

Research paper

Long-term effects of COVID-19 on mental health: A systematic review



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ABSTRACT

**Background:** Acute effects of COVID-19 can be life-threatening. Alterations in mental health during the active infection have been documented, but the long-term consequences are less clear.

**Method:** A systematic review was undertaken to investigate the effect of COVID-19 infection on long-term mental health outcomes. Three databases [PubMed, Medline (Ovid) and Cochrane library] were searched between 1st October 2019 and 29th August 2021 with additional hand searching to identify all published studies reporting symptoms of generalised anxiety, depression, post-traumatic stress disorder (PTSD), or sleep disturbance in participants at least one month after COVID-19 infection. The prevalence and mean symptom score of each were assessed.

**Results:** Eight hundred and eighty five studies were found, of which 33 were included in the review involving a total of 6743 participants. The studies' risk of bias were typically fair quality. The median study age of participants was 57.8 years (IQR 49.3–60.7), with 63.0% male (IQR 57.0%–73.0%). Participants typically experienced no or mild symptoms of long-term anxiety (GAD-7, STAI-S, HADS) and depression (PHQ-9, BDI, PHQ-2, HADS). Prevalence varied depending on the measurement tool. Sleep disturbances (primarily insomnia) were most commonly reported as mild. PTSD prevalence was similar to anxiety and depression.

**Conclusion:** The overall effect of the pandemic has been linked with worsening psychiatric symptoms. However, the long-term effect from direct COVID-19 infection has been associated with no or mild symptoms. Studies exhibited the long-term prevalence of anxiety, depression, PTSD, and sleep disturbances to be comparable to general population levels.

## 1. Introduction

Prior to the COVID-19 pandemic, poor mental health in England already carried an annual economic and social cost of £105 billion ([England.nhs.uk](https://www.england.nhs.uk), 2021). After 18 months since the first cases emerged, the direct effects of COVID-19 on mental health are only starting to become apparent (NICE188, 2021). In addition, the indirect effects of COVID-19, such as disruption to mental health services, are also becoming evident (World Health Organization; 2020).

The acute effects of COVID-19 can be devastating and life-threatening, affecting a wide range of organ systems. Reports of effects on the brain include inflammation which have been linked with cognitive deficits and psychiatric manifestations (Boldrini et al., 2021). Long-term effects are only now being documented with one year follow-up studies just being published (Huang et al., 2020).

Data exist on the long-term mental health impacts of epidemics caused by other coronaviruses including MERS (Middle Eastern Respiratory Syndrome caused by MERS-CoV) and SARS (Severe Acute

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Respiratory Syndrome caused by SARS-CoV-1). These have demonstrated sustained long-term psychiatric illness in people who have recovered from the acute infection (Park et al., 2020a). Studies with up to 12-year follow-up have shown sustained mental health effects including anxiety, depression, trauma, and sleep disturbance (Tzeng et al., 2020).

A systematic review published early in the pandemic (search date 18th March 2020) explored psychiatric disorders following exposure to COVID-19 infection. It found similarities in the trajectory of other coronavirus epidemics with a low prevalence of mental health conditions (Rogers et al., 2020). With one year having passed since this first review, we aimed to re-examine the longer-term mental health impact of COVID-19 with a larger literature base.

## 2. Materials and methods

### 2.1. Study design

A systematic review of peer-reviewed observational studies was conducted. The protocol for this study was published in the PROSPERO register (CRD42021239505, 2021). We report the findings in adherence to the PRISMA guidelines.

### 2.2. Search strategy

We searched the following databases: Medline (Ovid), PubMed, and Cochrane library [1st October 2019–29th August 2021] as well as hand searching; for full details, see Supplement 1.

### 2.3. Inclusion and exclusion criteria

Long-term was defined as follow-up occurring at least one month after COVID-19 diagnosis as per the National Institute Clinical Excellence guidance (NICE188, 2021). The definition of ‘long-term’ was pre-specified in our protocol, and while this definition is still evolving, it has been implemented in other COVID-19 studies (Halpin, 2021; Lopez-Leon et al., 2021) with the current reasoning being the inability to detect infectious SARS-CoV-2 three weeks post-infection (Nalbandian et al., 2021). Included subjects were at least 18 years of age with a laboratory-confirmed diagnosis of COVID-19. Articles were limited to observational studies including cohort and case-control, and case series. Manuscripts were restricted to those in English and excluded any not specifying age ranges.

### 2.4. Data extraction

Two investigators (TS and NWB) independently screened articles for inclusion. The following study characteristics were subsequently extracted: study type, location, environment, sample characteristics, average age, timepoints of follow-up relative to COVID-19 diagnosis, sex, study size, and mental health outcomes.

### 2.5. Outcomes

Primary outcome: anxiety symptoms (herein described as anxiety).

Secondary outcomes included: depression symptoms (herein described as depression); post-traumatic stress disorder (PTSD); sleep disturbance.

The use of any validated patient-rated or investigator-rated symptom severity scale was included. Details of the scales assessed are detailed in Supplement 2 including abbreviations, score thresholds and references.

Mental health is a broad construct and is not necessarily the opposite of mental illness. We chose to focus on common mental health conditions (otherwise termed mental illness, or mental disorder) with pre-selected outcomes including: anxiety and depression, as usually included in the definition of common mental disorders, in addition to

the specific outcomes of sleep and post-traumatic stress disorder symptoms, which are common but also have been particularly implicated in COVID-19 illness. We decided to investigate anxiety as our primary outcome, *a priori*, due to early concerns that 1 month post-hospitalization anxiety was the driving force, as suggested by preliminary data from COVID-19 survivors (D'Cruz et al., 2020; Mazza et al., 2020)

Outcome severity was classified using thresholds specified in the included articles. These were in alignment between included studies as commonly used cut-off scores (see Supplement 2). Prevalence for each outcome was calculated as a percentage of patients with psychometric scores above a specified cut-off score for each symptom severity scale. An overall prevalence for each mental health outcome was calculated by adding the total patient numbers across studies using each symptom severity scale. Studies that included > 30% severe COVID-19 cases, defined as patients admitted to ICU, were pooled separately as they were not comparable.

### 2.6. Risk of bias assessment

Two independent authors (NWB and TS) assessed the risk of bias (RoB) using the Newcastle-Ottawa Scale (NOS) (Wells et al., 2000). The scale has three domains which were: selection (four items); comparability of groups (two items); and ascertainment of exposure/outcome (three items). The study level RoB rating of good (scored 7–9), fair (scored 4–6), or poor (scored 0–3) was assigned (Supplement 3). Discrepancies were resolved by consensus.

### 2.7. Data analysis

Clinically similar studies were pooled for each outcome to determine prevalence. Evidence strength was assessed in the results and discussion by sections addressing the studies’ limitations, directness, consistency, precision, and reporting bias. Meta-analysis, as outlined in the protocol, was not deemed appropriate due to the expected clinical heterogeneity between studies. A sensitivity analysis was conducted comparing outcome prevalence from at least 3 months post-diagnosis (excluding severe COVID-19 cases).

## 3. Results

### 3.1. Study selection and characteristics

The search resulted in a total of 885 articles (Fig. 1- PRISMA flow chart). After title, abstract and full text screening, thirty-three studies were included: two retrospective cohort studies (Kang et al., 2021; Taquet et al., 2021), twenty cohort studies (Albu et al., 2021; Alemanno et al., 2021; Bellan et al., 2021; Daher et al., 2020; Darley et al., 2021; D'Cruz et al., 2020; de Graaf et al., 2021; González et al., 2021; Hasan et al., 2021; Horn et al., 2020; Huang et al., 2021; Li et al., 2021; Mazza, 2021; Mazza et al., 2020; Morin et al., 2021; Naidu et al., 2021; Tarsitani et al., 2021; van den Borst et al., 2021; Venturelli et al., 2021; Wong et al., 2020) , a controlled cohort study (Noviello et al., 2021), five cross-sectional cohort studies (Mandal et al., 2021; Mendez et al., 2021; Poyraz et al., 2021; Tanriverdi et al., 2021; Tomasoni et al., 2021), three case-control (Guo et al., 2020; Ortelli et al., 2021; Xiong et al., 2021), and two case-series (Negrini et al., 2020; Park et al., 2020b) (see Supplement 4 for study characteristics).

All studies examined an adult sample from treatment centres or hospitals. The median study age of patients was 57.8 years old (interquartile range [IQR] 49.3 to 60.7 years old) and the median study proportion of male participants was 63.0% male (IQR 57.0% to 73.0%). It is important to note that there was heterogeneity related to the severity of COVID-19 within and between studies. The outcomes were assessed approximately one to six months after infection (see Supplement 4).

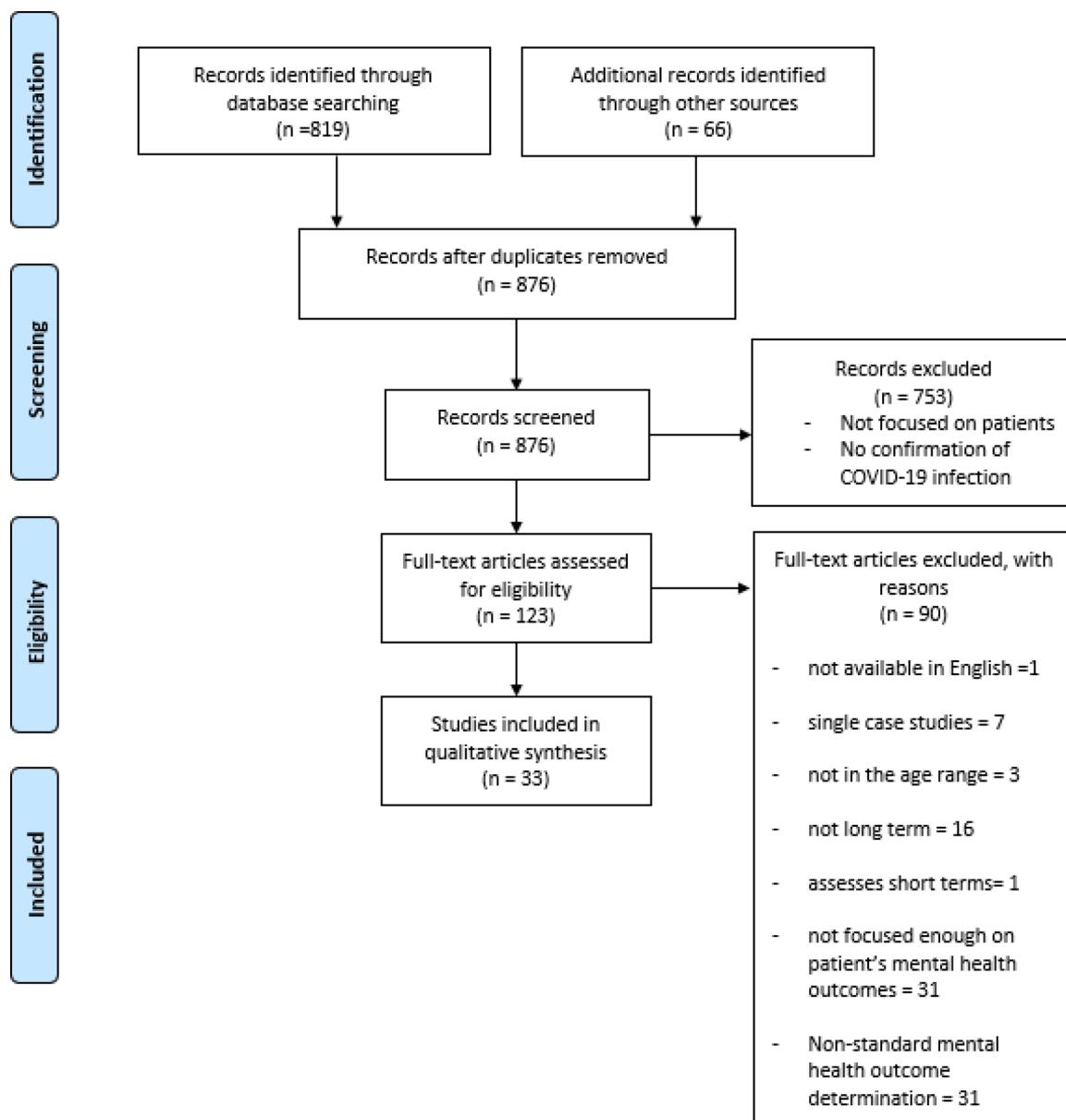


Fig. 1. PRISMA flow diagram.

Seven studies included participants with a lifetime psychiatric history (de Graaf et al., 2021; Horn et al., 2020; Kang et al., 2021; Park et al., 2020b; Poyraz et al., 2021; Tarsitani et al., 2021) with a prevalence of 40%, 13.9%, 30%, 15.4%, 10% and 8% respectively, and (Noviello et al., 2021) included 4.8% and 1.3% patients with anxiety and depression history respectively. None of these studies provided further detail regarding the nature or timeline of these psychiatric diagnoses. Kang et al., 2021 and Poyraz et al. (2021) reported that 27% and 6.3% of the cohort received psychotherapeutic intervention during admission. Patients with a positive psychiatric history were more likely to display higher symptoms scores of depression, anxiety, and PTSD. Nine studies excluded patients with a history of psychiatric disorders (Albu et al., 2021; Guo et al., 2020; Mazza, 2021; Mazza et al., 2020; Mendez et al., 2021; Negrini et al., 2020; Ortelli et al., 2021; Taquet et al., 2021; van den Borst et al., 2021), with the other seventeen studies not specifying.

### 3.2. Quality assessment

The risk of bias, assessed using the NOS, indicated seven studies were rated as good quality, eighteen rated as fair quality, and eight rated as poor quality (Supplement 3).

### 3.3. Outcomes

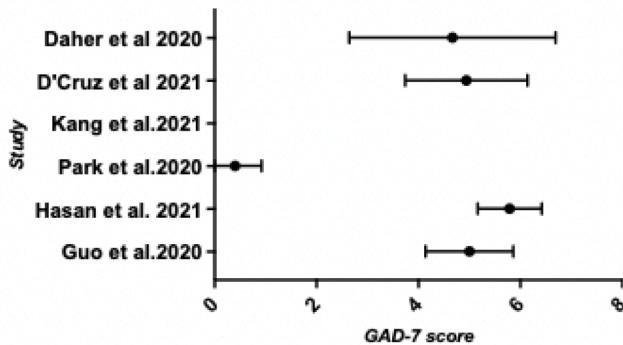
Outcomes with scoring thresholds for each of the outcome are shown in Supplement 2. The scores for Mazza, 2020 were excluded for calculation of prevalence percentages for anxiety, depression and PTSD outcomes due to being the same cohort with Mazza, 2021.

### 3.4. Primary outcome

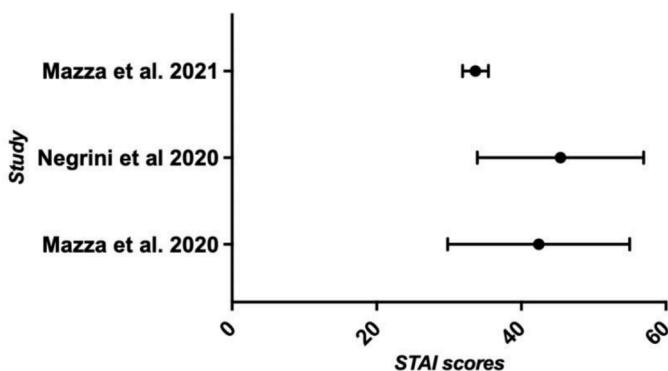
#### 3.4.1. Anxiety

Fifteen studies assessed anxiety in mild to moderate COVID-19 cases (see Fig. 2), five using the GAD-7 (Guo et al., 2020; Hasan et al., 2021; Kang et al., 2021; Li et al., 2021; Mendez et al., 2021), one using STAI-S

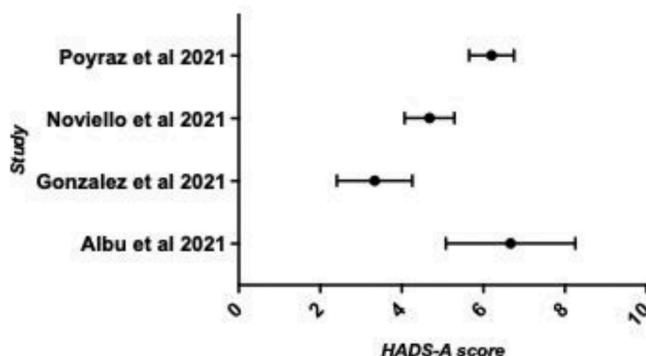
### Plot A: Generalized Anxiety (GAD-7)



### Plot B: State Trait Anxiety scale – state subscale (STAI-S)



### Plot C: Hospital Anxiety and Depression score – Anxiety (HADS-A)



**Fig. 2.** Plot A: Generalized Anxiety (GAD-7). Plot B: State Trait Anxiety scale – state subscale (STAI-S). Plot C: Hospital Anxiety and Depression score – Anxiety (HADS-A). Forest plot showing anxiety symptom severity scores across included studies. Plot A (upper panel) depicts GAD-7 scores; Plot B (intermediate panel) presents STAI-S scores; Plot C (lower panel) showcases HADS-A scores.

(Mazza, 2021), seven using HADS (Morin et al., 2021; Noviello et al., 2021; Poyraz et al., 2021; Tanriverdi et al., 2021; Tomasoni et al., 2021; van den Borst et al., 2021; Venturelli et al., 2021), and one using a clinical interview (Xiong et al., 2021). This included 3431 patients 17.52% of whom were experiencing at least mildly severe anxiety symptoms.

Seven studies assessed anxiety in severe COVID-19 cases, four using the GAD-7 (Daher et al., 2020; D'Cruz et al., 2020; de Graaf et al., 2021; Park et al., 2020b), one using the STAI-state (Negrini et al., 2020) and

two studies using the HADS scale for anxiety (Albu et al., 2021; González et al., 2021).

Anxiety prevalence in severe COVID-19 cases was 19.03% of 309 patients that were experiencing at least mild anxiety symptoms (see Supplement 6 for more details).

Two studies using GAD-7 (Guo et al., 2020; Hasan et al., 2021) reported on average mild anxiety with a mean score of 5.00 (95% CI = 4.14, 5.86) and 5.79 (95% CI = 5.16, 6.42). One study reported no anxiety with an average score of 1.88 (95% CI = 0.68, 3.08; (Kang et al.,

2021) while Li et al. (2021) and (Mendez et al., 2021) did not report average GAD-7 scores. The only study using the STAI-S identified minor symptoms of anxiety with Mendez et al., 2021 reporting 33.66 (95% CI = 31.88, 35.44) while two HADS studies (Noviello et al., 2021; Poyraz et al., 2021) reported minimal anxiety with overall scores of 4.68 (95% CI = 4.07, 5.29) and 6.2 (95% CI = 5.65, 6.75) respectively.

Out of the six studies that used the HADS, only two reported mean scores both indicating an overall normal level of anxiety. Taquet et al. (2021) reported a prevalence of anxiety disorder of 7.11% (95% CI = 6.82, 7.41).

Sensitivity analysis showed a decrease in prevalence from 20.68% to 11.11% between one to three months follow-up and more than three months follow-up (Supplement 8).

### 3.5. Secondary outcomes

#### 3.5.1. Depression

Twenty studies assessed symptoms of depression in non-severe COVID-19 cases, five using the PHQ-9 (Guo et al., 2020; Hasan et al., 2021; Kang et al., 2021; Li et al., 2021; Wong et al., 2020), three using the BDI (Mazza, 2021; Morin et al., 2021; Ortelli et al., 2021), three using PHQ-2 (Mandal et al., 2021; Mendez et al., 2021; Naidu et al., 2021), six using the HADS (Noviello et al., 2021; Poyraz et al., 2021; Tanriverdi et al., 2021; Tomasoni et al., 2021; van den Borst et al., 2021; Venturelli et al., 2021), one using HRSD (Alemanno et al., 2021), one using DMI-10 (Darley et al., 2021) and one using a clinical interview (Xiong et al., 2021). From a total of 4935 participants, 18.85% exhibited at least mild symptoms of depression (Supplement 7).

Seven studies assessed symptoms of depression in severe COVID-19 cases, four using the PHQ-9 (Daher et al., 2020; D'Cruz et al., 2020; de Graaf et al., 2021; Park et al., 2020a), one using the BDI (Negrini et al., 2020), and two using the HADS instrument for depression (Albu et al., 2021; González et al., 2021). Depression prevalence in severe COVID-19 cases was 20.39% out of 309 patients, averaging none to mild symptoms of depression.

Similar to the reporting for anxiety symptoms, Guo et al. (2020) and Hasan et al., 2021 reported an average mild depression severity, with a mean PHQ-9 score of 5.00 (95% CI = 4.71, 5.29) and 5.64 (95% CI = 4.98, 6.30). Kang et al. (2021) and Wong et al. (2020) reported no depression overall, with average scores of 2.75 (95% CI = 1.21, 4.29) and 5.31 (95% CI = 4.23, 6.38). The two BDI studies, Mazza et al. (2021) and Ortelli et al. (2021) reported minimal depression, with average scores of 1.93 (95% CI = 1.34, 2.52) and 3.80 (95% CI = 2.16, 5.44) respectively. Finally, only two HADS studies reported mean scores, both indicating minimal depression with scores of 3.81 (95% CI = 3.227, 4.35) for Noviello et al., 2021 and 6.3 (95% CI = 5.79, 6.81) for Poyraz et al., (2021).

Cohorts followed up for more than three months had half the prevalence of depression compared to those that were followed up for less than three months, reporting a prevalence of 10.36% and 20.84% respectively. A total of 3954 and 1187 participants were assessed in the sensitivity analysis respectively (Supplement 8).

#### 3.5.2. PTSD

Thirteen studies measured PTSD in non-severe COVID-19 cases, seven studies using the DSM-5 derived PCL-5 questionnaire (Guo et al., 2020; Horn et al., 2020; Kang et al., 2021; Mazza, 2021; Morin et al., 2021; Tarsitani et al., 2021; van den Borst et al., 2021), one study using the TSQ (Naidu et al., 2021), two studies using the DTS (Alemanno et al., 2021; Mendez et al., 2021), and three studies using the IES-R (Bellan et al., 2021; Poyraz et al., 2021; Venturelli et al., 2021). Average PCL-5 scores of 8.00 (95% CI = 6.57, 9.43), 10.99 (95% CI = 9.37, 12.61) and 8.77 (95% CI = 6.42, 11.12) were reported by Guo et al. (2020), Mendez et al., 2021 and Kang et al. (2021) respectively. Only one study (Poyraz et al., 2021) reported an average score of IES-R of 22.2 (95% CI = 20.48, 23.92). The overall prevalence of positive PTSD screen was 17.68% of

3405 participants.

Two studies measured PTSD in severe COVID-19 cases, one using PCL-5 (de Graaf et al., 2021) and the other one the TSQ (D'Cruz et al., 2020). The prevalence of PTSD in severe cases of COVID-19 was 19% from 200 patients.

PTSD prevalence in cohorts followed up longer than three months was slightly higher than less than three months follow-up at 18.99% and 12.19% respectively (Supplement 8).

#### 3.5.3. Sleep

A total of six studies assessed sleep in mild to moderate COVID-19 cases (Li et al., 2021; Mazza et al., 2020; Morin et al., 2021; Poyraz et al., 2021; Tanriverdi et al., 2021; Wong et al., 2020). An average MOS-SS score of 20.58 (95% CI = 19.95, 21.21) was reported representing mild symptoms of sleep disturbance (Mazza et al., 2020). Two studies used the ISI with an overall insomnia prevalence of 34.64% (Li et al., 2021; Morin et al., 2021). Three studies used the PSQI with an overall prevalence of 41.97% (Poyraz et al., 2021; Tanriverdi et al., 2021; Wong et al., 2020). An overall prevalence of sleep disturbances of 36.59% of 1454 participants was obtained. Finally, D'Cruz et al. (2021) reported a prevalence of 57%, however, since a validated tool was not used, this was excluded from the statistical summary.

Two studies assessed sleep in severe COVID-19 cases using the PSQI (Albu et al., 2021; Huang et al., 2021). However, only Albu et al. (2021) presented prevalence results hence the prevalence of sleep quality disturbance was 40% out of 30 cases, with most participants indicating no poor sleep.

## 4. Discussion

This systematic review included thirty-three studies of mixed quality. The included participants typically exhibited no worse than mild symptoms of anxiety and depression. Past epidemics caused by SARS, MERS, or ebola have demonstrated that half of the survivors suffered from at least one of the psychiatric conditions examined in this review (Chua et al., 2004; Keita et al., 2017). However, one year on from the (Rogers et al., 2020) systematic review of May 2020, the predicted mild trajectory of psychiatric illness would seem to have been borne out.

Anxiety findings (mean GAD-7, STAI-S and HADS scores) were comparable to the general population. Anxiety prevalence percentage was highest in GAD-7 studies, likely due to the low cut-off score used; Kang et al. (2021) reported that scores of  $\geq 5$  represent significant anxiety with many other studies using a cut-off score of 10 for diagnosis as a clinical case. Conversely, Xiong et al. (2021) had the lowest prevalence which is likely to be due to clinical interviews which are less likely to result in overestimation compared to self-rated questionnaires. Overall, there was inconsistency findings in anxiety prevalence between different diagnostic tools.

Even when disregarding the potential for over-sensitivity of diagnosis in the included studies, the overall prevalence for anxiety was lower compared with SARS, MERS, and ebola epidemics (Chua et al., 2004; Keita et al., 2017; Jeong et al., 2016) than studies that looked at short-term symptoms (Krishnamoorthy et al., 2020). Symptoms were lower than the prevalence reported in a control group from one of the included studies (Noviello et al., 2021) and comparable to similar studies in the general public during the pandemic (Salari et al., 2020; Zhang et al., 2020; Krishnamoorthy et al., 2020), indicating relatively limited long-term anxiety in COVID-19 patients. Compared to clinical diagnoses reported by Taquet et al. (2021), self-reported anxiety prevalence was significantly higher, further indicating the disparities between clinical diagnosis and patient-reported screening questionnaires. Moreover, the average GAD-7 scores from Hasan et al., 2021 and Gou et al. (2020) were higher than the general public before the COVID-19 pandemic in a German population (Löwe et al., 2008) while the average scores from Park et al., (2020b) and Kang et al. (2021) were lower indicating uncertainty. Finally, the sensitivity analysis revealed a

decrease in anxiety with follow-up greater than three months.

Overall, the evidence presented does not suggest any increase in anxiety after COVID-19 infection. This was also found within Klaser et al. (2021) who recruited a large cohort of SARS-CoV-2 positive individuals and found a slightly higher prevalence of anxiety and depression disorders at three months compared to pre-pandemic levels.

Similar to anxiety, depression mean scores for each study indicated levels from none to mild. All except PHQ-9 and HRSD reported lower than expected prevalence compared to other studies that examined the general population and healthcare workers during the COVID-19 pandemic using a mild disease severity threshold (Salari et al., 2020; Zhang et al., 2020; Krishnamoorthy et al., 2020). The PHQ-9 prevalence percentages may be over-sensitive in the included studies due to the low cut-off scores employed (Hasan et al., 2021). As with anxiety, the clinical interview implemented by Xiong et al. (2021) yielded a much lower depression prevalence compared to the questionnaires.

When pooled, the combined prevalence of all studies reporting depression was no higher than would be expected in the general public during the COVID-19 pandemic (Salari et al., 2020; Zhang et al., 2020; Krishnamoorthy et al., 2020). Taquet et al. (2021) reported a low prevalence of mood disorders, with other studies stating that long-term anxiety and depression in COVID-19 patients are similar to pre-pandemic levels (Klaser et al., 2021). Sensitivity analysis showed a halving of depression prevalence in studies with a longer follow-up.

As for PTSD, overall PCL-5 and TSQ scores were lower compared to DTS and IES-R scores. The pooled prevalence was also lower compared to rates reported in the MERS (Park et al., 2020a) and SARS epidemics (Mak et al., 2009). While this is not a fair comparison due to the different follow-up timeframes, the low prevalence does not support an association between COVID-19 and long-term PTSD. Finally, the sensitivity analysis revealed a decrease in PTSD prevalence with longer follow-up. This confirms results from Mazza et al. (2021) where PTSD reported using PCL-5 decreased with longer follow-up in COVID-19 patients.

In the case of sleep disturbances, evidence of minor levels of sleep disturbances was presented by Mazza et al. (2020). The prevalence of insomnia reported using the ISI was lower than that in patients with acute COVID-19, and comparable to the general population during the early stages of the pandemic in China, when measured using the same instrument (Deng et al., 2020; Yu et al., 2020). PSQI prevalence was also comparable to that in the general population during the outbreak determined using the same tool (Jahrami et al., 2021). Overall, although sleep disturbance prevalence is higher than the other outcomes, this is not pertaining to disorders and does not appear substantially different from general population estimates.

The appearance of some mental health symptoms following COVID-19 may be resultant of infection. Studies of previous coronaviruses (Netland et al., 2008), animal models (Burks et al., 2021), and brain analysis at post-mortem of COVID-19 patients (Paniz-Mondolfi et al., 2020) provide evidence that SARS-CoV-2 can penetrate the blood-brain barrier. Once in the brain, the virus can trigger an immune response resulting in the secretion of interleukins, tumour necrosis factor and nitric oxide (Cesuglio et al., 2021). These have been linked to mood disorders (Dantzer, 2018; Miller and Raison, 2016) and sleep disturbances (Cesuglio et al., 2021) providing some indications of neurological mechanisms through which viral infection may have causal effects on psychiatric disorder onset.

It is possible that indirect psychosocial factors may be the overriding mechanism for any increased level of anxiety and depression (Brooks et al., 2020; Yu et al., 2020). External environmental factors such as quarantine and lockdown measures introduced during the onset of the pandemic have been shown to act as risk factors for psychiatric disorders. In addition, psychological, social, and job-related factors have also been shown to be associated with poor mental health outcomes (Vindgaard and Benros, 2020). This renders the mechanism for psychiatric effects complex and not easily disentangled with these included studies. From the results of our study, current data seem to indicate limited

association between long-term follow-up after COVID-19 infection and psychiatric disorders. This suggests that the global increase in mental health sequelae reported by Santomauro et al. (2021) is more likely due to psychosocial factors rather than a direct long-term effect of the virus.

#### 4.1. Strengths and limitations

Only seven of thirty-three studies were rated as good in the RoB assessment. Longer-term assessment may also offer more reliable estimates and may also account for participants' psychiatric history, the severity of COVID-19, and the lack of comparable controls.

#### 4.2. Conclusion

Most studies reported anxiety, depression and sleep disturbances in the short term following COVID-19. However, symptoms at longer term were consistent with the general population suggesting deterioration could be attributed to indirect effects of COVID-19 psychosocial factors.

#### Declarations

##### Ethics approval

Not required

##### Funding

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##### Data availability

Data is available on request from the corresponding author.

##### Author contributions

Conceived the study (BC, PB), developed the protocol (BC, NB, PB, TS), collected the data (NB, TS), searched the literature (NB, TS) analysed the data (BC, NB, RS, TS), interpreted the findings (BC, NB, RS, TS), drafted the initial manuscript (BC, NB, RS, TS), all authors approved the final manuscript.

BC is the guarantor of the study findings.

##### Conflict of interest

RS has in the last three years received an honorarium from Lundbeck. BC, NB, TS and PB declare no conflicts of interest.

#### Declaration of Competing Interest

All authors declare no conflicts of Interest.

#### Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.jad.2021.11.031.

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