

# Association Between Mental Health Disorders and Mortality Among Patients With COVID-19 in 7 Countries

## A Systematic Review and Meta-analysis

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**IMPORTANCE** Heterogeneous evidence exists for the association between COVID-19 and the clinical outcomes of patients with mental health disorders. It remains unknown whether patients with COVID-19 and mental health disorders are at increased risk of mortality and should thus be targeted as a high-risk population for severe forms of COVID-19.

**OBJECTIVE** To determine whether patients with mental health disorders were at increased risk of COVID-19 mortality compared with patients without mental health disorders.

**DATA SOURCES** For this systematic review and meta-analysis, MEDLINE, Web of Science, and Google Scholar were searched from inception to February 12, 2021. Bibliographies were also searched, and the corresponding authors were directly contacted. The search paradigm was based on the following combination: (mental, major[MeSH terms]) AND (COVID-19 mortality[MeSH terms]). To ensure exhaustivity, the term *mental* was replaced by *psychiatric*, *schizophrenia*, *psychotic*, *bipolar disorder*, *mood disorders*, *major depressive disorder*, *anxiety disorder*, *personality disorder*, *eating disorder*, *alcohol abuse*, *alcohol misuse*, *substance abuse*, and *substance misuse*.

**STUDY SELECTION** Eligible studies were population-based cohort studies of all patients with identified COVID-19 exploring the association between mental health disorders and mortality.

**DATA EXTRACTION AND SYNTHESIS** Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) reporting guideline was used for abstracting data and assessing data quality and validity. This systematic review is registered with PROSPERO.

**MAIN OUTCOMES AND MEASURES** Pooled crude and adjusted odds ratios (ORs) for the association of mental health disorders with mortality were calculated using a 3-level random-effects (study/country) approach with a hierarchical structure to assess effect size dependency.

**RESULTS** In total, 16 population-based cohort studies (data from medico-administrative health or electronic/medical records databases) across 7 countries (1 from Denmark, 2 from France, 1 from Israel, 3 from South Korea, 1 from Spain, 1 from the UK, and 7 from the US) and 19 086 patients with mental health disorders were included. The studies covered December 2019 to July 2020, were of good quality, and no publication bias was identified. COVID-19 mortality was associated with an increased risk among patients with mental health disorders compared with patients without mental health disorders according to both pooled crude OR (1.75 [95% CI, 1.40-2.20];  $P < .05$ ) and adjusted OR (1.38 [95% CI, 1.15-1.65];  $P < .05$ ). The patients with severe mental health disorders had the highest ORs for risk of mortality (crude OR: 2.26 [95% CI, 1.18-4.31]; adjusted OR: 1.67 [95% CI, 1.02-2.73]).

**CONCLUSIONS AND RELEVANCE** In this systematic review and meta-analysis of 16 observational studies in 7 countries, mental health disorders were associated with increased COVID-19-related mortality. Thus, patients with mental health disorders should have been targeted as a high-risk population for severe forms of COVID-19, requiring enhanced preventive and disease management strategies. Future studies should more accurately evaluate the risk for patients with each mental health disorder. However, the highest risk seemed to be found in studies including individuals with schizophrenia and/or bipolar disorders.

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More than 100 million people have been infected with SARS-CoV-2, and almost 2.5 million have died of COVID-19 worldwide.<sup>1</sup> These numbers probably underestimate COVID-19 deaths by 50% owing to misclassified dementia and cardiovascular or metabolic deaths.<sup>2</sup> Patients with mental health disorders may be at particular risk of poor COVID-19 outcomes. Patients with mental health disorders can have multiple comorbidities that have been identified as risk factors for severe COVID-19: diabetes, hypertension, chronic obstructive respiratory disease, and end-stage kidney disease.<sup>3</sup> Mental health disorders are also associated with socioeconomic deprivation<sup>4</sup> and reduced access to care,<sup>5</sup> 2 important factors of poor COVID-19 outcomes.<sup>6</sup>

Data on the risks of poor COVID-19 outcomes among patients with mental health disorders continue to evolve from the first reports. Several population-based studies from South Korea, the US, and France revealed that severe mental health disorders (defined across studies by schizophrenia spectrum disorders and/or bipolar disorders) are risk factors for increased COVID-19 mortality.<sup>7-9</sup> The results were less clear for other mental health disorders (ie, depressive disorders, anxiety disorders, eating disorders, and personality disorders).<sup>8-11</sup> Determining whether patients with mental health disorders are at high risk of severe COVID-19 is an urgent research priority and can alert health policy makers and lead to adaptations in preventive care and disease management strategies to meet their health needs.<sup>12</sup> A preliminary meta-analysis has concluded that patients with mental health disorders were at increased risk of COVID-19 mortality.<sup>13</sup> However, this meta-analysis had methodological issues because the interdependency of effect sizes was not handled, in particular within each country. Moreover, mental health disorders were not analyzed separately, and there may be important discrepancies between diagnoses, which should guide health strategy priorities.

We carried out a systematic review and meta-analysis to synthesize the accumulating research on mental health disorders and COVID-19. The primary objective was to determine whether patients with mental health disorders are at increased risk of COVID-19 mortality compared with patients without mental health disorders. The secondary objectives were to determine whether patients with mental health disorders are at increased risk of intensive care unit (ICU) admission and which specific mental health disorders were associated with the risk of COVID-19 mortality.

## Methods

### Literature Search Strategy

This meta-analysis was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) reporting guideline.<sup>14</sup> Systematic bibliographic searches were carried out according to the Cochrane methodology. This project was registered in PROSPERO (CRD42021238038).

The search paradigm was based on the PubMed interface (MEDLINE database) and adapted for 2 databases: ScienceDirect and Google Scholar. The search paradigm was

### Key Points

**Question** Is there a significant association between mental health disorders and COVID-19-related mortality?

**Findings** In this systematic review and meta-analysis of 16 observational studies in 7 countries with 19 086 patients, mental health disorders were associated with increased COVID-19 mortality according to both pooled crude and adjusted odds ratios. Patients with severe mental health disorders had the highest odds ratios.

**Meaning** These findings suggest that patients with COVID-19 and mental health disorders should be targeted as a high-risk population for severe forms of COVID-19, requiring enhanced preventive and disease management strategies.

based on the following combination: (mental, major[MeSH terms]) AND (COVID-19 mortality[MeSH terms]). To ensure exhaustivity, the term *mental* was replaced by *psychiatric, schizophrenia, psychotic, bipolar disorder, mood disorders, major depressive disorder, anxiety disorder, personality disorder, eating disorder, alcohol abuse, alcohol misuse, substance abuse, and substance misuse*.

The last search was carried out on February 22, 2021. The reference lists and bibliographies of relevant reviews and articles retrieved from the database searches were manually searched for additional eligible articles. The authors of the relevant studies were contacted when additional data or clarifications were required.

### Eligibility

The inclusion criteria were as follows: (1) articles in any language and with any date of publication; (2) original research articles; (3) population-based studies based on medico-administrative health databases or a health care data warehouse; (4) studies that included participants with a diagnosis of mental health disorders according to the *DSM* or any version of the *International Classification of Diseases (ICD)*; (5) studies on patients with clinical or biological diagnosis of COVID-19; and (6) articles with mortality and ICU admission data.

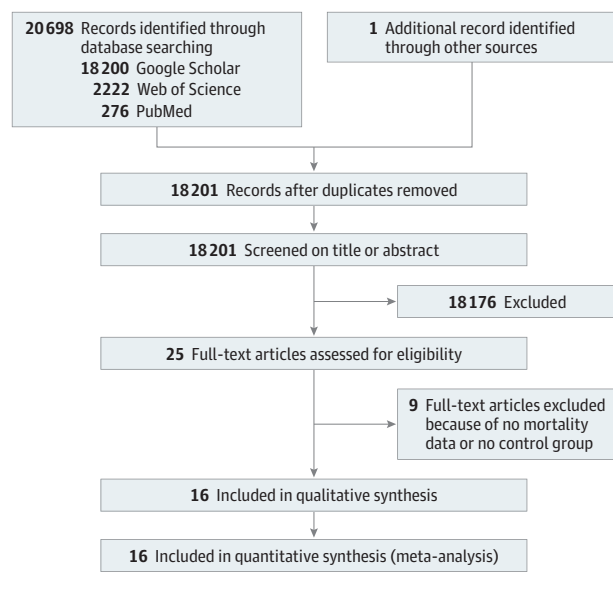
The titles and abstracts were screened by 2 researchers (G.F. and D.E.-E.). The full texts of the articles were then reviewed to determine whether they would be included by authors (G.F., D.E.-E., and L.B.).

### Data Extraction

The following data were extracted: first author, timing (period of inclusion of cases and follow-up), databases, population, study setting, COVID-19 criteria inclusion, mental health disorders group definition, mean age, percentage of men, mortality rate, mortality crude odds ratio (OR), mortality adjusted OR, ICU admission crude OR, and ICU admission adjusted OR.

Two researchers (G.F. and D.E.-E.) extracted data from the included studies systematically using a predesigned extraction form. Each discrepancy in data extraction was examined by the first and last authors (G.F. and L.B.) to reach a consensus.

Figure 1. Flowchart



### Assessment of Risk of Bias

To assess the risk of bias, we used the Newcastle-Ottawa Quality Assessment Scale. A good quality score required 3 or 4 stars for the selected item, 1 or 2 stars for the comparability item, and 2 or 3 stars for the outcomes item. A fair quality score required 2 stars for selection, 1 or 2 stars for comparability, and 2 or 3 stars for outcomes. A poor quality score required 0 or 1 star(s) for the selection, 0 stars for comparability, or 0 or 1 star(s) for outcome.

### Statistical Analyses

A random-effects model was used to calculate the pooled crude and adjusted log ORs with 95% CIs for mortality and ICU admission. When available, we used the numbers of events and the sample sizes instead of the value of the crude ORs.<sup>15</sup> Because studies may show a certain degree of overlap in observations (several ORs per study and a potential higher-level unit by country), we used a 3-level random-effects (study/country) approach with a hierarchical structure.

We also investigated sources of heterogeneity using Cochran *Q* and *I*<sup>2</sup> statistics. *I*<sup>2</sup> is reported as a percentage out of 100%, whereby 0% to 40% denotes that the heterogeneity might not be important, 30% to 60% indicates moderate heterogeneity, 50% to 90% represents to substantial heterogeneity, and 75% to 100% indicates considerable heterogeneity.<sup>16</sup> Publication bias was assessed graphically with a funnel plot and statistically with modified Egger regression test computed by including the standard error as a predictor of effect sizes in the multilevel model.<sup>17</sup>

For subgroup analyses, we explored the association of the following study characteristics with outcomes: mean age older than 65 years vs 65 years and younger; inpatients and outpatients vs only inpatients; laboratory-confirmed COVID-19 vs ICD criteria inclusion; and severe mental health disorders (defined as schizophrenia spectrum disorder ± bipolar disorders

if bipolar disorders were distinguished from other mood disorders) vs nonsevere mental health disorders (defined as mood disorders, anxiety disorders, personality disorders, eating disorders, and alcohol and substance misuses). All analyses were performed in R using the metafor package.<sup>18</sup> Two-sided *P* values were significant at .05.

## Results

### Search Strategy

We identified 18200 studies from the database search and no additional records through other sources. Sixteen studies met the eligibility criteria<sup>7-11,19-27</sup> (1 unpublished study by G.F. et al based on the French national hospital database) and were included in the quantitative analysis (Figure 1). A Swedish study<sup>28</sup> was not included because no data on patients with COVID-19 were available at the time of the analyses of the present work. Overall, the data of 19 086 patients with mental health disorders and COVID-19 were analyzed. It was not possible to determine the total number of individual patients, as some studies had overlaps in their samples.

### Study Characteristics

The study and patient characteristics are presented in Table 1 and Table 2. One study was carried out in Denmark,<sup>24</sup> 2 in France (including the unpublished study by G.F. et al),<sup>7</sup> 1 in Israel,<sup>26</sup> 3 in South Korea,<sup>9-11</sup> 1 in Spain,<sup>19</sup> 1 in the UK,<sup>24</sup> and 7 in the US.<sup>8,20-23,27,29</sup> The definition of the mental health disorders group varied across countries. The 3 South Korean studies,<sup>9-11</sup> 2 US studies,<sup>21,27</sup> and the UK study<sup>25</sup> included a large definition of mental health disorders (almost all F00-F90 codes) with addictions mixed with mental health disorders. Two US studies<sup>22,23</sup> included only patients with addictions (with no information on their mental status), and the Danish study<sup>24</sup> analyzed addictions separately from mental health disorders. No study reported on patients with the combination of a mental health disorder and addiction. It was possible to distinguish severe mental health disorders (as defined in the Methods section) in 6 studies (including the unpublished study by G.F. et al).<sup>7-9,24,26</sup> Only patients with schizophrenia were analyzed in the French and Israeli studies,<sup>7,26</sup> and patients with schizophrenia were included in a schizophrenia spectrum diagnosis group in 3 studies<sup>8,9,26</sup> and were combined with patients with bipolar disorders in 1 study.<sup>24</sup> Patients with bipolar disorders were analyzed separately in only 1 unpublished study by G.F. et al, and were included in the mood disorder group in 2 studies.<sup>8,19</sup> The last study, published as a letter, did not describe the mental health disorders of the patients in the mental health disorders group.<sup>20</sup>

### Quality assessment

The study quality is presented in eTable 1 in the Supplement. All studies had a good quality score.

### Meta-analysis

The forest plots of the adjusted ORs are presented in Figure 2 (mental health disorders) and Figure 3 (severe mental health

Table 1. Study Characteristics

Source	Timing	Database	Population	Study setting	COVID-19 criteria inclusion	Mental health disorders group definition
<b>Denmark</b>						
Reilev et al, <sup>24</sup> 2020	February 27 to May 19, 2020	Danish Microbiology Database linked to the Danish administrative and health care registries	Whole Danish population tested for SARS-CoV-2 infection	Inpatients and outpatients	Positive reverse transcription-polymerase chain reaction test	Mental health disorders (including schizophrenia and bipolar disorders); alcohol misuse; substance use
<b>France</b>						
Fond et al, <sup>7</sup> 2021	February 1 to June 9, 2020	French national hospital database for acute care	Whole French population hospitalized for COVID-19 aged ≥15 y	Inpatients	COVID-19 ICD-10 codes (U07.1 or U07.2), respiratory symptoms (U07.10 or U07.11), and a length of hospital stay >24 h	Schizophrenia
Unpublished study by Fond et al	February 1 to June 9, 2020	French national hospital database for acute care. In this unpublished study, data were anonymized and can be reused for research purposes. No informed consent was necessary because all data were anonymous. This study was declared to the French National Data Protection Commission in accordance with the methodological reference MR005 (declaration number: 2203797).	Whole French population hospitalized for COVID-19 aged ≥15 y	Inpatients	COVID-19 ICD-10 codes (U07.1 or U07.2), respiratory symptoms (U07.10 or U07.11), and a length of hospital stay >24 h	Bipolar disorders
<b>Israel</b>						
Tzur Bitan et al, <sup>26</sup> 2021	NA	Israeli health care database	5 Million citizens (half of the population)	Inpatients and outpatients	Positive reverse transcription-polymerase chain reaction test	Schizophrenia
<b>South Korea</b>						
Lee et al, <sup>9</sup> 2020	January 1 to May 15, 2020	South Korean national health insurance claims database	98% Of the whole population aged >20 y	Inpatients and outpatients	Positive reverse transcription-polymerase chain reaction test	One of the following mental health disorders: nonaffective psychotic disorders; affective psychotic disorders; anxiety- and stress-related disorders; alcohol or drug misuse; mood disorders without psychotic symptoms; eating disorders and personality disorders
Lee et al, <sup>11</sup> 2020	January 1 to April 10, 2020	South Korean National Health Insurance Review and Assessment Service database	Individuals aged ≥65 y	Inpatients and outpatients	Laboratory-confirmed COVID-19	Schizophrenia, psychotic disorders; bipolar disorders; depressive disorder; anxiety disorder; panic disorder, acute stress disorder; insomnia; dementia; organic mental disorder; psychoactive substance dependence; psychoactive substance use disorder; psychoactive substance-induced organic mental disorder; psychosomatic factor in physical condition
Jeon et al, <sup>10</sup> 2021	December 1, 2019, to May 15, 2020	South Korean national health insurance claims database linked to the Korea Disease Control and Prevention Agency database	Whole population without age restriction	Inpatients and outpatients	Diagnostic code (specific to the database)	Mental health disorders (included schizophrenia spectrum disorder and mood disorders)
<b>Spain</b>						
Poblador-Plou et al, <sup>19</sup> 2020	March 4 to May 17, 2020	PRECOVID database (created to follow patients with positive COVID-19 test results) linked to Aragon Health System	Spanish region of Aragon	Inpatients and outpatients	Laboratory-confirmed COVID-19	Bipolar disorders; depressive disorders; anxiety disorders
<b>United Kingdom</b>						
Yang et al, <sup>25</sup> 2020	January 31 to May 31, 2020	The UK Biobank	502 507 Participants, aged 40 to 69 y, from England, Scotland, and Wales	Inpatients	Positive reverse transcription-polymerase chain reaction test	Psychotic disorders; depressive disorders; anxiety; stress-related disorder; alcohol and substance misuse

(continued)

Table 1. Study Characteristics (continued)

Source	Timing	Database	Population	Study setting	COVID-19 criteria inclusion	Mental health disorders group definition
<b>United States</b>						
Allen et al, <sup>22</sup> 2020	January 1 to October 26, 2020	NYULH linked to NYULH's COVID-19 deidentified clinical database, which includes data from 4 acute care hospitals	Individuals in greater New York City	Inpatients and outpatients	Positive reverse transcription-polymerase chain reaction test	Any alcohol or substance use disorder excluding nicotine dependence
Baillargeon et al, <sup>23</sup> 2021	February 20 to July 31, 2020	TriNetX Research Network platform database, which includes data from 35 health care organizations including hospitals, primary care clinics, and specialty treatment institutions	Approximately 54 million patients aged ≥18 y	Inpatients and outpatients	COVID-19 ICD-10 codes (B34.2, B97.29, J12.81, U07.1, U07.2) or laboratory-confirmed COVID-19	Substance use disorder
Egede et al, <sup>21</sup> 2021	Unknown beginning to July 2020	Froedtert/Medical College of Wisconsin Epic medical record database, which includes data from 5 hospitals and 40 health centers and clinics	One-quarter of the population of southeastern Wisconsin	Inpatients and outpatients	Positive reverse transcription-polymerase chain reaction test	Any mental health disorders with or without physical illness including schizophrenia spectrum disorder, mood disorders (including bipolar disorders and depressive disorders), alcohol misuse and drug misuse
Nemani et al, <sup>8</sup> 2021	March 3 to May 31, 2020	NYULH electronic health record system database, which includes data from more than 260 outpatient office sites and 4 acute care hospitals	Individuals from Manhattan, Brooklyn, and Long Island, New York	Inpatients and outpatients	Positive reverse transcription-polymerase chain reaction test	Schizophrenia spectrum disorder mood disorders (including bipolar disorders and depressive disorders); anxiety disorders
Li et al, <sup>20</sup> 2020	February 15 to May 27, 2020	Yale New Haven Health System database, which includes data from a 5-hospital system	Individuals in the northeast of the United States	Inpatients and outpatients	NA	Psychiatric diagnoses (nonspecified)
Wang et al, <sup>27</sup> 2021	Unknown beginning to July 29, 2020	IBM-Watson Health Explorys database, which includes data from a 360-hospital system across 50 states	20% Of the United States population	Inpatients and outpatients	Diagnostic code (specific to the database)	Psychiatric diagnoses; schizophrenia; bipolar disorders; depressive disorders; attention-deficit/hyperactivity disorder; substance use disorder

Abbreviations: ICD-10, *International Statistical Classification of Diseases and Related Health Problems, Tenth Revision*; NA, not available; NYULH, NYU Langone Health.

disorders). The funnel plot is presented in eFigure 1 in the Supplement and shows no publication bias (Egger test > 0.05). COVID-19 mortality was associated with an increase in patients with mental health disorders compared with patients without mental health disorders (pooled adjusted OR, 1.38 [95% CI, 1.15-1.65];  $I^2 = 0\%$ ). In the studies including only patients with severe mental health disorders (schizophrenia spectrum disorders and/or bipolar disorders), the pooled adjusted OR was 1.67 (95% CI, 1.02-2.73;  $I^2 = 27.3\%$ ). In the other studies that included patients with all mental health disorders and addictions, the pooled adjusted OR was 1.34 (95% CI, 1.08-1.65;  $I^2 = 0\%$ ). All  $P$  values were significant ( $P < .05$ ). The ICD codes are presented in eTable 2 in the Supplement and adjustment factors are in eTable 3 in the Supplement.

The forest plots of the crude ORs are presented in eFigure 2 in the Supplement and confirm the abovementioned results (pooled crude OR, 1.75 [95% CI, 1.40-2.19];  $I^2 = 26.1\%$ ). In studies including only patients with severe mental health disorders, the pooled crude OR was 2.26 (95% CI, 1.18-4.31;  $I^2 = 55.5\%$ ; eFigure 3 in the Supplement). In the other studies that included patients with all mental health disorders and addictions, the pooled crude OR was 1.72 (95% CI, 1.45-2.04;  $I^2 = 0\%$ ). All  $P$  values were significant ( $P < .05$ ).

The subgroup analyses did not report any significant difference in either the crude or adjusted OR. Comparing patients with each mental health disorder in head-to-head comparisons or patients with severe mental health disorders

with those with nonsevere mental health disorders was not possible because in all studies including patients with nonsevere mental health disorders except 1,<sup>8</sup> patients with nonsevere mental health disorders were combined with patients severe mental health disorders.<sup>9,19-21,27,30</sup>

The number of studies reporting ICU admission (4 studies) was not sufficient to perform a meta-analysis. Among this small number of studies, the results were very heterogeneous and contradictory between countries, with an OR less than 1 in France<sup>7</sup> for schizophrenia, 1 in South Korea<sup>9</sup> for all mental health disorders (1 unpublished study by G.F. et al), and more than 1 in the US for patients with alcohol and substance misuse.<sup>22</sup>

## Discussion

We confirmed that mental health disorders were associated with increased COVID-19-related mortality from population-based data from 7 countries on 3 continents (North America, Europe, and Asia). Thus, patients with mental health disorders should have been targeted as a high-risk population for severe forms of COVID-19, requiring enhanced preventive and disease management strategies. However, future studies should evaluate the risk for each mental health disorder, which could not be determined with the current published data.

Table 2. Crude and Adjusted Mortality Odds Ratio

Source	Topic	No.	Age, mean (SD)	% Men	Mortality	OR (95% CI)			
						Mortality		ICU admission	
						Crude	Adjusted	Crude	Adjusted
<b>Denmark</b>									
Reilev et al, <sup>24</sup> 2020	SZ and BD	76	NA	NA	2.3	3.8 (2.1-7.0)	2.5 (1.2-5.1)	NA	NA
	Alcohol misuse	298	NA	NA	6.4	2.7 (1.9-3.9)	1.8 (1.2-2.7)	NA	NA
	Substance use	185	NA	NA	3.6	2.4 (1.5-3.8)	1.8 (1.1-3.2)	NA	NA
<b>France</b>									
Fond et al, <sup>7</sup> 2021	SZ	823	69.2 (14.6)	48.8	25.6	1.25 (1.05-1.49)	1.30 (1.08-1.56)	0.78 (0.65-0.94)	0.75 (0.62-0.91)
Unpublished study by Fond et al	BD	480	70.9 (13.5)	37.9	26.0	1.30 (1.16-1.45)	1.29 (1.15-1.44)	1.08 (0.97-1.20)	1.02 (0.91-1.14)
<b>Israel</b>									
Tzur-Bitan et al, <sup>26</sup> 2021	SZ	649	NA	NA	3.4	NA	NA	NA	NA
<b>South Korea</b>									
Lee et al, <sup>9</sup> 2020	MD	1443	59.5 (17.2)	39.6	6.7	1.39 (1.01-1.95)	1.38 (1.00-1.95)	1.17 (0.82-1.68)	1.18 (0.82-1.70)
	Severe MD <sup>a</sup>	404 <sup>a</sup>	58.7 (17.3) <sup>a</sup>	55.9 <sup>a</sup>	NA <sup>a</sup>	NA <sup>a</sup>	NA <sup>a</sup>	NA <sup>a</sup>	NA <sup>a</sup>
Lee et al, <sup>11</sup> 2020	MD	255	77.2 (7.5)	42.7	13.7	1.38 (0.86-2.21)	NA	NA	NA
Jeon et al, <sup>10</sup> 2021	MD	928	61.2 (18.2)	40.2	6.03	7.12 (4.87-10.39)	3.93 (2.57-6.03)	NA	NA
	SZ <sup>a</sup>	159 <sup>a</sup>	NA <sup>a</sup>	NA <sup>a</sup>	3.8 <sup>a</sup>	NA <sup>a</sup>	2.25 (0.36-14.03) <sup>a</sup>	NA <sup>a</sup>	NA <sup>a</sup>
	BD and MDD <sup>a</sup>	273 <sup>a</sup>	NA <sup>a</sup>	NA <sup>a</sup>	4.4 <sup>a</sup>	NA <sup>a</sup>	2.33 (0.96-5.66) <sup>a</sup>	NA <sup>a</sup>	NA <sup>a</sup>
<b>Spain</b>									
Poblador-Plou et al, <sup>19</sup> 2020	Men with BD and MDD	70	NA	100	NA	NA	1.38 (0.98-1.95)	NA	NA
	Men with AD	38	NA	100	NA	NA	0.80 (0.53-1.21)	NA	NA
	Women with BD and MDD	132	NA	0	NA	NA	1.46 (1.12-1.91)	NA	NA
	Women with AD	83	NA	0	NA	NA	1.21 (0.90-1.64)	NA	NA
<b>United Kingdom</b>									
Yang et al, <sup>25</sup> 2020	MD	442	NA	NA	27.1	NA	NA	NA	NA
<b>United States</b>									
Allen et al, <sup>22</sup> 2020	Alcohol and substance use disorder	395	NA	NA	NA	1.20 (0.76-1.90)	0.91 (0.53-1.57)	3.20 (2.29-4.48)	2.61 (1.80-3.79)
Baillargeon et al, <sup>23</sup> 2020	Substance use disorder	5450	53.8 (17.3)	52.4	4.7	NA	1.00 (0.84-1.20)	NA	NA
Egede et al, <sup>21</sup> 2021	MD with physical illness	505	54.0 (17.8)	33.5	7.7	1.52 (0.99-2.32)	1.35 (0.85-2.08)	NA	NA
	MD without physical illness	52	37.7 (15.8)	34.6	1.9	0.39 (0.05-2.86)	1.08 (0.15-8.05)	NA	NA
Nemani et al, <sup>8</sup> 2021	SZ	75	59.7 (15.0)	56.0	26.7	2.93 (1.75-4.92)	2.67 (1.48-4.80)	NA	NA
	BD and MDD	564	62.3 (18.7)	39.9	18.4	1.82 (1.45-2.29)	1.14 (0.87-1.49)	NA	NA
	AD	360	54.9 (19.3)	39.7	10.8	0.98 (0.70-1.38)	0.96 (0.65-1.40)	NA	NA
Li et al, <sup>20</sup> 2020	MD	473	NA	NA	44.8	2.3 (1.8-2.9)	1.5 (1.1-1.9)	NA	NA
Wang et al, <sup>27</sup> 2021	MD	3430	NA	NA	8.5	NA	NA	NA	NA
	Alcohol and substance use disorder	1880	NA	NA	9.6	NA	NA	NA	NA

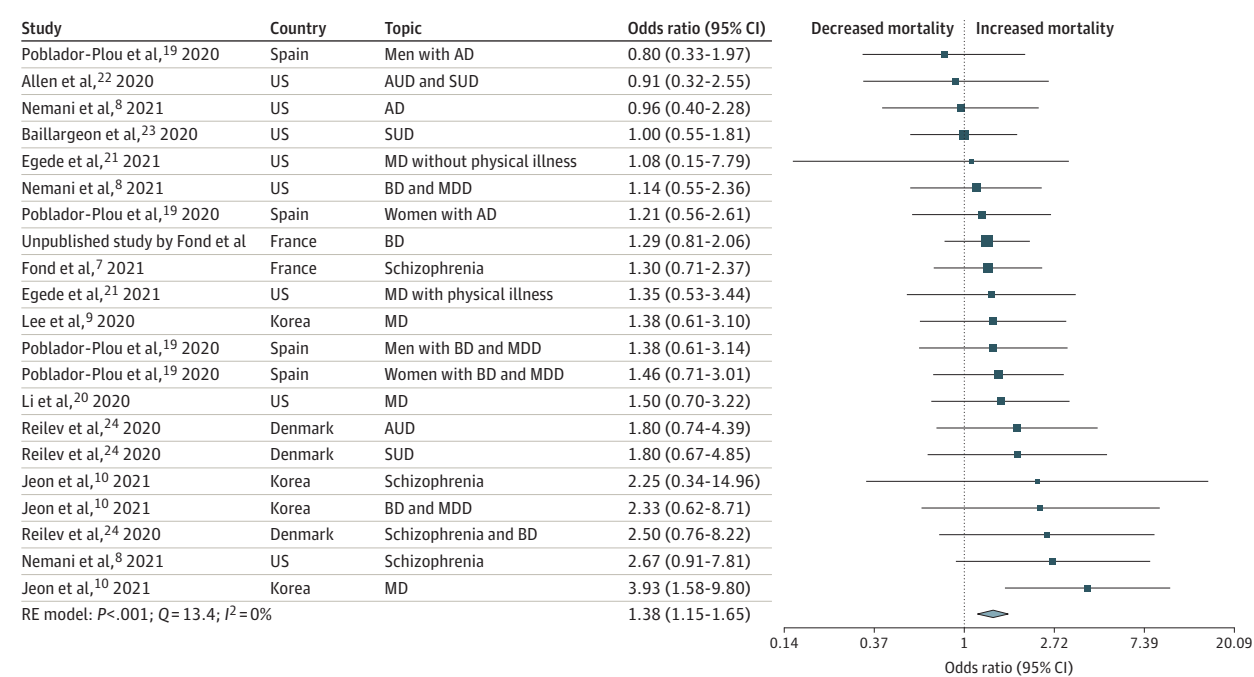
Abbreviations: AD, anxiety disorder; BD, bipolar disorder; ICU, intensive care unit; MD, mental health disorder; MDD, major depressive disorder; NA, not available; OR, odds ratio; SZ, schizophrenia.

<sup>a</sup> Subgroup analyses.

The different random-effects models confirmed the association between mental health disorders and increased COVID-19-related mortality for both pooled crude and adjusted ORs.

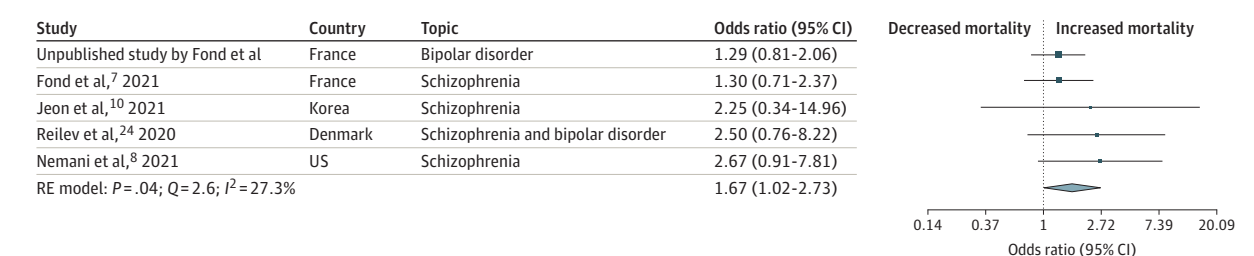
The confirmation of increased mortality by adjusted ORs suggests that patients with mental health disorders are at higher risk of poor COVID-19 outcomes than patients without

Figure 2. Forest Plot of the Association Between Mental Health Disorders and Mortality (Adjusted Odds Ratio)



AD indicates anxiety disorder; AUD, alcohol use disorder; BD, bipolar disorder; MD, mental health disorder; MDD, major depressive disorder; SUD, substance use disorder.

Figure 3. Forest Plot of the Association Between Severe Mental Health Disorders and Mortality (Adjusted Odds Ratio)



Severe mental health disorders were defined as schizophrenia spectrum disorder and/or bipolar disorder.

mental health disorders independent of the main clinical risk factors for severe COVID-19 (eg, age, obesity, smoking addiction, kidney disease, cardiovascular and cerebrovascular disease, and chronic obstructive pulmonary disease). This suggests that other factors lead to this health inequity in patients with mental health disorders, including several factors such as barriers to access to care, social determinants of health, immunological disturbances, and the effects of psychotropic drugs.

Several studies have reported important barriers to COVID-19-related somatic care in patients with mental health disorders in various countries.<sup>31-36</sup> Therefore, it is likely that these barriers may have influenced access to care during the pandemic and thus had an effect on COVID-19 prognosis in patients with mental health disorders. A wide range of social factors (eg, socioeconomic status, family or household composition, and environmental factors) were also reported to be

associated with increased COVID-19 mortality<sup>37</sup> and are known to be highly influential in patients with mental health disorders.<sup>38</sup> These factors need to be explored in depth in future works on mental health disorders and COVID-19, and they need to be considered for health policies.

Patients with schizophrenia and/or bipolar disorders had the highest risk of COVID-19 mortality. This may be explained by the particular immunological profile of these patients. Variation in the human leukocyte antigen complex is one of the most consistently replicated findings in genome-wide association studies in patients with schizophrenia and bipolar disorders.<sup>39</sup> Human leukocyte antigen predominantly regulates viral infection, especially COVID-19.<sup>40</sup> Genetic variability across major human leukocyte antigen class I genes may contribute to differences in the immune response to COVID-19, and an inappropriate T-cell response has been implicated in severe COVID-19 outcomes.<sup>39,41</sup> Abnormal cytokine levels have also

been found in the cerebrospinal fluid of patients with schizophrenia and bipolar disorders,<sup>42</sup> who are also at higher risk of hypovitaminosis D,<sup>43,44</sup> contributing to poor COVID-19 prognosis.<sup>45,46</sup> Antipsychotic treatments have shown inconsistent pro- or anti-inflammatory properties, modulating anti-inflammatory (interleukin 4 and interleukin 10) or pro-inflammatory cytokines (interleukin 17, tumor necrosis factor, interferon  $\gamma$ ), which results in immune function alterations.<sup>47,48</sup>

In all studies that analyzed patients with depressive disorders, patients with acute major depressive disorder (F32\*) and those with recurrent major depressive disorder (F33\*) were combined,<sup>8-10</sup> but it is probable that patients with these different forms of the disorder have different risks of COVID-19 mortality. An acute major depressive episode is common, and patients can achieve full remission with or without treatment and without later consequences. In contrast, recurrent major depressive disorder is a severe mental health disorder that may strongly affect functioning and vulnerability to severe COVID-19 events, even between acute episodes. Patients with recurrent major depressive episodes have impaired immune defenses from the onset of illness.<sup>49</sup> However, the administrative databases included in the present work did not include information on the mood state of the patients. It is possible that a current major depressive disorder at COVID-19 onset was the real culprit of increased COVID-19 mortality, and this hypothesis should be further explored. Anxiety disorders have also been associated with immune-inflammatory disturbances<sup>50</sup>; however, the only study that separately explored patients with anxiety disorders did not find an increased risk of COVID-19 mortality in this population.<sup>8</sup>

While addictions are classically distinguished from mental health disorders, patients with addiction were combined with those with mental health disorders in some studies.<sup>10,11,51</sup> Studies analyzing patients misusing alcohol and substances found an increased risk in those patients,<sup>22,23</sup> suggesting that attention should be paid to these patients. Long-term use of tobacco, alcohol, and other drugs is associated with cardiovascular (arrhythmias, cardiac insufficiency, and myocardial infarction), pulmonary (chronic obstructive pulmonary disease, pulmonary hypertension), and metabolic (diabetes, hypertension) diseases,<sup>52,53</sup> all of which are risk factors for COVID-19 infection and worse outcomes. Of note, opioid use disorder is a particular concern in the US. It is estimated that approximately 70 000 people died of an opioid overdose in 2019, and opioids have respiratory depressant effects that could be particularly lethal in the case of COVID-19.<sup>29</sup> As addictions and mental health disorders are frequently comorbid, the contribution of each to mortality risk should be clarified in future studies.

Our study has highlighted that there is a lack of data and discrepant data on ICU admission. Increased ICU admission was found in US patients with COVID-19 with alcohol and/or substance use disorders<sup>22</sup>, while decreased ICU admission was found in French patients with COVID-19 with schizophrenia.<sup>7</sup> ICU admission is an important indicator because it can provide information on the allocation of scarce medical resources. Triage may become necessary when the demand for ICU resources exceeds supply.<sup>54</sup> Severity of illness, initial ward or team the patient was referred from, and do-not-

resuscitate order status/patient preference are modifiable factors that could be improved in patient with mental health disorders.<sup>55</sup> Addressing a do-not-resuscitate order is complicated in mental health disorders owing to increased social isolation and the absence of relatives. Advance directives should be implemented in routine mental health to guarantee the respect of patients' wishes, but this remains challenging.<sup>56</sup> Reducing the time of access to the hospital for mental health disorders may prevent them from being admitted with very serious conditions. Specific training on mental health disorders for ICU staff could also deeply reduce mental illness stigma and improve ICU admission of patients with mental health disorders.<sup>57</sup> Future studies should determine the ability of patients with mental health disorders in obtaining health resources in the COVID-19 pandemic.

### Strengths and Limitations

The publication bias was reduced at its minimum by the inclusion of population-based approaches of unselected cohorts. Population-based studies allowed complete individual-level ascertainment without restricting analysis to those treated at hospitals and irrespective of socioeconomic differences. Studies yielding no data on patients with positive COVID-19 test results<sup>28</sup> were not included to reduce the heterogeneity of the findings.

Overall, these results should be interpreted with several caveats. Most of the included studies were carried out during the first peak of the COVID-19 pandemic. At this time, testing was largely restricted in some countries (such as the US and France) to symptomatic and high-risk people, while it was provided to all citizens in South Korea, which may explain discrepancies in mortality rates. However, it did not seem to influence the risk of increased mortality in patients with mental health disorders. The important variations in mental health disorder definitions across studies limited our analyses for each mental health disorder and contributed to the heterogeneity of our findings. One study included patients with insomnia and dementia in the mental health disorder group.<sup>11</sup> Insomnia is very common, while dementia is associated with COVID-19 prognosis and should be analyzed separately.<sup>58</sup> One study (published as a letter) did not clearly define its mental health disorder groups.<sup>20</sup>

In light of these issues, we recommend distinguishing data for patients with different mental health disorders in future studies to better understand which patients are at increased risk of COVID-19 mortality. The definition of control groups also varied across studies: some control groups excluded patients with mental health disorders, while others only included patients with or without 1 disorder in a direct head-to-head comparison. We did not obtain information on the stage of illness (acute vs stabilized), which could have affected the risk for severe COVID-19 outcomes. Comorbidities such as obesity or tobacco smoking may often be underreported in medicoadministrative databases, thus causing an underestimation of the prevalence of these specific issues. Most of the studies lacked data on social deprivation, which is likely to influence the risk of developing severe COVID-19 or dying.<sup>59</sup> It was not possible to determine if the deaths were directly caused by



COVID-19. No treatment was proven to be effective during the first wave of the COVID-19 pandemic; thus, no treatment data were included in the present analysis because they were available in only 1 study.

## Conclusions

In this systematic review and meta-analysis of 16 observational studies involving 19 086 patients with mental health

disorders in 7 countries, mental health disorders were associated with increased COVID-19–related mortality after adjustment for the main clinical risk factors for severe COVID-19. Thus, patients with mental health disorders should have been targeted as a high-risk population for severe forms of COVID-19, requiring enhanced preventive and disease management strategies. Future studies should evaluate the risk for each mental health disorder and confirm that patients with schizophrenia and bipolar disorders are at the highest risk of mortality.

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