60) | 0 (0.00) | 0 (0.00) | 2010 (2006-2014) | 2010 (2006-2014) |
| Connective tissue disorders | 800 | 160 | 52.65 (14.52) | 52.61 (14.54) | 540 (67.50) | 108 (67.50) | 2010.5 (2006-2013) | 2010.5 (2006-2013) |
| Cancers | 18 120 | 3 624 | 60.87 (11.82) | 60.77 (11.87) | 11 630 (64.18) | 2 326 (64.18) | 2011 (2007-2014) | 2011 (2007-2014) |
| Diseases of the neurological system | 9 130 | 1 826 | 49.79 (17.28) | 49.77 (17.23) | 4 735 (51.86) | 947 (51.86) | 2010 (2006-2014) | 2010 (2006-2014) |
| Epilepsy | 6 764 | 1 353 | 46.85 (16.55) | 46.81 (16.49) | 3 264 (48.26) | 653 (48.26) | 2010 (2006-2014) | 2010 (2006-2014) |
| Parkinson's disease | 1 875 | 391 | 65.62 (11.32) | 63.93 (13.04) | 1 081 (57.65) | 225 (57.54) | 2011 (2006-2014) | 2011 (2006.5-2014) |
| Multiple sclerosis | 585 | 117 | 40.87 (11.90) | 41.01 (11.89) | 425 (72.65) | 85 (72.65) | 2009 (2005-2014) | 2009 (2005-2014) |
| Infectious and parasitic diseases | 1 135 | 227 | 42.69 (15.98) | 42.63 (16.12) | 370 (32.60) | 74 (32.60) | 2008 (2004-2012) | 2008 (2004-2012) |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| Tuberculosis | 500 | 100 | 53.47 (14.54) | 53.34 (14.62) | 140 (28.00) | 28 (28.00) | 2008 (2005-2012) | 2008 (2005-2012) |
| Chronic viral hepatitis | 592 | 119 | 34.03 (11.48) | 34.19 (11.60) | 202 (34.12) | 41 (34.45) | 2007 (2003-2011) | 2007 (2003-2011) |

Individuals with and without severe mental illness were exactly-matched on sex, age (± 3 years), and discharge year.

638 Table 2 Sensitivity analyses of all-cause mortality following the onset of physical health conditions in people with pre-existing severe mental
639 illness compared with matched counterparts without severe mental illness
640

| Cohort | Adjusting for past history of other studied physical health conditions | Adjusting for number of past hospitalizations | Adjusting for number of past hospitalizations, excluding those for severe mental illness | Adjusting for past history of disorders due to psychoactive substance use | Adjusting for additional socio-demographic characteristics | Unnatural cause of death as competing risk |
|---|---|---|---|---|---|---|
| Diseases of the circulatory system | 1.86 (1.78; 1.95) | 1.57 (1.49; 1.64) | 1.75 (1.67; 1.83) | 1.87 (1.79; 1.96) | 1.66 (1.58; 1.74) | 1.88 (1.79; 1.96) |
| Hypertension | 1.78 (1.61; 1.98) | 1.54 (1.38; 1.71) | 1.67 (1.50; 1.85) | 1.80 (1.62; 1.99) | 1.61 (1.45; 1.79) | 1.77 (1.60; 1.96) |
| Ischemic heart disease | 1.90 (1.76; 2.05) | 1.57 (1.45; 1.71) | 1.76 (1.63; 1.90) | 1.95 (1.81; 2.10) | 1.75 (1.62; 1.89) | 1.92 (1.78; 2.07) |
| Atrial fibrillation | 1.78 (1.56; 2.04) | 1.61 (1.40; 1.84) | 1.72 (1.50; 1.97) | 1.79 (1.57; 2.05) | 1.75 (1.53; 2.01) | 1.79 (1.56; 2.05) |
| Heart failure | 1.36 (1.26; 1.46) | 1.23 (1.14; 1.33) | 1.30 (1.20; 1.40) | 1.34 (1.24; 1.44) | 1.23 (1.14; 1.33) | 1.33 (1.23; 1.43) |
| Peripheral artery occlusive disease | 1.41 (1.29; 1.54) | 1.22 (1.11; 1.33) | 1.30 (1.19; 1.42) | 1.38 (1.26; 1.50) | 1.30 (1.19; 1.41) | 1.38 (1.26; 1.50) |
| Stroke | 1.52 (1.42; 1.62) | 1.34 (1.25; 1.44) | 1.44 (1.34; 1.54) | 1.50 (1.40; 1.60) | 1.39 (1.30; 1.49) | 1.51 (1.41; 1.61) |
| Diseases of the endocrine system | 1.76 (1.61; 1.92) | 1.45 (1.32; 1.59) | 1.63 (1.49; 1.79) | 1.70 (1.56; 1.86) | 1.47 (1.34; 1.62) | 1.70 (1.55; 1.86) |
| Diabetes mellitus | 1.31 (1.19; 1.44) | 1.11 (1.01; 1.22) | 1.23 (1.12; 1.35) | 1.26 (1.15; 1.38) | 1.14 (1.03; 1.25) | 1.26 (1.15; 1.38) |
| Thyroid disorder | 3.02 (2.27; 4.01) | 2.13 (1.58; 2.85) | 2.63 (1.99; 3.46) | 2.92 (2.23; 3.83) | 2.50 (1.89; 3.32) | 2.70 (2.05; 3.56) |
| Chronic pulmonary diseases | 1.52 (1.39; 1.68) | 1.36 (1.23; 1.50) | 1.44 (1.31; 1.58) | 1.49 (1.35; 1.63) | 1.33 (1.21; 1.46) | 1.49 (1.36; 1.64) |
| Diseases of the gastrointestinal system | 1.40 (1.28; 1.54) | 1.21 (1.10; 1.33) | 1.29 (1.18; 1.42) | 1.32 (1.20; 1.45) | 1.15 (1.04; 1.26) | 1.34 (1.22; 1.48) |
| Ulcer or chronic gastritis | 1.46 (1.27; 1.67) | 1.26 (1.10; 1.45) | 1.36 (1.18; 1.56) | 1.42 (1.24; 1.62) | 1.27 (1.10; 1.46) | 1.40 (1.22; 1.60) |
| Chronic liver disease | 1.11 (0.95; 1.31) | 1.00 (0.84; 1.18) | 1.03 (0.87; 1.21) | 1.05 (0.89; 1.23) | 0.96 (0.82; 1.14) | 1.07 (0.91; 1.26) |
| Inflammatory bowel disease | 2.72 (1.75; 4.22) | 1.85 (1.20; 2.87) | 2.16 (1.42; 3.28) | 2.50 (1.65; 3.78) | 2.07 (1.32; 3.23) | 2.22 (1.45; 3.41) |
| Diverticular disease of intestine | 2.08 (1.65; 2.63) | 1.75 (1.39; 2.21) | 1.81 (1.45; 2.27) | 1.91 (1.53; 2.38) | 1.75 (1.39; 2.20) | 1.79 (1.42; 2.24) |
| Diseases of the urogenital system | 1.31 (1.15; 1.49) | 1.06 (0.92; 1.21) | 1.18 (1.03; 1.35) | 1.26 (1.11; 1.44) | 1.10 (0.96; 1.26) | 1.24 (1.09; 1.42) |
| Chronic kidney disease | 1.24 (1.05; 1.46) | 1.10 (0.93; 1.30) | 1.15 (0.98; 1.36) | 1.23 (1.04; 1.44) | 1.17 (0.99; 1.38) | 1.24 (1.06; 1.46) |
| Prostate disorders | 1.68 (1.35; 2.09) | 1.33 (1.06; 1.66) | 1.52 (1.22; 1.88) | 1.66 (1.35; 2.05) | 1.40 (1.13; 1.75) | 1.59 (1.28; 1.98) |
| Connective tissue disorders | 1.26 (0.84; 1.89) | 1.02 (0.67; 1.57) | 1.20 (0.80; 1.80) | 1.48 (1.01; 2.17) | 1.24 (0.83; 1.85) | 1.35 (0.91; 2.00) |
| Cancers | 1.46 (1.39; 1.54) | 1.35 (1.27; 1.42) | 1.42 (1.35; 1.50) | 1.47 (1.39; 1.55) | 1.32 (1.25; 1.39) | 1.46 (1.39; 1.54) |
| Diseases of the neurological system | 1.29 (1.17; 1.42) | 0.99 (0.89; 1.09) | 1.13 (1.02; 1.24) | 1.16 (1.05; 1.27) | 1.08 (0.98; 1.19) | 1.16 (1.05; 1.28) |
| Epilepsy | 1.12 (1.00; 1.26) | 0.89 (0.79; 1.01) | 1.01 (0.90; 1.13) | 1.05 (0.94; 1.18) | 0.96 (0.85; 1.07) | 1.05 (0.93; 1.18) |
| Parkinson's disease | 0.97 (0.82; 1.16) | 0.91 (0.76; 1.08) | 0.95 (0.80; 1.13) | 0.98 (0.82; 1.16) | 0.93 (0.79; 1.11) | 0.99 (0.83; 1.18) |
| Multiple sclerosis | 3.17 (1.64; 6.13) | 2.13 (1.12; 4.06) | 2.67 (1.44; 4.97) | 2.68 (1.45; 4.94) | 2.84 (1.38; 5.84) | 2.15 (1.12; 4.12) |
| Infectious and parasitic diseases | 1.26 (0.93; 1.72) | 1.15 (0.83; 1.58) | 1.23 (0.90; 1.67) | 1.25 (0.92; 1.70) | 1.10 (0.80; 1.52) | 1.20 (0.87; 1.66) |
| Tuberculosis | 1.26 (0.85; 1.85) | 1.11 (0.76; 1.63) | 1.17 (0.81; 1.70) | 1.22 (0.84; 1.77) | 1.12 (0.77; 1.64) | 1.24 (0.86; 1.80) |
| Chronic viral hepatitis | 1.45 (0.79; 2.67) | 0.98 (0.52; 1.86) | 1.12 (0.61; 2.02) | 1.29 (0.71; 2.34) | 1.23 (0.67; 2.25) | 1.17 (0.58; 2.37) |

641
642   The results are expressed as hazard ratios with 95% confidence intervals. Past history of other studied physical health conditions, past history of
643   disorders due to psychoactive substance use, and the number of past hospitalizations refer to the period of five-years prior to the first hospitalization
644   for the respective physical health condition. The additional socio-demographic characteristics were work status and marital status, both recorded
645   at the first hospitalization for the respective physical health condition. Unnatural causes of death included suicides, accidents and assaults.

646    Figure 1 Flowchart
647



All inpatient visits between 1st January
1994 and 31st December 2017
(n = 56 229 563)

Excluding records with missing information on key
variables or invalid admission and discharge date
(n = 34 761)

56 194 802 included

Excluding all records of individuals who have
more than one date of death available or have hospitalizations
following the date of death
(n = 283 330)

55 911 472 included

All records where a hospitalization began before the end
of a previous one (i.e., overlapping hospitalizations)
(n = 661 255)

55 250 217 included

Excluding records where admission or discharge date
occurred before 1st January 1999, or after 31 December
2017
(n =11 019 241)

44 230 976 included

Establishing the 28 study cohorts

648

649    Figure 2 Adjusted hazard ratios (aHR) of all-cause mortality following the onset of physical health conditions in people with pre-existing severe
650    mental illness compared with matched counterparts without severe mental illness
651

| | Unexposed events/total | Exposed events/total | aHR (95% CI) |
|---|---|---|---|
| Diseases of the circulatory system | 10193/31635 | 3071/6327 | 1.91 (1.83; 2.00) |
| Hypertension | 1900/7290 | 582/1458 | 1.83 (1.65; 2.02) |
| Ischemic heart disease | 3706/11000 | 1103/2200 | 1.97 (1.83; 2.12) |
| Atrial fibrillation | 1188/3810 | 341/762 | 1.83 (1.61; 2.09) |
| Heart failure | 4498/8015 | 1020/1603 | 1.34 (1.24; 1.44) |
| Peripheral artery occlusive disease | 3450/6395 | 808/1279 | 1.39 (1.27; 1.51) |
| Stroke | 5114/11575 | 1301/2315 | 1.52 (1.42; 1.62) |
| Diseases of the endocrine system | 2499/11115 | 746/2223 | 1.76 (1.61; 1.92) |
| Diabetes mellitus | 2800/8735 | 665/1747 | 1.29 (1.18; 1.41) |
| Thyroid disorder | 192/2620 | 95/524 | 3.01 (2.30; 3.93) |
| Chronic pulmonary diseases | 2564/6735 | 664/1347 | 1.52 (1.38; 1.67) |
| Diseases of the gastrointestinal system | 2568/8080 | 648/1616 | 1.40 (1.28; 1.53) |
| Ulcer or chronic gastritis | 1202/3515 | 317/703 | 1.45 (1.27; 1.66) |
| Chronic liver disease | 973/2540 | 210/508 | 1.10 (0.94; 1.29) |
| Inflammatory bowel disease | 97/760 | 40/152 | 2.54 (1.70; 3.79) |
| Diverticular disease of intestine | 390/1710 | 124/342 | 1.92 (1.54; 2.39) |
| Diseases of the urogenital system | 1396/3845 | 331/769 | 1.28 (1.12; 1.45) |
| Chronic kidney disease | 965/1805 | 211/361 | 1.24 (1.06; 1.46) |
| Prostate disorders | 410/2109 | 127/422 | 1.66 (1.34; 2.05) |
| Connective tissue disorders | 140/800 | 38/160 | 1.46 (1.00; 2.14) |
| Cancers | 8443/18120 | 2100/3624 | 1.48 (1.40; 1.56) |
| Diseases of the neurological system | 2617/9130 | 598/1826 | 1.20 (1.09; 1.32) |
| Epilepsy | 1929/6764 | 409/1353 | 1.08 (0.97; 1.21) |
| Parkinson's disease | 957/1875 | 188/391 | 0.99 (0.83; 1.17) |
| Multiple sclerosis | 33/585 | 18/117 | 2.79 (1.53; 5.09) |
| Infectious and parasitic diseases | 253/1135 | 59/227 | 1.30 (0.96; 1.75) |
| Tuberculosis | 205/500 | 41/100 | 1.25 (0.87; 1.79) |
| Chronic viral hepatitis | 66/592 | 17/119 | 1.36 (0.77; 2.38) |



aHR (95% CI)

652
653
654    The models were adjusted for sex, age, and discharge year listed on the first hospitalization for the respective physical health condition.
655    Figure 3 Differences in life-years lost following the onset of physical health conditions between people with pre-existing severe mental illness and
656    matched counterparts without severe mental illness

657



Difference in life−years lost (95% CI)

658

# Mortality and life-years lost following subsequent physical comorbidity in people with pre-existing substance use disorders: a national registry-based retrospective cohort study of hospitalised individuals in Czechia

*Tomáš Formánek, Dzmitry Krupchanka, Karolína Mladá, Petr Winkler, Peter B Jones*

## Summary

**Background** Substance use disorders constitute a major global public health problem, attributable largely to their subsequent comorbidity with other health conditions. This study aimed to investigate the risk of all-cause death and life-years lost following hospitalisation for 28 subsequent physical comorbid conditions in people with a previous hospitalisation for substance use disorder, compared with matched counterparts without substance use disorder.

**Methods** We did a retrospective cohort study on data from Czech nationwide registers of all-cause hospitalisations and deaths during the period from Jan 1, 1994, to Dec 31, 2017. The cohorts consisted of individuals who had initially been hospitalised between 15 and 70 years of age (index hospitalisation) and who were subsequently hospitalised with one or more of 28 comorbid physical health conditions. We included individuals with an index hospitalisation for substance use disorders and up to three counterparts without substance use disorders with a subsequent hospitalisation for the same physical health condition, with matching on sex, age (±3 years), work status, and discharge year at first hospitalisation for the subsequent condition. Data on ethnicity were not available. Risk of death due to any cause following the first hospitalisation for each physical health condition until Dec 31, 2017, and life-years lost after disease onset at ages 30, 45, and 60 years, and before 81 years of age, were examined.

**Findings** From a total 56229563 records of hospitalisations identified, we included 121153 people with hospitalisation for substance use disorders and 6742134 people without hospitalisation for substance use disorders in the study. The 28 condition-specific cohorts comprised a median of 6444 individuals (IQR 2033–12358), ranging from 444 for multiple sclerosis to 36356 for diseases of the circulatory system. Across the cohorts, the proportion of males ranged from 31·4% for thyroid disorder to 100·0% for prostate disorders. The mean baseline age ranged from 30·0 years (SD 9·1) for chronic viral hepatitis in people with pre-existing substance use disorders to 62·2 years (9·7) for Parkinson's disease in people without pre-existing substance use disorders. After adjusting for potential confounders using stratified Cox proportional hazards models, individuals with a pre-existing substance use disorder had an increased risk of death due to any cause after the onset of 26 out of 28 physical health conditions, relative to their counterparts without substance use disorders, with adjusted hazard ratios ranging from 1·15 (1·09–1·21) for chronic liver disease to 3·86 (2·62–5·67) for thyroid disorder. For seven subsequent health conditions, the risk of death was more than doubled in the group with pre-existing substance use disorders. When compared with the general population via mortality tables, people with pre-existing substance use disorders had substantial losses in life-years after the onset of most of the subsequent physical health conditions regardless of age of onset, and, for the majority of comorbidities, lost considerably more life-years than their counterparts without substance use disorders.

**Interpretation** A history of hospitalisation for substance use disorders appears to have a significant negative effect on prognosis following the development of various subsequent physical health conditions. These findings strongly suggest that clinical vigilance and high-quality integrated treatment for people with substance use disorders could be life-saving and should be given higher priority on the public health agenda.

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## Introduction

Worldwide estimates suggest that more than 283 million (5%) people aged 15 years or older live with alcohol use disorders,[1] and about 35·6 million individuals have psychoactive drug use disorders.[2] Global estimates also suggest that 4·2% of disability-adjusted life-years (DALYs) are attributable to alcohol use and 1·3% to psychoactive drug use.[3] Although substance use disorders

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**Research in context**

**Evidence before this study**
We searched Web of Science and MEDLINE, until April 11, 2022, for studies published in English, containing the terms (mental disorder* OR substance use disorder* OR alcohol use disorder* OR drug use disorder* OR substance use OR alcohol use OR drug use) AND (comorbid* OR co-occurr*) AND (somatic OR physical OR general medical) AND (mortality OR death* OR life-years lost OR years lost OR LYL) AND (health register* OR nationwide register* OR electronic record* OR electronic health record*). We found one recent nationwide cohort study from Denmark that examined the risk of mortality and life-years lost in individuals with substance use disorders with comorbid physical health conditions compared with unmatched individuals having only those physical health conditions. Without considering any direction of causality, it reported elevated mortality rate ratios across all the examined physical health conditions, and substantially more life-years lost in people with substance use disorders than in individuals without substance use disorders. We identified no study that used nationwide health registers matching individuals with pre-existing substance use disorders to those with no history of substance use disorders to estimate the risk of death and life-years lost following the development of specific physical health conditions.

**Added value of this study**
To the best of our knowledge, this is the first study using data from nationwide health registers that estimated the risk of all-cause death and life-years lost after the onset of multiple specific physical health conditions in individuals with a history of hospitalisation for substance use disorders, when compared with matched counterparts without substance use disorder but with the same physical health condition. Among people with pre-existing substance use disorders, an elevated risk of death was found after the onset of 26 out of 28 physical health conditions; for seven conditions, the risk was more than doubled. For most subsequent health conditions, people with substance use disorders lost substantially more life-years than did their counterparts without substance use disorders.

**Implications of all the available evidence**
Past history of hospitalisation for substance use disorders appears to adversely influence the prognosis after the onset of various physical health conditions. Clinicians should take note of such clinical histories and ensure that patients with previous hospital admission for substance use disorders are given high-quality integrated treatment.

have considerable direct effects on health, a large proportion of this burden is ascribed to their effects on other health conditions.[3]

Physical and mental health comorbidities are common in people with a substance use disorder.[4,5] Almost half of people diagnosed with a substance use disorder have other chronic health conditions,[6] and 47–100% have another current mental disorder.[7] Individuals with a substance use disorder and a comorbid health condition are more likely than those with a substance use disorder alone to undergo psychiatric emergency hospitalisation,[8] to be rehospitalised within 30 days of discharge,[9] to die by suicide[10] or have a higher suicide risk,[11] to die prematurely,[4] and to have worse proximal outcomes at discharge from treatment.[12] These increased risks are despite national and international strategies, such as the UN Sustainable Developmental Goals, emphasising the need to scale up public health actions to improve access to high-quality treatment for people with substance use disorders.[13] To succeed with these goals, comorbid health conditions in people with substance use disorders must be addressed, as recently emphasised in a statement by the Informal Scientific Network, UN Commission on Narcotic Drugs.[14]

Although the burden of comorbid health conditions in people with substance use disorders is widely recognised, most existing studies lack breadth of perspective, focusing solely on either psychiatric comorbidities or selected physical health conditions, or rely on analysis of isolated registers of patients with substance use disorders. To the best of our knowledge, no study to date has used

individual-level, nationwide data covering long time periods to investigate outcomes in people with pre-existing substance use disorders following the onset of different physical health conditions and compared these outcomes with matched counterparts without substance use disorders. In the present study, we used the Czech nationwide health registers of all-cause hospitalisations and all-cause deaths to assess the risk of all-cause death and life-years lost in people with a history of hospitalisation for a substance use disorder following the onset of nine broadly defined and 19 specific subsequent physical health conditions requiring hospitalisation, in the period from 1994 to 2017. We hypothesised that, following hospitalisation for a subsequent physical health condition, individuals who had previously been hospitalised with substance use disorder would have a higher risk of all-cause mortality and more life-years lost than their counterparts without hospitalisation for substance use disorder.

## Methods

### Data and sources
We used individual-level, de-identified data from two Czech nationwide health registers: the register of all-cause hospitalisations and the register of all-cause deaths. Both registers are maintained by the state-funded Institute of Health Information and Statistics (IHIS) of Czechia and cover the entire Czech population (approximately 10·7 million inhabitants). A unique identifier assigned after birth included in both datasets allows

linkage. The IHIS granted the Czech National Institute of Mental Health (NIMH) access to complete data covering the period from Jan 1, 1994 (the earliest available), to Dec 31, 2017.

The records in the register of all-cause hospitalisations are created by health professionals routinely completing a standard, mandatory form when patients are discharged from all Czech health-care settings.[15] Key clinical characteristics are collected, including the dates of admission and discharge, the primary diagnosis, and up to five secondary diagnoses, coded according to the WHO ICD-10. Basic sociodemographic information (such as sex, marital status, occupation, and region of residence) is also collected; however, patients are not required to provide information other than age and sex. Data on ethnicity were not present. The information in the register of all-cause deaths is based on death certificates that are routinely filled by physicians for all deaths occurring in Czechia.[15] The date of death, the ICD-10 cause, and, if applicable, the external cause of death, age at death, and sex are available for each individual.

This study was approved by the ethics committee of the NIMH (code number 105/18).

### Cohort construction

We screened records of all hospitalisations occurring during the specified study period. First, we excluded records with missing information on key variables (sex, age, work status, admission and discharge dates, region of residence, and primary diagnosis) or invalid dates; all records of individuals who were recorded as dying more than once or as being hospitalised after the date of death; and all records in which the discharge date of one hospitalisation occurred after the admission date of another hospitalisation (ie, overlapping hospitalisations). We applied the first two criteria to avoid invalid records due to administrative or technical errors, and the third to avoid severe identification problems (negative time-to-events). Next, we excluded all hospitalisations for which the admission occurred before Jan 1, 1999, or the discharge occurred after Dec 31, 2017. We restricted the analysis to individuals aged 15–70 years, based on the typical onset age of mental disorders[16] and life expectancy in Czechia. To avoid loss to follow-up, we excluded individuals residing outside of Czechia; foreign citizens allowed to stay in Czechia on a visa for up to 90 days and Czech citizens who have their permanent residence outside of Czechia were excluded on the basis of this criterion. When an individual fulfilled all the above conditions on multiple occasions, we used the first instance as the index hospitalisation. In cases with multiple admissions and discharges on the same date for an individual, we used a procedure that randomly sampled one record.

From all included records, we defined the cohort with substance use disorders as comprising all individuals hospitalised with a main ICD-10 diagnosis code of F1x, excluding those related to acute intoxication (ICD-10 codes F100, F110, F120, F130, F140, F150, F160, F170, F180 and F190), and defined the comparison cohort as comprising all hospitalised individuals without hospitalisation for substance use disorder during the entire examined period.

### Assessment of subsequent physical health conditions and mortality

For every individual, we identified the presence of subsequent physical health conditions arising during the period from the end of index hospitalisation until the end of dataset (Dec 31, 2017). We defined a subsequent health condition as an ICD-10 primary diagnosis code at any subsequent hospitalisation that differed from the one listed as the primary diagnosis on the index hospitalisation (appendix p 7) We separately examined nine broadly defined categories of health conditions and 19 specific health conditions (appendix p 1). To facilitate international comparison, which is still lacking in register-based research, the selected health conditions largely correspond to the ones used in two Danish nationwide studies on mental disorders and subsequent physical health conditions.[17,18] However, we added several codes relevant specifically to substance use disorders and removed certain health conditions that we considered to have a low likelihood of resulting in death (eg, migraine). We did not consider somatic multimorbidity, psychiatric comorbidity, or somatic and psychiatric polymorbidity because we believe that these constitute distinct problems that are beyond the scope of a single study.

To reduce the likelihood of including individuals who already had the health condition and severe misspecification of disease onset age, we established whether a health condition occurred in the period of 5 years before the admission date of the index hospitalisation (appendix p 7). When there was an occurrence, we did not consider it to be a subsequent health condition, and we did not include the affected individuals in the analysis for that given health condition.

Finally, we assessed whether an individual died in the period from the end of a hospitalisation for a subsequent health condition until the end of dataset (Dec 31, 2017), specifically for each health condition.

### Matching

We matched up to three individuals without a substance use disorder to every person with a substance use disorder; to do this we used exact matching on sex, age (±3 years), work status (not working *vs* employed), and discharge year of the first hospitalisation related to a given subsequent physical health condition (appendix p 8). When the person with a substance use disorder had more than three potential matched counterparts, we used a procedure that randomly sampled three of them. We matched on sex, age, and work status at the first hospitalisation for a given subsequent physical health condition because each of them is strongly associated with the exposure and the

See **Online** for appendix

```
┌─────────────────────────────────────────────────┐
│ 56 229 563 records of hospitalisations between   │
│         Jan 1, 1994, and Dec 31, 2017 identified │
└─────────────────────────────────────────────────┘
          │
          │        ┌─────────────────────────────────────────────┐
          ├───────▶│ 34 761 excluded (missing information on any   │
          │        │ key variables or invalid admission or         │
          │        │ discharge date)                               │
          ▼        └─────────────────────────────────────────────┘
┌─────────────────────────┐
│ 56 194 802 included     │
└─────────────────────────┘
          │
          │        ┌─────────────────────────────────────────────┐
          ├───────▶│ 283 330 excluded (records relating to         │
          │        │ individuals who had more than one date of     │
          │        │ death, or hospitalisation date occurring      │
          │        │ after date of death)                          │
          ▼        └─────────────────────────────────────────────┘
┌─────────────────────────┐
│ 55 911 472 included     │
└─────────────────────────┘
          │
          │        ┌─────────────────────────────────────────────┐
          ├───────▶│ 661 255 excluded (overlapping records with    │
          │        │ discharge date occurring after admission date │
          │        │ of another hospitalisation)                   │
          ▼        └─────────────────────────────────────────────┘
┌─────────────────────────┐
│ 55 250 217 included     │
└─────────────────────────┘
          │
          │        ┌─────────────────────────────────────────────┐
          ├───────▶│ 11 019 241 excluded (admission or discharge   │
          │        │ date occurred before Jan 1, 1999, or after    │
          │        │ Dec 31, 2017)                                 │
          ▼        └─────────────────────────────────────────────┘
┌─────────────────────────┐
│ 44 230 976 included     │
└─────────────────────────┘
          │
          │        ┌─────────────────────────────────────────────┐
          ├───────▶│ 16 679 884 excluded (patient age <15 or >70   │
          │        │ years)                                        │
          ▼        └─────────────────────────────────────────────┘
┌─────────────────────────┐
│ 27 551 092 included     │
└─────────────────────────┘
          │
          │        ┌─────────────────────────────────────────────┐
          ├───────▶│ 158 551 excluded (place of residence outside  │
          │        │ of Czechia)                                   │
          ▼        └─────────────────────────────────────────────┘
┌─────────────────────────┐
│ 27 392 541 included     │
└─────────────────────────┘
          │
          ├──────────────────────────────────────────────┐
          ▼                                               │
┌────────────────────────────────┐                       │
│ 1 374 866 records of            │                       │
│ individuals with a history of   │                       │
│ substance use disorder          │                       │
└────────────────────────────────┘                       │
          │                                               │
          │        ┌──────────────────────────────┐       │
          ├───────▶│ 975 747 records excluded      │       │
          │        │ (substance use disorder not   │       │
          │        │ listed as the primary         │       │
          │        │ diagnosis)                    │       │
          ▼        └──────────────────────────────┘       │
┌────────────────────────────────┐                       │
│ 399 119 records with substance  │                       │
│ use disorder listed as the      │                       │
│ primary diagnosis               │                       │
└────────────────────────────────┘                       │
          │                                               │
          │        ┌──────────────────────────────┐       │
          ├───────▶│ 103 823 records excluded      │       │
          │        │ (relating to acute            │       │
          │        │ intoxications)                │       │
          ▼        └──────────────────────────────┘       │
┌────────────────────────────────┐  ┌────────────────────────────────┐
│ 121 153 individuals             │  │ 6 742 134 individuals           │
│ (295 296 records) included in   │  │ (26 017 675 records) included   │
│ final cohort of people with     │  │ in final cohort of people       │
│ substance use disorder          │  │ without substance use disorders │
└────────────────────────────────┘  └────────────────────────────────┘
```

*Figure 1:* **Construction of cohorts of people hospitalised with and without substance use disorder**

outcome, and, thus, constitutes an important confounder. We matched on the year of first hospitalisation for a given subsequent health condition to ensure that individuals in matched pairs had approximately the same likelihood of having the outcome and to control for cohort effects.

For some of the individuals with pre-existing substance use disorders and particular subsequent health conditions, no matching counterparts without substance use disorder were present in the data (ranging from one [0·06%] of 1643 for hypertension, to 623 [44·47%] of 1399 for chronic viral hepatitis; appendix p 2). We did not include unmatched individuals in the analysis of those health conditions. For a small proportion of individuals with substance use disorder, only one to two matching coun-terparts without substance use disorder were available.

## Statistical analysis
We computed descriptive statistics, expressed as counts with proportions, means with SDs, and medians with IQRs. We used stratified Cox proportional hazards models to assess the risk of all-cause death in people with pre-existing substance use disorders who developed a subsequent health condition compared with people who developed a similar subsequent health condition but who had no history of substance use disorders. We considered groups of individuals with substance use disorders and their matched counterparts without substance use disorders as different strata, making it possible for the baseline hazards to vary across these groups.[19] By using this approach, the comparisons were done within each group, thus allowing us to control for the matched characteristics.[19] We fitted models for each subsequent health condition separately. We considered the event as the occurrence of death, and time-to-event as the time between discharge for a given subsequent health condition and either death or the end of follow-up for mortality (Dec 31, 2017). We fitted models adjusted for sex, age, work status, and discharge year of the first hospitalisation for the given subsequent health condition. We assessed whether the proportionality assumption was satisfied using Schoenfeld residuals, and found this assumption to be violated in a number of models. Consequently, hazard ratios (HRs) must be interpreted as weighted averages of the time-varying HRs over the entire follow-up period.[20] Survival plots are presented in the appendix (pp 9–36). Additionally, we fitted sex-stratified models, adjusting for age, work status, and discharge year of the first hospitalisation for the given subsequent health condition.

We computed life-years lost with 95% CIs established using 10 000 bootstrap iterations for individuals with and without substance use disorders who also developed a sub-sequent physical health condition based on comparison

| | Patients with substance use disorders | | | | | | | Patients without substance use disorders | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Total, n | Sex, n (%) | | Employment status, n (%) | | Mean age, years (SD) | Discharge year of first hospitalisation, median (IQR) | Total, n | Sex, n (%) | | Employment status, n (%) | | Mean age, years (SD) | Discharge year of first hospitalisation, median (IQR) |
| | | Male | Female | Employed | Not employed | | | | Male | Female | Employed | Not employed | | |
| Atrial fibrillation | 1274 | 1000 (78·49%) | 274 (21·51%) | 329 (25·82%) | 945 (74·18%) | 58·17 (10·13) | 2012 (2008–2015) | 3819 | 2998 (78·50%) | 821 (21·50%) | 987 (25·84%) | 2832 (74·16%) | 58·62 (10·09) | 2012 (2008–2015) |
| Cancers | 5405 | 3867 (71·54%) | 1538 (28·46%) | 1384 (25·61%) | 4021 (74·39%) | 56·54 (9·90) | 2011 (2007–2015) | 16215 | 11601 (71·54%) | 4614 (28·46%) | 4152 (25·61%) | 12063 (74·39%) | 56·94 (9·93) | 2011 (2007–2015) |
| Circulatory system diseases | 9089 | 6978 (76·77%) | 2111 (23·23%) | 2305 (25·36%) | 6784 (74·64%) | 55·80 (10·38) | 2011 (2007–2014) | 27267 | 20934 (76·77%) | 6333 (23·23%) | 6915 (25·36%) | 20352 (74·64%) | 56·18 (10·37) | 2011 (2007–2015) |
| Connective tissue disorders | 166 | 98 (59·04%) | 68 (40·96%) | 66 (39·76%) | 100 (60·24%) | 48·87 (13·29) | 2011 (2007–2014·75) | 497 | 293 (58·95%) | 204 (41·05%) | 198 (39·84%) | 299 (60·16%) | 49·17 (13·27) | 2011 (2007–2015) |
| Diabetes | 1648 | 1224 (74·27%) | 424 (25·73%) | 387 (23·48%) | 1261 (76·52%) | 52·29 (11·61) | 2011 (2007–2014) | 4944 | 3672 (74·27%) | 1272 (25·73%) | 1161 (23·48%) | 3783 (76·52%) | 52·67 (11·62) | 2011 (2007–2014) |
| Diverticular disease of the intestine | 340 | 229 (67·35%) | 111 (32·65%) | 101 (29·71%) | 239 (70·29%) | 55·82 (11·70) | 2012 (2008–2015) | 1018 | 685 (67·29%) | 333 (32·71%) | 303 (29·76%) | 715 (70·24%) | 55·98 (11·65) | 2012 (2008–2015) |
| Endocrine system diseases | 2011 | 1335 (66·38%) | 676 (33·62%) | 542 (26·95%) | 1469 (73·05%) | 51·61 (11·86) | 2011 (2007–2014) | 6033 | 4005 (66·38%) | 2028 (33·62%) | 1626 (26·95%) | 4407 (73·05%) | 51·94 (11·87) | 2011 (2007–2014) |
| Epilepsy | 5785 | 4280 (73·98%) | 1505 (26·02%) | 1682 (29·08%) | 4103 (70·92%) | 45·52 (11·81) | 2010 (2006–2014) | 17327 | 12812 (73·94%) | 4515 (26·06%) | 5045 (29·12%) | 12282 (70·88%) | 46·10 (12·10) | 2010 (2006–2014) |
| Gastrointestinal system diseases | 8735 | 6116 (70·02%) | 2619 (29·98%) | 2183 (24·99%) | 6552 (75·01%) | 45·15 (13·94) | 2009 (2005–2013) | 26161 | 18310 (69·99%) | 7851 (30·01%) | 6549 (25·03%) | 19612 (74·97%) | 45·68 (14·21) | 2009 (2005–2013) |
| Heart failure | 1581 | 1230 (77·80%) | 351 (22·20%) | 239 (15·12%) | 1342 (84·88%) | 59·70 (9·82) | 2012 (2009–2015) | 4741 | 3689 (77·81%) | 1052 (22·19%) | 716 (15·10%) | 4025 (84·90%) | 60·16 (9·75) | 2012 (2009–2015) |
| Hypertension | 1642 | 1159 (70·58%) | 483 (29·42%) | 372 (22·66%) | 1270 (77·34%) | 54·66 (11·01) | 2010 (2006–2014) | 4925 | 3476 (70·58%) | 1449 (29·42%) | 1116 (22·66%) | 3809 (77·34%) | 55·05 (11·00) | 2010 (2006–2014) |
| Chronic kidney disease | 532 | 397 (74·62%) | 135 (25·38%) | 92 (17·29%) | 440 (82·71%) | 54·22 (12·07) | 2011 (2006–2014) | 1596 | 1191 (74·62%) | 405 (25·38%) | 276 (17·29%) | 1320 (82·71%) | 54·50 (12·21) | 2011 (2006–2014) |
| Chronic liver disease | 6007 | 4095 (68·17%) | 1912 (31·83%) | 1574 (26·20%) | 4433 (73·80%) | 45·79 (13·23) | 2009 (2005–2013) | 17660 | 12049 (68·23%) | 5611 (31·77%) | 4673 (26·46%) | 12987 (73·54%) | 47·14 (13·02) | 2009 (2005–2013) |
| Chronic pulmonary diseases | 2054 | 1509 (73·47%) | 545 (26·53%) | 351 (17·09%) | 1703 (82·91%) | 54·23 (12·95) | 2010 (2006–2014) | 6161 | 4526 (73·46%) | 1635 (26·54%) | 1053 (17·09%) | 5108 (82·91%) | 54·67 (13·03) | 2010 (2006–2014) |
| Chronic viral hepatitis | 776 | 485 (62·50%) | 291 (37·50%) | 255 (32·86%) | 521 (67·14%) | 29·98 (9·10) | 2007 (2003–2011) | 1962 | 1230 (62·69%) | 732 (37·31%) | 660 (33·64%) | 1302 (66·36%) | 30·84 (9·09) | 2006 (2003–2010) |
| Infectious diseases | 1444 | 1005 (69·60%) | 439 (30·40%) | 415 (28·74%) | 1029 (71·26%) | 34·93 (12·58) | 2007 (2004–2012) | 4068 | 2848 (70·01%) | 1220 (29·99%) | 1177 (28·93%) | 2891 (71·07%) | 36·11 (12·45) | 2007 (2004–2012) |
| Inflammatory bowel disease | 187 | 128 (68·45%) | 59 (31·55%) | 77 (41·18%) | 110 (58·82%) | 44·39 (14·61) | 2011 (2006–2015) | 561 | 384 (68·45%) | 177 (31·55%) | 231 (41·18%) | 330 (58·82%) | 44·38 (14·88) | 2011 (2006–2015) |
| Ischaemic heart disease | 3025 | 2481 (82·02%) | 544 (17·98%) | 831 (27·47%) | 2194 (72·53%) | 56·36 (9·76) | 2011 (2007–2014) | 9074 | 7443 (82·03%) | 1631 (17·97%) | 2493 (27·47%) | 6581 (72·53%) | 56·75 (9·73) | 2011 (2007–2014) |
| Multiple sclerosis | 111 | 53 (47·75%) | 58 (52·25%) | 48 (43·24%) | 63 (56·76%) | 41·41 (10·98) | 2010 (2006·5–2014) | 333 | 159 (47·75%) | 174 (52·25%) | 144 (43·24%) | 189 (56·76%) | 41·36 (11·08) | 2010 (2006–2014) |
| Neurological system diseases | 6015 | 4432 (73·68%) | 1583 (26·32%) | 1750 (29·09%) | 4265 (70·91%) | 45·64 (11·94) | 2010 (2006–2014) | 18037 | 13288 (73·67%) | 4749 (26·33%) | 5249 (29·10%) | 12788 (70·90%) | 46·07 (12·23) | 2010 (2006–2014) |
| Parkinson's disease | 119 | 80 (67·23%) | 39 (32·77%) | 24 (20·17%) | 95 (79·83%) | 60·65 (10·60) | 2011 (2008–2015) | 341 | 231 (67·74%) | 110 (32·26%) | 66 (19·35%) | 275 (80·65%) | 62·16 (9·69) | 2011 (2008–2015) |

(Table 1 continues on next page)

| | Patients with substance use disorders | | | | | | | Patients without substance use disorders | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Total, n | Sex, n (%) | | Employment status, n (%) | | Mean age, years (SD) | Discharge year of first hospitalisation, median (IQR) | Total, n | Sex, n (%) | | Employment status, n (%) | | Mean age, years (SD) | Discharge year of first hospitalisation, median (IQR) |
| | | Male | Female | Employed | Not employed | | | | Male | Female | Employed | Not employed | | |
| (Continued from previous page) | | | | | | | | | | | | | | |
| Peripheral artery occlusive disease | 2074 | 1660 (80·04%) | 414 (19·96%) | 415 (20·01%) | 1659 (79·99%) | 57·75 (9·70) | 2011 (2007–2014) | 6218 | 4976 (80·03%) | 1242 (19·97%) | 1245 (20·02%) | 4973 (79·98%) | 58·20 (9·63) | 2011 (2007–2014) |
| Prostate disorders | 542 | 542 (100·00%) | 0 (0·00%) | 149 (27·49%) | 393 (72·51%) | 61·06 (7·42) | 2011 (2007–2015) | 1626 | 1626 (100·00%) | 0 (0·00%) | 447 (27·49%) | 1179 (72·51%) | 61·46 (7·18) | 2011 (2007–2015) |
| Stroke | 3284 | 2471 (75·24%) | 813 (24·76%) | 624 (19·00%) | 2660 (81·00%) | 57·36 (10·26) | 2011 (2007–2015) | 9849 | 7410 (75·24%) | 2439 (24·76%) | 1872 (19·01%) | 7977 (80·99%) | 57·81 (10·27) | 2011 (2007–2015) |
| Thyroid disorder | 373 | 117 (31·37%) | 256 (68·63%) | 158 (42·36%) | 215 (57·64%) | 48·66 (12·49) | 2010 (2007–2014) | 1118 | 350 (31·31%) | 768 (68·69%) | 474 (42·40%) | 644 (57·60%) | 48·85 (12·49) | 2010 (2007–2014) |
| Tuberculosis | 447 | 374 (83·67%) | 73 (16·33%) | 87 (19·46%) | 360 (80·54%) | 47·67 (10·67) | 2009 (2005·5–2013) | 1302 | 1098 (84·33%) | 204 (15·67%) | 248 (19·05%) | 1054 (80·95%) | 48·26 (10·71) | 2009 (2005–2013) |
| Ulcer or chronic gastritis | 2107 | 1577 (74·85%) | 530 (25·15%) | 524 (24·87%) | 1583 (75·13%) | 50·36 (11·92) | 2010 (2006–2014) | 6320 | 4730 (74·84%) | 1590 (25·16%) | 1572 (24·87%) | 4748 (75·13%) | 50·78 (12·07) | 2010 (2006–2014) |
| Urogenital system diseases | 1054 | 919 (87·19%) | 135 (12·81%) | 234 (22·20%) | 820 (77·80%) | 57·48 (10·63) | 2011 (2007–2014) | 3162 | 2757 (87·19%) | 405 (12·81%) | 702 (22·20%) | 2460 (77·80%) | 57·90 (10·68) | 2011 (2007–2014) |

Age, work status, and year are those at the time of the first hospitalisation for the given subsequent health condition.

*Table 1:* Descriptive statistics of matched individuals with and without substance use disorders who developed subsequent physical health conditions

with the general population of the same sex and age via mortality tables. The reference year for mortality tables was 2008 (ie, the middle study year). We computed differences in life-expectancy as life-years lost[21] for onset of subsequent physical health condition at ages 30, 45, and 60 years, and before reaching the age of 81 years. We proceeded with life-years lost calculation only when the number of at-risk individuals was ten or more.

To quantitively assess the level of unmeasured confounding, we computed E-values for each of the models. The E-values indicate what the HR would need to be for an unmeasured confounder, or set of confounders, to explain away the associations observed in the models.[22]

All analyses were done with R (version 4.0.3), using the libraries survival (version 3.2-7), lillies (version 0.2.9),[21] and EValue (version 4.1.3). Reflecting the statement from the American Statistical Association on p values,[23] we did not conduct null-hypothesis significance tests.

### Role of the funding source
The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

### Results
From the total 56 229 563 records of hospitalisations between Jan 1, 1994, and Dec 31, 2017, 27 392 541 records met all inclusion criteria. 399 119 were records of hospitalisations with substance use disorder listed as the primary diagnosis and 26 017 675 were records of hospitalised individuals with no history of hospitalisation for substance use disorder (figure 1). After exclusion of records of hospitalisations related to acute intoxication, the final cohorts consisted of 121 153 hospitalised individuals with and 6 742 134 without substance use disorder. 29 329 (24·2%) people with and 1 430 970 (21·2%) people without substance use disorder were subsequently hospitalised with at least one physical health condition during the examined period (appendix pp 3–4).

Cohort characteristics by subsequent physical health condition are shown in table 1. The number of individuals in disease-specific cohorts ranged from 444 for multiple sclerosis (333 individuals without and 111 with substance use disorders) to 36 365 for diseases of the circulatory system (27 267 individuals without and 9089 with substance use disorders), with a median of 6444 (IQR 2033–12 358) individuals. Across the cohorts, the proportion of males ranged from 31·4% (467 of 1491) for thyroid disorder to 100% (2168) for prostate disorders, while the mean baseline age ranged from 30·0 years (SD 9·1) for chronic viral hepatitis in people with pre-existing substance use disorders to 62·2 years (9·7) for Parkinson's disease in people without pre-existing substance use disorders.

In 26 of the 28 subsequent individual or broadly defined health conditions examined, individuals with pre-existing substance use disorder had an elevated risk of all-cause
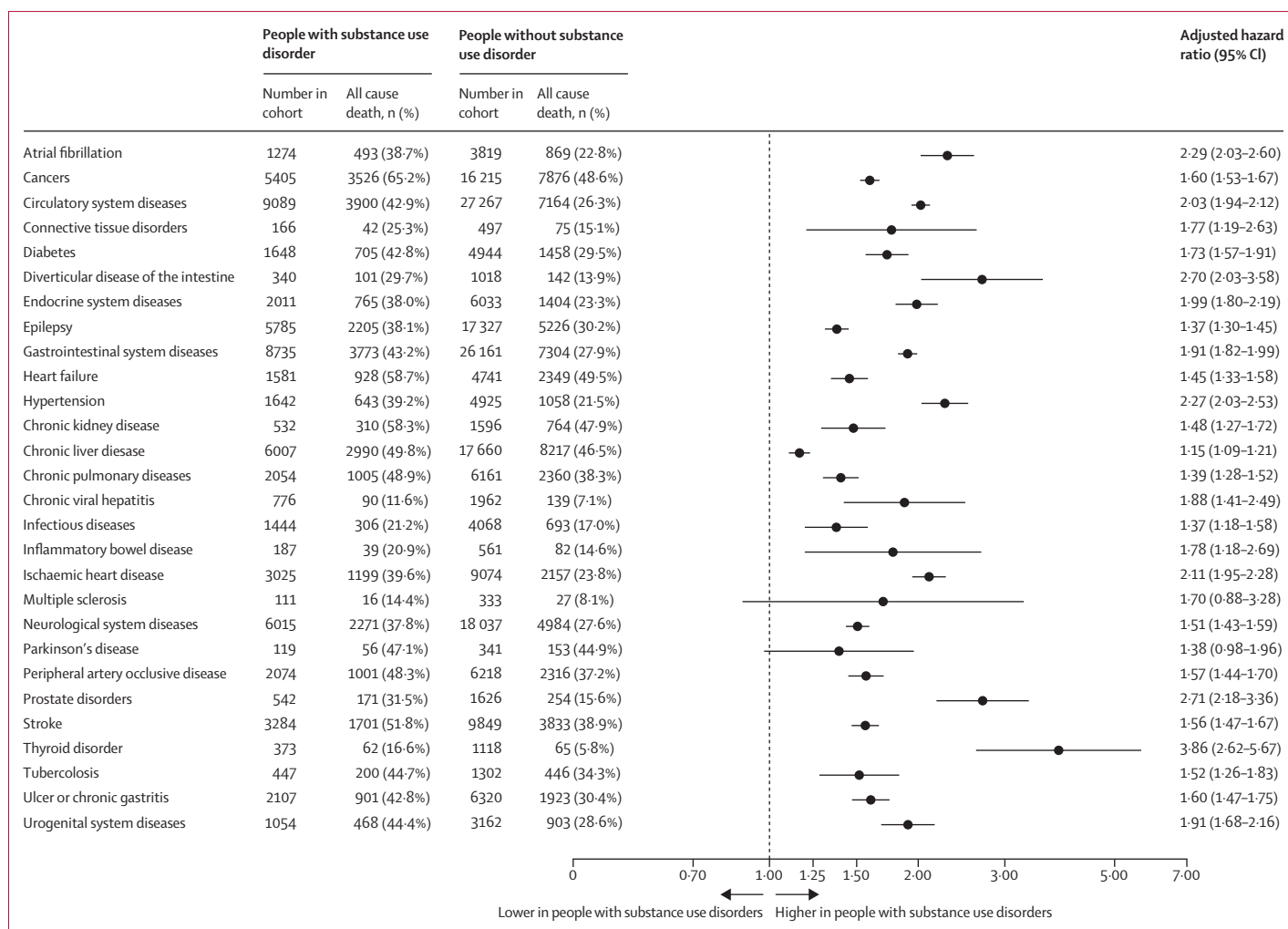
| | People with substance use disorder | | People without substance use disorder | | | Adjusted hazard ratio (95% CI) |
|---|---|---|---|---|---|---|
| | Number in cohort | All cause death, n (%) | Number in cohort | All cause death, n (%) | | |
| Atrial fibrillation | 1274 | 493 (38·7%) | 3819 | 869 (22·8%) | | 2·29 (2·03–2·60) |
| Cancers | 5405 | 3526 (65·2%) | 16 215 | 7876 (48·6%) | | 1·60 (1·53–1·67) |
| Circulatory system diseases | 9089 | 3900 (42·9%) | 27 267 | 7164 (26·3%) | | 2·03 (1·94–2·12) |
| Connective tissue disorders | 166 | 42 (25·3%) | 497 | 75 (15·1%) | | 1·77 (1·19–2·63) |
| Diabetes | 1648 | 705 (42·8%) | 4944 | 1458 (29·5%) | | 1·73 (1·57–1·91) |
| Diverticular disease of the intestine | 340 | 101 (29·7%) | 1018 | 142 (13·9%) | | 2·70 (2·03–3·58) |
| Endocrine system diseases | 2011 | 765 (38·0%) | 6033 | 1404 (23·3%) | | 1·99 (1·80–2·19) |
| Epilepsy | 5785 | 2205 (38·1%) | 17 327 | 5226 (30·2%) | | 1·37 (1·30–1·45) |
| Gastrointestinal system diseases | 8735 | 3773 (43·2%) | 26 161 | 7304 (27·9%) | | 1·91 (1·82–1·99) |
| Heart failure | 1581 | 928 (58·7%) | 4741 | 2349 (49·5%) | | 1·45 (1·33–1·58) |
| Hypertension | 1642 | 643 (39·2%) | 4925 | 1058 (21·5%) | | 2·27 (2·03–2·53) |
| Chronic kidney disease | 532 | 310 (58·3%) | 1596 | 764 (47·9%) | | 1·48 (1·27–1·72) |
| Chronic liver diesase | 6007 | 2990 (49·8%) | 17 660 | 8217 (46·5%) | | 1·15 (1·09–1·21) |
| Chronic pulmonary diseases | 2054 | 1005 (48·9%) | 6161 | 2360 (38·3%) | | 1·39 (1·28–1·52) |
| Chronic viral hepatitis | 776 | 90 (11·6%) | 1962 | 139 (7·1%) | | 1·88 (1·41–2·49) |
| Infectious diseases | 1444 | 306 (21·2%) | 4068 | 693 (17·0%) | | 1·37 (1·18–1·58) |
| Inflammatory bowel disease | 187 | 39 (20·9%) | 561 | 82 (14·6%) | | 1·78 (1·18–2·69) |
| Ischaemic heart disease | 3025 | 1199 (39·6%) | 9074 | 2157 (23·8%) | | 2·11 (1·95–2·28) |
| Multiple sclerosis | 111 | 16 (14·4%) | 333 | 27 (8·1%) | | 1·70 (0·88–3·28) |
| Neurological system diseases | 6015 | 2271 (37·8%) | 18 037 | 4984 (27·6%) | | 1·51 (1·43–1·59) |
| Parkinson's disease | 119 | 56 (47·1%) | 341 | 153 (44·9%) | | 1·38 (0·98–1·96) |
| Peripheral artery occlusive disease | 2074 | 1001 (48·3%) | 6218 | 2316 (37·2%) | | 1·57 (1·44–1·70) |
| Prostate disorders | 542 | 171 (31·5%) | 1626 | 254 (15·6%) | | 2·71 (2·18–3·36) |
| Stroke | 3284 | 1701 (51·8%) | 9849 | 3833 (38·9%) | | 1·56 (1·47–1·67) |
| Thyroid disorder | 373 | 62 (16·6%) | 1118 | 65 (5·8%) | | 3·86 (2·62–5·67) |
| Tubercolosis | 447 | 200 (44·7%) | 1302 | 446 (34·3%) | | 1·52 (1·26–1·83) |
| Ulcer or chronic gastritis | 2107 | 901 (42·8%) | 6320 | 1923 (30·4%) | | 1·60 (1·47–1·75) |
| Urogenital system diseases | 1054 | 468 (44·4%) | 3162 | 903 (28·6%) | | 1·91 (1·68–2·16) |

*Figure 2:* Stratified Cox proportional hazards models of all-cause mortality following the onset of physical health conditions in people with substance use disorder

death when compared with their counterparts without substance use disorder (figure 2). The adjusted HRs ranged from 1·15 (95% CI 1·09–1·21) for chronic liver disease to 3·86 (2·62–5·67) for thyroid disorder. For seven health conditions, the risk of all-cause death in individuals with a history of substance use disorders was more than two times higher than that for people without substance use disorder. Multiple sclerosis had a wide 95% CI for risk of all-cause death, ranging from a 12% decrease in risk to a more than three times higher risk (0·88–3·28). For Parkinson's disease, the 95% CI ranged from a 2% lower risk to a 96% higher risk of all-cause death (0·98–1·96). Sex-specific models are presented in the appendix (p 5).

E-values ranged from 1·44 for chronic liver disease to 4·44 for thyroid disorder, with a median of 2·30 (appendix p 6). These values mean that, to explain away the observed associations between substance use disorder and risk of death, an unmeasured confounder (or set of confounders) would, itself, need to be associated

with both the exposure and outcome by HRs ranging from 1·44 to 4·44, in addition to the confounders included in the models.

Across most subsequent physical health conditions in males and females, substance use disorder was associated with a loss in life-years (table 2). For males with pre-existing substance use disorder and any of the subsequent physical health conditions, disease onset at age 30 years was associated with loss of life-years, ranging from 10·12 years (95% CI 6·42–14·71) for prostate disorders to 37·17 years (32·26–41·88) for heart failure. For females with substance use disorder, the onset of 25 of the 27 health conditions at age 30 years was associated with loss of life-years, ranging from 10·01 years (1·15–18·19) for multiple sclerosis to 41·49 years (35·72–46·06) for heart failure. For chronic viral hepatitis, the 95% CI ranged from a gain of 3·13 life-years to a loss of 11·18 life-years. For inflammatory bowel disease, the 95% CI ranged from a gain of 2·55 life-years to a loss of 9·06 life-years.

| | Males | | | | | | Females | | | | | |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| | Onset age 30 years | | Onset age 45 years | | Onset age 60 years | | Onset age 30 years | | Onset age 45 years | | Onset age 60 years | |
| | With substance use disorders | Without substance use disorders | With substance use disorders | Without substance use disorders | With substance use disorders | Without substance use disorders | With substance use disorders | Without substance use disorders | With substance use disorders | Without substance use disorders | With substance use disorders | Without substance use disorders |
| Atrial fibrillation | 24·99 (19·55 to 31·96) | 11·67 (9·68 to 13·77) | 15·27 (13·67 to 16·92) | 8·02 (7·01 to 9·05) | 7·74 (6·97 to 8·50) | 3·58 (3·06 to 4·10) | 24·43 (12·83 to 40·98) | 11·51 (3·96 to 21·55) | 19·33 (12·21 to 30·55) | 5·40 (3·36 to 7·70) | 9·20 (7·47 to 10·81) | 2·76 (1·86 to 3·66) |
| Cancers | 33·35 (31·77 to 35·02) | 30·19 (29·16 to 31·21) | 24·27 (23·82 to 24·72) | 21·78 (21·40 to 22·17) | 12·59 (12·31 to 12·86) | 9·79 (9·54 to 10·04) | 34·78 (31·62 to 38·20) | 28·16 (26·24 to 30·17) | 25·20 (24·21 to 26·19) | 19·12 (18·31 to 19·89) | 13·11 (12·46 to 13·70) | 9·00 (8·53 to 9·45) |
| Circulatory system diseases | 25·32 (23·89 to 26·86) | 15·93 (14·92 to 16·99) | 16·56 (16·04 to 17·10) | 9·97 (9·60 to 10·35) | 8·26 (7·96 to 8·54) | 3·99 (3·78 to 4·19) | 29·86 (26·73 to 33·07) | 15·14 (13·49 to 16·88) | 19·12 (17·73 to 20·53) | 10·16 (9·30 to 11·03) | 8·60 (7·98 to 9·22) | 4·11 (3·76 to 4·47) |
| Connective tissue disorders | 18·06 (10·97 to 24·57) | 11·92 (7·59 to 16·41) | 14·44 (7·99 to 20·35) | 8·15 (5·13 to 11·34) | 5·26 (0·82 to 8·65) | 4·14 (1·93 to 6·10) | 18·34 (9·70 to 28·66) | 12·20 (3·48 to 22·46) | 14·66 (8·50 to 20·18) | 3·98 (0·20 to 8·11) | 7·11 (1·53 to 12·17) | 0·94 (-1·73 to 3·92) |
| Diabetes | 27·57 (25·06 to 30·17) | 15·98 (14·65 to 17·44) | 18·07 (17·03 to 19·11) | 12·12 (11·45 to 12·79) | 8·67 (7·92 to 9·43) | 6·38 (5·90 to 6·85) | 32·46 (26·97 to 37·78) | 15·10 (12·68 to 17·70) | 17·95 (15·34 to 20·49) | 12·29 (10·78 to 13·86) | 7·80 (6·30 to 9·27) | 6·46 (5·59 to 7·33) |
| Diverticular disease of the intestine | 15·46 (11·53 to 19·82) | 4·67 (2·03 to 7·77) | 13·30 (10·44 to 16·07) | 4·49 (2·37 to 6·67) | 7·11 (5·09 to 8·97) | 1·30 (0·19 to 2·45) | 12·75 (5·11 to 22·74) | 1·92 (-0·64 to 4·72) | 13·16 (5·58 to 22·71) | 2·33 (-0·22 to 5·16) | 4·92 (1·80 to 8·00) | 0·13 (-1·02 to 1·36) |
| Endocrine system diseases | 26·39 (24·02 to 28·88) | 14·80 (13·51 to 16·13) | 17·41 (16·35 to 18·46) | 10·91 (10·23 to 11·58) | 8·23 (7·46 to 8·94) | 5·70 (5·23 to 6·17) | 23·89 (20·11 to 27·80) | 6·23 (4·89 to 7·69) | 14·79 (12·71 to 16·88) | 5·45 (4·46 to 6·48) | 6·75 (5·49 to 7·98) | 3·54 (2·85 to 4·25) |
| Epilepsy | 24·58 (23·81 to 25·38) | 19·59 (19·07 to 20·12) | 17·42 (16·92 to 17·92) | 14·38 (14·03 to 14·73) | 8·76 (8·21 to 9·30) | 7·38 (7·05 to 7·70) | 25·79 (24·04 to 27·50) | 19·53 (18·55 to 20·54) | 16·85 (15·63 to 18·02) | 14·91 (14·17 to 15·64) | 8·32 (7·23 to 9·38) | 7·79 (7·17 to 8·43) |
| Gastrointestinal system diseases | 25·89 (25·35 to 26·44) | 19·04 (18·62 to 19·46) | 20·01 (19·58 to 20·44) | 15·28 (14·95 to 15·61) | 9·72 (9·30 to 10·14) | 6·53 (6·24 to 6·82) | 28·48 (27·45 to 29·49) | 16·42 (15·61 to 17·22) | 22·42 (21·58 to 23·22) | 12·83 (12·15 to 13·50) | 9·75 (8·95 to 10·54) | 4·70 (4·24 to 5·17) |
| Heart failure | 37·17 (32·26 to 41·88) | 32·82 (29·24 to 36·55) | 21·97 (20·61 to 23·34) | 19·80 (18·95 to 20·67) | 11·37 (10·84 to 11·87) | 9·83 (9·47 to 10·20) | 41·49 (35·72 to 46·06) | 37·48 (34·20 to 40·35) | 25·20 (21·15 to 29·41) | 23·28 (20·93 to 25·76) | 12·47 (11·14 to 13·76) | 11·34 (10·56 to 12·11) |
| Hypertension | 21·79 (19·10 to 24·70) | 11·63 (9·82 to 13·57) | 15·47 (14·31 to 16·61) | 7·35 (6·51 to 8·17) | 7·70 (7·00 to 8·41) | 3·00 (2·50 to 3·51) | 25·40 (19·55 to 31·84) | 7·16 (4·79 to 9·93) | 15·93 (12·85 to 18·99) | 5·66 (4·20 to 7·17) | 6·24 (4·99 to 7·51) | 2·25 (1·59 to 2·92) |
| Chronic kidney disease | 28·03 (25·07 to 31·42) | 22·50 (20·16 to 25·04) | 21·80 (20·24 to 23·37) | 17·20 (16·12 to 18·24) | 10·14 (8·96 to 11·25) | 9·66 (9·05 to 10·24) | 29·17 (23·47 to 33·54) | 23·56 (19·44 to 28·22) | 24·76 (18·22 to 31·92) | 19·22 (16·81 to 21·68) | 12·86 (11·17 to 14·49) | 12·18 (11·03 to 13·26) |
| Chronic liver disease | 27·45 (26·77 to 28·14) | 25·47 (25·07 to 25·89) | 21·25 (20·78 to 21·70) | 20·82 (20·53 to 21·10) | 10·65 (10·20 to 11·09) | 10·40 (10·15 to 10·66) | 30·08 (29·03 to 31·13) | 27·07 (26·34 to 27·77) | 23·95 (23·14 to 24·74) | 21·73 (21·12 to 22·31) | 11·34 (10·45 to 12·19) | 10·12 (9·60 to 10·63) |
| Chronic pulmonary diseases | 23·06 (21·38 to 24·78) | 18·05 (16·92 to 19·22) | 18·65 (17·58 to 19·71) | 14·62 (13·99 to 15·23) | 10·00 (9·50 to 10·52) | 8·60 (8·25 to 8·94) | 19·39 (16·83 to 22·07) | 11·93 (10·28 to 13·68) | 17·10 (15·08 to 19·16) | 10·63 (9·36 to 11·96) | 11·03 (9·86 to 12·12) | 6·82 (6·05 to 7·62) |
| Chronic viral hepatitis | 17·45 (13·64 to 19·31) | 9·52 (6·03 to 12·58) | 15·28 (11·07 to 17·14) | 7·37 (3·71 to 10·72) | NA | NA | 3·19 (-3·13 to 11·18) | 1·65 (-1·71 to 6·06) | NA | -0·70 (-4·02 to 3·81) | NA | NA |

(Table 2 continues on next page)

| | Males | | | | | | Females | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Onset age 30 years | | Onset age 45 years | | Onset age 60 years | | Onset age 30 years | | Onset age 45 years | | Onset age 60 years | |
| | With substance use disorders | Without substance use disorders | With substance use disorders | Without substance use disorders | With substance use disorders | Without substance use disorders | With substance use disorders | Without substance use disorders | With substance use disorders | Without substance use disorders | With substance use disorders | Without substance use disorders |
| (Continued from previous page) | | | | | | | | | | | | |
| Infectious diseases | 19·45 (18·11 to 20·78) | 16·04 (15·11 to 16·94) | 16·12 (14·82 to 17·32) | 13·48 (12·61 to 14·33) | 9·41 (7·69 to 10·97) | 7·31 (6·33 to 8·27) | 18·14 (14·12 to 21·65) | 12·17 (9·65 to 14·64) | 16·45 (12·24 to 20·05) | 10·39 (7·80 to 12·83) | 8·75 (3·49 to 13·06) | 5·31 (2·89 to 7·79) |
| Inflammatory bowel disease | 19·07 (13·41 to 24·62) | 10·19 (6·51 to 14·01) | 13·41 (9·30 to 17·22) | 4·86 (2·25 to 7·45) | 8·54 (4·91 to 11·34) | 3·38 (1·13 to 5·69) | 3·52 (-2·55 to 9·06) | 9·38 (3·53 to 15·81) | 3·94 (-2·13 to 9·58) | 5·88 (2·30 to 9·42) | 2·78 (-2·80 to 7·91) | 5·23 (2·31 to 7·85) |
| Ischaemic heart disease | 21·31 (18·74 to 24·32) | 12·16 (10·15 to 14·52) | 14·77 (13·86 to 15·70) | 7·77 (7·10 to 8·43) | 7·54 (7·02 to 8·04) | 3·05 (2·72 to 3·38) | 26·27 (18·94 to 34·50) | 13·32 (9·22 to 18·22) | 15·99 (13·20 to 19·06) | 9·35 (7·78 to 11·04) | 7·40 (6·27 to 8·53) | 3·97 (3·33 to 4·62) |
| Multiple sclerosis | 14·20 (2·50 to 24·41) | 11·70 (6·60 to 16·24) | 2·63 (-7·78 to 7·91) | 10·18 (4·70 to 14·72) | NA | 6·96 (1·28 to 11·97) | 10·01 (1·15 to 18·19) | 6·41 (-3·13 to 9·07) | 9·07 (0·11 to 17·61) | 6·83 (-2·66 to 9·53) | NA | NA |
| Neurological system diseases | 24·55 (23·80 to 25·32) | 18·52 (18·01 to 19·03) | 17·36 (16·86 to 17·86) | 13·73 (13·39 to 14·07) | 8·75 (8·22 to 9·25) | 7·39 (7·08 to 7·71) | 25·24 (23·53 to 27·00) | 15·64 (14·75 to 16·53) | 16·59 (15·44 to 17·75) | 12·97 (12·25 to 13·69) | 8·26 (7·16 to 9·32) | 7·14 (6·56 to 7·73) |
| Parkinson's disease | 20·38 (9·40 to 35·72) | 8·05 (5·86 to 10·41) | 14·28 (9·08 to 21·17) | 8·89 (6·71 to 11·31) | 8·73 (6·33 to 11·14) | 8·58 (7·22 to 10·00) | 22·78 (6·68 to 44·05) | 13·76 (7·61 to 22·22) | 12·56 (5·01 to 19·41) | 14·17 (7·90 to 22·23) | 9·31 (2·88 to 15·30) | 8·28 (5·60 to 11·08) |
| Peripheral artery occlusive disease | 24·00 (20·97 to 27·12) | 20·76 (18·34 to 23·34) | 17·81 (16·65 to 18·97) | 13·08 (12·25 to 13·91) | 8·98 (8·46 to 9·48) | 6·07 (5·71 to 6·41) | 27·17 (20·11 to 34·43) | 18·13 (14·77 to 21·78) | 19·44 (15·26 to 23·82) | 14·70 (12·36 to 17·14) | 9·62 (8·46 to 10·78) | 7·20 (6·46 to 7·96) |
| Prostate disorders | 10·12 (6·42 to 14·71) | -0·29 (-1·68 to 1·29) | 10·92 (7·26 to 15·17) | 0·55 (-0·82 to 2·17) | 4·47 (3·41 to 5·55) | -0·25 (-0·82 to 0·34) | ·· | ·· | ·· | ·· | ·· | ·· |
| Stroke | 30·03 (27·30 to 32·92) | 22·81 (21·10 to 24·67) | 19·93 (19·00 to 20·88) | 15·84 (15·19 to 16·52) | 9·85 (9·40 to 10·28) | 7·09 (6·79 to 7·40) | 32·66 (27·69 to 37·79) | 21·18 (18·74 to 23·76) | 22·27 (20·22 to 24·26) | 16·04 (14·76 to 17·37) | 10·48 (9·53 to 11·40) | 7·63 (7·02 to 8·24) |
| Thyroid disorder | 11·72 (5·53 to 17·77) | -0·22 (-2·62 to 2·44) | 8·10 (3·43 to 12·79) | 0·62 (-1·70 to 3·25) | 3·06 (-0·45 to 5·98) | 0·36 (-1·35 to 2·13) | 10·13 (5·73 to 14·51) | -0·68 (-2·10 to 1·02) | 8·48 (4·89 to 11·98) | -0·76 (-1·98 to 0·61) | 3·70 (1·09 to 6·16) | -0·72 (-1·69 to 0·44) |
| Tuberculosis | 25·25 (22·11 to 28·38) | 17·81 (16·11 to 19·63) | 17·52 (15·91 to 19·07) | 14·60 (13·55 to 15·64) | 9·40 (7·51 to 11·03) | 7·78 (6·74 to 8·79) | 23·97 (18·17 to 29·61) | 11·50 (7·53 to 15·72) | 20·42 (15·57 to 24·93) | 10·05 (6·72 to 13·42) | 9·52 (4·32 to 13·96) | 4·41 (1·83 to 7·08) |
| Ulcer or chronic gastritis | 23·97 (22·52 to 25·49) | 17·31 (16·34 to 18·35) | 17·91 (17·03 to 18·79) | 13·52 (12·88 to 14·14) | 8·61 (7·82 to 9·37) | 6·24 (5·74 to 6·73) | 28·35 (24·77 to 32·32) | 16·04 (13·74 to 18·71) | 20·89 (18·77 to 23·03) | 12·40 (11·14 to 13·72) | 8·58 (7·16 to 9·96) | 6·38 (5·50 to 7·24) |
| Urogenital system diseases | 26·11 (22·59 to 29·73) | 20·97 (17·73 to 24·29) | 18·37 (16·52 to 20·23) | 11·63 (10·37 to 12·86) | 6·43 (5·56 to 7·30) | 2·28 (1·75 to 2·83) | 29·17 (23·33 to 33·54) | 24·23 (20·05 to 28·42) | 24·76 (18·04 to 31·92) | 20·18 (17·26 to 23·11) | 12·86 (11·15 to 14·49) | 9·15 (7·77 to 10·49) |

Data are life-years lost (95% CI), calculated from 10 000 bootstrap iterations, for individuals with and without substance use disorders who also developed a subsequent physical health condition, based on comparison with the general population of the same sex and age. NA=not applicable (number of at-risk individuals was less than ten).

Table 2: Life-years lost following the onset of subsequent physical health conditions in people with and without substance use disorders

With onset age at 45 years, males with substance use disorder showed a loss of life-years across 27 out of 28 subsequent physical health conditions, ranging from 8·10 (3·43–12·79) for thyroid disorder to 24·27 (23·82–24·72) for cancers. For multiple sclerosis, the 95% CI ranged from gain of 7·78 life-years to a loss of 7·91 life-years. Females with substance use disorder and disease onset at age 45 years showed a loss of life-years in 25 of 26 subsequent physical health conditions, ranging from 8·48 (4·89–11·98) for thyroid disorder to 25·20 (21·15–29·41) for heart failure. For inflammatory bowel disease, the 95% CI covered a range from gain of 2·13 life-years to loss of 9·58 life-years.

Considering disease onset at age 60 years, males with substance use disorder had life-years lost in 25 out of 26 subsequent physical health conditions, ranging from 4·47 (3·41–5·55) for prostate disorders to 12·59 (12·31–12·86) for cancers. For thyroid disorder, the 95% CI ranged from a gain of 0·45 life-years to a loss of 5·98 life-years. For females with substance use disorder, disease onset at age 60 years was associated with a loss of life-years in 24 of 25 subsequent health conditions, ranging from 3·70 (1·09–6·16) for thyroid disorder to 13·11 (12·46–13·70) for cancers. The 95% CI for inflammatory bowel disease ranged from a gain of 2·80 life-years to a loss of 7·91 life-years. Individuals with a pre-existing substance use disorder had a higher number of life-years lost than their counterparts without substance use disorder for most health conditions and onset ages.

## Discussion

In this retrospective cohort study based on Czech nationwide health registers, we observed that people with a history of hospitalisation for a substance use disorder were more likely to die during the follow-up period than their counterparts without a history of hospitalisation for a substance use disorder, after the onset of 26 of the 28 examined physical health conditions. For seven subsequent physical health conditions, the risk of death due to any cause in people with pre-existing substance use disorders was twice as high or greater. Correspondingly, individuals with a pre-existing substance use disorder had substantial losses of life-years after the onset of most of the subsequent physical health conditions, and, in most cases, considerably larger losses than those of their counterparts without substance use disorder. These results strongly suggest that substance use disorder has a profound negative impact on mortality and life-years lost following the onset of subsequent health conditions.

A previous nationwide cohort study from Denmark used categories of physical health conditions consistent with those used in the present study to examine the risk of death and life-years lost in individuals with substance use disorder with comorbid physical health conditions when compared with unmatched individuals having only those physical health conditions.[18] That study showed elevated mortality rate ratios in people with substance use disorder who had any of the nine examined groups of physical health conditions, ranging from 2·42 (95% CI 2·36–2·48) for diseases of the haematological system to 3·81 (3·74–3·87) for diseases of the gastrointestinal system, when compared with individuals who only had the specific physical health conditions.[18] In our study, the observed risks were lower than in the Danish study, which could be related to intrinsic differences in the studied populations or underlying health-care systems, and to differences in study designs. The present study lacks data from outpatient settings, whereas the Danish study did not consider the direction of causality or match individuals with substance use disorder with those without substance use disorder. Results from Swedish nationwide registers imply that individuals with psychoactive drug use disorders had an increased risk for fatal prostate cancer when compared with their counterparts without drug use disorders.[24] Similarly, results from Finish nationwide registers suggest that men with colorectal cancer who had a history of a substance use disorder had increased risk of death when compared with their counterparts without substance use disorders.[25] Findings from Swedish nationwide registers also showed substantial premature mortality (defined as death before age 66 years; 23·3–28·7% of individuals) among people with chronic respiratory diseases, cardiovascular diseases, or diabetes in addition to comorbid substance use disorders.[19]

Since our dataset contains only a very small number of variables, we cannot establish the mechanisms responsible for the effect of pre-existing substance use disorders on mortality following the development of subsequent physical health conditions. However, the direct adverse effect of substance use on physical health could be a major factor, probably amplified by several other factors. First, substance use is associated with lifestyle factors such as smoking, lack of exercise, and suboptimal dietary habits, which are known risk factors for several adverse health outcomes. Next, people with substance use disorders are less likely to participate in screening and prevention programmes for diseases such as cancer and diabetes.[26,27] Thus, the observed differences in risk of death between people with and without substance use disorders could be, in part, due to differing clinical characteristics of hospitalised individuals, with more timely diagnoses and less severe or chronic cases among individuals without substance use disorder. However, in a study using data from Swedish nationwide registers, no association was found between drug use disorders and prostate cancer stage at diagnosis.[24] Additionally, previous research has shown that individuals with substance use disorder are less likely to use preventive medication, such as lipid-lowering and antihypertensive drugs,[28] exacerbating the risk of adverse outcomes. Finally, people with mental disorders, including people with substance use disorders, are more likely to be subject to diagnostic overshadowing (ie, the misattribution of physical symptoms to mental disorders),[29]

which can subsequently contribute to under-diagnosis, late diagnosis, and delayed treatment in affected individuals.

There are several limitations to this study that need to be considered. First, we had no data related to outpatient services. Consequently, we did not capture data on people who were receiving treatment without hospitalisation, and we cannot rule out that this approach led to the introduction of substantial selection bias.

Second, given the large treatment gap in people with substance use disorders in Czechia,[30] the number of undetected cases of substance use disorders (false negatives) is likely to be considerable. This bias is likely to have led to an underestimation of the true effects. In addition, we cannot rule out that some individuals hospitalised for a substance use disorder before Jan 1, 1999, were included in the cohort of people without substance use disorders.

Third, by restricting the analysis to only individuals who were hospitalised for substance use disorders as the primary diagnosis, individuals hospitalised with a secondary diagnosis of substance use disorders were undetected and potentially included in the group of people without substance use disorders. However, it is reasonable to assume that these two groups are dissimilar and combining them would result in a heterogeneous cohort of patients, potentially violating the consistency assumption.[31]

Fourth, we checked for the presence of examined health conditions 5 years before the first substance use disorder-related hospitalisation; however, we had no complete life histories available to establish the precise sequences of disease onsets. Thus, we cannot rule out the possibility that some individuals with a substance use disorder developed their substance use disorder after the onset of other health problems, perhaps, in part, as a strategy to cope with such problems (ie, reverse causality).

Fifth, although we tried to consider all relevant confounders, the pool of variables present in the registers is very limited, and it is likely that unaccounted confounding is still present. However, we believe that the size of the E-values calculated provides a reasonably strong indication that our results are unlikely to be attributable to unmeasured cofounding. Furthermore, people with other mental disorders often have comorbid substance use disorders with bidirectional association. Because of the complex relationships between substance use disorders, other mental disorders, and physical health conditions, we believe that including other mental disorders as confounders might result in overadjustment bias[32] or other complex design problems. Therefore, we opted for a cautious approach and did not consider them in the current study. Similarly, the worse prognosis in people with pre-existing substance use disorders might be partially related to potentially higher rates of multimorbidity, which we did not consider in the present study.

Sixth, for a non-negligible proportion of people with pre-existing substance use disorders and subsequent chronic viral hepatitis, chronic liver disease, and infectious diseases, we were not able to find any matching counterparts without substance use disorders. Thus, the results might not be generalisable to the entire population.

Finally, information on emigration status was not present in the registers, and we cannot rule out that some individuals left the country during the follow-up period, resulting in being lost to follow-up. However, the number of individuals emigrating from Czechia is very low (up to 0·2% per year), making it unlikely to have substantially biased the results.

The findings of this study warrant further investigation and public health action. The need to scale up public health actions to improve access to and quality of treatment has repeatedly been outlined in national and international agendas such as target 3·5 of UN Sustainable Development Goal 3 on strengthening the prevention and treatment of substance abuse; these aims should be addressed, with a particular emphasis on somatic comorbidity in people with substance use disorders. From the clinical perspective, there is an opportunity when individuals with substance use disorders are hospitalised or otherwise identified in the health-care system to address their physical and mental health in an integrated way.[33,34] An integrated approach to prevention and treatment and the so-called "no wrong door" principle have been suggested as ways to properly address the complexity of each individual patient with substance use disorder and ensure that patients receive comprehensive therapeutic interventions regardless of their entry point into the health-care system.[35] Nevertheless, more research is required to understand how to assure the feasibility, acceptability, affordability, and effectiveness of integrated care provision in different socioeconomic settings.

In summary, a history of hospitalisation for substance use disorders was associated with a profound negative impact on prognosis following the development of subsequent physical health conditions requiring hospitalisation. When compared with individuals without substance use disorders, people with pre-existing substance use disorders were more likely to die after developing a subsequent physical health condition in 26 of 28 physical health conditions examined. Likewise, people with pre-existing substance use disorders had substantial losses in life-years and, in most cases, lost markedly more life-years than their counterparts without substance use disorders. These results emphasise the need for clinical vigilance and high-quality integrated treatment when people with substance use disorders are hospitalised or otherwise identified.

results and provided critical revisions to the manuscript. PBJ contributed to study design and interpretation of results, provided supervision, and wrote a substantial portion of the manuscript. TF, KM and PW had full access to all data. TF and KM take responsibility for the integrity of the data and the accuracy of the data analysis. All authors approved the decision to submit for publication.

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