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Association Between Mood Disorders and Risk of COVID-19 Infection, Hospitalization, and Death
A Systematic Review and Meta-analysis

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IMPORTANCE Preexisting noncommunicable diseases (eg, diabetes) increase the risk of COVID-19 infection, hospitalization, and death. Mood disorders are associated with impaired immune function and social determinants that increase the risk of COVID-19. Determining whether preexisting mood disorders represent a risk of COVID-19 would inform public health priorities.

OBJECTIVE To assess whether preexisting mood disorders are associated with a higher risk of COVID-19 susceptibility, hospitalization, severe complications, and death.

DATA SOURCES Systematic searches were conducted for studies reporting data on COVID-19 outcomes in populations with and without mood disorders on PubMed/MEDLINE, The Cochrane Library, PsycInfo, Embase, Web of Science, Google/Google Scholar, LitCovid, and select reference lists. The search timeline was from database inception to February 1, 2021.

STUDY SELECTION Primary research articles that reported quantitative COVID-19 outcome data in persons with mood disorders vs persons without mood disorders of any age, sex, and nationality were selected. Of 1950 articles identified through this search strategy, 21 studies were included in the analysis.

DATA EXTRACTION AND SYNTHESIS The modified Newcastle-Ottawa Scale was used to assess methodological quality and risk of bias of component studies. Reported adjusted odds ratios (ORs) were pooled with unadjusted ORs calculated from summary data to generate 4 random-effects summary ORs, each corresponding to a primary outcome.

MAIN OUTCOMES AND MEASURES The 4 a priori primary outcomes were COVID-19 susceptibility, COVID-19 hospitalization, COVID-19 severe events, and COVID-19 death. The hypothesis was formulated before study search. Outcome measures between individuals with and without mood disorders were compared.

RESULTS This review included 21 studies that involved more than 91 million individuals. Significantly higher odds of COVID-19 hospitalization (OR, 1.31; 95% CI, 1.12-1.53; $P = .001$; n = 26 554 397) and death (OR, 1.51; 95% CI, 1.34-1.69; $P < .001$; n = 25 808 660) were found in persons with preexisting mood disorders compared with those without mood disorders. There was no association between mood disorders and COVID-19 susceptibility (OR, 1.27; 95% CI, 0.73-2.19; n = 65 514 469) or severe events (OR, 0.94; 95% CI, 0.87-1.03; n = 83 240). Visual inspection of the composite funnel plot for asymmetry indicated the presence of publication bias; however, the Egger regression intercept test result was not statistically significant.

CONCLUSIONS AND RELEVANCE The results of this systematic review and meta-analysis examining the association between preexisting mood disorders and COVID-19 outcomes suggest that individuals with preexisting mood disorders are at higher risk of COVID-19 hospitalization and death and should be categorized as an at-risk group on the basis of a preexisting condition.

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Supplemental content

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Despite ongoing public health efforts, the devastating impact of COVID-19 continues to be observed worldwide. In October 2020, the World Health Organization estimated that approximately 10% of the global population had been infected with COVID-19, representing 20 times the number of recorded cases.[1] An early study[2] reported that approximately 14% of affected individuals experienced severe COVID-19–associated symptoms, whereas 5% presented as critically unwell and required intensive care. Established risk factors for severe COVID-19 include preexisting cardiovascular disease, obesity, diabetes, cancers, and respiratory disease.[3,4]

Individuals with mood disorders may be at greater risk (and vice versa) for COVID-19 because of a confluence of factors known to increase the risk in the general population.[5] For example, the finding that a subpopulation of individuals with mood disorders exhibit evidence of dysregulated immune function has been replicated in several studies.[6,7] Moreover, persons with mood disorders are differentially affected by noncommunicable diseases (eg, obesity and cardiovascular disease) known to increase the risk of COVID-19.[8,9] In addition, social determinants of risk (eg, poverty and insufficient access to timely and preventive health care) are also more commonly observed in persons with mood disorders.

The fact that COVID-19 is associated with complex and, in some cases, enduring neuropsychiatric manifestations has been amply documented.[10-12] A related but separate question is whether individuals with mood disorders are at higher risk of contracting COVID-19 and/or experiencing complications and death from the disease.[13-15] A higher risk of infection and/or complications attributable to COVID-19 in individuals with psychiatric illnesses has been reported[16]; however, to our knowledge, no meta-analysis has delimited its focus to persons with mood disorders. Empirical evidence addressing this question is crucial given the high global lifetime prevalence of mood disorders in the general population and the need to prioritize public health strategies to mitigate the risk of COVID-19 and associated complications.[17] In this study, we hypothesized that individuals with preexisting mood disorders are at higher risk of COVID-19 susceptibility, hospitalization, severe events, and death.

Key Points

Question Are preexisting mood disorders associated with higher risk of COVID-19 infection, hospitalization, severe complications, and death?

Findings In this systematic review and meta-analysis of more than 91 million people, individuals with preexisting mood disorders, compared with those without mood disorders, had significantly higher pooled odds ratios for COVID-19 hospitalization and death. There were no associations between preexisting mood disorders and risk of COVID-19 infection or severe events.

Meaning These results suggest that individuals with mood disorders should be categorized as an at-risk group for COVID-19 hospitalization and death, providing basis for vaccine prioritization.

Methods

Search Strategy

The protocol pertaining to this study was registered on PROSPERO (CRD42020220502). A systematic search was conducted from database inception to February 1, 2021, for primary research articles. The following databases were searched systematically: PubMed/MEDLINE, the Cochrane Library, PsycInfo, Embase, and Web of Science. We manually searched the references of relevant articles as well as Google Scholar/Google and LitCovid for additional studies. No language restrictions were imposed. Sample search strategies are provided in eAppendix 1 in the Supplement. A total of 1950 articles were identified through this search strategy. This study followed the Meta-analysis of Observational Studies in Epidemiology (MOOSE)[18] and Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA)[19] reporting guidelines.

Titles and abstracts were independently screened by 2 reviewers (F.C. and D.N.), articles identified as potentially relevant by at least 1 reviewer were retrieved, and duplicates were removed. Full-text articles were independently screened by 2 reviewers (F.C. and D.N.), with discrepancies resolved through discussion.

Inclusion and Exclusion Criteria

We compared COVID-19 test positivity, hospitalizations, severe events (including intensive care unit admission, mechanical ventilatory support, oxygen therapy, extracorporeal membrane oxygenation, acute respiratory distress syndrome, and/or cardiopulmonary resuscitation), and/or death in populations with mood disorders vs without mood disorders of any age, sex, and nationality. Inclusion criteria were established before article review and were as follows: (1) a diagnosis of depression or bipolar disorder using standardized diagnostic criteria (eg, *DSM-5* or *International Statistical Classification of Diseases and Related Health Problems, Tenth Revision [ICD-10]*); (2) mood disorder diagnosis documented before COVID-19 event or present as of the index date (ie, comorbid); (3) COVID-19 ascertained according to laboratory testing, *ICD-10*, electronic health record (EHR), and/or clinical judgment; (4) available complete quantitative data relevant to at least 1 primary outcome (**Table 1**); (5) discrete outcome data for mood disorders; (6) primary research; and (7) presentation as a full-text article (which included preprints). Exclusion criteria were as follows: (1) mood disorders that were self-reported or otherwise did not follow standardized diagnostic criteria; (2) mood disorder outcomes grouped with those for other mental illnesses; (3) unpublished study or abstract; (4) and nonprimary research.

Assessment of Bias and Methodological Quality

Methodological quality and risk of bias were assessed using the Newcastle-Ottawa Scale (NOS),[20] modified for applicable retrospective cohort and case-control studies using patient EHR data (eAppendix 2 in the Supplement). Each included study was independently rated by 2 reviewers (F.C. and D.N.) and results were corroborated, with discrepancies resolved through

Table 1. Definition of Study Variables

COVID-19 event (primary outcome)	Definition	Cases (ie, event)	Controls (ie, nonevent)[a]
Susceptibility	COVID-19 test positivity as ascertained by laboratory testing, *ICD-10*, EHR, and/or clinical judgment	COVID-19 positive	COVID-19 negative or untested (assumed negative)
Hospitalization	Inpatient admission for COVID-19	Inpatient COVID-19 positive	COVID-19 positive or untested; not inpatient
Severe events	Any or a combination of the following COVID-19–related events indicating severe disease progression: ICU admission, mechanical ventilatory support, oxygen therapy, ECMO, ARDS, and/or cardiopulmonary resuscitation	COVID-19 positive and experiencing severe event(s)	COVID-19 positive or untested; not experiencing the corresponding severe event(s)
Death	COVID-19–related death or discharge to hospice or all-cause death after COVID-19 hospitalization; within a specified follow-up period	COVID-19 positive and death (including in-hospital)	COVID-19 positive or entire cohort (tested and untested); no death

Abbreviations: ARDS, acute respiratory distress syndrome; ECMO, extracorporeal membrane oxygenation; EHR, electronic health record; *ICD-10*, *International Statistical Classification of Diseases and Related Health Problems, Tenth Revision*; ICU, intensive care unit.

[a] When unadjusted odds ratio were calculated, the first of the 2 options listed were selected as the control groups.

discussion. Studies ranking 7 to 9 stars on the case-control NOS or 6 to 7 stars on the cohort NOS were deemed high quality, those ranking 5 to 6 (case-control) or 5 (cohort) stars were moderate, and 4 or fewer stars were low quality.

Data Extraction

Data from included articles were independently extracted by 2 reviewers (F.C. and D.N.) using a pilot-tested data extraction form and then corroborated, with discrepancies resolved through discussion. Information to be extracted was established a priori and included study characteristics, participant characteristics and subgroups, sample source and collection period, modes of ascertainment, methods of data analysis, selection of cases and controls, and quantitative data pertaining to any primary outcomes along with adjusted factors.

Statistical Analysis

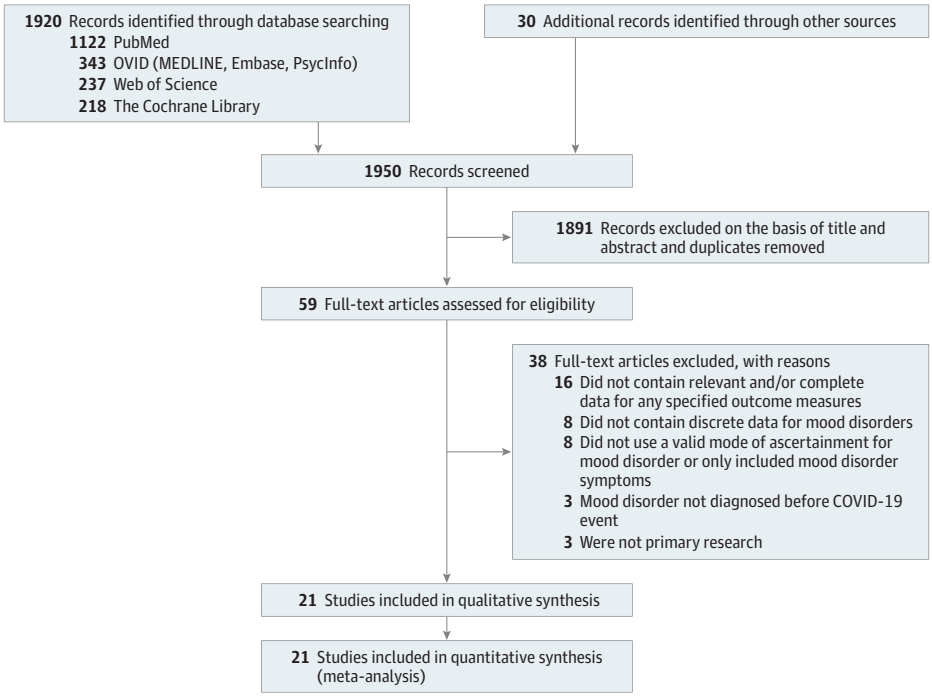
Odds ratios (ORs) with 95% CIs and/or summary data for COVID-19 test positivity, hospitalizations, severe events, and/or death in corresponding study populations with and without preexisting mood disorders were extracted. Where available, adjusted ORs (aORs) were preferentially used to reduce confounding, as recommended by the *Cochrane Handbook*.[21] When relevant studies did not report an applicable OR, unadjusted ORs were calculated from summary data and combined with reported aORs. The meta-analyses included 21 studies; aORs were derived from 11 studies,[22-32] crude summary data from 6 studies,[33-38] and both measures from 4 studies.[39-42] Authors of potentially eligible studies were contacted and asked to provide clarification and/or supplementary data where necessary; 4 study authors provided eligible summary data[34-36] and 1 provided aORs.[42] Among multiple statistical models within 1 study, the aOR most similar to that adjusted for age, sex, and comorbidities was used because these were the most common corrections and represent established COVID-19 risk factors. When aORs were reported only for subgroups, composite values for the aggregate research populations were calculated. Recent diagnoses of mood disorders were preferred over lifetime diagnoses if both were reported.

Pooled ORs with 95% CIs and prediction intervals (PIs) representing the range of values expected to contain a future observation have been provided (except for analyses in which all studies shared a common effect size), and forest plots were generated for 4 prespecified COVID-19 events: (1) susceptibility, (2) hospitalization, (3) severe events, and (4) deaths (Table 1). An α level of .05 was chosen to indicate statistical significance. The comparative groups were individuals with preexisting mood disorders (ie, exposure) vs those without mood disorders as of the index date. Study participants who experienced more than 1 COVID-19 outcome were not censored from precursory event counts. Summary data that encompassed varying intrasample follow-up times[31,36] (ie, where hazards ratios would be appropriate) were not used to calculate unadjusted ORs owing to high daily COVID-19 event rates. Measures that pertain to specific mood disorders (assessed independently) were combined with those for mood disorder subgroups and all mood disorders grouped. When measures for overlapping categories were available (eg, major depressive disorder and depression), the data that would encompass a greater range of exposures were used.

Observational studies are susceptible to interstudy differences in exposure and participants, justifying the use of the random-effects model of DerSimonian and Laird, which assumes varying effect sizes that arise from heterogeneity.[43] Furthermore, heterogeneity was evaluated using the I^2 statistic, where a 30% cutoff denotes moderate heterogeneity, 50% denotes substantial heterogeneity, and 75% denotes considerable heterogeneity, as recommended by GRADE (grading of recommendations, assessment, development and evaluation) criteria and the *Cochrane Handbook*'s interpretation of heterogeneity scores.[44,45] Exploratory post hoc sensitivity analyses were undertaken for subgroups of studies to ascertain the impact of moderator variables, and a meta-regression was performed to investigate heterogeneity.

To consider the impact of possible data duplication caused by identical sample source, sensitivity analyses retaining the study with the largest sample size derived from each duplicate database were conducted. The Egger regression intercept test and visual inspection of funnel plots for each COVID-19 event, as well as for all component data (including some overlap if 1 study reported multiple types of COVID-19 events as defined in Table 1), was performed to assess publication bias. All statistical analyses were conducted using Comprehensive Meta-Analysis, version 3.0 (BioStat Inc). A narrative synthe-

Figure 1. Study Selection Flowchart



sis was included for relevant results excluded from the meta-analyses.[31,36]

Results

Search Results and Study Characteristics

The literature search yielded 1950 articles of which 59 were eligible after screening titles and abstracts and removing duplicates. Of these eligible studies, 38 were further excluded after full-text screening. Details of study selection are provided in **Figure 1**. Twenty-one studies were included in the review: 8 retrospective case-control studies[22-24,27,28,38,41] (including 1 phenome-wide association study[42]), 12 retrospective cohort studies,[25,26,29-32,34-37,39,40] and 1 exposure-crossover study.[33] All studies contributed to at least 1 meta-analysis. Twelve studies analyzed data from the US,[22-25,31,33,34,38-42] 2 from South Korea,[26,27] 2 from Spain,[29,30] and 1 each from Italy,[28] Turkey,[37] the UK,[35] England,[32] and Israel.[36] Sample sizes ranged from 398 to 69.8 million, and data acquisition periods spanned from December 1, 2019, to September 30, 2020. **Table 2** provides detailed characteristics and summaries of applicable findings for all component studies.

Risk of Bias

Methodological quality of the included studies was moderate to high, evidenced by a mean score of 6.7 of 9 for case-control studies and 5.7 of 7 for cohort studies. The NOS rankings within each category for individual studies organized by design are provided in eTable 1 in the Supplement.

Synthesis of Results

Meta-analyses of the 4 primary outcomes revealed significantly higher odds of COVID-19 hospitalization and death among individuals with preexisting mood disorders compared with those without mood disorders. No significant associations between COVID-19 susceptibility or severe events were observed. Visual inspection of the composite funnel plot for asymmetry indicated the presence of publication bias. However, the Egger regression intercept test result was not statistically significant (eFigure 1 in the Supplement).

COVID-19 Susceptibility

There was no association between COVID-19 susceptibility and preexisting mood disorders (OR, 1.27; 95% CI, 0.73-2.19; P = .40; PI, 0.11-14.23; n = 65 514 469) (**Figure 2**A). Furthermore, no sensitivity analyses produced any statistically significant associations (**Table 3**), with the exception of the analysis restricted to moderate- to low-quality studies (OR, 2.16; 95% CI, 1.28-3.66; P = .004) (Table 3).

COVID-19 Hospitalization

The odds of COVID-19 hospitalization were significantly greater for individuals with preexisting mood disorders when compared with those without mood disorders (OR, 1.31; 95% CI, 1.12-1.53; P = .001; PI, 0.78-2.20; n = 26 554 397) (Figure 2B). All sensitivity analyses produced statistically significant higher odds of COVID-19 hospitalization (Table 3), with the exception of the analysis restricted to case-control studies (OR, 1.16; 95% CI, 0.95-1.43; P = .15) (Table 3).

Table 2. Characteristics of Component Studies and Summary of Relevant Findings

Study	Country	Study design	Sample source	Data acquisition period	Sample size	Sample characteristics	Exposure(s)	Mode(s) of ascertainment	Summary of findings
Azar et al,[39] 2020	US	Retrospective cohort	Sutter Health	January 1, 2020, to April 8, 2020	14 036 Tested	Age range: ≥18 y; mean (SD) age: 50.7 (18.1) y; sex, F/M 60.7%/39.3%	Depression	*ICD-10* diagnosis for mood disorder; EHR of laboratory test or *ICD-10* diagnosis for COVID-19	There were significantly lower odds of COVID-19 susceptibility (OR, 0.53; 95% CI, 0.41-0.70)[a] for individuals with comorbid depression. There were no associations for COVID-19 hospital admission (aOR, 1.18; 95% CI, 0.57-2.41) or ICU admission (OR, 1.24; 95% CI, 0.58-2.68)[a] among COVID-19-positive patients. There were significantly higher odds of death (OR, 2.64; 95% CI, 1.14-6.11)[a] for individuals with comorbid depression among COVID-19-positive patients.
Chang et al,[22] 2020[b]	US	Retrospective case-control	UCLA Health	March 9, 2020, to June 14, 2020	26 602 Tested, 10 000 untested controls	Age range: NA; mean (SD) age: 49 (20) y[c]; sex, F/M: 55%/44%[c]	MDD, depression	*ICD-9* or *ICD-10* diagnosis for mood disorder; RT-PCR for COVID-19	There were significantly higher odds of COVID-19 susceptibility (aOR, 2.1; 95% CI, 1.6-2.8) in individuals with preexisting MDD, although there was no association with preexisting depression (aOR, 1.23; 95% CI, 0.98-1.52).
Chang et al,[23] 2021	US	Retrospective case-control	Centers for Medicare & Medicaid Services	January 1, 2020, to September 30, 2020	710 980 COVID-19 positive	Age range: NA; mean age: NA (>50%->75 y of age); sex, F/M: 56.1%/43.9%	Depression	Chronic Conditions Data Warehouse diagnosis for mood disorder; *ICD-10* diagnosis for COVID-19	Comorbid depression was associated with significantly higher odds (aOR, 1.07; 95% CI, 1.06-1.08) of COVID-19-related hospitalization among COVID-19-positive patients.
Douville et al,[38] 2020	US	Retrospective case-control	Michigan Medicine, Academic Quaternary Care Centre	March 1, 2020, to May 5, 2020	398 COVID-19-positive inpatients	Age range: NA; mean (SD) age, 60 (17) y; sex, F/M: 47%/53%	Depression	*ICD-9*/*ICD-10* diagnosis for mood disorders	There were no associations between comorbid depression and COVID-19-related mechanical ventilatory support (OR, 1.09; 95% CI, 0.69-1.77)[a] or death (OR, 1.71; 95% CI, 0.87-3.37)[a] among the inpatient COVID-19-positive cohort.
Haimovich et al,[24] 2020	US	Retrospective case-control	Yale New Haven Health (8 emergency departments)	March 1, 2020, to April 8, 2020	2182 Emergency department inpatients	Age range: NA; median (IQR) age: 66 (53-78) y[d]; median (IQR) age: 65.0 (51.0-78.2) y[e]; sex, F/M: 41.8%/51.9%	Depression	*ICD-10* diagnosis for mood disorder; nucleic acid detection methods for COVID-19	There was no association between comorbid depression and COVID-19 susceptibility (aOR, 0.83; 95% CI, 0.61-1.13) among emergency department inpatients.
Izurieta et al,[25] 2020	US	Retrospective cohort	Medicare Parts A and B	April 1, 2020, to May 8, 2020	25 333 329 Medicare fee-for-service enrolled beneficiaries	Age range: ≥65 y; median age: 73 y; sex, F/M: 55.6%/44.4%	Depression	*ICD-10* diagnosis for mood disorder; *ICD-10* diagnosis for COVID-19	Preexisting depression was associated with significantly higher odds of COVID-19 hospitalization (aOR, 1.26; 95% CI, 1.22-1.30) and COVID-19-related death (aOR, 1.32; 95% CI, 1.26-1.38) among Medicare recipients.
Jeon et al,[26] 2021	South Korea	Retrospective cohort	Health Insurance Review & Assessment Service, linked to Korea Disease Control and Prevention Agency	December 1, 2019, to May 15, 2020	230 565 Tested, 126 075 analyzed	Age range: NA; mean (SD) age: 53.74 (20.04) y[f]; sex, F/M: 54.3%/45.7%[f]	Mood disorder(s)	*ICD-10* diagnosis for mood disorder; RT-PCR for COVID-19	Preexisting mood disorders were associated with significantly lower odds of COVID-19 susceptibility (aOR, 0.76; 95% CI, 0.66-0.88). There were no associations between COVID-19 severe events (aOR, 0.71; 95% CI, 0.32-1.58) or related death (aOR, 2.33; 95% CI, 0.96-5.66).
Ji et al,[27] 2020	South Korea	Retrospective case-control	Health Insurance Review & Assessment Service, linked to Korea Disease Control and Prevention Agency	Until May 15, 2020	219 961 Tested (analyzed)	Age range: ≥18 y; mean (SD) age: 49.40 (19.88) y; sex, F/M: 52.7%/47.3%	Mood disorder(s)	*KCD-7* diagnosis for mood disorder; RT-PCR for COVID-19	There were no associations between preexisting mood disorders and COVID-19 susceptibility (aOR, 0.93; 95% CI, 0.84-1.02) or severe COVID-19 (aOR, 1.04; 95% CI, 0.81-1.33).

(continued)

Table 2. Characteristics of Component Studies and Summary of Relevant Findings (continued)

Study	Country	Study design	Sample source	Data acquisition period	Sample size	Sample characteristics	Exposure(s)	Mode(s) of ascertainment	Summary of findings
Kundi et al,[37] 2020	Turkey	Retrospective cohort	Public Health Management System and e-Pulse	March 11, 2020, to July 20, 2020	18 234 Elderly COVID-19–positive inpatients	Age range: ≥65 y; mean (SD) age: 74.1 (7.4) y; sex, F/M: 53.4%/46.6%	Depression	*ICD-10* diagnosis for mood disorder; RT-PCR for COVID-19	Preexisting depression was associated with significantly higher odds of COVID-19–related death (OR, 1.30; 95% CI, 1.19-1.42)[a] among COVID-19–positive elderly inpatients.
Murk et al,[33] 2021	US	Exposure-crossover	HealthVerity Marketplace	March 1, 2020, to April 30, 2020	70 288 COVID-19–positive patients	Age range: NA; median (IQR) age: 65 (51-77) y; sex, F/M: 55.8%/42.7%	BD or depression	*ICD-10* diagnosis for mood disorder; *ICD-10* diagnosis for COVID-19	Baseline BD or depression (grouped) was associated with significantly higher odds of COVID-19 hospitalization (OR, 1.56; 95% CI, 1.49-1.62)[a], although there was no association with ICU admission (OR, 0.92; 95% CI, 0.84-1.02)[a] among the COVID-19–positive cohort.
Nemani et al,[40] 2021	US	Retrospective cohort	New York University Langone Health	March 3, 2020, to May 31, 2020; final date of patient follow-up was July 15, 2020	26 540 Tested	Age range: ≥18 y; mean (SD) age: 54 (18.6) y[d]; sex, F/M: 53%/47%[d]	Mood disorder(s)	*ICD-10* diagnosis for mood disorder; RT-PCR for COVID-19	Preexisting mood disorder was associated with significantly lower odds of COVID-19 susceptibility (OR, 0.88; 95% CI, 0.80-0.97).[a] There was no association between recent diagnosis of preexisting mood disorder (aOR, 1.27; 95% CI, 0.94-1.73) and death.
Orlando et al,[28] 2021	Italy	Retrospective case-control	Campania Region Database	Until June 10, 2020	3497 COVID-19–positive patients, 17 358 random controls	Age range: ≥30 y; mean age: NA; sex: NA	Depression	*ICD-9* diagnosis for mood disorder; RT-PCR for COVID-19	There were no associations between preexisting depression and COVID-19 susceptibility (aOR, 0.98; 95% CI, 0.86-1.12) or death (aOR, 1.21; 95% CI, 0.88-1.67).
Poblador-Plou et al,[29] 2020	Spain	Retrospective cohort	Aragon Health System	March 4, 2020, to May 17, 2020, or date of patient death	14 724 Tested, 1.3 million inhabitants as reference population	Age range: NA; mean (SD) age: 67.7 (20.7) y[d]; sex, F/M: 58.8%/41.2%[d]	Mood disorder(s)	*ICD-9* diagnosis for mood disorder; laboratory tests for COVID-19	Preexisting mood disorders were associated with significantly higher odds of death (aOR, 1.43; 95% CI, 1.16-1.76)[g] within at least 30 d of testing COVID-19 among the entire study population.
Rodriguez-Molinero et al,[30] 2020	Spain	Retrospective cohort	Consorci Sanitari de l'Alt Penedès i Garraf	March 12, 2020, to May 2, 2020	418 COVID-19–positive inpatients	Age range: NA; mean (SD) age: 65.4 (16.6) y; sex, F/M: 43.1%/56.9%	Depression	Health care record for mood disorder; PCR for COVID-19	There were no associations between preexisting depression and COVID-19 severe events (aOR, 0.96; 95% CI, 0.56-1.66) or death (aOR, 1.93; 95% CI, 1.02-3.53) among the hospitalized COVID-19–positive patients.
Salvatore et al,[42] 2021	US	Disease-disease PheWAS case-control	Michigan Medicine	March 10, 2020, to April 22, 2020	4622 Tested, 13 351 controls	Age range: NA[c]; mean (SD) age: 47.4 (20.6) y[c]; sex, F/M: 63.7%/36.3%[c]	Major depressive disorder, depression, mood disorder(s)	Phecode mapped to *ICD-9* or *ICD-10* diagnosis for mood disorder; Phecode mapped to *ICD-9* or *ICD-10* diagnosis for COVID-19	Preexisting MDD (aOR, 0.85; 95% CI, 0.73-0.98),[h] depression (aOR, 0.84; 95% CI, 0.73-0.97),[h] and mood disorders (aOR, 0.85; 95% CI, 0.74-0.98)[h] were associated with significantly lower odds of COVID-19 susceptibility. There were no associations for BD (aOR, 0.74; 95% CI, 0.52-1.05)[h] or PDD (aOR, 1.02; 95% CI, 0.78-1.33).[h] Preexisting MDD was associated with significantly higher odds of COVID-19 death (aOR 2.95, $P < .05$). There were no associations between preexisting mood disorders and COVID-19 hospitalization (OR, 1.00; 95% CI, 0.73-1.38),[a] ICU admission (OR, 0.96; 95% CI, 0.62-1.48),[a] or death (OR, 1.67; 95% CI, 0.65-4.29).[a]
Tang et al,[31] 2020	US	Retrospective cohort	Skilled nursing facilities EHR	March 1, 2020, to June 12, 2020	1970 Tested skilled nursing facility residents	Age range: NA; median (IQR) age: 73.9 (21.9-105.4) y; sex, F/M: 57%/43%	Depression	*ICD-10* diagnosis for mood disorder; RT-PCR for COVID-19	Preexisting depression was associated with significantly higher odds of COVID-19 susceptibility (aOR, 1.33; 95% CI, 1.07-1.65), and hospitalization (SHR, 1.33; 95% CI, 1.01-1.75), but there was no association with COVID-19–related death (HR, 1.08; 95% CI, 0.77-1.50).

(continued)

Table 2. Characteristics of Component Studies and Summary of Relevant Findings (continued)

Study	Country	Study design	Sample source	Data acquisition period	Sample size	Sample characteristics	Exposure(s)	Mode(s) of ascertainment	Summary of findings
Taquet et al,[34] 2021	US	Retrospective cohort	TriNetX Analytics Network	January 20, 2020, to August 1, 2020	62 354 COVID-19-positive patients, 69.8 million in database	Age range: ≥18 y[d]; mean (SD) age: 49.3 (19.7) y[d]; sex, F/M: 55.4%/45.1%[d]	Mood disorder(s)	*ICD-10* diagnosis for mood disorder; *ICD-10* diagnosis for COVID-19	Preexisting mood disorders were associated with significantly higher odds of COVID-19 susceptibility (OR, 1.75; 95% CI, 1.68-1.82).[a]
van der Meer et al,[35] 2020	UK	Retrospective cohort	UK BioBank	March 16, 2020, to April 16, 2020	1474 Tested	Age range: NA; mean (SD) age: 58.2 (8.8) y; sex, F/M: 45.6%/54.4%	Depression	ICD-10 for mood disorder; RT-PCR for COVID-19	There were no associations between preexisting depression and COVID-19 test positivity (OR, 0.84; 95% CI, (0.60-1.18).[a]
Wang et al,[41] 2021	US	Retrospective case-control	IBM Watson Health Explorys	Until July 29, 2020	15 120 COVID-19-positive patients, 61 783 950 in database	Age range: ≥18 y; mean age: NA; sex, F/M: 54%/45%	Depression, bipolar disorder	SNOMED-CT diagnosis for mood disorder; SNOMED-CT diagnosis for COVID-19	Recent diagnosis of preexisting depression was associated with significantly higher odds of COVID-19 susceptibility (aOR, 7.64; 95% CI, 7.45-7.83), as was recent diagnosis of preexisting BD (aOR, 5.72; 95% CI, 5.35-6.10). Preexisting depression was not associated with higher odds of COVID-19 hospitalization (OR, 1.39; 95% CI, 1.23-1.57)[a] or death (OR, 1.56; 95% CI, 1.28-1.91).[a]
Yang et al,[32] 2020	England	Retrospective cohort	UK BioBank, linked to Public Health England	Jan 31, 2020, to July 26, 2020	13 502 Tested, 421 014 total	Age range: 40-69 y; mean (SD) age: 67.8 (8.12) y; sex, F/M: 55.1%/44.9%	Depression	*ICD-9* or *ICD-10* diagnosis for mood disorder; RT-PCR for COVID-19	Preexisting depression was associated with significantly higher odds of COVID-19 susceptibility (aOR, 1.62; 95% CI, 1.40-1.87), related hospitalization (aOR, 1.70; 95% CI, 1.43-2.01), and related death (aOR, 2.68; 95% CI, 2.03-3.54).
Yanover et al,[36] 2020	Israel	Retrospective cohort	Maccabi Health Services	Test results until April 22, 2020; follow-up until April 30, 2020, or patient death	100 609 Tested	Age range: NA; median (IQR) age: 35 (22-54)[d]; sex, F/M: 44.5%/55.5%[d]	Depression	MHS-coded diagnosis for mood disorder; PCR for COVID-19	Preexisting depression was associated with significantly lower odds of COVID-19 susceptibility (OR, 0.85; 95% CI, 0.78-0.93).[a] There was no association between preexisting depression and COVID-19 complications, including death (aOR, 1.58; 95% CI, (0.70-3.70).

Abbreviations: aOR, adjusted odds ratio (differentially adjusted by authors of component studies); BD, bipolar disorder; EHR, electronic health record; HR, hazard ratio; *ICD-9*, *International Classification of Diseases, Ninth Revision*; *ICD-10*, *International Statistical Classification of Diseases and Related Health Problems, Tenth Revision*; ICU, intensive care unit; IQR, interquartile range; *KCD-7*, Korean version of *ICD-10*; MDD, major depressive disorder; MHS, Maccabi Health Services; NA, not available; OR, odds ratio; PCR, polymerase chain reaction; PDD, persistent depressive disorder; PheWAS, phenome-wide association study; RT-PCR, reverse transcription–polymerase chain reaction; SHR, subhazard ratio; SNOMED-CT, Systematized Nomenclature of Medicine Clinical Terms.

[a] Unadjusted ORs calculated from summary data.

[b] This article was a preprint as of July 28, 2021.

[c] Tested.

[d] COVID-19 positive.

[e] COVID-19 negative.

[f] Matched cohort.

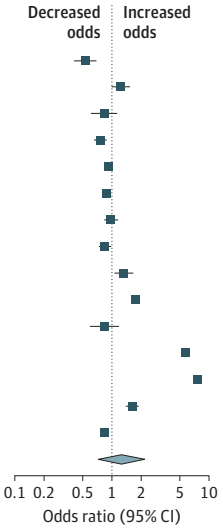
[g] Composite ORs calculated from reported subgroup ORs.

[h] Data from revised data set provided by study author on February 19, 2021. All other values from Salvatore et al[42] are from the unrevised data set published July 1, 2020 (preprint).

Figure 2. Pooled Odds Ratios for COVID-19 Susceptibility, Hospitalization, Severe Events, and Death in Individuals With vs Without Preexisting Mood Disorders

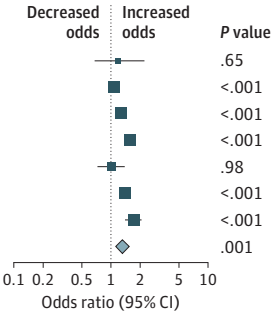
A COVID-19 susceptibility

Study name	Odds ratio (95% CI)	P value
Azar et al,[39] 2020	0.53 (0.41-0.69)	<.001
Chang et al,[22] 2020	1.23 (0.99-1.53)	.06
Haimovich et al,[24] 2020	0.83 (0.61-1.13)	.24
Jeon et al,[26] 2021	0.76 (0.66-0.88)	<.001
Ji et al,[27] 2020	0.93 (0.84-1.02)	.11
Nemani et al,[40] 2021	0.88 (0.80-0.97)	.01
Orlando et al,[28] 2021	0.98 (0.84-1.15)	.80
Salvatore et al,[42] 2021	0.85 (0.74-0.98)	.02
Tang et al,[31] 2020	1.33 (1.07-1.65)	.01
Taquet et al,[34] 2021	1.75 (1.68-1.82)	<.001
van der Meer et al,[35] 2020	0.84 (0.60-1.18)	.31
Wang et al,[41] 2021	5.72 (5.36-6.11)	<.001
Wang et al,[41] 2021	7.64 (7.45-7.83)	<.001
Yang et al,[32] 2020	1.62 (1.40-1.87)	<.001
Yanover et al,[36] 2020	0.85 (0.78-0.93)	<.001
Total	1.27 (0.73-2.19)	.40



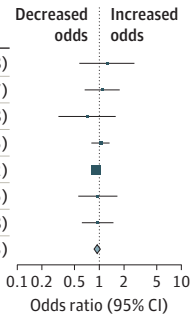
B COVID-19 hospitalization

Study name	Odds ratio (95% CI)	P value
Azar et al,[39] 2020	1.18 (0.57-2.43)	.65
Chang et al,[23] 2021	1.07 (1.06-1.08)	<.001
Izurieta et al,[25] 2020	1.26 (1.22-1.30)	<.001
Murk et al,[33] 2021	1.56 (1.49-1.62)	<.001
Salvatore et al,[42] 2021	1.01 (0.73-1.38)	.98
Wang et al,[41] 2021	1.39 (1.23-1.57)	<.001
Yang et al,[32] 2020	1.70 (1.41-2.06)	<.001
Total	1.31 (1.12-1.53)	.001



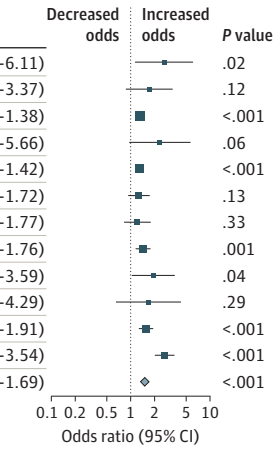
C COVID-19 severe events

Study name	Odds ratio (95% CI)	P value
Azar et al,[39] 2020	1.24 (0.58-2.68)	.58
Douville et al,[38] 2020	1.09 (0.67-1.77)	.74
Jeon et al,[26] 2021	0.71 (0.32-1.58)	.40
Ji et al,[27] 2020	1.04 (0.81-1.33)	.79
Murk et al,[33] 2021	0.92 (0.84-1.02)	.11
Rodriguez-Molinero et al,[30] 2020	0.96 (0.56-1.65)	.88
Salvatore et al,[42] 2021	0.96 (0.62-1.48)	.84
Total	0.94 (0.87-1.03)	.19



D COVID-19 death

Study name	Odds ratio (95% CI)	P value
Azar et al,[39] 2020	2.64 (1.14-6.11)	.02
Douville et al,[38] 2020	1.71 (0.87-3.37)	.12
Izurieta et al,[25] 2020	1.32 (1.26-1.38)	<.001
Jeon et al,[26] 2021	2.33 (0.96-5.66)	.06
Kundi et al,[37] 2020	1.30 (1.19-1.42)	<.001
Nemani et al,[40] 2021	1.27 (0.94-1.72)	.13
Orlando et al,[28] 2021	1.21 (0.83-1.77)	.33
Poblador-Plou et al,[29] 2020	1.43 (1.16-1.76)	.001
Rodriguez-Molinero et al,[30] 2020	1.93 (1.04-3.59)	.04
Salvatore et al,[42] 2021	1.67 (0.65-4.29)	.29
Wang et al,[41] 2021	1.56 (1.28-1.91)	<.001
Yang et al,[32] 2020	2.68 (2.03-3.54)	<.001
Total	1.51 (1.34-1.69)	<.001



A, There was no association between COVID-19 susceptibility and preexisting mood disorders (n = 65 514 469). B, The odds of COVID-19 hospitalization were significantly greater for individuals with preexisting mood disorders when compared with those without mood disorders (n = 26 554 397). C, There was no association between COVID-19 severe events or preexisting mood disorders (n = 83 240). D, The odds of COVID-19-related death were significantly greater for individuals with preexisting mood disorders when compared with those without mood disorders (n = 25 808 660). Squares represent effect sizes of individual studies, lines indicate the 95% CIs, and the diamond represents the summary effect size (ie, statistical combination of the effect sizes of component studies via the random-effects model).

COVID-19 Severe Events

There was no association between COVID-19 severe events and preexisting mood disorders (OR, 0.94; 95% CI, 0.87-1.03; P = .19; n = 83 240) (Figure 2C). Furthermore, sensitivity analyses restricted to depression, comparing unadjusted vs aORs, based on study design or quality, and excluding possible data duplication did not find any associations (Table 3).

COVID-19–Related Death

The odds of COVID-19-related death were significantly greater for individuals with preexisting mood disorders when compared with those without mood disorders (OR, 1.51; 95% CI, 1.34-1.69; P < .001; PI, 1.09-2.07; n = 25 808 660) (Figure 2D). Compared with the foregoing OR, the summary effect size was greater when the meta-analysis was restricted to aORs (OR, 1.57; 95% CI, 1.26-1.95; P < .001) (Table 3) and markedly so when restricting analysis to high-quality studies (OR, 1.80; 95% CI, 1.30-2.51; P < .001) (Table 3). Furthermore, the effect size modestly increased when the exposure was restricted to depression (OR, 1.55; 95% CI, 1.34-1.79; P < .001) and did not markedly change depending on study design (Table 3).

Heterogeneity

The meta-analysis for COVID-19 hospitalization exhibited considerable heterogeneity (I^2 = 98.5%). The meta-analysis for COVID-19-related death exhibited substantial heterogeneity (I^2 = 67.2%). Meta-regression results are provided in eTable 2 in the Supplement.

Publication Bias

Visual inspection of funnel plot asymmetry for the COVID-19 hospitalization meta-analysis indicated the pres-

Table 3. Random-Effects Sensitivity Analyses by Study Subgroup

Moderator[a]	No. of Studies	OR (95% CI)	*P* value	Heterogeneity (I^2)[b]
COVID-19 susceptibility				
Exposure: depression	9	1.23 (0.49-3.09)	.66	99.8
ORs				
Adjusted	9	1.50 (0.75-2.99)	.25	99.8
Unadjusted	5	0.91 (0.58-1.41)	.66	100
Study design				
Case-control studies	6	1.66 (0.75-3.67)	.21	99.8
Cohort studies	8	1.00 (0.72-1.38)	>.99	98.5
No duplicate databases[c]	12	1.36 (0.76-2.43)	.31	99.9
NOS rating				
High	10	0.98 (0.75-1.28)	.90	98.4
Moderate/low	4	2.16 (1.28-3.66)	.004	99.4
COVID-19 hospitalization				
Exposure: depression	5	1.30 (1.13-1.48)	<.001	96.9
ORs				
Adjusted	4	1.27 (1.09-1.47)	.002	97.4
Unadjusted	3	1.38 (1.17-1.63)	<.001	79.8
Study design				
Case-control studies	3	1.16 (0.95-1.42)	.15	88.1
Cohort studies	3	1.41 (1.09-1.82)	.008	78.4
NOS rating				
High	5	1.30 (1.00-1.69)	.05	98.7
Moderate/low	2	1.30 (1.19-1.41)	<.001	53.3
COVID-19 severe events				
Exposure: depression	3	1.06 (0.77-1.48)	.71	…
ORs				
Adjusted	3	0.99 (0.80-1.24)	.96	…
Unadjusted	4	0.93 (0.85-1.03)	.16	…
Study design				
Case-control studies	3	1.03 (0.84-1.25)	.80	…
Cohort studies	3	0.95 (0.65-1.41)	.81	…
No duplicate databases[c]	6	0.93 (0.85-1.02)	.13	…
NOS rating				
High	6	0.94 (0.86-1.03)	.16	…
Moderate/low	1	1.09 (0.67-1.77)	.74	…
COVID-19–related death				
Exposure: depression	8	1.55 (1.34-1.79)	<.001	77.7
ORs				
Adjusted	7	1.57 (1.26-1.95)	<.001	78.4
Unadjusted	5	1.44 (1.23-1.68)	<.001	29.5
Study design				
Case-control studies	4	1.50 (1.26-1.77)	<.001	…
Cohort studies	8	1.53 (1.33-1.77)	<.001	77.0
NOS rating				
High	7	1.80 (1.30-2.51)	<.001	67.1
Moderate/low	5	1.33 (1.28-1.38)	<.001	…

Abbreviations: aOR, adjusted odds ratio (adjusted by authors of included studies for variable combinations of factors, such as age, sex, and comorbidities); NOS, Newcastle-Ottawa Scale; OR, odds ratio.

[a] Variable that the analysis is restricted to (ie, analysis only includes studies that exhibit the specific characteristic or report the specified outcome).

[b] Heterogeneity values that were not statistically significant ($P > .05$) and reported by the statistical software as 0 are represented by ellipses.

[c] If multiple studies derived data from the same database, only the study with the largest analyzed sample size from each duplicate database was retained in the no duplicate databases subgroup analysis to eliminate the possibility of data overlap, regardless of data acquisition period.

ence of publication bias, and the Egger regression intercept test was statistically significant (eFigure 2 in the Supplement). Likewise, visual inspection of funnel plot asymmetry for the COVID-19–related death meta-analysis indicated the presence of publication bias, and the Egger regression intercept test result was statistically significant (eFigure 3 in the Supplement). Although the Egger regression intercept test result was not statistically significant (eFigure 1 in the Supplement), visual inspection of the composite funnel plot (ie, for all data sets included in the review, including both aORs and unadjusted ORs) indicated the presence of publication bias.

Excluded Results

Relevant results from Tang et al[31] could not be incorporated into the COVID-19 hospitalization meta-analysis because of variant intrastudy follow-up times; however, this study similarly established a higher subhazard ratio of 1.33 (95% CI, 1.01-1.75; $P < .05$) of COVID-19 hospitalization for skilled nursing facility residents with preexisting mood disorders vs those without mood disorders. Relevant results from Yanover et al[36] could not be incorporated into the COVID-19 severe events meta-analysis because of variant intrastudy follow-up times; however, there was no association between preexisting depression and COVID-19 complications (including death) (aOR, 1.58; 95% CI, 0.70-3.70). Finally, relevant results from Tang et al[31] could not be included in the COVID-19–related death meta-analysis because of variant intrastudy follow-up times; however, the reported result was not statistically significant (hazard ratio, 1.08; 95% CI, 0.77-1.50) for COVID-19–related death.

Discussion

This systematic review and meta-analysis identified higher odds of COVID-19 hospitalization and death in individuals with preexisting mood disorders compared with individuals without mood disorders. However, no significant associations between COVID-19 susceptibility and severe events were identified. The foregoing results are in accordance with a recent meta-analysis that examined all grouped psychiatric illnesses by Toubasi et al,[16] which reported a higher risk of COVID-19 death, although the current meta-analysis does not similarly report a higher risk of severe events.

There are multiple pathways by which persons with mood disorders may be at greater risk for COVID-19 hospitalization and death. Social determinants, including economic insecurity, insufficient access to primary preventive health care, and lower health literacy, may portend COVID-19 risk.[46,47] For example, many individuals with mood disorders reside in congregate facilities, such as psychiatric inpatient units, homeless shelters, community housing, and prisons, where risk of COVID-19 transmission is increased because of the inability to effectively socially distance and/or quarantine.[48,49] Moreover, symptoms of mood disorders, including disinhibition, apathy, avolition, and cognitive deficits, may presage nonconcordance with healthy behaviors and possibly public health directives. However, some of the possible mediators discussed may act as confounders; hence, causal inferences with respect to social determinants of health, mood disorders, and COVID-19 outcomes cannot be established.

Furthermore, cigarette smoking[50,51] and substance use disorders,[52] established risk factors for COVID-19 infection and complications, are significantly more prevalent among individuals with mood disorders. In addition, persons with mood disorders are differentially affected by noncommunicable diseases that are established risk factors for COVID-19 (eg, obesity and cardiovascular disease[8,9]) as well as behaviors (eg, sleep dysregulation and habitual inactivity) that may presage COVID-19 risk.[53]

Disturbance in immune regulation is also a well-documented abnormality in subpopulations of persons with mood disorders.[6,7] For example, it has been reported that subsets of populations with mood disorders exhibit increases in central and peripheral levels of acute-phase proteins, such as C-reactive peptide, and proinflammatory cytokines, such as interleukin 6 and tumor necrosis factor α.[6,54-57] The inflammatory signature of mood disorders overlaps with clinical reports[57,58] of increased cytokine activity in persons affected with severe COVID-19. It is hypothesized that the cytokine disturbance intrinsic to mood disorders may be exacerbated in situations of COVID-19 infection, increasing the risk of death and complications from COVID-19.

Pharmacotherapy prescribed to individuals with mood disorders exerts disparate effects on the immune inflammatory system. Benzodiazepines and select atypical antipsychotics have been associated with a higher risk of pneumonia and/or COVID-19.[59-62] Interpretation of this finding is, however, complicated by confounding by indication as well as by other lines of research reporting that some antipsychotics exert anti-inflammatory effects.[63] Moreover, lithium exerts substantial immune-modulating and anti-inflammatory effects,[64] and valproate has been associated with a lower risk of respiratory infections.[65] Preliminary results from controlled and observational studies[66-70] also suggest that conventional antidepressants provide protective effects against COVID-19 complications. The foregoing finding would be in accordance with preclinical work documenting anti-inflammatory and/or anti-SARS-CoV-2 replication effects of select selective serotonin reuptake inhibitors.[71,72]

It warrants consideration that the risk of being infected and possibly experiencing complications from COVID-19 in adults with mood disorders may have overlapping but different determinants. For example, individuals with mood disorders report higher rates of social isolation, unemployment, and reduced interpersonal contact, which would be hypothesized to decrease their risk of COVID-19 exposure and/or complications. In addition, individuals with mood disorders are also more likely to have insufficient access to primary preventive health care, live in congregate settings, and engage in behaviors (eg, smoking cigarettes) that would place them at higher risk of contracting COVID-19 and experiencing complications, as previously discussed.

Moreover, it is counterintuitive that the OR for the intermediary of COVID-19 severe events was not statistically significant, whereas the ORs for hospitalization and death were statistically significant. Possible explanations for this finding include interstudy variation in how severe events were defined (Table 1), differences across studies in event reporting and coding, and heterogeneity in statistical approaches. Furthermore, the COVID-19 severe events analysis included a relatively small sample size.

The calculated OR for COVID-19–related death is comparable to reported unadjusted ORs and aORs for other preexisting conditions that are risk factors for COVID-19 (eg, diabetes,[73,74] liver disease[74] cancer,[75] and obesity[4,76]). Notably, the higher COVID-19 risk in individuals with mood disorders cannot be fully accounted for by medical comorbidity.

Limitations

This study has limitations. There are several methodological aspects that may affect inferences and interpretations of the results. The pathways highlighted are not definitive and thus may not adequately address associations among the primary outcomes. First, component studies were observational, and therefore causal relationships cannot be inferred. Second, data missing because of factors such as publication bias and the possibility of grouping of mood disorders with other mental disorders could confound interpretation. Third, the lack of distinction in multiple studies as to whether an individual with a mood disorder had major depressive disorder or bipolar disorder is also a substantial limitation insofar as there are differences between the 2 conditions in their overall risk of medical comorbidity.[77] Fourth, it was not possible to quantify the extent of unexplained heterogeneity or assess the causes of the substantial to considerable heterogeneity among studies included in our random-effects meta-analytic model. We recognize that high heterogeneity in meta-analytic studies may belie study findings. Fifth, it is not certain whether, in some cases, the dependent measures (eg, hospitalization) were confounded by other factors (eg, health care systems, staffing, local standard operating procedures, policies regarding hospitalization and testing, and attribution of cause of death),[78] and a quantitative characterization of the influence of mediators (eg, comorbidities) was not possible because sufficient information was not provided by the included studies. Sixth, many component studies had insufficient characterization of patient sociodemographic characteristics, as well as clinical, psychiatric, comorbidity, and smoking histories, which may have confounded or limited results. Seventh, there is a possibility that the component studies may have misdiagnosed patients or misentered patient information into administrative data records, which is an inherent limitation of observational data and administrative data sets. In addition, there was variability in how controls were defined (Table 1); notably, this study included individuals ascertained as not having COVID-19 who may not have had a laboratory confirmation. Furthermore, the Egger regression test is suboptimal toward the characterization of publication bias in analyses that involve ORs.[79] An additional methodological aspect that may affect interpretation of our findings relates to our inability to fully characterize the temporality of events. For example, it is possible that, in some cases, COVID-19 was not a subsequent event in an individual with a previously declared mood disorder. Instead, in some cases COVID-19 may have been an antecedent to the onset of mood disorders because it is well established that COVID-19 infection results in a significant increase in a variety of neuropsychiatric disorders.[12] Moreover, some of the included studies were preprints (Table 2) and thus not yet peer reviewed. In addition, the possibility that some studies included overlapping samples cannot be excluded. Notwithstanding, results from the sensitivity analyses, wherein studies that may have had overlapping samples were excluded, were consistent with the overall findings (Table 3). Most of the included studies were conducted within the first 6 to 9 months of the pandemic, which possibly oversampled persons with symptomatic COVID-19 because of prioritized testing and thus may underestimate the associations between mood disorders and COVID-19 complications. Selective COVID-19 testing and a lack of adjudication in databases or accuracy of the original clinical diagnoses were not accounted for by either of the modified NOSs.

Conclusions

In this systematic review and meta-analysis examining the association between preexisting mood disorders and COVID-19 outcomes, results of analyses of more than 91 million people indicated that individuals with preexisting mood disorders are at a higher risk of COVID-19 hospitalization and death. These results suggest that individuals with mood disorders, like persons with other preexisting conditions (eg, obesity), should be categorized as an at-risk group on the basis of a preexisting condition. Future research should address whether COVID-19 vaccinations exhibit differential efficacy in persons with mood disorders and whether COVID-19 infection affects the longitudinal trajectory of the underlying mental disorder.[80,81]

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Supervision: Nogo, Lee, Mansur, Lin, Rosenblat, Ho, McIntyre.

Conflict of Interest Disclosures: Ms Lee reported receiving personal fees from Braxia Scientific Corp outside the submitted work. Ms Lui is a contractor to Braxia Scientific Corp. Ms Teopiz reported receiving personal fees from Braxia Scientific Corp

outside the submitted work. Dr Rosenblat is the medical director of Braxia Health (formally known as the Canadian Rapid Treatment Center of Excellence and is a fully owned subsidiary of Braxia Scientific Corp), which provides ketamine and esketamine treatment for depression, and has received research grant support from the American Psychiatric Association, American Society of Psychopharmacology, Canadian Cancer Society, Canadian Psychiatric Association, Joseph M. West Family Memorial Fund, Timeposters Fellowship, University Health Network Centre for Mental Health, and University of Toronto and speaking, consultation, or research fees from Allergan, COMPASS, Janssen, Lundbeck, and Sunovion. Dr McIntyre reported receiving grant support from Canadian Institutes of Health Research, Global Alliance for Chronic Diseases, and Chinese National Natural Research Foundation and speaker/consultation fees from Lundbeck, Janssen, Purdue, Pfizer, Otsuka, Takeda, Neurocrine, Sunovion, Bausch Health, Novo Nordisk, Kris, Sanofi, Eisai, Intra-Cellular, NewBridge Pharmaceuticals, and AbbVie. Dr McIntyre is a chief executive officer of Braxia Scientific Corp.

REFERENCES

1. Keaten J. WHO: 10% of world's people may have been infected with virus. Associated Press website. Updated 2020. Accessed February 15, 2020. https://apnews.com/article/virus-outbreak-archive-united-nations-54a3a5869c9ae4ee623497691e796083

2. Wiersinga WJ, Rhodes A, Cheng AC, Peacock SJ, Prescott HC. Pathophysiology, transmission, diagnosis, and treatment of coronavirus disease 2019 (COVID-19): a review. *JAMA*. 2020;324(8):782-793. doi:10.1001/jama.2020.12839

3. Jordan RE, Adab P, Cheng KK. Covid-19: risk factors for severe disease and death. *BMJ*. 2020;368:m1198. doi:10.1136/bmj.m1198

4. Huang Y, Lu Y, Huang YM, et al. Obesity in patients with COVID-19: a systematic review and meta-analysis. *Metabolism*. 2020;113:154378. doi:10.1016/j.metabol.2020.154378

5. Xiong J, Lipsitz O, Nasri F, et al. Impact of COVID-19 pandemic on mental health in the general population: a systematic review. *J Affect Disord*. 2020;277:55-64. doi:10.1016/j.jad.2020.08.001

6. Rosenblat JD, Cha DS, Mansur RB, McIntyre RS. Inflamed moods: a review of the interactions between inflammation and mood disorders. *Prog Neuropsychopharmacol Biol Psychiatry*. 2014;53:23-34. doi:10.1016/j.pnpbp.2014.01.013

7. Rosenblat JD, McIntyre RS. Bipolar disorder and inflammation. *Psychiatr Clin North Am*. 2016;39(1):125-137. doi:10.1016/j.psc.2015.09.006

8. Fenton WS, Stover ES. Mood disorders: cardiovascular and diabetes comorbidity. *Curr Opin Psychiatry*. 2006;19(4):421-427. doi:10.1097/01.yco.0000228765.33356.9f

9. McIntyre RS, Carvalho AF. Mood disorders and general medical comorbidities: shared biology and novel therapeutic targets. *Curr Mol Med*. 2016;16(2):104-105. doi:10.2174/1566524016999160127110934

10. Varatharaj A, Thomas N, Ellul MA, et al. Neurological and neuropsychiatric complications of COVID-19 in 153 patients: a UK-wide surveillance study. *Lancet Psychiatry*. 2020;7(10):875-882. doi:10.1016/S2215-0366(20)30287-X

11. Mukaetova-Ladinska E, Kronenberg G. Psychological and neuropsychiatric implications of COVID-19. *Eur Arch Psychiatry Clin Neurosci*. 2021;271(2):235-248. doi:10.1007/s00406-020-01210-2

12. Taquet M, Geddes JR, Husain M, Luciano S, Harrison PJ. 6-month neurological and psychiatric outcomes in 236 379 survivors of COVID-19: a retrospective cohort study using electronic health records. *Lancet Psychiatry*. 2021;8(5):416-427. doi:10.1016/S2215-0366(21)00084-5

13. Yao H, Chen JH, Xu YF. Patients with mental health disorders in the COVID-19 epidemic. *Lancet Psychiatry*. 2020;7(4):e21. doi:10.1016/S2215-0366(20)30090-0

14. Shinn AK, Viron M. Perspectives on the COVID-19 pandemic and individuals with serious mental illness. *J Clin Psychiatry*. 2020;81(3):20. doi:10.4088/JCP.20com13412

15. Mazereel V, Van Assche K, Detraux J, De Hert M. COVID-19 vaccination for people with severe mental illness: why, what, and how? *Lancet Psychiatry*. 2021;8(5):444-450. doi:10.1016/S2215-0366(20)30564-2

16. Toubasi AA, AbuAnzeh RB, Tawileh HBA, Aldebei RH, Alryalat SAS. A meta-analysis: the mortality and severity of COVID-19 among patients with mental disorders. *Psychiatry Res*. 2021;299:113856. doi:10.1016/j.psychres.2021.113856

17. Steel Z, Marnane C, Iranpour C, et al. The global prevalence of common mental disorders: a systematic review and meta-analysis 1980-2013. *Int J Epidemiol*. 2014;43(2):476-493. doi:10.1093/ije/dyu038

18. Stroup DF, Berlin JA, Morton SC, et al. Meta-analysis of observational studies in epidemiology: a proposal for reporting. *JAMA*. 2000;283(15):2008-2012. doi:10.1001/jama.283.15.2008

19. Moher D, Liberati A, Tetzlaff J, Altman DG; PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *BMJ*. 2009;339:b2535. doi:10.1136/bmj.b2535

20. Stang A. Critical evaluation of the Newcastle-Ottawa scale for the assessment of the quality of nonrandomized studies in meta-analyses. *Eur J Epidemiol*. 2010;25(9):603-605. doi:10.1007/s10654-010-9491-z

21. Higgins JPT, Li T, Deeks JJ. *Choosing effect measures and computing estimates of effect*. In: *Cochrane Handbook for Systematic Reviews of Interventions*. Cochrane; 2019:143-176. doi:10.1002/9781119536604.ch6

22. Chang TS, Ding Y, Freund MK, et al. Prior diagnoses and medications as risk factors for COVID-19 in a Los Angeles Health System. Preprint posted online July 4, 2020. *medRxiv*. doi:10.1101/2020.07.03.20145581

23. Chang M, Moonesinghe R, Truman BI. COVID-19 hospitalization by race and ethnicity: association with chronic conditions among Medicare beneficiaries, January 1-September 30, 2020. *J Racial Ethn Health Disparities*. 2021:1-10. doi:10.1007/s40615-020-00960-y

24. Haimovich AD, Warner F, Young HP, et al. Patient factors associated with SARS-CoV-2 in an admitted emergency department population. *Ann Emerg Med*. 2020;1(4):569-577. doi:10.1002/emp2.12145

25. Izurieta HS, Graham DJ, Jiao Y, et al. Natural history of coronavirus disease 2019: risk factors for hospitalizations and deaths among >26 million US Medicare beneficiaries. *J Infect Dis*. 2021;223(6):945-956. doi:10.1093/infdis/jiaa767

26. Jeon HL, Kwon JS, Park SH, Shin JY. Association of mental disorders with SARS-CoV-2 infection and severe health outcomes: nationwide cohort study. *Br J Psychiatry*. 2021:1-8. doi:10.1192/bjp.2020.251

27. Ji W, Huh K, Kang M, et al. Effect of underlying comorbidities on the infection and severity of COVID-19 in Korea: a nationwide case-control study. *J Korean Med Sci*. 2020;35(25):e237. doi:10.3346/jkms.2020.35.e237

28. Orlando V, Rea F, Savaré L, et al. Development and validation of a clinical risk score to predict the risk of SARS-CoV-2 infection from administrative data: a population-based cohort study from Italy. *PLoS One*. 2021;16(1):e0237202. doi:10.1371/journal.pone.0237202

29. Poblador-Plou B, Carmona-Pírez J, Ioakeim-Skoufa I, et al; EpiChron Group. Baseline chronic comorbidity and mortality in laboratory-confirmed COVID-19 cases: results from the PRECOVID study in Spain. *Int J Environ Res Public Health*. 2020;17(14):5171. doi:10.3390/ijerph17145171

30. Rodríguez-Molinero A, Gálvez-Barrón C, Miñarro A, et al; COVID-19 Research Group of CSAPG. Association between COVID-19 prognosis and disease presentation, comorbidities and chronic treatment of hospitalized patients. *PLoS One*. 2020;15(10):e0239571. doi:10.1371/journal.pone.0239571

31. Tang O, Bigelow BF, Sheikh F, et al. Outcomes of nursing home COVID-19 patients by initial symptoms and comorbidity: results of universal testing of 1970 residents. *J Am Med Dir Assoc*. 2020;21(12):1767-1773.e1. doi:10.1016/j.jamda.2020.10.011

32. Yang H, Chen W, Hu Y, et al. Pre-pandemic psychiatric disorders and risk of COVID-19: a UK Biobank cohort analysis. *Lancet Healthy Longev*. 2020;1(2):e69-e79. doi:10.1016/S2666-7568(20)30013-1

33. Murk W, Gierada M, Fralick M, Weckstein A, Klesh R, Rassen JA. Diagnosis-wide analysis of COVID-19 complications: an exposure-crossover study. *CMAJ*. 2021;193(1):E10-E18. doi:10.1503/cmaj.201686

34. Taquet M, Luciano S, Geddes JR, Harrison PJ. Bidirectional associations between COVID-19 and psychiatric disorder: retrospective cohort studies of 62 354 COVID-19 cases in the USA. *Lancet Psychiatry*. 2021;8(2):130-140. doi:10.1016/S2215-0366(20)30462-4

35. van der Meer D, Pinzón-Espinosa J, Lin BD, et al. Associations between psychiatric disorders, COVID-19 testing probability and COVID-19 testing results: findings from a population-based study. *B J Psych Open*. 2020;6(5):e87. doi:10.1192/bjo.2020.75

36. Yanover C, Mizrahi B, Kalkstein N, et al. What factors increase the risk of complications in SARS-CoV-2-infected patients? a cohort study in a nationwide Israeli health organization. *JMIR Public Health Surveill*. 2020;6(3):e20872. doi:10.2196/20872

37. Kundi H, Çetin EHÖ, Canpolat U, et al. The role of frailty on adverse outcomes among older patients with COVID-19. *J Infect*. 2020;81(6):944-951. doi:10.1016/j.jinf.2020.09.029

38. Douville NJ, Douville CB, Mentz G, et al. Clinically applicable approach for predicting mechanical ventilation in patients with COVID-19.

Br J Anaesth. 2021;126(3):578-589. doi:10.1016/j.bja.2020.11.034

39. Azar K, Shen Z, Romanelli RJ, et al. Disparities in outcomes among COVID-19 patients in a large health care system in California. *Health Aff (Millwood)*. 2020;39(7):1253-1262. doi:10.1377/hlthaff.2020.00598

40. Nemani K, Li C, Olfson M, et al. Association of psychiatric disorders with mortality among patients with COVID-19. *JAMA Psychiatry*. 2021;78(4):380-386. doi:10.1001/jamapsychiatry.2020.4442

41. Wang Q, Xu R, Volkow ND. 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;20(1):124-130. doi:10.1002/wps.20806

42. Salvatore M, Gu T, Mack JA, et al. A phenome-wide association study (PheWAS) of COVID-19 outcomes by race using the electronic health records data in Michigan Medicine. *J Clin Med*. 2021;10(7):1351. doi:10.3390/jcm10071351

43. Barili F, Parolari A, Kappetein PA, Freemantle N. Statistical Primer: heterogeneity, random- or fixed-effects model analyses? *Interact CardioVasc Thorac Surg*. 2018;27(3):317-321. doi:10.1093/icvts/ivy163

44. Deeks JJ, Higgins JPT, Altman DG, eds. Analysing data and undertaking meta-analyses. In: *Cochrane Handbook for Systematic Reviews of Interventions*. Cochrane; 2008:243-296. doi:10.1002/9780470712184.ch9

45. Schünemann H.J., Higgins JPT, Vist GE, et al, eds. *Completing 'Summary of findings' tables and grading the certainty of the evidence*. In: *Cochrane Handbook for Systematic Reviews of Interventions*. Cochrane; 2019:375-402. doi:10.1002/9781119536604.ch14

46. Paakkari L, Okan O. COVID-19: health literacy is an underestimated problem. *Lancet Public Health*. 2020;5(5):e249-e250. doi:10.1016/S2468-2667(20)30086-4

47. Abrams EM, Szefler SJ. COVID-19 and the impact of social determinants of health. *Lancet Respir Med*. 2020;8(7):659-661. doi:10.1016/S2213-2600(20)30234-4

48. Zhu Y, Chen L, Ji H, Xi M, Fang Y, Li Y. The risk and prevention of novel coronavirus pneumonia infections among inpatients in psychiatric hospitals. *Neurosci Bull*. 2020;36(3):299-302. doi:10.1007/s12264-020-00476-9

49. Kar SK, Arafat SMY, Marthoenis M, Kabir R. Homeless mentally ill people and COVID-19 pandemic: the two-way sword for LMICs. *Asian J Psychiatr*. 2020;51:102067. doi:10.1016/j.ajp.2020.102067

50. Dickerson F, Schroeder J, Katsafanas E, et al. Cigarette smoking by patients with serious mental illness, 1999–2016: an increasing disparity. *Psychiatr Serv*. 2018;69(2):147-153. doi:10.1176/appi.ps.201700118

51. Covey LS, Glassman AH, Stetner F. Cigarette smoking and major depression. *J Addict Dis*. 1998;17(1):35-46. doi:10.1300/J069v17n01_04

52. Wang QQ, Kaelber DC, Xu R, Volkow ND. COVID-19 risk and outcomes in patients with substance use disorders: analyses from electronic health records in the United States. *Mol Psychiatry*. 2021;26(1):30-39. doi:10.1038/s41380-020-00880-7

53. Hert MDE, Correll CU, Bobes J, et al. Physical illness in patients with severe mental disorders, I: prevalence, impact of medications and disparities in health care. *World Psychiatry*. 2011;10(1):52-77. doi:10.1002/j.2051-5545.2011.tb00014.x

54. Brietzke E, Stertz L, Fernandes BS, et al. Comparison of cytokine levels in depressed, manic and euthymic patients with bipolar disorder. *J Affect Disord*. 2009;116(3):214-217. doi:10.1016/j.jad.2008.12.001

55. Miller AH. Depression and immunity: a role for T cells? *Brain Behav Immun*. 2010;24(1):1-8. doi:10.1016/j.bbi.2009.09.009

56. Howren MB, Lamkin DM, Suls J. Associations of depression with C-reactive protein, IL-1, and IL-6: a meta-analysis. *Psychosom Med*. 2009;71(2):171-186. doi:10.1097/PSY.0b013e3181907c1b

57. Dowlati Y, Herrmann N, Swardfager W, et al. A meta-analysis of cytokines in major depression. *Biol Psychiatry*. 2010;67(5):446-457. doi:10.1016/j.biopsych.2009.09.033

58. Giamarellos-Bourboulis E, Netea MG, Rovina N, et al. Complex immune dysregulation in COVID-19 patients with severe respiratory failure. *Cell Host Microbe*. 2020;27(6):992-1000.e3. doi:10.1016/j.chom.2020.04.009

59. Obiora E, Hubbard R, Sanders RD, Myles PR. The impact of benzodiazepines on occurrence of pneumonia and mortality from pneumonia: a nested case-control and survival analysis in a population-based cohort. *Thorax*. 2013;68(2):163-170. doi:10.1136/thoraxjnl-2012-202374

60. Dzahini O, Singh N, Taylor D, Haddad PM. Antipsychotic drug use and pneumonia: systematic review and meta-analysis. *J Psychopharmacol*. 2018;32(11):1167-1181. doi:10.1177/0269881118795333

61. de Leon J, Ruan CJ, Verdoux H, Wang C. Clozapine is strongly associated with the risk of pneumonia and inflammation. *Gen Psychiatr*. 2020;33(2):e100183. doi:10.1136/gpsych-2019-100183

62. Govind R, Fonseca de Freitas D, Pritchard M, Hayes RD, MacCabe JH. Clozapine treatment and risk of COVID-19 infection: retrospective cohort study. *Br J Psychiatry*. 2020:1-7. doi:10.1192/bjp.2020.151

63. Raison CL, Pikalov A, Siu C, Tsai J, Koblan K, Loebel A. C-reactive protein and response to lurasidone in patients with bipolar depression. *Brain Behav Immun*. 2018;73:717-724. doi:10.1016/j.bbi.2018.08.009

64. Beurel E, Jope RS. Inflammation and lithium: clues to mechanisms contributing to suicide-linked traits. *Transl Psychiatry*. 2014;4(12):e488. doi:10.1038/tp.2014.129

65. Landén M, Larsson H, Lichtenstein P, Westin J, Song J. Respiratory infections during lithium and valproate medication: a within-individual prospective study of 50,000 patients with bipolar disorder. *Int J Bipolar Disord*. 2021;9(1):4. doi:10.1186/s40345-020-00208-y

66. Nobile B, Durand M, Olié E, et al. Clomipramine could be useful in preventing neurological complications of SARS-CoV-2 infection. *J Neuroimmune Pharmacol*. 2020;15(3):347-348. doi:10.1007/s11481-020-09939-2

67. Hoertel N, Sánchez-Rico M, Vernet R, et al; AP-HP / Universities/INSERM COVID-19 Research Collaboration and AP-HP COVID CDR Initiative. Association between antidepressant use and reduced risk of intubation or death in hospitalized patients with COVID-19: results from an observational study. *Mol Psychiatry*. 2021. doi:10.1038/s41380-021-01021-4

68. Zimering MB, Razzaki T, Tsang T, Shin JJ. Inverse association between serotonin 2A receptor antagonist medication use and mortality in severe COVID-19 infection. *Endocrinol Diabetes Metab J*. 2020;4(4):1-5. https://pubmed.ncbi.nlm.nih.gov/33117497.

69. Seftel D, Boulware DR. Prospective cohort of fluvoxamine for early treatment of coronavirus disease 19. *Open Forum Infect Dis*. 2021;8(2):ofab050. doi:10.1093/ofid/ofab050

70. Lenze EJ, Mattar C, Zorumski CF, et al. Fluvoxamine vs placebo and clinical deterioration in outpatients with symptomatic COVID-19: a randomized clinical trial. *JAMA*. 2020;324(22):2292-2300. doi:10.1001/jama.2020.22760

71. Lu Y, Ho CS, Liu X, et al. Chronic administration of fluoxetine and pro-inflammatory cytokine change in a rat model of depression. *PLoS One*. 2017;12(10):e0186700. doi:10.1371/journal.pone.0186700

72. Zimniak M, Kirschner L, Hilpert H, Seibel J, Bodem J. The serotonin reuptake inhibitor fluoxetine inhibits SARS-CoV-2. Published online June 17, 2020. *bioRxiv* 5809.

73. Rosenthal N, Cao Z, Gundrum J, Sianis J, Safo S. Risk factors associated with in-hospital mortality in a US national sample of patients with COVID-19. *JAMA Netw Open*. 2020;3(12):e2029058. doi:10.1001/jamanetworkopen.2020.29058

74. Li M, Cheng B, Zeng W, et al. Analysis of the risk factors for mortality in adult COVID-19 patients in Wuhan: a multicenter study. *Front Med (Lausanne)*. 2020;7:545. doi:10.3389/fmed.2020.00545

75. Kim W, Han JM, Lee KE. Predictors of mortality in patients with COVID-19: a systematic review and meta-analysis. *Korean J Clin Pharmacy*. 2020;30(3):169-176. doi:10.24304/kjcp.2020.30.3.169

76. Zhang F, Xiong Y, Wei Y, et al. Obesity predisposes to the risk of higher mortality in young COVID-19 patients. *J Med Virol*. 2020;92(11):2536-2542. doi:10.1002/jmv.26039

77. McIntyre RS, Berk M, Brietzke E, et al. Bipolar disorders. *Lancet*. 2020;396(10265):1841-1856. doi:10.1016/S0140-6736(20)31544-0

78. Yoo JY, Dutra SVO, Fanfan D, et al. Comparative analysis of COVID-19 guidelines from six countries: a qualitative study on the US, China, South Korea, the UK, Brazil, and Haiti. *BMC Public Health*. 2020;20(1):1853. doi:10.1186/s12889-020-09924-7

79. Page MJ, Higgins JPT, Sterne JAC. Assessing risk of bias due to missing results in a synthesis. In: *Cochrane Handbook for Systematic Reviews of Interventions*. Cochrane; 2019:349-374.

80. Liao YH, Fan BF, Zhang HM, et al. The impact of COVID-19 on subthreshold depressive symptoms: a longitudinal study. *Epidemiol Psychiatr Sci*. 2021;30:e20. doi:10.1017/S2045796021000044

81. Wang C, Pan R, Wan X, et al. A longitudinal study on the mental health of general population during the COVID-19 epidemic in China. *Brain Behav Immun*. 2020;87:40-48. doi:10.1016/j.bbi.2020.04.028