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## **Risk of SARS-CoV-2 infection, severe COVID-19 illness and COVID-19 mortality in people with pre-existing mental disorders: an umbrella review**

Federico Bertolini, Anke B Witteveen, Susanne Young, Pim Cuijpers, Jose Luis Ayuso-Mateos, Corrado Barbui, María Cabello, Camilla Cadorin, Naomi Downes, Daniele Franzoi, et al.

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1 Title:

2 **Risk of SARS-CoV-2 infection, severe COVID-19 illness and COVID-19 mortality in people with**  
3 **pre-existing mental disorders: an umbrella review**

4

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1 **Abstract:**

2 Introduction: The COVID-19 pandemic has posed a serious health risk, especially in vulnerable populations.  
3 Even before the pandemic, people with mental disorders had worse physical health outcomes compared to  
4 the general population. This umbrella review investigated whether having a pre-pandemic mental disorder  
5 was associated with worse physical health outcomes due to the COVID-19 pandemic.

6 Methods: Following a pre-registered protocol available on the Open Science Framework platform, we  
7 searched Ovid MEDLINE All, Embase (Ovid), PsycINFO (Ovid), CINAHL, and Web of Science up to the 6<sup>th</sup> of  
8 October 2021 for systematic reviews on the impact of COVID-19 on people with pre-existing mental  
9 disorders. The following outcomes were considered: risk of contracting the SARS-CoV-2 infection, risk of  
10 severe illness, COVID-19 related mortality risk, risk of long-term physical symptoms after COVID-19. For  
11 meta-analyses, we considered adjusted odds ratio (OR) as effect size measure. Screening, data extraction  
12 and quality assessment with the AMSTAR 2 tool have been done in parallel and duplicate.

13 Results: We included five meta-analyses and four narrative reviews. The meta-analyses reported that  
14 people with any mental disorder had an increased risk of SAR-CoV-2 infection (OR: 1.71, 95% CI 1.09-2.69),  
15 severe illness course (OR from 1.32 to 1.77, 95%CI between 1.19-1.46 and 1.29-2.42, respectively) and  
16 COVID-19 related mortality (OR from 1.38 to 1.52, 95%CI from 1.15-1.65 to 1.20-1.93) as compared to the  
17 general population. People with anxiety disorders had an increased risk of SAR-CoV-2 infection, but not  
18 increased mortality. People with mood and schizophrenia spectrum disorders had an increased COVID-19  
19 related mortality but without evidence of increased risk of severe COVID-19 illness. Narrative reviews were  
20 consistent with findings from the meta-analyses.

21 Discussion and conclusions: As compared to the general population, there is strong evidence showing that  
22 people with pre-existing mental disorders suffered from worse physical health outcomes due to the COVID-  
23 19 pandemic and may therefore be considered a risk group similar to people with underlying physical  
24 conditions. Factors likely involved include living accommodations with barriers to social distancing,

1 cardiovascular comorbidities, psychotropic medications and difficulties in accessing high-intensity medical  
2 care.

3 **Keywords:**

- 4 • Umbrella review
- 5 • Covid-19
- 6 • Sars-CoV-2
- 7 • Mental health
- 8 • Mortality
- 9 • Pre-existing mental health disorders

10

11 **Background**

12 The COVID-19 pandemic has affected most of the population worldwide. Disadvantaged population groups  
13 are thought to have suffered the most, with possibly among those, people affected by mental disorders.  
14 The physical health repercussions have been a particular point of concern, as many known risk factors for  
15 severe COVID-19 illness course and COVID-19 related mortality are common in people with mental  
16 disorders [1-3]. Firstly, it is unclear whether this population, or specific subgroups, had an increased risk of  
17 contracting the SARS-CoV-2 virus than the general population [4, 5]. Shared living accommodations  
18 represented contexts in which adhering to social distancing might have been not possible or difficult.  
19 Secondly, there has been a focus on the disease course in people with mental disorders. Obesity, diabetes  
20 mellitus and cardiovascular disease are common in this population [6, 7]. In addition to that, many  
21 psychotropic medications have the potential of a detrimental effect on the respiratory function [8, 9].  
22 Given these premises, it seems highly relevant to assess if and how the COVID-19 pandemic has affected  
23 the physical health of people with pre-existing mental disorders. Against this background, an umbrella  
24 review was performed aiming to summarize evidence from systematic reviews (SR) and meta-analyses

1 (MAs). This work builds on a wider project of evidence synthesis on the impact of the Covid-19 pandemic  
2 on mental health, performed to inform a WHO Scientific Brief [10].

### 3 **Methods**

#### 4 *Umbrella review design*

5 We followed published guidelines on performing umbrella reviews [11-13]. An umbrella review consists of a  
6 systematic search and assessment of systematic reviews on a specific research question. This allows for the  
7 comparison of results of clinical outcomes and provides a clear picture on broad healthcare areas, possibly  
8 revealing whether the evidence base is consistent or contradictory. We registered a protocol to define the  
9 research methodology to inform the WHO scientific brief that is publicly available on the Open Science  
10 Framework platform [14]. The present work is based on the 'Question 3 - Are people living with pre COVID-  
11 19 existing mental health disorders at (increased) risk of severe illness and mortality and/or of contracting  
12 SARS-CoV-2 compared to any other population?' of the protocol, with the addition of focusing on estimates  
13 that have adjusted for confounding.

#### 14 *Literature search and study selection*

15 An information specialist performed a systematic search on Ovid MEDLINE All, Embase (Ovid), PsycINFO  
16 (Ovid), CINAHL, and Web of Science, from December 31, 2019 until October 6, 2021, using a search strategy  
17 based on a combination of keywords and text words for reviews, COVID-19, and mental disorders or  
18 problems. The search strategy can be found in the supplementary material. This search was designed to  
19 inform a wide panel of different research questions on COVID-19 and mental health. We deduplicated  
20 search results using Endnote software [15]. Entries were divided into groups, each screened in parallel and  
21 independently by two different authors using Rayyan [16]. In case of disagreement, records were  
22 conserved. The full text of the remaining articles was assessed against the inclusion and exclusion criteria,  
23 again in duplicate and independently. Disagreement was resolved by discussion or with a senior review  
24 author.

#### 25 *Eligibility criteria and data extraction*

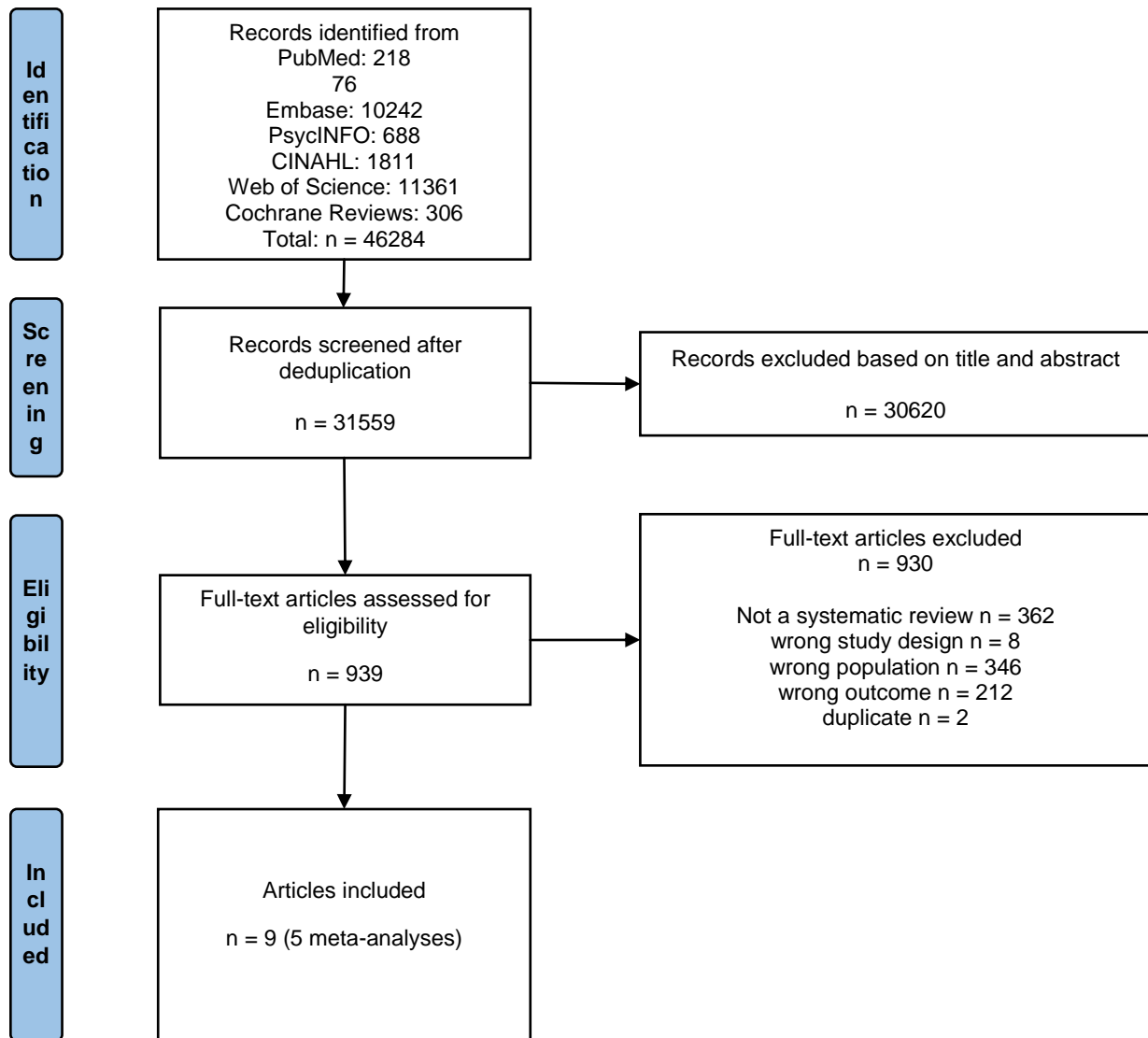
1 We considered for inclusion reviews that: 1) were systematic, as defined by having a systematic search on  
2 at least one bibliographic database, explicitly reporting primary studies selection criteria and providing a list  
3 and synthesis of included studies; 2) considered as primary studies either cohort or cross-sectional or case-  
4 control studies; 3) have been published in a peer-reviewed journal; 4) compared people with pre-existing  
5 mental disorders (i.e., with a diagnosis of mental disorder established before the pandemic onset) with  
6 those without a pre-existing mental disorder; and 5) assessed at least one of the following outcomes: a) risk  
7 of contracting SARS-Cov-2 infection, b) risk of severe COVID-19 illness, c) risk of long-term physical  
8 symptoms after COVID-19 illness, d) mortality from SARS-CoV-2 infection. For the outcome 'risk of severe  
9 illness', we considered definitions as provided by original systematic reviewers, or proxy outcomes such as  
10 hospitalization. We did not exclude reviews on the basis of language of publication. In the case of reviews  
11 considering several pandemics, we planned to include only those that reported separated data for the  
12 COVID-19 pandemic. We considered systematic reviews independently of whether a meta-analysis was  
13 performed. Two authors independently and in parallel extracted the following data: author, date of  
14 publication, timeframe covered by the search, population and comparator, design of included studies,  
15 inclusion and exclusion criteria, outcomes, risk of bias assessment strategy, how exposure to SARS-CoV-2  
16 was established, number of included studies and participants, and outcomes of interest with  $I^2$  statistic as a  
17 measure of heterogeneity. In terms of meta-analysis, we aimed to summarize effect size in terms of  
18 adjusted Odds Ratio (aOR), if that was not available, we considered the most adjusted model available.

### 19 *Assessment of quality*

20 Two independent authors assessed the quality of the included systematic reviews using the AMSTAR 2 tool  
21 [17]. For systematic reviews that did not perform a meta-analysis, items 11, 12 and 15 were not considered.  
22 Also, small adaptations to some items were performed to make them more suitable to score (see the  
23 supplementary material). For an overall rating, we used the proposed scheme by Shea and colleagues that  
24 provides judgments of high, moderate, low or critically low confidence [17].

## 25 **Results**

1 *Selection and inclusion of systematic reviews*



2 The systematic search provided 46,284 record entries, reduced to 31,559 after deduplication. 939 records  
3 were selected for full text retrieval by screening titles and abstracts. Of these, nine were finally included  
4 after comparing full texts against inclusion and exclusion criteria. Figure 1 reports the details of the study  
5 selection process.

6 **Figure 1.** PRISMA flowchart of studies selection.

7



1 *Characteristics of included systematic reviews*

2 Of the nine included reviews, five performed a meta-analysis on at least one of the outcomes of interest  
 3 [18-22], while the remaining four were of a narrative nature [23-26]. Table 1 summarises the characteristics  
 4 of the included reviews.

Author, year	Design	Timeframe covered by bibliographic search	Design of included studies	Population / comparator	Countries	Effect size estimation methods	Number of included Studies	Outcomes
Ceban 2021	Systematic review with meta-analysis	From inception to February 1, 2021	Case-control and cohort studies	People with a mood disorder / people without mood disorders	USA, South Korea, Spain, Italy, Turkey, UK, Israel	Random effect model pooling adjusted and crude ORs. Preference given to adjusted ORs when available. Subgroups analyses according to adjustment status	21 (15 aOR, 6 crude ORs)	1- Susceptibility (laboratory testing, ICD-10, EHR, and/or clinical judgment) 2- Hospitalization 3- Occurrence of severe events (includes oxygen therapy) 4- Death
Fond 2021	Systematic review with meta-analysis	From inception to February 12, 2021	Population-based cohort studies based on medico-administrative health databases or a health care data warehouse	People with any mental disorder (includes substance abuse disorders and ADHD) / people without a mental disorder	Denmark, France, Israel, South Korea, Spain, UK, USA	Random effects models, separate pooling of aORs and crude ORs	21	1- Mortality 2- ICU admission
Fornaro 2021	Scoping review (no meta-analysis)	From inception up to April 24, 2021	Cross-sectional, prospective cohort, retrospective cohort studies, case reports/series	People with Bipolar disorder / NA	Italy, UK, Australia, USA, the Netherlands, India, China		14	Identified themes: 1- Impact of COVID-19-related stressors on BD 2- Impact of COVID-19 on mental health service utilization among people with BD 3- Impact of BD on the risk of acquiring SARS-cov-2 infection 4- Engagement in preventative behaviors among people with BD
Karaoulanis 2021	Systematic review without meta-analysis	From inception up to 21 March 2021	Unreported	People with Schizophrenia / people without Schizophrenia	USA, Korea, France, Israel		7	1- Susceptibility (being infected) 2- Mortality
Lemieux 2020	Rapid review	From December 2019 up 18 August 2020	Opinion pieces by experts (editorials, letters to the editor, position papers and other correspondences), rapid literature reviews, narrative (i.e., Non-systematic) literature reviews, empirical studies (surveys and descriptive/case studies)	People with mental illness in secure settings / NA	USA, China, Italy, UK, France, Germany, Ireland, Singapore, Brazil, Canada, Spain, Australia, India, Israel, Poland, New Zealand, South Korea, Scandinavia, Switzerland		69	Narrative review on strategies, challenges and recommendations for dealing with the COVID-19 outbreak in secure settings for persons with mental illness

Liu 2021	Systematic review with meta-analysis	From inception to January 16, 2021	Cohort, case-control, cross-sectional studies and case series	People with mental disorders (includes sleep disorders and ADHD) / people without mental disorders	USA, Italy, Korea, UK, China, Iran, Brazil, Spain, Turkey, Israel, Switzerland, the Netherlands, Denmark, France, Belgium, Sweden, Russia, Peru, Germany, Malaysia, Poland	Random effect models pooling adjusted and crude ORs. Subgroups analyses according to adjustment status for 'any mental disorder' population only	149	1- Susceptibility (positive laboratory results, diagnosis in conjunction with clinical presentation) 2- Illness severity (hospitalization, ICU admission, or requirement for other special treatment (e.g., oxygen therapy, mechanical ventilator, extracorporeal membrane oxygenation, and cardiopulmonary resuscitation)) 3- Death
Murphy 2021	Scoping review	From 1 January to 31 December 2020	Primary research papers including qualitative, quantitative and mixed methods study designs	People with mental disorders / NA	Italy, USA, China, Canada, Germany, Spain, UK, Ireland, Australia, India, Switzerland, France, Iran, Turkey, Poland, Pakistan, Bosnia and Herzegovina		30	Narrative review of factors influencing health outcomes in people with pre-existing mental health conditions during the pandemic; impact of the pandemic on the health of people with pre-existing mental health conditions; Strategies or measure to support people with pre-existing mental health conditions during the pandemic
Toubasi 2021	Systematic review with meta-analysis	From inception to 15 February 2021	Cohort, case control	People with mental disorders / people without mental disorders	UK, Japan, South Korea, France, Scotland, Israel, USA	Random effects models, pooling both adjusted and crude ORs. Sensitivity analysis including aOR only	16 (aOR: 5)	1- Death or Severe illness (ICU admission and ventilation)
Vai 2021	Systematic review with meta-analysis	From 1 January 2020 to 5 March 2021	Cross-sectional, longitudinal studies	People with mental disorders (includes substance use disorders and intellectual disabilities)/ people without mental disorders	UK, Japan, South Korea, France, Scotland, Sweden, USA	Random effects models pooling crude ORs. Sensitivity analysis polling aORs only.	23	1- Death 2- Hospitalization 3- ICU admission
aORs: adjusted Odds Ratios, ADHD: Attention-deficit hyperactivity disorder, BP: Bipolar disorder, ICU: intensive care unit, NA: Not applicable, ORs: Odds Ratios, UK: United Kingdom, USA: United States of America,								

1 **Table 1.** Characteristics of included systematic reviews

2 Systematic reviews with meta-analyses (MAs) generally had a search covering up to the first quarter of  
3 2021. They included primary studies with mainly a cohort design, with the notable exceptions of the review  
4 by Liu and colleagues which considered case-series too and the review by Fond and colleagues which  
5 considered population-based cohort studies. MAs included a mean of 45 studies and a median of 21, the  
6 review by Liu and colleagues being an outlier with 149 included studies. Most of the MAs considered  
7 people with any mental disorder, possibly providing subgroups for specific disorders groups, while the  
8 review by Ceban and colleagues only focused on people with a mood disorder. Included studies covered a

1 wide range of countries but with a general lack of representation from low- and middle-income countries.  
2 Infection by SARS-CoV-2 was defined as by laboratory testing, ICD-10, electronic health records, or clinical  
3 judgment in the review by Ceban and colleagues and as by laboratory results and diagnosis in conjunction  
4 with clinical presentation in the review by Liu and colleagues. Severe illness was defined as ICU admission,  
5 mechanical ventilatory support, oxygen therapy, extracorporeal membrane oxygenation, acute respiratory  
6 distress syndrome, and/or cardiopulmonary resuscitation by Ceban and colleagues and as hospitalization,  
7 ICU admission, or requirement for other special treatment (including oxygen therapy) by Liu and  
8 colleagues. For the review by Vai and colleagues, which does not have a “severe illness” outcome, we  
9 considered the outcome ‘hospitalisation’. For the review by Toubasi and colleagues, we considered the  
10 pooled mortality and severe illness outcome, as a separate estimate for mortality only was not available.  
11 Notably, no review was available to inform on the long-term physical symptoms after SARS-CoV2 infection.  
12 Four reviews reported estimates based on pooling adjusted ORs only [18, 19, 21, 22]. The review by Vai and  
13 colleagues reported a fully adjusted model only when considering people with any mental disorder, for the  
14 diagnostic groups we have then considered the ‘partially adjusted model’, where review authors  
15 considered aORs pooled together with crude ORs when an adjusted figure was not available from primary  
16 studies.

17 The four narrative reviews varied in their specific design, with two scoping reviews [25, 26], one rapid  
18 review [23], and one systematic review without meta-analysis [24]. They considered a wide range of study  
19 designs with the review by Lemieux and colleagues considering opinion pieces and other reviews; as for  
20 population of interest, they considered people with bipolar disorder [25], people with schizophrenia [24],  
21 people with mental illness in secure settings [23], and generally people with mental disorders [26].

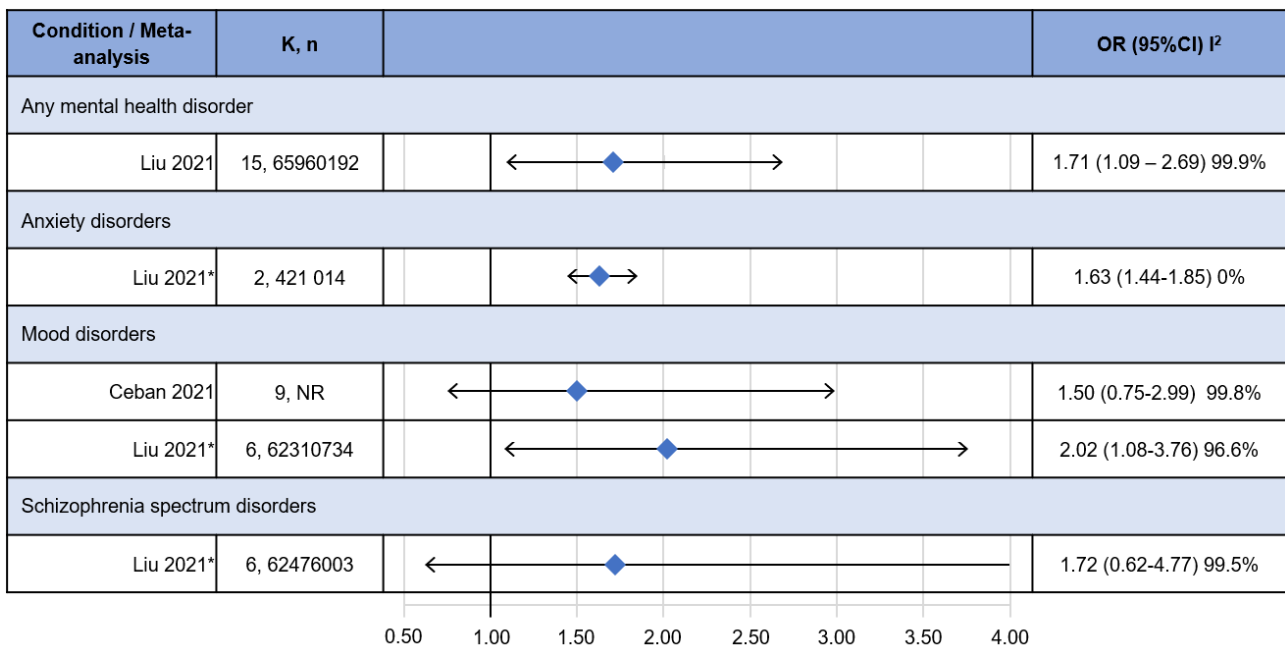
## 22 *Quality of included reviews*

23 The AMSTAR 2 rated level of quality for all the MAs was “low”, with the exception of the review by Liu and  
24 colleagues with “high” and the review by Fond and colleagues with “critically low”. The review by Liu and  
25 colleagues did not have any weaknesses in critical items, while all other MAs did not report the list of

1 excluded studies with reasons for exclusion; the review by Fond and colleagues also did not account for the  
 2 impact of risk of bias in primary studies on the results. The level of quality for the narrative reviews was  
 3 “critically low” with the exception of the review by Fornaro and colleagues (“low”), mainly because of a lack  
 4 of risk of bias assessment and protocol registration. See the supplementary material for detailed AMSTAR 2  
 5 evaluation of the included reviews.

6 *Risk of SARS-CoV-2 infection*

7 Two MAs informed on the association between Sars-CoV-2 infection and having a pre-existing mental  
 8 disorder compared to not having a pre-existing mental disorder (Figure 2) [18, 19].



9

10 **Figure 2.** Risk of contracting SARS-CoV-2 infection.

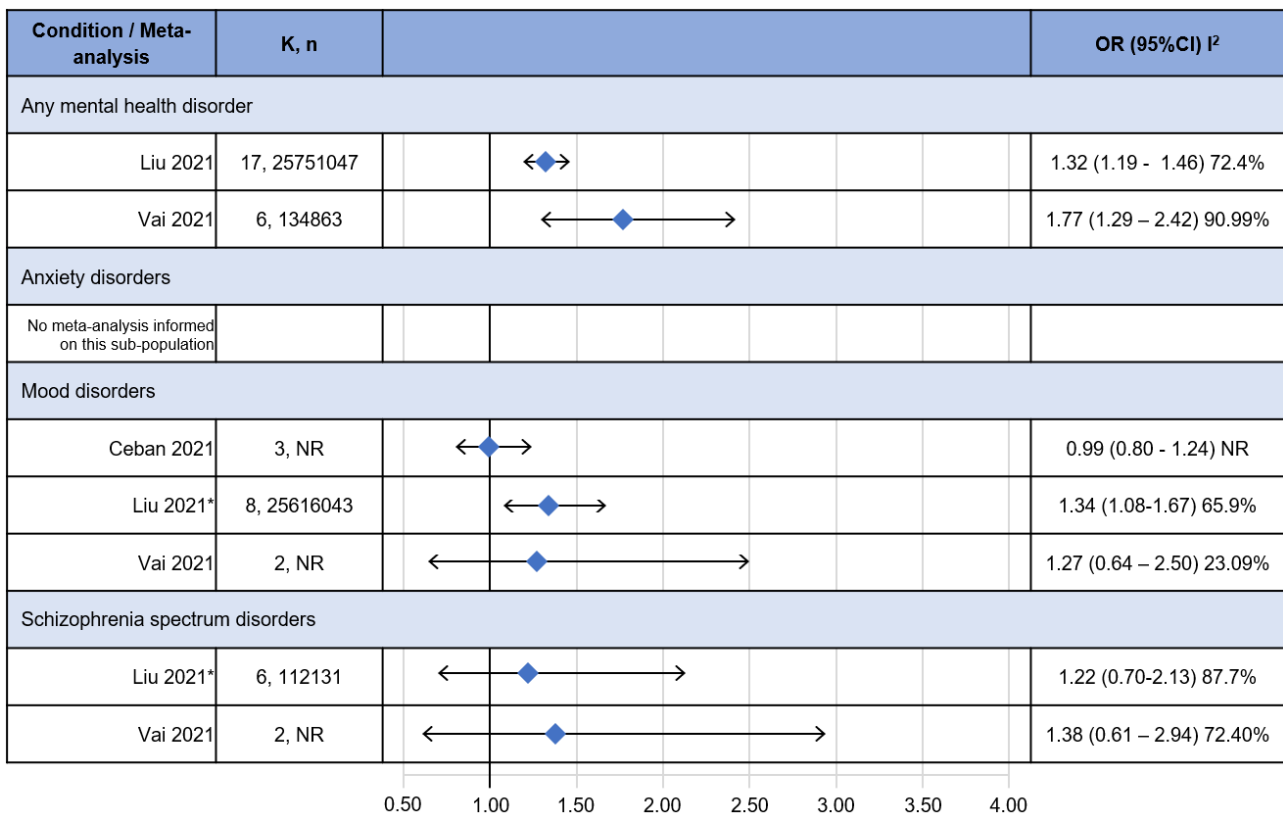
11 CI: confidence interval; K: number of included studies; OR: Odds ratio; n: total number of included participants; NR: not reported; \*: partially  
 12 adjusted model

13 For people with any mental disorder, Liu and colleagues found a statistically significant positive association  
 14 (OR: 1.71, 95% CI 1.09-2.69). For people with anxiety disorders, Liu 2021 and colleagues in a partially  
 15 adjusted model found a statistically significant positive association although this effect size relies on two  
 16 studies only (OR 1.63, 95%CI 1.44-1.85). For people with mood disorders, Liu 2021 and colleagues in a  
 17 partially adjusted model found a statistically significant positive association (OR: 2.02, 95%CI 1.08-3.76),

1 while Ceban and colleagues did not find a statistically significant association (OR: 1.50, 95%CI 0.75-2.99).  
 2 For people with schizophrenia spectrum disorders, Liu and colleagues, in a partially adjusted model, did not  
 3 find a statistically significant association (OR: 1.72, 95%CI 0.62-4.77). The level of statistical heterogeneity  
 4 has been generally very high, with most  $I^2$  statistics over 95%, with the exception of the estimate for people  
 5 with mood disorders by Liu and colleagues (0%).  $I^2$  was not reported in Ceban et al., 2021.

6 *Risk of severe illness*

7 Three MAs informed on the association between a severe course of COVID-19 and having a pre-existing  
 8 mental disorder compared to not having a pre-existing mental disorder (Figure 3) [18-20].



10 **Figure 3.** Risk of severe COVID-19 illness.

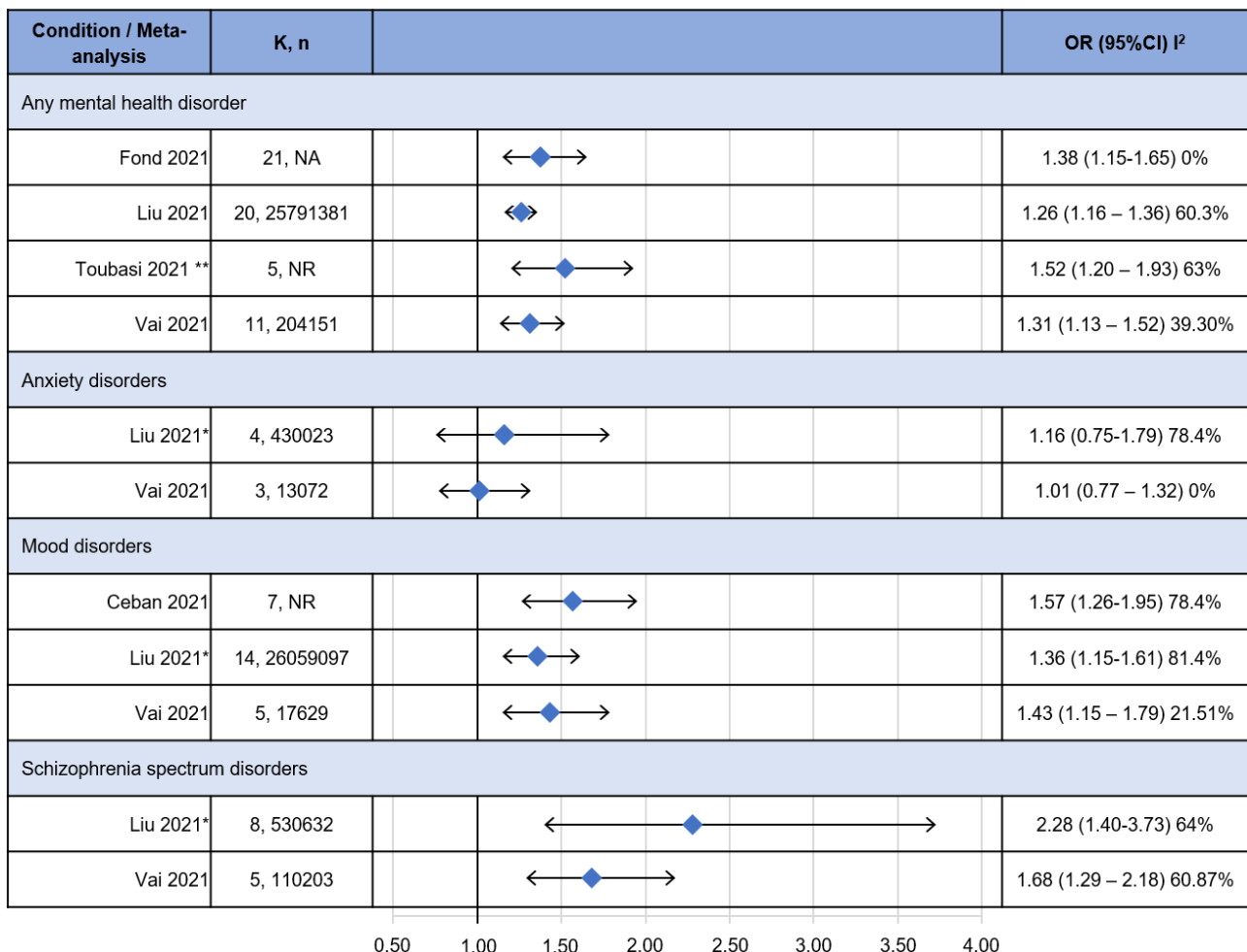
11 CI: confidence interval; K: number of included studies; OR: Odds ratio; n: total number of included participants; NR: not reported; \*: partially  
 12 adjusted model

13 For people with any mental disorder, both the review by Liu and colleagues and Vai and colleagues found a  
 14 statistically significant positive association (OR: 1.32, 95%CI 1.19-1.46 and OR: 1.77, 95%CI 1.29-2.42,  
 15 respectively). No study informed on people with anxiety disorders. For people with a mood disorder, Ceban

1 and colleagues found no association (OR: 0.99, 95%CI: 0.80-1.24), Liu and colleagues in a partially adjusted  
 2 model found a statistically significant positive association (OR: 1.34, 95%CI 1.08-1.67) while Vai and  
 3 colleagues did not find a statistically significant association (OR 1.27, 95%CI 0.64-2.50). For people with a  
 4 schizophrenia spectrum disorder, both the reviews by Liu and colleagues and Vai and colleagues did not  
 5 find a statistically significant association (OR: 1.22, 95%CI 0.70-2.13 and OR: 1.38, 95%CI 0.61-2.94,  
 6 respectively). The level of statistical heterogeneity was moderate to very high, with an  $I^2$  statistic between  
 7 65% to 100%, but low for the estimate for people with mood disorders by Vai and colleagues (23%).  $I^2$  was  
 8 not reported in Ceban et al., 2021.

9 *COVID-19 related mortality*

10 Four MAs informed on the association between mortality and having a pre-existing mental disorder  
 11 compared to not having a pre-existing mental disorder (Figure 4) [19-22].



12

1 **Figure 4.** COVID-19 related mortality risk.

2 CI: confidence interval; K: number of included studies; OR: Odds ratio; n: total number of included participants; NR: not reported; \*: partially  
3 adjusted model; \*\*: considers mortality and severe illness together

4 For people with any mental disorder all four MAs found a statistically significant positive association,  
5 ranging from an OR of 1.38 (95%CI: 1.15-1.65) for the review by Fond and colleagues to 1.52 (95%CI: 1.20-  
6 1.93) for the review by Toubasi and colleagues (which however considered in this outcome severe illness  
7 cases as well). For people with anxiety disorders both the reviews by Liu and colleagues, in a partially  
8 adjusted model, and by Vai and colleagues did not find a statistically significant association (OR: 1.16,  
9 95%CI 0.75-1.79 and OR: 1.01, 95%CI 0.77–1.32, respectively). For people with mood disorders, all three  
10 informing MAs found a statistically significant positive association with ORs ranging from 1.36 (95%CI: 1.15-  
11 1.79, Liu and colleagues, partially adjusted model) to 1.57 (95%CI: 1.26-1.95 Vai and colleagues). For people  
12 with schizophrenia spectrum disorders both the reviews by Liu and colleagues, in a partially adjusted  
13 model, and by Vai and colleagues found a positive association (OR 2.28, 95%CI 1.40-3.73, and OR 1.68,  
14 95%CI 1.29-2.18, respectively). The level of statistical heterogeneity has been generally moderate to  
15 considerable, with an  $I^2$  statistic between 60% and 81.4%, but for the review by Vai and colleagues for the  
16 estimate for people with any mental disorder (39%), and low for the estimate for people with anxiety  
17 disorders (0%) and mood disorders (22%). The  $I^2$  has not been reported in Ceban et al., 2021.

18 *Narrative reviews*

19 The narrative reviews corroborated meta-analytic findings by indicating that patients with serious pre-  
20 COVID-19 mental disorders show adverse health outcomes related to COVID-19 infection in terms of higher  
21 severity and mortality. Fornaro and colleagues [25] performed a scoping review on clinical and public  
22 health themes for people with bipolar disorder. They identified four major themes from the 14 included  
23 papers, among which was the impact of having bipolar disorder on the risk of contracting the SARS-CoV-2  
24 infection. For this theme, one study reported an increased risk of infection contraction for people with  
25 bipolar disorder [27]. This study was considered by the MAs previously reported. Karaoulanis and  
26 Christodoulou performed a systematic review without meta-analysis on infection rates and mortality in

1 people with schizophrenia spectrum disorders. The included studies suggest an increased infection and  
2 mortality risk; these studies have been included in the MAs previously reported. Lemieux and colleagues  
3 performed a rapid review on the management of COVID-19 for people with mental illness in secure  
4 settings. They considered a wide range of publications including opinion pieces and other reviews and  
5 report greater morbidity and mortality. Murphy and colleagues conducted a scoping review on the impact  
6 of COVID-19 and related restrictions on people with pre-existing mental disorders. They reported an  
7 increased infection risk in this population.

## 8 **Discussion**

9 To our knowledge this is the first umbrella review aimed at summarizing evidence on the impact of the  
10 COVID-19 pandemic on health outcomes in people with pre-existing mental disorders. Compared to the  
11 individual systematic reviews previously published, this umbrella review contextualizes the single piece of  
12 evidence, and provides an overview for different mental disorders, while systematic reviews have so far  
13 focused on specific diagnostic groups or considered only some of the outcomes of interest on the physical  
14 health repercussions of people with mental disorders. Two reviews considered several diagnostic groups  
15 and outcomes, however one employed only partially adjusted models within diagnostic groups [19], and  
16 the other could include a considerably smaller number of studies [20]. Overall, we found consistent results  
17 across the various reviews. Of interest, we found no previous reviews exploring the long-term effects of  
18 SARS-CoV-2 infection.

19 Having any mental disorder was found to be associated with a higher likelihood of contracting the SARS-  
20 CoV-2 infection, a more severe COVID-19 illness, and higher mortality. We found different risks for different  
21 disorder groups. People with pre-existing anxiety disorders had an increased risk of contracting the SARS-  
22 CoV-2 infection; for people with mood disorders there was conflicting evidence of increased risk for severe  
23 COVID-19 course, and evidence of increased mortality; people with schizophrenia spectrum disorders had  
24 an increased risk of mortality, but there was no clear evidence of increased severe illness course for people



1 with schizophrenia spectrum disorders. Notably, we found no review assessing the association between  
2 long-term physical symptoms after COVID-19 and having a pre-existing mental disorder.

3 Having any mental disorder has been associated with an increased risk of contracting the SARS-CoV-2  
4 infection. Looking at the data for the specific diagnostic groups, however, we observe that the association is  
5 confirmed for people with an anxiety disorder (and in an estimate based on only two studies) only, while  
6 for people with mood disorders the evidence is not consistent across reviews, and for people with a  
7 schizophrenia spectrum disorder the association is not statistically significant with a very wide confidence  
8 interval, making it hard to draw clear conclusions. Many people with a mental disorder live in shared  
9 households, nursing homes, therapeutic communities, or are inpatients. It has been noted that such  
10 settings pose challenges in putting into practice infection control measures [28]. In addition to that, people  
11 in an acute phase of a mental disorder might find it difficult to understand the need for and adhere to  
12 behavioural means of social distancing [29]. Still, these considerations regard mostly people with serious  
13 mental illness such as bipolar disorder or schizophrenia, adding difficulty to the interpretation of these  
14 results.

15 Having a mental disorder was associated with having a more severe illness course and increased mortality.  
16 This could be partially explained by the increased risk of contracting the SARS-CoV-2 infection, but as the  
17 three disorder groups showed differential patterns, we argue that additional factors may have influenced  
18 this outcome. In particular, anxiety disorders were not associated with increased mortality despite an  
19 increased infection risk, and indeed the results are compatible with a random distribution in terms of effect  
20 sizes and confidence intervals. Mood disorders and schizophrenia spectrum disorders have been associated  
21 with increased mortality from COVID-19 without conclusive evidence of increased infection risk. Several  
22 factors might come into play in determining such a negative outcome. People with severe mental illness,  
23 such as bipolar disorder and schizophrenia, more frequently present with high BMI, diabetes mellitus,  
24 generally limited exercise tolerance, and are more likely to also smoke and have substance abuse disorders  
25 [6, 7, 30]. All of these are known risk factors for severe COVID-19 and for COVID-19 related mortality [2, 3,  
26 31]. Although the use of adjusted odds ratios should have mitigated the impact of these risk factors in the

1 estimate of effect sizes there was high heterogeneity in terms of adjusted factors used by primary studies.  
2 Therefore, it is possible that some factors, such as BMI, might not have been appropriately accounted for  
3 [32]. Many people with these disorders would have received an antipsychotic (and potentially  
4 benzodiazepines), with a possible negative impact on respiratory function [8]. However, there is limited  
5 evidence to support these hypotheses and future research is needed to fill this gap in knowledge.  
6 Moreover, we should take into consideration that socio-economic factors and stigma might have influenced  
7 the access to medical care of these persons [33]. Many primary studies were conducted during the initial  
8 phases of the pandemic when medical resources were scarce compared to needs, access to intensive care  
9 units was limited and subject to stringent triage, and no vaccine was available yet. The finding that for  
10 people with schizophrenia spectrum disorders there was no increased risk for a more severe disease  
11 course, but higher risk for COVID-19 related mortality, is somewhat puzzling. The reviews have used slightly  
12 different definitions of “severe illness”, but all considered it as an operational composite outcome where  
13 many different events qualified, including oxygen therapy. Oxygen therapy has been a widespread need in  
14 COVID-19 patients, as arterial hypoxemia is a major feature of the disease [34]. It is possible that the  
15 definition of severe illness was therefore excessively sensitive and did not allow for the identification of  
16 differences between people with and without a pre-existing mental disorder. Another possible explanation  
17 is that people with schizophrenia might have been disproportionately affected by sudden death events. We  
18 know that cardiac sudden death events have been shown to be associated with COVID-19 [35] and that  
19 people with schizophrenia have a higher frequency of cardiovascular disease which may predispose to such  
20 events [36]. However, there is no direct evidence, and the use of adjusted estimates should have  
21 compensated for the increased cardiovascular burden. Overall, the mismatch between the risk of severe  
22 disease and mortality reinforces the need to better investigate factors associated with the increased  
23 mortality risk.

24 The findings of this umbrella review should be put into the context of some limitations. For the various  
25 diagnostic groups, the number of included primary studies has been limited, especially for anxiety  
26 disorders. Mood disorders include both depression and bipolar disorder, two disorders with different

1 pharmacological approaches and neuro-inflammatory profiles. Additionally, information on the disease  
2 status of participants (remission or relapse) has generally not been considered. Low- and middle-income  
3 countries have been scarcely represented in the primary studies included by the reviews. The publication  
4 timeframe covered by the meta-analyses span to the first quarter of 2021; as such, these findings depict  
5 the first year of the pandemic. The general landscape has since changed, thanks to health care systems  
6 adaptations, improved COVID-19 treatments and importantly, the introduction of vaccines. There is,  
7 however, conflicting evidence regarding vaccine uptake rates in people with mental disorders, possibly due  
8 to regional differences [37, 38]. The reviews considered different study designs for inclusion; notably, Liu  
9 and colleagues considered case series. The review by Vai and colleagues informed on many diagnostic  
10 groups, but in only partially adjusted models. There has been considerable heterogeneity across all  
11 outcomes, which the meta-analyses struggled to explain. Heterogeneity likely reflects methodological and  
12 qualitative differences among the primary studies. Moreover, this high heterogeneity and the generally  
13 wide confidence intervals limit the accuracy of the estimates.

14 In light of these findings, there are relevant questions for future research. The new Omicron variant of the  
15 SARS-CoV-2 virus spreads more easily but usually causes less severe illness [39]. Assessing if this holds true  
16 for people with a pre-existing mental disorder as a risk factor would be valuable. In parallel, there is still  
17 limited evidence on vaccine hesitancy and uptake rate in this population. Moreover, the topic of long-term  
18 physical symptoms after COVID-19 in people with mental disorders remains scarcely investigated.  
19 Addressing these three points would allow for more effective health care planning and possibly targeted  
20 intervention to address vaccine hesitancy.

## 21 **Conclusions**

22 The COVID-19 pandemic has affected people with pre-existing mental disorders more severely than people  
23 without in terms of physical health. People with pre-existing mental disorders, and especially those with  
24 mood or schizophrenia spectrum disorders, should have been considered at risk of severe course and

1 increased mortality from COVID-19, similar to other identified risk groups such as patients with somatic  
2 health conditions.

3 **Disclaimer:** The authors alone are responsible for the views expressed in this article and they do not  
4 necessarily represent the views, decisions, policy, or views of WHO or the institutions with which the  
5 authors are affiliated.

6 **List of abbreviations:**

7 aOR: adjusted Odds Ratio; ICU: Intensive Care Unit; MAs: Meta-Analyses; OR: Odds Ratio; SR: Systematic  
8 Review

9 **Declarations:**

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11 Consent for publication: not applicable.

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