Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Journal of Psychiatric Research 144 (2021) 129–137

Contents lists available at ScienceDirect

Journal of Psychiatric Research

journal homepage: www.elsevier.com/locate/jpsychires

Onset and frequency of depression in post-COVID-19 syndrome: A systematic review

Olivier Renaud-Charest [a,b], Leanna M.W. Lui [a,c], Sherry Eskander [a,d], Felicia Ceban [a], Roger Ho [e,f], Joshua D. Di Vincenzo [a,g], Joshua D. Rosenblat [a,c,h], Yena Lee [a], Mehala Subramaniapillai [a], Roger S. McIntyre [a,c,g,h,*]

[a] Mood Disorder Psychopharmacology Unit, University Health Network; University of Toronto, Toronto, ON, Canada
[b] Faculty of Medicine and Health Sciences, McGill University, Montreal, QC, Canada
[c] Institute of Medical Science, University of Toronto, Toronto, ON, Canada
[d] Faculty of Science, University of Toronto, Mississauga, ON, Canada
[e] Department of Psychological Medicine, Yong Loo Lin School of Medicine, National University of Singapore, Singapore
[f] Institute of Health Innovation and Technology (iHealthtech), National University of Singapore, 119228, Singapore
[g] Department of Pharmacology and Toxicology, University of Toronto, Toronto, ON, Canada
[h] Department of Psychiatry, University of Toronto, Toronto, ON, Canada

ARTICLE INFO

Keywords:
Depression
Post-COVID-19 syndrome
Post-acute sequelae of COVID-19
COVID-19
SARS-CoV-2
Population health

ABSTRACT

Following recovery from COVID-19, an increasing proportion of individuals have reported the persistence and/or new onset of symptoms which collectively have been identified as post-COVID-19 syndrome by the National Institute for Health and Care Excellence. Although depressive symptoms in the acute phase of COVID-19 have been well characterized, the frequency of depression following recovery of the acute phase remains unknown. Herein, we sought to determine the frequency of depressive symptoms and clinically-significant depression more than 12 weeks following SARS-CoV-2 infection. A systematic search of PubMed, Ovid Medline and Google Scholar for studies published between January 1, 2020 and June 5, 2021 was conducted. Frequency and factors associated with depression in post-COVID-19 syndrome were recorded and qualitatively assessed through narrative synthesis. Methodological quality and risk of bias was assessed using a modified version of the Newcastle-Ottawa Scale (NOS) for prospective cohort studies. Of 316 articles identified through our systematic search, eight studies were included. The frequency of depressive symptoms +12 weeks following SARS-CoV-2 infection ranged from 11 to 28%. The frequency of clinically-significant depression and/or severe depressive symptoms ranged from 3 to 12%. The severity of acute COVID-19 was not associated with the frequency of depressive symptoms. However, the component studies were highly heterogeneous with respect to mode of ascertainment, time of assessment, and location and age of patients. The majority of studies did not include an unexposed control group. Future research should endeavour to produce a standardized classification of post-COVID-19 syndrome, and as well as include unexposed control groups.

1. Introduction

The coronavirus disease 2019 (COVID-19) pandemic has affected more than 194 million individuals as of July 26, 2021 and continues to spread globally ("WHO Coronavirus (COVID-19) Dashboard," 2021). Replicated studies have indicated the persistence of COVID-19 symptoms following recovery of the acute infection despite clearance of the virus from the body (Nalbandian et al., 2021; Nasserie et al., 2021). Moreover, individuals who were symptomatic or asymptomatic during the acute phase of COVID-19 have experienced persistent symptoms (Huang et al., 2021).

This phenomenon has been characterized by the National Institute for Health and Care Excellence (NICE) as "post-COVID-19 syndrome", which refers to new and/or persistent signs and symptoms more than 12 weeks following severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection (COVID-19, 2021). Most patients with persisting and/or new onset symptoms after acute COVID-19 are resolved by 12 weeks (COVID-19, 2021). Hitherto, the NICE criteria for post-COVID-19

* Corresponding author. University Health Network 399 Bathurst Street, MP 9-325, Toronto, ON, Canada.
E-mail address: roger.mcintyre@uhn.ca (R.S. McIntyre).

https://doi.org/10.1016/j.jpsychires.2021.09.054
Received 27 July 2021; Received in revised form 18 September 2021; Accepted 29 September 2021
Available online 30 September 2021

syndrome provide a more rigorous threshold for defining this phenomenon. High rates of neuropsychiatric symptoms (e.g., fatigue, depression) have been reported among individuals affected by COVID-19, suggesting an effect of COVID-19 on the central nervous system (CNS) (e.g., neurotropism of SARS-CoV-2, hyperinflammatory state and hypercoagulability following infection, especially in severe cases) (Troyer et al., 2020; Zubair et al., 2020).

Depression is a leading cause of disability globally (Incidence, 2017). Accordingly, depressive symptoms and clinically-significant depression in post-COVID-19 syndrome may have severe implications as it relates to quality of life outcomes.

Recent reviews have investigated the neuropsychiatric sequelae of COVID-19, but to our knowledge, none have reported on the frequency of depression, specifically, in accordance with NICE-defined post-COVID-19 syndrome (Shanbehzadeh et al., 2021; Sinanović, 2021; Vanderlind et al., 2021). Notwithstanding, studies reporting on the survivors of the severe acute respiratory syndrome (SARS) pandemic in 2003 have indicated the presence of depression for up to 12 months following hospital discharge (Liu et al., 2021). Thus, it may be hypothesized that depression is a significant outcome among survivors of coronavirus infections. Taken together, there is a need to characterize the relationship between depression and post-COVID-19 syndrome. Herein, the aim of this paper is to synthesize the extant evidence reporting on the frequency and factors associated with depression in post-COVID-19 syndrome.

2. Methods

This review was prospectively registered on PROSPERO (CRD42021254534) and the protocol was updated throughout the writing process. Methods adhere to the Preferred Reporting Item for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (Page et al., 2021).

2.1. Search strategy

A systematic search was conducted on PubMed, OvidMedline and Google Scholar for studies published between January 1, 2020 and June 5, 2021. The title and abstract of each identified article were screened for relevance according to our selection criteria. Following the initial screen, full-text articles were assessed for eligibility. Two reviewers (OR and SE) screened articles independently and consensus was reached through discussion.

The search string used for PubMed and OvidMedline is as follows: ("depression" OR mood disorders) AND ("COVID-19" OR "SARS-CoV-2" OR "Coronavirus disease 2019") AND (follow up OR prospective) AND (sequelae OR recover* OR surviv*). To limit the search to relevant articles only on Google Scholar, a more restrictive search string was used: "depression" AND "psychiatric" AND "mental health" AND "after COVID-19" AND "virus" AND "follow up" AND "sequelae". Additionally, reference lists of included articles and identified reviews on the COVID-19 neuropsychiatric sequelae were manually reviewed.

2.2. Inclusion and exclusion criteria

The inclusion criteria for this review are as follows: 1) English language articles, 2) case-control studies, cohort studies, uncontrolled observational studies, cross-sectional studies, and retrospective chart reviews, 3) SARS-CoV-2 infection confirmed by reverse transcriptase polymerase chain reaction (RT-PCR) of nasopharyngeal or saliva swabs, or confirmed by antibody assays of blood, 4) depressive symptoms and clinically-significant depression assessed using a validated and standardized scale (e.g., HADS-D, PHQ-9) or criteria from the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV or DSM-V), and 5) depressive symptoms and clinically-significant depression assessed more than 12 weeks following SARS-CoV-2 infection. If the follow-up time was counted from the time of discharge from the hospital, an equivalent of 12 weeks must have passed from time of infection. Ten weeks or more from time of discharge were required for inclusion if the research article did not clearly specify for how long patients were hospitalized.

The exclusion criteria for this review are as follows: 1) animal studies, 2) case reports, unpublished data sets, review articles, meta-analyses, 3) SARS-CoV-2 infection not confirmed by RT-PCR of nasopharyngeal or saliva swabs, or antibody assays of blood, and 4) depressive symptoms and clinically-significant depression in the general population reported as socioeconomic consequences of the COVID-19 pandemic.

2.3. Data extraction

Two reviewers (OR and SE) used a standard data extraction form for the following study characteristics: 1) first author, 2) year of publication, 3) sample size, 4) gender distribution, 5) location, 6) mean or median age, 7) study design, 8) severity of COVID-19 symptoms, 9) method of assessment for measures of depressive symptoms and clinically-significant depression, 10) time of assessment, 11) frequency of depressive symptoms and clinically-significant depression, 12) factors associated with depression, and 13) other significant findings.

2.3.1. Quality assessment

The methodological quality of the articles was evaluated using a modified version of The Newcastle-Ottawa Scale (NOS) for prospective cohort studies (Wells et al., 2000). There are eight criteria and a possibility of obtaining up to eight stars if all criteria are met. The characteristics assessed fall into three categories: selection of the study groups, comparability of the groups, and assessment of outcome of interest. In the case of uncontrolled observational studies, two items did not apply due to the absence of a control group. A NOS score $\geq$5 reflects a high NOS ranking, whereas a score of 3–4 refers to a moderate score, and score $<$3 is categorically low. Two reviewers (OR and SE) assessed the quality of the included articles independently. Disagreements were resolved through discussion.

3. Results

3.1. Systematic search results

Databases were searched from inception until June 5, 2021. The initial search yielded a total of 316 articles, of which 87 were identified as duplicates. The remaining 229 titles and abstracts were screened for eligibility. Thirty studies met criteria for full-text assessment and 23 studies were excluded. One additional study identified from the reference lists of relevant articles met inclusion criteria. A total of eight studies were included in the present review (Fig. 1).

3.2. Methodological quality and risk of bias

Five studies had a high NOS rank (i.e., NOS scores of 5 or 6), and three had a moderate NOS rank (i.e., NOS scores of 4). The mean NOS score was 4.75. The three studies with a moderate NOS rank were uncontrolled observational studies. Two studies lost points because not all patients had a SARS-CoV-2 infection confirmed by RT-PCR or antibody assay, and depressive symptoms were not assessed at baseline (van den Borst et al., 2020; Morin et al., 2021). The third study also lost a point as depressive symptoms were not assessed at baseline, and a second point was lost as no description was provided of patients who were not assessed for depressive symptoms at follow-up (Rass et al., 2021). Rankings for individual studies are summarized in Table 1.

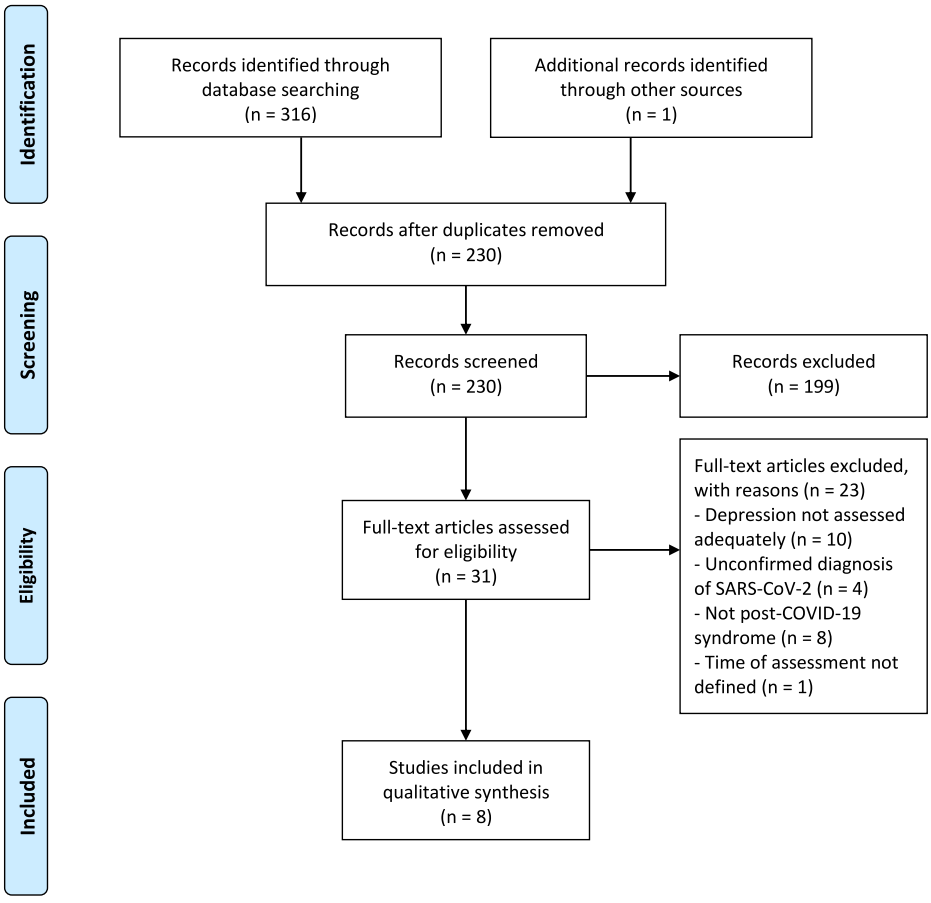

Fig. 1. PRISMA study selection flow diagram.

Table 1
Quality assessment of included publications.

Study	Selection				Comparability	Outcome			Score
	Representativeness of exposed cohort	Selection of non-exposed cohort	Ascertainment of exposure	Demonstration that outcome of interest was not present at start of study	Control for age and sex	Assessment of outcome	Follow-up	Adequacy of follow-up	
Uncontrolled observational studies									
Mazza et al. (2021)	b*	N/A	a*	b	N/A	a*	a*	b*	5
Rass et al. (2021)	a*	N/A	a*	b	N/A	b*	a*	c	4
González et al. (2021)	a*	N/A	a*	b	N/A	b*	a*	b*	5
Morin et al. (2021)	b*	N/A	b	b	N/A	b*	a*	b*	4
van den Borst et al. (2020)	a*	N/A	b	b	N/A	b*	a*	a*	4
Daher et al. (2021)	b*	N/A	a*	b	N/A	b*	a*	a*	5
Prospective cohort studies									
Frontera et al. (2021)	a*	a*	a*	b	a*	b*	a*	c	6
Mattioli et al. (2021)	c	a*	a*	b	a*	b*	b	a*	5

3.3. Study characteristics

Six of the eight included studies used an uncontrolled observational design and two used a prospective cohort design. The six uncontrolled observational studies measured the frequency of depressive symptoms and clinically-significant depression in post-COVID-19 syndrome whereas the two cohort studies only compared the depression scores between the main cohort and the control group. The DSM-V criteria (n = 1) and the following validated scales were used for the assessment of depression: 13-items Beck's Depression Inventory (BDI-13) (n = 2), Zung Self-Rating Depression Scale (ZSDS) (n = 1), Depression, Anxiety and Stress Scale (DASS-21) (n = 1), Hospital Anxiety and Depression Scale (HADS) (n = 3), Patient Health Questionnaire (PHQ-9) (n = 1), and Quality of Life in Neurological Disorders (Neuro-QoL) (n = 1). The included studies took place in seven different countries: Italy (n = 2), Spain (n = 1), Austria (n = 1), France (n = 1), Germany (n = 1), the United States (n = 1), and the Netherlands (n = 1). No regional disparity analysis was performed due to the limited number of articles. Other characteristics of the included studies are presented in Table 2.

3.4. Frequency of depression

Considerable rates of depressive symptoms and clinically-significant depression in post-COVID-19 syndrome were reported. The frequency of depressive symptoms more than 12 weeks following SARS-CoV-2 infection ranged from 11 to 28% (Daher et al., 2021; González et al., 2021; Mazza et al., 2021; Rass et al., 2021; van den Borst et al., 2020; Morin et al., 2021). When only considering clinically-significant depression and/or severe depressive symptoms (i.e., DSM-V criteria, BDI-13 score ≥9, PHQ-9 score >14, or HADS-D score >10), the reported rates ranged from 3 to 12% (Daher et al., 2021; González et al., 2021; Mazza et al., 2021; Rass et al., 2021; van den Borst et al., 2020).

Most studies measured the frequency of depressive symptoms and clinically-significant depression three to four months after diagnosis or hospital discharge; however, Daher et al. (2021) measured it at 6.5 months ($\bar{x}$ = 197 days) after hospital discharge and obtained a frequency of 27% for moderate depressive symptoms, and 5% for severe depressive symptoms. Only one study had a control group unexposed to SARS-CoV-2 and reported significantly higher depression scores among COVID-19 subjects (i.e., $\bar{x}$ = 3 vs. $\bar{x}$ = 1 on the DASS-21 depression scale, p = 0.036) (Mattioli et al., 2021). However, time of assessment in that study ranged from 12 to 215 days from diagnosis, meaning that not all patients qualified for post-COVID-19 syndrome. A meta-analysis was not performed due to the significant heterogeneity in regard to the tools used for the assessment of depression, and the time points of assessment following COVID-19 diagnosis.

3.5. Factors associated with depression

The main factors associated with depression were sex, previous psychiatric history, psychopathology at one-month follow-up, and systemic inflammation during the acute phase, while age was only a potential factor, and severity of acute COVID-19 was not. Indeed, female sex (Wilks' λ = 0.92; F = 5.76; p = 0.003), a previous psychiatric diagnosis (Wilks' λ = 0.93; F = 5.29; p = 0.006), and psychopathology at one-month follow-up (Wilks' λ = 0.82; F = 15.16; p < 0.001) were moderators of depression in post-COVID-19 syndrome (Mazza et al., 2021). Interestingly, depression persisted between one-month follow-up and three-month follow-up while significant decreases in PTSD symptoms, anxiety, and insomnia were observed (Mazza et al., 2021).

Importantly, Mazza et al. (2021) demonstrated that the severity of depressive symptomatology in post-COVID-19 syndrome was proportional to systemic inflammation measured at baseline during acute infection. Systemic immune-inflammation index (SII) at baseline (SII = (platelets x neutrophils)/lymphocytes) explained the variation of depression severity in models when assessing the influence of age, sex and hospitalization (ZSDS: χ^2 = 42.417, p < 0.0001; BDI-13: χ^2 = 56.536, p < 0.0001). The changes in SII also significantly predicted changes in depression scores (ZSDS: Wald W^2 = 6.881, p = 0.0087; BDI-13: Wald W^2 = 14.304, p = 0.0002). A decrease of SII between hospital admission and 3-month follow-up led to a decrease in depression severity in contrast to small changes of SII that led to persistent or worse depression scores (Mazza et al., 2021).

Age was a potential moderator in the study by the Consultation Multi-Expertise de Bicêtre Après COVID-19 (COMEBAC) group. Patients aged 75 years and older were more affected; 30.8% had significant depressive symptoms as part of post-COVID-19 syndrome compared to 19.7% of patients younger than 75 years (Morin et al., 2021). Although, it is important to note that age did not have a significant impact on depression scores in the study by Mazza et al. (2021).

Three studies reported that severity of acute COVID-19 according to symptoms and treatment required did not have an influence on the frequency of depressive symptoms in post-COVID-19 syndrome (Daher et al., 2021; Rass et al., 2021; van den Borst et al., 2020). Notably, in one study, patients with mild COVID-19 disease reported greater frequency of depressive symptoms than patients with a critical form of the disease (22% vs 10%) 13.0 weeks after onset of symptoms (van den Borst et al., 2020).

A fourth study had similar results wherein nonintubated patients suffered more from depressive symptoms than intubated patients (21.7% vs. 18.0%) at a median of 125 days after hospital discharge (Morin et al., 2021). However, no statistical analysis was performed. Additionally, Mazza et al. (2021) reported an inverse correlation between length of hospital stay and depression at three months post-discharge (ZSDS: r = −0.23, p = 0.005, q = 0.01; BDI-13: r = −0.21, p = 0.010, q = 0.015) insofar as shorter hospitalization was associated with worse depressive symptomatology in post-COVID-19 syndrome.

3.6. Depression and neurocognitive functioning

Neurocognitive impairment in the acute phase of COVID-19 was not a moderator of depression. However, depressive symptoms significantly influenced neurocognitive functioning in post-COVID-19 syndrome. Frontera et al. (2021) compared a cohort of patients who had suffered from neurological complications during hospitalization to a control group of COVID-19 patients with no neurological complications. There was no significant difference in the depression scores between the two cohorts 6.7 months after the onset of the neurological symptoms. Two separate studies investigated the association between depression and neurocognitive functioning in post-COVID-19 syndrome and reported that patients with depression tended to perform worse on neurocognitive tests compared to those without depression (Mattioli et al., 2021; Mazza et al., 2021).

In the study by Mazza et al. (2021), high ZSDS scores predicted worse performance in selective attention and processing speed (symbol coding test: Wald = 8.37, p = 0.003). A study by Mattioli et al. (2021) found that DASS-21 depression scores negatively influenced general cognitive functioning (Mini-Mental State Examination: β = −0.039, p = 0.007) and performance on tests assessing immediate recall in verbal memory (California Verbal Learning Test: β = −0.432, p = 0.016), visual reaction times (Test of Everyday Attention: β = 6.298, p = 0.007), executive abilities (Tower of London test: β = −0.149, p = 0.008) and visuospatial abilities (Rey figure copy and recall: β = −0.096, p = 0.044).

4. Discussion

Depressive symptoms and clinically-significant depression were commonly reported among individuals as part of post-COVID-19 syndrome. Factors that were associated with the onset and frequency of depression included sex, previous psychiatric history, and psychopathology at one-month follow-up (Mazza et al., 2021). In particular,

Table 2
Summaries of included publications.

Study	Design	Population	Age	Time of assessment	Location	Diagnostic Tool	Findings
Mazza et al. (2021)	Uncontrolled observational study	226 patients (67% hospitalized) 66% male	Mean = 58.5 SD = 12.8 Range: 26-87	Mean of 90 days post discharge or ED evaluation (SD = 13.4), previous assessment at one-month follow-up	Milan, Italy	DSM-5, BDI-13, ZSDS	Frequency: • 8.9% of patients diagnosed with clinically-significant depression (DSM-5), same result with BDI-13 (≥9). • 28% of patients with depressed mood based on ZSDS (≥50). Factors: • Female sex (Wilks' $\lambda = 0.92$, $F = 5.76$, $p = 0.003$), previous psychiatric history (Wilks' $\lambda = 0.93$, $F = 5.29$, $p = 0.006$), and psychopathology at one-month follow-up (Wilks' $\lambda = 0.82$; $F = 15.16$; $p < 0.001$) were predictors of depression at three-month follow-up in a multivariate analysis. • No effect of age on self-reported depression scores. • Length of hospital stay is inversely correlated with ZSDS ($r = -0.23$, $p = 0.005$, $q = 0.01$) and BDI-13 scores ($r = -0.21$, $p = 0.010$, $q = 0.015$). • Baseline systemic immune-inflammation index (SII) (ZSDS: $\chi 2 = 42.417$, $p < 0.0001$; BDI-13: $\chi 2 = 56.536$, $p < 0.0001$) and changes of SII (ZSDS: Wald $W^2 = 6.881$, $p = 0.0087$; BDI-13: Wald $W^2 = 14.304$, $p = 0.0002$) were predictors of depression and changes of depression at three-month follow-up. Other findings: • Persistent depressive symptoms from one-month follow-up to three-month follow-up, in contrast with significant decrease of PTSD symptoms, anxiety and insomnia. • Depression had a significant effect on neurocognitive functioning and ZSDS scores specifically predicted performance in selective attention and processing speed (Wald = 8.37, $p = 0.003$).
Mattioli et al. (2021)	Prospective cohort study	120 patients with mild-moderate COVID-19 (2% hospitalized), health care workers 30 controls, matched for age, sex and main comorbidities, health care workers 25% male	Mean = 47.9 Range: 26-65	Mean of 126 days from diagnosis (Range: 12–215)	Brescia, Italy	DASS-21	Frequency: • DASS-21 depression scores were significantly higher in COVID-19 subjects than in controls ($\bar{x} = 3$ vs. $\bar{x} = 1$, $p = 0.036$). Other findings: • DASS-21 depression scores significantly influenced many neuropsychological test scores: MMSE ($\beta = -0.039$, $p = 0.007$) CVLT immediate recall ($\beta = -0.432$, $p = 0.016$), TEA visual RT ($\beta = 6.298$, $p = 0.007$), TOL ($\beta = -0.149$, $p = 0.008$), Rey figure copy and recall ($\beta = -0.096$, $p = 0.044$).
Rass et al. (2021)	Uncontrolled observational study	98 out of 135 patients (23% required ICU care, 53% were admitted to the regular ward, 24% were outpatients) 61% male	Median = 56 IQR: 48-68 Range: 19-87	Median of 102 days from diagnosis (IQR: 91–110)	Tyrol, Austria	HADS-D	Frequency: • 11% of patients with depressive symptoms: o 7% with mild depressive symptoms (HADS-D score >7) o 3% with clinically-significant depression (HADS-D score >10) Factors: • Severity of the disease does not significantly influence the frequency of depressive symptoms at 3-month follow-up.
		59 of 62 patients who required ICU admission for	Mean = 60	3 months after hospital discharge	Lleida, Spain	HADS-D	Frequency:

(*continued on next page*)

Table 2 (*continued*)

Study	Design	Population	Age	Time of assessment	Location	Diagnostic Tool	Findings
González et al. (2021)	Uncontrolled observational study	ARDS secondary to COVID-19 74.2% male	Range: 48-65				• 15.2% of patients with depressive symptoms: o 10.2% with borderline abnormal scores (HADS-D score >7 and ≤ 10) o 5.0% with clinically-significant depression (HADS-D score >10)
Morin et al. (2021)	Uncontrolled observational study	170 out of 177 hospitalized patients (54.8% required ICU care) 62% male	Mean = 56.9 SD = 13.2	Median of 125 days after hospital discharge (IQR: 94–128)	Paris region, France	BDI-13	Frequency: • 20.6% of patients with depressive symptoms (BDI-13 > 7), notably 18.1% of ICU patients. • Depressive symptoms observed in 18.0% of intubated patients and in 21.7% of non-intubated patients. • 30.8% of patients ≥75 yr with depressive symptoms vs 19.7% of patients <75 yr.
van den Borst et al. (2020)	Uncontrolled observational study	124 patients (16.1% with critical disease, 20.9% with severe disease, 41.1% with moderate disease, 21.7% with mild disease) 60% male	Mean = 59 SD = 14	Mean of 13.0 weeks after onset of symptoms (SD = 2.2) Mean of 9.1 weeks after discharge for hospitalized patients (SD = 1.6)	Nijmegen, Netherlands	HADS-D	Frequency: • 12% of patients with clinically-significant depression (HADS-D > 10), notably 22% of patients with mild disease and 10% of patients with critical disease. Factors: • Severity of the disease does not significantly influence the frequency of depression at 13-week follow-up.
Frontera et al. (2021)	Prospective cohort study	136 of 196 patients with neurological complications during hospitalization for COVID-19 143 of 186 COVID-19 controls, matched for age, sex, race/ethnicity, and intubation status 65% male	Median = 68 IQR: 55-77	Median of 6.7 months from neurological symptom onset (or COVID-19 symptom in controls) (IQR: 6.5–6.8)	New York, USA	Neuro-QoL	Frequency: • 29% of patients with neurological complications scored worse than average on depression section of Neuro-QoL (T score >50) • 22% of COVID-19 controls scored worse than average on depression section of Neuro-QoL (T score >50) Factors: • No significant difference between both groups.
Daher et al. (2021)	Uncontrolled observational study	18 patients who required ICU admission for ARDS secondary to COVID-19 61% male	Mean = 61 SD = 7	Mean of 197 days after hospital discharge (SD = 15)	Aachen, Germany	PHQ-9	Frequency: • 27% of patients with moderate to severe depressive symptoms (PHQ-9 > 9), all with type L pneumonia (less severe cases than patients with type H pneumonia): o 22% with moderate depressive symptoms (PHQ-9 > 9 and ≤ 14) o 5% with severe depressive symptoms (PHQ-9 > 14) Factors: • No significant difference in depression scores of patients with type H or L pneumonia.

DSM-V, Diagnostic and Statistical Manual of Mental Disorders; BDI-13, 13-items Beck's Depression Inventory; ZSDS, Zung Self-rating Depression Scale; DASS-21, Depression, Anxiety and Stress Scale; HADS-D, Hospital Anxiety and Depression Scale - Depression; Neuro-QoL, Quality of Life in Neurological Disorders; PHQ-9, Patient Health Questionnaire; MMSE, Mini–Mental State Examination; CVLT immediate recall, California Verbal Learning Test immediate recall for verbal memory; TEA visual RT, visual reaction times section of the TEA attention test; TOL, Tower of London test for executive abilities.

female sex (Parker and Brotchie, 2010), previous history of depression, and other mental disorders (Christensen et al., 2011) are risk factors for depression commonly observed in the general population. However, findings on age as a moderator were inconsistent.

Systemic inflammation at baseline, as measured by platelet count, and levels of neutrophils and lymphocytes (SII), and their change over time were shown to predict depressive symptoms at 3-month follow-up post-discharge (Mazza et al., 2021). Available literature suggests that the level of inflammation in patients with COVID-19 is associated with severity of symptoms in the acute phase (Zeng et al., 2020). However, in this review, the severity of acute COVID-19 (i.e., symptom severity and level of care required) was not associated with a higher frequency of depressive symptoms in post-COVID-19 syndrome (Daher et al., 2021; Rass et al., 2021; van den Borst et al., 2020). Similarly, hospitalizations for COVID-19 with neurological complications, compared to hospitalizations with no complications, did not lead to significantly higher rates of depressive symptoms in the long term (Frontera et al., 2021).

It remains unclear whether a relationship exists between systemic inflammation at baseline and depressive symptomatology in post-COVID-19 syndrome with respect to severity of COVID-19 symptoms. A hypothesis of depression in post-COVID-19 syndrome is then only partially explained by systemic inflammation as a consequence of acute infection. Indeed, it has been reported that COVID-19 induces a hyper-inflammatory state, which may cause persistent low-grade inflammation (Mazza et al., 2020, 2021). More specifically, Han et al. (2020) reported high levels of TNF-α, IFN-γ, IL-2, IL-4, IL-6, IL-10 and CRP in COVID-19 patients compared to controls, with IL-6 as the most frequently reported cytokine increased among COVID-19 patients (Ragab et al., 2020). Moreover, the positive association between depression and

inflammation has been thoroughly characterized (Lee and Giuliani, 2019; Rosenblat et al., 2014). More specifically, studies have reported elevated levels of pro-inflammatory cytokines (e.g., interleukin-6 (IL-6)) among patients suffering from mood symptoms and disorders (Liu et al., 2012).

Extant literature indicates that pro-inflammatory cytokines moderate serotonin levels, hypothalamic–pituitary–adrenal (HPA) axis self-regulation, microglial cells, and neuroplasticity, leading to negative regulation of brain function (Rosenblat et al., 2014). This phenomenon has been commonly observed among the elderly (Ng et al., 2018), who are known to be more at risk for increased inflammation and serious complications following SARS-CoV-2 infection due to cytokine storms (Fajgenbaum and June 2020; Mueller et al., 2020). Further research is needed to elucidate the effect of antidepressants (Lu et al., 2017) and mindfulness interventions (Ng et al., 2020) on inflammation and depression among survivors of COVID-19. For example, animal models may be developed to identify treatment targets of depression in post-COVID-19 syndrome (Muñoz-Fontela et al., 2020).

Furthermore, it remains to be determined whether the high frequency of depression among individuals with post-COVID-19 syndrome is a long-term consequence of the viral infection or a result of the social and/or economic outcomes of the pandemic. Indeed, the COVID-19 pandemic has proven detrimental to measures of mental health within the general population. For example, higher rates of depressive symptoms have been reported since the onset of the pandemic (Xiong et al., 2020). The foregoing rates of depressive symptoms vary across regions and were potentially even higher at the beginning of the pandemic due to the establishment of new restrictive public health measures (Ho et al., 2020; Lee et al., 2021; Wang et al., 2021; Xiong et al., 2020). Notably, Ettman et al. (2020) demonstrated that the prevalence of depressive symptoms in the United States was more than 3-fold higher during the COVID-19 pandemic compared to before, based on data collected in the first two weeks of April 2020.

Longitudinal studies of COVID-19 patients with a non-infected control group are critical to compare the frequency of depression in post-COVID-19 syndrome to that of the general population. However, only one of the included studies had a non-infected control group. While the study reported greater depressive symptoms among COVID-19 patients, the time of assessment in this study did not correspond to post-COVID-19 syndrome classification in all patients (i.e., time of assessment ranged from 12 to 215 days from diagnosis, with a mean of 126 days) (Mattioli et al., 2021). As such, results from this study should be interpreted with caution.

Notwithstanding, Taquet et al. (2021) reported that the incidence of mood disorders 6 months after a COVID-19 diagnosis was significantly greater than the incidence of mood disorders after influenza or other respiratory tract infections over a similar time period. While this retrospective chart review was not included in our results as it did not provide data on depression specifically, its results reinforce the hypothesis that SARS-CoV-2 infection increases the risk for depression in the long term.

Lastly, social, economic and spatial factors may have a significant effect on the development and persistence of depressive symptoms among individuals with post-COVID-19 syndrome. In addition to the fear of the virus, the pandemic has led to job and housing uncertainty, school closures, and social isolation (Chirumbolo et al., 2021; Sepúlveda-Loyola et al., 2020; Szlamka et al., 2021).

Higher rates of depression have been reported among lower socioeconomic populations given the particularly pronounced social and economic consequences of the pandemic (Xiong et al., 2020). A similar observation was reported among students, potentially due to the significant transition from in-person to online schooling (Cao et al., 2020; Xiong et al., 2020). Isolation due to social distancing restrictions has prevented social networking and physical participation in family and community activities increasing rates of loneliness, which has a negative effect on mental health (Loades et al., 2020; Sepúlveda-Loyola et al., 2020). Of note, it has been suggested that younger individuals (i.e., <40 years) experience higher rates of depression as a result of isolation measures (Pieh et al., 2020; Xiong et al., 2020). The foregoing psychosocial stressors are pro-inflammatory (Berk et al., 2013). Taken together, the social and economic consequences of the pandemic should be assessed in the purview of biological stressors.

4.1. Limitations

This systematic review has several limitations which may affect interpretation of our results. First, the included studies were highly heterogeneous. Depression was assessed through various validated self-report questionnaires, at different time points after COVID-19 diagnosis, and in patients from different countries and age groups. Second, most studies did not include a control group (i.e., unexposed to SARS-CoV-2). As such, it is a testable hypothesis whether depression is a residual consequence of acute COVID-19 infection or result of the social and/or economic outcomes of the pandemic. Furthermore, depression during the pandemic is confounded by numerous factors (e.g., increased stress levels, economic hardship, etc.). Third, studies did not assess depression or depressive symptoms at the start of the study (i.e., week 0) nor prior to acute infection. These limitations may have resulted in the overestimation of the true frequency of clinically-significant depression and depressive symptoms.

4.2. Implications for research

The current literature on the frequency and factors associated with depression in post-COVID-19 syndrome is limited. Taken together, there is a need to conduct studies assessing the impact of post-COVID-19 syndrome in larger populations, as well as include control groups. Assessments of depression should be performed using validated clinician-rated scales complimented with validated self-report questionnaires. Administering validated clinician-rated scales would reduce the risk of overestimating and/or underestimating the true frequency of clinically-significant depression and depressive symptoms associated with post-COVID-19 syndrome. Assessments of depression should also occur at time of diagnosis and at multiple time points during the recovery process to observe symptom variation over time. Furthermore, future studies should aim to increase methodological consistency by adhering to a single post-COVID-syndrome classification to allow for adequate comparison between studies.

5. Conclusion

This systematic review suggests a high frequency of clinically-significant depression and depressive symptoms associated with post-COVID-19 syndrome. Moderators include female sex, previous psychiatric history, and psychopathology at one-month follow-up. The severity of COVID-19 and cognitive impairment in the acute phase of the disease are not associated with worsening depressive symptoms in post-COVID-19 syndrome. Nevertheless, it cannot be concluded that depression is more frequent in patients suffering from post-COVID-19 syndrome than in the general population. Further research should therefore take into consideration post-COVID-19 syndrome classification and include control groups unexposed to SARS-CoV-2. Moreover, the overlap of depressive symptoms in individuals with post-COVID-19 syndrome and its differentiation from manifestations of long COVID syndrome is a priority research vista.

Disclosures

LMWL is a contractor to Braxia Scientific Corp. JDR is the medical director of the Braxia Health (formally known as the Canadian Rapid Treatment Center of Excellence and is a fully owned subsidiary of Braxia Scientific Corp) which provides ketamine and esketamine treatment for

depression; he has received research grant support from the American Psychiatric Association, the American Society of Psychopharmacology, the Canadian Cancer Society, the Canadian Psychiatric Association, the Joseph M. West Family Memorial Fund, the Timeposters Fellowship, the University Health Network Centre for Mental Health, and the University of Toronto and speaking, consultation, or research fees from Allergan, COMPASS, Janssen, Lundbeck, and Sunovion. YL is the chief research officer of Braxia Scientific Corp. RSM has received research grant support from CIHR/GACD/Chinese National Natural Research Foundation; speaker/consultation fees from Lundbeck, Janssen, Purdue, Pfizer, Otsuka, Takeda, Neurocrine, Sunovion, Bausch Health, Novo Nordisk, Kris, Sanofi, Eisai, Intra-Cellular, NewBridge Pharmaceuticals, Abbvie. RSM is a CEO of Braxia Scientific Corp. All other authors report no disclosures.

CRediT authorship contribution statement

Olivier Renaud-Charest: Conceptualization, Methodology, Investigation, Writing – original draft, Writing – review & editing. **Leanna M. W. Lui:** Conceptualization, Writing – original draft, Writing – review & editing, Project administration. **Sherry Eskander:** Investigation, Writing – review & editing. **Felicia Ceban:** Writing – review & editing. **Roger Ho:** Writing – review & editing. **Joshua D. Di Vincenzo:** Writing – review & editing. **Joshua D. Rosenblat:** Writing – review & editing. **Yena Lee:** Writing – review & editing. **Mehala Subramaniapillai:** Writing – review & editing. **Roger S. McIntyre:** Conceptualization, Methodology, Writing – review & editing, Supervision.

References

COVID-19, 2021. Rapid Guideline: Managing the Long-Term Effects of COVID-19. National Institute for Health and Care Excellence (UK), London.

Berk, M., Williams, L.J., Jacka, F.N., O'Neil, A., Pasco, J.A., Moylan, S., Allen, N.B., Stuart, A.L., Hayley, A.C., Byrne, M.L., Maes, M., 2013. So depression is an inflammatory disease, but where does the inflammation come from? BMC Med. 11, 200.

Cao, W., Fang, Z., Hou, G., Han, M., Xu, X., Dong, J., Zheng, J., 2020. The psychological impact of the COVID-19 epidemic on college students in China. Psychiatr. Res. 287, 112934.

Chirumbolo, A., Callea, A., Urbini, F., 2021. The effect of job insecurity and life uncertainty on Everyday consumptions and broader life projects during COVID-19 pandemic. Int. J. Environ. Res. Publ. Health 18. https://doi.org/10.3390/ijerph18105363.

Christensen, K.S., Sokolowski, I., Olesen, F., 2011. Case-finding and risk-group screening for depression in primary care. Scand. J. Prim. Health Care 29, 80–84.

Daher, A., Cornelissen, C., Hartmann, N.-U., Balfanz, P., Müller, A., Bergs, I., Aetou, M., Marx, N., Marx, G., Simon, T.-P., Müller-Wieland, D., Hartmann, B., Kersten, A., Müller, T., Dreher, M., 2021. Six months follow-up of patients with invasive mechanical ventilation due to COVID-19 related ARDS. Int. J. Environ. Res. Publ. Health 18. https://doi.org/10.3390/ijerph18115861.

Ettman, C.K., Abdalla, S.M., Cohen, G.H., Sampson, L., Vivier, P.M., Galea, S., 2020. Prevalence of depression symptoms in US adults before and during the COVID-19 pandemic. JAMA Netw Open 3, e2019686.

Fajgenbaum, D.C., June, C.H., 2020. Cytokine storm. N. Engl. J. Med. 383, 2255–2273.

Frontera, J.A., Yang, D., Lewis, A., Patel, P., Medicherla, C., Arena, V., Fang, T., Andino, A., Snyder, T., Madhavan, M., Gratch, D., Fuchs, B., Dessy, A., Canizares, M., Jauregui, R., Thomas, B., Bauman, K., Olivera, A., Bhagat, D., Sonson, M., Park, G., Stainman, R., Sunwoo, B., Talmasov, D., Tamimi, M., Zhu, Y., Rosenthal, J., Dygert, L., Ristic, M., Ishii, H., Valdes, E., Omari, M., Gurin, L., Huang, J., Czeisler, B. M., Kahn, D.E., Zhou, T., Lin, J., Lord, A.S., Melmed, K., Meropol, S., Troxel, A.B., Petkova, E., Wisniewski, T., Balcer, L., Morrison, C., Yaghi, S., Galetta, S., 2021. A prospective study of long-term outcomes among hospitalized COVID-19 patients with and without neurological complications. J. Neurol. Sci. 426, 117486.

González, J., Benítez, I.D., Carmona, P., Santisteve, S., Monge, A., Moncusí-Moix, A., Gort-Paniello, C., Pinilla, L., Carratalá, A., Zuil, M., Ferrer, R., Ceccato, A., Fernández, L., Motos, A., Riera, J., Menéndez, R., Garcia-Gasulla, D., Peñuelas, O., Bermejo-Martin, J.F., Labarca, G., Caballero, J., Torres, G., de Gonzalo-Calvo, D., Torres, A., Barbé, F., CIBERESUCICOVID Project (COV20/00110, ISCIII), 2021. Pulmonary function and radiologic features in survivors of critical COVID-19: a 3-month prospective cohort. Chest. https://doi.org/10.1016/j.chest.2021.02.062.

Han, H., Ma, Q., Li, C., Liu, R., Zhao, L., Wang, W., Zhang, P., Liu, X., Gao, G., Liu, F., Jiang, Y., Cheng, X., Zhu, C., Xia, Y., 2020. Profiling serum cytokines in COVID-19 patients reveals IL-6 and IL-10 are disease severity predictors. Emerg. Microb. Infect. 9, 1123–1130.

Ho, C.S.H., Chee, C.Y.I., Ho, R.C.M., 2020. Mental health strategies to combat the psychological impact of Coronavirus disease 2019 (COVID-19) beyond paranoia and panic. Ann. Acad. Med. Singapore 49, 155–160.

Huang, Y., Pinto, M.D., Borelli, J.L., Mehrabadi, M.A., Abrihim, H., Dutt, N., Lambert, N., Nurmi, E.L., Chakraborty, R., Rahmani, A.M., Downs, C.A., 2021. COVID Symptoms, Symptom Clusters, and Predictors for Becoming a Long-Hauler: Looking for Clarity in the Haze of the Pandemic. https://doi.org/10.1101/2021.03.03.21252086 medRxiv.

GBD 2016 Disease and Injury Incidence and Prevalence Collaborators, 2017. Global, regional, and national incidence, prevalence, and years lived with disability for 328 diseases and injuries for 195 countries, 1990-2016: a systematic analysis for the Global Burden of Disease Study 2016. Lancet 390, 1211–1259.

Lee, C.-H., Giuliani, F., 2019. The role of inflammation in depression and fatigue. Front. Immunol. 10, 1696.

Lee, Y., Lui, L.M.W., Chen-Li, D., Liao, Y., Mansur, R.B., Brietzke, E., Rosenblat, J.D., Ho, R., Rodrigues, N.B., Lipsitz, O., Nasri, F., Cao, B., Subramaniapillai, M., Gill, H., Lu, C., McIntyre, R.S., 2021. Government response moderates the mental health impact of COVID-19: a systematic review and meta-analysis of depression outcomes across countries. J. Affect. Disord. 290, 364–377.

Liu, Y., Ho, R.C.-M., Mak, A., 2012. Interleukin (IL)-6, tumour necrosis factor alpha (TNF-α) and soluble interleukin-2 receptors (sIL-2R) are elevated in patients with major depressive disorder: a meta-analysis and meta-regression. J. Affect. Disord. https://doi.org/10.1016/j.jad.2011.08.003.

Liu, D., Baumeister, R.F., Zhou, Y., 2021. Mental health outcomes of coronavirus infection survivors: a rapid meta-analysis. J. Psychiatr. Res. 137, 542–553.

Loades, M.E., Chatburn, E., Higson-Sweeney, N., Reynolds, S., Shafran, R., Brigden, A., Linney, C., McManus, M.N., Borwick, C., Crawley, E., 2020. Rapid systematic review: the impact of social isolation and loneliness on the mental health of children and Adolescents in the context of COVID-19. J. Am. Acad. Child Adolesc. Psychiatry 59, 1218–1239 e3.

Lu, Y., Ho, C.S., Liu, X., Chua, A.N., Wang, W., McIntyre, R.S., Ho, R.C., 2017. Chronic administration of fluoxetine and pro-inflammatory cytokine change in a rat model of depression. PLoS One 12, e0186700.

Mattioli, F., Stampatori, C., Righetti, F., Sala, E., Tomasi, C., De Palma, G., 2021. Neurological and cognitive sequelae of Covid-19: a four month follow-up. J. Neurol. https://doi.org/10.1007/s00415-021-10579-6.

Mazza, M.G., De Lorenzo, R., Conte, C., Poletti, S., Vai, B., Bollettini, I., Melloni, E.M.T., Furlan, R., Ciceri, F., Rovere-Querini, P., COVID-19 BioB Outpatient Clinic Study group, Benedetti, F., 2020. Anxiety and depression in COVID-19 survivors: role of inflammatory and clinical predictors. Brain Behav. Immun. 89, 594–600.

Mazza, M.G., Palladini, M., De Lorenzo, R., Magnaghi, C., Poletti, S., Furlan, R., Ciceri, F., , COVID-19 BioB Outpatient Clinic Study group, Rovere-Querini, P., Benedetti, F., 2021. Persistent psychopathology and neurocognitive impairment in COVID-19 survivors: effect of inflammatory biomarkers at three-month follow-up. Brain Behav. Immun. 94, 138–147.

Writing Committee for the COMEBAC Study Group, Morin, L., Savale, L., Pham, T., Colle, R., Figueiredo, S., Harrois, A., Gasnier, M., Lecoq, A.-L., Meyrignac, O., Noel, N., Baudry, E., Bellin, M.-F., Beurnier, A., Choucha, W., Corruble, E., Dortet, L., Hardy-Leger, I., Radiguer, F., Sportouch, S., Verny, C., Wyplosz, B., Zaidan, M., Becquemont, L., Montani, D., Monnet, X., 2021. Four-month clinical status of a cohort of patients after hospitalization for COVID-19. J. Am. Med. Assoc. 325, 1525–1534.

Mueller, A.L., McNamara, M.S., Sinclair, D.A., 2020. Why does COVID-19 disproportionately affect older people? Aging 12, 9959–9981.

Muñoz-Fontela, C., Dowling, W.E., Funnell, S.G.P., Gsell, P.-S., Riveros-Balta, A.X., Albrecht, R.A., Andersen, H., Baric, R.S., Carroll, M.W., Cavaleri, M., Qin, C., Crozier, I., Dallmeier, K., de Waal, L., de Wit, E., Delang, L., Dohm, E., Duprex, W.P., Falzarano, D., Finch, C.L., Frieman, M.B., Graham, B.S., Gralinski, L.E., Guilfoyle, K., Haagmans, B.L., Hamilton, G.A., Hartman, A.L., Herfst, S., Kaptein, S.J.F., Klimstra, W.B., Knezevic, I., Krause, P.R., Kuhn, J.H., Le Grand, R., Lewis, M.G., Liu, W.-C., Maisonnasse, P., McElroy, A.K., Munster, V., Oreshkova, N., Rasmussen, A.L., Rocha-Pereira, J., Rockx, B., Rodríguez, E., Rogers, T.F., Salguero, F.J., Schotsaert, M., Stittelaar, K.J., Thibaut, H.J., Tseng, C.-T., Vergara-Alert, J., Beer, M., Brasel, T., Chan, J.F.W., García-Sastre, A., Neyts, J., Perlman, S., Reed, D.S., Richt, J.A., Roy, C.J., Segalés, J., Vasan, S.S., Henao-Restrepo, A.M., Barouch, D.H., 2020. Animal models for COVID-19. Nature 586, 509–515.

Nalbandian, A., Sehgal, K., Gupta, A., Madhavan, M.V., McGroder, C., Stevens, J.S., Cook, J.R., Nordvig, A.S., Shalev, D., Sehrawat, T.S., Ahluwalia, N., Bikdeli, B., Dietz, D., Der-Nigoghossian, C., Liyanage-Don, N., Rosner, G.F., Bernstein, E.J., Mohan, S., Beckley, A.A., Seres, D.S., Choueiri, T.K., Uriel, N., Ausiello, J.C., Accili, D., Freedberg, D.E., Baldwin, M., Schwartz, A., Brodie, D., Garcia, C.K., Elkind, M.S.V., Connors, J.M., Bilezikian, J.P., Landry, D.W., Wan, E.Y., 2021. Post-acute COVID-19 syndrome. Nat. Med. 27, 601–615.

Nasserie, T., Hittle, M., Goodman, S.N., 2021. Assessment of the frequency and variety of persistent symptoms among patients with COVID-19: a systematic review. JAMA Netw Open 4, e2111417.

Ng, A., Tam, W.W., Zhang, M.W., Ho, C.S., Husain, S.F., McIntyre, R.S., Ho, R.C., 2018. IL-1β, IL-6, TNF- α and CRP in elderly patients with depression or Alzheimer's disease: systematic review and meta-analysis. Sci. Rep. https://doi.org/10.1038/s41598-018-30487-6.

Ng, T.K.S., Fam, J., Feng, L., Cheah, I.K.-M., Tan, C.T.-Y., Nur, F., Wee, S.T., Goh, L.G., Chow, W.L., Ho, R.C.-M., Kua, E.H., Larbi, A., Mahendran, R., 2020. Mindfulness improves inflammatory biomarker levels in older adults with mild cognitive impairment: a randomized controlled trial. Transl. Psychiatry 10, 21.

Page, M.J., McKenzie, J.E., Bossuyt, P.M., Boutron, I., Hoffmann, T.C., Mulrow, C.D., Shamseer, L., Tetzlaff, J.M., Akl, E.A., Brennan, S.E., Chou, R., Glanville, J., Grimshaw, J.M., Hróbjartsson, A., Lalu, M.M., Li, T., Loder, E.W., Mayo-Wilson, E., McDonald, S., McGuinness, L.A., Stewart, L.A., Thomas, J., Tricco, A.C., Welch, V.A.,

Whiting, P., Moher, D., 2021. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. PLoS Med. 18, e1003583.
Parker, G., Brotchie, H., 2010. Gender differences in depression. Int. Rev. Psychiatr. 22, 429–436.
Pieh, C., Budimir, S., Probst, T., 2020. The effect of age, gender, income, work, and physical activity on mental health during coronavirus disease (COVID-19) lockdown in Austria. J. Psychosom. Res. 136, 110186.
Ragab, D., Salah Eldin, H., Taeimah, M., Khattab, R., Salem, R., 2020. The COVID-19 cytokine storm; what we know so far. Front. Immunol. 11, 1446.
Rass, V., Beer, R., Schiefecker, A.J., Kofler, M., Lindner, A., Mahlknecht, P., Heim, B., Limmert, V., Sahanic, S., Pizzini, A., Sonnweber, T., Tancevski, I., Scherfler, C., Zamarian, L., Bellmann-Weiler, R., Weiss, G., Djamshidian, A., Kiechl, S., Seppi, K., Loeffler-Ragg, J., Pfausler, B., Helbok, R., 2021. Neurological outcome and quality of life 3 months after COVID-19: a prospective observational cohort study. Eur. J. Neurol. https://doi.org/10.1111/ene.14803.
Rosenblat, J.D., Cha, D.S., Mansur, R.B., McIntyre, R.S., 2014. Inflamed moods: a review of the interactions between inflammation and mood disorders. Prog. Neuro-Psychopharmacol. Biol. Psychiatry 53, 23–34.
Sepúlveda-Loyola, W., Rodríguez-Sánchez, I., Pérez-Rodríguez, P., Ganz, F., Torralba, R., Oliveira, D.V., Rodríguez-Mañas, L., 2020. Impact of social isolation due to COVID-19 on health in older people: mental and physical effects and recommendations. J. Nutr. Health Aging 24, 938–947.
Shanbehzadeh, S., Tavahomi, M., Zanjari, N., Ebrahimi-Takamjani, I., Amiri-Arimi, S., 2021. Physical and mental health complications post-COVID-19: scoping review. J. Psychosom. Res. 147, 110525.
Sinanović, O., 2021. LONG-TERM neuropsychiatric consequences OF SARS-COV infections. Psychiatr. Danub. 33, S309–S317.
Szlamka, Z., Kiss, M., Bernáth, S., Kámán, P., Lubani, A., Karner, O., Demetrovics, Z., 2021. Mental health support in the time of crisis: are we prepared? Experiences with the COVID-19 counselling programme in Hungary. Front. Psychiatr. 12, 655211.
Taquet, M., Geddes, J.R., Husain, M., Luciano, S., Harrison, P.J., 2021. 6-month neurological and psychiatric outcomes in 236 379 survivors of COVID-19: a retrospective cohort study using electronic health records. Lancet Psychiatry 8, 416–427.
Troyer, E.A., Kohn, J.N., Hong, S., 2020. Are we facing a crashing wave of neuropsychiatric sequelae of COVID-19? Neuropsychiatric symptoms and potential immunologic mechanisms. Brain Behav. Immun. 87, 34–39.
van den Borst, B., Peters, J.B., Brink, M., Schoon, Y., Bleeker-Rovers, C.P., Schers, H., van Hees, H.W.H., van Helvoort, H., van den Boogaard, M., van der Hoeven, H., Reijers, M.H., Prokop, M., Vercoulen, J., van den Heuvel, M., 2020. Comprehensive health assessment three months after recovery from acute COVID-19. Clin. Infect. Dis. https://doi.org/10.1093/cid/ciaa1750.
Vanderlind, W.M., Rabinovitz, B.B., Miao, I.Y., Oberlin, L.E., Bueno-Castellano, C., Fridman, C., Jaywant, A., Kanellopoulos, D., 2021. A systematic review of neuropsychological and psychiatric sequalae of COVID-19: implications for treatment. Curr. Opin. Psychiatr. 34, 420–433.
Wang, C., Chudzicka-Czupała, A., Tee, M.L., Núñez, M.I.L., Tripp, C., Fardin, M.A., Habib, H.A., Tran, B.X., Adamus, K., Anlacan, J., García, M.E.A., Grabowski, D., Hussain, S., Hoang, M.T., Hetnał, M., Le, X.T., Ma, W., Pham, H.Q., Reyes, P.W.C., Shirazi, M., Tan, Y., Tee, C.A., Xu, L., Xu, Z., Vu, G.T., Zhou, D., Chan, N.A., Kuruchittham, V., McIntyre, R.S., Ho, C.S.H., Ho, R., Sears, S.F., 2021. A chain mediation model on COVID-19 symptoms and mental health outcomes in Americans, Asians and Europeans. Sci. Rep. 11, 6481.
Wells, G., Shea, B., O'Connell, D., Robertson, J., Peterson, J., Welch, V., Losos, M., Tugwell, P., 2000. The Newcastle-Ottawa Scale (NOS) for Assessing the Quality of Nonrandomized Studies in Meta- Analysis [WWW Document]. URL. http://www3.med.unipmn.it/dispense_ebm/2009-2010/Corso%20Perfezionamento%20EBM_Faggiano/NOS_oxford.pdf (accessed 9.17.2021).
WHO Coronavirus, 2021 (COVID-19) Dashboard [WWW Document], URL. https://covid19.who.int/ (accessed 7.12.2021).
Xiong, J., Lipsitz, O., Nasri, F., Lui, L.M.W., Gill, H., Phan, L., Chen-Li, D., Iacobucci, M., Ho, R., Majeed, A., McIntyre, R.S., 2020. Impact of COVID-19 pandemic on mental health in the general population: a systematic review. J. Affect. Disord. 277, 55–64.
Zeng, F., Huang, Y., Guo, Y., Yin, M., Chen, X., Xiao, L., Deng, G., 2020. Association of inflammatory markers with the severity of COVID-19: a meta-analysis. Int. J. Infect. Dis. 96, 467–474.
Zubair, A.S., McAlpine, L.S., Gardin, T., Farhadian, S., Kuruvilla, D.E., Spudich, S., 2020. Neuropathogenesis and neurologic manifestations of the coronaviruses in the age of coronavirus disease 2019: a review. JAMA Neurol 77, 1018–1027.