Univerzita Karlova
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Dlouhodobé výstupy u pacientů s duševním onemocněním

Long-term outcomes in patients with mental health disorders

Disertační práce

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Abstract

The presented dissertation is a compilation of four studies published or accepted for publication in international journals with an impact factor, supplemented by a framing introduction and summary comments on each of these studies.

In the first part of the introduction section, the author states the main descriptive statistics related to Czech mental health care, from the prevalence of mental health disorders and the treatment gap to the utilized mental health care.

In the second part, the author introduces topics in psychiatric epidemiology with missing evidence, covered by four studies presented below.

The first presented study focuses on victimization of people with mental health disorders and provides evidence of the significant effects of the experienced assault and the number of previous hospitalizations on the following course of a patient's severe mental illness.

The second presented study provides evidence of a lower survival following SARS-CoV-2 infection in people with pre-existing psychotic disorders and in people with pre-existing substance use disorders when compared to the Czech general population.

The final two presented studies provide the first evidence of the higher risk of death and the first quantification of life-years lost after the onset of a physical health condition in people with a history of hospitalization for severe mental illness and in people with a history of hospitalization for substance use disorders, both compared to the Czech general population.

All presented studies are based on the Czech routinely collected data from nationwide health registers maintained by the Institute of Health Information and Statistics.

Abstrakt

Předkládaná disertační práce je kompilátem čtyř studií publikovaných nebo přijatých k publikaci v impaktovaných mezinárodních časopisech, doplněných o rámcový úvod a souhrnný komentář ke každé z těchto studií.

V první části úvodu autorka předkládá hlavní popisné statistické údaje týkající se českého prostředí péče o duševní zdraví, od prevalence duševních onemocnění, přes poměr lidí nevyhledávajících odbornou pomoc, až po čerpanou zdravotní péči o duševní zdraví.

Ve druhé části autorka představuje témata psychiatrické epidemiologie, u kterých dosud chyběla evidence a kterými se zabývají čtyři níže uvedené studie.

První prezentovaná studie se zaměřuje na téma viktimizace osob s duševním onemocněním a poskytuje evidenci o významném vlivu napadení a počtu předchozích hospitalizací na další průběh závažného duševního onemocnění pacienta.

Druhá prezentovaná studie uvádí evidenci nižšího přežití po infekci SARS-CoV-2 u osob s psychotickým onemocněním a u osob s poruchami způsobenými užíváním návykových látek, ve srovnání s českou obecnou populací.

Poslední dvě prezentované studie poskytují první evidenci vyššího rizika úmrtí a první kvantifikaci ztracených roků života po vypuknutí fyzického onemocnění u osob s historií hospitalizace pro závažné duševní onemocnění a u osob s historií hospitalizace pro poruchy způsobené užíváním návykových látek, ve srovnání s českou obecnou populací.

Všechny prezentované studie jsou založené na českých rutinně sbíraných datech z celostátních zdravotních registrů spravovaných Ústavem zdravotnických informací a statistiky.

Acknowledgment

Contents

Introduction

Patients with mental health disorders

Prevalence of mental health disorders in Czechia

As we stated in the study (Potocar, Mlada et al. 2024), the COVID-19 pandemic and the associated mitigation strategies, consisting, among others, of closures of non-essential services and businesses and stay-at-home-orders, exposed large parts of the Czech population to levels of known risk factors of mental disorders (e.g., social isolation, stress, financial hardship, and uncertainty about the future) that were unprecedented in the last decades. To provide timely evidence on the state of the population mental health, we conducted two nationally representative surveys during the pandemic, using the Mini International Neuropsychiatric Interview to assess current mental disorders. The data collection for the first survey coinciding with the first wave of the pandemic (May 2020), when both the cumulative number of COVID-19-related hospitalizations and deaths was very low (Kasal, Kuklova et al. 2023). On the other hand, the second data collection was realized during November 2020, aligned with the second wave of the pandemic, during which Czechia was hit particularly hard, leaving the healthcare system overloaded for months (Kasal, Kuklova et al. 2023). Data for both surveys were collected using a mixed computer-assisted web interviewing (CAWI) and computer-assisted telephone interviewing approach (CATI), with individuals randomly drawn from a panel. When compared with pre-pandemic data collection from 2017 utilized by household sampling and paper and pencil interviewing (PAPI), we found that the prevalence of mental disorders increased from 20,02 % to 29,63 % and 32,94 % during the first and second data collection, respectively (Formanek, Kagstrom et al. 2019), (Winkler, Formanek et al. 2020), (Winkler, Mohrova et al. 2021). While these results suggest that the mental health of the Czech population worsened during the first year of pandemic, the potential longer-term impacts of the pandemic on the population mental health were not known.

The study we conducted in 2022 (Potocar, Mlada et al. 2024), investigated the Czech adults' mental health following the COVID-19 pandemic and the potential influence of data collection methodology on prevalence estimates. Data from representative surveys on Czech adults, conducted in November 2017 ($n = 3\ 306$), in May ($n = 3\ 021$) and November 2020 ($n = 3\ 000$), and in November and December 2022 ($n = 7\ 311$), were collected. In 2017 and 2022, 20,02 % and 27,22 % of individuals had at least one mental disorder, respectively. The 2022 panel

sampling and online and telephone interviewing estimates (34,29 % and 26,7 %) were substantially higher than those from household sampling and personal interviewing (19,9 %). Prevalence rates based on the same sampling and interviewing strategy were broadly consistent in 2017 and 2022. This study showed that overall prevalence rates were still elevated in 2022, but suggests that data collection methodology influenced the estimates (Potocar, Mlada et al. 2024).

When assessing the overall prevalence of mental disorders, relative to the 2017 baseline, the prevalence of current major depressive episode increased by almost 8 percentage points in November 2020 (3,96 %; 3,29 to 4,62 vs 12,15 %; 10,92 to 13,39), and remained elevated up to 2022 (8,82 %; 8,17 to 9,47). Similarly, the prevalence of anxiety disorders increased by approximately 5 percentage points in November 2020, when compared with 2017 (7,79 %; 6,87 to 8,7 vs. 12,84; 11,61 to 14,08), and remained elevated until 2022 (12,28 %; 11,52 to 13,04), and the proportion of individuals scoring positively for suicide risk increased between 2017 and November 2022 by more than 10 percentage points (3,88 %; 3,22 to 4,55 vs 14,26 %; 12,88 to 15,64), and decreased only slightly to 10,47 %, (9,77 to 11,18) in 2022. Then, the proportion of individuals meeting criteria for alcohol use disorders was 10,84 %, (9,76 to 11,91) in 2017 and 11,51 % (10,77 to 12,25) in 2022, suggesting consistency in time. More details can be found in (Potocar, Mlada et al. 2024).

Treatment gap and barriers in help-seeking in Czechia

In the study (Potocar, Mlada et al. 2024), we also investigated help-seeking and associated barriers and the treatment gap was established in participants scoring positively. In help-seeking individuals, encountering barriers was investigated.

Almost 60 % of individuals who sought professional help in the last 12 months reported that they were confronted with structural barriers such as long waiting lists and unavailability of services (56,97 %; 95% CI = 53,37 to 60,56). Individual barriers, such as worries and feelings of fear and shame, were present in 20,36 % (17,43 to 23,28) of individuals who sought professional help.

Then, out of those individuals who never sought help during their lifetime or who did not seek help in the past 12 months, 8,53 % (7,85 to 9,20) and 4,59 % (4,08 to 5,1) reported individual and structural barriers in their potential help-seeking.

The treatment gap was around 80 % from 2017 to 2022. We found that the levels of treatment gap are broadly consistent with the 2017 levels, remaining still very high. In addition, worryingly, more than 50 % of individuals reported encountering structural barriers when actually seeking help in 2022. More details can be found in (Potocar, Mlada et al. 2024).

Number of people utilizing mental health care in Czechia

Based on information provided by the Czech Institute of Health Information and Statistics, there were 504 490 people older than 19 years who utilized mental health care in outpatient care in Czechia in 2022, excluding those treated for Alzheimer's disease (Institute of Health Information and Statistics 2023). Compared to the 2012, this number increased by approximately 100 000 people during the last decade.

In 2022, more than 18 600 hospitalizations of people with mental health disorders (excluding Alzheimer's disease), older than 19 years, were recorded in inpatient care facilities and 24 666 cases were treated at psychiatric acute care beds. Within the last decade, the number of hospitalizations in mental health care inpatient facilities decreased by 30 %. The number of psychiatric acute care beds existing in the Czech facilities increased by 70 %, resulting in an 80 % increase in cases treated at psychiatric acute care beds in Czechia (Institute of Health Information and Statistics 2023). More details on the trends in inpatient care use for adult mental disorders in Czechia can be found in (Potocar, Winkler et al. 2024).

Mental health related long-term outcomes and missing evidence in psychiatric epidemiology

Mortality, life-years lost and physical comorbidities

Mental health disorders are still associated with stigma which negatively correlates with help-seeking behavior, it's associated with limited access to and provision of physical health care and therefore it contributes to worse health outcomes (Gronholm, Thornicroft et al. 2017, Schnyder, Panczak et al. 2017, Schomerus, Leonhard et al. 2022).

There is an evidence proving a higher risk of developing a wide range of physical health conditions in people with mental health disorders, relative to their counterparts without these disorders (Scott, Lim et al. 2016, Schneider, Erhart et al. 2019, Momen, Plana-Ripoll et al. 2020). Higher mortality rates and shorter life expectancies in people with mental health disorders than in the general population were shown in multiple studies (Plana-Ripoll, Pedersen et al. 2019, Schneider, Erhart et al. 2019), including our study (Krupchanka, Mlada et al. 2018) where we presented standardized mortality ratios for people with mental health disorders compared with the general population (from 1,6; 95% CI: 1,5-1,7 for mood disorders to 3,5; 95% CI 3,4–3,7 for substance use disorders). However, these studies did not assess the impact of mental health disorder presence on individuals' mortality by comparing people having the same physical health problem while having or not having mental health disorder.

Worse physical health in people with mental health disorders was an important issue during the COVID-19 pandemic epoch, related to the lower survival following SARS-CoV-2 infection in people with pre-existing mental disorders. Later since the COVID-19 outbreak, it was unknown whether these poorer outcomes persisted at later stages of the pandemic, following the broad introduction of vaccines. Furthermore, no study had used national data covering almost all inpatient and outpatient services and laboratory-confirmed SARS-CoV-2 infections to study these associations in matched cohorts.

Victimization and relapses of mental health disorders

Although relapses of mental health disorders are associated with an increased risk of long-term disability and suicide attempts (Lauriello 2020), evidence of some factors affecting the quality of the patient's life and long-term development of her/his mental health disorder was missing. Namely, trauma is considered to be one of the risk factors not only in development

of psychotic disorder but also in affecting the course of this illness. Concurrently, people with severe mental illness experience victimization more often than the general population (de Vries, van Busschbach et al. 2019). Nevertheless, the former study showed that only 23 % of studies published on Pub-Med until 2007 focused on victimization while 72 % focused on violence in people with mental health (Vevera, Černý et al. 2011). The systematic review (Latalova K, Kamaradova D et al. 2014) showed that the life-time prevalence of victimization in patients with psychotic disorder varied from 4,3 % to 92 % and the prevalence of victimization in the last 12 months varied from 7,1 % to 56 %. Current following systematic review based on studies published from 2014 to 2021 showed that the prevalence of victimization in the last 12 months in people with psychotic disorder was 24,8 % (with 95% confidence interval from 22,1 to 27,6) (Nichtova, Vevera 2024). Few studies provided the evidence of the risk and protective factors for victimization in people with psychotic disorder in the Czech Republic (Cerny, Hodgins et al. 2018; Vevera, Černý et al. 2018) but there was no evidence substantiating the effect of victimization on the patient's prognosis based on nationwide data.

Within the Ph.D. study, my research activities focused mainly on the recent topics mentioned above and on the filling the evidence gap in psychiatric epidemiology. Studies presented in the Results section elaborate these topics more.

Goals and hypotheses

In the current studies presented below, we aimed to provide the evidence for the Czech mental health care system but also to supply the evidence missing for people with mental health disorders worldwide. We used the Czech nationwide health registers:

1) to investigate the effect of being an assault victim on the further trajectory of a patient's severe mental illness, specifically on the risk of rehospitalization for severe mental illness.

   We hypothesized that individuals who had been hospitalized for injury sustained in the assault would have a higher risk of rehospitalizations for severe mental illness than their matched counterparts who had not been hospitalized for injury sustained in the assault.

2) to investigate the risk of death with COVID-19 and all-cause mortality in individuals with mental health disorders, compared to the rest of the general population.

   We hypothesized that individuals with pre-existing mental disorders would have a higher risk of death with COVID-19 and from all-cause following first-ever laboratory-confirmed infection with SARS-CoV-2 compared with matched counterparts without mental disorders, at five distinct pandemic epochs.

3) to assess the risk of all-cause death and loss of life years in people with physical health conditions who had a pre-existing severe mental illness compared with matched counterparts who had the same physical health condition but did not have a severe mental illness.

   We hypothesized that people with pre-existing severe mental illness would have an increased risk of all-cause death as well as larger losses of life-years following the onset of physical health conditions than their matched counterparts without a history of severe mental illness.

4) to assess the risk of all-cause death and life-years lost in people with physical health conditions who had a pre-existing substance use disorder compared with matched counterparts who had the same physical health condition but did not have a substance use disorder.

We hypothesized that people with pre-existing substance use disorder would have a consistently increased risk of all-cause death as well as larger losses of life-years following the onset of physical health conditions than their matched counterparts without a history of substance use disorder.

Data sources

In all four studies presented below, we used the Czech nationwide health register data. While there are no registers of people with mental health disorders in the Czech Republic, the data on utilized care are the most representative nationwide source of data enabling to assess the long-term outcomes in people with mental health disorders in Czechia.

For assessing the effect of victimization on the course of a patient's severe mental illness and for assessing the mortality and life-years lost in patients with mental health disorders (severe mental illness; substance use disorders), with regards to physical health condition, we used the National Registry of Hospitalized Patients containing data on inpatient services and the registry of all-cause mortality, maintained by the state-funded Institute of Health Information and Statistics of Czechia. Both registries cover the period from 1994 to 2017 and can be interlinked using a common unique identifier. More information about these registers can be found in (Krupchanka, Mlada et al. 2018).

For assessing the risk of death with COVID-19 and all-cause mortality following first-ever laboratory-confirmed infection with SARS-CoV-2, we used data from three registries, parts of the Czech National Health Information System.

The National Registry of Reimbursed Health Services contains data on all services covered by public health insurance (outpatient and inpatient services, medicine prescriptions, etc.) starting from 2010. The register covers virtually the entire Czech population (approximately 10.7 million inhabitants). Administratively, all records are created by health professionals who complete information on diagnosis per International Classification of Diseases 10th Revision, date of treatment, Anatomical Therapeutic Chemical (ATC) classification codes for prescription medications (except common medications administered during inpatient treatment), and sociodemographic information. Additionally, we used data from the Information System of Infectious Diseases covering nationwide testing for SARS-CoV-2 and COVID-19 vaccination status. Furthermore, we used data from the Register of All-cause Mortality, containing information on the date of death, the ICD-10 cause, and, if applicable, the external cause of death. All three registers can be interlinked using a common unique identifier, and are maintained by the state-funded Institute of Health Information and Statistics of Czechia.

Results

The results of the dissertation are documented by the four original papers presented below. Each paper has its own page numbering.

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

In the initiation part of my Ph.D. study, I focused on the topic of the victimization of people with mental health disorders. This phenomenon is strongly related to the stigma and destigmatization of people with mental health disorders which are the subject of my activities focused on increasing mental health literacy in the Czech public and of an implementation project conducted under our research program Public Mental Health, at the National Institute of Mental Health, for more information see (Guerrero 2024). Although the prejudice picturing people with severe mental illness as often acting violently is still present in the Czech general population, victimization is more common in people with severe mental illness than in the general population (de Vries, van Busschbach et al. 2019). The original motivation of our study was to describe the role of victimization in the individual's mental health disorder development. Since we aimed to provide the evidence based on the whole Czech population data, instead of a facility-specific patient cohort with the limited generalization of the results, we used nationwide health register data. While the data available in 2019 were based on the inpatient care records only, we defined the victimization as being hospitalized for an injury sustained in an assault.

We sampled people hospitalized for ICD codes F20, F25, F31, F32 or F33 (SMI; schizophrenia, schizoaffective disorder, bipolar and depressive disorder), discharged from inpatient facilities from 2002 until 2007. Then we divided these patients into two groups: those hospitalized for injury sustained in an assault (exposure; ICD codes X93–95, X99, Y00–Y05) after their SMI hospitalization and those who were not subsequently exposed to an assault resulting in hospitalization. These two groups of patients were individually matched based on sex, age (+-3 years), and SMI diagnosis of individual's index hospitalization. For every exposed individual, we randomly chose five unexposed counterparts.

Using this procedure, we obtained 248 individuals with a history of hospitalization for SMI who were assaulted and their 1 240 non-assaulted counterparts. Both groups of patients were

followed up for SMI rehospitalization within 6 months after the discharge from the assault-related hospitalization (or corresponding timepoint for non-assaulted individuals). We considered the number of previous SMI hospitalizations and an occurrence of substance use disorder hospitalization within the last seven years as potential confounders and we adjusted for them in the regression model. The effect of sex, age, and specific SMI diagnosis was annulled by individual matching of exposed and unexposed counterparts.

In the final adjusted mixed effects logistic regression model, the effect of experiencing an assault on being rehospitalized for SMI was 3,07 (with a 95% confidence interval from 2,10 to 4,49). The effect of the number of SMI hospitalizations in the last 7 years was also significant with an odds ratio of 1,27 on one previous SMI hospitalization (95% CI: 1,20; 1,35).

These results are important for psychiatric clinical praxis and the public mental health field. They show the need to prevent relapses, as these play a significant role in the further course of a patient's mental health disorder. Concurrently, the results of our study show the need for assault victims to be evaluated by a mental health professional, as violent victimization may have an essential impact of the further development of their mental health disorder.

Deaths with COVID-19 and from all-causes following first-ever SARS-CoV-2 infection in individuals with pre-existing mental disorders: A national cohort study

In addition to the negative effects of the COVID-19 disease pandemic on the population mental health, the direct effects of the disease COVID-19 on people with an existing mental illness were also identified. The results of a meta-analysis conducted in 2021 indicated more than two times increased risk of hospitalization and mortality associated with COVID-19 in people with mental disorders compared with counterparts without these diseases (Vai, Mazza et al. 2021). An increased risk of mortality was found specifically for psychotic disorders, mood disorders, substance use disorders, and developmental disorders (Vai, Mazza et al. 2021). The exact mechanisms behind the increased mortality associated with COVID-19 in people with mental illness were unknown, however, factors contributing to this association were thought to include an increased incidence of comorbidities identified as risk factors for a more severe course of COVID-19 (e.g. diabetes), poorer access to care or poorer care, and immunological disorders related to mental illnesses or their treatment (De Picker, Yolken et al. 2021, Nemani, Li et al. 2021, Vai, Mazza et al. 2021).

In collaboration with the Czech Institute of Health Information and Statistics, we implemented a project supported by the Czech Health Research Council assessing the impact of the COVID-19 pandemic on natural causes of death in individuals with a history of mental disorders. We aimed to describe the situation in the Czech Republic and concurrently to provide missing evidence for later stages of the pandemic worldwide.

We used Czech national, whole population, all healthcare encompassing register-based data using data covering inpatient and outpatient services reimbursed by Czech health insurance companies, including primary care, as well as prescription medications. We defined five epochs of the COVID-19 pandemic covering the period from March 2020 to February 2022 and retrieved all individuals with first-ever laboratory-confirmed SARS-CoV-2 infection occurring during these epochs. Within the individuals, we identified people with a history of mental health disorders and matched them with individuals who had no history of mental health disorders, based on age, sex, month, and year of infection as well as the Charlson Comorbidity Index. Both groups were followed up for the risk of death with COVID-19 and all-cause death, both within 28 and 60 days after a positive test for SARS-CoV-2.

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Based on the stratified Cox proportional hazards models adjusting for all considered confounders, including vaccination uptake and clinically-recorded physical comorbidities, people with psychotic disorders had an elevated risk of death with COVID-19 and an elevated risk of all-cause death in all epochs (except the first epoch where the models could not be fit reliably), both 28 days and 60 days following SARS-CoV-2 infection. People with substance use disorders had an elevated risk of death with COVID-19 in the epoch from 27th December 2020 to 31st March 2021 (third epoch; the beginning of the national vaccination program to the end of the second wave of the pandemic), both within 28 and 60 days after a positive test for SARS-CoV-2. This group of people had an elevated risk of all-cause death in all epochs (except the first epoch where the models could not be fit reliably), both 28 days and 60 days following SARS-CoV-2 infection.

In contrast, people with anxiety disorders had a decreased risk of death with COVID-19 and a decreased risk of all-cause death in 3 of 5 epochs, both 28 days and 60 days following SARS-CoV-2 infection. People with affective disorders had a decreased risk of death with COVID-19 and a decreased risk of all-cause death in the epoch from 27th December 2020 to 31st March 2021. All other adjusted models were broadly consistent with a null effect.

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

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

Studies using nationwide health registers show that people with severe mental illness have an elevated risk of developing a large number of physical health conditions compared with people without severe mental illness. These people are also more likely to die prematurely, with deaths from comorbid physical health conditions far outweighing the impact of suicides and accidents. However, it is uncertain as to whether people with severe mental illness experience premature mortality solely because they are more likely to develop a larger number of physical illnesses, or whether those illnesses are also more likely to result in death due to biological, behavioral, socio-demographic, and structural factors that are related to this patient group. No national study of people with severe mental illness has considered the temporal order of mental and physical health conditions and the contribution of severe mental illness to the fatally deleterious effects of physical illness.

We used individual-level, de-identified data from the Czech nationwide registers of all-cause hospitalizations to identify all people hospitalized with specific physical health conditions between 1999 and 2017, separately for each health condition. We considered people hospitalized for severe mental illness (schizophrenia, schizotypal and delusional disorders, F20-F29; bipolar affective disorder, F31; depressive episode, F32; recurrent depressive disorder, F33) before the hospitalization for the studied physical health conditions as the exposed cohort. The comparison cohort consisted of individuals not hospitalized for a severe mental illness between 1999 and the onset of the studied physical health condition. We exactly matched each individual with severe mental illness with counterparts without severe mental illness on sex, age (± 3 years), and discharge year of the hospitalization for a physical health condition. By using a register of all-cause deaths, we investigated the risk of all-cause death and life years lost following the onset of specific physical health condition in people with severe mental illness, compared with counterparts without a history of severe mental illness.

The number of individuals in disease-specific cohorts ranged from 600 (100 with and 500 without severe mental illness) for tuberculosis to 37 962 (6 327 with and 31 635 without severe mental illness) for diseases of the circulatory system. Stratified Cox proportional hazards models detected an elevated risk of all-cause death in people with severe mental illness

following the onset of seven out of nine studied broadly defined physical health conditions when compared with matched counterparts. The hazard ratios for these conditions ranged from 1,20 for diseases of the neurological system to 1,91 for diseases of the circulatory system. Considering specific physical health conditions subgroups, the models detected an increased risk of all-cause death in people with severe mental illness following the onset of 14 out of 19. The hazard ratios ranged from 1,24 for chronic kidney disease to 3,01 for thyroid disorder.

We detected that people with severe mental illness had shorter life expectancy after the onset of a physical health condition than people without severe mental illness for eight out of nine broadly defined physical health conditions. The additional losses of life-years ranged from 1,73 for diseases of the neurological system to 4,38 for connective tissue disorders. Considering specific physical health conditions, people with severe mental illness lost more life-years following the onset of 13 out of 19 specific physical health conditions. The additional losses of life-years ranged from 1,40 for heart failure to 8,94 for inflammatory bowel disease.

These findings demonstrate that people with severe mental illnesses are particularly vulnerable and should be a high priority not only within psychiatric but also within broader health services. To the best of our knowledge, this is the first national study to systematically investigate mortality and loss of life-years in people with severe mental illness who subsequently develop physical health conditions.

Physical and mental health comorbidities are common in people with a substance use disorder (Aldridge, Story et al. 2018, Wu, Zhu et al. 2018). These studies had limitations as focusing solely on either psychiatric comorbidities or selected physical health conditions, or relying on analysis of isolated registers of patients with substance use disorders. Therefore we conducted a study based on individual-level, nationwide data covering a long time period to investigate long-term outcomes in people with pre-existing substance use disorders (excluding acute intoxication), following the onset of different physical health conditions. We compared these outcomes with those of matched counterparts without substance use disorders to describe the difference between people with substance use disorders and the rest of the general population.

We used individual-level Czech data from the register of all-cause hospitalizations and the register of all-cause deaths. We selected 121 153 people with a history of hospitalization for substance use disorder discharged between 1994 and 2017, defined the comparison cohort as all hospitalized individuals without hospitalization for substance use disorder during the entire examined period (6 742 134 people), and matched these two groups based on sex, age (+-3 years), work status, and year of discharge. For every individual, we assessed the presence of subsequent physical health conditions and whether an individual had died, both until the end of 2017.

Number of people 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 9 089 with substance use disorders). Stratified Cox proportional hazards models showed that in 26 of the 28 groups of subsequent health conditions examined, individuals with pre-existing substance use disorder had an elevated risk of all-cause death when compared with their counterparts without substance use disorder. The adjusted hazard ratios ranged from 1,15 (95% CI: 1,09–1,21) for chronic liver disease to 3,86 (2,62–5,67) for thyroid disorder.

Across most subsequent physical health conditions in males and females, substance use disorder was associated with a loss in life-years. 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 years for prostate disorders to 37 years 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 years for multiple sclerosis to 41 years for heart failure. Considering disease onset at ages 40 and 60 years, males and females with substance use disorder had significant life-years lost in the majority of groups of subsequent physical health conditions.

A history of hospitalization 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.

Conclusion

The Ph.D. thesis concludes studies in psychiatric epidemiology, published or accepted for publication in international journals with an impact factor from 3 (Annals of General Psychiatry) to 64 (Lancet Psychiatry).

These studies provide evidence of long-term outcomes in people with mental health disorders, assessing the effect of experienced assault on the further course of an individual's severe mental illness and the risk of death with COVID-19 or all-cause death following the SARS-CoV-2 infection in people with mental health disorders. Presented studies also provided important evidence of significant differences between people with mental health disorders and the rest of the population in terms of mortality and life-years lost, while having the same specific physical health comorbidity.

References

Aldridge, R. W., A. Story, S. W. Hwang, M. Nordentoft, S. A. Luchenski, G. Hartwell, E. J. Tweed, D. Lewer, S. Vittal Katikireddi and A. C. Hayward (2018). "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 **391**(10117): 241-250.

Cerny M, S. Hodgins, R. Kučíková, L. Kážmér, A. Lambertová, A. Nawka, L. Nawková, A. Parzelka, J. Raboch, P. Bob, J. Vevera (2018). Violence in persons with and without psychosis in the Czech Republic: risk and protective factors. Neuropsychiatr Dis Treat; 14: 2793-2805.

De Picker, L. J., R. Yolken, F. Benedetti, A. Borsini, I. Branchi, P. Fusar-Poli, J. Carlos Leza, C. Pariante, T. Pollak, R. Tamouza, B. Vai, A. C. Vernon, M. E. Benros, M. Leboyer and E. I.-N. TWG (2021). "Viewpoint | European COVID-19 exit strategy for people with severe mental disorders: Too little, but not yet too late." Brain Behav Immun **94**: 15-17.

de Vries, B., J. T. van Busschbach, E. C. D. van der Stouwe, A. Aleman, J. J. M. van Dijk, P. H. Lysaker, J. Arends, S. A. Nijman and G. H. M. Pijnenborg (2019). "Prevalence Rate and Risk Factors of Victimization in Adult Patients With a Psychotic Disorder: A Systematic Review and Meta-analysis." Schizophr Bull **45**(1): 114-126.

Formanek, T., A. Kagstrom, P. Cermakova, L. Csemy, K. Mlada and P. Winkler (2019). "Prevalence of mental disorders and associated disability: Results from the cross-sectional CZEch mental health Study (CZEMS)." Eur Psychiatry **60**: 1-6.

Gronholm, P. C., G. Thornicroft, K. R. Laurens and S. Evans-Lacko (2017). "Mental health-related stigma and pathways to care for people at risk of psychotic disorders or experiencing first-episode psychosis: a systematic review." Psychological medicine **47**(11): 1867-1879.

Guerrero, Z. (2024). "Vývoj a pilotáž programů proti stigmatizaci v České republice." Česká a slovenská psychiatrie. Retrieved May 24, 2024, from http://www.cspsychiatr.cz/detail.php?stat=1576.

Institute of Health Information and Statistics (2023). "Psychiatrická ročenka 2022." Retrieved May 22, 2024, from https://www.uzis.cz/res/f/008442/psych2022.pdf.

Kasal, A., M. Kuklova, A. Kagstrom, P. Winkler and T. Formanek (2023). "Suicide Risk in Individuals With and Without Mental Disorders Before and During the COVID-19 Pandemic: An Analysis of Three Nationwide Cross-Sectional Surveys in Czechia." Arch Suicide Res **27**(2): 671-685.

Krupchanka, D., K. Mlada, P. Winkler, Y. Khazaal and E. Albanese (2018). "Mortality in people with mental disorders in the Czech Republic: a nationwide, register-based cohort study." Lancet Public Health **3**(6): e289-e295.

Latalova K, D. Kamaradova, J. Prasko (2014). "Violent victimization of adult patients with severe mental illness: a systematic review". Neuropsychiatr Dis Treat. 10:1925-1939.

Lauriello, J. (2020). "Prevalence and Impact of Relapse in Patients With Schizophrenia." J Clin Psychiatry **81**(2).

Momen, N. C., O. Plana-Ripoll, E. Agerbo, M. E. Benros, A. D. Børglum, M. K. Christensen, S. Dalsgaard, L. Degenhardt, P. de Jonge, J.-C. P. G. Debost, M. Fenger-Grøn, J. M. Gunn, K. M. Iburg, L. V. Kessing, R. C. Kessler, T. M. Laursen, C. C. W. Lim, O. Mors, P. B. Mortensen, K. L. Musliner, M. Nordentoft, C. B. Pedersen, L. V. Petersen, A. R. Ribe, A. M. Roest, S. Saha, A. J. Schork, K. M. Scott, C. Sievert, H. J. Sørensen, T. J. Stedman, M. Vestergaard, B. Vilhjalmsson, T. Werge, N. Weye, H. A. Whiteford, A. Prior and J. J. McGrath (2020). "Association between Mental Disorders and Subsequent Medical Conditions." New England Journal of Medicine **382**(18): 1721-1731.

Nemani, K., C. Li, M. Olfson, E. M. Blessing, N. Razavian, J. Chen, E. Petkova and D. C. Goff (2021). "Association of Psychiatric Disorders With Mortality Among Patients With COVID-19." JAMA Psychiatry **78**(4): 380-386.

Nichtová A, J. Vevera (2024). "Victimization of patients with psychotic disorder (I.)" Česká a slovenská psychiatrie. 2/2024. Retrieved June 13, 2024, from http://www.cspsychiatr.cz/detail.php?stat=1571

Plana-Ripoll, O., C. B. Pedersen, E. Agerbo, Y. Holtz, A. Erlangsen, V. Canudas-Romo, P. K. Andersen, F. J. Charlson, M. K. Christensen, H. E. Erskine, A. J. Ferrari, K. M. Iburg, N. Momen, P. B. Mortensen, M. Nordentoft, D. F. Santomauro, J. G. Scott, H. A. Whiteford, N. Weye, J. J. McGrath and T. M. Laursen (2019). "A comprehensive analysis of mortality-related health metrics associated with mental disorders: a nationwide, register-based cohort study." The Lancet **394**(10211): 1827-1835.

Potocar, L., K. Mlada, M. Kucera, P. Mohr, P. Winkler and T. Formanek (2024). "Population mental health, help-seeking and associated barriers following the COVID-19 pandemic: Analysis of repeated nationally representative cross-sectional surveys in Czechia." Psychiatry Res **331**: 115641.

Potocar, L., P. Winkler, P. Mohr and T. Formanek (2024). "Temporal trends in inpatient care use for adult mental disorders in Czechia: a nationwide register-based study from 1994 to 2015." Soc Psychiatry Psychiatr Epidemiol.

Scott, K. M., C. Lim, A. Al-Hamzawi, J. Alonso, R. Bruffaerts, J. M. Caldas-de-Almeida, S. Florescu, G. de Girolamo, C. Hu, P. de Jonge, N. Kawakami, M. E. Medina-Mora, J. Moskalewicz, F. Navarro-Mateu, S. O'Neill, M. Piazza, J. Posada-Villa, Y. Torres and R. C. Kessler (2016). "Association of Mental Disorders With Subsequent Chronic Physical Conditions: World Mental Health Surveys From 17 Countries." JAMA Psychiatry **73**(2): 150-158.

Schneider, F., M. Erhart, W. Hewer, L. A. K. Loeffler and F. Jacobi (2019). "Mortality and medical comorbidity in the severely mentally ill - a German registry study." Dtsch Arztebl International **116**(23-24): 405-411.

Schnyder, N., R. Panczak, N. Groth and F. Schultze-Lutter (2017). "Association between

mental health-related stigma and active help-seeking: systematic review and meta-analysis." The British Journal of Psychiatry **210**(4): 261-268.

Schomerus, G., A. Leonhard, J. Manthey, J. Morris, M. Neufeld, C. Kilian, S. Speerforck, P. Winkler and P. W. Corrigan (2022). "The stigma of alcohol-related liver disease and its impact on healthcare." Journal of Hepatology.

Vai, B., M. G. Mazza, C. Delli Colli, M. Foiselle, B. Allen, F. Benedetti, A. Borsini, M. Casanova Dias, R. Tamouza, M. Leboyer, M. E. Benros, I. Branchi, P. Fusar-Poli and L. J. De Picker (2021). "Mental disorders and risk of COVID-19-related mortality, hospitalisation, and intensive care unit admission: a systematic review and meta-analysis." Lancet Psychiatry **8**(9): 797-812.

Vevera J, M. Černý, L. Kážmér, K. Příhodová, R. Ptáček, H. Ptáčková (2018). Viktimizace pacientů trpících psychózou. Postgraduální medicína; 20 (6): 573-579.

Vevera J, M. Černý, P. Král (2011). "Agrese a násilné chování." Postgraduální medicína (on-line), from http://zdravi.e15.cz/clanek/postgradualni-medicina/agrese-a-nasilne-chovani-457912

Winkler, P., T. Formanek, K. Mlada, A. Kagstrom, Z. Mohrova, P. Mohr and L. Csemy (2020). "Increase in prevalence of current mental disorders in the context of COVID-19: analysis of repeated nationwide cross-sectional surveys." Epidemiol Psychiatr Sci **29**: e173.

Winkler, P., Z. Mohrova, K. Mlada, M. Kuklova, A. Kagstrom, P. Mohr and T. Formanek (2021). "Prevalence of current mental disorders before and during the second wave of COVID-19 pandemic: An analysis of repeated nationwide cross-sectional surveys." J Psychiatr Res **139**: 167-171.

Wu, L. T., H. Zhu and U. E. Ghitza (2018). "Multicomorbidity of chronic diseases and substance use disorders and their association with hospitalization: Results from electronic health records data." Drug Alcohol Depend **192**: 316-323.

Author's publications

Presented papers

Mlada K, Formanek T, Vevera J, Latalova K, Winkler P, Volavka J. Serious physical assault and subsequent risk for rehospitalization in individuals with severe mental illness: a nationwide, register-based retrospective cohort study. Ann Gen Psychiatry. 2021 Sep 18;20(1):44. doi: 10.1186/s12991-021-00358-y. PMID: 34537054; PMCID: PMC8449895.

Formánek T, Potocar L, Wolfova K, Melicharova H, Mladá K., Wiedemann A, Chen D, Mohr P, Winkler P, Jones P, Jarkovský J. Deaths with COVID-19 and from All-causes following First-ever SARS-CoV-2 Infection in Individuals with Pre-existing Mental Disorders: A National Cohort Study from Czechia. PLOS Medicine. Accepted for publication 2024 May.

Formánek T, Krupchanka D, Perry I. P, Mladá K, Osimo F. E, Masopust J, Jones B. P, Plana-Ripoll O. Severe mental illness contributing to fatally deleterious effects of physical disorders: A national cohort study. BJPsych. Accepted for publication 2024 May.

Formánek T, Krupchanka D, Mladá K, Winkler P, Jones PB. 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. Lancet Psychiatry. 2022 Dec;9(12):957-968. doi: 10.1016/S2215-0366(22)00335-2. Epub 2022 Nov 3. PMID: 36335974.

Other author's publications related to the topic of Ph.D. thesis

Potočár L, Mladá K, Kučera M, Mohr P, Winkler P, Formánek T. Population mental health, help-seeking and associated barriers following the COVID-19 pandemic: Analysis of repeated nationally representative cross-sectional surveys in Czechia. Psychiatry Res. 2023 Nov 27;331:115641. doi: 10.1016/j.psychres.2023.115641. Epub ahead of print. PMID: 38042095.

Flodin P, Sörberg Wallin A, Tarantino B, Cerchiello P, Mladá K, Kuklová M, Kondrátová L, Parimbelli E, Osika W, Hollander AC, Dalman C. Differential impact of the COVID-19 pandemic on primary care utilization related to common mental disorders in four European countries: A retrospective observational study. Front Psychiatry. 2023 Jan 9;13:1045325. doi: 10.3389/fpsyt.2022.1045325. PMID: 36699500; PMCID: PMC9868724.

Winkler P, Formánek T, Mladá K, Evans Lacko S. Development of public stigma toward people with mental health problems in Czechia 2013-2019. Eur Psychiatry. 2021 Aug 16;64(1):e52. doi: 10.1192/j.eurpsy.2021.2226. PMID: 34392840; PMCID: PMC8446069.

Winkler P, Mohrova Z, Mlada K, Kuklova M, Kagstrom A, Mohr P, Formanek T. Prevalence of current mental disorders before and during the second wave of COVID-19 pandemic: An analysis of repeated nationwide cross-sectional surveys. J Psychiatr Res. 2021 Jul;139:167-171. doi: 10.1016/j.jpsychires.2021.05.032. Epub 2021 May 26. PMID: 34062293; PMCID: PMC8769682.

Kuklová M, Kagstrom A, Kučera M, Mladá K, Winkler P, Cermakova P. Educational inequalities in mental disorders in the Czech Republic: data from CZEch Mental health Study (CZEMS). Soc Psychiatry Psychiatr Epidemiol. 2021 May; 56(5):867-877. doi: 10.1007/s00127-020-01930-9. Epub 2020 Aug 12. PMID: 32789560.

Winkler P, Formanek T, Mlada K, Kagstrom A, Mohrova Z, Mohr P, Csemy L. Increase in prevalence of current mental disorders in the context of COVID-19: analysis of repeated nationwide cross-sectional surveys. Epidemiol Psychiatr Sci. 2020 Sep 29;29:e173. doi: 10.1017/S2045796020000888. PMID: 32988427; PMCID: PMC7573458.

Bakstein E, Mladá K, Fárková E, Kolenič M, Španiel F, Manková D, Korčáková J, Winkler P, Hajek T. Cross-sectional and within-subject seasonality and regularity of hospitalizations: A population study in mood disorders and schizophrenia. Bipolar Disord. 2020 Aug;22(5):508-516. doi: 10.1111/bdi.12884. Epub 2020 Jan 22. PMID: 31883178.

Formánek T, Kagström A, Cermakova P, Csémy L, Mladá K, Winkler P. Prevalence of mental disorders and associated disability: Results from the cross-sectional CZEch mental health Study (CZEMS). Eur Psychiatry. 2019 Aug;60:1-6. doi: 10.1016/j.eurpsy.2019.05.001. Epub 2019 May 13. PMID: 31096115.

Kagstrom A, Alexova A, Tuskova E, Csajbók Z, Schomerus G, Formanek T, Mladá K, Winkler P, Cermakova P. The treatment gap for mental disorders and associated factors in the Czech Republic. Eur Psychiatry. 2019 Jun;59:37-43. doi: 10.1016/j.eurpsy.2019.04.003. Epub 2019 Apr 19. PMID: 31009916.

Kondrátová L, König D, Mladá K, Winkler P. Correlates of Negative Attitudes towards Medication in People with Schizophrenia. Psychiatr Q. 2019 Mar;90(1):159-169. doi: 10.1007/s11126-018-9618-z. PMID: 30478641.

Winkler P, Formánek T, Mladá K, Cermakova P. The CZEch Mental health Study (CZEMS): Study rationale, design, and methods. Int J Methods Psychiatr Res. 2018 Sep;27(3):e1728. doi: 10.1002/mpr.1728. Epub 2018 Jun 21. PMID: 29926999; PMCID: PMC6877135.

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 Jun;3(6):e289-e295. doi: 10.1016/S2468-2667(18)30077-X. PMID: 29884434.