Prevalence of mental health conditions and brain fog in people with long COVID: A systematic review and meta-analysis

Christina van der Feltz-Cornelis a,b,c,e, Fidan Turk a,1, Jennifer Sweetman a,1, Kamlesh Khunti d, Mark Gabbay e, Jessie Shepherd a, Hugh Montgomery e, W. David Strain s, Gregory Y.H. Lip b,i,1, Dan Wootton j,k, Caroline Leigh Watkins l,m, Daniel J. Cuthbertson n, Nefyn Williams s, Amitava Banerjee c,g,p

a Department of Health Sciences, University of York, York, United Kingdom
b Hull York Medical School, (HYMS), University of York, York, United Kingdom
c Institute of Health Informatics, University College London, London, United Kingdom
d Diabetes Research Centre, University of Leicester, Leicester, UK
e Department of Primary Care and Mental Health University of Liverpool, Liverpool, United Kingdom
f Department of Medicine, University College London, London, United Kingdom
g Diabetes and Vascular Medicine Research Centre, Institute of Clinical and Biomedical Science and College of Medicine and Health, University of Exeter, Exeter, UK
h Liverpool Centre for Cardiovascular Science at University of Liverpool John Moores University and Liverpool Heart & Chest Hospital, Liverpool, United Kingdom
i Danish Center for Health Services Research, Department of Clinical Medicine, Aalborg University, Aalborg, Denmark
j Institute of Infection Veterinary and Ecological Sciences and NIHR HPRU in Emerging and Zoonotic Infections, University of Liverpool, Liverpool, United Kingdom
k Liverpool University Hospitals NHS Foundation Trust, Liverpool, United Kingdom
l Lancashire Clinical Trials Unit, University of Central Lancashire, Preston, United Kingdom
m School of Nursing and Midwifery, University of Central Lancashire, Preston, United Kingdom
n Institute of Cardiovascular and Metabolic Medicine, University of Liverpool, Liverpool, United Kingdom
o Department of Cardiology, University College London Hospitals NHS Trust, London, United Kingdom
p Department of Cardiology, Barts Health NHS Trust, London, United Kingdom

ARTICLE INFO

Keywords:
Long COVID
Mental health conditions
Brain fog
COVID-19
SARS-CoV-2
Meta-analysis

ABSTRACT

Objective: Long COVID can include impaired cognition (‘brain fog’; a term encompassing multiple symptoms) and mental health conditions. We performed a systematic review and meta-analysis to estimate their prevalence and to explore relevant factors associated with the incidence of impaired cognition and mental health conditions.

Methods: Searches were conducted in Medline and PsycINFO to cover the start of the pandemic until August 2023. Included studies reported prevalence of mental health conditions and brain fog in adults with long COVID after clinically-diagnosed or PCR-confirmed SARS-CoV-2 infection.

Findings: 17 studies were included, reporting 41,249 long COVID patients. Across all timepoints (3–24 months), the combined prevalence of mental health conditions and brain fog was 20-4% (95% CI 11-1%-34-4%), being lower among those previously hospitalised than in community-managed patients(19-5 vs 29-7% respectively; p = 0-047). The odds of mental health conditions and brain fog increased over time and when validated instruments were used. Odds of brain fog significantly decreased with increasing vaccination rates (p = 0-000).

Conclusions: Given the increasing prevalence of mental health conditions and brain fog over time, preventive interventions and treatments are needed. Research is needed to explore underlying mechanisms that could inform further research in development of effective treatments. The reduced risk of brain fog associated with vaccination emphasizes the need for ongoing vaccination programs.

* Corresponding author at: Department of Health Sciences, HYMS, University of York, ARRC Building, T204, Heslington, York, United Kingdom.
E-mail address: christina.vanderfeltz-cornelis@york.ac.uk (C. van der Feltz-Cornelis).

Joint second authorship. Both authors contributed equally to the manuscript.

https://doi.org/10.1016/j.genhospsych.2024.02.009
Received 10 January 2024; Received in revised form 16 February 2024; Accepted 19 February 2024
Available online 27 February 2024
0163-8343/© 2024 The Author(s). Published by Elsevier Inc. This is an open access article under the CC BY license (http://creativecommons.org/licenses/by/4.0/).
1. Introduction

‘Long COVID,’ the presence of symptoms ≥12 weeks after acute COVID-19 disease [1,2], affects an estimated 45% of COVID-19 survivors worldwide, regardless of hospitalization status [3]. The most prevalent symptoms include fatigue/muscle aches, shortness of breath and neurocognitive impairment [4,5].

The prevalence of mental health conditions (International Classification of Diseases 11th Revision (ICD-11) [6]) has been explored in studies on COVID and some studies presented such symptoms in COVID over time, without taking into account when they occur specifically in long COVID [7]. The impact of hospitalization rather than community care for acute COVID-19 or of prior vaccination on the prevalence of mental health conditions in long COVID is unknown, as well as whether their prevalence varies over time after acute COVID-19 disease.

For this review we used the World Health Organisation (WHO) definition of a mental health condition as a mental disorder: ‘characterized by a clinically significant disturbance in an individual’s cognition, emotional regulation, or behaviour. It is usually associated with distress or impairment in important areas of functioning.’ Mental disorders are listed as mental, behavioural or neurodevelopmental disorders in Chapter 6 of the International Classification of Diseases 11th Revision (ICD-11) developed by the WHO. ‘Mental health conditions is a broader term covering mental disorders, psychosocial disabilities and (other) mental states associated with significant distress, impairment in functioning, or risk of self-harm.’ Such subthreshold symptoms are associated with distress or impairment in functioning without reaching the full criteria for a disorder. They are listed as mental or behavioural symptoms and signs in Chapter 21, symptoms, signs or clinical findings, not elsewhere classified, in the ICD-11 [6]. This definition seems the most suitable, as it allows for exploring the prevalence of mental disorders as diagnosed medical conditions, but also subthreshold symptoms such as anxiety or low mood, associated with distress or impairment in functioning or future incidence of full disorder without reaching the full criteria for a mental disorder at that time [8].

‘Brain fog’ is not a medical term but is a term used to encompass a range of symptoms including poor concentration, feeling confused, thinking more slowly than usual, fuzzy thoughts, forgetfulness, lost words and mental fatigue [9]. It can occur in many medical conditions; but, to date has been mentioned especially in the context of long COVID.

It can lead to impaired functioning or distress [10]. However, so far no research has explored the full range of its comprised elements and their prevalence, whereas indications are that they impact severely on work functioning. Such knowledge is important, given the high incidence of long COVID [3] and its impact on healthcare costs and workforce [11,12].

To date, there have been no systematic reviews exploring prevalence rates of mental health conditions in long COVID. Also, no studies addressed prevalence of brain fog as a composite measure of cognitive symptoms in long COVID so far. We thus sought to estimate the prevalence of any mental health condition or brain fog in long COVID, and to explore potential risk factors for their presence, covering studies published over the first 2.5 years of the pandemic.

2. Method

This systematic review and meta-analysis followed a preregistered protocol (PROSPERO registration: CRD42023394105) [13]. Results are reported following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement (Supplementary Table 1) [14].

2.1. Search strategy (See supplementary table 2)

Medline and PsycINFO were searched to cover the start of the pandemic until August 31st 2023, to identify cross-sectional or longitudinal adult human studies relating to long COVID. No date or language restrictions were applied. Title and abstract screening used the Rayyan platform [15]. Observational studies were included that reported prevalence rates, odds ratios, or hazard ratios for any mental health conditions, cognitive symptoms or brain fog ≥12 weeks after acute SARS-CoV-2 infection. We excluded abstracts, conference reports, or letters to editors; case studies, case series, qualitative studies, surveys, and intervention trials; and studies with <50 participants (to avoid small study effects) [16].

2.2. Quality assessment

Criteria for low risk-of-bias (assessed independently by two reviewers [FT, JSw] using cohort, cross-sectional and prevalence checklists from the Joanna Briggs Institute as appropriate) [17] included:

- Long COVID and control groups comparable and drawn from the same population
- COVID-19 measured consistently in individuals in exposed/unexposed groups
- Valid instruments to assess COVID-19, long COVID and mental health conditions or brain fog, such as the medical diagnosis of COVID infection [18], a positive PCR test [19], and clear definition of long COVID in the manuscript; use of the PHQ9 [20], GAD7 [21] or another validated questionnaire for establishing depressive or anxiety symptoms; ICD codes for mental disorders [22]; and MoCA [23] or other cognitive tests to establish cognitive symptoms.
- Identification of confounding factors and addressing their management within the study
- Completion of follow-up, exploration of reasons for attrition, addressing incomplete follow-up within the study
- Utilization of appropriate statistical analysis techniques
- Participants being free of long COVID at onset of the study to only report incident cases.

Discrepancies in appraisal were resolved through discussion with a third reviewer [CFC].

2.3. Screening

2.3.1. Stage 1

Search results were uploaded to Rayyan [13] and after removing duplicates, titles and abstracts were screened against the concrete, predefined inclusion and exclusion criteria described in 2.1 independently by three reviewers [JSw, JSh, FT]. In several stages, inclusion and exclusion criteria were discussed for clarification with an independent reviewer [CFC]. Clear, pre-defined criteria, inter-rater reliability checks and regular discussions about any uncertainties in screening were incorporated into this process to decrease the risks of mistakes in inclusion [24].

Duplicate blind screening of a random 10% of references was undertaken (from pairs of JSw, JSh, FT) to confirm inter-reviewer consistency. The level of agreement, rated as include or exclude, ranged from 97% [Jsw & FT] to 100% [Jsw & JSh], with Cohen’s unweighted kappa 0.59 [Jsw & FT] to 1 [Jsw & JSh], indicating at least moderate levels of screening reliability [25]. As agreement and consistency were high, it was considered acceptable to single-screen remaining references [26]. Any uncertainties were discussed and adjudicated by an independent reviewer [CFC]. Where insufficient information was available to make a clear decision, references were retained for further screening.

2.3.2. Stage 2

Full texts of included articles were reviewed independently [JSw, JSh, FT]. A random 10% of total papers were checked by a second reviewer to ensure reliability. Disagreements were discussed and arbitrated by an alternative reviewer [CFC]. To ensure transparency, all
papers excluded during full-text screening and the associated reasons for exclusion are listed in Supplementary List 1.

2.4. Data extraction

A data extraction format was designed to extract (independently by each) (1) general study information (e.g. author, year of publication, title, country) (2) study aim (3) design (e.g. control group, timeframe, sample size, sampling method and description, COVID-19 assessment method) (4) reporting of comorbidities (5) prevalence rates of mental health and cognitive symptoms or conditions (6) long COVID definition and diagnostic method (7) method of mental health assessment (e.g. interview, validated or non-validated questionnaire, routine medical data) (8) cut-off criteria for mental health assessments to meet the criteria for a mental health condition or cognitive symptoms of brain fog; and (9) main findings. Uncertainties were decided by an independent reviewer [CFC]. Where additional information was required, corresponding authors were contacted. Where authors did not respond or did not have relevant data, studies were excluded from analysis (Supplementary list 1).

In general, we assumed that if a study reported cognitive symptoms separately from anxiety/depression, those cognitive symptoms stood alone and were not reported as part of the mental health conditions themselves. However, as overlap between mental health conditions and cognitive symptoms might exist (e.g. concentration problems and anxiety), we showed the amount of overlap (Results, Fig. 1). We assessed mental and physical fatigue where differentiated, or if fatigue was listed as a physical or general symptom.

Country and time vaccination and COVID-19 period data were identified using Our World in Data [27] and the Johns Hopkins University Coronavirus Resource Centre [28]; virus strain from the Nextstrain project [29]; and variants of concern from the European Centre for Disease Prevention and Control [30,31].

2.5. Data analysis

Pooled prevalence rates of mental health conditions and brain fog were assessed by random effects meta-analysis (Comprehensive Meta-Analysis Version 2) [32]. The effect size was the event rate, reported as prevalence rates in percentages with 95% Confidence Interval (CI) and weights provided. Between-study variability was examined for heterogeneity, using the Q statistic for quantifying inconsistency. We planned a moderator analysis exploring the influence of several potential factors on prevalence (e.g. post-hospitalization versus non-hospitalised (community-managed) COVID-19 patients; presence/absences of pre-COVID-19 mental health conditions and brain fog). Overlapping symptoms such as fatigue or fatiguability can occur in mental health and other medical conditions as they are intertwined, and attention has been drawn to the diagnostic issues with that [33]. To deal with this issue, we planned to run the analysis for mental health conditions with a random model without fatigue, ‘Brain Fog’ was assessed as the combined presence of cognitive symptoms and of mental fatigue [9,34] where data concerning mental fatigue were available, or as the presence of one or more cognitive symptom if not.

We conducted meta-regression to estimate changes in the prevalence of mental health conditions and brain fog over time after acute COVID-19 disease, and their association with geographically-specific vaccination rates at the time of the study, and with diagnosis from medical files.
versus that derived from validated instruments. Tau-squared was calculated to establish the variance of true effect sizes in logit units. A sensitivity analysis excluding studies with high risk-of-bias was planned.

**2.6. Role of the funding source**

The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

**3. Results**

Searches yielded 7541 studies: 7415 were excluded (582 duplicates; 6833 not meeting criteria for progression to stage 2), leaving 126 studies of which 109 were excluded by full-text screening (reasons in Supplementary Fig. 1, Supplementary List 1). Seventeen studies with data allowing the estimation of prevalence rates were thus included in the meta-analysis (9 prospective observational cohort studies, 5 observational, 3 cross-sectional). Three were Spanish, 3 British, 3 German, 2 French and 2 Chinese, with one study each from South Korea, Switzerland, Luxembourg, and India. Full details of included studies are shown in Supplementary Figure 1 [14].

The number of COVID-19 patients per study ranged from 72 to 86,157, with 41,249 of the total 146,231 (28%) suffering from long COVID. Seven studies included long COVID patients never hospitalised for SARS-CoV-2 infection (n = 38,774, 94%). Ten included those who had been hospitalised (2475, 6%). Twelve studies (n = 4609) reported the gender of long COVID sufferers (female 2660: 58%). Subramanian and colleagues [35] failed to respond to our inquiries regarding healthy control data, making it impossible to compare the prevalence of mental health conditions and brain fog between long COVID and non-COVID-19 control subjects. There were insufficient data to include mental fatigue in a composite measure of brain fog, so we included only cognitive symptoms encompassing concentration difficulties, memory impairment and mental confusion. Characteristics of included studies are shown in Table 1.

Although cut scores for clinical levels of depression (PHQ9) and anxiety disorder (GAD7), (HADS) exist, studies reported depression and anxiety at symptom level, not as clinical diagnosis, except in case of one study using ICD codes [36]. Only two studies [37,38] used a validated test for cognitive symptoms (the MOCA). We have included concentration difficulties, memory loss and mental confusion as cognitive symptoms of brain fog.

In addition, long COVID was only diagnosed if symptoms were present >12 weeks after acute COVID-19, but the included studies had heterogeneous long COVID definitions (Table 1); some [38–42] proposed the presence of any one symptom, while one [43] required >three symptoms; five studies [43–47] used predefined lists of 10–64 symptoms.

The combined prevalence of all mental health conditions and brain fog reported in all studies over all follow-up periods was 20–4% (95% CI 11–1%–34 4%; 17 studies). There was significant and large heterogeneity (99%, p < .001) between studies. When differentiating between specific mental health conditions and brain fog; however, there was no significant heterogeneity (p = .92).

Overall prevalence of anxiety was 21.9% (95% CI 11–39%; 13 studies); concentration problems 23.7% (95% CI 10–%–51%; six studies); depression 21.4% (95% CI 11–38%; 14 studies); insomnia 11.6% (95% CI 3%–30%; four studies); irritability 30.2% (95% CI 2%–7%; one study); memory loss 21% (95% CI 7%–50%; five studies); mental confusion 25.3% (95% CI 7%–60%; four studies); psychological distress 10.5% (95% CI 4%–56%; three studies); and PTSD symptoms 7.3% (95% CI 1%–31%; three studies). (See Fig. 1).

At 12 months follow-up, the prevalence of all mental health conditions and brain fog taken together was 27.4% (95% CI 23%–32%; 9 studies). Prevalence rates per condition or symptom are shown in the Forest Plot (Fig. 2). At the 12-month time point, the prevalence of brain fog was 23.3% (95% CI 7.3%–54.0%; 8 studies). Prevalence rates per cognitive symptom are shown in the Forest Plot (Fig. 3). No significant heterogeneity was observed (p = .99).

By moderator analyses, the prevalence was higher in non-hospitalised patients (29.7%; 95% CI 21.2%–39.9%; seven studies vs (19.5%, 95% CI 11.2%–26.1%; ten studies: p < .05).

Meta-regression showed that brain fog was twice as likely to be reported when validated assessment instruments were used (p < .001), compared to being diagnosed from medical files (Fig. 4). For mental health conditions, probability was higher if validated measures were used, however to a smaller degree (p < .001) (Fig. 5).

By meta-regression analysis, the probability of brain fog, but not of mental health conditions, decreased with increasing vaccination rates by up to 3.7 times (p < .001) (Supplemental Fig. 2, and Supplemental Fig. 3).

Meta-regression indicated brain fog was more prevalent with longer duration after acute SARS-CoV-2 infection (p < .001), with the probability rising 2.5 from onset of long COVID to 24 months after infection. (Supplemental Fig. 4). For mental health conditions, the increase was approximately 1.2 times (p < .001). (Supplemental Fig. 5).

The majority of included papers (n = 15; 88%) reported the information expected for the study design-type and were rated to have low risk-of-bias. Eight studies had unclear reporting regarding follow-up and missing data. Two [1,25] had moderate risk, with unclear reporting of three and four out of ten criteria respectively. None were rated high-risk, precluding the need to perform a sensitivity analysis. Full quality assessment results in Supplementary Table 3.

As there was no control group without COVID-19, we could not run a publication bias analysis. However, the estimate of the prediction interval for true effects was 0.02 to 0.72 with the true effect size in 95% of all comparable populations falling within this interval [56]. This supports the validity and generalizability of our findings as there are no indications of publication bias.

**4. Discussion**

This systematic review and meta-analysis of 17 studies and 41,249 long COVID patients infected in the first 30 months of the pandemic across three continents is the first to specifically assess the prevalence of any mental health condition or brain fog in long COVID, and to compare between the two when exploring factors that may be relevant to their manifestation.

To summarize, mental health conditions and brain fog both occurred in around one in five of patients between three months and two years after COVID-19 infection. This is a major public health problem. Given the high percentage of people developing long COVID in most studies, this finding is concerning and should have implications for provision of care, that seems to be stretched currently [57]. The findings may also be important for recovery as comorbid mental health conditions in chronic conditions are known to impair both recovery and participation in rehab programmes. The increase of prevalence over time after acute infection occurs both in brain fog and in mental health conditions and would potentially allow preventive approaches. Given that vaccination appears to be protective for brain fog, this calls for sustained vaccination programs.

Regarding the interpretation of the findings, it is known that depression or cognitive symptoms can occur following other infective conditions such as pneumonia [58] and stroke in similar percentages and with a similar increase over time as in long COVID [59]. Alternatively, mental health conditions in long COVID might be reactive to the presence of long-term illness. In addition, long COVID may be a chronic condition that clusters with depression and anxiety as it does for other disease states like diabetes, COPD and cardiovascular disorder [60–62].

Brain fog is not listed as a mental disorder in the ICD-11, but as ‘clouding of consciousness’ (with brain fog being listed as a synonym) in the ICD-11 chapter ‘Symptoms, signs or clinical findings’ [ICD-11]
Table 1
Characteristics of included studies.

<table>
<thead>
<tr>
<th>Paper</th>
<th>Design</th>
<th>Setting(s)</th>
<th>Country</th>
<th>Data collection</th>
<th>COVID-19 assessment</th>
<th>COVID-19 additional information</th>
<th>Total N</th>
<th>LC N [LC%] (m/f)</th>
<th>(Term and Classification)</th>
<th>F/U</th>
<th>Mental health assessment; method</th>
<th>LC mental health prevalence N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ariza et al., (2023) [38]</td>
<td>Cross-sectional observational study</td>
<td>Community settings</td>
<td>Spain</td>
<td>Jun 2021 - Jun 2022</td>
<td>Confirmed diagnosis of COVID-19; method NA.</td>
<td>Wave 4 &amp; 5. Viral strains: 201; 21J (VOC); 21 K (VOC); 21L; 22B (VUM)</td>
<td>428,319 [74.5%] (120/199)</td>
<td>Post-coronavirus disease: confirmed COVID-19 diagnosis with signs/symptoms during the acute phase and at least 12 weeks after infection.</td>
<td>320 days</td>
<td>After infection</td>
<td>PHQ-9, GAD-7, MoCA; trained neuro-psychologist.</td>
<td>Combined total: 382 (38.7) Depression: 155 (49), Anxiety 160 (50.2), Mental confusion: 67 (21)</td>
</tr>
<tr>
<td>Becker et al., (2021) [48]</td>
<td>Prospective bicentric cohort study</td>
<td>Hospital follow-up (after inpatient admission)</td>
<td>Switzerland</td>
<td>Mar 2020 - Jun 2020</td>
<td>NA</td>
<td>Wave 1</td>
<td>Viral strain: 20B (VUM).</td>
<td>90,63 [70%] (42/21)</td>
<td>LC: one or more persisting or new symptoms related to COVID-19, from a predefined list of symptoms, after 1 year of hospitalization for COVID.</td>
<td>12 m</td>
<td>After hospital discharge</td>
<td>IES-R and HADS; interviews by trained interviewers.</td>
</tr>
<tr>
<td>Evans, PHOSP-COVID Collaborative et al., (2022) [49]</td>
<td>Prospective observational study</td>
<td>Hospital follow-up (after inpatient admission)</td>
<td>UK</td>
<td>Mar 2020 - Apr 2021</td>
<td>Clinician-diagnosed COVID-19</td>
<td>Wave 1 &amp; 2</td>
<td>Viral strains: 20E (VOC); 20I (VOC); 20A; 20E; 20B(VUM);</td>
<td>2320,392 [16.9%] (224/145)</td>
<td>Long COVID: self-report not fully recovered from COVID-19.</td>
<td>12 m</td>
<td>After hospital discharge</td>
<td>PHQ-9, GAD-7, PCL-5; questionnaires administered to patients who visited hospital.</td>
</tr>
</tbody>
</table>

(continued on next page)
<table>
<thead>
<tr>
<th>Paper</th>
<th>Design</th>
<th>Setting(s)</th>
<th>Country</th>
<th>Data collection</th>
<th>COVID-19 assessment</th>
<th>COVID-19 additional information</th>
<th>Total N</th>
<th>LC N [%] (m/f)</th>
<th>(Term and Classification)</th>
<th>F/U</th>
<th>Mental health assessment; method</th>
<th>LC mental health prevalence N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Huang et al., (2022) [40]</td>
<td>Longitudinal cohort study</td>
<td>Hospital follow-up</td>
<td>China</td>
<td>Jan – May 2020</td>
<td>Laboratory confirmed COVID-19</td>
<td>Wave 1 Viral strain: C-Tan-RCoV Wuhan Strain; N5 Novel β genus coronavirus as per (Wei et al., 2020) [56]</td>
<td>1127</td>
<td>960 [57.7%] NA</td>
<td>Long COVID: at least one sequelae symptom during follow-up.</td>
<td>24 m After infection</td>
<td>GAD-7, PHQ-9, PCL-C; HRQoL telephone or face-to-face interviews with trained clinicians.</td>
<td>Combined total: 180 (8 4) Depression: 70 (10 3) Anxiety: 83 (12 8) PTSD: 27 (4 2)</td>
</tr>
<tr>
<td>Kim et al., (2022) [47]</td>
<td>Prospective cohort study</td>
<td>Community settings</td>
<td>South Korea</td>
<td>Feb – Mar 2020</td>
<td>Positive SARS-CoV-2 PCR</td>
<td>Wave 1 Viral strain B41 as per (Park et al., 2022) [51].</td>
<td>170</td>
<td>83 [48.8%] NA</td>
<td>Persistent COVID-19-related symptoms: newly identified symptoms that did not exist before the acute COVID-19 infection, comprising a total of 38 symptoms.</td>
<td>12 m After infection</td>
<td>PHQ-9, GAD-7, PCL-5; administered to patients who visited the hospital.</td>
<td>Combined total: 88 (34 8) Anxiety: 22 (26 5) Memory loss: 41 (49 4) Insomnia: 25 (30 1)</td>
</tr>
<tr>
<td>Ladlow et al., (2023) [52]</td>
<td>Prospective observational cohort study</td>
<td>Military hospital (Hos-pitalized and non-hospitalised)</td>
<td>UK</td>
<td>Aug 2020 – Mar 2021</td>
<td>Positive for COVID-19 antigen PCR or clinically adjudicated COVID-19</td>
<td>Wave 2 20; 20E 20F (VOC); 20U (VOC); Vac. Rate 46%</td>
<td>88</td>
<td>53 [60.2%] NA</td>
<td>Non recovery: the presence of one or more “new” post-COVID-19 symptom(s) reported at 5 months (baseline), using a</td>
<td>5 m, 12 m After infection</td>
<td>PHQ-9, GAD-7, PCL-5, FAS; administered to patients who visited the hospital.</td>
<td>Combined total: 50 (27 6) Memory loss: 17 (32 1)</td>
</tr>
</tbody>
</table>

(continued on next page)
<table>
<thead>
<tr>
<th>Paper</th>
<th>Design</th>
<th>Setting(s)</th>
<th>Country</th>
<th>Data collection</th>
<th>COVID-19 assessment</th>
<th>COVID-19 additional information</th>
<th>Total N LC N [LC%] (m/f)</th>
<th>(Term and Classification)</th>
<th>F/U</th>
<th>Mental health assessment; method</th>
<th>LC mental health prevalence N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Messin et al., (2021) [41]</td>
<td>Retrospective observational descriptive study</td>
<td>Hospital follow-up (after inpatient admission)</td>
<td>France</td>
<td>Mar 2020</td>
<td>Positive SARS-CoV-2 PCR</td>
<td>Wave 1 Viral strain: 20C. Vac. Rate 0%</td>
<td>74 53 [71.6%] (23/30)</td>
<td>Persistent post-COVID symptoms: at least one symptom related to COVID-19 infection and not explained by another pathology. 6 m after infection</td>
<td>Non-validated questionnaire, telephone interview.</td>
<td>Combined total: 21 (16-4) Anxiety: 17 (32-1) Psychological distress: 4 (7-5) Combined total: 10 (2-6) Depression: 2 (1-6) Anxiety:4 (3-3) Insomnia: 4 (3-3) Fatigue: 22 (18-0)</td>
<td></td>
</tr>
<tr>
<td>Naik et al., (2021) [39]</td>
<td>Prospective observational study</td>
<td>Hospital follow-up</td>
<td>India</td>
<td>Oct 2020</td>
<td>Confirmed COVID-19 infection</td>
<td>Wave 1 Viral strain: Delta B1, 617 as per (Pascarella et al., 2021) [53]. Vac. Rate 0%</td>
<td>1234 122 [9.6%] NA</td>
<td>Post-COVID-19 sequelae: any symptoms related to COVID-19 that persist for &gt;12 weeks. 3.6 m after hospital discharge</td>
<td>Interview with a trained interviewer with a non-validated questionnaire.</td>
<td>Combined total: 128 (8-3) Depression: 35 (6-9) Anxiety: 54 (10-6) Insomnia: 30 (7-17) Fatigue: 175 (34-4)</td>
<td></td>
</tr>
<tr>
<td>Romero-Duarte et al., (2021) [44]</td>
<td>Retrospective longitudinal observational follow-up study</td>
<td>Hospital follow-up (after inpatient admission)</td>
<td>Spain</td>
<td>Mar – Apr 2020</td>
<td>Positive SARS-CoV-2 PCR</td>
<td>Wave 1 Viral strains: 19A; 19B 20A; 20B 20C as per (Lopez et al., 2021) [54]. Vac. Rate 0%</td>
<td>797 509 [63.7%] (267/424)</td>
<td>Persistent symptomatology: the presence of sequelae/per persistent symptoms related to COVID-19, comprising 46 symptoms, during the 6 months after discharge from COVID-19. 6 m after hospital discharge</td>
<td>Medical files</td>
<td>Combined total: 128 (8-3) Depression: 35 (6-9) Anxiety: 54 (10-6) Insomnia: 30 (7-17)</td>
<td></td>
</tr>
<tr>
<td>Stallmach et al., (2022) [37]</td>
<td>Prospective cohort study</td>
<td>Hospital follow-up</td>
<td>Germany</td>
<td>Aug 2020 - Jul 2021</td>
<td>Diagnosed SARS-CoV-2 infection; method NA.</td>
<td>Wave 2 &amp; 3 Viral strain: 211 (VOC) 201 (VOC) Vac. Rate 62%.</td>
<td>627 355 [56.6%] (142/213)</td>
<td>Post-COVID: a collection of symptoms and conditions experienced after SARS-CoV-2 infection. Median 160 days after infection</td>
<td>FAS, BFI, PHQ-9, MOCA; administered to patients who visited the hospital.</td>
<td>Combined total: 338 (53-6) Depression: 274 (81-3) Concentration problems 64 (23-5) Fatigue: 315 (88-7)</td>
<td></td>
</tr>
<tr>
<td>Subramanian et al., (2022) [35]</td>
<td>Retrospective matched cohort study</td>
<td>Non-hospitalised Primary care Clinical Practice Research Datalink Aurum</td>
<td>UK</td>
<td>Jan 2020 - Apr 2021</td>
<td>Coded record of SARS-COV-2</td>
<td>Wave 1 &amp; 2 20L (VOC) 20J (VOC) 20A, 20B 20B (VOI) Vac. Rate 48.3%.</td>
<td>86,157 35,705 [41.4%] NA</td>
<td>Persistent symptoms: at least one of the symptoms associated with COVID-19 for a duration of ≥12 weeks after infection, from a list of 62 symptoms. 3 m after infection</td>
<td>Clinical Practice Research Datalink Aurum database codes.</td>
<td>Combined total: 8341 (2-4) Depression: 3441 (9.6) Anxiety: 3732 (10.5)</td>
<td></td>
</tr>
</tbody>
</table>

(continued on next page)
### Table 1 (continued)

<table>
<thead>
<tr>
<th>Paper</th>
<th>Design</th>
<th>Setting</th>
<th>COVID-19 assessment</th>
<th>COVID-19 additional information</th>
<th>Total N</th>
<th>(m/f)</th>
<th>LC mental health assessment</th>
<th>LC mental health prevalence N (%)</th>
<th>Data collection</th>
</tr>
</thead>
<tbody>
<tr>
<td>Zhang et al., Prospective follow-up study</td>
<td>Prospective follow-up study</td>
<td>China</td>
<td>Wave 1/2 (Gao et al., 2020)</td>
<td>SARS-CoV-2 by false-time RT-PCR</td>
<td>259/49</td>
<td>No</td>
<td>Impact of Event Scale-revised Hospital (IES-r)</td>
<td>17%</td>
<td>Long COVID: one or more long-term symptoms and clinical indices in COVID-19 patients at hospital discharge; participants who visited the hospital.</td>
</tr>
</tbody>
</table>

Notes: Number of participants, F/U = follow up, LC = Long COVID, m/f = number of males and females, NA = Not available, m = months, Y = Year, B = Blood, Vac. = Vaccination, Rate = Vaccination rate, (IES-r) = Impact of Event Scale-revised Hospital (IES-r), SF36; administered one year, (interview) to patients who visited the hospital. *Concentration problems: 221 ⋅ (220 6) from Zhang et al., (2023) [42]; Long COVID: one or more long-term symptoms and clinical indices in COVID-19 patients at hospital discharge; participants who visited the hospital. |

4.2 Limitations

Our prevalence estimates and rates should be interpreted with caution. The lack of matched studies reporting the prevalence rate of [6,22]. Also, brain fog is not listed as a medical condition but as a set of symptoms that can occur in long COVID [9]. Nevertheless, overlap among mental health conditions and brain fog might occur as cognitive symptoms are part of depressive and anxiety disorder and this could affect the findings. We assumed that if a study reported anxiety or depression and also cognitive symptoms, those cognitive symptoms were independent of the mental health conditions, as this is common in mental health conditions and brain fog might be strongly intertwined in brain fog in long COVID; both should be addressed.

Prevalence rates were lower in patients who had been admitted to hospital with acute COVID-19. The potential influence of bias seems low as the use of validated instruments for classifying mental health conditions and brain fog did not differ between these study populations, which were seemingly screened and reported in the same way. Survivor bias might help explain our findings. Likewise, those hospitalised might have received medication [63] that reduced acute symptoms and hence later prevalence rates. Hospitalised patients may also have been ‘grateful to be alive’, with those ill in the community being more socially isolated. Finally, those who stayed in the community may have had less access to medical care [64,65].

4.1 Strengths of the review

Study strengths include the fact that both mental health conditions and brain fog were simultaneously studied and that factors associated with their presence in long COVID were compared. The most common approach for assessment was the use of standardized assessments such as GAD-7 [21] and PHQ-9 [20] in an interview [38,40,43,45,48] or for self-reporting [41,46,50], for mental health conditions, and the use of valid tests such as the MOCA for cognitive symptoms. The size, timing, geographical spread and methodology of included studies makes the risk of bias low to moderate. Heterogeneity was low 12 months after infection and when type of mental health condition or brain fog were taken into account. We explored the association between prevalence rates and follow-up time and vaccination, and hospital admission versus community management in the acute phase. We also explored potential factors affecting prevalence rates separately for brain fog and mental health conditions.
mental health conditions in long COVID with non-COVID-19 subjects is a limitation. Although the COVID-19 pandemic seems associated with a 27.6% increase (95% uncertainty interval: 25.1–30.3) in cases of major depressive disorder and a 25.6% increase (95% uncertainty interval: 23.2–28.0) in cases of anxiety disorders worldwide in 2020 [66,67], how many of these patients suffered long COVID is unknown. Another limitation is that COVID disease affected some groups disproportionately but we could not get data by ethnicity, age, socio-economic group.

Fig. 2. Forest plot event rates grouped by mental health conditions and cognitive symptoms at 12 months.

Fig. 3. Forest plot event rates of brain fog as a composite measure of cognitive symptoms.
to explore this. In addition, regarding the negative association between vaccination rates and prevalence of brain fog, as these analyses are based on approximations at country level, we could not explore an association between virus strain and the prevalence of mental health conditions or brain fog as virus strain data for included study samples were not reported, and most studies in this review were performed during waves with several strains. So this finding is exploratory and should be confirmed in further research. In addition, although overlap between brain fog and mental health conditions seems to have been limited, nevertheless its potential occurrence is a limitation of the study. Because no studies reported mental fatigue explicitly, we could only provide an estimate of brain fog prevalence based on a composite of cognitive measures. We lacked information on a history of previous COVID-19, brain fog or of mental health conditions.

It should be noted that the research summarised in this review is fundamentally descriptive, so causal attribution to acute COVID-19 disease is not possible. However, our findings that approximately one in five to one in four of long COVID cases experience mental health conditions or brain fog suggest there is a high demand for effective and accessible treatments. Funding for research into effective treatments for mental health conditions and brain fog in people with long COVID is urgently needed.

This is the first systematic review to determine the prevalence rates of both mental health conditions and brain fog in long COVID, and to compare factors that may be associated with their presence. Both are common, with prevalence rising with time after SARS-CoV-2 infection. The prevalence of brain fog, but not of mental health conditions, is inversely related to vaccination rates, suggesting some degree of

Fig. 4. Meta-regression of probability that brain fog will occur in relation to diagnostic method.

1 = routine medical file/database; 2 = non-validated questionnaire; 3 = validated instruments.

Area proportional to study weight.

Fig. 5. Prevalence of mental health conditions association with diagnostic methods.

Area proportional to study weight.
pathogenic independence. Research is required to better characterise the neurocognitive features of brain fog, their pathogenesis, and brain fog's relationship (if any) to other mental health conditions, such that therapeutic targets might be identified. As our findings emphasize the value of vaccination in preventing brain fog as a core symptom of long COVID, ongoing vaccination programmes should be encouraged and reinforce the need for effective treatments to manage mental health conditions and brain fog in long COVID. Furthermore, given the increasing prevalence of mental health conditions over time, and their potential negative impact on recovery, preventive treatment for mental health conditions in long COVID may be helpful.

Funding source

This study was funded by the NIHR (COV-LT2-0043) as part of the STIMULATE-ICP study. The views expressed in this publication are those of the author(s) alone and not necessarily those of the National Institute for Health Research or the Department of Health and Social Care.

CRediT authorship contribution statement

Christina van der Feltz-Cornelis: Writing – review & editing, Writing – original draft, Methodology, Funding acquisition, Formal analysis, Data curation, Conceptualization. Fidan Turk: Writing – review & editing, Writing – original draft, Methodology, Formal analysis, Data curation. Jennifer Sweetman: Writing – review & editing, Writing – original draft, Methodology, Data curation, Conceptualization. Kamlesh Khunti: Writing – review & editing, Methodology, Funding acquisition. Mark Gabbay: Writing – review & editing, Funding acquisition. W. David Strain: Writing – review & editing, Formal analysis, Gregory Y.H. Lip: Writing – review & editing, Funding acquisition. Dan Wootton: Writing – review & editing, Funding acquisition. Caroline Leigh Watkins: Writing – review & editing, Funding acquisition. Daniel J. Cuthbertson: Writing – review & editing, Funding acquisition. Nefyn Williams: Writing – review & editing, Funding acquisition. Amitava Banerjee: Writing – review & editing, Funding acquisition.

Declaration of competing interest

Unless otherwise stated, funding for this project was paid to author institutions. In addition, CFC has had recent or current involvement with grants from the British Medical Association (CANDO Study), EU Horizon (EMPOWER Study), the Netherlands Organisation for Health Research and Development (Regional systems intervention for suicide prevention (SUPREMCOL) in Noord-Brabant, the Netherlands), and NIHR HS&DR (Frequent Users of the Emergency Department: Improving and Standardising Services—a mixed methods study). CFC has received royalties for standardising Services—a mixed methods study). CFC has received royalties for original draft, Methodology, Funding acquisition. The Metoclopramide for Avoiding Pneumonia after Stroke (MAPS-2) Trial: a single-blinded, randomised controlled trial of metoclopramide for the prevention of pneumonia in patients with dysphagia after an acute stroke), a Study Steering Committee 7 - Predicting AF after Cardiac Surgery - the PARADISE Score A Clinical Prediction Rule for Post-operative Atrial Fibrillation in Patients Undergoing Cardiac Surgery, and sat on a Trial Steering Committee - COVID NURSE: evaluation of the effects of a COVID-specific fundamental nursing care protocol compared to care as usual on experience of care for non-invasively ventilated patients in hospital with the SARS-CoV-2 virus: a randomised controlled trial. DJC has received investigator-initiated research funding, conference and/or consultancy fees and support for attending meetings/travel from NovoNordisk, Astra Zeneca and Ipsen. NW is Deputy Chair NIHR HTA Programme Funding Committee (Commissioned Research); payments are paid to institution. NW is GP partner in Llanfairfechan Group Practices; drawings are made to NW. AB has had recent or current involvement with NIHR, BMA, Astra Zeneca and UKRI research grants. AB is an unpaid Trustee for the South Asian Health Foundation. All other authors have no COIs to report.

Data availability

The datasets generated during and/or analysed during the current study are displayed in the manuscript and are available in the original studies taken up in this review.

Acknowledgments

We thank the Stimulate-ICP PPI group for their thorough review of this article.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.genhosppsych.2024.02.009.

References


