Heightened COVID-19 Mortality in People With Severe Mental Illness Persists After Vaccination: A Cohort Study of Greater Manchester Residents

Lamiece Hassan1,*, Chelsea Sawyer1, Niels Peek2,3,*, Karina Lovell4, Andre F. Carvalho5, Marco Solmi6–8,*, George Tilston2,9, Matthew Sperrin2, and Joseph Firth1,10

1Division of Psychology and Mental Health, The University of Manchester, Manchester Academic Health Science Centre, Manchester, M13 9PL, UK; 2Centre for Health Informatics, Division of Informatics, Imaging and Data Sciences, The University of Manchester, M13 9PL, UK; 3NIHR Greater Manchester Patient Safety Translational Research Centre, The University of Manchester, Manchester, UK; 4Division of Nursing, Midwifery and Social Work, University of Manchester, Manchester Academic Health Science Centre, Manchester, M13 9PL, UK; 5IMPACT (Innovation in Mental and Physical Health and Clinical Treatment) Strategic Research Centre, School of Medicine, Barwon Health, Deakin University, Geelong, Victoria, Australia; 6Psychiatry Department, University of Ottawa, Ottawa, ON, Canada; 7The Ottawa Hospital, University of Ottawa, Ottawa, ON, Canada; 8Clinical Epidemiology Program, Ottawa Hospital Research Institute (OHRI), University of Ottawa, Ottawa, ON, Canada; 9Manchester Academic Health Science Centre, National Institute for Health Research Manchester Biomedical Research Centre, The University of Manchester, Manchester, M13 9PL, UK; 10Greater Manchester Mental Health NHS Foundation Trust, Manchester Academic Health Science Centre, Manchester, M13 9PL, UK

*To whom correspondence should be addressed; Jean McFarlane Building, Division of Psychology and Mental Health, University of Manchester, Manchester Academic Health Science Centre, Manchester, M13 9PL, UK; tel: +44 (0) 161 306 6000, e-mail: lamiece.hassan@manchester.ac.uk.

Introduction

People with severe mental illness (SMI) die approximately 15 years younger than the general population, primarily due to the heightened morbidity and mortality from physical diseases among this vulnerable group.1–4 This elevated risk applies to both noncommunicable and infectious diseases and recent evidence from around the world—summarized in several recent systematic reviews and meta analyses5–11—has now shown that people with SMI are also disproportionately affected by COVID-19.

While people with mental illnesses appear to be more vulnerable to COVID-19,5–11 the extent to which disparities in outcomes apply across different diagnostic groups of mental illness, and the reasons underpinning this, is a complex and dynamic subject, not fully elucidated by research. Available evidence points towards a combination of sociodemographic factors, preexisting comorbidities, and disease related factors (eg, psychotropic medication) as possible explanatory factors contributing towards increased risks of COVID-19 related infection, hospitalization, and mortality among people with SMI.5–8 Despite
well-conducted and thorough studies, however, gaps and methodological limitations apply to several areas. For example, a recent systematic review of 23 studies on COVID-19 in mental illness reported that only a minority adjusted for preexisting conditions. Moreover, systematic reviews and meta-analyses have adopted varying search strategies and definitions of key variables, including COVID-19 infection itself, complicating efforts to synthesize knowledge in this area.

Two of the largest UK studies to date used the UK Biobank (UKB) cohort, a longitudinal cohort study linking primary care, hospital data, and death records for half a million older adults. These both reported higher rates of COVID-19 related hospitalization and mortality among people with mental illness, including schizophrenia, in the period prior to the UK vaccine roll-out. While considered a valuable resource, UKB participants are well known to be older, healthier and less ethnically diverse than the general population. Thus, while studies have generated some useful evidence, there remains a need to conduct research using more representative samples of the population, particularly those that include ethnically diverse groups and younger populations.

Concerns have led to calls for people with schizophrenia and certain other severe mental illnesses to be prioritized for access to vaccinations; advice which has been followed by several countries, including the United Kingdom. However, given the combination of biopsychosocial factors that may affect vaccine uptake and immune response among people with mental illness, evidence is still needed to demonstrate whether these disparities in COVID-19 mortality risks still persist following vaccination. In England, the NHS started administering COVID-19 vaccinations on December 8, 2020, with people with SMI prioritized for vaccination alongside people aged 70 years and over on advice from an independent expert advisory committee. By April 12, 2021, all people aged over 50 years (including SMI groups) had been offered a first vaccination; second vaccinations were offered 3–12 weeks after the individual’s first dose. An early analysis of vaccination uptake nationally in England, albeit limited to patients over 80 up until March 17, 2021, showed that vaccination was initially lower among people with severe mental illnesses and learning disabilities. A more recent study by Bitan that followed up people with schizophrenia in Israel throughout the first year of the pandemic found that mortality rates declined in these populations following mass vaccination efforts, though they remained relatively higher compared to controls. The same study also noted that people with schizophrenia were less likely to be vaccinated.

In this study we aimed to examine COVID-19 related mortality among people with schizophrenia and other SMIs, compared to similar people without SMI, over a 20-month period (February 2020 to September 2021). This covered the period prior to, during, and after the initial vaccine roll-out in the United Kingdom. We also aimed to account for the influence of sociodemographic characteristics, preexisting clinical conditions, and vaccination status on the risks of COVID-19 related mortality among people with SMI. In doing so, we build upon previous studies to support enhanced understanding of the size and nature of the risks posed by COVID-19 to people with mental illness to inform public health strategies in a postvaccine world.

Methods

Design and Participants

We used de-identified patient data from the Greater Manchester Care Record (GMCR), a city wide, integrated digital care record containing information related to 3.2 million residents. Used by over 500 health and social care organizations to provide direct care to patients, the GMCR also includes details of primary care, hospital stay episodes, and deaths.

Using the GMCR, we compared COVID-19 mortality in three overlapping samples of patients with SMI (each with matched controls), namely people with schizophrenia, BD, and/or MDD (supplementary material - figure S1). All patients who were alive, aged 18 years and over and registered with a general practitioner in GM as of January 31, 2020 (the date of the first UK COVID-19 related death) were eligible for inclusion in the samples. Participants were followed up for up to 20 months in total; from the start of the pandemic (February 1, 2020) until September 30, 2021 or death, whichever occurred first.

This study was approved via the GMCR’s secondary uses and research governance process, which involved review against legal, ethical, and information governance criteria. A patient and public involvement (PPI) group of 14 regular members with experience of mental illness (including service users and carers) provided feedback on design and interpretation throughout. The RECORD guidelines, a checklist devised for studies using routinely collected health data, were used to guide reporting.

Mental Health Diagnoses

We selected all patients with primary care-recorded diagnoses of schizophrenia or other related psychoses (henceforth “schizophrenia”) at any point in their lifetime up until January 31, 2020. Similarly, all patients with BD were selected for the second sample. The third sample included all individuals with recurrent major depressive disorder (henceforth “MDD”), thereby ruling out patients with single depressive episodes. For comparison purposes, we obtained records for age–sex (ie matched on sex at birth and year of birth) matched people with no prior evidence of mental illness up until January 31, 2020, sampled at a 4:1 ratio against cases (henceforth
referred to as “controls”). Hence, individuals could be included in more than one sample as a case if they had multiple relevant lifetime diagnoses, though never as controls. Individuals with no prior mental illness could also appear in more than one sample as a control. For the purposes of this study, diagnoses for mental health problems following January 31, 2020 were ignored. Clinical code sets for concepts and diagnoses were developed using OpenCodelists (https://www.opencodelists.org), a tool created by OpenSAFEly to improve transparency and reusability in coding curation, and are available in our online GitHub repository (https://github.com/rw251/gm-idcr/tree/master/shared/clinical-code-sets; supplementary material – table S1). Mental health diagnostic codes corresponded with ICD codes F20-29 (schizophrenia, schizotypal, and delusional disorders), F31 (bipolar affective disorder), and F33 (recurrent depressive disorder).

Outcomes and Covariates

The primary outcome was COVID-19 related mortality, defined as all deaths reported via NHS Digital’s personal demographics service within 28 days of a positive, lab-confirmed COVID-19 test entering the primary care record. This measure is consistent with Public Health England’s definition of COVID-19 related mortality and has been used in the United Kingdom as a standard indicator for surveillance purposes. Vaccination status was determined for each individual on a monthly basis from their primary care record as either doubly vaccinated (ie, 2 or more doses by the preceding month) or not doubly vaccinated (ie, 0 doses or 1 dose). As the booster vaccination campaign only began in September 2021 in the United Kingdom, we did not account for this in this analysis.

We also explored how demographic and clinical factors affected risk of COVID-19 related mortality among people with and without SMI. Demographic data included age (in years), sex and ethnicity (Asian; Black; mixed; White; other). Index of multiple deprivation (IMD) deciles were provided as a measure of material deprivation, calculated based on patients’ residential postcode data, decile 1 representing the most deprived and decile 10 representing the least deprived.

Comorbidity data was based on recorded primary care diagnoses (lifetime, up until January 31, 2020) for the following conditions: alcohol misuse, atrial fibrillation, cancer, chronic kidney disease, chronic liver disease, chronic obstructive pulmonary disease (COPD), coronary heart disease (CHD), dementia, diabetes, epilepsy, heart failure, learning disability, multiple sclerosis, Parkinson’s disease, peripheral vascular disease, stroke, and substance (psychoactive drug) misuse. These conditions have previously all been used to predict COVID-19 mortality.

Statistical Analysis

We investigated associations between different mental illnesses and mortality due to COVID-19, adjusted for a range of demographic and clinical variables, described herein. In preparation for analysis, data validation checks were performed to exclude invalid codes and data ranges. Owing to low counts for people with BD in certain subgroup analyses, statistical disclosure control techniques (mainly rounding to base 5) have been applied to some table cells and figures where indicated. Missing sociodemographic data were imputed using multiple imputation with chained equations under the assumption that they were missing at random.

Monthly mortality rates from February 2020 through until September 30, 2021 were calculated and visualized as line charts with 95% confidence intervals (CIs). Sample denominators were calculated on a monthly basis, taking into account reductions in denominators due to deaths resulting from COVID-19 or other causes.

Separate Poisson regression models for each psychiatric diagnosis were used to generate crude and adjusted risk ratios (RRs) and 95% CIs for mortality related to (1) COVID-19 and (2) other causes. For these models, an individual’s follow up was divided into months. In each month, the outcome was death within that month. Data for 83 COVID-19 related deaths where the date of death was missing were excluded from regression analyses. Diagnoses were treated as binary variables in all analyses. To allow vaccinations to take effect, a 1-month lag was applied meaning that vaccinations were only counted in the calendar month following the month that the dose was administered. Vaccination status was the only time-updated variable, all other variables remained at the baseline values. In multivariable adjusted models, psychiatric diagnoses were combined with vaccination status and entered as interaction terms, to investigate potential differential effects of vaccination among people with mental illnesses versus controls. Sex and comorbid diagnoses (excluding psychiatric diagnoses) were included in adjusted models as binary variables, while age and IMD decile were entered as continuous variables, and ethnicity was entered as a categorical variable.

To further test the robustness of our findings, we performed a sensitivity analysis using hierarchically defined (rather than overlapping) diagnoses of BD and MDD to generate unadjusted and adjusted RRs and 95% CIs for COVID-19 related mortality. For this analysis, each case with SMI was assigned to one of three groups: schizophrenia; BD (excluding schizophrenia); or MDD, excluding schizophrenia or BD).

All statistical analyses were conducted using R version 4.0.0. Statistical tests were conducted with significance set at \( p < .05 \) (two-sided).
Results

Sample Characteristics

Table 1 describes the demographic and clinical characteristics of the 3 samples (total $N = 967,169$). These included 48,912 people with a diagnosis of schizophrenia, 13,932 with BD and 152,489 with MDD. There was a degree of overlap between people with different psychiatric diagnoses, particularly among people with BD, 82.2% ($n = 11,459$) of whom had more than one diagnosis (supplementary material - figure S2). Compared to people with BD and MDD, people with schizophrenia were more likely to be male (54.1% vs 38.4%; $\chi^2 = 3686.6, df = 1, p < .001$) and less likely to be White (77.2% vs 82.0%; $df = 4, \chi^2 = 1694.7, p < .001$).

Across the 3 samples, 773,734 people were included as age–sex matched controls; these had no prior evidence of schizophrenia, BD, or depressive disorders recorded in their records by January 31, 2020. For the 5 most commonly recorded physical comorbidities, physical illnesses were less common in controls in comparison with people with SMI, specifically: history of diabetes (13.3% vs 19.7%; $\chi^2 = 5088.4, p < .001$), cancer (9.2% vs 19.2%; $\chi^2 = 15514.0, p < .001$), CHD (3.3% vs 5.6%; $\chi^2 = 2297.4, p < .001$), COPD (2.6% vs 5.3%; $\chi^2 = 5238.8, p < .001$), and stroke (2.8% vs 5.3%; $\chi^2 = 3005.7, p < .001$). In addition, alcohol use (2.1% vs 9.5%; $\chi^2 = 30114.0, p < .001$) and substance use (1.2% vs 8.6%; $\chi^2 = 39513.0, p < .001$) were also less common in controls compared with people with SMI. Overall, missing sociodemographic data were evident for sex ($N = 112, <0.01%$), ethnicity ($N = 90,344, 9.3%$), and IMD decile ($N = 1239, <0.1%$).

Changes in COVID-19 Mortality Over Time

A total of 5442 people across the 3 samples died due to COVID-19 during the study observation period; 1083 had schizophrenia, 136 had BD, 2334 had MDD, and 3570 had none of these. For reference, 14,423 people died of causes other than COVID-19 during the same period; 1980 had schizophrenia, 329 had BD, 2334 had MDD and 10,365 had none of these. Figure 1 shows how mortality rates due to COVID-19 and other causes varied over time. Clear peaks in COVID-19 mortality rates across all groups were observable in April 2020 (peak rates ranging from 29 to 168 deaths per 100,000 people) and November to February 2021 (34–179 deaths per 100,000). Broadly similar patterns were observable among deaths due to other causes over the same period; it is, however, notable that the first “peak” in rates in April 2020 (121–497 deaths per 100,000) occurred prior to the full roll-out of COVID-19 testing.

Compared to matched controls, vaccination rates as of September 31, 2021 were highest among people with MDD (74.0% vs 67.7%; RR 1.09, CI 1.09–1.10), followed by people with BD (72.2% vs 67.0%; RR 1.08, CI 1.05–1.10), and finally schizophrenia (65.8% vs 64.8%; RR 1.02, CI 1.00–1.03). After the vaccine roll-out began in December 2020, COVID-19 mortality rates showed significant declines across all diagnostic subgroups from January 2021 onwards, specifically

---

Table 1. Baseline Sample Demographic Characteristics (as of January 31, 2020, Unless Otherwise Indicated)*

|                      | Schizophrenia ($N = 48,912$) | Matched Control Group, SZb ($N = 195,645$) | Matched Control Group, BDb ($N = 55,728$) | MDD ($N = 152,489$) | Matched Control Group, MDDb ($N = 609,953$) |
|----------------------|-----------------------------|--------------------------------------------|--------------------------------------------|-------------------|--------------------------------------------|
|                      | $n$                         | $\%$                                      | $n$                                       | $\%$             | $n$                                       | $\%$                                      | $n$                                      | $\%$                                      | $n$                                      | $\%$                                      |
| Sex                  |                             |                                            |                                            |                  |                                            |                                            |                                            |                                            |                                            |                                            |
| Female               | 22,455                      | 45.9                                      | 89,817                                    | 45.9             | 8340                                      | 59.9                                      | 33,360                                   | 59.9                                      | 93,212                                   | 61.1                                      | 372,848                                   | 61.1                                      |
| Male                 | 26,448                      | 54.1                                      | 105,792                                   | 54.1             | 5,590                                     | 40.1                                      | 22,356                                   | 40.1                                      | 59,264                                   | 38.9                                      | 237,056                                   | 38.9                                      |
| Age group            |                             |                                            |                                            |                  |                                            |                                            |                                            |                                            |                                            |                                            |                                            |                                            |
| Mean, SD             | 50.7                        | 19.6                                      | 50.7                                      | 19.6             | 50.0                                      | 16.2                                      | 50.0                                     | 16.2                                      | 50.4                                     | 16.0                                      | 50.4                                     | 16.0                                      |
| Ethnicity            |                             |                                            |                                            |                  |                                            |                                            |                                            |                                            |                                            |                                            |                                            |                                            |
| Asian                | 3663                        | 7.5                                       | 16,103                                    | 8.2              | 820                                       | 5.9                                       | 4705                                     | 8.4                                       | 6929                                     | 4.5                                       | 50,855                                   | 8.3                                       |
| Black                | 1576                        | 3.2                                       | 5,635                                     | 2.9              | 270                                       | 2.0                                       | 1744                                     | 3.1                                       | 2096                                     | 1.4                                       | 17,833                                   | 2.9                                       |
| Mixed                | 861                         | 1.8                                       | 2,404                                     | 1.2              | 240                                       | 1.7                                       | 704                                      | 1.3                                       | 1590                                     | 1.0                                       | 7,547                                    | 1.2                                       |
| Other                | 4,185                       | 8.6                                       | 2,298,323,841                            | 12.2             | 1,055                                     | 7.1                                       | 6600                                     | 11.8                                      | 13,005                                   | 8.53                                      | 72,419                                   | 11.9                                      |
| White                | 37,749                      | 77.2                                      | 124,798                                   | 63.8             | 11,305                                    | 82.0                                      | 35,743                                   | 64.1                                      | 124,759                                  | 81.8                                      | 395,427                                  | 64.8                                      |
| IMD decile           | Mean, SD                    | 3.3                                       | 2.6                                       | 4.3             | 2.9                                       | 3.7                                       | 2.8                                       | 4.3                                       | 2.9                                       | 3.8                                       | 2.8                                       |

*Cell counts and percentages may not add up to 100% of totals due to missing data and rounding (to 1 dp).

bMatched on age (year of birth) and sex at birth.

cCounts, except total, are rounded to base 5 for disclosure control purposes.
COVID-19 Mortality in People With SMI

people with schizophrenia ($\beta = -13.47$, $p = .005$), BD ($\beta = -3.95$, $p = .048$), and/or MDD ($\beta = -2.97$, $p = .007$). Mortality rate ratios, however, remained relatively stable (figure 2).

COVID-19 Mortality in SMI vs General Population

Table 2 shows the RRs for the primary outcome of COVID-19 mortality associated with different SMI diagnoses. When compared against their respective matched control groups, COVID-19 mortality rates were significantly higher among people with schizophrenia (OR 3.18, CI 2.94–3.44), BD (RR 2.69, CI 2.16–3.34) and MDD (RR 1.59, CI 1.47–1.71). Relative risks of mortality due to other causes were 2.12 times higher among people with schizophrenia (CI 2.01–2.24), 2.12 times higher among people with BD (CI 1.86–2.42), and 1.32 times higher among people with MDD (CI 1.26–1.38).

After adjustment for vaccination, demographic and clinical variables, RRs for COVID-19 related mortality were reduced but remained significantly associated with schizophrenia (aRR 1.61, 95% CI 1.45–1.79) and BD (aRR 1.92, 95% CI 1.47–2.50), but not recurrent MDD (aRR 1.08, 95% CI 0.99–1.17). In a sensitivity analysis performed using hierarchically defined diagnoses (supplementary table S2), these results were found to be robust in the case of unadjusted associations with COVID-19 related mortality for both BD (RR 1.93, CI 1.20–3.12).
and MDD (RR 1.45, CI 1.34–1.58). In the case of adjusted mortality RRs, however, neither MDD (aRR 1.05 CI 0.95–1.15) nor BD (aRR 1.54, CI 0.87–2.73) reached the threshold for statistical significance.

In multivariable adjusted regression models, COVID-19 mortality was consistently and positively associated with male gender and older age (table 3). Double vaccination was significantly associated with lower risk for COVID-19 mortality among schizophrenia and MDD, but not BD (table 3). The negative interaction effect between vaccination status and mental illness status was significant only for BD (table 3). In terms of comorbidities, history of dementia, COPD, and substance misuse all consistently showed significant associations of RR 1.5 or greater with COVID-19 related mortality regardless of diagnosis.

**Discussion**

This study has investigated COVID-19 related disparities over time for people with schizophrenia, BD, and/or MDD in GM. Compared to age–sex matched controls, unadjusted COVID-19 mortality rates were significantly higher overall among people with any of the aforementioned mental illnesses. In the case of people with schizophrenia and/or BD, these remained significantly elevated even following adjustment for demographic factors, pre-existing physical illnesses, and vaccination status.
It is well-established in the wider literature that all-cause mortality rates are higher among people with mental illness, particularly those with SMI.3,4 In line with several previous studies, COVID-19 mortality rates were particularly high among people with schizophrenia and/or BD.5–7 Moreover, the relative risk of COVID-19 mortality among people with SMI exceeded the risk of death due to other causes; indeed their relative risk of COVID-19 mortality remained consistently higher than matched controls throughout the study period, against the backdrop of raised risk of death due to other causes. The latter findings are consistent with those of Das Munshi et al.25 who have reported that all-cause mortality among a sample of 167,122 Londoners with a range of mental disorders and intellectual disabilities, was already higher compared with the general population, and further increased during the COVID-19 pandemic.

The reduction in RRs seen between unadjusted and adjusted models indicate that a sizeable proportion of the elevated mortality risk among people with SMI

### Table 2. Relative Risk (RR) of Mortality Due to COVID-19, by Diagnosis

| Diagnosis                        | Deathsa | Unadjustedb | Adjusteda |
|----------------------------------|---------|-------------|-----------|
| Schizophrenia                    | 1083 (2.2) | 3.18 (2.94–3.44)* | 1.61 (1.45–1.79)* |
| Matched control group for SZ BD   | 1402 (0.7) | – | – |
| MDD                              | 2352 (0.4) | 1.59 (1.47–1.71)* | 1.08 (0.99–1.17) |

*aIncludes all deaths.

*bIncludes deaths with month and year data.

*cIncludes deaths with month and year data. Adjusted for age, sex, ethnicity, deprivation (IMD decile), and preexisting comorbidities and vaccination status.

*p < .05.

### Table 3. Adjusteda Multivariable Model for Relative Risk (RR) of Mortality Due to COVID-19, by Diagnosis

| Variable               | Schizophrenia aRR (95% CI) | BD aRR (95% CI) | MDD aRR (95% CI) |
|------------------------|----------------------------|----------------|------------------|
| Mental illness status  | 1.61 (1.45–1.79)*          | 1.92 (1.47–2.50)* | 1.08 (0.99–1.17) |
| Doubly vaccinated vs not vaccinated | 0.76 (0.67–0.87)* | 0.82 (0.59–1.16) | 0.73 (0.66–0.81)* |
| Mental illness status* doubly vaccinated (interaction) | 1.19 (0.97–1.44) | 0.52 (0.28–0.97)* | 0.91 (0.75–1.11) |
| Age (years)            | 1.09 (1.09–1.10)*          | 1.09 (1.08–1.10)* | 1.10 (1.09–1.10)* |
| Female (ref) vs Male    | 1.22 (1.11–1.33)*          | 1.34 (1.07–1.68)* | 1.32 (1.22–1.42)* |
| Ethnicity              |                            |                |                  |
| White (ref) vs Asian    | 0.86 (0.70–1.07)           | 0.96 (0.57–1.62) | 1.6 (0.99–1.36) |
| White (ref) vs Black    | 1.29 (0.99–1.68)           | 1.78 (0.96–3.31) | 1.28 (0.99–1.64) |
| White (ref) vs mixed    | 1.25 (0.78–1.99)           | 1.55 (0.57–4.18) | 1.17 (0.75–1.82) |
| White (ref) vs other    | 1.05 (0.92–1.19)           | 0.93 (0.64–1.36) | 1.05 (0.94–1.18) |
| Deprivationb           | 0.93 (0.92–0.95)*          | 0.92 (0.88–0.96)* | 0.92 (0.91–0.93)* |
| Comorbidity            |                            |                |                  |
| Alcohol misuse         | 1.41 (1.18–1.70)*          | 1.81 (1.24–2.64)* | 1.70 (1.47–1.97)* |
| Atrial fibrillation     | 1.15 (1.03–1.29)*          | 1.25 (0.88–1.77) | 1.24 (1.11–1.38)* |
| Cancer                 | 1.57 (1.44–1.70)*          | 1.40 (1.11–1.77)* | 1.75 (1.62–1.89)* |
| CKD                    | 1.19 (1.08–1.30)           | 1.09 (0.82–1.44) | 1.23 (1.12–1.34)* |
| Chronic liver disease   | 1.33 (0.99–1.78)           | 1.76 (0.94–3.29) | 1.80 (1.46–2.21)* |
| COPD                   | 1.56 (1.39–1.74)*          | 1.50 (1.11–2.02)* | 1.57 (1.43–1.73)* |
| CHD                    | 1.13 (1.02–1.25)*          | 0.96 (0.70–1.32) | 1.01 (0.92–1.11) |
| Dementia               | 2.40 (2.16–2.67)*          | 2.81 (2.07–3.83)* | 3.39 (3.07–3.73)* |
| Diabetes               | 0.99 (0.91–1.08)           | 1.25 (0.99–1.58) | 1.06 (0.98–1.15) |
| Epilepsy               | 1.45 (1.18–1.78)*          | 0.82 (0.42–1.62) | 1.29 (1.03–1.60)* |
| Heart failure          | 1.42 (1.24–1.62)*          | 1.80 (1.22–2.69)* | 1.50 (1.32–1.71)* |
| Learning disability    | 2.79 (2.01–3.87)*          | 1.87 (0.69–5.09) | 3.53 (2.43–5.15)* |
| Multiple sclerosis     | 1.49 (0.71–3.12)           | 2.24 (0.56–0.90)* | 1.73 (1.07–2.79)* |
| Parkinson’s disease    | 1.66 (1.31–2.11)*          | 1.75 (0.89–3.45) | 1.46 (1.09–1.97)* |
| Peripheral vascular disease | 1.26 (1.06–1.50)*     | 1.80 (1.17–2.78)* | 1.65 (1.43–1.89)* |
| Stroke                 | 1.17 (1.06–1.29)*          | 1.33 (0.99–1.79) | 1.34 (1.22–1.47)* |
| Substance misuse       | 1.55 (1.29–1.87)*          | 1.52 (1.01–2.29)* | 1.56 (1.31–1.87)* |

*aAdjusted for demographic variables plus atrial fibrillation, cancer, chronic kidney disease (CKD), chronic liver disease, chronic obstructive pulmonary disease (COPD), coronary heart disease (CHD), dementia, diabetes, epilepsy, heart failure, learning disability, multiple sclerosis, Parkinson’s disease, peripheral vascular disease, and stroke.

*bLower deciles indicate higher levels of deprivation.

*p < .05.
could be due to demographic factors (particularly those not used in the matching process eg, ethnicity and deprivation), alcohol and substance misuse, and underlying physical health conditions, which are known risk factors for COVID-19 mortality in the general population.28 Even so, controlling for demographic factors and comorbidities did not account for all of the excess risk. While a proportion of the excess risk observed could well be due to unmeasured factors—including lifestyle factors such as smoking and obesity, and the severity of physical diseases—our findings arguably add weight to the hypothesis that SMI, or its treatment, confers additional COVID-19 mortality risk independent of comorbid conditions. Unlike a previous larger, UK study of ethnic differences on COVID-19 related mortality,26 we found no significant effect of ethnicity. Though we included all available SMI cases and used higher-level ethnicity categories, COVID-19 deaths are (fortunately) relatively rare events, especially when considering ethnic subgroups; thus, it is possible this finding was a type 2 error resulting from insufficient statistical power.

Double vaccination was associated with significantly lower COVID-19 mortality among people with schizophrenia and MDD, though the significance threshold was not reached among people with BD (our smallest sample). The interaction between vaccination and mental illness status on COVID-19 mortality was significant only among people with BD, indicating that the protective effect of vaccination was relatively stronger in people with BD than for their matched controls. These are interesting results, which arguably warrant further investigation. Though evidence surrounding vaccination response among people with mental illness is lacking,17 emerging conceptual frameworks do point towards immuno-inflammatory dysregulation as a component underpinning certain mental health conditions.27 Mediation analysis was outside the scope of our study, and so we did not account for psychotropic medication use. This could be important given recent research suggesting that antidepressants and antipsychotics might have varying effects on COVID-19 related outcomes.28,29

In summary, despite population vaccination efforts that have prioritized people with SMI—and significantly higher vaccination uptake in some SMI groups—disparities still remain in COVID-19 mortality for people with SMI compared to the general population. While vaccination uptake appeared to have attenuated absolute mortality rates across the board during 2021, people with SMI continued to show higher mortality rate ratios compared to controls during the final period of our study. The results of our study therefore arguably warrant further cause for concern in the context of ongoing diagnoses. A sensitivity analysis using stricter, hierarchical definitions of BD and MDD that excluded co-occurring other affective disorders, an area where more evidence is required.7,8 Finally, we had access to vaccination data and were able to examine mortality outcomes during the vaccination roll-out period, permitting analyses of how vaccination status affected COVID-19 related mortality among people with mental illness.

There are several limitations to our research. Though GM represents a sizeable, urban population in Northern England, this limits broader generalisability. Limited testing capacity during the first wave of coronavirus in the United Kingdom (initially testing was focused in hospitals) mean that rates of COVID-19 related mortality have likely been underestimated during this period. To preserve patient confidentiality, COVID-19 deaths and vaccinations were rounded to the nearest month preventing more fine-grained time to event analyses. Diagnoses of mental and physical illnesses were on a lifetime basis (ever/never) and derived from coded data in electronic health records (EHRs), not created specifically for research. As such, we were unable to account for the differences in the severity and burden of health problems. Furthermore, EHR diagnoses may have been under-recorded the true prevalence of SMI, leading to the potential for reduced sample sizes and/or misclassification bias. Incident diagnoses of mental illness after January 31, 2020 were ignored. This definition may have masked differential risks between those with historical (possibly resolved) illnesses and those with more recent, ongoing diagnoses.

Some people with multiple psychiatric diagnoses, particularly those with BD, were included as cases in more than one sample. Thus, a proportion of the elevated rates in people with BD and MDD may have been attributable to other (ie, BD and/or schizophrenia) diagnoses. A sensitivity analysis using stricter, hierarchical definitions of BD and MDD that excluded co-occurring schizophrenia diagnoses showed significantly elevated mortality RRs for unadjusted, but not adjusted analyses. We note, however, that the BD sample size in the sensitivity analysis performed was much reduced (by over two-thirds) and that the direction and size of the differences between unadjusted and adjusted RRs
looked proportionate with those presented in the main analyses. Grouping people with affective disorders (i.e., BD and MDD) was considered to avoid small sample sizes, especially for fine-grained monthly analyses; however, after consultation with our PPI group, permitting overlapping samples was, on balance, viewed as less artificial and allowed separate examination of a sizeable group of people with BD.

To date, research consistently indicates that people with mental illness, and particularly SMI, are at increased risk of poorer outcomes related to COVID-19, prompting calls for prioritizing screening, treatment and access to vaccination for such groups. Our study confirms that people with schizophrenia and BD in particular show increased risk of COVID-19 mortality compared to matched controls, even following population vaccination efforts. These findings strengthen the case for addressing the life-shortening, physical health needs of people with mental illnesses and continued research into the source of vulnerability to COVID-19 to protect these groups from further health disparities.

Supplementary Material
Supplementary material is available at https://academic.oup.com/schizophreniabulletin/.

Funding
J.F. is supported by a University of Manchester Presidential Fellowship and a UK Research and Innovation Future Leaders Fellowship (grant numbers PI23958 and MR/T021780/1). N.P. is supported by the National Institute for Health Research (NIHR) Greater Manchester Patient Safety Translational Research Centre and the NIHR Manchester Biomedical Research Centre. The views expressed are those of the author(s) and not necessarily those of the NIHR or the Department of Health and Social Care.

Acknowledgments
The authors recognise the Greater Manchester Care Record (a partnership of Greater Manchester Health and Social Care Partnership, Health Innovation Manchester and Graphnet Health, on behalf of Greater Manchester localities) in the provision of data required to undertake this work. This work uses data provided by patients and collected by the NHS as part of their care and support. We would also like to thank members of the COVID-19 Lived Experience Advisory Group for their invaluable contributions towards design, analysis and interpretation. Marco Solmi received honoraria/has been a consultant for Angelini, Lundbeck, Otsuka. Joseph Firth has received honoraria/has been a consultant for Atheneum, ParachuteBH and Nirakara.

References
1. Hughes E, Bassi S, Gilbody S, Bland M, Martin F. Prevalence of HIV, hepatitis B, and hepatitis C in people with severe mental illness: a systematic review and meta-analysis. Lancet Psychiatry. 2016;3(1):40–48.
2. Vancampfort D, Correll CU, Galling B, et al. Diabetes mellitus in people with schizophrenia, bipolar disorder and major depressive disorder: a systematic review and large scale meta-analysis. World Psychiatry. 2016;15(2):166–174.
3. Firth J, Siddiqi N, Koyanagi A, et al. The Lancet Psychiatry Commission: a blueprint for protecting physical health in people with mental illness. Lancet Psychiatry. 2019;6(8):675–712.
4. Thornicroft G. Physical health disparities and mental illness: the scandal of premature mortality. Br J Psychiatry. 2011;199(6):441–442.
5. Fond G, Nemani K, Etchecopar-etchard D, et al. Association between mental health disorders and mortality among patients with COVID-19 in 7 countries. JAMA Psychiatry. 2021;78(11):1202–1217.
6. Toubasi AA, AbuAnzeh RB, Tawileh HBA, Aldebei RH, Alryalat SAS. A meta-analysis: Mar 3, 2021. The mortality and severity of COVID-19 among patients with mental disorders. Psychiatry Res. 2021. doi:10.1016/j.psychres.2021.113856.
7. Vai B, Mazza MG, Deli Colli C, et al. Mental disorders and risk of COVID-19-related mortality, hospitalisation, and intensive care unit admission: a systematic review and meta-analysis. Lancet Psychiatry. 2021;8(9):797–812.
8. De Hert M, Mazereel V, Stroobants M, De Picker L, Van Assche K, Detraux J. COVID-19-related mortality risk in people with severe mental illness: a systematic and critical review. Front Psychiatry. 2022;12:2436.
9. Pardamean E, Roan W, Iskandar KTA, Prayangga R, Hariyanto TI. Mortality from coronavirus disease 2019 (Covid-19) in patients with schizophrenia: a systematic review, meta-analysis and meta-regression. Gen Hosp Psychiatry. 2022;75:61–67.
10. Liu L, Ni SY, Yan W, et al. Mental and neurological disorders and risk of COVID-19 susceptibility, illness severity and mortality: a systematic review, meta-analysis and call for action. EClinicalMedicine. 2021;40:101111.
11. Ceban F, Nogo D, Carvalho IP, et al. Association between mood disorders and risk of COVID-19 infection, hospitalization, and death: a systematic review and meta-analysis. JAMA Psychiatry. 2021;78(10):1079–1091.
12. Yang H, Chen W, Hu Y, et al. Pre-pandemic psychiatric disorders and risk of COVID-19: a UK Biobank cohort analysis. Lancet Healthy Longev. 2020;1(2):e69–e79.
13. Hassan L, Peek N, Lovell K, et al. Disparities in COVID-19 infection, hospitalisation and death in people with schizophrenia, bipolar disorder, and major depressive disorder: a cohort study of the UK Biobank. Mol Psychiatry. 2022;27:1248–1255.
14. Fry A, Littlejohns TJ, Sudlow C, et al. Comparison of sociodemographic and health-related characteristics of UK biobank participants with those of the general population. Am J Epidemiol. 2017;186(9):1026–1034.
15. De Hert M, Mazereel V, Detraux J, Van Assche K. Prioritizing COVID-19 vaccination for people with severe mental illness. World Psychiatry. 2021;20(1):54–55.
16. De Picker LJ, Dias MC, Benros ME, et al. Severe mental illness and European COVID-19 vaccination strategies. Lancet Psychiatry. 2021;8(5):356–359.
17. Mazereel V, Van Assche K, Detraux J, De Hert M. COVID-19 vaccination for people with severe mental illness: why, what, and how? *Lancet*. 2021;8(5):444–450.

18. Warren N, Kisely S, Siskind D. Maximizing the uptake of a COVID-19 vaccine in people with severe mental illness: a public health priority. *JAMA Psychiatry*. 2021;78(6):589–590.

19. Department of Health and Social Care. Joint Committee on Vaccination and Immunisation: Advice on Priority Groups for COVID-19 Vaccination. 2020. https://www.gov.uk/government/publications/priority-groups-for-coronavirus-covid-19-vaccination-advice-from-the-jcvi-30-december-2020. Accessed December 30, 2020.

20. Curtis HJ, Inglesby P, Morton E, et al. Trends and clinical characteristics of COVID-19 vaccine recipients: a federated analysis of 57.9 million patients’ primary care records in situ using OpenSAFELY. *Br J Gen Pract*. 2022;72(714):e51–e62.

21. Tzur Bitan D, Kridin K, Cohen AD, Weinstein O. COVID-19 hospitalisation, mortality, vaccination, and postvaccination trends among people with schizophrenia in Israel: a longitudinal cohort study. *Lancet Psychiatry*. 2021;8(10):901–908.

22. Benchimol EI, Smeeth L, Guttmann A, et al. The REporting of studies Conducted using Observational Routinely-collected health Data (RECORD) Statement. *PLoS Med*. 2015;12(10):e1001885.

23. UK Health Security Agency. Technical Summary: UK Health Security Agency Data Series on Deaths in People with COVID-19. 2022. https://www.gov.uk/government/publications/. Accessed March 30, 2022.

24. Clift AK, Coupland CAC, Keogh RH, et al. Living risk prediction algorithm (QCOVID) for risk of hospital admission and mortality from coronavirus 19 in adults: national derivation and validation cohort study. *BMJ*. 2020;371.

25. Das-Munshi J, Chang CK, Bakolis I, et al. All-cause and cause-specific mortality in people with mental disorders and intellectual disabilities, before and during the COVID-19 pandemic: cohort study. *Lancet Reg Health Eur*. 2021;11:100228.

26. Mathur R, Rentsch CT, Morton CE, et al. Ethnic differences in SARS-CoV-2 infection and COVID-19-related hospitalisation, intensive care unit admission, and death in 17 million adults in England: an observational cohort study using the OpenSAFELY platform. *Lancet*. 2021;397(10286):1711–1724.

27. Miller AH, Raison CL. The role of inflammation in depression: From evolutionary imperative to modern treatment target. *Nat Rev Immunol*. 2016;16(1):22–34.

28. Oskotsky T, Marić I, Tang A, et al. Mortality risk among patients with COVID-19 prescribed selective serotonin reuptake inhibitor antidepressants. *JAMA Netw Open*. 2021;4(11):e2133090.

29. Govind R, Fonseca de Freitas D, Protchard M, et al. Clozapine treatment and risk of COVID-19 infection: retrospective cohort study. *Br J Psychiatry*. 2021;219(1):368–374.

30. Peckham E, Spanakis P, Heron P, et al. A year into the pandemic: the diversity of experience amongst people with severe mental ill health. *Front Psychiatry*. 2022;12:2546.