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 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 6444 individuals (IQR 2033–12 358), 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.

Funding National Institute for Health and Care Research Applied Research Collaboration East of England at Cambridge and Peterborough National Health Service Foundation Trust.

Lancet Psychiatry 2022; 9: 957–68

Published Online November 3, 2022 https://doi.org/10.1016/S2215-0366(22)00335-2

See Comment page 931

Department of Public Mental Health, National Institute of Mental Health, Klecany, Czechia (T Formánek MSc, K Mladá MSc, P Winkler PhD); **Department of Psychiatry, University of Cambridge, Cambridge, UK** (T Formánek, Prof P B Jones PhD); **Department of Mental Health and Substance Use, World Health Organization, Geneva, Switzerland** (D Krupchanka PhD); **Department of Psychiatry, Faculty of Medicine, University Hospital in Pilsen, Charles University Prague, Pilsen, Czechia** (K Mladá); **Health Service and Population Research Department, Institute of Psychiatry, Psychology and Neuroscience, King's College London, London, UK** (P Winkler)

Correspondence to: Mr Tomáš Formánek, Department of Psychiatry, University of Cambridge, Cambridge CB2 8AH, UK **tf363@cam.ac.uk**

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

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.

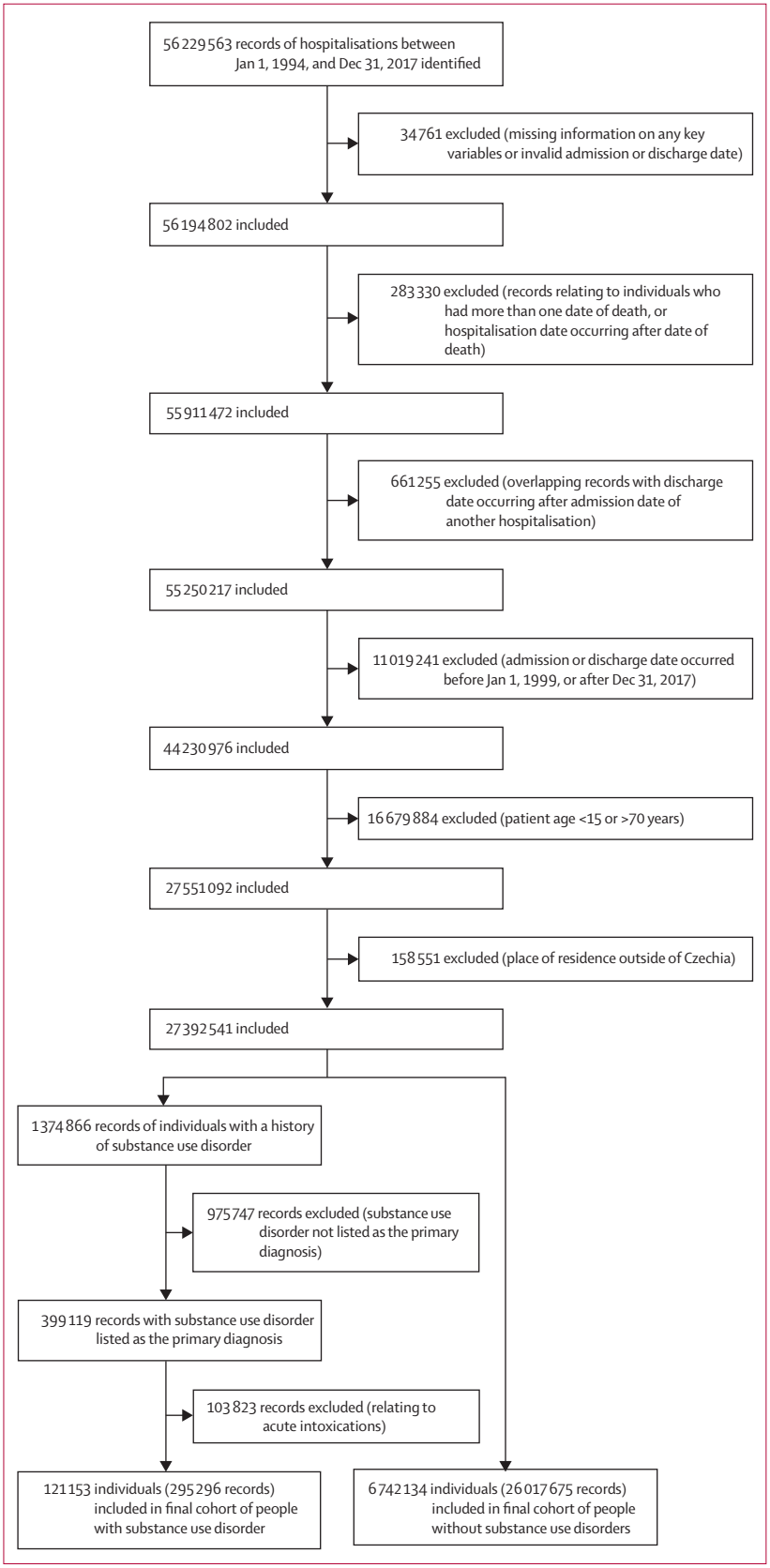
See Online for appendix

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.[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 subsequent physical health condition based on comparison

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

	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)	16 215	11 601 (71·54%)	4614 (28·46%)	4152 (25·61%)	12 063 (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)	27 267	20 934 (76·77%)	6333 (23·23%)	6915 (25·36%)	20 352 (74·64%)	56·18 (10·37)	2011 (2007–2014)
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)	17 327	12 812 (73·94%)	4515 (26·06%)	5045 (29·12%)	12 282 (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)	26 161	18 310 (69·99%)	7851 (30·01%)	6549 (25·03%)	19 612 (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)	17 660	12 049 (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)	18 037	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

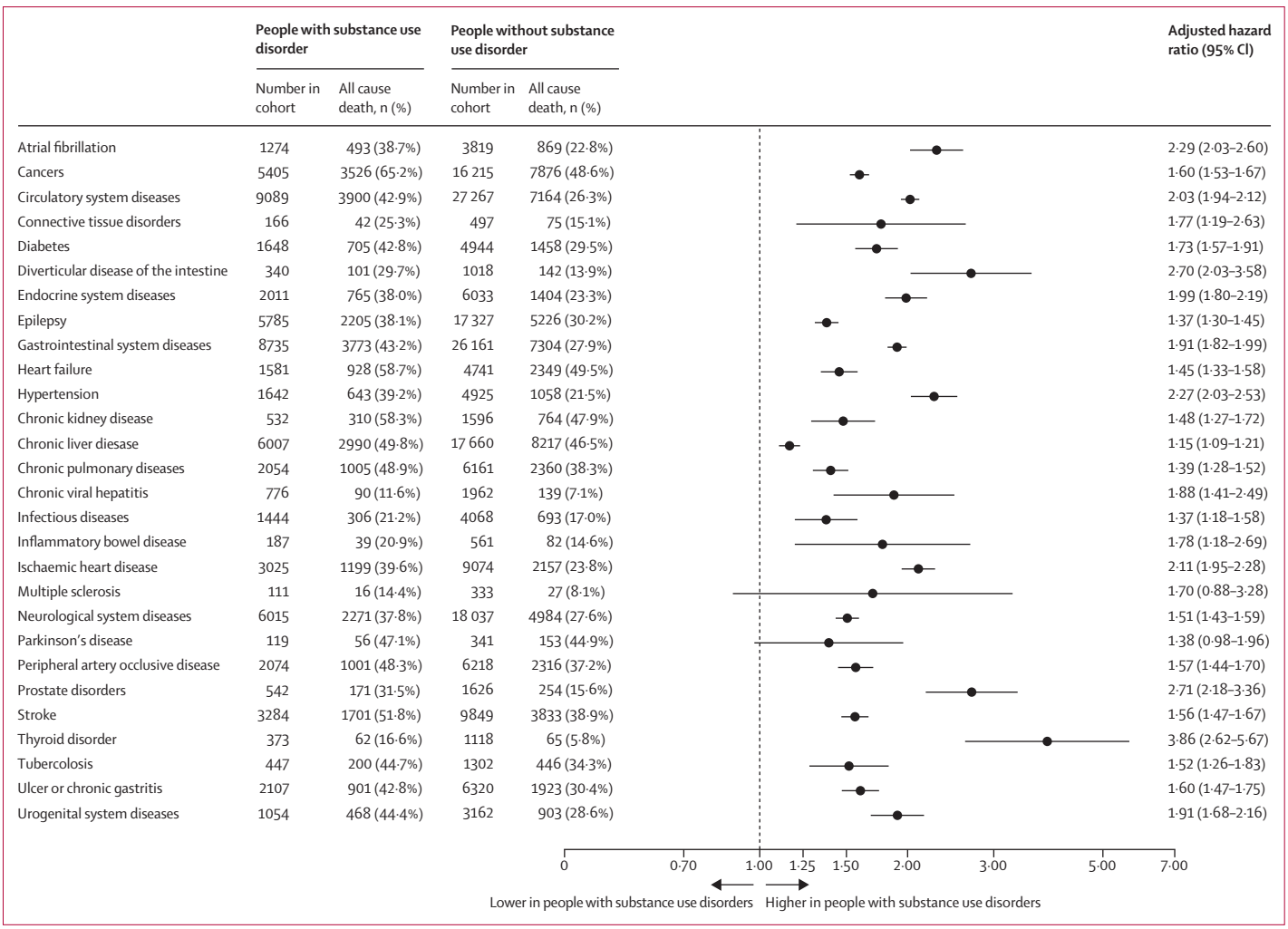


Figure 2: **Stratified Cox proportional hazards models of all-cause mortality following the onset of physical health conditions in people with substance use disorder**

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.

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.

Acknowledgments

TF is supported by the National Institute for Health and Care Research (NIHR) Applied Research Collaboration East of England at Cambridge and Peterborough NHS Foundation Trust. DK is a staff member of WHO. The views expressed in this article are those of the authors and do not necessarily reflect the views of the NIHR, the Department of Health and Social Care, or WHO.

References

1 WHO. Global status report on alcohol and health 2018. Sept 27, 2018. https://www.who.int/publications/i/item/9789241565639 (accessed Sept 29, 2022).
2 UN Office on Drugs and Crime. World drug report 2020. https://wdr.unodc.org/wdr2020/en/index2020.html (accessed Sept 29, 2022).
3 Degenhardt L, Charlson F, Ferrari A, et al. The global burden of disease attributable to alcohol and drug use in 195 countries and territories, 1990–2016: a systematic analysis for the Global Burden of Disease Study 2016. *Lancet Psychiatry* 2018; **5:** 987–1012.
4 Plana-Ripoll O, Musliner KL, Dalsgaard S, et al. Nature and prevalence of combinations of mental disorders and their association with excess mortality in a population-based cohort study. *World Psychiatry* 2020; **19:** 339–49.
5 Aldridge RW, Story A, Hwang SW, et al. Morbidity and mortality in homeless individuals, prisoners, sex workers, and individuals with substance use disorders in high-income countries: a systematic review and meta-analysis. *Lancet* 2018; **391:** 241–50.
6 Wu L-T, Zhu H, Ghitza UE. Multicomorbidity of chronic diseases and substance use disorders and their association with hospitalization: results from electronic health records data. *Drug Alcohol Depend* 2018; **192:** 316–23.
7 Kingston REF, Marel C, Mills KL. A systematic review of the prevalence of comorbid mental health disorders in people presenting for substance use treatment in Australia. *Drug Alcohol Rev* 2017; **36:** 527–39.
8 Martín-Santos R, Fonseca F, Domingo-Salvany A, et al. Dual diagnosis in the psychiatric emergency room in Spain. *Eur J Psychiatry* 2006; **20:** 147–56.
9 Becker MA, Boaz TL, Andel R, Hafner S. Risk of early rehospitalization for non-behavioral health conditions among adult Medicaid beneficiaries with severe mental illness or substance use disorders. *J Behav Health Serv Res* 2017; **44:** 113–21.
10 Brent DA, Perper JA, Moritz G, et al. Psychiatric risk factors for adolescent suicide: a case-control study. *J Am Acad Child Adolesc Psychiatry* 1993; **32:** 521–29.
11 Szerman N, Lopez-Castroman J, Arias F, et al. Dual diagnosis and suicide risk in a Spanish outpatient sample. *Subst Use Misuse* 2012; **47:** 383–89.
12 Boden MT, Moos R. Dually diagnosed patients' responses to substance use disorder treatment. *J Subst Abuse Treat* 2009; **37:** 335–45.
13 UN Department of Economic and Social Affairs. Transforming our world: the 2030 agenda for sustainable development. 2015. https://sustainabledevelopment.un.org/post2015/transformingourworld/publication (accessed Sept 29, 2022).
14 Volkow ND, Torrens M, Poznyak V, et al. Managing dual disorders: a statement by the Informal Scientific Network, UN Commission on Narcotic Drugs. *World Psychiatry* 2020; **19:** 396–97.
15 Krupchanka D, Mladá K, Winkler P, Khazaal Y, Albanese E. Mortality in people with mental disorders in the Czech Republic: a nationwide, register-based cohort study. *Lancet Public Health* 2018; **3:** e289–95.
16 Pedersen CB, Mors O, Bertelsen A, et al. A comprehensive nationwide study of the incidence rate and lifetime risk for treated mental disorders. *JAMA Psychiatry* 2014; **71:** 573–81.
17 Momen NC, Plana-Ripoll O, Agerbo E, et al. Association between mental disorders and subsequent medical conditions. *N Engl J Med* 2020; **382:** 1721–31.
18 Momen NC, Plana-Ripoll O, Agerbo E, et al. Mortality associated with mental disorders and comorbid general medical conditions. *JAMA Psychiatry* 2022; **79:** 444–53.
19 Sariaslan A, Sharpe M, Larsson H, Wolf A, Lichtenstein P, Fazel S. Psychiatric comorbidity and risk of premature mortality and suicide among those with chronic respiratory diseases, cardiovascular diseases, and diabetes in Sweden: a nationwide matched cohort study of over 1 million patients and their unaffected siblings. *PLoS Med* 2022; **19:** e1003864.
20 Stensrud MJ, Hernán MA. Why test for proportional hazards? *JAMA* 2020; **323:** 1401–02.
21 Plana-Ripoll O, Canudas-Romo V, Weye N, Laursen TM, McGrath JJ, Andersen PK. lillies: an R package for the estimation of excess life years lost among patients with a given disease or condition. *PLoS One* 2020; **15:** e0228073.
22 VanderWeele TJ, Ding P. Sensitivity analysis in observational research: introducing the E-value. *Ann Intern Med* 2017; **167:** 268–74.
23 Wasserstein RL, Lazar NA. The ASA statement on p-values: context, process, and purpose. *Am Stat* 2016; **70:** 129–33.
24 Dahlman D, Li X, Crump C, Sundquist J, Sundquist K. Drug use disorder and risk of incident and fatal prostate cancer among Swedish men: a nationwide epidemiological study. *Cancer Causes Control* 2022; **33:** 213–22.
25 Manderbacka K, Arffman M, Lumme S, et al. The effect of history of severe mental illness on mortality in colorectal cancer cases: a register-based cohort study. *Acta Oncol* 2018; **57:** 759–64.
26 Spithoff S, Kiran T, Khuu W, et al. Quality of primary care among individuals receiving treatment for opioid use disorder. *Can Fam Physician* 2019; **65:** 343–51.
27 Lasser KE, Kim TW, Alford DP, Cabral H, Saitz R, Samet JH. Is unhealthy substance use associated with failure to receive cancer screening and flu vaccination? A retrospective cross-sectional study. *BMJ Open* 2011; **1:** e000046.
28 de Weert-van Oene GH, Termorshuizen F, Buwalda VJA, Heerdink ER. Somatic health care utilization by patients treated for substance use disorders. *Drug Alcohol Depend* 2017; **178:** 277–84.
29 van Nieuwenhuizen A, Henderson C, Kassam A, et al. Emergency department staff views and experiences on diagnostic overshadowing related to people with mental illness. *Epidemiol Psychiatr Sci* 2013; **22:** 255–62.
30 Kagstrom A, Alexova A, Tuskova E, et al. The treatment gap for mental disorders and associated factors in the Czech Republic. *Eur Psychiatry* 2019; **59:** 37–43.
31 Rehkopf DH, Glymour MM, Osypuk TL. The consistency assumption for causal inference in social epidemiology: when a rose is not a rose. *Curr Epidemiol Rep* 2016; **3:** 63–71.
32 van Zwieten A, Tennant PWG, Kelly-Irving M, Blyth FM, Teixeira-Pinto A, Khalatbari-Soltani S. Avoiding overadjustment bias in social epidemiology through appropriate covariate selection: a primer. *J Clin Epidemiol* 2022; **149:** 127–36.
33 Magura S. Effectiveness of dual focus mutual aid for co-occurring substance use and mental health disorders: a review and synthesis of the "double trouble" in recovery evaluation. *Subst Use Misuse* 2008; **43:** 1904–26.
34 Flynn PM, Brown BS. Co-occurring disorders in substance abuse treatment: issues and prospects. *J Subst Abuse Treat* 2008; **34:** 36–47.
35 UN Office on Drugs and Crime. Comorbidities in drug use disorders: no wrong door. March 9, 2022. https://www.unodc.org/documents/drug-prevention-and-treatment/UNODC_Comorbidities_in_drug_use_disorders.pdf (accessed Sept 29, 2022).