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

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Summary

Background Mental disorders might be a risk factor for severe COVID-19. We aimed to assess the specific risks of COVID-19-related mortality, hospitalisation, and intensive care unit (ICU) admission associated with any pre-existing mental disorder, and specific diagnostic categories of mental disorders, and exposure to psychopharmacological drug classes.

Methods In this systematic review and meta-analysis, we searched Web of Science, Cochrane, PubMed, and PsycINFO databases between Jan 1, 2020, and March 5, 2021, for original studies reporting data on COVID-19 outcomes in patients with psychiatric disorders compared with controls. We excluded studies with overlapping samples, studies that were not peer-reviewed, and studies written in languages other than English, Danish, Dutch, French, German, Italian, and Portuguese. We modelled random-effects meta-analyses to estimate crude odds ratios (OR) for mortality after SARS-CoV-2 infection as the primary outcome, and hospitalisation and ICU admission as secondary outcomes. We calculated adjusted ORs for available data. Heterogeneity was assessed using the I^2 statistic, and 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 assess study quality. We also did 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. This study is registered with PROSPERO, CRD42021233984.

Findings 841 studies were identified by the systematic search, of which 33 studies were included in the systematic review and 23 studies in the meta-analysis, comprising 1 469 731 patients with COVID-19, of whom 43 938 had mental disorders. The sample included 130 807 females (8·9% of the whole sample) and 130 373 males (8·8%). 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 also observed for psychotic disorders (2·05 [1·37–3·06]; I^2=80·81%), mood disorders (1·99 [1·46–2·71]; I^2=68·32%), substance use disorders (1·76 [1·27–2·44]; I^2=47·90%), and intellectual disabilities and developmental disorders (1·73 [1·29–2·31]; I^2=90·15%) but not for anxiety disorders (1·07 [0·73–1·56]; I^2=11·05%). COVID-19 mortality was associated with exposure to antipsychotics (3·71 [1·74–7·91]; I^2=90·31%), anxiolytics (2·58 [1·22–5·44]; I^2=96·42%), and antidepressants (2·23 [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 associated with increased risk of hospitalisation (2·24 [1·70–2·94]; I^2=88·80%). No significant associations with mortality were identified for ICU admission. Subgroup analyses and meta-regressions showed significant associations of baseline COVID-19 treatment setting (p=0·013) and country (p<0·0001) with mortality. No significant associations with mortality were identified for other covariates. No evidence of publication bias was found. GRADE assessment indicated high certainty for crude mortality and hospitalisation, and 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. Although further research is required to determine the underlying mechanisms, our findings highlight the need for targeted approaches to manage and prevent COVID-19 in at-risk patient groups identified in this study.

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Introduction

According to WHO, as of May 22, 2021, 166 million confirmed cases of COVID-19 and more than 3 million deaths had been reported.[1] Several risk factors for severe COVID-19 illness and mortality, including age, male sex, obesity, and cardiovascular disease have been identified

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For the Italian translation of the abstract see Online for appendix 1

For the French translation of the abstract see Online for appendix 2

For the Portuguese translation of the abstract see Online for appendix 3

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Research in context

Evidence before this study

Several studies have found that patients with psychiatric disorders are at increased risk of severe COVID-19, but results are conflicting in the context of different patient groups and COVID-19 outcomes. Reliable risk estimates of separate COVID-19 outcomes, including mortality, hospitalisation, and intensive care unit (ICU) admission, by specific mental disorders and psychopharmacological drug classes, are required for actionable risk stratification. We searched PubMed from database inception to March 5, 2021, using the search terms "(psychiatr* OR mental OR psychopharm* OR psychotrop*) AND COVID* AND (meta-analysis OR systematic review)", without language restrictions. Eligible publications were meta-analyses of studies investigating risks of COVID-19 mortality, hospitalisation, or ICU admission associated with pre-existing mental disorders or chronic use of psychopharmacological treatments. We excluded study protocols. Of 271 records, only one meta-analysis was identified, which provided a pooled estimate of fatal and severe COVID-19 outcomes in patients with any mental disorder. No studies investigated the risks associated with exposure to psychopharmacological compounds, or differentiated between diagnostic groups.

Added value of this study

We identified strong evidence that patients with mental disorders are at higher risk of mortality and hospitalisation, but not ICU admission, after SARS-CoV-2 infection. Psychotic and mood disorders were consistently associated with COVID-19-associated mortality, as were exposure to antipsychotic and anxiolytic treatments. Patients with substance use disorders were at increased risk of hospitalisation, whereas no increased risk of hospitalisation was identified among patients with psychotic disorders. Our findings show marked differentiation in COVID-19 outcomes among different mental disorders.

Implications of all the available evidence

Our meta-analysis confirms an increased risk of mortality and hospitalisation after SARS-CoV-2 infection among patients with pre-existing mental disorders. Public health authorities should prioritise vaccination and ensure access to physical health care among at-risk individuals identified in this study.

since the early phases of the pandemic.[2] Evidence from a meta-analysis 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 could contribute to this association, including a higher prevalence of somatic comorbid risk factors, reduced access to appropriate physical health care among patients with mental disorders, and immunological disturbances associated with psychiatric disorders or treatment.[4,5]

The risks of poor COVID-19 outcomes might differ between psychiatric disorders, and patients with severe mental illness (usually including psychotic and mood disorders) have been suggested to be particularly susceptible.[6] Increased risks of COVID-19 mortality and intensive care unit (ICU) admission have also been associated with psychopharmacological treatments.[7,8] Although some studies have demonstrated higher COVID-19 mortality in patients with mental disorders, the studies did not identify higher risk of hospital admission or ICU admission.[7,9,10] Hence, providing summarised 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 might prompt new evidence-based action from clinicians and policy makers. Most European countries have not included psychiatric disorders as risk comorbidities eligible for vaccine prioritisation, which could lead to detrimental outcomes for patients and communities.[11] The primary aim of our systematic review and meta-analysis was to determine the mortality risk associated with COVID-19 in patients with pre-existing mental disorders or those exposed to psychopharmacological treatments. We also aimed to assess the risks of hospitalisation and ICU admission in these patients.

See Online for appendix 4

Methods

Overview

We did a systematic review and meta-analysis of studies reporting risk estimates for mortality, hospitalisation, and ICU admission in people with mental disorders compared with people without mental disorders after infection with SARS-CoV-2. This review was registered with PROSPERO (ICRD42021233984) and was reported according to the PRISMA reporting guidelines (appendix 4 pp 8–10).[12] Amendments to the protocol and associated sensitivity analyses are included in appendix 4 (pp 2–7).

Search strategy and selection criteria

We used a multistep procedure to search for articles published between Jan 1, 2020, and March 5, 2021, on Web of Science, Cochrane, PubMed, and PsycINFO databases in English, Danish, Dutch, French, German, Italian, or Portuguese languages. English language search terms were as follows: COVID, SARS-CoV-2, hospitalization, hospital admission, intensive care, emergency department, mortality, death, psychiatry*, mental*, neuropsych*, personality disorder*, mood disorder*, affective disorder*, depressi*, anxi*, obsessive compulsive, OCD, panic, post-traumatic*, PTSD, bipolar disorder*, mania, manic, schizophren*, mental

retardation, intellectual disability, autis*, attention deficit, ADHD, eating disorder*, substance abuse, substance dependence, alcohol use, anorexia, bulim*, alcohol use, schizoaffect*, psychotic, psychosis, DSM, antipsychotic*, antidepressant*, lithium, risk, odds ratio, and hazard ratio. Full search terms are included in appendix 4 (p 11). We additionally searched the references of published meta-analyses and included articles.

We included cross-sectional or longitudinal studies published in peer-reviewed journals; studies that included patients with mental disorders; studies in which psychiatric diagnosis and exposure to psychopharmacological treatments preceded SARS-CoV-2 infection (based on a positive PCR assay or clinical diagnosis made by physicians); and studies reporting association measures (odds ratio [OR], risk ratio, hazard ratio, or associated metrics) with COVID-19 mortality or associated hospitalisation, or ICU admission.

We excluded studies that did not include patients with pre-existing mental disorders or a control group without mental disorders; studies that did not investigate associations between mental disorders and severe COVID-19 outcomes; reviews, clinical case reports, abstracts, conference proceedings, preprints, or studies that had not been peer-reviewed; and duplicate publications. When two or more studies included the same clinical population and reported an overlapping sample, the study with the smallest dataset was excluded from the meta-analysis, but included in the narrative review (and classified as an overlapping sample).

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

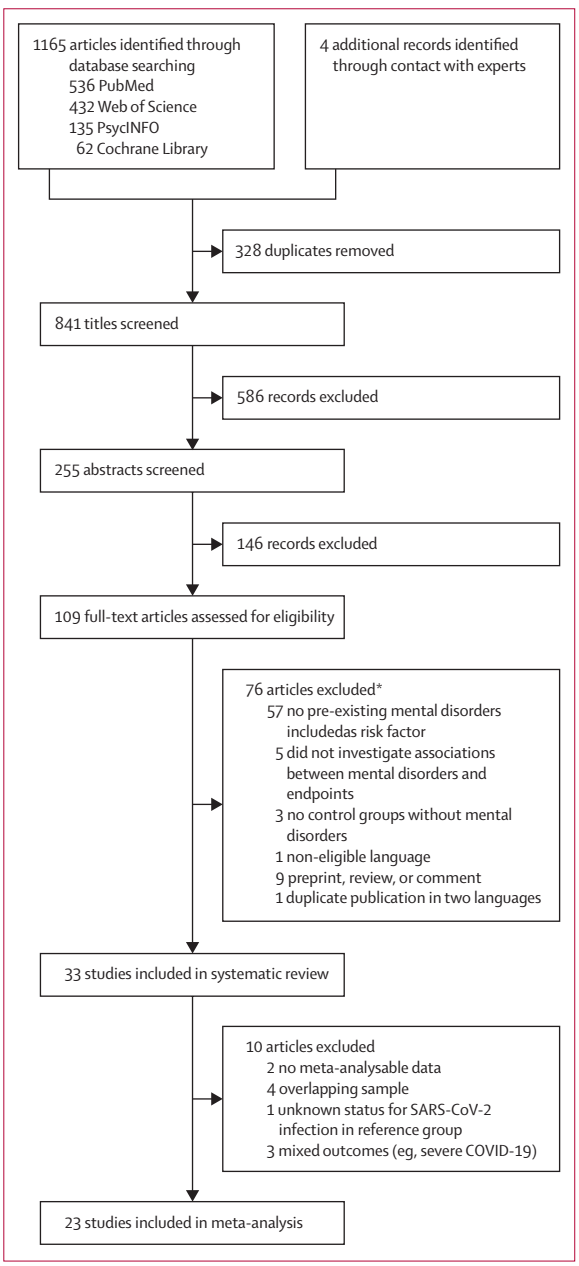

Figure 1: **Study selection**
*A full list of studies excluded after full-text screening is included in appendix 4 (pp 49–51).

Outcomes

The primary outcome was mortality after COVID-19. Secondary outcomes were hospitalisation and ICU admission after COVID-19. Risks were assessed through the estimation of pooled crude ORs and adjusted ORs (aORs) and associated 95% CIs. For each outcome, we considered the exposure variables: pre-existing mental disorders (ie, schizophrenia and psychotic disorders, bipolar and depressive disorders, anxiety and stress-related disorders, substance use disorders, and intellectual disability and developmental disorders), and treatment with psychopharmacological compounds (ie, antipsychotics, anxiolytics, and antidepressants) initiated before the individual contracted COVID-19 (appendix 4 pp 12). When crude ORs and aORs were concordant, exposures were considered to be consistently associated with the COVID-19 outcome.

We assessed the quality of eligible observational studies using the Newcastle Ottawa Scale for cohort studies,[13] whereby a higher score indicated higher methodological quality. Quality assessment was done independently by two authors (BV and MGM), and any disagreement was resolved by discussion.

Data extraction

For each study, we extracted meta-analytic data, including the following: country; age and male-to-female ratio of participants; diagnosis or psychopharmacological drug class; crude ORs, aORs, and related CIs for death, hospitalisation, and admission to ICU; index and group

	Setting	Study design	Study period	Mean age of participants, years (SD)	Study participants, n (%)	Sample size		Outcomes		
						Patients, n	Controls, n	Mortality OR (95% CI)	ICU admission OR (95% CI)	Hospitalisation OR (95% CI)
Allen et al (2020)[21]	USA	Retrospective	Jan 1–Oct 26, 2020	NA	6135 females (51·9%), 5695 males (48·1%)	..	..	..	..	..
Any substance use disorder	..	..	..	..	..	395	11 435	1·57 (1·17–2·10)	3·23 (2·54–4·09)	4·80 (3·76–6·12)
Alcohol use disorder	..	..	..	..	..	188	11 642	1·20 (0·76–1·90)	3·20 (2·29–4·48)	6·67 (4·51–9·88)
Opioid use disorder	..	..	..	..	..	70	11 760	1·59 (0·91–3·12)	3·02 (1·74–5·24)	5·46 (2·99–9·99)
Cannabis use disorder	..	..	..	..	..	74	11 756	0·54 (0·20–1·49)	1·13 (0·54–2·36)	3·60 (2·14–6·08)
Cocaine use disorder	..	..	..	..	..	40	11 790	0·77 (0·24–2·50)	1·04 (0·37–2·92)	2·57 (1·33–4·99)
Drug overdose	..	..	..	..	..	74	11 756	4·94 (3·04–8·03)	7·70 (4·85–12·23)	9·02 (4·49–18·12)
An et al (2020)[22]	South Korea	Retrospective cohort	Jan 23–April 2, 2020	45·0 (20)	6149 females (60·0%), 4088 males (40·0%)	..	..	..	..	..
Mental, behavioural, and neurodevelopmental disorders	..	..	..	..	..	497	9740	7·52 (5·50–10·28)	NA	NA
Baillargeon et al (2020)[24]	USA	Retrospective	Feb 20–June 30, 2020	50·0	31 091 females (57·1%), 22 926 males (42·0%)	..	..	..	..	..
Substance use disorder	..	..	..	..	..	5562	48 967	1·81 (1·58–2·07)	NA	2·29 (2·16–2·44)
Bellan et al (2020)[35]	Italy	Prospective cohort	March 1–June 29, 2020	60·3 (14·1)	96 females (40·0%), 142 males (60·0%)	..	..	..	..	..
Anxiety and depression	..	..	..	..	..	11	227	NA	3·03 (0·75–12·17)	NA
Bitan et al (2021)[37]	Israel	Retrospective cohort	March–October, 2020	51·4	19 934 females (39·0%), 31 144 males (61·0%)	..	..	..	..	..
Schizophrenia	..	..	..	..	..	25 539	25 539	3·14 (1·34–7·36)	NA	2·13 (1·62–2·81)
Canal-Riveiro et al (2021)[38]	Spain	Retrospective cohort	February–November, 2020	NA	NA	..	..	..	..	..
Mental illness	..	..	..	..	..	9	23 077	4·72 (0·27–81·32)	5·92 (0·34–101·99)	0·57 (0·03–9·78)
Fond et al (2020)[9]	France	Population based cohort	Feb 1–June 9, 2020	71 (57–83)*	21 932 females (46·0%), 28 818 males (54·0%)	..	..	..	..	..
Schizophrenia	..	..	..	..	..	823	49 927	1·25 (1·05–1·49)	0·78 (0·65–0·94)	NA
Geriatric Medicine Research Collaborative (2021)[39]	12 countries†	Observational	NA	74 (54–83)*	2562 females (45·0%), 3149 males (55·0%)	..	..	..	..	..
Any mental health disorder	..	..	..	..	..	482	5229	0·88 (0·71–1·09)	0·77 (0·56–1·06)	NA

(Table 1 continues on next page)

	Setting	Study design	Study period	Mean age of participants, years (SD)	Study participants, n (%)	Sample size		Outcomes		
						Patients, n	Controls, n	Mortality OR (95% CI)	ICU admission OR (95% CI)	Hospitalisation OR (95% CI)
(Continued from previous page)										
Genet et al (2020)[25]	France	Retrospective	March 17–April 18, 2020	86·3 (8)	135 females (67·0%), 66 males (33·0%)	..	..	..	..	..
Major depressive disorder	..	..	..	..	..	93	108	0·95 (0·53–1·72)	NA	NA
Antidepressant	..	..	..	..	..	108	93	0·73 (0·40–1·32)	NA	NA
Antipsychotics	..	..	..	..	..	47	154	1·37 (0·69–2·71)	NA	NA
Benzodiazepines	..	..	..	..	..	110	91	1·19 (0·66–2·15)	NA	NA
Huls et al (2021)[36]	Brazil, India, Italy, France, Spain, UK, USA, Other	Case-control study	April 9–Oct 22, 2020	NA	712 females (52·4%), 647 males (47·6%)	..	..	..	..	..
Down syndrome	..	..	..	..	..	959	400	1·36 (0·98–1·89)	NA	NA
Jeon et al (2021)[10]	South Korea	Cohort study	Dec 1, 2019–May 15, 2020	45·99	4199 females (59·0%), 2878 males (41·0%)	..	..	..	..	..
Mental and behavioural disorder	..	..	..	..	..	928	6149	7·12 (4·87–10·39)	2·31 (1·63–3·27)	0·73 (0·45–1·18)
Landes et al (2020)[26]	USA	Retrospective cohort	Up to May 28, 2020	NA	NA	..	..	..	..	..
Intellectual and developmental disabilities	..	..	..	..	..	1602	371 559	2·05 (1·78–2·35)	NA	NA
Landes et al (2021)[28]	USA	Retrospective cohort	May 2–Oct 2, 2020	NA	NA	..	..	..	..	..
Intellectual and developmental disabilities	..	..	..	..	..	2948	816 488	2·93 (2·50–3·43)	NA	NA
Lee et al (2020)[29]	South Korea	Cohort	Jan 1–May 15, 2020	47·8 (18·7)	4291 females (60·0%), 2869 males (40·0%)	..	..	..	..	..
Any mental disorders	..	..	..	..	..	1443	5717	4·85 (3·71–6·33)	2·44 (1·83–3·25)	NA
Li et al (2020)[30]	USA	Prospective cohort	Feb 15–April 25, 2020	65·2 (18·4)	798 females (47·0%), 887 males (53·0%)	..	..	..	..	..
Any psychiatric disorders	..	..	..	..	..	473	1212	2·61 (2·03–3·36)	NA	NA
Nemani et al (2021)[4]	USA	Retrospective cohort	March 3–May 31, 2020	54 (18·6)	3891 females (53·0%), 3457 males (47·0%)	..	..	..	..	..
Schizophrenia–lifetime	..	..	..	..	..	75	6349	2·93 (1·75–4·92)	2·18 (1·33–3·58)	NA
Lifetime mood disorders	..	..	..	..	..	564	6349	1·82 (1·45–2·29)	1·45 (1·18–1·78)	NA
Lifetime anxiety disorders	..	..	..	..	..	360	6349	0·98 (0·70–1·38)	1·07 (0·81–1·41)	NA

(Table 1 continues on next page)

	Setting	Study design	Study period	Mean age of participants, years (SD)	Study participants, n (%)	Sample size		Outcomes		
						Patients, n	Controls, n	Mortality OR (95% CI)	ICU admission OR (95% CI)	Hospitalisation OR (95% CI)
(Continued from previous page)										
Poblador-Plou et al (2020)[8]	Spain	Retrospective cohort	March 4–April 17, 2020	67·7 (20·7)	2593 females (59·0%), 1821 males (41·0%)	..	..	..	..	..
Mood disorders	..	..	..	..	..	728	3684	2·10 (1·75–2·53)	NA	NA
Anxiety disorders	..	..	..	..	..	714	3684	0·96 (0·77–1·18)	NA	NA
Developmental disorders	..	..	..	..	..	110	4302	1·56 (1·00–2·42)	NA	NA
Antidepressants	..	..	..	..	..	714	3698	2·63 (2·19–3·16)	NA	NA
Antipsychotics	..	..	..	..	..	348	4064	4·32 (3·43–5·42)	NA	NA
Psychostimulants	..	..	..	..	..	55	4357	3·47 (2·02–5·96)	NA	NA
Anxiolytic	..	..	..	..	..	508	3904	2·12 (1·71–2·61)	NA	NA
Reilev et al (2020)[7]	Denmark	Cohort	Feb 27–May 19, 2020	48 (33–62)*	6430 females (57·8%), 4692 males (42·2%)	..	..	..	..	..
Alcohol abuse	..	..	..	..	..	298	10 824	2·70 (1·90–3·90)	1·87 (1·10–3·18)	2·50 (2·00–3·20)
Major psychiatric disorder	..	..	..	..	..	76	11 046	3·80 (2·10–7·00)	2·99 (1·29–6·93)	3·00 (1·90–4·80)
Substance abuse	..	..	..	..	..	185	10 937	2·40 (1·50–3·80)	NA	1·80 (1·30–2·40)
Benzodiazepines	..	..	..	..	..	538	10 584	6·00 (4·80–7·50)	1·90 (1·27–2·84)	4·00 (3·40–4·70)
Antipsychotics	..	..	..	..	..	262	10 860	7·10 (5·30–9·50)	1·83 (1·04–3·24)	3·20 (2·50–4·10)
Antidepressants	..	..	..	..	..	996	10 126	4·80 (3·90–5·80)	1·78 (1·29–2·45)	2·90 (2·50–3·30)
Siso-Almirall et al (2020)[31]	Spain	Retrospective cohort	Feb 29–April 4, 2020	56·7 (17·8)	161 females (50·0%), 161 males (50·0%)	..	..	..	..	..
Depression	..	..	..	..	..	18	304	2·25 (0·48–10·64)	0·83 (0·18–3·72)	9·13 (2·06–40·38)
Turk et al (2020)[27]	USA	Retrospective cohort	Jan 20–May 14, 2020	NA	16 728 females (55·2%), 13 546 males (44·7%)	..	..	..	..	..
Intellectual and developmental disability	..	..	..	..	..	474	29 808	0·93 (0·62–1·41)	NA	NA
Yanover et al (2020)[33]	Israel	Cohort	Up to April 22, 2020	38·4 (20·6)	1939 females (44·5%), 2414 males (55·5%)	..	..	..	..	..
Depression	..	..	..	..	..	578	3775	7·30 (3·09–17·28)	3·13 (1·85–5·29)	2·71 (2·16–3·39)

(Table 1 continues on next page)

	Setting	Study design	Study period	Mean age of participants, years (SD)	Study participants, n (%)	Sample size		Outcomes		
						Patients, n	Controls, n	Mortality OR (95% CI)	ICU admission OR (95% CI)	Hospitalisation OR (95% CI)
(Continued from previous page)										
Yang et al (2020)[32]	UK	Prospective cohort	Jan 31–July 26, 2020	67·8 (8·1)	1031 females (52·8%), 920 males (47·2%)	..	..	..	..	..
Any psychiatric disorders	..	..	..	..	..	442	1509	1·82 (1·42–2·34)	NA	1·60 (1·25–2·04)
Depression	..	..	..	..	..	231	1720	1·91 (1·40–2·60)	NA	1·34 (0·98–1·83)
Anxiety disorders	..	..	..	..	..	165	1786	1·33 (0·91–1·94)	NA	1·38 (0·96–1·99)
Stress-related disorders	..	..	..	..	..	10	1941	1·80 (0·46–7·00)	NA	1·04 (0·27–4·03)
Substance misuse	..	..	..	..	..	212	1739	1·38 (0·98–1·93)	NA	2·12 (1·48–3·04)
Psychotic disorders	..	..	..	..	..	19	1932	3·09 (1·23–7·74)	NA	0·96 (0·36–2·55)
Zimering et al (2020)[34]	USA	Retrospective cohort	March– June, 2020	70·6 (11·5)	53 males (100·0%)	..	..	..	..	..
Psychiatric disorders	..	..	..	..	..	11	42	0·36 (0·07–1·89)	NA	NA

The leftmost column shows the exposure variables investigated within a study. ICU=intensive care unit. NA=not available. OR=odds ratio. *Median (IQR). †Egypt, Greece, Ireland, Iraq, Italy, Libya, Saudi Arabia, Spain, Sudan, Turkey, the UK, and the USA.

Table 1: **Characteristics of studies included in the meta-analysis**

sample sizes; and covariates included in the models for aOR (appendix 4 p 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, we applied modified Haldane-Anscombe correction.[14] 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 model 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 independent authors (BV and MGM) cross-checked the data extraction.

Data analysis

For both primary and secondary outcomes, effect size measures were crude and adjusted ORs. We applied DerSimonian and Laird random-effects models, considering the possible high heterogeneity related to the outcomes, which was assessed using the Cochran's Q and I^2 statistics (with heterogeneity classified as low [I^2=25–49%], moderate [I^2=50–74%], or high [I^2>75%]).[15] To assess the evidence for causality between the exposure and outcome variables, we calculated E-values (defined as "the minimum strength of association, on the risk ratio scale, that an unmeasured confounder would need to have with both the exposure and the exposure-outcome to fully explain away a specific treatment–outcome association, conditional on the measured covariates").[16] Larger E-values indicate a greater amount of unmeasured confounding is needed to explain away an effect estimate.[16]

For each outcome, the primary meta-analysis assessed the risks associated with any pre-existent mental disorder; findings were presented in forest plots. Different clinical samples comparing the same or overlapping control groups were combined creating a single pair-wise comparison.[15] We did leave-one-out and Hartung-Knapp-Sidik-Jonkman random-effects meta-analyses as sensitivity analyses.[15]

For secondary analyses, we stratified 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: country of the population studied; COVID-19 pandemic phase (meta-regression with two predictors: starting month of recruitment from December, 2019, and duration of recruitment in months); Newcastle Ottawa Scale quality assessment; minimum age of the recruited cohort (studies that recruited only participants aged ≥45 years *vs* cohorts with a wider age

range); and sample size of patients with psychiatric disorders and control populations. For mortality and ICU admission, we assessed the effect of the baseline COVID-19 treatment setting of the study sample (hospitalised or not hospitalised). For the aOR analysis, we assessed differences between models with and without adjustment for relevant covariates (age, sex, race or ethnicity, and other comorbidities).

Publication bias was assessed using visual inspection of funnel plots and Egger linear regression tests.[15] The overall

	Setting	Study design	Study period	Mean age of participants, years (SD)	Study participants, n (%)	Patients, n	Controls, n	Point estimate (95% CI) for outcome	Covariates
Atkins et al (2020)[23]*	UK	Retrospective cohort	March 16–April 26, 2020	73·1 (4·38)	121 401 females (54·9%), 147 661 males (45·1 %)	19 546	249 516	..	..
Exposure: depression									
Hospitalisation OR	..	..	..	..	..	..	..	2·15 (1·68–2·76)	NA
Hospitalisation aOR	..	..	..	..	..	..	..	2·42 (1·89–3·11)	Age and sex
Hospitalisation aOR	..	..	..	..	..	..	..	2·33 (1·80–3·01)	Age group, sex, ethnicity, education, and baseline assessment centre
Mortality OR	..	..	..	..	..	..	..	2·11 (1·32–3·39)	NA
Mortality aOR	..	..	..	..	..	..	..	2·54 (1·58–4·08)	Age and sex
Mortality aOR	..	..	..	..	..	..	..	2·52 (1·54–4·11)	Age group, sex, ethnicity, education, and baseline assessment centre
Fond et al (2020)[40]†	France	Case-control	Feb 27–April 15, 2020	62·5 (51–76)‡	499 females (46·0%), 593 males (54·0%)	15	1077	..	..
Exposure: schizophrenia									
Mortality OR	..	..	..	..	..	..	..	3·80 (1·19–12·18)	NA
Mortality aOR	..	..	..	..	..	..	..	4·36 (1·09–17·44)	Age, sex, smoking status, obesity, Charlson Comorbidity Index
Mortality aOR	..	..	..	..	..	..	..	4·28 (1·07–17·2)	Age, sex, smoking status, obesity, Charlson Comorbidity Index, and hydroxychloroquine
Mortality aOR	..	..	..	..	..	..	..	4·33 (1·08 –17·34)	Age, sex, smoking status, obesity, Charlson Comorbidity Index, and hydroxychloroquine–azithromycin combination
ICU admission OR	..	..	..	..	..	..	..	0·72 (0·16–3·23)	NA
ICU admission aOR	..	..	..	..	..	..	..	0·46 (0·10–2·18)	Age, sex, smoking status, obesity, and Charlson Comorbidity Index
ICU admission aOR	..	..	..	..	..	..	..	0·53 (0·11–2·61)	Age, sex, smoking status, obesity, Charlson Comorbidity Index, and hydroxychloroquine
ICU admission aOR	..	..	..	..	..	..	..	0·46 (0·10–2·23)	Age, sex, smoking status, obesity, Charlson Comorbidity Index, and hydroxychloroquine–azithromycin combination
Hirashima et al (2020)[41]‖	Japan	Retrospective cohort	Feb 20–April 30, 2020	47·51	21 females (34·4%), 40 males (65·6%)	2	59	..	..
Exposure: panic disorder and or obsessive-compulsive disorder									
Critical or severe COVID-19 OR	..	..	..	..	..	..	..	0·53 (0·02–11·57)	NA

(Table 2 continues on next page)

	Setting	Study design	Study period	Mean age of participants, years (SD)	Study participants, n (%)	Patients, n	Controls, n	Point estimate (95% CI) for outcome	Covariates
(Table 2 continued from previous page)									
Ji et al (2020)[42]§	South Korea	Case-control	Up to May 15, 2020	47·05 (19)	4371 females (59·5%), 2970 males (40·5%)	..	..	..	Sex, age, residence, Charlson Comorbidity Index, and health-care utilisation**
Exposure: substance use disorders									
Severe COVID-19 OR	..	..	..	..	..	86	7255	1·42 (0·81–2·49)	NA
Severe COVID-19 aOR	..	..	..	..	..	86	7255	0·58 (0·31–1·06)	As described above
Exposure: schizophrenia									
Severe COVID-19 OR	..	..	..	..	..	263	7078	1·64 (1·2–2·25)	NA
Severe COVID-19 aOR	..	..	..	..	..	263	7078	1·21 (0·82–1·76)	As described above
Exposure: mood disorders									
Severe COVID-19 OR	..	..	..	..	..	796	6545	2·64 (2·21–3·15)	NA
Severe COVID-19 aOR	..	..	..	..	..	796	6545	1·01 (0·81–1·25)	As described above
Exposure: anxiety and stress-related disorders									
Severe COVID-19 OR	..	..	..	..	..	931	6401	2·54 (2·15–3·00)	NA
Severe COVID-19 aOR	..	..	..	..	..	931	6401	0·98 (0·80–1·21)	As described above
Exposure: personality disorders									
Severe COVID-19 OR	..	..	..	..	..	13	7328	4·20 (1·37–12·87)	NA
Severe COVID-19 aOR	..	..	..	..	..	13	7328	1·44 (0·41–5·08)	As described above
Exposure: intellectual disabilities									
Severe COVID-19 OR	..	..	..	..	..	37	7304	0·81 (0·29–2·29)	NA
Severe COVID-19 aOR	..	..	..	..	..	37	7304	1·00 (0·32–3·06)	As described above
Lee et al (2020)[43]§	South Korea	Case-control	Jan 1–April 10, 2020	74·8	105 females (12·8%), 709 males (87·2%)	255	559	..	..
Exposure: mental disorders									
Mortality OR	..	..	..	..	..	..	..	1·96 (1·22–3·15)	NA
Mortality aOR	..	..	..	..	..	..	..	2·0 (1·20–3·20)	Propensity score (age, sex, index months)
McKeigue et al (2020)[45]‖	Scotland	Case-control	Up to June 6, 2020	NA	NA	..	..	..	..
Exposure: mental disorders									
Severe or fatal COVID-19 RR	..	..	..	..	..	656	19 082	4·46 (3·34–5·95)	NA
Exposure: mood disorders									
Severe or fatal COVID-19 RR	..	..	..	..	..	72	18 666	4·94 (2·24–10·92)	NA
McKeigue et al (2021)[44]‖	Scotland	Case-control	Up to June 6, 2020	NA	NA	..	..	..	Other drugs and socioeconomic status**
Exposure: anxiolytics									
Severe or fatal COVID-19 RR	..	..	..	..	..	1492	34 668	2·17 (1·46–3·23)	NA
Severe or fatal COVID-19 aRR	..	..	..	..	..	1492	34 668	1·25 (1·04–1·51)	As described above
Exposure: antipsychotic drugs									
Severe or fatal COVID-19 RR	..	..	..	..	..	677	35 483	4·18 (3·42–5·11)	NA
Severe or fatal COVID-19 aRR	..	..	..	..	..	677	35 483	2·80 (2·24– ·51)	As described above
Exposure: tricyclic and related antidepressant drugs									
Severe or fatal COVID-19 RR	..	..	..	..	..	3029	33 131	1·86 (1·36–2·54)	NA
Severe or fatal COVID-19 aRR	..	..	..	..	..	3029	33 131	1·10 (0·94–1·27)	As described above
Exposure: selective serotonin reuptake inhibitors									
Severe or fatal COVID-19 RR	..	..	..	..	..	3213	32 947	1·60 (1·40–1·83)	NA
Severe or fatal COVID-19 aRR	..	..	..	..	..	3213	32 947	1·18 (1·03–1·36)	As described above

(Table 2 continues on next page)

	Setting	Study design	Study period	Mean age of participants, years (SD)	Study participants, n (%)	Patients, n	Controls, n	Point estimate (95% CI) for outcome	Covariates
(Table 2 continued from previous page)									
Exposure: drugs used for mania and hypomania									
Severe or fatal COVID-19 RR	..	..	..	..	..	77	36 083	2·53 (1·26–5·10)	NA
Severe or fatal COVID-19 aRR	..	..	..	..	..	77	36 083	0·93 (0·43–1·98)	As described above
Exposure: other antidepressant drugs									
Severe or fatal COVID-19 RR	..	..	..	..	..	1820	34 340	2·71 (2·34–3·14)	NA
Severe or fatal COVID-19 aRR	..	..	..	..	..	1820	34 340	1·76 (1·50–2·07)	As described above
Maripuu et al (2020)[18]††	Sweden	Cohort	March 11–June 15, 2020	NA	NA	103 999	7 819 860	..	..
Exposure: severe mental illness									
Mortality OR	..	..	..	..	..	..	..	1·98 (1·66–2·35)	NA
Mortality aOR	..	..	..	..	..	..	..	2·24 (0·99–5·07)	Age 40–59 years
Mortality aOR	..	..	..	..	..	..	..	4·52 (2·90–7·03)	Age 60–69 years
Mortality aOR	..	..	..	..	..	..	..	4·16 (3·14–5·52)	Age 70–79 years
Mortality aOR	..	..	..	..	..	..	..	2·22 (1·69–2·93)	Age ≥80 years
Wang et al (2020)[19]	USA	Case-control	Up to June 15, 2020	NA	7160 females (60·0%), 4840 males (40·0%)	1880	10 150	..	..
Exposure: substance use disorder (lifetime diagnosis)									
Mortality	..	..	..	..	..	..	..	NA‡‡	NA
Hospitalisation	..	..	..	..	..	..		NA‡‡	NA
Wang et al (2021)[20]	USA	Case-control	Up to July 29, 2020	NA	8980 females (59·0%), 6090 males (40·0%)	3430	11 680	..	..
Exposure: recent mental disorders (diagnosed in the past year)									
Mortality	..	..	..	..	..	..	..	NA‡‡	NA
Hospitalisation	..	..	..	..	..	..	..	NA‡‡	NA

The leftmost column lists the outcome variables investigated for each exposure variable within a study. ICU=intensive care unit. NA=not available or not applicable. OR=odds ratio. aOR=adjusted odds ratio. *Sample overlapped with Yang et al (2020).[32] †Sample overlapped with Fond et al (2020).[9] ‡Median (IQR). §Sample overlapped with Jeon et al (2020)[10] and Lee et al (2020).[29] ||Mixed outcomes. **The same covariates were used in the adjusted models for all outcomes within the study. ††Unknown status for SARS-CoV-2 infection in reference group. ‡‡No meta-analysable data.

Table 2: **Characteristics of studies included in the systematic review**

strength of the evidence was assessed according to the GRADE approach.[17] All analyses were two-sided and were done using Comprehensive Meta-Analysis (version 3.3.070), with the exception of Hartung-Knapp-Sidik-Jonkman analysis, which was done using R software (version 4.0.5). The statistical threshold was Bonferroni corrected, so that $p<0·0167$ was considered significant to account for multiple testing of the three COVID-19 outcomes.

Role of the funding source

There was no funding source for this study.

Results

Our search identified 841 studies, 33 of which met the inclusion criteria for the systematic review (figure 1, tables 1, 2; appendix 4 pp 14–20),[4,7–10,18–45] including data from 22 countries (tables 1, 2) with outcomes registered between Dec 1, 2019, and Nov 30, 2020.

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-analysable data;[19,20] three did not differentiate between death, hospitalisation, or ICU admission;[41,44,45] and one included a control group with unknown SARS-CoV-2 infection status[18] (table 2; appendix 4 p 23). Thus, 23 studies[4,7–10,21,22,24–39] were included in the meta-analyses. This sample comprised 1 469 731 participants, of whom 43 938 had psychiatric disorders, 130 807 (8·9%) were female, and 130 373 (8·8%) were male. Nine studies included data for race or ethnicity (appendix 4 pp 21–22). 22 studies reported mortality outcome data (table 1; appendix 4 pp 14–20), nine studies reported data on hospitalisation, and ten reported ICU admission data.

The presence of any comorbid mental illness was associated with an increased risk of death after SARS-CoV-2 infection (OR 2·00, 95% CI 1·58–2·54; I^2=92·66; figure 2; appendix 4 p 24). In sensitivity analyses, all results remained statistically significant (appendix 4 pp 25–26), suggesting consistent effects across samples and models. E-values of 3·41 for crude models and 1·95 for adjusted

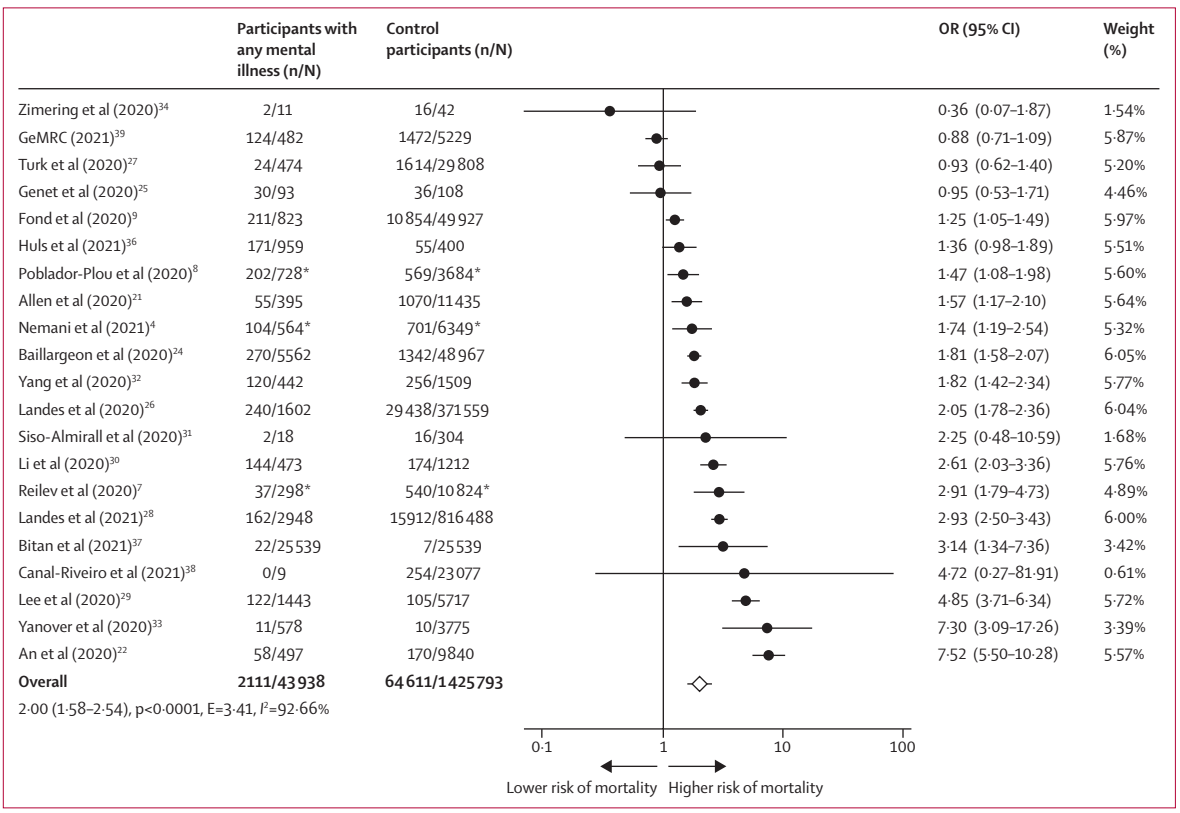

Figure 2: **Forest plot of pooled ORs for mortality for any mental disorder**
OR=odds ratio. *Sample size for any mental disorder was not available, thus we included data for the specific mental disorder with the largest sample size.

models indicated that substantial confounding would be required to account for the observed effect. Heterogeneity was high for unadjusted models (I^2=92·66%, Cochran's Q=272·58, p=0·00011) and low for adjusted models (I^2=39·30%, Q=16·47, p=0·087).

When stratifying mortality risk by psychiatric disorder type, the most robust associations were found for psychotic and mood disorders (figure 3; appendix 4 pp 27–30). Substance use disorders and intellectual disabilities and developmental disorders were associated with higher mortality only in crude estimates. No significant associations with death were found for anxiety disorders. Antipsychotics were consistently associated with an increased risk of mortality (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 (OR 2·58 [1·22–5·44], I^2=96·42%, E=4·60; aOR 1·47 [1·15–1·88], I^2=0%, E=4·29; appendix 4 pp 28–30). Antidepressant exposure was associated with increased mortality risk only in crude estimates (OR 2·23 [1·06–4·71], I^2=95·45%, E=3·89; aOR 1·18 [0·93–1·50], I^2=0%, E=1·64).

The risk of hospitalisation after SARS-CoV-2 infection was significantly higher in people with any pre-existing mental disorder than people without any pre-existing mental disorder (figure 4; appendix 4 pp 31). Significant associations were confirmed in all the sensitivity analyses (appendix 4 pp 32–33). Heterogeneity was high for both crude models (OR I^2=88·85%, Q=71·72, p<0·0001) and adjusted models (aOR I^2=90·99%, Q=55·5, p<0·0001), warranting further exploration of covariates. After stratification by disorder (appendix 4 pp 34), the most robust association with hospitalisation was identified in patients with a comorbid substance use disorder (OR 2·66 [1·79–3·95], I^2=91·31%, E=4·76; aOR 1·87 [1·16–3·03], I^2=94·51%, E=2·24), whereas psychotic disorders were not significantly associated (OR 1·68 [0·86–3·29], I^2=57·62%, E=2·75; aOR 1·34 [0·61–2·94], I^2=72·40%, E=2·01). The association between mood disorders and hospitalisation after SARS-CoV-2 was significant on the basis of the crude estimate (OR 2·26 [1·33–3·86], I^2=87·9%, E=3·95) but not the adjusted estimate (aOR 1·26 [0·64–2·50], I^2=23·09%; E=1·83).

We found no robust evidence of an increased risk of ICU admission for patients with mental disorders (OR 1·77 [1·09–2·89]; aOR 1·33 [0·87–2·04]; appendix 4 pp 35–36). Sensitivity analyses highlighted an effect of single studies on the overall estimates (appendix 4 pp 37–38). A high proportion of unexplained heterogeneity was identified (OR I^2=93·01%, Q=128·76, p<0·0001; aOR I^2=89·51%, Q=57·21, p<0·0001), and a subgroup analysis was done to explore whether the diagnostic category explained a

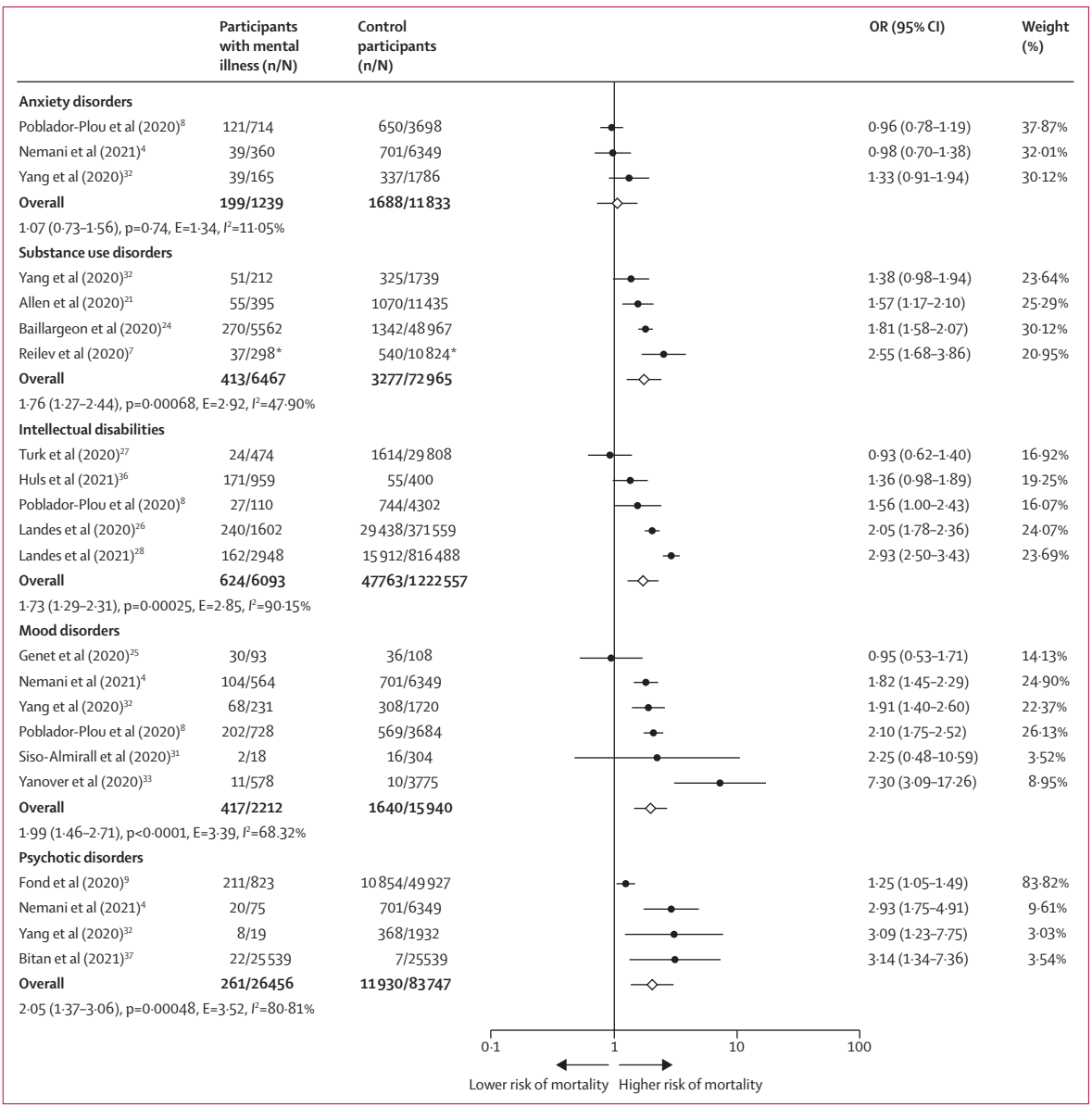

Figure 3: **Forest plot of ORs for mortality stratified by diagnostic category**
OR=odds ratio. *Sample size for any mental disorder was not available, thus we included data for the specific mental disorder with the largest sample size.

proportion of the heterogeneity (appendix 4 pp 39–40). After correction for multiple comparisons, none of the diagnostic categories were found to be consistently associated with an increased risk for ICU admission. Insufficient data were available to estimate the risk of hospitalisation and ICU admission associated with exposure to psychopharmacological drug classes.

Patients with severe mental illness had higher mortality estimates (OR 2·21 [1·63–2·99], I^2=81·93%, E=3·85; aOR 1·55 [1·30–1·85], I^2=28·78%, E=2·47, appendix 4 pp 28-30) than did patients with other mental disorders (OR 1·62 [1·27–2·08], I^2=88·63%, E=2·62; aOR 1·09 [0·92–1·29], I^2=0%, E=1·40) with a significant difference identified between adjusted estimates (OR, p=0·13; aOR, p=0·0047). No significant differences were identified in the incidence of hospitalisation and ICU admission (appendix 4 pp 34, 39–40).

Baseline treatment setting for COVID-19 significantly affected crude effect size estimates for mortality and ICU admission (p=0·013 for mortality; p<0·0001 for ICU admission) and reduced the initially identified heterogeneity (appendix 4 pp 28–30, 39–40). The ORs for mortality and ICU admission were significantly higher in individuals who were not admitted to hospital (OR 2·34 [95% CI 1·82–3·00] for mortality, I^2=90·92%; OR 2·39 [1·81–3·15] for ICU admission, I^2=62·05%) than

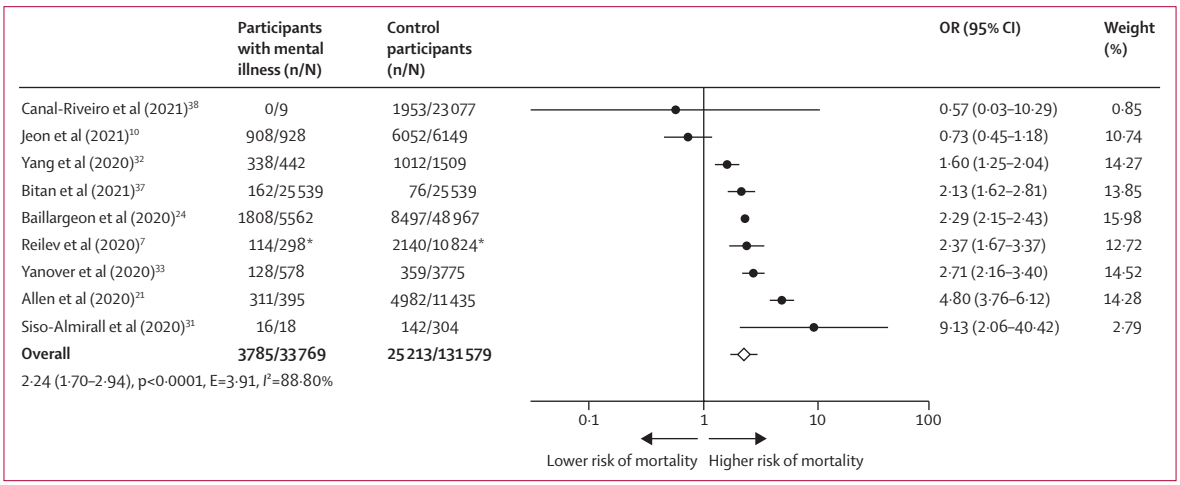

Figure 4: **Forest plot of pooled ORs for hospitalisation for all mental disorders**
OR=odds ratio. *Sample size for any mental disorder was not available, thus we included data for the specific mental disorder with the largest sample size.

were those who were admitted to hospital (OR 1·21 [0·77–1·90] for mortality, I^2=91·26%; OR 0·85 [0·58–1·24], for ICU admission, I^2=44·62%). For study samples that included only individuals who had been admitted to hospital, no significant differences between patients and controls in terms of mortality or ICU admission were identified (OR 1·21 [0·77–1·90] for mortality, I^2=91·26%; OR 0·85 [0·58–1·24], for ICU admission, I^2=44·62%).

The country of the population studied had a significant effect on both crude mortality estimates (p<0·0001) and adjusted mortality estimates (p=0·0071), with the lowest mortality effect sizes identified in samples from European countries and the USA (appendix 4 pp 28–30). No significant effects were identified by country for ICU risk, or for COVID-19 pandemic phases, Newcastle Ottawa Scale quality assessment, the minimum age of the recruited sample, or the study sample sizes for any outcome. No significant differences were identified between covariate-adjusted models with and without adjustment for race or ethnicity or other comorbidities.

In the quality assessment of the 33 peer-reviewed studies included in the systematic review, 22 were rated as high quality, eight as moderate quality, and three as low quality (appendix 4 pp 41–42). GRADE assessment indicated high certainty for estimates of the primary outcome and of crude hospitalisation, moderate certainty for adjusted hospitalisation and crude ICU admission. Adjusted ICU admission estimates were rated as very low certainty (appendix 4 pp 43–44). Visual inspection of funnel plots and the Egger test did not indicate publication bias (appendix 4 pp 45–48).

Discussion

Our results indicate an increased risk of COVID-19 mortality for patients with mental disorders. We found consistent evidence that patients with psychotic and mood disorders, and those taking antipsychotics or anxiolytics, represent susceptible subgroups. Patients with psychiatric disorders, especially substance use disorders, but not those with psychotic disorders, had a higher risk of hospitalisation than did individuals without psychiatric disorders, however, no differences were identified for ICU admission risk. Patients with severe mental illness (including psychotic and mood disorders) had a higher risk of death than patients with other mental disorders.

Our findings reflect the evidence of high all-cause mortality in people with mental disorders, in particular those with psychotic disorders, followed by mood disorders.[46] An increased risk of COVID-19 mortality might reflect biological processes, such as immune-inflammatory alterations, including immunogenetic abnormalities, raised cytokine concentrations, auto-antibodies, acute-phase proteins, and aberrant counts of leukocyte cell types, which characterise psychiatric disorders.[47–49] We found that exposure to antipsychotic and anxiolytic drug treatments initiated before contracting COVID-19 was associated with severe COVID-19 outcomes. Antipsychotics might precipitate cardiovascular and thromboembolic risk, might interfere with an adequate immune response, and might cause pharmacokinetic and pharmacodynamic interactions with drugs used to treat COVID-19.[50,51] Anxiolytics, especially benzodiazepines, are associated with respiratory risk, and are known to be associated with all-cause mortality.[52] By contrast, antidepressants are associated with a lower risk of severe respiratory and cardiovascular side-effects, and previous findings support possible anti-inflammatory and antiviral properties of serotonergic antidepressants investigated as potential treatments for COVID-19.[53,54] Although we found no evidence for such a protective effect of antidepressants, this could have been confounded by the psychiatric indication. In contrast to antipsychotics and anxiolytics,

the mortality risk associated with antidepressants was not increased after adjustment for age, sex, and other covariates.

Social and lifestyle factors (eg, diet, physical inactivity, social isolation, high alcohol and tobacco use, and sleep disturbances) and a higher prevalence of somatic comorbidities (eg, diabetes, cardiovascular disease, and respiratory disease)[19,55] might also have detrimental effects on COVID-19 prognosis.[56]

The increased mortality of patients with psychiatric disorders—in particular, patients with psychotic disorders—observed in our study might also reflect reduced access to care, which has previously been described in relation to nearly every aspect of somatic health care in this population.[57] However, although mortality was increased among patients with psychiatric disorders who were not admitted to hospital for COVID-19, we found no evidence of increased in-hospital mortality in patients with mental disorders versus those without, based on the results of subgroup analyses by baseline clinical setting (ie, samples of patients in hospital versus those not in hospital for COVID-19).

Mortality was also significantly different among countries, with a lowest risk in Europe and the USA. This difference might be attributable to several factors, including differences in health-care systems or accessibility to care among countries, which could also be associated with the dynamics of the pandemic or possible interactions with race and ethnicity.[58,59] Although our data did not allow us to explore these associations specifically, models adjusted for ethnicity and race were not found to be significantly different from unadjusted models, and variables associated with 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] overall heterogeneity in this analysis was high, and was substantially reduced in adjusted estimates and after 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. Most of the included studies (22 [67%] of 33) were rated as high quality, and we found no evidence of publication bias. A strength of this study is that we included only patients with confirmed SARS-CoV-2 infection status, thus, we can assume that the observed risks for severe or fatal COVID-19 were not due to patients with psychiatric disorders being more likely to be infected with SARS-CoV-2.[32,60]

Several study limitations should be acknowledged. Although we stratified risk estimates for psychiatric diagnosis, pharmacological drug class, and baseline treatment setting for COVID-19, it was not possible to disentangle the specific risks attributable to each of these variables. Specifically, we were unable to differentiate 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 might not allow a fine-grained analysis of clinical variables.[61] For example, no studies included in our meta-analysis distinguished between unipolar and bipolar mood disorders. 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.

Some studies were of low quality or included small samples of patients with psychiatric disorders, contributing to a low certainty of evidence for ICU admission. More evidence is needed to determine the validity and generalisability of our results, and we recommend accounting for psychiatric comorbidities 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 previous exposure to psychopharmacological compounds were associated with poor COVID-19 outcomes. Public health authorities should consider priority vaccination for all groups of at-risk patients identified in this study. Additionally, close monitoring and adequate hospital referral in patients with psychiatric disorders who develop COVID-19 is needed to counteract possible reduced access to care.

Contributors

BV, LDP, PF-P, and IB conceptualised and initiated the study. BV, CDC, MF, and MGM screened the text. BV and MGM analysed the data. LDP created the forest plots. BV, LDP, and MGM wrote the first draft of the manuscript with input from MCD, IB, PF-P, and MEB. BA proofread the manuscript. All authors contributed to the design of the study and the final manuscript. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Declaration of interests

LDP reports grants from Boehringer-Ingelheim and Janssen, outside the submitted work. PFP reports grants from Lundbeck; personal fees from Angelini and Menarini; and non-financial support from Boehringer Ingelheim, outside the submitted work. BV, FB, AB, RT, ML, MEB, IB, PFP and LDP are members of the ECNP Immunopsychiatry Thematic Working Group. All other authors declare no competing interests.

Data sharing

Study data are available on request to the corresponding author at livia.depicker@uantwerp.be.

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