Title: **Mental disorders and risk of COVID-19 related mortality, hospitalization and intensive care unit admission: a systematic review and meta-analysis**

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Summary

Background: Mental disorders may represent a risk factor for severe COVID-19. This study aims to provide new insight into the specific risks of COVID-19 mortality, hospitalization, and intensive care unit (ICU) admission associated with any pre-existing mental disorder, as well as specific categories of mental disorders (i.e., psychotic disorders, mood disorders, substance use disorders, anxiety disorders, intellectual disabilities and developmental disorders), and exposure to psychopharmacological drug classes (antidepressants, antipsychotics, and anxiolytics).

Methods: In this PRISMA-compliant systematic review and meta-analysis (PROSPERO-CRD42021233984), we searched Web of Science, PsycINFO, Cochrane, PubMed, and Ovid/PsycINFO databases through 5th March 2021. We included original studies reporting data on COVID-19 outcomes in psychiatric patients compared to controls. We excluded overlapping samples, studies that were not peer-reviewed, and studies written in languages other than English, Danish, Dutch, French, German, Italian, and Portuguese. We modeled random-effects meta-analyses to estimate crude odds ratios (OR) for COVID-19 mortality as primary outcome, and hospitalization and ICU admission as secondary outcomes. Analyses for adjusted OR on available data were also performed. Heterogeneity was assessed using the I^2 statistic, publication bias was tested with Egger regression and visual inspection of funnel plots. We used the GRADE approach to assess the overall strength of the evidence and the Newcastle Ottawa Scale to explore study quality. We also conducted subgroup analyses and meta-regressions to assess the effects of baseline COVID-19 treatment setting, patient age, country, pandemic phase, quality assessment score, sample sizes, and adjustment for confounders.

Findings: A total of 33 studies were included in the systematic review, with 23 studies included in the meta-analysis, representing 1,469,731 patients with COVID-19 (43,938 patients with mental disorders). The sample was composed of 130,807 females (8·90% of the whole sample) and 130,373 males (8·87%). Nine studies provided data on patient race and ethnicity, and 22 studies were rated as high quality.

The presence of any mental disorder was associated with an increased risk of COVID-19 mortality (OR 2·00, 95% CI 1·58-2·54; I^2=92·66). This association was confirmed in psychotic disorders (OR 2·05, 95% CI 1·37-3·06; I^2=80·81), mood disorders (OR 1·99, 95% CI 1·46-2·71; I^2=68·32), substance use disorders (OR 1·76, 95% CI 1·27-2·44; I^2=47·90), and intellectual disabilities and developmental disorders (OR 1·73, 95% CI 1·29-2·31; I^2=90·15). We detected no significant effect for anxiety disorders (OR 1·07, 95% CI 0·73-1·56; I^2=11·05). COVID-19 mortality was also associated with exposure to antipsychotics (OR 3·71, 95% CI 1·74-7·91; I^2=90·31), anxiolytics (OR 2·58, 95% CI 1·22-5·44; I^2=96·42), and antidepressants (OR 2·23, 95% CI 1·06-4·71; I^2=95·45). For psychotic disorders, mood disorders, antipsychotics, and anxiolytics, the association remained significant after adjustment for age, sex, and other confounders.

Mental disorders were found to be associated with increased risk of hospitalization (OR: 2·24, 95% CI 1·70-2·94; I^2=88·80). No significant effects were found for ICU admission. Subgroup analyses and meta-regressions showed significant effects of baseline COVID-19 treatment setting (p=0·013) and country (p<0·0001) on mortality. No significant effects were found for other covariates. No evidence of publication bias was found. GRADE assessment revealed high certainty for crude mortality and hospitalization, with moderate certainty for crude ICU admission.

Interpretation: Pre-existing mental disorders, in particular psychotic and mood disorders, and exposure to antipsychotics and anxiolytics were associated with COVID-19 mortality in both crude and adjusted models. While further research is required to determine the underlying mechanisms, our findings call for targeted approaches to manage and prevent COVID-19 in at-risk patient groups identified in this study.

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Evidence before this study

Several studies have found that patients with psychiatric disorders are at increased risk of severe COVID-19, but their results are conflicting when focusing on different patient groups and COVID-19 outcomes. Reliable risk estimates of separate COVID-19 outcomes, including mortality, hospitalization, and intensive care unit (ICU) admission, by specific mental disorders and psychopharmacological drug classes, are required for actionable risk stratification. To address these issues, we searched PubMed databases using the keywords "(psychiatr* OR mental OR psychopharm* OR psychotrop*) AND COVID* AND (meta-analysis OR systematic review)", from inception until March 5th 2021, and without language restriction. Selection criteria were meta-analyses of studies examining risks of COVID-19 mortality, hospitalization, or ICU admission associated with pre-existing mental disorders or chronic use of psychopharmacological treatments. Study protocols were excluded. Of 271 records, only one meta-analysis was identified, resulting in a pooled estimate of both fatal and severe COVID-19 outcomes in patients with any mental disorder. No studies examined the risks associated with exposure to psychopharmacological compounds, or differentiated between diagnostic groups.

Added value of this study

Our study provides new compiled evidence differentiating and comparing specific COVID-19 risks among different psychiatric exposure variables, and assesses the strength of the available evidence. We identified strong evidence that patients with mental disorders are at higher risk of mortality and hospitalization, but not ICU admission, following COVID-19. Psychotic and mood disorders were consistently associated with COVID-19 mortality, as were patients exposed to antipsychotic and anxiolytic treatments. Patients with substance use disorders were at increased risk of hospitalization, whereas no increased hospitalization risks were found among patients with psychotic disorders. Our findings show marked differentiation in COVID-19 outcomes among different mental disorders, and highlight possible reduced access to care.

Implication of all the available evidence

Our meta-analysis confirms an increased mortality and hospitalization risk following COVID-19 among patients with pre-existing mental disorders. This study may inform public health authorities' preventive management of the COVID-19 pandemic, including support for policies that prioritize vaccination and counteract reduced access to care among at-risk individuals identified in this study.

Introduction

According to the World Health Organization, as of the 22nd May 2021, there were 166 million confirmed cases of Coronavirus disease 2019 (COVID-19) and more than three million deaths.[1] Several risk factors for severe COVID-19 illness and mortality, including age, male sex, obesity, and cardiovascular disease have been identified since the early phases of the pandemic.[2] Preliminary meta-analytic evidence demonstrated an increased risk of severe or fatal COVID-19 among patients with a pre-existing mental disorder (OR=1·76, 95% CI=1·29-2·41).[3] Several factors may underlie this association, including a higher prevalence of somatic comorbid risk conditions, and reduced access to appropriate physical health care among patients with mental disorders, besides immunological disturbances related to the psychiatric disorder or its treatment.[4,5]

Notably, recent findings have suggested the risks of poor COVID-19 outcomes may differ between psychiatric disorders, and patients with severe mental illness (usually including psychotic and mood disorders) have been indicated as particularly vulnerable.[6] Increased COVID-19 mortality and intensive care unit (ICU) admission have also been associated with psychopharmacological treatments.[7,8] Furthermore, although some studies have demonstrated higher COVID-19 mortality in patients with mental disorders, they did not detect higher rates of hospital or ICU admission.[7,9,10] Hence, there is a need to stratify the risks of specific COVID-19 outcomes by psychiatric disorders and psychopharmacological treatments.

Providing summarized evidence for the risks of adverse COVID-19 outcomes associated with mental disorders, while addressing potential sources of heterogeneity, will advance our understanding of patient risk and may prompt new evidence-based action from clinicians and policymakers.[11] The majority of European countries have not included psychiatric disorders as risk comorbidities eligible for vaccination priority,[11] leading to potentially detrimental outcomes for patients and communities. Given the recent availability of studies with large sample sizes, the primary aim of our systematic review and meta-analysis was to determine the mortality risk related to COVID-19 in patients affected by pre-existing mental disorders or exposed to psychopharmacological treatments. As secondary outcomes, we assessed the risks of hospitalization and ICU admission. We further explored the potential role of confounders (e.g. baseline treatment setting for COVID-19, pandemic phase, quality assessment, minimum age of the recruited sample, sample sizes, and adjustment for age, sex, race/ethnicity, and comorbidities) not previously assessed as possible sources of heterogeneity.

Methods

We performed a systematic review and meta-analysis of risk estimates for mortality, hospitalization, and ICU admission among people with mental disorders compared to people without mental disorders following infection with COVID-19 (PROSPERO ID:CRD42021233984, for updates to protocol, and related sensitivity analyses see appendix pp 2-7). The study was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-analysis PRISMA 2020 standard (appendix pp 8-10).[12]

Eligibility criteria

Inclusion criteria were: a) original articles published in peer-reviewed journals reporting any cross-sectional or longitudinal data; b) studies including patients affected by mental disorders; c) psychiatric diagnosis and exposure to psychopharmacological treatments preceded SARS-CoV-2 infection; d) studies reporting association measures (odds ratio, risk ratio, hazard ratio, or associated metrics) with COVID-19 mortality or related hospitalization, or ICU admission; and e) studies written in languages intelligible for the authors: English, Danish, Dutch, French, German, Italian, and Portuguese.

Exclusion criteria were: a) studies not including patients with pre-existing mental disorders or a control group without mental disorders; b) studies not investigating associations between mental disorders and severe COVID-19 outcomes; c) reviews, clinical case reports, abstracts, conference proceedings, preprints, or studies that did not undergo a peer-review process; and d) duplicate publications. When two or more studies investigated the same clinical population and reported an overlapping sample, the study with the smallest dataset was excluded from meta-analysis but included in the narrative review, as studies not reporting meta-analyzable data.

Search strategy for identification of studies

We conducted an independent and systematic multi-step search procedure including all eligible articles published from 1st January 2020 to 5th March 2021 on Web of Science (Clarivate Analytics), Cochrane, PubMed, and Ovid/PsycINFO databases. The search terms are available in the appendix (appendix pp 11). We additionally searched the references of published meta-analyses and included articles.

After the removal of duplicates, two authors independently completed the preliminary screening (BV and MGM) based on titles and abstracts according to the eligibility criteria. In cases of disagreement, studies were retained for the next stage. Disagreements on the full-text article were resolved through consensus.

Choice of primary outcome measures

The primary outcome was mortality as the worst COVID-19 endpoint. Secondary outcomes were hospitalization and ICU admission. Risks were assessed through crude and adjusted odds ratios (OR, aOR) with related 95% confidence intervals (CI). While ORs provide information on observed outcomes, aORs provide insight into the direct risks after controlling for possible confounders. An OR and its 95% CIs greater than 1 indicate an increased likelihood of severe COVID-19 outcomes in psychiatric patients compared to controls. For each outcome, we considered different exposure variables: pre-existing mental disorders (i.e., schizophrenia and psychotic disorders, bipolar and depressive disorders, anxiety and stress-related disorders, substance use disorders, and intellectual disability and developmental disorders), as well as treatment with psychopharmacological compounds (i.e., antipsychotics, anxiolytics, and antidepressants; appendix pp 12). When crude and adjusted OR were concordant, exposures were considered to be consistently associated with the COVID-19 outcome.

Data extraction

For each study, we extracted meta-analytic data (appendix pp 13). When crude ORs were not reported in the full text, they were calculated using sample sizes for groups of interest. For zero count cells, modified Haldane-Anscombe correction was applied.[13] To account for the effect of relevant covariates, when multiple aORs were reported in the same study, we selected the model most similar to the one adjusted for age, sex, and comorbidities.

To reduce the risk of selective reporting bias, when studies did not present sufficient meta-analytical data, corresponding authors were contacted by email to retrieve additional information. Two authors extracted data independently (CDC and MF) and two other independent authors (BV and MGM) cross-checked the data extraction.

Data Analyses

For both primary and secondary outcomes, effect size measures were crude and adjusted ORs, indexing the association between exposure variables and severe COVID-19 outcomes. We applied DerSimonian and Laird random-effects models expecting high heterogeneity, which was assessed through the I^2 statistics (25% low, 50% moderate, 75% high).[14] E-values were calculated to assess evidence for causality between the exposure and outcome variables.[15]

For each outcome, the primary meta-analysis assesses the risks associated with any pre-existent mental disorder; findings are presented in forest plots. Different clinical samples compared to the same or overlapped control group, were combined creating a single pair-wise comparison.[14] We performed leave-one-out and Hartung-Knapp-Sidik-Jonkman (HKSJ) random-effects meta-analyses as sensitivity analyses.[14]

Secondary analyses were performed stratifying by diagnostic category and psychopharmacological drug class. We also tested the between-group effect of severe mental illness (defined as psychotic and mood disorders) versus other mental disorders.

For all outcome measures, we tested the effect of the following covariates in subgroup analyses or meta-regressions: a) country of the population studied; b) COVID-19 pandemic phase (meta-regression with two predictors: starting month of recruitment from December 2019 and duration of recruitment in months); c) NOS quality assessment; d) minimum age of the recruited cohort, comparing studies which recruited only participants aged 45 years or above to those with a wider aged cohort; and e) sample size of psychiatric and control populations. For mortality and ICU admission, we additionally evaluated the effect of the baseline COVID-19 treatment setting of the study sample (hospitalized or not). For the aOR analysis, we explored differences between models that did or did not adjust for relevant covariates (age, sex, race/ethnicity, and other comorbidities).

Publication bias was explored using visual inspection of funnel plots and with Egger linear regression test.[14] The overall strength of the evidence was assessed according to the GRADE approach.[16] All analyses were performed two-sided in Comprehensive Meta-Analysis Version 3.3.070 (Copyright ©2006-2021Biostat, Inc.), except for HKSJ, which was performed in R. The statistical threshold was Bonferroni corrected ($p<0.05/3=0.0167$) to account for multiple testing of the three COVID-19 outcomes.

Study quality

We assessed the quality of eligible observational studies using the Newcastle Ottawa Scale for cohort studies (NOS).[17] A higher score indicates higher methodological quality. Quality assessment was independently conducted by two authors (BV and MGM), and any disagreement was resolved by discussion.

Results

The systematic search identified 841 studies, 33 of which met the inclusion criteria (Figure 1, Tables 1, 2, appendix pp 14-20).[4,7-10,18-45] The total meta-analysis sample included 1,469,731 participants affected by COVID-19 (43,938 psychiatric patients), recruited in 22 countries (Tables 1, 2) with outcome data between 1 December 2019 and 30 November 2020. The sample was composed of 130,807 females (8·90% of the whole sample) and 130,373 males (8·87%). Nine studies included data for race/ethnicity (appendix pp 21-22). Ten studies included in the systematic review were excluded from the meta-analysis: four reported overlapping samples,[23,40,42,43] two had no meta-analyzable data,[19,20] three did not differentiate between death, hospitalization, or ICU admission,[41,44,45] and one included a control group with unknown SARS-CoV-2 infection status[18] (Table 2, appendix pp 23). A final number of 23 studies was included in the meta-analyses. 22 reported mortality outcome data (Table 1, appendix pp 14-20), while the rates of hospitalization and ICU admission were reported in nine and ten studies, respectively.

The presence of any comorbid mental illness was significantly associated with an increased risk of death following COVID-19 (Figure 2 and appendix pp 24). In sensitivity analyses all the results remained statistically significant (appendix pp 25-26), suggesting consistent effects across samples and models. E-values of 3·41 for crude models and 1·95 for adjusted models indicate that substantial confounding would be required to explain away the observed effect. Heterogeneity was high for crude ($I^2=92·66$, $Q=272·58$, $df=20$, $p=0·00011$) and low for adjusted models ($I^2=39·30$,

Q=16·47, df=10, p=0·087). Exploring COVID-19 mortality by psychiatric disorders (Figure 3 and appendix pp 27-30), the most robust significant associations were found for mortality risk in psychotic and mood disorders. Substance use disorders and intellectual disabilities and developmental disorders were associated with higher mortality only in crude estimates. No significant effects were found for anxiety disorders. For exposure to drug classes (appendix pp 28-30), antipsychotics were consistently associated with the highest mortality risks (Crude OR: 3·71, 95% CI 1·74-7·91, I^2=90·31, E=6·88; aOR: 2·43, 95% CI 1·81-3·25, I^2=61·35, E=4·29), as were anxiolytics (Crude OR: 2·58, 95% CI 1·22-5·44, I^2=96·42, E=4·60; aOR: 1·47, 95% CI 1·15-1·88, I^2=0, E=4·29). Antidepressant exposure was only associated with increased mortality risk in crude estimates (Crude OR: 2·23, 95% CI 1·06-4·71, I^2=95·45, E=3·89; aOR: 1·18, 95% CI 0·93-1·50, I^2=0, E=1·64).

The risk of hospitalization following SARS-CoV-2 infection was significantly higher in people with any pre-existing mental disorder (Figure 4 and appendix pp 31). Sensitivity analyses detected significant effects in all the results (appendix pp 32-33). High heterogeneity was detected for both crude and adjusted models (Crude OR: I^2=88·85, Q=71·72, df=8, p<0·0001; aOR: I^2=90·99, Q=55·5, df=5, p<0·0001), warranting further exploration of covariates. Stratifying for disorders (appendix pp 34), the most robust finding was found in patients with a comorbid substance use disorder (Crude OR: 2·66, 95% CI 1·79-3·95, I^2=91·3, E=4·76; aOR: 1·87, 95% CI 1·16-3·03, I^2=94·5, E=2·24), whereas effects for psychotic disorders were not significant (Crude OR: 1·68, 95% CI 0·86-3·29, I^2=57·62, E=2·75; aOR: 1·34, 95% CI 0·61-2·94, I^2=72·4, E=2·01). The evidence for mood disorders was inconsistent between crude and adjusted estimates (Crude OR: 2·26, 95% CI 1·33-3·86, I^2=87·9, E=3·95; aOR: 1·26, 95% CI 0·64-2·50, I^2=23·1; E=1·83).

We did not find robust evidence of an increased risk of ICU admission for patients with mental disorders (Crude OR: 1·77, 95% CI 1·09-2·89; aOR: 1·33, 95% CI 0·87-2·04, appendix pp 35-36). Sensitivity analyses highlighted an effect of single studies on the overall estimates (appendix pp 37-38). A high degree of unaccounted heterogeneity was present (Crude OR: I^2=93·01, Q=128·76, df=9, p<0·0001; aOR: I^2=89·51, Q=57·21, df=6, p<0·0001) and explored through diagnostic categories (appendix pp 39-40). After correction for multiple comparisons, no diagnostic category was found to be consistently associated with an increased risk for ICU admission. There was insufficient evidence to estimate the hospitalization and ICU admission risks associated with exposure to psychopharmacological drug classes. Patients with severe mental illness had higher mortality estimates (Crude OR: 2·21, 95% CI 1·63-2·99, I^2=81·93, E=3·85; aOR: 1·55, 95% CI 1·30-1·85, I^2=28·78, E=2·47, appendix pp 28-30) than patients with other mental disorders (Crude OR: 1·62, 95% CI 1·27-2·08, I^2=88·63, E=2·62; aOR: 1·09, 95% CI 0·92-1·29, I^2=0, E=1·40) with a significant difference between adjusted estimates (Crude OR: p=0·13; aOR: p=0·0047). Differences in hospitalization and ICU admission rates were not significant (appendix pp 34, 39-40).

Baseline treatment setting for COVID-19 significantly affected crude effect size estimates for mortality and ICU admission (Mortality: p=0·013; ICU admission: p<0·0001) and reduced the initially detected heterogeneity (appendix pp 28-30, 39-40). Significantly higher mortality and ICU admission estimates were found among non-hospitalized samples (Mortality OR 2·34, 95% CI: 1·82-3·00, I^2=90·92; ICU admission OR 2·39, 95% CI 1·81-3·15, I^2=62·05). In study samples that included only hospitalized patients, odds ratios of mortality and ICU admission were not significantly increased compared to controls (Mortality OR: 1·21, 95% CI 0·77-1·90, I^2=91·26; ICU admission OR: 0·85, 95% 0·58-1·24, I^2=44·62). The country of the population studied had a significant effect on both crude and adjusted mortality estimates (Crude OR: p<0·0001; aOR: p=0·0071), with lower mortality effect sizes in samples from European countries and the US (appendix pp 28-30). No significant effects were detected by country for ICU risk, nor for COVID-19 pandemic phases, NOS quality assessment, the minimum age of the recruited sample, or the

study sample sizes for any outcome. Exploring differences between covariate-adjusted models, no significant differences were detected between models which did and did not adjust for race/ethnicity or other comorbidities.

In the quality assessment of the 33 peer-reviewed studies, 22 were rated as high quality, eight as moderate quality, and three as low quality (appendix pp 41-42). GRADE assessment revealed high certainty for estimates of the primary outcome and of crude hospitalization, moderate certainty for adjusted hospitalization and crude ICU admission. Adjusted ICU admission estimates, however, were rated as very low certainty (appendix pp 43-44). Visual inspection of funnel plots (appendix pp 45-47) and the Egger test did not reveal evidence of publication bias (appendix pp 48).

Discussion

Our results highlight the increased risk of COVID-19 mortality for patients affected by mental disorders. We found consistent evidence that patients with psychotic and mood disorders, as well as those taking antipsychotics or anxiolytics, represent vulnerable subgroups. While psychiatric patients, especially with substance use disorders, demonstrated higher risks of hospitalization, these effects were not detected for ICU admission risk and psychotic patients. A similar pattern emerged for mortality in severe mental illness: patients with psychotic and mood disorders, when pooled together, had larger odds ratios for mortality but not for hospitalization and ICU admission compared to other mental disorders.

Our findings reflect the overall evidence of increased all-cause mortality in people with mental disorders, in particular in psychotic disorders, followed by mood disorders.[46] Notably, emerging preliminary data (not peer-reviewed as of 22 May 2021) showed that mortality risk related to COVID-19 is higher compared to other conditions for psychiatric patients, especially those with schizophrenia or bipolar disorder.[47] An increased risk of COVID-19 mortality may reflect biological processes: immune-inflammatory alterations, including immunogenetic abnormalities, elevated cytokines, autoantibodies, acute-phase proteins, and aberrant counts of leukocyte cell types characterize psychiatric disorders.[48,49]Abnormalities in these processes have been reported in patients with severe mental illness,[50] consistent with our findings. Moreover, chronic exposure to antipsychotics and anxiolytics was consistently associated with severe COVID-19 outcomes. Antipsychotics may precipitate cardiovascular and thromboembolic risk, may interfere with an adequate immune response, and may cause pharmacokinetic and pharmacodynamic interactions with drugs used to treat COVID-19.[51,52] Anxiolytics, especially benzodiazepines, are notably associated with respiratory risk, and are known to be associated with all-cause mortality.[53] On the other hand, antidepressants are associated with a lower risk of severe respiratory and cardiovascular side effects, and recent findings support possible anti-inflammatory and antiviral properties of serotonergic antidepressants repurposed for COVID-19.[54,55] Although we did not find evidence for such a protective effect of antidepressants, this could have been confounded by the psychiatric indication. Unlike antipsychotics and anxiolytics, the mortality risk associated with antidepressants was not increased after adjustment for age, sex, and other covariates.

Besides the pathophysiological underpinnings of the psychiatric illness and/or its treatment, social and lifestyle factors (e.g., diet, physical inactivity, social isolation, elevated alcohol and tobacco use, and sleep disturbances) and a higher prevalence of somatic comorbidities (e.g., diabetes, cardiovascular disease, and respiratory disease)[19,56] may also exert detrimental effects on COVID-19 prognosis.[57]

Our findings indicate that the increased mortality of psychiatric patients—in particular, patients with psychotic disorders—may also reflect reduced access to optimal care, previously described in relation to nearly every aspect of somatic healthcare in this population.[58] Supporting the detrimental potential role of poor access to COVID-19 healthcare, we did not observe that a higher mortality risk was paralleled by a higher risk of ICU admission in all

psychiatric patients or a higher risk of hospitalization in psychotic patients. Furthermore, while mortality was increased among non-hospitalized psychiatric patients, we did not find evidence of increased in-hospital mortality.

Mortality was also significantly different among countries, with lower risk in Europe and the US. This effect may be related to several factors, including differences in healthcare systems or accessibility to care among countries, also related to the dynamics of the pandemic or possible interactions with race and ethnicity.[59,60] Although our data did not allow us to specifically explore these associations, models adjusting for ethnicity and race were not found to be significantly different from models not controlling for this factor, and variables related to COVID-19 pandemic phase, such as starting month of study recruitment and its duration, did not influence our results

Similar to a previously published meta-analysis,[3] we detected an overall high heterogeneity, that we significantly reduced in adjusted estimates and by stratification for mental disorders, pharmacological treatments, baseline COVID-19 treatment setting, and country. This confirms the relevance of these variables in affecting COVID-19 outcomes and the strength of the current study. Moreover, most of the included studies (67%) were rated as high quality, and we did not find evidence of publication bias. A further advantage of the current study is that we only included patients with confirmed SARS-CoV-2 infection status, thus, the observed risks for severe or fatal COVID-19 are not caused by higher infection rates previously observed in psychiatry.[32,61]

Nevertheless, several limitations should be acknowledged. Although we stratified risk estimates for psychiatric diagnosis, pharmacological drug class, and baseline treatment setting for COVID-19, we cannot disentangle the specific risks attributable to each of these variables. Specifically, we cannot disentangle the association of COVID-19 prognosis with psychotropic medications from that of the underlying psychiatric conditions. Most of the included evidence relied on electronic medical records that may not allow a fine-grained analysis of clinical variables.[62] For example, no studies included in our meta-analysis distinguished between unipolar and bipolar mood disorders. These disorders may be subject to different COVID-19 outcomes, as suggested by emerging preliminary data showing higher mortality in bipolar disorders compared to other mood disorders.[47] Notwithstanding the evidence compiled in this review, we observe that mental disorders remain unaccounted for in many studies assessing COVID-19 outcomes, even when psychotropic compounds are included as exposure variables, thus impeding a full assessment of confounding. Furthermore, it is possible that unmeasured confounders associated with both the COVID-19 outcome and the psychiatric disorders by a risk ratio of twofold each for mortality and threefold each for hospitalization, above and beyond those included in our analyses, could explain away a direct causal relationship.

Finally, although non-significant associations may suggest evidence of unchanged risk in mental disorders, they can also relate to a lack of power to confirm significant effects, especially in subgroup analyses. Some studies showed low quality or included small samples of psychiatric patients, contributing to a low certainty of evidence for ICU admission. More evidence is needed to determine the validity and generalizability of our results, and we recommend taking account of psychiatric comorbidity in all observational studies and prediction models of COVID-19 outcomes.

In conclusion, pre-existing mental disorders, in particular severe mental illness, intellectual disability, and substance use disorders, and chronic exposure to psychopharmacological compounds were associated with poor COVID-19 outcomes. In some European countries, patients with severe mental illness and/or intellectual disability are offered priority vaccination, while the US Centers for Disease Control and Prevention is currently recommending priority status for patients with substance use disorders.[63] The present findings should warrant public health authorities to consider priority vaccination for all groups of at-risk patients identified in this study. In addition, close monitoring and adequate hospital referral in psychiatric patients who develop COVID-19 is needed to counteract possible reduced access to care.

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There was no funding source for this study. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Ethics approval

No human subject participants were involved. The study was exempt from ethics approval.

Contribution

BV, LDP, PF-P, and IB conceptualized and initiated the study. BV, CDC, MF, and MGM screened the text. BV and MGM analyzed the data. LDP created the forest plots. BV, LDP, MGM wrote the first draft of the manuscript with input from MCD, IB, PF-P, MEB. BA proofread the manuscript as native English speaker. All authors contributed to the design of the study and the final manuscript.

Declaration of interest

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Data sharing

Study data are available on request to the authors.

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Figures

Figure 1 PRISMA Flow Diagram.

*for a detailed list of exclude studies at full-text see Appendix pp 49-51. ICU, Intensive Care Unit.

Figure 2 Forest plot of crude odds ratios of mortality pooling all mental disorders

*sample size for any mental disorder was not available, we considered data for the specific mental disorder with the largest sample size; OR, odds ratio.

Figure 3 Forest plot of crude odds ratios of mortality stratified by diagnostic category.

*sample size for any mental disorder was not available, we considered data for the specific mental disorder with the largest sample size; OR, odds ratio.

Figure 4 Forest plot of crude odds ratios of hospitalization pooling all mental disorders

*sample size for any mental disorder was not available, we considered data for the specific mental disorder with the largest sample size; OR, odds ratio.

Tables

Table 1: Studies included in meta-analysis

GeMRC, Geriatric Medicine Research Collaborative; ICU, Intensive Care Unit; NA, Not Available; OR, Odds Ratio. Age is presented as mean and standard deviations, *Median and interquartile range, **Egypt, Greece, Ireland, Iraq, Italy, Libya, Saudi Arabia, Spain, Sudan, Turkey, UK, US

Table 2: Studies included in the systematic review

Adj, Adjusted; ICU, Intensive Care Unit, NA, Not Available; OR, Odds Ratio; SSRI, Selective Serotonin Reuptake Inhibitors; SUD, Substance Use Disorder.