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Research paper

Mental and neurological disorders and risk of COVID-19 susceptibility, illness severity and mortality: A systematic review, meta-analysis and call for action

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ABSTRACT

Background: Coronavirus disease 2019 (COVID-19) has evolved into a worldwide pandemic, and has been found to be closely associated with mental and neurological disorders. We aimed to comprehensively quantify the association between mental and neurological disorders, both pre-existing and subsequent, and the risk of susceptibility, severity and mortality of COVID-19.

Methods: In this systematic review and meta-analysis, we searched PubMed, Web of Science, Embase, PsycINFO, and Cochrane library databases for studies published from the inception up to January 16, 2021 and updated at July 7, 2021. Observational studies including cohort and case-control, cross-sectional studies and case series that reported risk estimates of the association between mental or neurological disorders and COVID-19 susceptibility, illness severity and mortality were included. Two researchers independently extracted data and conducted the quality assessment. Based on I^2 heterogeneity, we used a random effects model to calculate pooled odds ratios (OR) and 95% confidence intervals (95% CI). Subgroup analyses and meta-regression analysis were also performed. This study was registered on PROSPERO (registration number: CRD 42021230832).

Finding: A total of 149 studies (227,351,954 participants, 89,235,737 COVID-19 patients) were included in this analysis, in which 27 reported morbidity (132,727,798), 56 reported illness severity (83,097,968) and 115 reported mortality (88,878,662). Overall, mental and neurological disorders were associated with a

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significant high risk of infection (pre-existing mental: OR 1·67, 95% CI 1·12-2·49; and pre-existing neurological: 2·05, 1·58-2·67), illness severity (mental: pre-existing, 1·40, 1·25-1·57; sequelae, 4·85, 2·53-9·32; neurological: pre-existing, 1·43, 1·09-1·88; sequelae, 2·17, 1·45-3·24), and mortality (mental: pre-existing, 1·47, 1·26-1·72; neurological: pre-existing, 2·08, 1·61-2·69; sequelae, 2·03, 1·66-2·49) from COVID-19. Subgroup analysis revealed that association with illness severity was stronger among younger COVID-19 patients, and those with subsequent mental disorders, living in low- and middle-income regions. Younger patients with mental and neurological disorders were associated with higher mortality than elders. For type-specific mental disorders, susceptibility to contracting COVID-19 was associated with pre-existing mood disorders, anxiety, and attention-deficit hyperactivity disorder (ADHD); illness severity was associated with both pre-existing and subsequent mood disorders as well as sleep disturbance; and mortality was associated with pre-existing schizophrenia. For neurological disorders, susceptibility was associated with pre-existing dementia; both severity and mortality were associated with subsequent delirium and altered mental status; besides, mortality was associated with pre-existing and subsequent dementia and multiple specific neurological diseases. Heterogeneities were substantial across studies in most analysis.

Interpretation: The findings show an important role of mental and neurological disorders in the context of COVID-19 and provide clues and directions for identifying and protecting vulnerable populations in the pandemic. Early detection and intervention for neurological and mental disorders are urgently needed to control morbidity and mortality induced by the COVID-19 pandemic. However, there was substantial heterogeneity among the included studies, and the results should be interpreted with caution. More studies are needed to explore long-term mental and neurological sequela, as well as the underlying brain mechanisms for the sake of elucidating the causal pathways for these associations.

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Research in context

Evidence before this study

We reviewed evidence of association of mental and neurological disorders with susceptibility and prognosis of COVID-19 published before July 7, 2021. PubMed, Web of Science, Embase, PsycINFO, and Cochrane library databases were searched, terms included synonyms of (1) mental disorder, neurological disorder, or a particular type of disease belong to them; (2) COVID-19; (3) susceptibility, severity or mortality. Although several previous meta-analyses reported the association of mental disorders and certain neurological diseases such as dementia and Parkinson's disease with prognosis of COVID-19, a comprehensive meta-analysis and systematic evidence on the association between mental and neurological disorders and the risk of susceptibility, severity and mortality of COVID-19 is lacking.

Added value of this study

To our knowledge, this is the first meta-analysis with a large sample size (over 227 million from 21 countries) examining the association of **pre-existing and subsequent** mental and neurological disorders with the susceptibility, illness severity, and mortality of COVID-19. Results in our study suggested that mental and neurological disorders were associated with COVID-19 infection, severity, and mortality. Subgroup analysis found the association with illness severity was significantly stronger in younger COVID-19 patients with mental sequalae, living in low- and middle-income regions, while younger cases with mental and neurological disorders were associated with mortality in a higher level.

Implications of all the available evidence

This study suggests that early detection and intervention for neurological and mental disorders are important for controlling the morbidity and mortality of the COVID-19 pandemic. More studies are needed to explore the psychiatric and neurological long-term sequela and underlying brain mechanisms and elucidate the causal pathways for these associations.

1. Introduction

Coronaviruses disease 2019 (COVID-19) has evolved into a worldwide pandemic with more than 200 million individuals infected and 4 million deaths as of August 2021, resulting in a burden of over a decade in terms of potential years of life lost [1,2]. To reduce the morbidity and mortality of the COVID-19 pandemic effectively, factors associated with high susceptibility to infection and high risks of progressing to severe illness and death in COVID-19 patients have been identified including various comorbidities [3,4]. Meanwhile, the link between mental and neurological disorders with COVID-19 have been concerned as well [5,6].

Mental and neurological disorders are common among COVID-19 patients [7]. The COVID-19 virus belongs to the genus of beta coronaviruses which also includes SARS-CoV-1 and MERS-CoV; causative agents for severe acute respiratory syndrome (SARS) in 2002 and Middle East respiratory syndrome (MERS) in 2012, respectively. Beta-coronaviruses cause diseases in the central and peripheral nervous systems and commonly include mental and neurological complications [5,6,8]. The most common neurologic complaints in COVID-19 patients are anosmia, ageusia, and headache, but more serious adverse events, such as stroke, impairment of consciousness, seizure, and encephalopathy, were also reported [5]. Mental disorders among COVID-19 cases during the pandemic additionally resulted from stress and psychological problems partially due to social isolation [9-14]. A meta-analysis that included 31 studies of the psychological status of COVID-19 patients revealed that the most common psychiatric problems among patients were anxiety (47%), followed by depression (45%) and sleep disorders (34%) [15].

These mental and neurological presentations, either pre-existing or developing during coronavirus infection, were associated with illness deterioration and mortality among COVID-19 cases. A meta-analysis of 16 studies noted the likelihood of increased severity and mortality of COVID-19 with the previous history of mental illness [16]. Another recent meta-analysis suggested that the presence of pre-existing mental disorders was associated with an increased risk of COVID-19 mortality and hospitalization and the association between mortality and specific diseases such as mood disorders and substance use disorders were also observed [17]. Neurological signs after infection including delirium, confusion, agitation, and altered

consciousness have already been considered to be associated with severe clinical outcomes among infections with SARS and MERS [6]. For COVID-19 patients, dementia and Parkinson's disease were also found to be predictors of increased mortality, whereas, there was no evidence for other specific neurological disorders [18,19].

It also remains controversial whether individuals with mental and neurological disorders have a higher risk of susceptibility to COVID-19 infection. A cohort from the US showed psychiatric diagnosis might be an independent risk factor for infection with COVID-19 [20]. However, another cohort from South Korea suggested a non-significant difference [21]. Similarly, as some neurological disorders such as dementia and Parkinson's disease were associated with increased susceptibility to COVID-19 [22,23], others may show insignificant results or even relation with lower incidence of COVID-19 infection in different studies [24]. The disparities in findings across studies could be explained by differences in study outcomes, demographics and clinical characteristics, as well as socioeconomic status. In addition, different types of specific neurological and psychiatric disorders may further confound the relationships, given that the biological and neurological mechanisms of the diseases may also differ.

In view of these complicated interactions of COVID-19 infection and mental and neurological disorders, a comprehensive, rigorously conducted meta-analysis is needed to assess the overall and type-specific risk of mental and neurological disorders for COVID-19 infection and clinical outcomes. We reviewed and conducted a quantitative meta-analysis on the association between mental and neurological disorders and the risk of COVID-19 incidence, illness severity and mortality for overall and type-specific disorders. We had three main objectives. (1) We calculated the pooled overall estimates of association between mental and neurological disorders and susceptibility, illness severity and death from COVID-19. (2) We evaluated the correlation between specific mental and neurological disorders and the risk of three COVID-19 outcomes. (3) We explored the sources of heterogeneity and risk factors influencing the associations. These analyses should provide evidence for preventing and managing the brain disorders morbidity and mortality associated with the COVID-19 pandemic.

2. Methods

2.1. Search Strategy and Selection Criteria

This review was conducted using parameters consistent with PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) [25] and GATHER (Guidelines for Accurate and Transparent Health Estimates Reporting) [26]. This study was registered on PROSPERO (registration number: CRD42021230832).

In this meta-analysis, we searched PubMed, Web of Science, Embase, PsycINFO, and Cochrane library databases for studies published from inception up to January 16, 2021 and updated at July 7, 2021. We used the following keywords to identify human studies: ("Mental Disorders" OR "Psychiatric Disease" OR "Psychiatric Disorders" OR "Anxiety" OR "Depression" OR "Insomnia" OR "Sleep disturbance" OR "Bipolar" OR "Mood Disorders" OR "Neurocognitive Disorders" OR "Dementia") AND ("COVID-19" OR "SARS-CoV-2" OR "coronavirus" OR "severe acute respiratory syndrome coronavirus 2") AND ("Susceptibility" OR "Prevalence" OR "Infection", "Incidence" OR "Critical illness" OR "Severity" OR "ICU", "mortality" OR "fatality" OR "death"). Neurological disorders such as stroke, seizures, degenerative dementias and delirium were all included as neuropsychiatric disorders, but peripheral neuropathies, inherited childhood neurological disorders and many other specific neurological syndromes and diseases were not specifically included in these searches. The search terms that were used to search the titles and abstracts are listed in the Appendix. We also scanned reference lists and review articles for additional studies that might meet the inclusion criteria.

Eight researchers (Liu L, Ni SY, Zhao YM, Xu YY, Mei H, Zeng N, Zheng YB, and Yang BN) worked in pairs to independently assess the articles for their eligibility for inclusion. They included observational studies regarding mental and neurological diseases and COVID-19 susceptibility, illness severity, and mortality, which also met the following six criteria: (1) peer-reviewed articles written in English; (2) population: general population or COVID-19 patients; (3) exposure: pre-existing and post-infection neurological and mental disorders based on standard clinical criteria or measurement tools such as the international diagnostic criteria, actual medical records, and standard questionnaires or instruments; (4) comparison: general population or COVID-19 patients without neurological and mental disorders; (5) outcomes: COVID-19 infection, illness severity, or mortality; the risk estimates of odds ratio [OR], relative risk ratio [RR], or hazard ratio [HR] should be reported or able to be calculated through provided data. The criteria for COVID-19 infection included positive laboratory results and diagnosis in conjunction with clinical presentation. Illness severity for COVID-19 was defined as hospitalization, ICU admission, or requirement for other special treatment (e.g., oxygen therapy, mechanical ventilator, extracorporeal membrane oxygenation, and cardiopulmonary resuscitation). (6) study design: cohort studies, case-control studies, case series and cross-sectional studies. We excluded reviews, case reports and studies without control groups or without available full text or data. If the same sample was used in more than one publication, only the dataset with the most comprehensive information was included to avoid data duplication in the meta-analysis.

2.2. Date Extraction

Two researchers independently conducted data extraction and quality assessment using detailed information forms. A third researcher (Bao YP) addressed any unresolved disagreement on the extracted data or its quality. The data extraction included basic study information such as first author, year of publication, country where study was conducted, survey time, study design, resources, type of participants, total sample size, mean or median age with standard deviation (SD) or interquartile range (IQR), gender distribution; other details of the analyses involving follow-up time, exposures (mental illness or neuropsychiatric disorder, and specific illness if any), temporal relationship of exposure and COVID-19 infection (pre-existing and sequelae), control group, outcomes (infection, illness severity and mortality), OR (adjusted preferred to unadjusted; if not available, replaced with number of cases in each group and each outcomes), and the statistical model used in the study.

We used the 9-star Newcastle-Ottawa Scale (NOS) to assess the study quality. We assessed the selection, comparability, and exposure in case-control studies, and similarly, the selection, comparability, and outcomes in cohort studies. Only studies with a NOS score greater than 5 were included in data synthesis.

2.3. Statistical Analysis

We calculated the pooled OR of COVID-19 susceptibility, illness severity, and mortality in different populations, each accompanied by the 95% confidence interval (95% CIs). We calculated log OR and the corresponding standard errors (SE), and then we weighted the effect size by the inverse of the standard deviation. To estimate the risk for COVID-19 incidence, the comparative groups were individuals with a diagnosis of mental or neurological disorders versus people without these diagnoses among the general or community population or from a data-linkage study. For illness severity or mortality as outcome, all participants were COVID-19 cases; COVID-19 with mental or neurological disorder versus COVID-19 cases without these problems. In studies without available OR, other risk measure (e.g., RR or HR) or exact number of each outcome in different groups were

extracted and used to convert to OR. We used an I^2 statistic of ≥ 50% as an indicator of large statistical heterogeneity and because of the substantial heterogeneity, we used a random effects model to calculate pooled odds ratios and 95% confidence intervals (CIs).

Subgroup analyses and meta-regression analyses were also performed to explore potential sources of heterogeneity. We conducted subgroup analyses categorized by the following variables: type of disease (mental and neurological disorder, specific disease), temporal relationship of exposure and COVID-19 infection (pre-existing vs. sequela), sex ratio (male <50% vs. male ≥50%) of the study sample, mean age (mean age <60 vs. mean age ≥60), income level of regions (high vs. low- and middle-income countries based on World Bank standard) [27], literature quality (NOS ≥7 vs. <7) and adjustment of OR (adjusted vs. unadjusted). Evidence for differences in associations between the subgroups was quantified by the ratios of OR comparing associations in the subgroups and the corresponding P values for interaction. Studies that clearly provided essential information were included in corresponding subgroups analyses. Meta-regression for the relation between mental and neurological disorders and mean age and sex ratio (percentage male) were conducted for each outcome.

We assessed the possibility of publication bias and small-study effects of each outcome using visual examinations of funnel plots, and Egger's test. Sensitivity analyses were also conducted to identify the influence of individual studies on the pooled estimates by excluding each of the studies from the pooled estimate. All of the analyses used the statistical package Meta-Analysis in Stata 12 software.

2.4. Role of the funding source

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

3. Results

We conducted the search on January 16, 2021 and updated on July 7, 2021. 13,475 records were included in the initial search and 9,369 remained after duplicates were removed. After excluding articles that did not meet the inclusion criteria, 286 studies (including 4 study from references) were full-text screened and finally 149 articles [20-24,28-171] were eligible and included in this analysis (Figure 1).

3.1. The characteristics of eligible studies

Among the 149 eligible articles, 227,351,954 participants were included in our meta-analysis; and 89,235,737 were COVID-19 patients. We included 27 studies (132,727,798 participants) for susceptibility [20-24,30-37,108-119,132,166], 56 studies (83,097,968 participants) for illness severity [21,24,28,31,32,34,38-41,43-62,83,108,110,116,117,120-138,167,169], and 115 studies (88,878,662 participants) for mortality [21,23,28,29,31,32,34,35,38-44,46-48,51,52,54,56,58,59,62-107,112,114-117,119,122,124,125,129-132, 139-165,167-171]. Among the 149 studies, 117 involved neurological disorders and 49 involved mental disorders. Among the 117 neurological disorder**s** articles, 11 specific types of disorders were covered: dementia (65 studies, 43·6%), stroke (33 studies, 22·1%), Parkinson's disease (20 studies, 13·4%), delirium (15 studies), epilepsy (10 studies), altered mental status (6 studies), cognitive disorders (6 studies), and one study each for hemiplegia, neurosis, encephalopathy, and intellectual and developmental disability. 94 studies involved pre-existing neurological disorders and 36 included neurological sequelae that appeared or had been screened during hospitalization or the course of COVID-19. Among the 49 mental disorder**s** articles, 6 types of disorders were covered: mood disorders (23 studies, 15·4%, including depression and bipolar disorder), schizophrenia (12 studies, 8·1%), anxiety (8 studies, 5·4%), sleep disturbance (7 studies), attention-deficit hyperactivity disorder (ADHD, 2 studies) and stress related disorder (2 studies). 46 studies involved pre-existing mental disorders

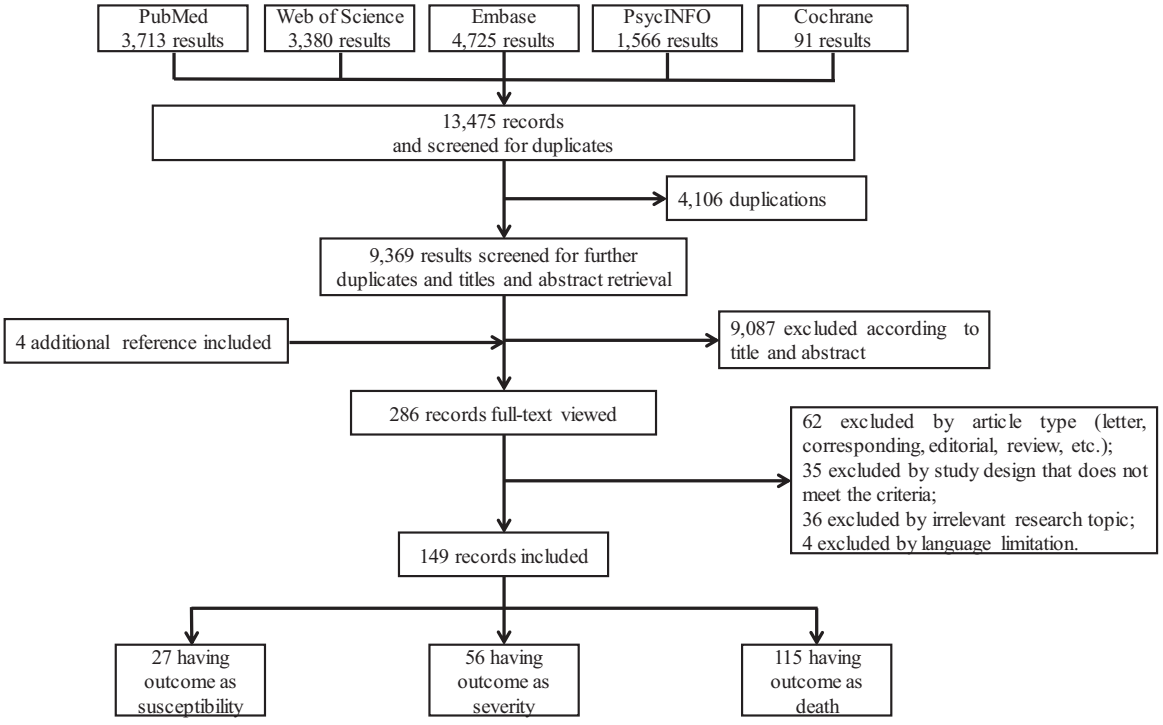

Figure 1. Flow chart of study selection.
13,475 records from PubMed, Web of Science, Embase, PsycINFO, and Cochrane library databases were included in the initial search and 149 articles were finally included after full-text screen.

and 5 included mental symptoms during hospitalization or the course of COVID-19, including anxiety, mood disorders and sleep disturbance. These studies covered 21 countries, including the US (39 studies), Italy (19 studies), Korea (15 studies), the United Kingdom (13 studies), China (11 studies), Iran, Brazil, Spain, Turkey, Israel, Switzerland, Netherlands, Denmark, France, Belgium, Sweden, Russian, Peru, Germany, Malaysia and Poland, and 8 studies were multinational. For the three different outcomes, most studies were retrospective. The sample size of these studies ranged from 26[162] to 61,783,950[37], and mean age ranged from 8·8 [SD 6·7] [30] to 87 years (IQR 92·9-91·1) [69], as shown in Table 1 and supplementary.

3.2. The effect of mental and neurological disorders on susceptibility of COVID-19 infection

The meta-analysis results of 27 studies showed that overall pre-existing mental (1·67, 1·12-2·49, 18 studies, n=72,464,308, I^2=99·8%) and neurological disorders (2·05, 1·58-2·67, 15 studies, n=128,363,844, I^2=99·7%) were associated with increased risk for COVID-19 infection. Subgroup analyses based on age, sex ratio, income region, adjusted for OR of overall mental and neurological disorder with COVID-19 susceptibility did not reveal any significant relationship (P>0·05). However, the association between neurological disorders and susceptibility was significantly stronger in studies with high literature quality than those with low literature quality (2·81, 2·07-3·10 vs. 1·18, 0·86-1·60; P=0·008; Figure 2). Meta-regression of mean age and sex ratio found that among individuals with neurological disorders, strength of the association with susceptibility increased as the male proportion increased (P=0·005). Other results from meta-regression were not significant (Figure 3).

As for specific disorders, pre-existing mood disorders (2·02, 1·08-3·76, 6 studies, I^2=99·6%), anxiety (1·63, 1·44-1·85, 2 studies, I^2=0), ADHD (5·82, 5·46-6·20, 1 study) and dementia (2·65, 1·45-4·85, 9 studies, I^2=99·7%) were associated with high susceptibility to COVID-19 (Table 1).

3.3. The effect of mental and neurological disorders on illness severity of COVID-19

The meta-analysis results of 21 studies showed that mental disorders (pre-existing: 1·40, 1·25-1·57, 19 studies, I^2=79·7%; sequelae: 4·85, 2·53-9·32, 2 studies, I^2=14·0%) among COVID-19 cases had a significant association with illness severity. Similarly, pooled analysis of 44 studies showed that neurological disorders (pre-existing: 1·43, 1·09-1·88, 39 studies, I^2=99·4%; sequelae: 2·17, 1·45-3·24, 5 studies, I^2=58·1%, P>0·05) in COVID-19 patients were significantly associated with higher illness severity. Subgroup analysis found that the association with subsequent mental disorders was significantly stronger than association with pre-existing mental disorders (P=0·002). However, there was no significant difference between pre-existing neurological disorders and neurological sequelae (P>0·05).

Further subgroup analyses showed that the association between mental disorders and illness severity was higher in the middle-aged cases (mean age <60 years: 1·92, 1·48-2·51 vs. ≥60 years: 1·20, 1·04-1·37; P=0·046) and higher in low- and middle-income regions (4·85, 2·53-9·32 vs. high-income region: 1·39, 1·24-1·55; P=0·002). Meta-regression also found that strength of association between COVID-19 severity and mental disorders reduced as the mean age of study population increased (P=0·049). The association in studies with unadjusted OR (2·73, 1·66-4·48) was stronger than those with adjusted OR (1·32, 1·19-1·46; P=0·007). Other results from subgroups analysis and meta-regressions were not significant (Figure 2, 3).

For specific diseases, both mood disorders (pre-existing, 1·34, 1·08-1·67, 8 studies, I^2=65·9%; sequelae, 3·55, 1·41-8·93, 1 study) and sleep disturbance (pre-existing, 1·62, 1·36-1·94, 2 studies, I^2=0; sequelae, 12·21, 3·81-39·18, 2 studies, I^2=0) were significantly associated with illness severity. Moreover, the association with illness severity was stronger in COVID-19 patients with subsequent sleep disturbance than those with pre-existing sleep disturbance (p=0·044). For pre-existing specific disorders, ADHD (1·93, 1·06-3·51, 1 study) and cognitive disorders (1·63, 1·54-1·73, 1 study) were associated with COVID-19 illness severity. As for sequelae, anxiety (3·23, 1·18-8·86, 1 study), altered mental status (17·28, 3·56-84·02, 2 studies, I^2=68·5%) and delirium (2·29, 1·17-4·48, 2 studies, I^2=85·2%) were related to illness severity (Table 1).

3.4. The effect of mental and neurological disorders on mortality of COVID-19

The meta-analysis results of 29 studies showed that pre-existing mental disorders were associated with mortality of COVID-19 patients (1·47, 1·26-1·72, 28 studies, I^2=92·7%), while subsequent mental disorders were not associated with mortality (1·17, 0·97-1·43, 3 studies, I^2=0·4%). For neurological disorders from 101 eligible studies, both pre-existing neurological disorders (2·08, 1·61-2·69, 74 studies, I^2=99·3%) and neurological sequelae (2·03, 1·66-2·49, 34 studies, I^2=84·2%) were associated with mortality, and there was no significant difference between them (p>0·05).

We further conducted subgroup analysis to explore the heterogeneity. Both mental disorders (mean age <60 years: 2·04, 0·96-4·33 vs. ≥60 years: 1·25, 1·13-1·38; P=0·046) and neurological (mean age <60 years: 3·29, 2·07-5·25 vs. ≥60 years: 1·78, 1·58-2·00; P=0·003) were related to mortality more strongly in middle-aged population. Meta-regression showed that the strength of association between neurological disorders and mortality decreased with age (P<0·001). (Figure 3) There was no significant difference between subgroups based on gender ratio, region based on income, adjusted for OR, literature quality for overall mental and neurological disorders (p>0·05) (Figure 2).

Analyses for specific disease showed that pre-existing disorders including mood disorders (1·36, 1·15-1·61, 14 studies, I^2=81·4%), schizophrenia (2·28, 1·40-3·73, 8 studies, I^2=64·0%), cognitive disorders (1·92, 1·24-2·99, 4 studies, I^2=87·6%), Parkinson's disease (1·50, 1·06-2·10, 12 studies, I^2=91·4%) and epilepsy (2·26, 1·84-2·78, 3 studies, I^2=41·0%) were significantly associated with mortality. For symptoms and disorders appeared or had been screened after COVID-19 infection, subsequent altered mental status (2·09, 1·23-3·55, 6 studies, I^2=76·7%), delirium (1·60, 1·17-2·19, 10 studies, I^2=68·1%) and stroke (2·82, 1·74-4·57, 11 studies, I^2=88·3%) were associated with higher mortality of COVID-19. Both pre-existing dementia (2·54, 2·11-3·05, 46 studies, I^2=90·9%) and subsequent dementia (1·91, 1·38-2·64, 4 studies, I^2=33·5%) were associated with mortality. (Table 1)

3.5. Publication bias and quality control

Almost all analyses except for a few subgroups showed high heterogeneity. The sensitivity analysis showed consistency on the three outcomes. Studies of severity and mortality showed publication bias (P<0·001 in Egger's test), while studies on susceptibility did not. Figure 4 shows funnel plots for these three outcomes.

4. Discussion

Our systematic review and meta-analysis provided a quantitative estimate of overall and type-specific association between mental and neurological disorders, both pre-existing and subsequent, and the risk of susceptibility to COVID-19 in the general population, as well as illness severity and mortality in COVID-19 patients. Overall, pre-existing mental and neurological disorders were related to higher incidence and worse prognosis of COVID-19. Subsequent neurological disorders were associated with increased risk of illness severity and

Table 1
Subgroup analysis of odds ratios (ORs) across specific types of disorders

Subgroup	Susceptibility					Severity					Death				
	No. of studies	Participants (risk group)	Participants (control)	OR (95%CI)	I^2(%)	No. of studies	Participants (risk group)	Participants (control)	OR (95%CI)	I^2(%)	No. of studies	Participants (risk group)	Participants (control)	OR (95%CI)	I^2(%)
Mental disorders															
Any mental disorders															
Pre-existing	18	3,325,988	69,138,320	**1·67 (1·12-2·49)**	99·8	19	3,045,593	22,722,005	**1·40 (1·25-1·57)**[a]	79·7	28	3,211,426	30,956,951	**1·47 (1·26-1·72)**	92·7
Sequelae	/	/	/	/	/	2	142	93	**4·85 (2·53-9·32)**	14·0	3	1,290	4,478	1·17 (0·97-1·43)	0·4
ADHD															
Pre-existing	1	99,230	61,684,720	**5·82 (5·46-6·20)**	/	1	231	1,639	**1·93 (1·06-3·51)**	/	/	/	/	/	/
Sequelae	/	/	/	/	/	/	/	/	/	/	/	/	/	/	/
Anxiety															
Pre-existing	2	50,809	370,205	**1·63 (1·44-1·85)**	0·0	/	/	/	/	/	4	51893	378130	1·16 (0·75-1·79)	78·4
Sequelae	/	/	/	/	/	1	67	33	**3·23 (1·18-8·86)**	/	1	606	2,382	1·05 (0·80-1·37)	/
Mood disorders															
Pre-existing	6	674,997	61,635,737	**2·02 (1·08-3·76)**	99·6	8	3,010,065	22,605,978	**1·34 (1·08-1·67)**	65·9	14	3,067,474	22,991,623	**1·36 (1·15-1·61)**	81·4
Sequelae	/	/	/	/	/	1	27	73	**3·55 (1·41-8·93)**	/	2	1,274	3,864	1·30 (0·90-1·90)	36·1
Schizophrenia															
Pre-existing	6	107,838	62,368,165	1·72 (0·62-4·77)	99·5	6	26,768	85,363	1·22 (0·70-2·13)	87·6	8	77,346	453,286	**2·28 (1·40-3·73)**	64·0
Sequelae	/	/	/	/	/	/	/	/	/	/	/	/	/	/	/
Sleep disturbance															
Pre-existing	1	172	103	2·31 (0·87-5·55)	/	2	812	9,165	**1·62 (1·36-1·94)**[b]	0·0	2	188	534	1·47 (0·92-2·35)	0·0
Sequelae	/	/	/	/	/	2	137	98	**12·21 (3·81-39·18)**	0·0	1	16	614	1·40 (0·53-3·68)	/
Stress-related disorder															
Pre-existing	2	175,025	414,021	1·05 (0·67-1·64)	58·6	/	/	/	/	/	1	50,809	370,205	2·75 (0·87-8·77)	/
Sequelae	/	/	/	/	/	/	/	/	/	/	/	/	/	/	/
Non-specific mental disorders															
Pre-existing	10	2,526,119	7,691,686	**1·23 (1·02-1·48)**	97·8	7	8,466	31,436	**1·54 (1·07-2·21)**	82·5	14	168,334	8,261,732	**1·63 (1·05-2·53)**	96·4
Sequelae	/	/	/	/	/	/	/	/	/	/	/	/	/	/	/
Neurological disorders															
Any neurological disorders															
Pre-existing	15	2,482,257	125,881,587	**2·05 (1·58-2·67)**	99·7	39	2,445,582	77,691,338	**1·43 (1·09-1·88)**	99·4	74	2,443,487	77,898,688	**2·08 (1·61-2·69)**	99·3
Sequelae	/	/	/	/	/	5	583	2,753	**·17 (1·45-3·24)**	58·1	34	5,726	31,728	**2·03 (1·66-2·49)**	84·2
Altered mental status															
Pre-existing	/	/	/	/	/	/	/	/	/	/	/	/	/	/	/
Sequelae	/	/	/	/	/	2	37	311	**17·28 (3·56-84·02)**	68·5	6	468	1,156	**2·09 (1·23-3·55)**	76·7
Delirium															
Pre-existing	/	/	/	/	/	2	1,729	272,749	1·97 (0·89-4·38)	66·4	3	1,742	272,857	1·59 (0·56-4·51)	74·6
Sequelae	/	/	/	/	/	2	460	1,064	**2·29 (1·17-4·48)**	85·2	10	992	4,603	**1·60 (1·17-2·19)**	68·1
Epilepsy															
Pre-existing	2	86,971	6,216,092	1·36 (0·41-4·51)	99·2	3	428	9,822	1·07 (0·71-1·62)	0·0	3	693	20,390	**2·26 (1·84-2·78)**	41·0
Sequelae	/	/	/	/	/	/	/	/	/	/	4	76	4,058	1·52 (0·83-2·79)	37·1
Cognitive disorder															
Pre-existing	/	/	/	/	/	1	177,333	25,155,996	**1·63 (1·54-1·73)**	/	4	177,980	25,160,107	**1·92 (1·24-2·99)**	87·6
Sequelae	/	/	/	/	/	/	/	/	/	/	1	119	116	1·03 (0·71-1·50)	/
Dementia															
Pre-existing	9	1,139,479	67,609,718	**2·65 (1·45-4·85)**	99·7	25	16,758	348,111	1·27 (0·94-1·71)	89·4	46	15,817	387,750	**2·54 (2·11-3·05)**	90·9
Sequelae	/	/	/	/	/	/	/	/	/	/	4	498	1,259	**1•91 (1·38-2·64)**	33·5
Parkinson's disease															
Pre-existing	5	90,532	11,438,994	1·89 (0·88-4·09)	99·3	8	1,217,223	24,133,244	1·37 (0·78-2·42)	87·8	12	1,218,444	24,239,914	**1·50 (1·06-2·10)**	91·4
Sequelae	/	/	/	/	/	/	/	/	/	/	1	8	227	0·77 (0·23-2·58)	/
Stroke															
Pre-existing	3	1,348,873	59,342,371	2·15 (0·83-5·55)	99·9	11	1,204,353	53,491,285	1·72 (0·82-3·61)	99·3	17	1,204,369	53,477,179	1·79 (0·82-3·90)	99·0
Sequelae	/	/	/	/	/	1	12	1,206	0·80 (0·22-2·97)	/	11	620	17,769	**2·82 (1·74-4·57)**	88·3
Non-specific neurological															
Pre-existing	4	19,638	6,076,805	1·38 (0·65-2·93)	98·3	6	9,309	31,523	**2·00 (1·50-2·67)**	52·0	10	4,224	31,677	**1·47 (1·19-1·83)**	49·3
Sequelae	/	/	/	/	/	2	111	483	**2·55 (1·49-4·38)**	0·0	8	3,011	8,277	**2·23 (1·38-3·60)**	92·2

[a] p=0·003; b: p=0·044
[Abbreviations]: ADHD, attention-deficit hyperactivity disorder; OR, odds ratio; 95% CI, 95% confidence intervals.

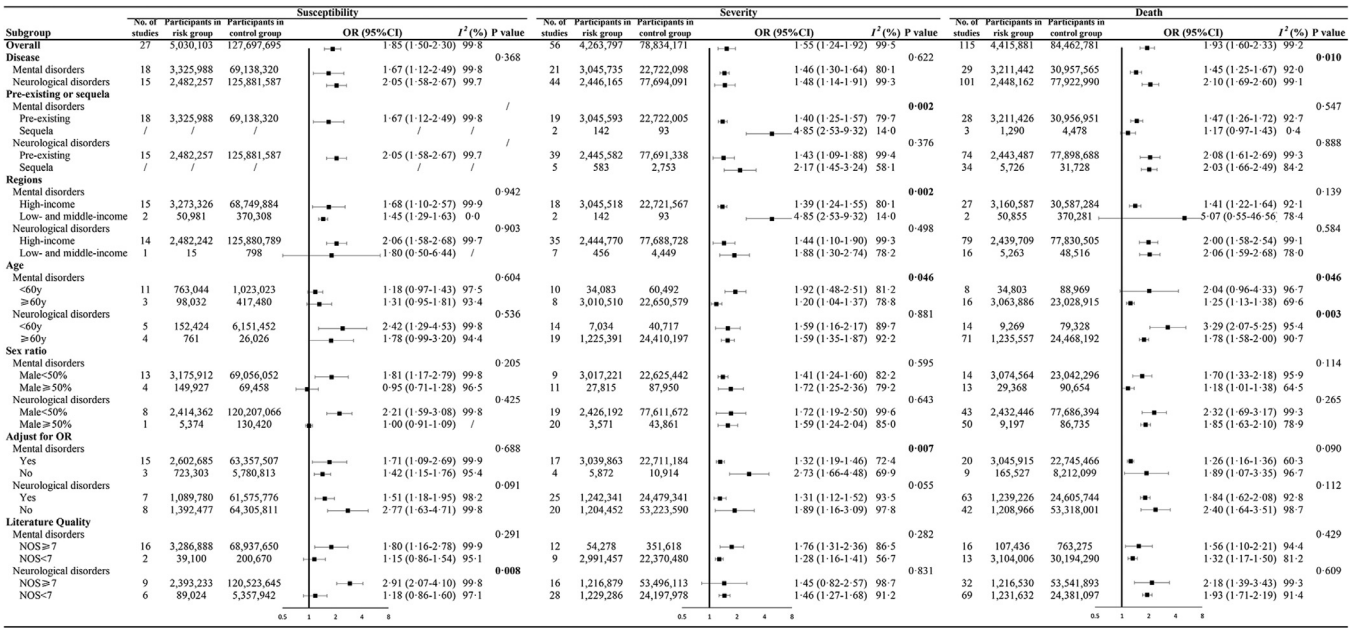

Figure 2. Subgroup analysis of odds ratios (ORs) across variables.

Mental and neurological disorders were both associated with higher COVID-19 susceptibility, illness severity and mortality. Subgroup analyses suggested that the associations of mental disorders and severity varied in subgroups by temporal relationship, geographic regions, mean age and adjustments applied to OR. The association between mental and neurological disorders and mortality differed by mean age. While, there was not statistical significance observed for other subgroup analysis.

mortality among COVID-19 cases, while subsequent mental disorders were only associated with illness severity, not mortality. Subgroup analyses found that the associations with illness severity were stronger in some vulnerable subgroups including younger COVID-19 patients, those with subsequent mental disorders and living in low- and middle- income countries. We further explored the association between type-specific mental and neurological disorders and each of three outcomes. These findings urge early detection and intervention in patients with mental and neurological disorders to control the morbidity and mortality of the COVID-19 pandemic.

Individuals with pre-existing mental disorders were associated with high susceptibility to be infected, as well as increased risk of illness severity and mortality once infected. This finding is consistent with a recent meta-analysis which showed pre-existing mental disorders were associated with COVID-19-related hospitalization, intensive care unit admission and mortality [17]. Similar to previous infectious diseases including SARS and MERS, the mental stress on the population could be caused and aggravated not only by the infection but also by indirect factors such as quarantine measures, social isolation, trauma related to the disease, insufficiency of medical resources, and high economic burden [172-175]. Mental disorders may further increase the vulnerability of infection in individuals with pre-existing mental illnesses, including mood disorder, anxiety and ADHD [176]. For example, in our results, mood disorders related to a higher COVID-19 incidence (OR=2·02) and also a poorer prognosis (1·41 for severity, 1·35 for mortality) after infection. These associations may reflect the known relationship between depression and inflammatory responses [177]. Susceptibility to infection is also critical in this special population, as patients with severe mental illness are often housed in nursing homes and psychiatric hospitals, where they are more densely packed and can be insufficiently cooperative with the protections of social distancing and properly using infection control materials necessary for preventing spread of infection [178]. However, a recent Mendelian Randomization study found that positive associations between psychiatric disorders and COVID-19 may have resulted from statistical models incompletely capturing body mass index (BMI) as a continuous covariate [179]. Further studies on mechanism of mental illness and COVID-19 susceptibility are in need.

Notably, in our subgroup analyses, the association between subsequent mental disorders and illness severity was significantly higher than that of pre-existing mental disorders, especially for sleep disturbance. Mental symptoms such as sleep disturbance are common among inpatients, especially those with severe illnesses. The causes of sleep problems are complex, including high psychological stress, environmental and other factors as well as COVID-19 itself [180]. In order to improve the prognosis of COVID-19 patients, it is essential to improve their sleep quality and other mental disorders. This finding indicates that mental disorders that developed during and after-infection should be detected and addressed early and urgently among COVID-19 cases. Other specific mental disorders except sleep disturbance appear to have similar association strength irrespective of being pre-existing or developing as a sequela. Possible reason might be the limited number of studies, as only one study for mood disorders and one for anxiety were included in this analysis. More research is needed to evaluate the risk of specific mental sequelae for the severe clinical outcome.

More attention should be paid to mortality among infected patients with schizophrenia, considering the strong association (2·28, 1·40-3·73). Schizophrenia was found to have no significant correlation with illness severity; however, these paradoxical associations may reflect selection bias and potential discrimination against those with disruptive serious mental illnesses. The schizophrenia patients appeared to have fewer chances to access advanced COVID treatments or enter ICUs, and this lack of access may be a prime contributor to their increased mortality [40]. A reduced ICU admission rate caused by discrimination against patients with schizophrenia during a time of limited allocation for medical resources would be a very serious structural problem within the world's healthcare system. COVID-19 patients with comorbid schizophrenia can over-tax the limited supply of psychiatric management that is needed along with these patients' COVID-19 treatment. A potential bias in this finding is the limited number of studies involving this special population, and specifically, one of the included studies driving this finding had a

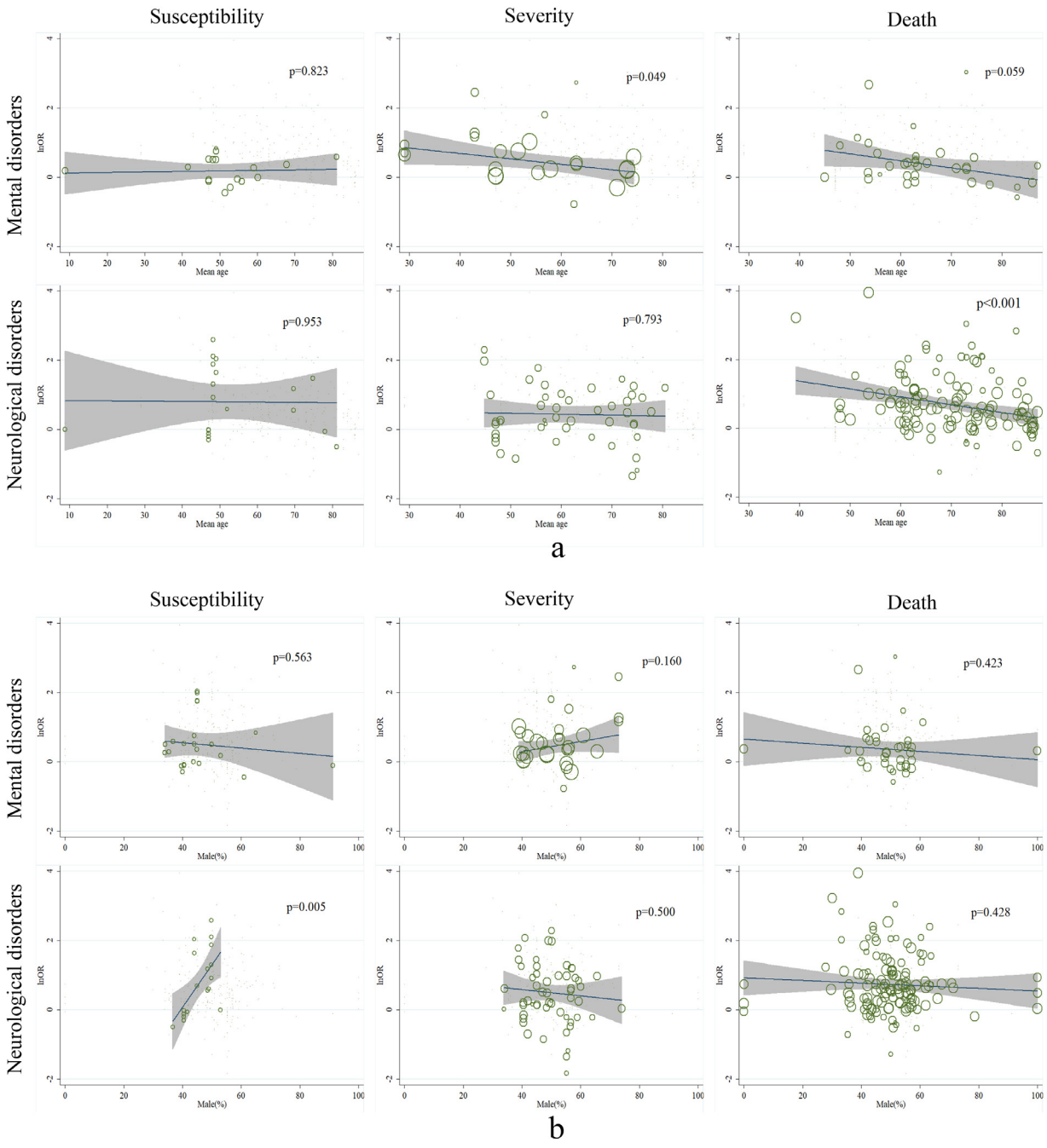

Figure 3. Meta-regression for COVID-19 susceptibility, illness severity and death by mental and neurological disorders. Meta-regression showed that the strength of association between mental disorders and severity, and between neurological disorders and mortality decreased with age.
(a). Meta-regression for mean age; (b). Meta-regression for sex ratio.

very large sample size. Clearly further studies are needed to verify this result. These findings for schizophrenia patients urgently indicate that public emergency plans in a pandemic should include consideration of structural and institutional discrimination against the seriously mentally ill patients in getting appropriate and life-saving medical care with our best technologies and medications.

COVID-19 patients with pre-existing and subsequent neurological disorders were associated with increased risk of illness severity and mortality. One basis for these two associations may be that both the SARS-CoV and SARS-CoV-2 viruses bind to the angiotensin-converting enzyme 2 (ACE2) receptors to enter human cells, and these receptors are expressed in glial cells and neurons in the brain causing changes and damage to the nervous system [181-183]. Conscious manifestations during the course of the disease, such as delirium, altered mental status and stroke, were associated with outcomes of COVID-19 patients, as well as pre-existing neurological disorders including epilepsy and cognitive disorders. Consistent with previous meta-analyses, dementia and Parkinson's disease were also related to a higher susceptibility to COVID-19 in our study [18,19]. It's worth noting that epilepsy appears to have a protective correlation with infection. It should not be ignored, however, that patients with some neurological diseases tend to be on long-term medication and have less social interaction, and this may reduce their exposure to infection [24]. Thus, reducing mortality and improving patients' prognosis requires actively monitoring nervous system changes and taking corresponding therapeutic measures once they occur.

Subgroup analyses suggested that the association of mental disorders with COVID-19 severity was significantly higher in some

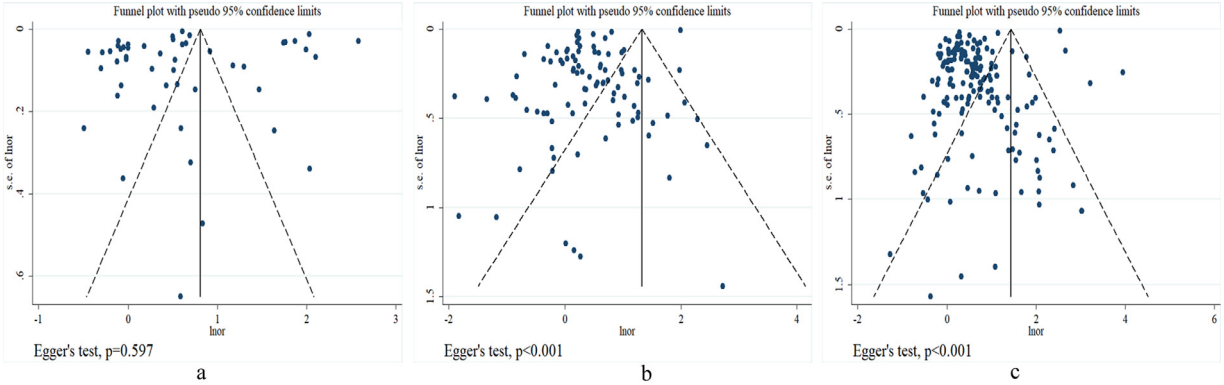

Figure 4. Funnel plot for Covid-19 susceptibility, illness severity and death.
Funnel plot and Egger's test suggested that there was publication bias among studies of COVID-19 severity and mortality, but not susceptibility.
(a). susceptibility; (b). severity; (c). death

vulnerable populations, including those with young ages, and living in low- and middle-income areas. This finding is consistent with the fact that young individuals and participants living in low- and middle-income regions had higher psychological stress and burden of mental disease [184]. Low-income areas need enhanced construction of their mental health systems. The WHO's "Building Back Better" proposed that emergency situations like this pandemic could become building opportunities with external assistance and cooperation. As the male proportion increasing, the association of neurological disorders and susceptibility became stronger. Furthermore, the associations between mental disorders and illness severity, neurological disorders and mortality appear to decrease with increasing age. Thus, the male population and middle-aged COVID-19 patients with mental and neurological disorders might be target individuals for early detection during the treatment period for COVID-19 cases. Other demographics and clinical factors did not appear to be a significant source of heterogeneity.

High heterogeneity and the lack of statistical significance in some subgroups analysis indicates that results should be interpreted cautiously. Common causes of heterogeneity were differences in study design, population demographic**s** (e.g., comorbid conditions), types of disease. Among studies on susceptibility, different sample sources (community vs. institution) and diagnosis of COVID-19 infection led to their heterogeneity; high heterogeneity among studies on severity include differences in medical systems of countries and definition of severe COVID-19 cases; and sample sources (normal patients vs. ICU patients) and limitation to death (whether included COVID-19 related death only) contributed to heterogeneity among studies on COVID-19 mortality. Further studies are needed to allow prediction of at-risk groups based on demographic data.

For clinical implementation, the association of mental and neurological disorders with the susceptibility and vulnerability of the population to COVID-19 is especially essential for individuals with some specific mental disorders including mood disorders, anxiety, sleep disturbance, schizophrenia and specific neurological disorders including dementia. They are important prognostic indicators, so rigorous detection and early intervention are important among community population during the pandemic. Facing the risk of mental and neurological disorders on susceptibility of COVID-19, the early prevention and intervention, and research priorities should be addressed. Under conditions of quarantine, social distancing and fear associated with infection, there is a need for timely monitoring and urgent public heath response**s** for the comprehensive management of mental and neurological disorders before potential infection [172]. Government and relevant departments should restore the routine medical services and help people face difficulties in pandemic conditions with the right attitude through health education and promotion. Actions also need to be taken to decrease the stigma associated with both mental illness and infection, while assuring regular treatment and alternative online consulting and intervention during the pandemic for vulnerable populations with certain disease like mood disorders and schizophrenia [185]. After infection, subsequent mood disorders, sleep disturbance, altered mental status and delirium were associated with severe clinical outcome, adequate supply of medical resources including experienced psychiatrists and neurologist are recommended. Identification of early signals for mental and neurological disorders in COVID-19 patients should be part of training for clinicians and other health care staff. Attention needs to be paid to specific signs during the course of the disease and targeted treatment programs should be implemented actively. In particular, the presence of psychiatric and neurological symptoms is still common in patients who have recovered from COVID-19; high burden of mental and neurological sequelae have been found in COVID-19 survivors even during recovery periods [186]. However, we did not find significant association between subsequent mental disorders and mortality among COVID-19 cases, and the possible reason is that only 3 studies were involved in this analysis. More studies of mental sequelae are needed in the future. Moreover, further research on pathological mechanisms of the neural and psychiatric disorders in COVID-19 cases, treatment protocol for patients with mental and neurological illness, and management and prevention of long-term sequelae is urgently needed (Figure 5).

This study has several limitations. First, the heterogeneity between studies is high, and publication bias was found in studies of illness severity and mortality. The extreme I^2 could also result from the small number of studies for each estimate [187]. Results in most subgroups were consistent, however, the association between mental and neurological disorders and COVID-19 should be interpreted with caution. Second, we only included studies in the English language and unpublished literatures were not included in our meta-analysis. Since we did not include all specific diseases in our search strategy, there might be omitted studies, leading to the limited generalizability in our findings. Third, the amount of research that is currently available remains inadequate, and short durations of follow up and unspecified severity of the mental and neurological disorders limited some subgroup analyses. Fourth, the number of studies on COVID-19 infection rates is relatively small, leading to a decrease in the reliability of the subgroup analyses. More specifically, few studies in low- and middle-income regions were available. Notably, a large number of participants (61 million) were from one study, which may decrease the credibility of our conclusion. Finally, as the studies were all observational and most retrospective, we cannot assign causality to the associations of neurological and mental disorders with susceptibility, illness severity or mortality of COVID-19.

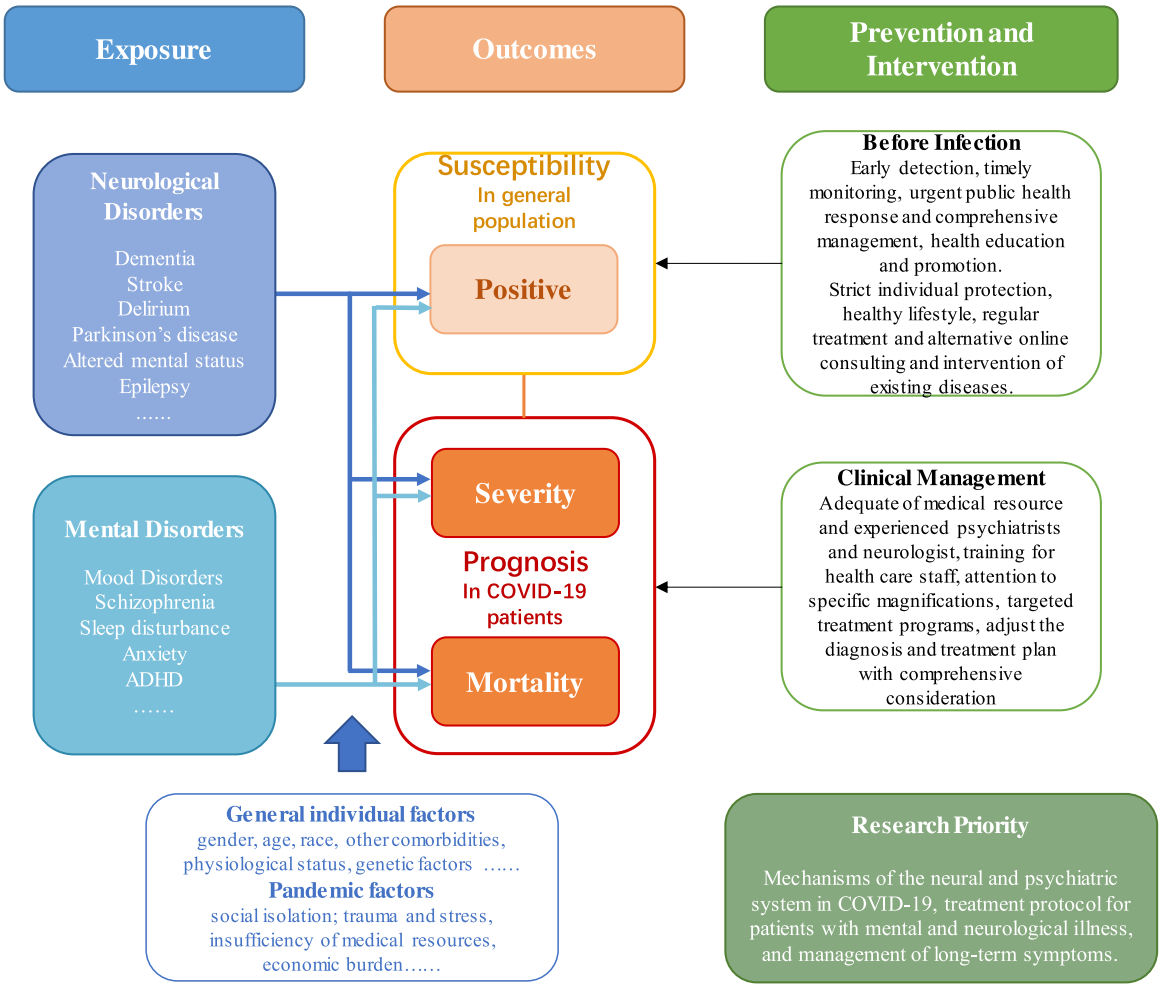

Figure 5. The association of mental and neurological disorders with the risk of susceptibility and prognosis of COVID-19, and the prevention and intervention
The blue arrows indicate potential associations between mental and neurological disorders and the three different outcomes, with light blue for mental disorders and dark blue for neurological disorders. The black arrows represent possible interventions for improving poor outcomes of COVID-19 susceptibility, severity and death.

To our knowledge, this is the first comprehensive meta-analysis using a large sample of more than 227 million people from 21 countries to examine the association of mental and neurological disorders, both pre-existing and subsequent, with the susceptibility, illness severity, and mortality of COVID-19. Early detection and intervention for neurological and mental disorders are urgently needed to control the morbidity and mortality of the COVID-19 pandemic. Furthermore, there was substantial heterogeneity among the included studies, and the results should be interpreted with caution. More studies are needed to explore the mental and neurological long-term sequelae and the underlying neural mechanisms, and to elucidate the causal pathways for these associations.

Declaration of Competing Interest

The authors declare that they do not have any conflicts of interest (financial or otherwise).

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Contributors

Liu L, Ni SY, and Yan W contributed equally to this article. Lu L, Bao YP and Shi J proposed the topic and main idea. Liu L and Ni SY were responsible for the literature search and study selection. Liu L, Ni SY, Zhao YM, Xu YY, Mei H, Zeng N, Zheng YB, Yang BN, and Yan W were responsible for the data extraction and quality assessment. Ni SY wrote the initial draft. Yan W, Yuan K, Sun YK, Shi L, Han Y, Deng JH, Meng SQ, Gong YM, Jiang ZD, Ravindran A, Kosten T, Wing YK, Tang XD, Yuan JL, Wu P, Shi J, Bao YP, and Lu L commented on and revised the manuscript. Lu L, Shi J, and Bao YP made the final version. All authors contributed to the final draft of the manuscript.

Data sharing

The collected study-level data and statistical analysis plan in this study are available for others after publication. Email for one of our corresponding authors.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.eclinm.2021.101111.

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