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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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 samples[1]. However, the emergence of new variants and the increased frequency of breakthrough infections[2], especially among vulnerable groups[3], 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 comorbidities[4]. 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 gender[9]. 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-

5.90, p=0.12).

To assess whether overall differences in risk between individuals with schizophrenia and controls changed during the fourth infection wave, we examined the RR of infection, hospitalization and mortality for the two groups between June and August 2022, and compared it with prior (January to May 2021) and subsequent (September to November 2022) periods. The results indicated that the RR for infection was slightly inverted during the fourth wave of infection (RR=1.021, 95% CI: 0.90-1.15) as compared with the prior (RR=0.98, 95% CI: 0.84-1.15) and subsequent (RR=0.62, 95% CI: 0.52-0.74) periods. The RR of COVID-19-related hospitalization was larger during the fourth infection wave (RR=4.19, 95% CI: 2.41-7.27) as compared with the prior (RR=3.65, 95% CI: 2.29-5.82) and subsequent (RR=3.15, 95% CI: 1.42-6.99) periods. Similarly, the RR of mortality was higher during the fourth infection wave (RR=7.61, 95% CI: 0.93-61.89) compared with the prior (RR=3.60, 95% CI: 0.99-13.08) and subsequent (RR=3.01, 95% CI: 0.60-14.95) periods.

Overall, these results suggest that vaccinated patients with schizophrenia are at increased risk for COVID-19-related hospitalization than are controls from the general population, even after controlling for demographic and clinical factors, and even when accounting for the extent of vaccination coverage through matching. Furthermore, although the overall mortality rates in the total sample were low and therefore affected the magnitude of incidence rate differences between the groups, mortality cases were more frequent in the schizophrenia group, and the RR tended to increase during the fourth infection wave. The increased risk of adverse COVID-19 outcomes for vaccinated individuals with schizophrenia during infection waves highlights the importance of conducting longitudinal studies to continuously monitor the extent of risk for patients with severe mental illness.

In this study we were not able to determine the type of COVID-19 variants. Additional studies are needed to explore whether specific variants present a greater risk for individuals with severe mental illness. Future studies should also aim to differentiate between complications that are fully related to COVID-19 and those that are secondary to other medical conditions.

The findings reported in this study indicate that individuals with schizophrenia, although taking advantage from vaccination, continue to be an at-risk group for adverse COVID-19 outcomes, which calls for the need to develop outreach programs aimed at facilitating prevention strategies for individuals with severe mental illness.

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The response pattern to SSRIs as assessed by the Montgomery-Åsberg Depression Rating Scale: a patient-level meta-analysis

The effect size for antidepressants vs. placebo varies considerably among the 17 symptoms rated by the Hamilton Depression Rating Scale (HDRS)[1]. Using patient-level data (N=~13,000) from the development programs of citalopram, duloxetine, paroxetine and sertraline, we reported that there are sizeable effects on HDRS items such as depressed mood and psychic anxiety, which appear already after one week of treatment, but negligible effects, throughout the treatment period, on items that may capture side effects of selective serotonin reuptake inhibitors (SSRIs), such as insomnia, somatic anxiety, gastrointestinal symptoms, genital symptoms, and weight change[1-3]. Other authors have reported similar findings[4,5].

While the Montgomery-Åsberg Depression Rating Scale (MADRS) overlaps with the HDRS[6], there are significant differences between the two scales with respect to how the various symptoms are described. Moreover, the MADRS includes some key depressive symptoms not explicitly rated by the HDRS, such as inability to feel and concentration difficulties. Patient-level analyses of the impact of SSRIs on individual MADRS items may thus allow us to assess to what extent symptom-level findings based on HDRS ratings generalize to other instruments, and may further our understanding of the effects of SSRIs on different depressive symptoms.

We report here symptom-level MADRS ratings from 4,243 subjects participating in twelve acute phase placebo-controlled trials of an SSRI in major depression (see supplementary information). Our aims were: a) to investigate the time-course and magnitude of the effects of SSRIs on individual MADRS items; b) to assess the relation of individual MADRS items to the MADRS total score; and c) to compare drug-placebo differences for the total score of