National Institute of Mental Health (NIMH)

Klecany, Czech Republic

MORTALITY GAP ASSOCIATED WITH MENTAL DISORDERS IN THE CZECH REPUBLIC

Protocol for a nation-wide register-based study

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ABSTRACT

Central and Eastern Europe is the world region with estimated highest level of Years of Life Lost due to mental, behavioral and substance use disorders. However, the evidence on mental disorders associated mortality in the region is patchy, and insufficient to inform policy actions and health systems reform.

We aim to explore the mortality associated with mental disorders in the Czech Republic. Using international guidelines and standards, we will link data from the Czech nation-wide health databases of patients' hospitalizations, and all-cause mortality between 1994 and 2014. We set out to assess life expectancy, standardized mortality ratios, and causes of deaths by mental and behavior disorders compared to the Czech general population, and accounting for life circumstances and other determinants.

The outcome of the project may stimulate and inform interventions and a structured national reform of mental health services and strategies, and provide the epidemiological evidence base for further hypothesis generation and testing as well as for cross-region collaborations.

Key words: mental disorders, mortality, life expectancy, mortality risks

PROJECT DESCRIPTION

BACKGROUND AND JUSTIFICATION

Excessive mortality among people with mental disorders has been consistently reported across studies attesting from a two- to three-folds higher risk of death compared to the general population (Grigoletti *et al.*, 2009; De Hert *et al.*, 2011). Some of these figures are comparable to those of heavy smoking related mortality (Chesney, Goodwin and Fazel, 2014).

The life expectancy gap between people with mental disorders and general population was defined **„The scandal of premature mortality"** because it is not only marked but avoidable and unjust (Thornicroft, 2011). Compared to the general population, men and women diagnosed with severe mental disorders have an average of 20 and 15 years shorter life expectancies, respectively (Wahlbeck *et al.*, 2011). A recent meta-analysis suggests that mental disorders rank among the most substantial causes of death worldwide (Walker, McGee and Druss, 2015). Moreover, this gap is likely increasing because different from the general population, lifespans in those affected by mental disorders have not increased in recent years (Lawrence, Hancock and Kisely, 2013).

The complex relationship between physical and mental health provides a number of potential explanations for this gap in life expectancy (Prince et al. 2007). Mental and somatic disorders often co-occur because of shared risk factors. Mental health may impact diagnosis, care and the prognosis of both communicable and non-communicable diseases. Chronic diseases may cause or worsen mental disorders because of the associated disability and burden. Further, there may be side effects of medications on the central nervous system, as well as of antipsychotics on peripheral organs, systems and metabolisms. Finally, schizophrenia and common mental disorders, like depression, alcohol and substance abuse, are the main proximal risk factors for suicide, which is a leading cause of death in young adults (<30 years of age) (De Hert *et al.*, 2011).

According to the Global Burden of Disease (GBD) figures, mental and behavioral disorders account for 0.5% of all Years of Life Lost (YLL) (Whiteford *et al.*, 2013). However, the methods used to calculate premature death in the GBD has been criticized, and it is widely recognized that mortality related to mental and behavioral disorders is substantially underestimated using the GBD approach (Whiteford *et al.*, 2015; Patel *et al.*, 2016). Importantly, the burden of neurological and mental health disorders accounted for up to a fourth of the total amount of the

Disability Adjusted Life Years (DALYs) in the GBD. This is largely explained by the chronic nature of this group of diseases, their relative early onset during the life course and high prevalence in the general population, and their remarkable impact on independence.

The GBD data revealed that Central and Eastern Europe (CEE) is the region with the world's highest level of DALYs (Whiteford *et al.*, 2013) and YLLs due to mental, behavioral and substance use disorders (Charlson *et al.*, 2015). Notably, YLLs were found to be especially high among males. This may be partly explained by the high prevalence of alcohol-use and substance-use disorders in the region (Leon, Shkolnikov and McKee, 2009; Charlson *et al.*, 2015). Yet, country level evidence from this CEE region is extremely patchy (Evans-Lacko *et al.*, 2014).

Most of the available evidence on disproportionate mortality comes from Scandinavia, Western Europe, North America, Asia and Australia with no studies from CEE (Walker, McGee and Druss, 2015). Issues of generalizability may exist because of the potential differences across the determinants, diagnostics and treatments of mental disorders and in systems responsiveness between countries and world regions. However, the causal role on standardized mortality ratio (SMR) of substance use disorders (opiate use - 14.7 (Degenhardt *et al.*, 2011), amphetamine – 6.2 (Singleton *et al.*, 2009), alcohol – 6.68 (Adrian and Barry)) and anorexia nervosa (5.86 (Arcelus *et al.*, 2011)) followed by other conditions (acute and transient psychosis – 4.7, bipolar disorder – 3.3 (Castagnini, Foldager and Bertelsen, 2013), schizophrenia – 2.5 to 4.6 (Saha, Chant and McGrath, 2007; Castagnini, Foldager and Bertelsen, 2013) depression (1.52) (Cuijpers *et al.*, 2014) is plausible and may therefore be ubiquitous. Nevertheless, whether any differences in region-specific risks factors distribution and associations with differential mortality exist is not known. Evidence from the CEE region is key to inform local action, and may also allow unprecedented comparisons across cultures and geographic regions that may provide further insight into the underlying mechanisms.

We maintain that sound research evidence on the anticipated excess mortality due to mental ill health, and on the potential underlying mechanisms is needed to inform health promotion, disease prevention, and policy and health systems responses aimed at addressing the ethical and moral implications of the existing life expectancy gap in people with mental disorders.

GOALS

- To inform decision and policy makers with a unique evidence-base to plan, develop and implement mental health care national strategies and services;
- To pose the basis of a rich, comprehensive and nationwide representative data repository that will facilitate international, comparative research, as well as hypothesis generation and testing in future collaborative studies.

To the best of our knowledge, this is the first study of this kind conducted in country of CEE, with potential great relevance for the ongoing mental health care reform in the Czech Republic, which ultimate aim is to improve quality and duration of life of people with mental disorders, and to reduce the impact of mental disorders on those affected, their families and society at large.

AIM

To study the excess mortality associated with mental and substance use disorders in the Czech Republic.

OBJECTIVES:

- Collect relevant information on Czech nation-wide routinely-collected health data on (1) patients' discharge from hospitals and (2) all-cause deaths;
- Provide a comprehensive description of the databases according to the existing international guidelines;
- Link the aforementioned databases, clean the data, and create a data repository and dictionary to allow the planned statistical analyses, and to facilitate further cross-linkage with other relevant databases;
- Estimate life expectancies, mortality ratios and causes of death for people with major mental and behavior disorders and compare these figures with those found in the Czech general population;
- Explore any differences in causes of mortality between those with and without the following conditions: Substance use disorders; Non-affective psychoses; Affective disorders; Anxiety and stress-related disorders; Personality disorders.

METHODS

STUDY POPULATION

This project is based on the analysis of two main sources of Czech nation-wide observational, routinely collected health data: (1) all-cause inpatient hospitalizations and (2) all-cause deaths. Both databases are maintained by the Institute of Health Information and Statistics of the Czech Republic, which has granted full access to both databases to the National Institute of Mental Health, for all calendar years between 1994 and 2014.

ALL-CAUSE INPATIENT HOSPITALIZATION DATABASE

The **all-cause inpatient hospitalization database** contains data routinely-collected by the Institute of Health Information and Statistics through the health information system to monitor the service provision in the country. The database contains about 2.3 million observations for each calendar year, about 2.5 % (about 60,000) of these data points are related to psychiatric hospitalizations. Psychiatric hospitalizations are detailed on a standard form, the "*Protocol of discharge*" report, which is filled out by health professionals at the time of patients discharge from the inpatient medical facility, and directly sent to the Institute of Health Information and Statistics. The completion of the *protocols* is mandatory for all health care facilities, and is used in every case of patients discharge because of any reasons, such as: a) the person dies during hospitalization; b) the person is transferred to another department within the same facility; c) the person is transferred to an acute physical health care facility; d) the person is re-institutionalized into either health or social care facility; e) the person is discharged home; or f) the person is discharged against the medical advice of the clinician. A summary of the key clinical and health care information of a person at the time of discharge from an inpatient facility is reported in the *protocol of discharge* for each patient. The resulting database includes various variables spanning data on date of birth; sex; marital status; occupation; place and reason of admission; main and comorbid diagnoses; date of admission and discharge; date of first symptoms; type of admission and discharge; destination of discharge.

ALL-CAUSE MORTALITY DATABASE

The **all-cause mortality database** is based on the *"Notification of deaths"*. These are sent to the Czech Statistical Office by the national Register Office which collects data from physicians who examine every deceased person in the Czech Republic and who then issue the "*Death Certificate"* to officially notify death occurrences, along with personal details and cause of death. The all-cause mortality database contains information about all deaths in the country. For each dead person the database includes following information: place of death; time and date of

death; age at death; sex; marital status; education; nationality; place of residence; primary cause of death (coded according to the 10th revision of the International Classification of Diseases and Related Health Problems (ICD-10)); whether an autopsy has been conducted (yes/no); age of spouse at death. The database contains about 1.2 million observations during the whole 1994-2014 period.

STUDY DESIGN

This is a whole population, observational, register-based study built upon the deterministic linkage of nation-wide medical data routinely collected in the Czech Republic between 1994 and 2014. The project consists of three main stages (see also Gantt chart presented in Table 1):

(1) DATA DESCRIPTION

We plan to conduct a qualitative study to fully understand the main characteristics and all possible limitations at each stage of the routine data collection. For this purpose a serious of expert consultations with relevant stakeholders will be conducted: with psychiatrists, heads of institutions, employees of the local and central statistical offices, people involved in data analysis and quality control. Data will be reported in accordance to the recent guidelines on the Reporting of studies Conducted using Observational Routinely-collected health Data (Benchimol *et al.*, 2015).

(2) DATA LINKAGE AND CLEANING

We will create a deterministic record-linkage of the two datasets based on the unique individual personal identifier, which is based on the date of birth and is used identically in both registries, and all official documents. The individual data in both databases are anonymized by the same encryption of 'birth numbers' assigned to each individual in the Czech Republic, so that it is possible to combine data on an individual basis while keeping them anonymized. The original 'birth numbers' is unique for each individual and consists of a combination of 8 numbers on date of birth and 4 random digits (i.e. yyyymmdd/xxxx). The resulting dataset will be cleaned to exclude repeating observations and assure completeness of data.

(3) DATA ANALYSIS.

Data analysis will be divided into two stages. At the first stage we will focus on calculation of standardized age- and sex-adjusted mortality ratios (SMR) and explore differences in causes of deaths. At the later stage, we will perform additional analysis of life expectancies and risks of deaths.

FIRST STAGE OF THE PROJECT IMPLEMENTATION

First, we will calculate SMR for each group of mental disorders dividing observed and expected deaths rates for 2014. **Second**, we will analyze excessive mortality due to specific causes of deaths. For each specific cause of death, we will calculate cause-specific SMR for 2014 for each group of mental diagnosis.

SECOND STAGE OF THE PROJECT IMPLEMENTATION

Third, to analyze differences in life expectancies, we will build life tables for people within each group of mental disorder. Based on the life tables, we will calculate life expectancy at 15 years (and its 95% CI) separately for males and females, for each diagnostic group. The life expectancies for different mental conditions will be compared with those of the general population. **Finally**, we will derive data separately for cohorts of people with particular category of mental illnesses (substance use disorders (F1x of the ICD-10); non-affective psychoses (F2x); affective

disorders (F3x); anxiety and stress-related disorders (F4x)) who were exposed to a hospitalization and discharged from mental inpatient facility in 1994-2014. We will separately follow the derived cohort of people with every group of disorders for one year and conduct a survival analysis of all cause death one year after discharge building Kaplan-Meier survival curve. Analysis of mortality risks will be calculated by estimating crude rate ratios and adjusted within a Cox regression model, accounting for relevant socio-demographic and service use characteristics.

STATISTICAL ANALYSIS

Statistical analyses will consist of analysis of life tables to calculate life expectancies and standardized mortality ratios, mortality ratios for causes of deaths; survival analysis and regression modeling in the analysis of mortality risk factors. Statistical analysis will be performed in Stata. Oracle database system will be used to account for the large sample sizes, and in all cases in which the number of cases will exceed the capacity of standard software for data management such as Microsoft Excel or Access.

RESULTS, IMPACT AND DISSEMINATION

We plan to disseminate our results in the larger scientific community through publication of relevant articles in peer-review journals. We also aim to report the exact stages of the project, including the assembling of the datalink system. Namely, articles shall describe the managing, linking and cleaning of the datasets, and the detailed description of the anticipated mortality gap among people with mental disorders in Czech Republic. Further, papers exploring life expectancies and mortality risks among people with mental and substance use disorders will be crafted as well.

Additionally, we will report results in the local Czech scientific journals and disseminate data among local stakeholders and policy-makers by preparing policy briefs, press releases, presenting key data through the general media and public lectures, through engagement with professionals' and users' organizations.

Attendance at national and international conferences is also anticipated to present and discuss the expected results and network with colleagues and other researchers in view of establishing collaborations.

Furthermore, the combined and cleaned database established within the current project will be available for future extended research of mortality and patients' hospital discharges.

ETHICAL CONSIDERATIONS

The project has been considered and approved by the Ethical Committee of the National Institute of Mental Health on 15 June 2016. According to the Committee decision, the project is fully in line with the Convention on Human Rights and Biomedicine and Act no. 101/2000 on protection of personal information. After legal review, the data were only made available for researchers in the group who meet the criteria for access to this type of sensitive data. Data are derived from two different registers. Therefore, no personal contact with the individuals will be established. Prior to approaching the databases, all birth numbers will be encrypted in a non-identifiable way resulting in a code consisting of 88 digits and letters. Therefore, the integrity of the persons is secured through de-identification of the individual information. Results will be presented on a group level without any possibility of backward identification. The research group applies high standards of data safety. Taking these rigorous safety measures into account, the benefits of identifying potential differences in mortality risk of individuals with mental disorders compared to the general population exceed the potential harm for the individual caused by the loss of integrity that could arise from using data on their mental disorders and mortality.

PROJECT IMPLEMENTATION

MILESTONES AND TIMEFRAME

M1. Literature reviews performed

M2. All necessary information on the databases is collected

M3. Registers linked and cleaned

M4. All data analyses performed

M4a. First stage of data analyses performed

M4b. Second stage of data analyses performed

M5. Articles accepted for publications

M5a. Results from the 1st stage submitted for publication

M5b. Results from the 2nd stage submitted for publication

Table 1. Gant chart of the project

Timeframe		2016									2017											2018											
	Activities	4	5	6	7	8	9	10	11	12	1	2	3	4	5	6	7	8	9	10	11	12	1	2	3	4	5	6	7	8	9	10	11	12
1	**Managing and coordination**																																	
2	**Literature reviews on CEE**											M1																						
3	**Describing datasets**											M2																						
4	**Linking datasets**															M3																		
5	**Data analysis**																														M4			
	1st stage of data analysis																				M4a												
	2nd stage of data analysis																													M4b				
8	**Working on publications**																																	M5
	Results from the 1st stage submitted																						M5a											
	Results from the 2nd stage submitted																																M5b	
9	**Dissemination**																																	

RESEARCH GROUP, ROLES AND RESPONSIBILITIES

BASIC INFORMATION ON THE CORE RESEARCH GROUP

Principal investigator: **Dzmitry Krupchanka** MD, MSc, PhD

Institution: **Department of Social Psychiatry, National Institute of Mental Health of the Czech Republic**

Researchers involved in this project:

- Petr Winkler;
- Karolína Mladá;
- Blanka Nechanská;

INTERNATIONAL COLLABORATION

Principal investigator, Dzmitry Krupchanka has a well-established scientific collaborations with several institutions that will be involved into the current project.

1. University of Geneva, Department of Psychiatry and Institute of Global health (Professor Emiliano Albanese and Professor Yasser Khazaal);
2. World Health Organization Collaborating Centre for training and research in Mental Health, University of Geneva; and Swiss School of Public Health plus (SSPH+) (Professor Emiliano Albanese)
3. Department of Clinical Neuroscience, Division of Insurance Medicine, Karolinska Institutet (Ellenor Mittendorfer-Rutz)

RESEARCH GROUP PREPAREDNESS TO IMPLEMENT THE PROJECT

Department of Social Psychiatry, National Institute of Mental Health (NIMH CZ) of the Czech Republic since its foundation in 2015 has become a national reference centre for research and innovation in mental health care, including the research related to the ongoing mental health care reform. The department employs more than two dozens of dedicated researchers, has broad scientific collaborations within and outside of EU and has all prerequisites to achieve the goals indicated in this project.

1. **Dzmitry Krupchanka MD MSc PhD** is a senior researcher at the Department of Social Psychiatry, NIMH CZ and an affiliated researcher at King's College London and London School of Hygiene and Tropical Medicine. He has gained medical degree with distinction (psychiatrist) in Minsk, Belarus and later achieved part of his education at the University of London and King's College London (MSc in Global Mental Health with distinction). He has successfully defended his PhD thesis on "Insight in psychosis". Area of his professional interests includes addiction medicine, global mental health, psychiatric epidemiology, mental health in Central and Eastern Europe and post-communist countries, mental health stigma and discrimination, human rights in mental health, community-based treatment, insight and compliance in patients with psychosis, non-pharmacological interventions in schizophrenia. Dr Krupchanka has advanced knowledge in psychiatric epidemiology and experience in managing and coordination big international projects.
2. **PhDr Petr Winkler** is the Head of the Department of Social Psychiatry at the NIMH CZ. After graduating in Social Policy and Social Work at the Charles University in Prague, he became one of the Bakala Foundation scholars and went to the Institute of Psychiatry, Psychology and Neuroscience, at King's College London, to pursue his PhD in mental health economics. Dr Winkler's main expertise is in psychiatric epidemiology, health economics, and mental health care systems, and he is also interested in suicidology and research on stigma and discrimination. In the past few years he has been involved in the development of the mental health care reform strategy in the Czech Republic; and currently he is working on a matrix of analyses that will enable informed decision making with regards to the reform and its evaluation. In close collaboration with international partners, Petr and his team at NIMH CZ are also working towards the establishment of the Centre of Research Excellence in Social Psychiatry for the region of post-communist Central and Eastern Europe.
3. **Mgr. Karolina Mlada** is a statistician at Department of Social Psychiatry at NIMH CZ. After obtaining her master degree in applied mathematics, statistics and data analysis at Masaryk University in Brno, she worked at Czech Statistical Office (CZSO). In recent years, she has been actively involved in register-based research while processing and analyzing routinely collected Czech medical datasets as well as was actively involved in other studies concerning mental health and psychiatric epidemiology.

The collaboration with **Institute of Health Information and Statistic (Ing. Blanka Nechanská)** will allow us to have an immediate access to both the raw data as they are kept in an Oracle database system within the institute. This will provide us with an excellent opportunity to work with huge databases and not be limited by the capacity of traditional software for data management and analysis. Additionally, collaboration with the Institute of Health Information and Statistic will assure best possible understanding of the databases and their management.

The project will be substantially strengthened by the intensive international collaboration with **(1) University of Geneva, (2) Swiss School of Public Health Plus (SSPH+) , (3) Karolinska Institute, (4) WHO collaborating centre for training and research in mental health.** International support will assure that all possible difficulties in data management and analysis will be appropriately addressed and solved by the team's collaborative efforts.

1. **Professor Emiliano Albanese** is a physician with a specialization in public health (University of Milan/London), a MPH at the London School of Hygiene and Tropical Medicine, and a MD-PhD in clinical neuropsychology. Emiliano is a strong, internationally renowned epidemiologist, who has trained and worked in the Department of Health Service and Population research of the Institute of Psychiatry (King's College London); the National Institute on Aging (NIH, Bethesda – USA) and the MRC Unit of Lifelong Health and Ageing (London/ UK). Prof. Albanese is a SSPH+ assistant professor of public mental health and the director of the WHO Collaborating Centre for training and research in mental health of the Department of Psychiatry of the University of Geneva. The participation of Professor Albanese in the project is expected to substantially strengthen the methodological and statistical components. In addition, Professor Albanese will contribute to disseminate the results of the project at the highest level as well as to drafting, revising and editing all relevant articles and contributing to the publication strategy.
2. **Professor Yasser Khazaal** is assistant professor of psychiatry at the University of Geneva. He is the current president of the Swiss Society of Social Psychiatry. He is involved in a number of studies related to cognitive and behavioral treatments, e-mental health, online addictive behaviors as well as in projects related to the development and assessment of games or computer-based treatments. Professor Khazaal will strengthen the project by contributing to the discussion of results and putting them into the clinical practice perspective and literature context.
3. **Professor Ellenor Mittendorfer-Rutz** is an associate professor in epidemiology at the Department of Clinical Neuroscience, Division of Insurance medicine, and a head of the research group MENTE ("Mental health and social integration"). She is the principal investigator of several large epidemiological studies, involving around 30 researchers both in Europe and the United States. Professor Mittendorfer-Rutz has broad experience in working with nation-wide register-based studies and will assist us with possible difficulties in working with huge health datasets.

The presented Czech research team strengthened by the extended local and international collaboration is highly capable to implement the project and achieve all expected outcomes as it is presented to have an impact on the Czech mental health care reform, which is currently developing its pilot version. The inception of the NIMH CZ and the ongoing mental health care reform presents a window of opportunity for this proposal.

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