

Mortality in persons with recent primary or secondary care contacts for mental disorders in Finland

Excess mortality among persons with mental disorders has been consistently documented^{1,2}, but the mortality risk over a full spectrum of mental disorders treated both in primary and secondary care remains to be explored at a nationwide level.

Integration of mental health care in primary care services is considered a priority in low-, middle-, and high-income countries³, and depression and anxiety are among the top ten most common reasons for visits in primary care⁴. The global shortage of mortality data concerning mental disorders in primary care may lead to an overestimation of the population-wide burden of the full spectrum of treated mental disorders^{5,6}.

Excess mortality is related to a variety of risk factors at the individual, health system and social levels⁷. Mental disorders are associated with socioeconomic factors and an increased vulnerability to several physical conditions, with complex bi-directional pathways⁸. Physical comorbidities contribute to the majority of life-years lost in people with mental disorders, and low socioeconomic position (SEP) associates with mental disorders and physical conditions, as well as with mortality in the general population⁹.

This national register-based open cohort study aimed to: a) assess the excess mortality in persons with mental disorders seen in both primary and secondary care, and compare these estimates with secondary care data only; b) determine the extent to which adjusting for physical comorbidities and individual-level socioeconomic factors affects the estimates.

We used individual-level register data concerning all citizens with Finnish background aged at least 20 years and living in Finland at some point between January 1, 2011 and December 31, 2017. We identified all deaths (using the Finnish Causes of Death Register), the dynamic population at risk of death (through Population Registers), and all mental health contacts (using Care Register for Health Care, in which primary care has been included since 2011) during that period. The ethical review board of the Finnish Institute for Health and Welfare approved the study protocol. Data were linked with the permission of Statistics Finland (TK-53-1696-16) and the Finnish Institute of Health and Welfare. Informed consent is not required for register-based studies in Finland.

A history of mental health related contacts was defined as having any contact with secondary care psychiatric inpatient or outpatient services, or with primary care, with a diagnosis of any mental disorder (i.e., ICD-10 chapter V, or International Classification of Primary Care-2 chapter P) within the previous year.

We collected data on the following individual-level variables: sex, urbanicity of residence area, region of residence, living alone status, level of educational attainment, economic activity, and equalized household net income deciles. Income measurement with a three-year lag was used to account for potential reverse causation. Physical comorbidity was assessed using the Charlson Comorbidity Index (CCI), categorized by previously used cut-points: none, 1-3, and ≥ 4 .

Three sets of data were collected and analyzed separately, con-

cerning: a) individuals seen in primary and secondary care combined, compared with those without such contacts; b) individuals seen in primary and secondary care separately, compared with those without such contacts; c) individuals seen in secondary care only, compared to all individuals without such contacts (including individuals with possible primary care treatments), which is the traditional approach.

Mortality rate ratios (MRRs) were estimated using a Poisson regression model. Men and women were analyzed separately. To investigate the association between physical comorbidities and mortality, a stratified analysis for the CCI categories was performed. In addition, the ICD-10 diagnostic blocks were analyzed separately. We performed sensitivity analyses using three- and five-year histories of mental health related contacts. R and Stata were used for the analyses.

During the period between 2011 and 2017, we observed 4,417,635 individuals (51.3% women), contributing 28,049,912 person-years. Along that period, 860,287 (19.5%) of all observed individuals had mental health related contacts, more commonly in primary care. Mood disorders was the most commonly used ICD-10 diagnostic block. Altogether, 357,119 persons died (50.3% women), of whom 44,364 (12.4%) had had some contact with psychiatric secondary or primary care within the previous year.

Age and calendar year adjusted MRRs of 2.83 (95% CI: 2.79-2.87) and 1.79 (95% CI: 1.76-1.82) were observed for men and women with a one-year history of primary or secondary care mental health contacts, compared to those without. After SEP adjustments, MRRs of 2.17 (95% CI: 2.13-2.20) and 1.71 (95% CI: 1.68-1.74) were observed. After further adjustments for physical comorbidities, the estimates decreased to 1.63 (95% CI: 1.60-1.65) and 1.20 (95% CI: 1.18-1.22), respectively. These SEP and comorbidity adjusted MRR estimates were 27% and 42% lower, respectively, compared to the MRRs of 2.24 (95% CI: 2.19-2.30) and 2.07 (95% CI: 2.01-2.12) obtained with the traditional approach considering secondary care only.

In diagnosis-specific analysis, the highest SEP and comorbidity adjusted MRRs were observed in disorders related to substance use. Excess mortality varied by age and turned to decrease in both men and women starting from the age of 35 years (see supplementary information).

Individuals with recent primary care mental health contacts had more commonly diagnosed physical comorbidities than individuals treated in psychiatric secondary care (24.5% vs. 18.1% of person-time). The presence of physical comorbidities modified the association between mortality and a one-year history of mental health contact: excess mortality related to mental disorders was the highest in people without comorbidities, and the lowest in people with multiple comorbidities. Sensitivity analysis with three- or five-year histories of treated mental disorders, instead of one year, showed only a little difference (see supplementary information).

These findings confirm the previously reported evidence of an excess mortality in people with mental disorders, but also suggest that the previously published MRR estimates would have been considerably lower if primary care had been included in those analyses. As mental disorders are commonly treated in primary care, the current results are likely to have generalizability, especially in high-income countries. They provide a more optimistic view of the burden of mental disorders and highlight the diversity of these disorders in the population.

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This study was supported by grants from the Jalmari and Rauha Ahokas Foundation, the Finnish Psychiatric Association, and the Signe och Ane Gyllenberg Foundation. The authors thank A. Solismaa for helpful comments on this letter. Supplementary information on the study is available at <https://kmmssk.github.io/mpsc>.

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DOI:10.1002/wps.21027

Severe breakthrough COVID-19 infections in vaccinated patients with schizophrenia in Israel

Patients with schizophrenia show a substantial reduction in risk of COVID-19 severe illness and related mortality when vaccinated, as compared to non-vaccinated samples¹. However, the emergence of new variants and the increased frequency of breakthrough infections², especially among vulnerable groups³, raise questions regarding the long-term effectiveness of vaccines in reducing overall morbidity and mortality in these patients.

In a study conducted in Scotland, the risk of COVID-19-related hospital admission was doubled in individuals infected with the B.1.617.2 (delta) when compared to the alpha variant, and was particularly increased in those with five or more relevant comorbidities⁴. These findings suggest that individuals with schizophrenia, who are known to suffer from an excess of physical comorbidities^{5,6}, might present a differential pattern of risk during infection waves even if vaccinated.

To explore whether vaccinated individuals with schizophrenia present a higher risk for breakthrough infections, severe course of illness, and mortality, compared with vaccinated controls from the general population, we utilized the database of Clalit Health Services (CHS), the largest health care organization in Israel. The database was mined at the end of November 2021, almost a year after the launch of the vaccination plan in Israel, and after the fourth infection wave in Israel began to subside^{7,8}.

A total of 34,797 individuals diagnosed with schizophrenia at the onset of the pandemic were extracted, along with a sample of individuals with no diagnosis of schizophrenia, matched for age and gender⁹. For the current study, individuals who were not vaccinated were removed, and the sample was then re-matched for age, sex, and number of vaccinations (first, second, and booster). After excluding cases with infection prior to the vaccination plan or with inaccurate dates (4.7% of the sample), the overall sample included 24,354 subjects in the schizophrenia group, and 24,196 controls, matched for age, sex and vaccination coverage at a 1:1

ratio (total N=48,550).

The study was approved by the CHS institutional review board. Informed consent was waived due to the anonymous nature of the data. Hazard ratios (HRs) were assessed with Cox proportional hazard regression. Crude and adjusted models were assessed to control for demographic and clinical risk factors. Estimated projections of the cumulative probability of the three outcomes were obtained with Kaplan-Meier analysis. Differences in incidence of outcomes between the study groups were calculated using the incidence rate ratio (RR). Statistical analyses were performed using SPSS software, version 25.

There were 2,233 individuals infected in the total sample (4.59%), with 1,019 in the schizophrenia group (4.18%) and 1,214 in the control group (5.01%). A total of 210 individuals were hospitalized due to COVID-19 (0.43%), including 164 (0.67%) from the schizophrenia group and 47 (0.19%) from the control group. There were 29 deceased cases (0.05%) due to COVID-19, including 23 from the schizophrenia group (0.09%) and 6 from the control group (0.02%).

Survival analyses indicated that individuals with schizophrenia exhibited a significantly lower estimated probability of being infected compared with controls (log-rank test = 4.33, $p=0.037$); after controlling for risk factors, this difference became non-significant (HR=0.93, 95% CI: 0.84-1.03, $p=0.14$). On the other hand, individuals with schizophrenia showed a significantly sharper increase in the probability of being hospitalized as time progressed (log-rank test = 62.93, $p<0.001$), and continued to present a significantly higher risk for hospitalization even after controlling for demographic and clinical risk factors (HR=2.68, 95% CI: 1.75-4.08, $p<0.001$). Estimated projections of cumulative probability of mortality also differed significantly between the groups: individuals with schizophrenia were more likely to die due to COVID-19 (log-rank = 11.04, $p=0.001$), although this difference became non-significant after controlling for risk factors (HR=2.18, 95% CI: 0.80-