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

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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 56,229,563 records of hospitalisations identified, we included 121,153 people with hospitalisation for substance use disorders and 6,742,134 people without hospitalisation for substance use disorders in the study. The 28 condition-specific cohorts comprised a median of 6,444 individuals (IQR 2,033–12,358), ranging from 444 for multiple sclerosis to 36,356 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
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 Almost half of people diagnosed with a substance use disorder have other chronic health conditions,⁵ and 47–100% have another current mental disorder.⁶ 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,⁷ to be rehospitalised within 30 days of discharge,⁸ to die by suicide⁹ or have a higher suicide risk,⁹ to die prematurely,⁹ and to have worse proximal outcomes at discharge from treatment.¹⁰ 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.¹¹ 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.¹²

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 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.

**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-occur*) 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.

**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
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. 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. 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 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 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. 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
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 counterparts 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. 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. 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.

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. 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 10000 bootstrap iterations for individuals with and without substance use disorders who also developed a subsequent physical health condition based on comparison.
| Patients with substance use disorders | Total, n | Sex, n (%) | Employment status, n (%) | Mean age, years (SD) | Discharge year of first hospitalisation, median (IQR) | Patients without substance use disorders |
|--------------------------------------|---------|------------|--------------------------|---------------------|-------------------------------------------------|------------------------------------------|
|                                      |         | Male       | Female                   |                     |                                                 |                                           |
| Atrial fibrillation                  | 1274    | 1090 (87·49%) | 224 (17·51%)             | 412 (33·54%)        | 84 (18·75%)                                     |                                           |
| Cancers                              | 5405    | 1000 (21·36%) | 224 (17·51%)             | 997 (33·54%)        | 1000 (21·36%)                                   |                                           |
| Circulatory system diseases          | 9089    | 6978 (77·0%)  | 1531 (17·0%)             | 5500 (33·54%)       | 5500 (33·54%)                                   |                                           |
| Connective tissue disorders          | 166     | 111 (71·0%)  | 35 (39·0%)                | 35 (39·0%)          | 35 (39·0%)                                      |                                           |
| Diabetes                             | 1648    | 1224 (75·7%)  | 424 (24·3%)               | 424 (24·3%)         | 424 (24·3%)                                     |                                           |
| Diverticular disease of the intestine| 340     | 229 (77·1%)  | 111 (33·9%)               | 111 (33·9%)         | 111 (33·9%)                                     |                                           |
| Endocrine system diseases            | 2011    | 1335 (66·3%)  | 676 (33·7%)               | 676 (33·7%)         | 676 (33·7%)                                     |                                           |
| Epilepsy                             | 5785    | 4280 (73·98%) | 1595 (26·02%)            | 4280 (73·98%)       | 4280 (73·98%)                                   |                                           |
| Gastrointestinal system diseases     | 8735    | 6116 (70·02%)  | 2619 (29·98%)            | 6116 (70·02%)       | 6116 (70·02%)                                   |                                           |
| Heart failure                        | 1581    | 1230 (78·1%)  | 351 (21·9%)               | 1230 (78·1%)        | 1230 (78·1%)                                    |                                           |
| Hypertension                         | 1642    | 1159 (70·58%)  | 483 (29·42%)             | 1159 (70·58%)       | 1159 (70·58%)                                   |                                           |
| Chronic kidney disease               | 532     | 397 (74·62%)  | 135 (25·38%)              | 397 (74·62%)        | 397 (74·62%)                                    |                                           |
| Chronic liver disease                | 6007    | 4095 (68·17%)  | 1912 (31·83%)            | 4095 (68·17%)       | 4095 (68·17%)                                   |                                           |
| Chronic pulmonary diseases           | 2054    | 1509 (73·47%)  | 545 (26·53%)              | 1509 (73·47%)       | 1509 (73·47%)                                   |                                           |
| Chronic viral hepatitis              | 776     | 485 (62·50%)  | 291 (37·50%)              | 485 (62·50%)        | 485 (62·50%)                                    |                                           |
| Infectious diseases                  | 1444    | 1005 (69·60%)  | 439 (30·40%)             | 1005 (69·60%)       | 1005 (69·60%)                                   |                                           |
| Inflammatory bowel disease           | 187     | 128 (68·45%)  | 59 (31·55%)               | 128 (68·45%)        | 128 (68·45%)                                    |                                           |
| Ischaemic heart disease              | 3025    | 2481 (82·02%)  | 544 (17·98%)             | 2481 (82·02%)       | 2481 (82·02%)                                   |                                           |
| Multiple sclerosis                   | 111     | 53 (47·75%)  | 58 (52·25%)               | 53 (47·75%)         | 53 (47·75%)                                     |                                           |
| Neurological system diseases         | 6035    | 442 (73·68%)  | 1583 (26·32%)            | 442 (73·68%)        | 442 (73·68%)                                    |                                           |
| Parkinson’s disease                  | 119     | 80 (67·23%)   | 29 (32·77%)               | 80 (67·23%)         | 80 (67·23%)                                     |                                           |
|                                      |         |             |                          |                     |                                                 | (Table 1 continues on next page)         |
### Table 1: Descriptive statistics of matched individuals with and without substance use disorders who developed subsequent physical health conditions

| Condition                                | Total, n | Sex, n (%) | Employment status, n (%) | Mean age, years (SD) | Discharge year of first hospitalisation, median (IQR) |
|------------------------------------------|----------|------------|--------------------------|----------------------|-----------------------------------------------------|
| Stroke                                   | 3284     | 2471       | 813 (25.6%)              | 62.06                | 2011 (2007–2014)                                    |
| Thyroid disorder                         | 373      | 117 (31.7%)| 256 (68.3%)             | 48.66                | 2010 (2007–2014)                                    |
| Tuberculosis                             | 447      | 111 (24.7%)| 336 (75.3%)             | 56.64                | 2010 (2007–2014)                                    |
| Ulcer or chronic gastritis                | 2107     | 959 (45.5%)| 1148 (54.5%)            | 54.44                | 2010 (2007–2014)                                    |
| Venous thromboembolic disease            | 2034     | 874 (42.9%)| 1160 (57.1%)            | 67.14                | 2010 (2007–2014)                                    |
| Tuberculosis, and age at the time of the first hospitalisation for the condition |            |             |                          |                      |                                                     |
| Thyroid disorder                         | 374      | 117 (31.7%)| 256 (68.3%)             | 48.66                | 2010 (2007–2014)                                    |
| Tuberculosis                             | 447      | 111 (24.7%)| 336 (75.3%)             | 56.64                | 2010 (2007–2014)                                    |
| Ulcer or chronic gastritis                | 2107     | 959 (45.5%)| 1148 (54.5%)            | 54.44                | 2010 (2007–2014)                                    |
| Venous thromboembolic disease            | 2034     | 874 (42.9%)| 1160 (57.1%)            | 67.14                | 2010 (2007–2014)                                    |

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 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 quantitatively 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.

All analyses were done with R (version 4.0.3), using the libraries survival (version 3.2-7), lillies (version 0.2.9), and EValue (version 4.1.3). Reflecting the statement from the American Statistical Association on p values, 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 56229563 records of hospitalisations between Jan 1, 1994, and Dec 31, 2017, 27392541 records met all inclusion criteria. 399119 were records of hospitalisations with substance use disorder listed as the primary diagnosis and 26017675 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 121153 hospitalised individuals with and 674234 without substance use disorder. 29329 (24–2%) people with and 1340970 (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 36365 for diseases of the circulatory system (27267 individuals without and 9089 with substance use disorders), with a median of 6444 (IQR 2033–13258) 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
E-values ranged from 1·44 for chronic liver disease to 4·44 for chronic viral hepatitis, 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 3·86 life-years to a loss of 9·06 life-years. For inflammatory bowel disease, the 95% CI ranged from a gain of 2·27 life-years to a loss of 9·06 life-years.

### Table 2

| Health Condition                        | Adjusted hazard ratio (95% CI) |
|-----------------------------------------|---------------------------------|
| Atrial fibrillation                     | 2·99 (2·03–2·66)                |
| Cancers                                 | 1·60 (1·53–1·67)                |
| Circulatory system diseases             | 2·03 (1·94–2·12)                |
| Connective tissue disorders             | 1·77 (1·19–2·63)                |
| Diabetes                                | 1·73 (1·57–1·91)                |
| Diverticular disease of the intestine   | 2·14 (2·03–3·38)                |
| Endocrine system diseases               | 1·99 (1·80–2·19)                |
| Epilepsy                                | 1·27 (1·30–1·45)                |
| Gastrointestinal system diseases        | 1·91 (1·82–1·99)                |
| Heart failure                           | 1·45 (1·33–1·58)                |
| Hypertension                            | 2·27 (2·03–2·53)                |
| Chronic kidney disease                  | 1·48 (1·27–1·71)                |
| Chronic liver disease                   | 1·15 (1·09–1·21)                |
| Chronic pulmonary diseases              | 1·39 (1·28–1·52)                |
| Chronic viral hepatitis                 | 1·88 (1·41–2·49)                |
| Infectious diseases                     | 1·37 (1·18–1·58)                |
| Inflammatory bowel disease              | 1·78 (1·18–2·69)                |
| Ischaemic heart disease                 | 2·11 (1·95–2·28)                |
| Multiple sclerosis                      | 1·70 (0·88–3·28)                |
| Neurological system diseases            | 1·51 (1·43–1·59)                |
| Parkinson’s disease                     | 1·38 (0·98–1·96)                |
| Peripheral artery occlusive disease     | 1·57 (1·44–1·70)                |
| Prostate disorders                      | 2·71 (2·18–3·36)                |
| Stroke                                  | 1·56 (1·47–1·67)                |
| Thyroid disorder                        | 1·86 (2·62–5·67)                |
| Tuberculosis                            | 1·52 (1·26–1·83)                |
| Ulcer or chronic gastritis              | 1·60 (1·47–1·75)                |
| Urogenital system diseases              | 1·91 (1·68–2·16)                |

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 was higher in people with substance use disorder compared with those without, ranging from 1·15 (95% CI 1·09–1·21) for chronic liver disease to 3·86 (2·62–5·67) for thyroid disorder. For eight health conditions, the risk of all-cause death was lower in people with substance use disorder compared with those without, ranging from 0·86 (95% CI 0·82–0·91) for Parkinson’s disease to 2·03 (1·94–2·12) for chronic liver disease. For 27 health conditions, the risk of all-cause death was no different between people with and without substance use disorder, ranging from 0·98 (95% CI 0·96–1·01) for heart failure to 1·00 (95% CI 0·99–1·01) for heart failure.

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| Illness                                | Males With substance use disorders | Males Without substance use disorders | Females With substance use disorders | Females Without substance use disorders |
|----------------------------------------|------------------------------------|--------------------------------------|--------------------------------------|---------------------------------------|
| **Atrial fibrillation**                | 11·67 (9·68 to 13·77)              | 8·02 (7·01 to 9·05)                  | 3·58 (2·96 to 4·10)                  | 4·00 (3·36 to 4·70)                  |
| **Cancers**                            | 15·27 (13·67 to 16·92)             | 12·59 (11·31 to 13·86)               | 9·79 (9·54 to 10·04)                 | 10·81 (10·35 to 11·30)               |
| **Circulatory system diseases**        | 11·51 (9·59 to 13·70)              | 8·26 (7·16 to 9·36)                  | 3·99 (3·78 to 4·20)                  | 3·66 (3·41 to 3·91)                  |
| **Connective tissue disorders**        | 11·51 (9·59 to 13·70)              | 8·26 (7·16 to 9·36)                  | 3·99 (3·78 to 4·20)                  | 3·66 (3·41 to 3·91)                  |
| **Diabetes**                           | 18·07 (16·45 to 19·41)             | 12·02 (11·45 to 12·60)               | 6·38 (6·09 to 6·68)                  | 6·36 (6·03 to 6·70)                  |
| **Diverticular disease of the intestine** | 12·30 (10·44 to 14·07)            | 8·12 (6·90 to 9·32)                  | 4·12 (3·90 to 4·34)                  | 4·12 (3·90 to 4·34)                  |
| **Endocrine system diseases**          | 17·41 (15·35 to 18·46)             | 14·71 (12·23 to 17·20)               | 7·86 (6·82 to 8·90)                  | 7·86 (6·82 to 8·90)                  |
| **Epilepsy**                           | 17·41 (15·35 to 18·46)             | 14·71 (12·23 to 17·20)               | 7·86 (6·82 to 8·90)                  | 7·86 (6·82 to 8·90)                  |
| **Gastrointestinal system diseases**    | 17·41 (15·35 to 18·46)             | 14·71 (12·23 to 17·20)               | 7·86 (6·82 to 8·90)                  | 7·86 (6·82 to 8·90)                  |
| **Heart failure**                      | 20·01 (18·58 to 21·44)             | 15·28 (14·95 to 15·61)               | 7·97 (7·64 to 8·32)                  | 7·97 (7·64 to 8·32)                  |
| **Hypertension**                       | 21·37 (19·85 to 23·67)             | 18·00 (16·51 to 19·47)               | 9·12 (8·78 to 9·46)                  | 9·12 (8·78 to 9·46)                  |
| **Chronic kidney disease**             | 21·37 (19·85 to 23·67)             | 18·00 (16·51 to 19·47)               | 9·12 (8·78 to 9·46)                  | 9·12 (8·78 to 9·46)                  |
| **Chronic liver disease**              | 21·37 (19·85 to 23·67)             | 18·00 (16·51 to 19·47)               | 9·12 (8·78 to 9·46)                  | 9·12 (8·78 to 9·46)                  |
| **Chronic pulmonary diseases**         | 21·37 (19·85 to 23·67)             | 18·00 (16·51 to 19·47)               | 9·12 (8·78 to 9·46)                  | 9·12 (8·78 to 9·46)                  |
| **Chronic viral hepatitis**            | 21·37 (19·85 to 23·67)             | 18·00 (16·51 to 19·47)               | 9·12 (8·78 to 9·46)                  | 9·12 (8·78 to 9·46)                  |

(Table 2 continues on next page)
|                           | Males Onset age 30 years | Males Onset age 45 years | Males Onset age 60 years | Females Onset age 30 years | Females Onset age 45 years | Females 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 |
| Infectious diseases       | 19.45 (18.11 to 20.87)  | 16.04 (15.11 to 16.94)  | 16.12 (14.82 to 17.32)  | 13.48 (12.64 to 14.33)  | 9.41 (7.69 to 10.97)   | 7.31 (6.33 to 8.27)    |
|                           | (2.25 to 7.45)          | (3.49 to 7.79)          | (14.12 to 21.65)        | (12.64)                   | (10.97)                   | (8.27)                   |
| Neurological system       | 12.24 (11.25 to 13.28)  | 16.24 (15.33 to 17.15)  | 18.14 (16.64)           | 12.17 (11.83)             | 8.75 (7.90)               | 7.79 (7.03)               |
|                           | (2.31 to 23.31)         | (11.83 to 12.31)        | (14.64)                  | (11.83)                   | (7.90)                    | (7.03)                    |
| Multiple sclerosis        | 12.24 (11.25 to 13.28)  | 16.24 (15.33 to 17.15)  | 18.14 (16.64)           | 12.17 (11.83)             | 8.75 (7.90)               | 7.79 (7.03)               |
|                           | (2.31 to 23.31)         | (11.83 to 12.31)        | (14.64)                  | (11.83)                   | (7.90)                    | (7.03)                    |
| Parkinson’s disease       | 23.84 (20.93 to 26.74)  | 32.15 (29.36 to 35.06)  | 27.54 (24.65 to 30.44)  | 30.36 (27.47 to 33.26)   | 25.66 (22.77 to 28.57)   | 23.76 (20.88 to 26.69)  |
|                           | (18.01 to 19.72)        | (16.11 to 17.82)        | (21.87)                  | (19.72)                   | (22.77)                   | (20.88)                   |
| Peripheral artery         | 24.00 (19.93 to 28.12)  | 27.12 (23.34 to 30.94)  | 27.12 (23.34)           | 27.12 (23.34)             | 27.12 (23.34)             | 27.12 (23.34)             |
|                           | (7.91 to 15.72)         | (7.91 to 15.72)         | (7.91 to 15.72)         | (7.91 to 15.72)           | (7.91 to 15.72)           | (7.91 to 15.72)           |
| Prostate disorders        | 10.12 (6.42 to 14.72)   | 11.72 (7.62 to 15.57)   | 10.12 (7.62 to 15.57)   | 11.72 (7.62 to 15.57)     | 10.12 (7.62 to 15.57)     | 11.72 (7.62 to 15.57)     |
|                           | (-1.68 to 12.99)        | (-1.68 to 12.99)        | (-1.68 to 12.99)        | (-1.68 to 12.99)          | (-1.68 to 12.99)          | (-1.68 to 12.99)          |
| Stroke                    | 30.03 (27.30 to 32.72)  | 22.81 (20.47 to 25.19)  | 21.90 (19.09 to 23.78)  | 15.84 (13.93 to 17.75)    | 9.85 (7.90 to 11.80)      | 7.90 (7.04 to 9.04)      |
|                           | (24.57 to 28.46)        | (24.57 to 28.46)        | (24.57 to 28.46)        | (24.57 to 28.46)          | (24.57 to 28.46)          | (24.57 to 28.46)          |
| Thyroid disorder          | 11.72 (5.30 to 17.79)   | 11.72 (5.30 to 17.79)   | 11.72 (5.30 to 17.79)   | 11.72 (5.30 to 17.79)     | 11.72 (5.30 to 17.79)     | 11.72 (5.30 to 17.79)     |
|                           | (-2.62 to 2.44)         | (-2.62 to 2.44)         | (-2.62 to 2.44)         | (-2.62 to 2.44)           | (-2.62 to 2.44)           | (-2.62 to 2.44)           |
| Tuberculosis              | 25.25 (23.13 to 27.38)  | 17.81 (15.63 to 19.97)  | 17.52 (15.35 to 19.64)  | 14.60 (12.55 to 16.65)    | 9.40 (7.38 to 11.42)      | 7.78 (6.76 to 8.80)      |
|                           | (21.13 to 13.63)        | (18.63 to 15.43)        | (19.64 to 15.43)        | (15.35 to 19.64)          | (12.55 to 16.65)          | (11.42)                  |
| Uterine chronic           | 23.97 (22.52 to 25.49)  | 17.21 (16.34 to 18.32)  | 17.21 (16.34 to 18.32)  | 14.32 (13.45 to 15.29)    | 9.61 (8.54 to 10.68)      | 7.54 (6.48 to 8.60)      |
|                           | (18.75 to 18.75)        | (18.75 to 18.75)        | (18.75 to 18.75)        | (18.75 to 18.75)          | (18.75 to 18.75)          | (18.75 to 18.75)          |
| Urogenital system         | 25.61 (22.59 to 29.73)  | 25.61 (22.59 to 29.73)  | 25.61 (22.59 to 29.73)  | 25.61 (22.59 to 29.73)    | 25.61 (22.59 to 29.73)    | 25.61 (22.59 to 29.73)    |
|                           | (22.59 to 29.73)        | (22.59 to 29.73)        | (22.59 to 29.73)        | (22.59 to 29.73)          | (22.59 to 29.73)          | (22.59 to 29.73)          |

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. 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. 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. 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.

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.

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. 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. 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, 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).
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, 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.

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 confounding. 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 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. 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. 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.

Contributors
TF initiated and designed the study, did the statistical analysis, and led the writing of the manuscript. DK contributed to study design and interpretation of results and wrote a substantial portion of the manuscript. KM contributed to the statistical analysis and interpretation of results, did the code review, and provided critical revisions to the manuscript. PW contributed to study design and interpretation of
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.

Declaration of interests
We declare no competing interests.

Data sharing
The data cannot be published or shared externally without permission granted by the Czech Institute of Health Information and Statistics. The full analytical code and raw results are available at https://github.com/tmfmnk/Mortality-and-LYL-in-Comorbid-SUD.

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