Bidirectional associations between COVID-19 and psychiatric disorder: retrospective cohort studies of 62 354 COVID-19 cases in the USA

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Summary

Background: Adverse mental health consequences of COVID-19, including anxiety and depression, have been widely predicted but not yet accurately measured. There are a range of physical health risk factors for COVID-19, but it is not known if there are also psychiatric risk factors. Two important research questions are whether a diagnosis of COVID-19 (compared to other health events) is associated with increased rates of subsequent psychiatric diagnoses, and whether patients with a history of psychiatric disorder are at a higher risk of being diagnosed with COVID-19.

Methods: We addressed both questions using retrospective real-world cohort studies derived from TriNetX, an electronic health records (EHR) network of 69 million patients in the USA including over 62,000 cases of COVID-19 between January 20, and August 1, 2020. We created cohorts of patients who had been diagnosed with COVID-19 or a range of other health events. Propensity score matching was used to control for confounding by risk factors for COVID-19 and for severity of illness. We measured the incidence of, and hazard ratios for, psychiatric disorders, dementia, and insomnia, during the 14-90 days after a diagnosis of COVID-19.

Findings: In patients with no prior psychiatric history, a diagnosis of COVID-19 was associated with an increased incidence of a first psychiatric diagnosis in the following 14-90 days compared to 6 other health events (hazard ratio [95% CI] 2·1 [1·8–2·5] *vs.* influenza; 1·7 [1·5–1·9] *vs.* other respiratory tract infections; 1·6 [1·4–1·9] *vs.* skin infection; 1·6 [1·3–1·9] *vs.* cholelithiasis; 2·2 [1·9–2·6] *vs.* urolithiasis, and 2·1 [1·9–2·5] *vs.* fracture of a large bone; all p<0·0001). The hazard ratio was greatest (~2-3-fold) for anxiety disorders, insomnia, and dementia. Similar findings, though with smaller hazard ratios, were seen when relapses as well as new diagnoses were measured. The incidence of any psychiatric diagnosis in the 14-90 days after COVID-19 was 18·1%, including 5·8% that were a first diagnosis. The incidence of a first diagnosis of dementia in the 14-90 days after COVID-19 was 1·6% in people aged over 65. A psychiatric diagnosis in the previous year was associated with a higher incidence of COVID-19 (relative risk 1·65, 95% CI: 1·59–1·71, p<0·0001), independent of known physical health risk factors for COVID-19 (but possibly confounded by residual socioeconomic factors).

Interpretation: Survivors of COVID-19 appear to be at increased risk of psychiatric sequelae, and a psychiatric diagnosis might be an independent risk factor for COVID-19. The findings, although preliminary, have implications for clinical services and call for prospective cohort studies.

Research in context

Evidence before this study: From January 1 to August 1, 2020, we searched PubMed with the terms: (COVID-19 OR SARS-CoV2 OR SARS-CoV-2) AND (pysch* OR cognit* OR mental) and MedRxiv with the terms COVID-19 OR SARS-CoV2 OR SARS-CoV-2 in the 'neurology' and/or 'psychiatry' categories. We also manually reviewed the references in the identified papers. Studies investigating the psychiatric consequences of COVID-19 lacked a control condition, consisted mostly of surveys, and mostly used self-reported symptoms (rather than diagnoses) as an outcome. No study has assessed the risk of developing psychiatric sequelae over time and only anecdotal evidence exists for the risk of dementia as a potential consequence of COVID-19. In terms of psychiatric risk factors for COVID-19, two case-control studies were identified. One study investigated risk factors for hospitalisation for (rather than diagnosis of) COVID-19. The other study used historical data (not acquired during the same period as COVID-19) as a control group. As these were case-control studies, only odds-ratios could be estimated rather than relative or absolute risks. In addition, in both studies, controls were not well matched to cases. Other surveys (such as the Australian COLLATE and the UK Household Longitudinal Study) have investigated the mental health challenges resulting from the COVID-19 pandemic rather than the COVID-19 illness.

Added value of this study: This is the first dataset allowing the psychiatric sequelae and antecedents of COVID-19 to be measured reliably in terms of clinical diagnoses. The study cohorts are orders of magnitude larger than previous studies producing more precise, more representative estimates of even small but important effects—such as the incidence of dementia. It uses propensity score matching to control for many variables, including established physical risk factors for COVID-19 and for more severe COVID-19 illness, and it uses large-scale real-world data thus providing more clinically relevant findings. We used time-to-event data for the analysis of psychiatric sequelae, thus providing the first evidence for their temporal evolution. Our findings show that COVID-19 survivors have significantly higher rates of psychiatric diagnoses and also show that a psychiatric history is a potential risk factor for being diagnosed with COVID-19 independent of known physical risk factors.

Implications of all the available evidence: The implications of the available evidence are three-fold. First, prospective cohort studies and longer term follow-up studies are urgently needed to confirm and extend the findings. Second, enhanced psychiatric follow up should be considered for patients who survived COVID-19. Third, past psychiatric history should be queried during the assessment of a patient presenting with COVID-19 symptoms to adjust pre-test probability.

Introduction

From the early stages of the coronavirus disease 2019 (COVID-19) pandemic, concerns have been raised about its impact on mental health[1–3] and on patients with mental illness[4]. Yet several months later, we still know little about the mental health consequences of COVID-19 (its psychiatric sequelae) and the susceptibility of patients with mental illness to COVID-19 (its psychiatric antecedents).

Several surveys have suggested that patients with COVID-19 experience symptoms of anxiety[5–8] (including post-traumatic stress disorder[7,8]), depression[5,6,9] and insomnia[6]. Cross-sectionally, it has been shown that 22.5% of patients with COVID-19 have a concurrent neuropsychiatric diagnosis[10]. CORONERVE, a UK-wide surveillance program identified 23 patients with a psychiatric diagnosis following infection with SARS-CoV-2[11]. A meta-analysis pooled data from studies estimating the incidence of psychiatric disorders following the severe acute respiratory syndrome (SARS) and Middle East respiratory syndrome (MERS), suggesting that coronavirus infections may lead to delirium, anxiety, depression, manic symptoms, poor memory, and insomnia[12]. However, cohort studies of patients with COVID-19 with adequate control and follow-up are urgently needed to quantify the incidence and relative risks of psychiatric sequelae following infection.

A separate question is whether pre-existing psychiatric disorder affects susceptibility to COVID-19 infection, as has been reported for some other infections including pneumonia[13]. A large case-control study based on electronic health records (EHR) of patients in the USA found that the odds of being diagnosed with COVID-19 were higher for patients with attention deficit hyperactivity disorder, bipolar disorder, depression, and schizophrenia[14]. But a Korean study found no such relationships except for schizophrenia[15]. However, reliable estimation of possible increased risk of COVID-19 among patients with a psychiatric illness requires large, well-controlled cohort studies.

In this EHR network cohort study using data from 69 million individuals, 62,354 of whom have had a diagnosis of COVID-19, we assessed whether a diagnosis of COVID-19 is associated with increased rates of subsequent

psychiatric diagnoses, and whether patients with a history of psychiatric illness are at a higher risk of being diagnosed with COVID-19.

Methods

Data and study design

We used the TriNetX Analytics Network (www.trinetx.com), a global federated network capturing anonymized data from EHR in 54 healthcare organizations (HCOs) in the USA, totalling 69·8 million patients. The TriNetX platform and its functionalities have been described elsewhere[16], and more details are provided in the appendix (pp. 1–2). Available data include demographics, diagnoses (using ICD-10 codes), procedures, and measurements (e.g. lab results, body mass index). The healthcare organizations are a mixture of hospitals, primary care, and specialist providers and contribute data from insured and uninsured patients alike. A single HCO frequently has more than one facility, including the main and satellite hospitals as well as outpatient clinics. Each HCO has 26 facilities on average and the majority (68%) have both inpatient and outpatient data. The data from a typical HCO goes back approximately 7 years, with some going back as long as 13 years. The data are continuously updated. HCOs update their data at various times with over 80% refreshing every 1, 2, or 4 weeks. To comply with legal frameworks and ethical guidelines guarding against data re-identification, the identity of participating HCOs and their individual contribution to each dataset are not disclosed.

Using the TriNetX user interface, cohorts can be created based on specified inclusion and exclusion criteria and compared for outcomes of interest over specified time periods. Cohorts were matched for confounding variables using the built-in propensity score matching capability. Outcomes of interest were then compared between matched cohorts. This study followed the RECORD reporting guidelines.

Variables of interest and their coding

We defined a diagnosis of COVID-19 as one of the following diagnoses, recorded on or after January 20, 2020 (date of the first recorded COVID-19 case in the USA): COVID-19 (U07.1 and U07.2); Pneumonia due to SARS-associated coronavirus (J12.81); Other coronavirus as the cause of disease classified elsewhere (B97.29);

or Coronavirus infection unspecified (B34.2). The latter three definitions (which make up 7·3% of the total COVID-19 sample) were included to capture the early stage of the pandemic when the ICD code for COVID-19 (U07) was not yet defined. We defined a psychiatric illness as any of the ICD-10 codes F20-F48, comprising psychotic (F20-F29), mood (F30-F39), and anxiety (F40-F48) disorders.

We identified a set of established and suspected risk factors for COVID-19[17–19]: age, sex, race, obesity, hypertension, diabetes, chronic kidney disease, asthma, chronic lower respiratory diseases, nicotine dependence, ischaemic heart disease, and other forms of heart disease. To capture these risk factors in patients' EHR, we used 28 variables (e.g. diabetes was separated into Type 1 and Type 2, hypertension was represented both as a diagnosis and as a measurement of systolic and diastolic blood pressure, etc.). We also identified an additional set of established risk factors for death due to COVID-19[20] (which we take to be risk factors for severe forms of COVID-19 illness): cancer (and haematological cancer in particular), chronic liver disease, stroke, dementia, organ transplant, rheumatoid arthritis, lupus, psoriasis, and other immunosuppression. These risk factors were captured using 22 variables from patients' EHR. More details are provided in the appendix, pp. 2–3.

Analysis of psychiatric sequelae

To assess the psychiatric sequelae of COVID-19, we produced matched cohorts of patients who had been diagnosed with another health event. The other health events were selected to represent a wide range of common acute presentations (some clinically similar to COVID-19 and others very different). These control health events comprised: (i) influenza, (ii) another respiratory tract infection, (iii) skin infection, (iv) cholelithiasis, (v) urolithiasis, and (vi) fracture of a large bone (see appendix, p. 3).

All seven cohorts (COVID-19 and six control health events) included all patients over the age of ten who had the corresponding health event on or after January 20, 2020. This age threshold was recommended by TriNetX for COVID-19 cohorts defined within the network to make results consistent across studies. We excluded patients who had died by the time of the analysis (August 1, 2020). In the primary analysis, we also excluded patients who had a psychiatric diagnosis recorded before the health event (COVID-19 or control health event).

Cohorts were matched (details shown below) for the 50 variables mentioned above: the 28 variables capturing risk factors for COVID-19 and the 22 variables capturing risk factors for more severe COVID-19 illness.

The primary outcome was the incidence of a first psychiatric diagnosis (defined as any of F20-F48 corresponding to psychotic [F20–F29], mood [F30-F39] and anxiety [F40–F48] disorders), over a period from 14 days to 90 days after a diagnosis of COVID-19, represented by a hazard ratio (HR) and by the estimated probability of outcome over that period. We also assessed for dementia and insomnia (see appendix p. 4 for ICD-10 codes) as they are potential sequelae of COVID-19[6,12]. For dementia, the analysis was repeated among patients over the age of 65 years. Finally, we also measured the incidence of *all* F20-F48 diagnoses over the same period (i.e. recurrences as well as first episodes).

We performed a range of sensitivity analyses in order to test the robustness of the findings, and to aid their interpretation (see appendix, pp. 4–7 for full details). We repeated the analysis in 7 scenarios: (a) excluding individuals whose race was unknown (in case this differentially affected cohorts), (b) adjusting for the ICD-10 code Z59 'Problems related to housing and economic circumstances' (as a proxy for extreme socioeconomic deprivation), (c) restricting the diagnosis of COVID-19 to confirmed diagnoses (ICD-10 code U07.1), (d) further restricting the diagnosis of COVID-19 to cases confirmed using RNA/antigen testing, (e) focusing on patients who made at least one healthcare visit between 14 and 90 days after the health event (in case of differential drop-out rates between cohorts), (f) comparing the rate of psychiatric sequelae to those observed before the COVID-19 pandemic, and (g) using unmatched cohorts.

Besides the explanation that COVID-19 itself leads to increased rates of psychiatric sequelae, we tested two alternative hypotheses which could explain differences in outcomes between cohorts. The "severity" hypothesis posits that differences in rates of psychiatric sequelae are due to differences in the severity of the health event (e.g. COVID-19 might lead to more severe presentations than the control health events). We tested this hypothesis by limiting the cohorts to patients with the least severe presentations (taken to be those not requiring inpatient admission). If the hypothesis were correct, the difference in rates of psychiatric sequelae between these cohorts would be substantially smaller than in the original cohorts. The "contextual factors" hypothesis posits

that COVID-19 was mostly diagnosed at a time when having *any* health event would have increased the risk of psychiatric sequelae (e.g. because of overwhelmed health services, fear of COVID-19, limited social support, etc.). Assuming that these contextual factors may have changed substantially between January and April 2020, we tested this hypothesis by comparing the rate of psychiatric sequelae of health events before *vs.* after April 1, 2020 and by comparing the rate of psychiatric sequelae between COVID-19 and control health events after April 1, 2020. See appendix, p. 6 for further details.

Analysis of psychiatric antecedents

We tested whether patients with a recent diagnosis of psychiatric illness were at a higher risk of developing COVID-19 compared to a matched cohort of patients with otherwise similar risk factors for COVID-19.

Two cohorts were defined. The first cohort included all patients over the age of 18 who had a diagnosis of a psychiatric illness recorded in their EHR in the past year (from January 21, 2019 to January 20, 2020). The second cohort had no psychiatric illness recorded in their EHR but did make a healthcare visit in the same period (thus excluding patients who made no contact with the participating healthcare organizations). We also defined separate cohorts for the three main classes of psychiatric illness (psychotic disorder [F20-F29], mood disorders [F30-F39], and anxiety disorders [F40-F48]). Patients who had died before January 20, 2020 were excluded from both cohorts.

Cohorts were matched for the 28 variables capturing risk factors for COVID-19 (see above). The primary outcome was the relative risk (RR) of being diagnosed with COVID-19 between matched cohorts. The robustness of the findings was tested by repeating the analysis in 6 scenarios: (a) limiting the cohorts to those with none of the physical risk factors for COVID-19, (b) extending the window for a psychiatric diagnosis from one to three years before January 20, 2020 (c) limiting the cohort to patients with a first diagnosis of psychiatric illness (i.e. with no diagnosis present before January 21, 2019), (d) excluding patients with unknown race, (e) adjusting for problems related to housing and economic circumstances using the ICD-10 code Z59, and (f) redefining the primary outcome as a confirmed (U07.1) COVID-19 diagnosis.

More details on the sensitivity analyses are provided in the appendix pp. 4–7.

Statistical analyses

Propensity score matching was used to create cohorts with matched baseline characteristics[21]. The propensity score was calculated using a logistic regression implemented by the function LogisticRegression of the scikit-learn package in Python. Propensity score 1:1 matching used a greedy nearest neighbour matching approach with a caliper distance of 0·1 pooled standard deviations of the logit of the propensity score (see further details in appendix p. 7). To eliminate the influence of ordering of records, the order of the records in the covariate matrix were randomised before matching. Any baseline characteristic with a standardized mean difference between cohorts lower than 0.1 is considered to be well matched[22]. For the analysis of psychiatric sequelae, propensity score matching was directly applied to each cohort pair. For the analysis of psychiatric antecedents, given their much larger sample sizes (which exceeded the maximum number of 1·5 million patients possible per matched cohort), cohorts were first stratified by sex and age (from 18 years old to 30, 31 to 45, 46 to 60, 61 to 75, and 76 and over) and propensity score matching (including for age) was achieved within each stratum separately.

In the analysis of psychiatric sequelae, Kaplan-Meier analysis was conducted to estimate the probability of outcomes from 14 to 90 days. Comparisons between cohorts were made using a log-rank test. The HR was calculated using a proportional hazard model (with the survival package 3.2.3 in R) wherein the cohort to which the patient belonged was used as the independent variable. The proportional hazard assumption was tested using the generalized Schoenfeld approach[23]. If the assumption was violated, a piecewise constant HR was estimated by calculating a separate HR for the early and late phases of the follow-up period and the assumption was tested again in each sub-period (see appendix p. 7).

In the analysis of the psychiatric antecedents, the relative risk (RR) of being diagnosed with COVID-19 were calculated for each stratum and for the whole cohort. The null hypothesis that the outcome rate is equal in the two cohorts was tested using a χ^2-test. A logistic regression was used to test for a potential association between age and RR (see appendix p. 8).

Statistical analyses were conducted in R version 3.4.3 except for the logrank tests which were performed within TriNetX. Statistical significance was set at two-sided p-values < 0·05.

Results

A total of 62,354 patients had a diagnosis of COVID-19 (Table 1 and appendix p. 9). For the analysis of psychiatric sequelae, a subset of 44,779 patients who had no prior psychiatric illness and who had not died was used as the COVID-19 cohort. Successful matching was achieved between this cohort and cohorts with other acute health events (appendix pp. 9–20). For the analysis of psychiatric antecedents, a cohort of 1,729,837 patients with a psychiatric diagnosis between January 21, 2019 and January 20, 2020 was defined and successfully matched to a cohort of 1,729,837 patients who never had a psychiatric diagnosis (appendix p. 21).

The estimated probabilities of psychiatric sequelae during the first 14-90 days following COVID-19 and other control health events are presented in Table 2 (the corresponding HR are reported in the appendix, p. 22). Compared to all six control health events, a diagnosis of COVID-19 led to significantly more first diagnoses of psychiatric illness (HR between 1·58 and 2·24, all p-values < 0·0001; Fig. 1 and appendix p. 23). At 90 days, the estimated probability of having been newly diagnosed with a psychiatric illness following COVID-19 was 5·8% (95% CI: 5·2–6·4). The proportional hazard assumption was valid for three out of six control health events (influenza, other respiratory tract infection, and urolithiasis). For the other three events (skin infection, cholelithiasis, and fracture), there was evidence of non-proportionality and the HR tended to increase over time (appendix p. 24). However, the HR remained significantly greater than 1 for both the early and late phases of the follow-up period (all p<0·0001, except for cholelithiasis in the early phase: p=0·0044). The most frequent psychiatric diagnosis following COVID-19 was anxiety disorder (HRs 1·59–2·62, all p-values < 0·0001) with a probability of outcome within 90 days of 4·7% (95% CI: 4·2–5·3). Among the anxiety disorders, adjustment disorder, generalized anxiety disorder, and to a lesser extent post-traumatic stress disorder and panic disorder were the most frequent (appendix pp. 25–26).

The probability of a first diagnosis of mood disorder within 14-90 days after COVID-19 was 2% (95% CI: 1·7–2·4). The corresponding hazard rate was comparable to that following a diagnosis of skin infection (HR 1·07, 95% CI: 0·87–1·31, p=0·55) or cholelithiasis (HR 1·22, 95% CI: 0·93–1·59, p=0·14) but was significantly higher than the hazard rate following a diagnosis of influenza (HR 1·79, 95% CI: 1·37–2·33, p<0·0001), another respiratory tract infection (HR 1·33, 95% CI: 1·09–1·63, p=0·0054), urolithiasis (HR 1·62, 95% CI: 1·26–2·07, p=0·00011), or a fracture (HR 1·35, 95% CI: 1·094–1·67, p=0·0050). Depressive episode was the most common first diagnosis of mood disorder (1·7%, 95% CI: 1·4–2·1; appendix p. 27).

There was a low probability of being newly diagnosed with a psychotic disorder in the 14-90 days following COVID-19 (0·1%, 95% CI: 0·08-0·2), broadly similar to the probability following control health events (Table 2). The probability of a first diagnosis of insomnia in the 14-90 days following COVID-19 was 1·9% (95% CI: 1·6–2·2), commoner than after control health events (HRs 1·85–3·29, all p-values < 0·0001). About 60% of the insomnia diagnoses were not accompanied by a concurrent diagnosis of an anxiety disorder (appendix p. 27). The probability of developing dementia was increased following a diagnosis of COVID-19 compared to all control health events (Table 2 and appendix p. 28); among patients over the age of 65 years the risk was 1·6% (95% CI: 1·2–2·1), with HR between 1·89 and 3·18 (p-values in Table 2).

The findings described above concern diagnoses of psychiatric disorder in people who had no prior psychiatric history. We also found that the rate of *all* diagnoses of psychiatric disorder (i.e. including relapses) was higher after COVID-19 than after control health events (Fig. 2, Table 3, and appendix p. 29). The estimated probability of having been diagnosed with any psychiatric illness in the 14-90 days following COVID-19 was 18·1% (95% CI: 17·6–18·6), significantly higher than for all control health events (HRs 1·24–1·49, all p < 0·0001). The most common psychiatric diagnosis following COVID-19 was anxiety disorder (12·8%, 95% CI: 12·4–13·3) followed by mood disorders (9·9%; 95% CI: 9·5–10·3). Both these rates were higher than those for all control health events (HRs 1·24–1·60 for anxiety disorders, and HRs 1·12–1·44 for mood disorders, all p < 0·0001). The rate of first or relapsed psychotic disorder diagnosis following COVID-19 was 0·9% (95% CI: 0·8–1·1),

significantly higher than that for all control health events (HRs 1·20–2·16, all $p < 0.05$ except for skin infection: p=0·44).

The increased risk of psychiatric sequelae after COVID-19 remained unchanged in all sensitivity analyses: (a) when the cohorts were limited to patients with known race (HR between 1·52 and 2·19, all $p < 0·0001$, appendix p. 30), (b) when controlling for problems related to housing and economic circumstances (HR between 1·53 and 2·09, all $p < 0·0001$, appendix p. 31), (c) when limiting cohorts to patients with confirmed COVID-19 (HR between 1·63 and 2·28, all $p < 0·0001$, appendix p. 32), (d) cohorts where COVID-19 was diagnosed by RNA/Antigen test (HR between 1·53 and 2·04, all $p < 0·0001$, appendix p. 33), (e) patients who made at least one healthcare visit between 14 and 90 days after their health event (HR between 1·66 and 1·77, all $p<0·0001$, appendix p. 34), (f) when comparing to the psychiatric sequelae of control health events before the COVID-19 pandemic (HR between 1·89 and 2·56, all $p < 0·0001$, appendix p. 35), and (g) when comparing unmatched cohorts (HR between 1·58 and 2·36, all $p < 0·0001$, appendix p. 36).

The elevated risk of psychiatric sequelae after COVID-19 compared to control health events could not be readily explained by differences in illness severity. Patients with COVID-19 requiring inpatient admission were more at risk of psychiatric sequelae than patients not needing an admission (HR 1·40, 95% CI: 1·06–1·85, p=0·019). However, when limiting cohorts to those not requiring inpatient admission, large differences in psychiatric sequelae remained between COVID-19 and the other cohorts (HR 1·54-2·23, all $p<0·0001$, appendix p. 37).

Contextual factors provide part of the explanation for the difference in psychiatric sequelae between COVID-19 and control health events. All health events had higher rates of psychiatric sequelae when they occurred after (*vs.* before) April 1, 2020 (HR comparing the period before to the period after April 1 ranging from 1·32 and 1·79, all $p<0·05$, appendix p. 38) and the HR between COVID-19 and control health events were lower when these events occurred after April 1, 2020 (HR 1·31–1·83 *vs.* 1·58–2·24 when considering the whole study period, appendix p. 39). However, these HR all remained statistically larger than 1 indicating that contextual factors alone are insufficient to explain differences in psychiatric sequelae. In other words, experiencing *any* health

event after (*vs.* before) April 1, 2020 led to a higher rate of psychiatric sequelae but this rate was higher still after experiencing COVID-19.

Having a diagnosis of psychiatric illness in the year before the COVID-19 outbreak was associated with a 65% increased risk of COVID-19 (RR 1·65, 95% CI: 1·59–1·71, p<0·0001) compared to a cohort matched for established physical risk factors for COVID-19 but without a psychiatric diagnosis (Fig. 3). The RR was higher in older patients (odds ratio 1·25, 95% CI: 1·14–1·38, p<0·0001).

These results were robust in all sensitivity analyses: (a) if this was a first psychiatric diagnosis (RR: 1·67, 95% CI: 1·57–1·79, p<0·0001, appendix p. 40), (b) among patients with a psychiatric diagnosis in the past three years (RR: 1·80, 95% CI: 1·74–1·86, p<0·0001, appendix p. 40), (c) among patients whose race was known (RR: 1·64, 95% CI: 1·58–1·70, p<0·0001, appendix p. 41), (d) if the cohorts were limited to patients without any of the physical comorbidities that are risk factors for COVID-19 (RR: 1·57, 95% CI: 1·39–1·76, p<0·0001, appendix p. 42), (e) if the outcome was limited to a confirmed diagnosis of COVID-19 (RR: 1·57, 95% CI: 1·51–1·64, p<0·0001, appendix p. 43) , and (f) if cohorts were matched for problems related to housing and economic circumstances (RR: 1·57, 95% CI: 1·52–1·61, p < 0·0001, appendix p. 44).

Only small differences in the RR of COVID-19 were observed when comparing classes of psychiatric diagnoses against each other: the RR among patients with a psychotic disorder were 1·17 (95% CI: 1·02–1·33, p=0·022) when compared a mood disorder and 1·08 (95% CI: 0·95–1·23, p=0·22) when compared to an anxiety disorder. When compared to an anxiety disorder, the RR among patients with a mood disorder was 0·95 (95% CI: 0·92–0·99, p=0·020).

Discussion

Using a large federated EHR network in the USA to create propensity score matched cohorts of patients, we provide evidence that COVID-19 survivors have a significantly elevated rate of psychiatric disorders as well as

dementia and insomnia. We also show that a psychiatric history is independently associated with an increased risk of being diagnosed with COVID-19.

In the period between 14 and 90 days after diagnosis, 5·8% of COVID-19 survivors had their first recorded diagnosis of psychiatric illness (F20-F48), compared to 2·5–3·4% of patients in the comparison cohorts. These data show that even relatively resilient adults have an approximately doubled risk of being newly diagnosed with a psychiatric disorder after COVID-19. The comparable figures when recurrences of prior diagnoses are included (18·1 *vs*. 12·7–15·1%, with HR of 1·24–1·49) are indicative of the rates of psychiatric disorder that may be anticipated in practice. Note that these incidence figures are minimum estimates, for three reasons. First, there will be patients who have not yet presented or received a diagnosis. Second, patients may seek healthcare from organisations not included in the network. Third, diagnostic rates overall in the network are about 30% lower for both psychiatric and physical disorders since the onset of COVID-19 (see appendix p. 45), consistent with other evidence for reduced presentations in the USA[24].

The psychiatric effects of COVID-19 were broad but not uniform. The HR was greater for anxiety disorders than for mood disorders. The particular impact of COVID-19 on anxiety is in line with expectations and highlights the need for effective and accessible interventions. The data show increased diagnoses in all major anxiety disorder categories, and so it remains unclear whether post-COVID-19 anxiety will have a particular PTSD-like picture. Rates of an insomnia diagnosis were also markedly elevated, again in keeping with predictions that circadian disturbances will follow COVID-19 infection. In contrast, we did not find a clear signal for newly diagnosed psychotic disorders despite case reports suggesting that this might occur[11,25]. The 2-3-fold increased risk of dementia after COVID-19 extends findings from previous case series[11,26] and is concerning. Some of the excess may reflect misdiagnosed cases of delirium, or transient cognitive impairments due to reversible cerebral events. However our exclusion of the first 14 days after COVID-19 diagnosis reduces this likelihood, and the incidence of dementia was not higher among inpatients (who are more prone to having delirium) than outpatients (see appendix p. 45), further suggesting that delirium misdiagnosis does not explain this finding. Detailed follow-up and investigation of this group should be a research priority, as should evaluation of other severe neuropsychiatric phenotypes which become apparent.

The HRs from COVID-19 were higher compared to all other cohorts, indicating that COVID-19 has an impact on psychiatric health above and beyond that which occurs following other acute health events. Since our 'severity' and 'contextual factors' hypotheses cannot explain most of the associations, it is necessary to explain the particular effect of COVID-19 on risk of psychiatric disorder. Despite various speculations, the mechanisms are unknown and require urgent investigation. The relationship between severity of the illness (as proxied by inpatient admission) and psychiatric outcomes, albeit modest, might represent a dose-response relationship suggesting that the association may at least partially be mediated by biological factors directly related to COVID-19 severity (e.g. viral load, breathlessness, or the nature of the immune response).[6,27,28]

We had not anticipated that psychiatric history would be an independent risk factor for COVID-19. The finding appears robust, being seen in all age strata, and in both sexes, and is substantial—a 1·65-fold excess. It is not related to any specific psychiatric diagnostic category, and it was similar regardless of whether the diagnosis was made within one or three years, and whether or not the known physical risk factors for COVID-19 were present. It persisted when problems related to housing and economic circumstances were controlled for. It is consistent with a recent case-control study using a different US EHR network, although they found much higher relative risks[14]. Nevertheless, we interpret the finding cautiously, since a Korean study did not find any clear association between psychiatric diagnosis and COVID-19 diagnosis, albeit in a much smaller sample and with less matching.[15] Possible explanations include behavioural factors (e.g. less adherence to social distancing recommendations) and residual socioeconomic and lifestyle factors (e.g. smoking) that are not sufficiently captured by the available data in any of the studies. It may also be that vulnerability to COVID-19 is increased by the pro-inflammatory state postulated to occur in some forms of psychiatric disorder, or be related to psychotropic medication.

The strengths of this study are the sample sizes, the amount of data available, the use of propensity score matching to control for confounding, the range of sensitivity analyses, and the real-world nature of the data. The study also has limitations. First, despite the matching and use of various comparison cohorts, there may well be residual confounding, particularly related to social and economic factors which are not captured in the

network and which might influence outcomes post COVID-19. Second, we do not know whether diagnoses were made in primary or secondary care, nor by whom. It is possible that some healthcare centres were closed as a result of lockdowns and this might influence where and how patients were diagnosed. Clearly, the study can provide no information about undiagnosed patients with COVID-19. Third, clinicians might be more likely to diagnose a psychiatric illness following a COVID-19 diagnosis than after the comparison events because of a difference in the nature or extent of assessments; this could also lead to improved detection of conditions (e.g. dementia) which had been present but undiagnosed prior to COVID-19. Fourth, some patients may receive additional care, especially for mental health, at locations not included in the network; this would reduce the absolute incidence figures, but unlikely to confound the relative risks associated with COVID-19. Fifth, propensity score matching raises some statistical issues, but these are unlikely to impact the results to any extent (see appendix p. 7); moreover, similar results were seen in the unmatched analyses (appendix p. 36). Sixth, we did not control statistically for multiple comparisons, although the large majority of results were significant at the $p<0.001$ level or lower. Finally, the results cannot necessarily be generalised to other populations or healthcare settings.

Nevertheless, the findings are of sufficient robustness and magnitude to have some immediate implications. The figures provide minimum estimates of the excess in psychiatric morbidity to be anticipated in survivors of COVID-19 and for which services need to plan.[29] As COVID-19 sample sizes and survival times increase, it will be possible to refine these findings and to identify rarer and delayed psychiatric presentations. Prospective cohort studies, and inclusive case registers, will be valuable to complement EHR analyses. It will also be important to explore additional risk factors for contracting COVID-19, and for developing psychiatric disorders thereafter, since some elements may prove to be modifiable.

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Declaration of interests

PJH and MT were granted unrestricted and free access to the TriNetX Analytics network for the purposes of research relevant to psychiatry, and with no constraints on the analyses performed nor the decision to publish. SL is an employee of TriNetX Inc.

Data sharing

The data presented in this paper and in the appendix can be freely accessed at https://osf.io/fjnw8. In addition, TriNetX will grant access to researchers if they have a specific concern (via the 'third party agreement' option).

Author contributions

PJH and MT designed the study and directly accessed the TriNetX Analytics web interface in order to carry it out. PJH and MT defined the inclusion and exclusion criteria for each cohort, checked all characteristics of the cohorts, and defined the outcome criteria and analytic approaches. MT carried out data analyses. SL and JRG assisted with data analysis and interpretation. MT and PJH wrote the paper with input from JRG and SL. PJH is the guarantor. The TriNetX system returned the results of these analyses as csv files, which were downloaded and archived.

Role of the funding source

The funders of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. MT and PJH had full access to all the data in the study and the corresponding author had final responsibility for the decision to submit for publication.

References

1 Xiang Y-T, Yang Y, Li W, *et al.* Timely mental health care for the 2019 novel coronavirus outbreak is urgently needed. *Lancet Psychiatry* 2020; 7: 228–9.

2 World Health Organization. Mental health and psychosocial considerations during the COVID-19 outbreak, 18 March 2020. World Health Organization, 2020 https://apps.who.int/iris/bitstream/handle/10665/331490/WHO-2019-nCoV-MentalHealth-2020.1-ng.pdf.

3 Holmes EA, O'Connor RC, Perry VH, *et al.* Multidisciplinary research priorities for the COVID-19 pandemic: a call for action for mental health science. *Lancet Psychiatry* 2020; published online April 15. DOI:10.1016/S2215-0366(20)30168-1.

4 Yao H, Chen J-H, Xu Y-F. Patients with mental health disorders in the COVID-19 epidemic. *Lancet Psychiatry* 2020; 7: e21.

5 Paz C, Mascialino G, Adana-Díaz L, *et al.* Anxiety and depression in patients with confirmed and suspected COVID-19 in Ecuador. *Psychiatry Clin Neurosci* 2020; published online July 1. DOI:10.1111/pcn.13106.

6 Gennaro Mazza M, De Lorenzo R, Conte C, *et al.* Anxiety and depression in COVID-19 survivors: role of inflammatory and clinical predictors. *Brain Behav Immun* 2020; published online July 29. DOI:10.1016/j.bbi.2020.07.037.

7 Halpin SJ, McIvor C, Whyatt G, *et al.* Post-discharge symptoms and rehabilitation needs in survivors of COVID-19 infection: a cross-sectional evaluation. *J Med Virol* 2020; published online July 30. DOI:10.1002/jmv.26368.

8 Bo H-X, Li W, Yang Y, *et al.* Posttraumatic stress symptoms and attitude toward crisis mental health services among clinically stable patients with COVID-19 in China. *Psychol Med* 2020; : 1–2.

9 Zhang J, Lu H, Zeng H, *et al.* The differential psychological distress of populations affected by the COVID-19 pandemic. *Brain Behav Immun* 2020; 87: 49–50.

10 Nalleballe K, Reddy Onteddu S, Sharma R, *et al.* Spectrum of neuropsychiatric manifestations in COVID-19. *Brain Behav Immun* 2020; 88: 71–4.

11 Varatharaj A, Thomas N, Ellul M, *et al.* UK-Wide Surveillance of Neurological and Neuropsychiatric Complications of COVID-19: The First 153 Patients. 2020; published online May 14. DOI:10.2139/ssrn.3601761.

12 Rogers JP, Chesney E, Oliver D, *et al.* Psychiatric and neuropsychiatric presentations associated with severe coronavirus infections: a systematic review and meta-analysis with comparison to the COVID-19 pandemic. The Lancet Psychiatry. 2020; 7: 611–27.

13 Seminog OO, Goldacre MJ. Risk of pneumonia and pneumococcal disease in people with severe mental illness: English record linkage studies. *Thorax* 2013; 68: 171–6.

14 Wang Q, Xu R, Volkow N. D., Increased risk of COVID-19 infection and mortality in people with mental disorders: analysis from electronic health records in the United States. *World Psychiatry* 2021; published online ahead of print. DOI: 10.1002/wps.20806.

15 Lee SW, Yang JM, Moon SY, et al. Association between mental illness and COVID-19 susceptibility and clinical outcomes in South Korea: a nationwide cohort study. *Lancet Psychiatry* 2020; published online Sept 17. DOI:10.1016/S2215-0366(20)30421-1.

16 Harrison PJ, Luciano S, Colbourne L. Rates of delirium associated with calcium channel blockers compared to diuretics, renin-angiotensin system agents and beta-blockers: An electronic health records network study. *J Psychopharmacol* 2020; 34: 848–55.

17 de Lusignan S, Dorward J, Correa A, *et al.* Risk factors for SARS-CoV-2 among patients in the Oxford Royal College of General Practitioners Research and Surveillance Centre primary care network: a cross-sectional study. *Lancet Infect Dis* 2020; published online May 15. DOI:10.1016/S1473-3099(20)30371-6.

18 Zhang J-J, Dong X, Cao Y-Y, *et al.* Clinical characteristics of 140 patients infected with SARS-CoV-2 in Wuhan, China. *Allergy* 2020. https://onlinelibrary.wiley.com/doi/abs/10.1111/all.14238.

19 Chen N, Zhou M, Dong X, *et al.* Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. *Lancet* 2020; 395: 507–13.

20 Williamson EJ, Walker AJ, Bhaskaran K, *et al.* OpenSAFELY: factors associated with COVID-19 death in 17 million patients. *Nature* 2020; published online July 8. DOI:10.1038/s41586-020-2521-4.

21 Austin PC. An Introduction to Propensity Score Methods for Reducing the Effects of Confounding in Observational Studies. *Multivariate Behav Res* 2011; 46: 399–424.

22 Haukoos JS, Lewis RJ. The Propensity Score. *JAMA* 2015; 314: 1637–8.

23 Grambsch PM, Therneau TM. Proportional hazards tests and diagnostics based on weighted residuals. *Biometrika*. 1994; 81: 515–26.

24 Jeffery MM, D'Onofrio G, Paek H, *et al.* Trends in Emergency Department Visits and Hospital Admissions in Health Care Systems in 5 States in the First Months of the COVID-19 Pandemic in the US. *JAMA Intern Med* 2020; published online Aug 3. DOI:10.1001/jamainternmed.2020.3288.

25 Parra A, Juanes A, Losada CP, *et al.* Psychotic symptoms in COVID-19 patients. A retrospective descriptive study. *Psychiatry Res* 2020; 291: 113254.

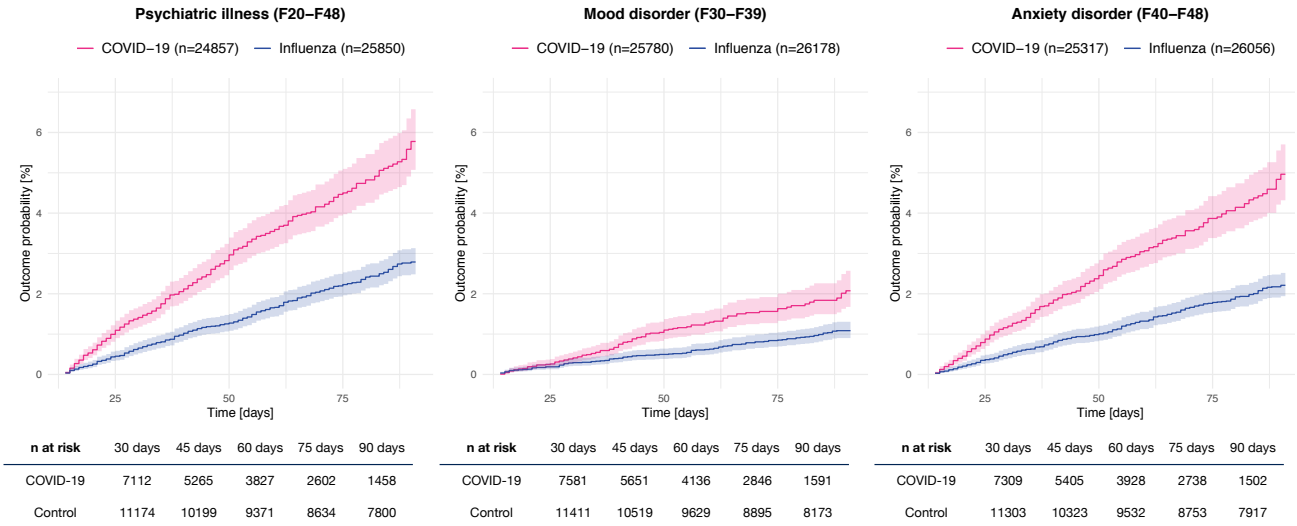
26 Pinna P, Grewal P, Hall JP, *et al.* Neurological manifestations and COVID-19: Experiences from a tertiary care center at the Frontline. *J Neurol Sci* 2020; 415: 116969.

27 Postolache TT, Benros ME, Brenner LA. Targetable Biological Mechanisms Implicated in Emergent Psychiatric Conditions Associated With SARS-CoV-2 Infection. *JAMA Psychiatry* 2020; published online July 31. DOI:10.1001/jamapsychiatry.2020.2795.

28 Gupta A, Madhavan MV, Sehgal K, *et al.* Extrapulmonary manifestations of COVID-19. *Nat Med* 2020; 26: 1017–32.

29 Greenhalgh T, Knight M, A'Court C, Buxton M, Husain L. Management of post-acute covid-19 in primary care. *BMJ* 2020; m3026.

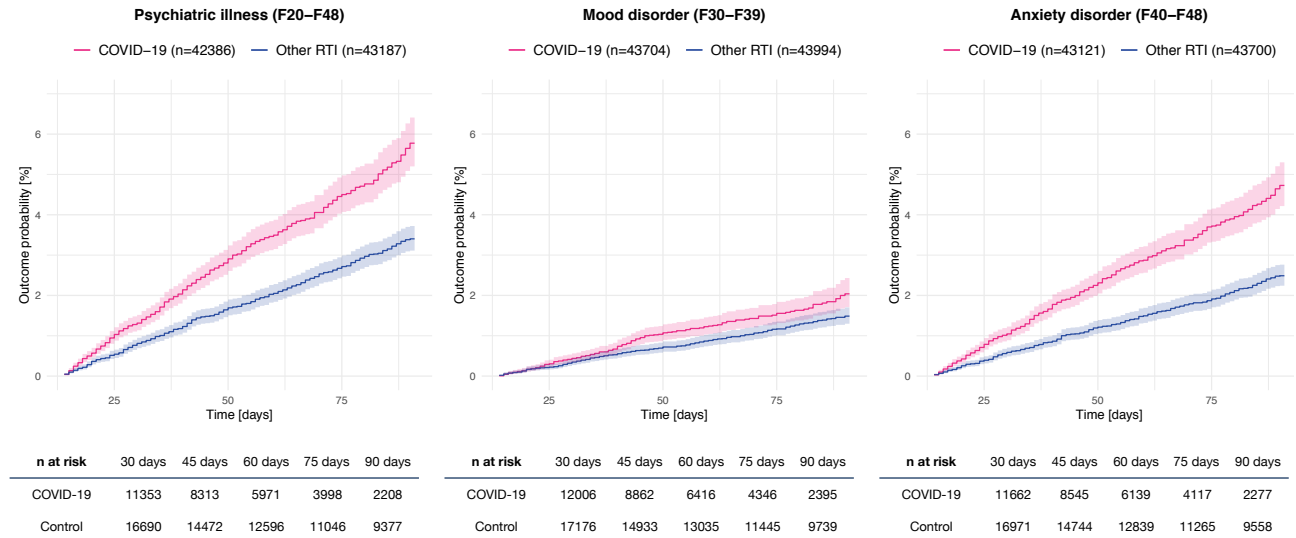
Tables and Figures



n at risk	30 days	45 days	60 days	75 days	90 days
COVID-19	7112	5265	3827	2602	1458
Control	11174	10199	9371	8634	7800

n at risk	30 days	45 days	60 days	75 days	90 days
COVID-19	7581	5651	4136	2846	1591
Control	11411	10519	9629	8895	8173

n at risk	30 days	45 days	60 days	75 days	90 days
COVID-19	7309	5405	3928	2738	1502
Control	11303	10323	9532	8753	7917



n at risk	30 days	45 days	60 days	75 days	90 days
COVID-19	11353	8313	5971	3998	2208
Control	16690	14472	12596	11046	9377

n at risk	30 days	45 days	60 days	75 days	90 days
COVID-19	12006	8862	6416	4346	2395
Control	17176	14933	13035	11445	9739

n at risk	30 days	45 days	60 days	75 days	90 days
COVID-19	11662	8545	6139	4117	2277
Control	16971	14744	12839	11265	9558

Fig. 1 - Kaplan-Meier curves representing the onset of first psychiatric diagnoses after COVID-19 compared to influenza and other respiratory tract infections (RTI). The same curves for the other control health events are presented in the appendix, p. 23. Shaded areas represent 95% confidence intervals. The number of subjects within each cohort corresponds to all those that did not have the outcome before the follow-up period.

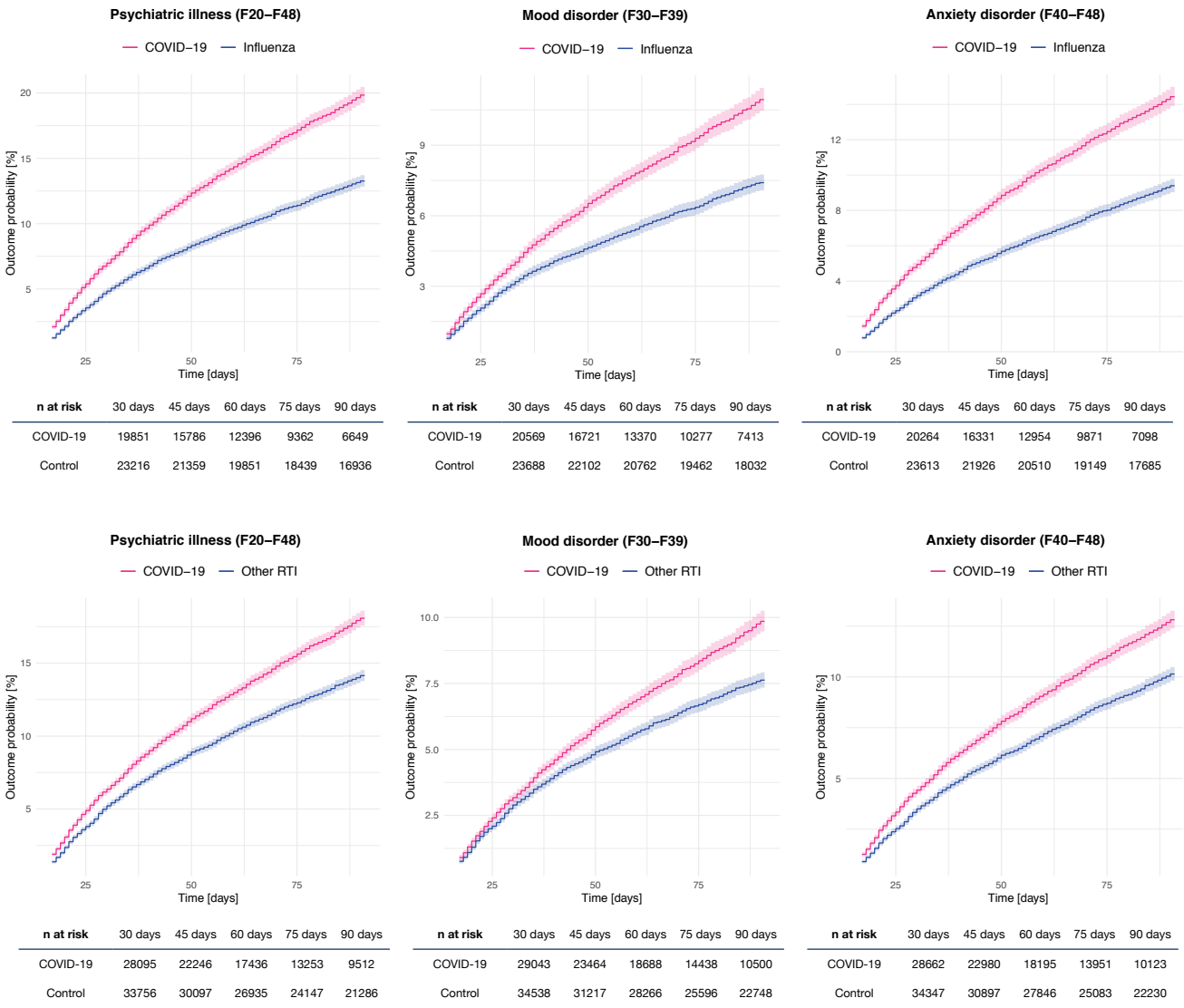


Fig. 2 - Kaplan-Meier curves for any (first or recurrent) psychiatric diagnoses after COVID-19 compared to influenza and other respiratory tract infections (RTI). The same curves for the other control health events are presented in the appendix, p. 29. Shaded areas represent 95% confidence intervals. The number of subjects within each cohort corresponds to all those that did not have the outcome before the follow-up period.

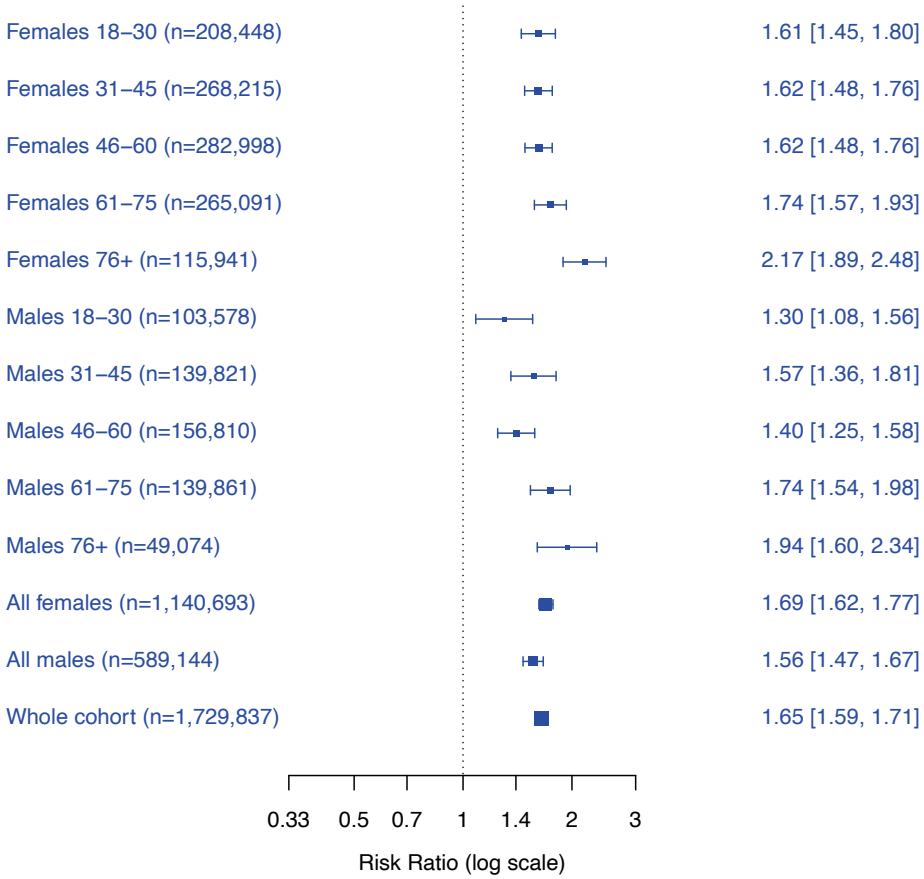


Fig. 3 - Relative risks of COVID-19 among patients with a psychiatric illness recorded in the past year compared to a matched cohort of patients with no history of psychiatric illness. Error bars and numbers in brackets represent 95% CI.

Table 1. Baseline characteristics of the patients with a COVID-19 diagnosis

	n (%), mean (SD)
COVID-19	
Diagnosis of COVID-19	62,354 (100.0)
of which confirmed diagnosis	57,821 (92.7)
DEMOGRAPHICS	
Age, mean (SD), y	49.3 (19.7)
Sex	
Female	34,461 (55.3)
Male	28,399 (45.5)
Other	261 (0.4)
Race	
White	31,789 (51.0)
Black or African American	14,700 (23.6)
Asian	1,554 (2.5)
American Indian or Alaska Native	329 (0.5)
Native Hawaiian or Other Pacific Islander	107 (0.2)
Unknown	13,875 (22.3)
Geographic region of the USA	
Northeast	22,817 (37)
Midwest	7,908 (13)
South	19,643 (32)
West	9,719 (16)
Other/Unknown	2,267 (4)
COMORBIDITIES	
Obesity	
Overweight and obesity	12,249 (19.6)
Body mass index, n with data (%) | mean (SD), kg/m^2	23,728 (38.1) | 28.1 (8.2)
Hypertension	
Systolic Blood Pressure, n with data (%) | mean (SD), mmHg	41,011 (65.8) | 128 (20.6)
Diastolic Blood Pressure, n with data (%) | mean (SD), mmHg	41,009 (65.8) | 76.9 (13.1)
Hypertensive diseases	21,228 (34.0)
Diabetes mellitus	
Type 1 diabetes mellitus	1,535 (2.5)
Type 2 diabetes mellitus	10,998 (17.6)
Chronic lower respiratory diseases	
Bronchitis; not specified as acute or chronic	3,125 (5.0)
Simple and mucopurulent chronic bronchitis	329 (0.5)
Unspecified chronic bronchitis	388 (0.6)
Emphysema	1,211 (1.9)
Other chronic obstructive pulmonary disease	3,582 (5.7)

Asthma	7,101 (11.4)
Bronchiectasis	384 (0.6)
Nicotine dependence	4,579 (7.3)
Heart diseases	
Ischemic heart diseases	6,579 (10.6)
Other forms of heart disease	12,633 (20.3)
Chronic kidney diseases	
Chronic kidney disease (CKD)	5,554 (8.9)
Hypertensive chronic kidney disease	2,890 (4.6)
Chronic liver diseases	
Alcoholic liver disease	351 (0.6)
Hepatic failure; not elsewhere classified	502 (0.8)
Chronic hepatitis; not elsewhere classified	83 (0.1)
Fibrosis and cirrhosis of liver	775 (1.2)
Fatty (change of) liver; not elsewhere classified	2,152 (3.5)
Chronic passive congestion of liver	388 (0.6)
Portal hypertension	322 (0.5)
Other specified diseases of liver	1,502 (2.4)
Cerebral infarction	1,910 (3.1)
Dementia	
Vascular dementia	558 (0.9)
Dementia in other diseases classified elsewhere	740 (1.2)
Unspecified dementia	1,794 (2.9)
Alzheimer's disease	672 (1.1)
Neoplasms	
Neoplasms	12,655 (20.3)
Malignant neoplasms of lymphoid; hematopoietic and related tissue	836 (1.3)
Organ transplant	
Renal Transplantation Procedures	137 (0.2)
Liver Transplantation Procedures	44 (0.1)
Psoriasis	669 (1.1)
Rheumatoid arthritis	
Rheumatoid arthritis with rheumatoid factor	301 (0.5)
Other rheumatoid arthritis	982 (1.6)
Systemic lupus erythematosus (SLE)	414 (0.7)
Disorders involving the immune mechanism	1,532 (2.5)
PSYCHIATRIC DIAGNOSES	
Psychiatric illness (F20-F48)	15,980 (25.6)
Psychotic disorders (F20-29)	1,219 (2.0)
Mood disorders (F30-F39)	9,921 (15.9)
Anxiety disorder (F40-F48)	12,145 (19.5)

Table 2. Estimated incidence of first psychiatric diagnoses during the 14-90 days after a diagnosis of COVID-19 compared to other health events.

	COVID-19	Influenza		Other RTI		Skin infection	
n in each matched cohort	-	26497		44775		38977	
	% (95% CI)	**% (95% CI)**	**p**	**% (95% CI)**	**p**	**% (95% CI)**	**p**
Psychiatric illness	5.8 (5.2-6.4)	2.8 (2.5-3.1)	<0.0001	3.4 (3.1-3.7)	<0.0001	3.3 (3-3.7)	<0.0001
Psychotic disorder	0.1 (0.08-0.2)	0.04 (0.01-0.10)	0.019	0.1 (0.06-0.16)	0.23	0.15 (0.096-0.24)	0.83
Mood disorder	2.0 (1.7-2.4)	1.1 (0.9-1.3)	<0.0001	1.5 (1.3-1.7)	0.0054	1.7 (1.5-1.9)	0.55
Anxiety disorder	4.7 (4.2-5.3)	2.2 (1.9-2.5)	<0.0001	2.5 (2.2-2.8)	<0.0001	2.4 (2.1-2.7)	<0.0001
Insomnia	1.9 (1.6-2.2)	0.6 (0.5-0.8)	<0.0001	0.8 (0.7-1.0)	<0.0001	0.89 (0.73-1.1)	<0.0001
Dementia	0.44 (0.33-0.60)	0.11 (0.06-0.20)	0.00044	0.25 (0.18-0.35)	0.00063	0.28 (0.20-0.39)	0.13
Dementia (among 65+)	1.6 (1.2-2.1)	0.66 (0.41-1.1)	0.0043	0.84 (0.61-1.1)	0.00071	0.70 (0.49-1.0)	0.00069

	Cholelithiasis		Urolithiasis		Fracture	
n in each matched cohort	19733		28827		37841	
	% (95% CI)	**p**	**% (95% CI)**	**p**	**% (95% CI)**	**p**
Psychiatric illness	3.2 (2.8-3.7)	<0.0001	2.5 (2.2-2.8)	<0.0001	2.5 (2.2-2.7)	<0.0001
Psychotic disorder	0.11 (0.054-0.24)	0.21	0.044 (0.016-0.12)	0.0051	0.16 (0.11-0.24)	0.77
Mood disorder	1.6 (1.3-1.9)	0.14	1.2 (1-1.4)	0.00011	1.4 (1.2-1.6)	0.0050
Anxiety disorder	2.6 (2.2-3)	<0.0001	1.8 (1.6-2.1)	<0.0001	1.6 (1.4-1.8)	<0.0001
Insomnia	1.1 (0.88-1.4)	<0.0001	0.57 (0.43-0.74)	<0.0001	0.7 (0.57-0.85)	<0.0001
Dementia	0.24 (0.14-0.38)	<0.0001	0.16 (0.09-0.28)	<0.0001	0.34 (0.25-0.44)	0.14
Dementia (among 65+)	0.58 (0.36-0.94)	<0.0001	0.60 (0.38-0.95)	<0.0001	0.94 (0.68-1.3)	0.0036

P-values are obtained using a logrank test. A breakdown of the results for different diagnoses of the anxiety disorders and mood disorders categories is provided in Table 10 and 11 respectively (appendix pp. 26–27).

Table 3. **Estimated incidence of all (first and recurrent) psychiatric diagnoses during the 14-90 days after a diagnosis of COVID-19 compared to other health events.**

	COVID-19	Influenza		Other RTI		Skin infection	
	% (95% CI)	% (95% CI)	p	% (95% CI)	p	% (95% CI)	p
Psychiatric illness	18.1 (17.6-18.6)	13.3 (12.8-13.7)	<0.0001	14.1 (13.8-14.5)	<0.0001	14.8 (14.4-15.2)	<0.0001
Psychotic disorder	0.94 (0.82-1.1)	0.49 (0.41-0.59)	<0.0001	0.60 (0.53-0.70)	<0.0001	0.92 (0.82-1.0)	0.44
Mood disorder	9.9 (9.5-10.3)	7.4 (7.1-7.8)	<0.0001	7.6 (7.3-7.9)	<0.0001	8.6 (8.3-9.0)	<0.0001
Anxiety disorder	12.8 (12.4-13.3)	9.4 (9.0-9.8)	<0.0001	10.1 (9.8-10.5)	<0.0001	10.0 (9.6-10.4)	<0.0001

	Cholelithiasis		Urolithiasis		Fracture	
	% (95% CI)	p	% (95% CI)	p	% (95% CI)	p
Psychiatric illness	15.1 (14.6-15.6)	<0.0001	13.7 (13.3-14.1)	<0.0001	12.7 (12.4-13.1)	<0.0001
Psychotic disorder	0.72 (0.61-0.86)	0.045	0.44 (0.37-0.53)	<0.0001	0.74 (0.65-0.84)	0.034
Mood disorder	9.2 (8.8-9.7)	<0.0001	8.3 (8.0-8.6)	<0.0001	8.1 (7.8-8.4)	<0.0001
Anxiety disorder	10.0 (9.6-10.5)	<0.0001	9.5 (9.2-9.9)	<0.0001	7.9 (7.6-8.3)	<0.0001