General Hospital Psychiatry 88 (2024) 10–22

Contents lists available at ScienceDirect

General Hospital Psychiatry

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

Review article

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

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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 = ·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.

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https://doi.org/10.1016/j.genhosppsych.2024.02.009
Received 10 January 2024; Received in revised form 16 February 2024; Accepted 19 February 2024
Available online 27 February 2024

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 world-wide, 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 never-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

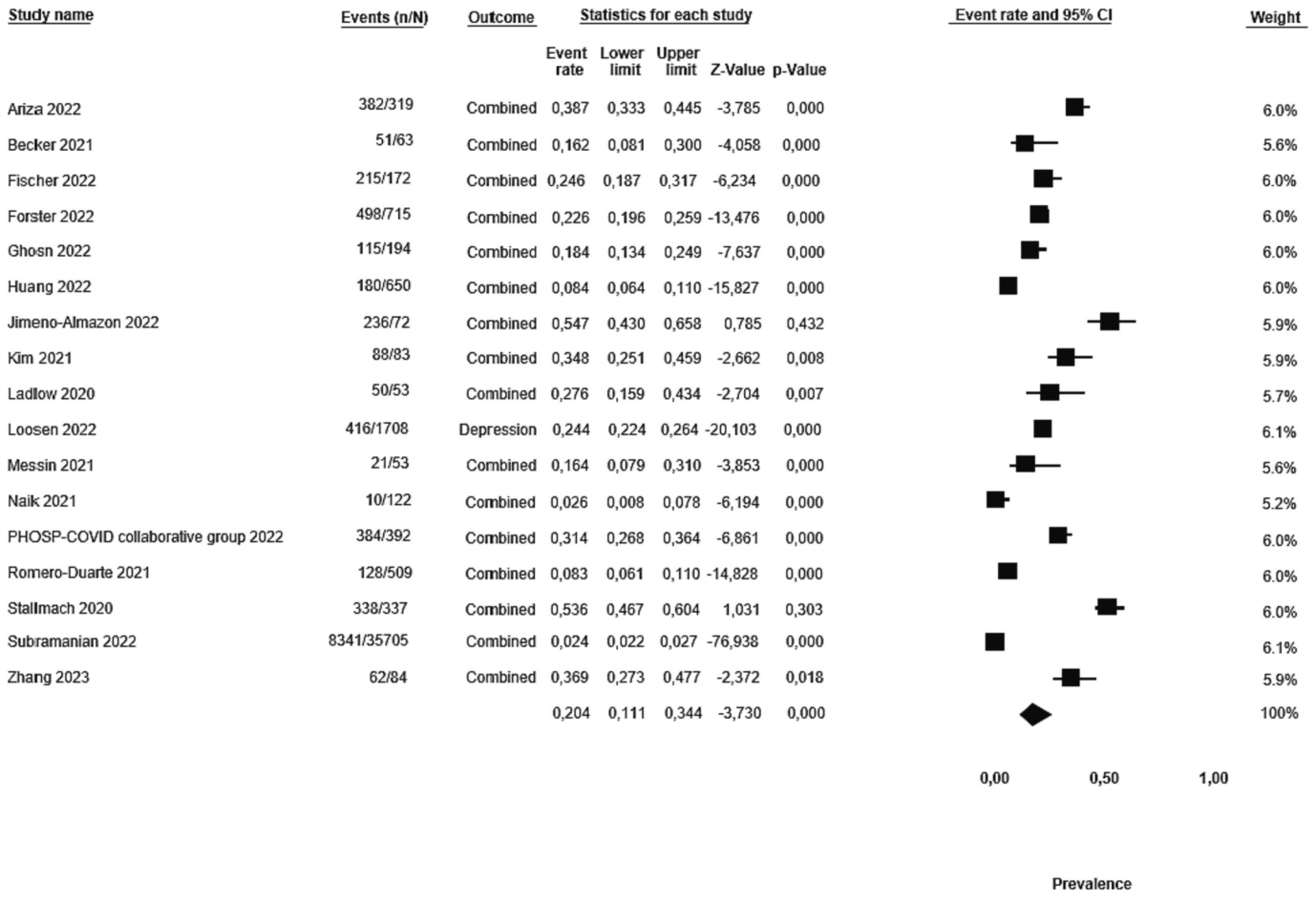

Fig. 1. Forest plot event rates of combined mental health conditions and brain fog cognitive symptoms at all timepoints.

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 18·5% (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 ($p \leq ·001$), 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.

Paper	Design	Setting(s)	Country Data collection	COVID-19 assessment	COVID-19 additional information	Total N *LC N [LC%] (m/f)*	(Term and Classification)	F/U	Mental health assessment; method	LC mental health prevalence N (%)
Ariza et al., (2023) [38]	Cross-sectional observational study	Community settings	Spain Jun 2021 -Jun 2022	Confirmed diagnosis of COVID-19; method NA.	Wave 4 & 5. Viral strains: 201; 21J (VOC); 21 K (VOC); 21L; 22B (VUM) Vac. Rate 70%	428,*319* [74·5%] *(120/199)*	Post-coronavirus disease: confirmed COVID-19 diagnosis with signs/symptoms during the acute phase and at least 12 weeks after infection.	320 days After infection	PHQ-9, GAD-7, MoCA; trained neuro-psychologist.	Combined total: 382 (38·7) Depression: 155 (49), Anxiety 160 (50·2), Mental confusion: 67 (21)
Becker et al., (2021) [48]	Prospective bicentric cohort study	Hospital follow-up (after inpatient admission)	Switzer-land Mar 2020 – Jun 2020	NA	Wave 1 Viral strain: 20B (VUM). Vac. Rate 0%.	90 *63* [70%] *(42/21)*	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.	12 m After hospital discharge	IES-R and HADS; interviews by trained interviewers.	Combined total: 51 (16·2) Depression: 9 (14·3) Anxiety: 11 (17·5) Concentration problems: 28 (44·4) Fatigue: 41 (65·1)
Evans, PHOSP-COVID Collabor-ative et al., (2022) [49]	Prospective observational study	Hospital follow-up (after inpatient admission)	UK Mar 2020 -Apr 2021	Clinician-diagnosed COVID-19	Wave 1 & 2 20I (VOC); 20J (VOC); 20A; 20E 20B(VOI); Vac. Rate 48·3%	2320 *392* [16·9%] *(224/145)*	Long COVID: self-report not fully recovered from COVID-19.	12 m After hospital discharge	PHQ-9, GAD-7, PCL-5; questionnaires administered to patients who visited hospital.	Combined total: 384 (31·4) Depression: 169 (43·1) Anxiety: 147 (37·5) PTSD: 68 (173) Fatigue: 36 (9·2)
Fischer et al., (2022) [46]	Prospective hybrid cohort study	Community PCR test	Luxem-bourg May – Nov 2020	Positive SARS-CoV-2 PCR	Wave 1 & 2. Viral strain: 20E. Vac. Rate 0%	289 *172* [59·5%] *(65/107)*	Long COVID: at least one persisting symptom from a list of 64 symptoms.	12 m After infection	Self-report by non-validated questionnaire.	Combined total: 215 (24·6) Depression: 27 (15·7) Anxiety:46 (26·7) Irritability: 52 (30·2) Mental confusion: 45 (26·2) Memory loss: 45 (26·2) Fatigue: 99 (57·6)
Förster et al., (2022) [50]	Population-based cohort study	Community PCR test (Hospitalised and non-hospitalised)	Germany Mar – Sept 2020	Positive SARS-CoV-2 PCR	Wave 1 Viral strains: 20D; 20E. Vac. Rate 0%	1459 *715* [49·0%] *(258/453)*	Post-COVID-19: any symptoms related to COVID-19 that persist for >12 weeks.	12 m After infection	Self-report; non-validated questionnaire.	Combined total: 498 (22·6) Depression: 112 (15·7) Concentration problems: 219 (30·6) Psychological

(*continued on next page*)

Table 1 (*continued*)

Paper	Design	Setting(s)	Country Data collection	COVID-19 assessment	COVID-19 additional information	Total N *LC N [LC%] (m/f)*	(Term and Classification)	F/U	Mental health assessment; method	LC mental health prevalence N (%)
										distress: 167 (23·4) Fatigue: 294 (41·1)
Ghosn et al., (2022) [43]	Prospective cohort	Hospital follow-up (after inpatient admission)	France Jan – Jul 2020	A virologically confirmed COVID-19	Wave 1 Viral strains: 19A; 20A. Vac. Rate 0%	710 *194* [27·3%] *(96/98)*	Post-acute COVID-19: at least three out of ten COVID-19-related symptoms.	12 m After hospital discharge	HADS; SF12; HRQol interview with a trained interviewer.	Combined total: 115 (18·4) Depression: 20 (10·3) Anxiety: 37 (19·1) Psychological distress: 58 (29·9)
Huang et al., (2022) [40]	Longitudinal cohort study	Hospital follow-up	China Jan – May 2020	Laboratory confirmed COVID-19	Wave 1 Viral strain: C-Tan-nCoV Wuhan StrainTaxonomy Novel β genus coronavirus as per (Wei et al., 2020) [56] Vac. Rate 0%	1127 *650* [57·7%] *NA*	Long COVID: at least one sequelae symptom during follow-up.	24 m After infection	GAD-7, PHQ-9, PCL—C; HRQol telephone or face-to-face interviews with trained clinicians.	Combined total: 180 (8·4) Depression: 70 (10·3) Anxiety: 83 (12·8) PTSD: 27 (4·2)
Jimeno-Almazán et al., (2022) [45]	Observational cross-sectional	Community settings – only non-hospitalised	Spain Feb – Nov 2021	Positive SARS-CoV-2 PCR or a positive rapid antigen test	Wave 3 Viral strains: 20I (VOC) 21J (VOC). Vac. Rate 70%	72 *72* *NA* *(25/47)*	Post-COVID-19: the presence of any of the 22 most frequent symptoms.	3 m After infection	GAD-7, PHQ-9, CFQ-11, FSS; interview with medical specialists.	Combined total: 236 (54·7) Depression: 38 (52·8) Anxiety: 31 (43·1) Memory problems:44 (61·1) Mental confusion: 40 (55·6) Insomnia: 42 (58·3) Concentration problems: 41 (56·9) Fatigue: 60 (83·3)
Kim et al., (2022) [47]	Prospective cohort study	Community settings	South Korea Feb -Mar 2020	Positive SARS-CoV-2 PCR	Wave 1 Viral strain B41 as per (Park et al., 2022) [51]. Vac. Rate 0%	170 *83* [48·8%] *NA*	Persistent COVID-19-related symptoms: newly identified symptoms that did not exist before the acute COVID-19 infection, comprising a total of 38 symptoms.	12 m After infection	PHQ-9, GAD-7, PCL-5-K; administered to patients who visited the hospital.	Combined total: 88 (34·8) Anxiety: 22 (26·5) Memory loss: 41 (49·4) Insomnia: 25 (30·1)
Ladlow et al., (2023) [52]	Prospective observational cohort study,	Military hospital (Hos-pitalised and non-hospitalised)	UK Aug 2020 – Mar 2021	Positive for COVID-19 antigen PCR or clinically adjudicated COVID-19	Wave 2 20°; 20E 20I (VOC); 20J (VOC); Vac. Rate 46%	88 *53* [60·2%] *NA*	Non recovery: the presence of one or more "new" post-COVID-19 symptom(s) reported at 5 months (baseline), using a	5 m, 12 m After infection	PHQ-9, GAD-7, PCL-5, FAS; administered to patients who visited the hospital.	Combined total: 50 (27·6) Memory loss: 17 (32·1) Concentration

(*continued on next page*)

Table 1 (*continued*)

Paper	Design	Setting(s)	Country Data collection	COVID-19 assessment	COVID-19 additional information	Total N *LC N [LC%] (m/f)*	(Term and Classification)	F/U	Mental health assessment; method	LC mental health prevalence N (%)
							symptom checklist (27 symptoms)			problems: 28 (52·8) Mental confusion: 5 (9·43) Fatigue: 24 (45·3)
Loosen et al., (2022) [36]	Retrospective observational cross-sectional	Disease Analyzer database	Germany Mar 2020 – Mar 2021	Confirmed diagnosis of COVID-19	Wave 1 & 2 20D; 20E. Vac. Rate 11%	50,402 *1708* [3·4%] *(652/1056)*	Long COVID syndrome: specified text documented 90 to 183 days after COVID-19*	3–6 m After infection	ICD-10 codes F32, F33.	Combined total: 416 (24·4) Depression: 416 (24·4)
Messin et al., (2021) [41]	Retrospective observational descriptive study	Hospital follow-up (after inpatient admission)	France Mar 2020	Positive SARS-CoV-2 PCR	Wave 1 Viral strain 20C. Vac. Rate 0%.	74 *53* [71·6%] *(23/30)*	Persistent post-COVID symptoms: at least one symptom related to COVID-19 infection and not explained by another pathology.	6 m after infection	Non-validated questionnaire, telephone interview.	Combined total: 21(16·4) Anxiety: 17 (32·1) Psychological distress: 4 (7·5)
Naik et al., (2021) [39]	Prospective observational study	Hospital follow-up	India Oct 2020	Confirmed COVID-19 infection	Wave 1 Viral strain: Delta B1·617 as per (Pascarella et al., 2021) [53]. Vac. Rate 0%.	1234 *122* [9·9%] *NA*	Post-COVID-19 sequelae: any symptoms related to COVID-19 that persist for >12 weeks.	3-6 m After hospital discharge	Interview with a trained interviewer with a non-validated questionnaire.	Combined total: 10 (2·6) Depression: 2 (1·6) Anxiety:4 (3·3) Insomnia: 4 (3·3) Fatigue: 22 (18·0)
Romero-Duarte et al., (2021) [44]	Retrospective longitudinal observational follow-up study	Hospital follow-up (after inpatient admission)	Spain Mar – Apr 2020	Positive SARS-CoV-2 PCR	Wave 1 Viral strains: 19A; 19B 20A; 20B 20C as per (Lopez et al., 2021) [54]. Vac. Rate 0%	797 *509* [63·7%] *(267/242)*	Persistent symptomatology: the presence of sequelae/ persistent symptoms related to COVID-19, comprising 46 symptoms, during the 6 months after discharge from COVID-19.	6 m After hospital discharge	Medical files	Combined total:128 (8·3) Depression: 35 (6·9) Anxiety: 54 (10·6) Insomnia: 39 (7·7) Fatigue: 175 (34·4)
Stallmach et al., (2022) [37]	Prospective cohort study	Hospital follow-up	Germany Aug 2020 -Jul 2021	Diagnosed SARS-CoV-2 infection; method NA.	Wave 2 & 3 Viral strain: 21I (VOC) 20J (VOC) Vac. Rate 62%.	627 *355* [56·6%] *(142/213)*	Post-COVID: a collection of symptoms and conditions experienced after SARS-CoV-2 infection.	Median 160 days after infection	FAS, BFI, PHQ-9, MOCA; administered to patients who visited the hospital.	Combined total: 338 (53·6) Depression: 274 (81·3) Concentration problems 64 (23·5) Fatigue: 315 (88·7)
Subramanian et al., (2022) [35] †	Retrospective matched cohort study	Non-hospitalised Primary care Clinical Practice Research Datalink Aurum	UK Jan 2020 -Apr 2021	Coded record of SARS-COV-2	Wave 1 & 2 20I (VOC) 20 J (VOC) 20A, 20E 20B (VOI) Vac. Rate 48·3%.	86,157 *35,705* [41·4%] *NA*	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	Clinical Practice Research Datalink Aurum database codes.	Combined total: 8341 (2·4) Depression: 3441 (9·6) Anxiety: 3732 (10·5)

(*continued on next page*)

Table 1 (*continued*)

Paper	Design	Setting(s)	Country Data collection	COVID-19 assessment	COVID-19 additional information	Total N *LC N [LC%] (m/f)*	(Term and Classification)	F/U	Mental health assessment; method	LC mental health prevalence N (%)
										Concentration problems: 221 (·6) Insomnia: 746 (2·1) Memory loss: 201 (·6)
Zhang et al., (2023) [42]	Prospective observational follow-up study	Hospital follow-up	China Dec 2020 -May 2021	SARS-CoV-2 by real-time RT-PCR	Wave 1 B.1 as per (Gao et al., 2023) [55] Vac. Rate 0%	187 *84* [44·9] *(35/ 49)*	Long COVID: one or more long-term symptoms and clinical indices in COVID-19 patients at one year.	12 m After hospital discharge	Zung SAS, Zung SDS; SF36; administered (interview) to patients who visited the hospital.	Combined total: 62 (36·9) Anxiety: 30 (35·7) Depression: 32 (38·1)

Notes. N = number of participants, F/U = follow up, LC = Long COVID, m/f = number of males and females, NA = Not available, m = months, Vac. Rate = Vaccination rate. (IES-r) = Impact of Event Scale-revised Hospital Anxiety and Depression Scale (HADS) PHQ-9 = Patient Health Questionnaire-9, GAD-7 = Generalized Anxiety Disorder-7, PCL-5-K = Korean version of the Posttraumatic Stress Disorder (PTSD) Checklist-5, PCL-5 = Post-traumatic stress disorder, MoCA: Montreal, Cognitive Assessment, (CFQ-11) = Chalder Fatigue Scale, Fatigue Severity Scale (FSS), Insomnia Severity Index questionnaire (ISI), Zung Self-Rating Anxiety Scale (SAS), and Zung Self-Rating Depression Scale (SDS), FAS = Fatigue Assessment Scale, BFI = Brief Fatigue Inventory = (BFI).
Studies reported depression and anxiety at symptom level, not as clinical diagnosis, except in case of studies using ICD codes.
* Original physician diagnosis texts ('long COVID syndrome,' 'post COVID syndrome,' 'post COVID complications'). ICD-10 diagnoses like chronic fatigue, breathing abnormalities, smell and taste disturbances, malaise and fatigue, and attention disturbances were surrogate markers for LCS.
† Control group included in this study: People in primary care without known SARS-COV-2 infection (n = 110,737). No prevalence data were provided in that group.

[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 diagnostic and classification procedure in clinical and research assessments. However, as this was not always clear from the studies included, such overlap might still have occurred, potentially leading to underreporting of cognitive symptoms in the context of brain fog. We therefore showed the n of the relevant symptom compared to the N of the sample per study in Fig. 1, and this shows that in four of the 17 studies there are indications that overlap may have occurred [38,41,45,47]. In those studies, the overall prevalence rates should not be interpreted as mutually exclusive. As the relative weight of those studies was similar to the other studies, this may however have had a small influence in the analysis.

Furthermore, the strong association with validated assessment methods for brain fog indicate that its diagnosis requires specific and valid neuropsychological testing. Prevalence rates were higher in studies that used validated diagnostic instruments versus routine medical data or databases which might (at the beginning of the pandemic) have suffered from underreporting. Taking 'brain fog' as a catch-all term to include mental health conditions would not be supported by our findings. Formal diagnostic criteria for the cognitive symptoms in brain fog are needed, which should separate them from mental health conditions such as anxiety, depression and psychological distress. Research is therefore needed to address the characteristics, and pathogenesis of brain fog in long COVID. As it seems that fatigue and cognitive aspects may 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.

4.2. *Limitations*

Our prevalence estimates and rates should be interpreted with caution. The lack of matched studies reporting the prevalence rate of

Group by Outcome	Study name	Events (n/N)	Outcome	Event rate	Lower limit	Upper limit	Z-Value	p-Value	Weight
Anxiety	Ariza 2022	160/319	Anxiety	0,502	0,447	0,556	0,056	0,955	7.8%
Anxiety	Becker 2021	11/63	Anxiety	0,175	0,099	0,288	-4,681	0,000	7.5%
Anxiety	Fischer 2022	46/172	Anxiety	0,267	0,207	0,338	-5,849	0,000	7.8%
Anxiety	Ghosn 2022	37/194	Anxiety	0,191	0,141	0,252	-7,909	0,000	7.8%
Anxiety	Kim 2021	22/83	Anxiety	0,265	0,181	0,370	-4,101	0,000	7.7%
Anxiety	PHOSP-COVID collaborative group 2022	147/392	Anxiety	0,375	0,328	0,424	-4,896	0,000	7.9%
Anxiety	Zhang 2023	30/84	Anxiety	0,357	0,262	0,465	-2,581	0,010	7.7%
Anxiety				0,299	0,204	0,415	-3,289	0,001	
Concentration difficulties	Becker 2021	28/63	Concentration difficulties	0,444	0,327	0,568	-0,880	0,379	16.5%
Concentration difficulties	Forster 2022	219/715	Concentration difficulties	0,306	0,274	0,341	-10,076	0,000	16.9%
Concentration difficulties	Ladlow 2020	28/53	Concentration difficulties	0,528	0,395	0,658	0,412	0,680	16.4%
Concentration difficulties				0,417	0,247	0,609	-0,840	0,401	
Depression	Ariza 2022	155/319	Depression	0,486	0,431	0,541	-0,504	0,614	7.3%
Depression	Becker 2021	9/63	Depression	0,143	0,076	0,252	-4,977	0,000	6.9%
Depression	Fischer 2022	27/172	Depression	0,157	0,110	0,219	-8,019	0,000	7.2%
Depression	Forster 2022	112/715	Depression	0,157	0,132	0,185	-16,361	0,000	7.3%
Depression	Ghosn 2022	20/194	Depression	0,103	0,067	0,154	-9,162	0,000	7.2%
Depression	PHOSP-COVID collaborative group 2022	169/392	Depression	0,431	0,383	0,481	-2,719	0,007	7.3%
Depression	Zhang 2023	32/84	Depression	0,381	0,284	0,489	-2,161	0,031	7.2%
Depression				0,244	0,163	0,349	-4,372	0,000	
Insomnia	Kim 2021	25/83	Insomnia	0,301	0,212	0,408	-3,517	0,000	20.2%
Insomnia				0,301	0,099	0,628	-1,209	0,227	
Irritability	Fischer 2022	52/172	Irritability	0,302	0,238	0,375	-5,037	0,000	100.0%
Irritability				0,302	0,104	0,619	-1,240	0,215	
Memory loss	Fischer 2022	45/172	Memory loss	0,262	0,201	0,332	-5,981	0,000	20.1%
Memory loss	Kim 2021	41/83	Memory loss	0,494	0,388	0,600	-0,110	0,913	20.0%
Memory loss	Ladlow 2020	17/53	Memory loss	0,321	0,210	0,457	-2,550	0,011	19.6%
Memory loss				0,353	0,199	0,545	-1,514	0,130	
Mental confusion	Ariza 2022	67/319	Mental confusion	0,210	0,169	0,258	-9,638	0,000	25.7%
Mental confusion	Fischer 2022	45/172	Mental confusion	0,262	0,201	0,332	-5,981	0,000	25.5%
Mental confusion	Ladlow 2020	5/53	Mental confusion	0,094	0,040	0,207	-4,813	0,000	23.6%
Mental confusion				0,188	0,094	0,341	-3,572	0,000	
Psychological distress	Forster 2022	167/715	Psychological distress	0,234	0,204	0,266	-13,444	0,000	34.6%
Psychological distress	Ghosn 2022	58/194	Psychological distress	0,299	0,239	0,367	-5,434	0,000	34.4%
Psychological distress				0,264	0,125	0,475	-2,174	0,030	
PTSD	PHOSP-COVID collaborative group 2022	68/392	PTSD	0,173	0,139	0,214	-11,704	0,000	50.2%
PTSD				0,173	0,054	0,437	-2,341	0,019	
PTSD (symptoms)	Becker 2021	3/63	PTSD (symptoms)	0,048	0,015	0,138	-5,064	0,000	100.0%
PTSD (symptoms)				0,048	0,009	0,220	-3,398	0,001	
Overall				0,272	0,225	0,324	-7,673	0,000	

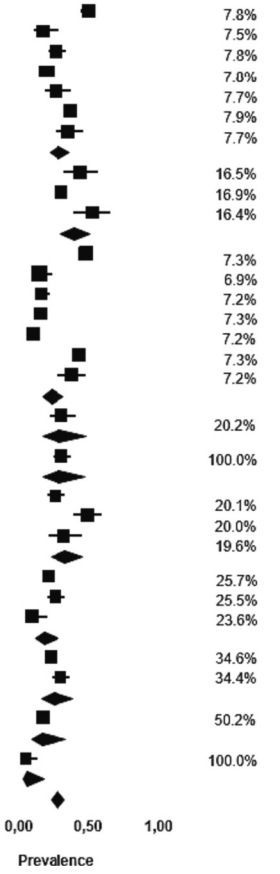

Fig. 2. Forest plot event rates grouped by mental health conditions and cognitive symptoms at 12 months.

Group by Outcome	Study name	Events (n/N)	Outcome	Event rate	Lower limit	Upper limit	Z-Value	p-Value	Relative weight
Concentration difficulties	Becker 2021	28/53	Concentration difficulties	0,444	0,327	0,568	-0,880	0,379	16,61
Concentration difficulties	Forster 2022	219/715	Concentration difficulties	0,306	0,274	0,341	-10,076	0,000	16,74
Concentration difficulties	Jimeno-Almazan 2022	41/72	Concentration difficulties	0,569	0,453	0,678	1,175	0,240	16,62
Concentration difficulties	Ladlow 2020	28/53	Concentration difficulties	0,528	0,395	0,658	0,412	0,680	16,58
Concentration difficulties	Stallmach 2020	64/272	Concentration difficulties	0,235	0,189	0,289	-8,246	0,000	16,71
Concentration difficulties	Subramanian 2022	221/35705	Concentration difficulties	0,006	0,005	0,007	-75,266	0,000	16,75
Concentration difficulties				0,239	0,036	0,727	-1,061	0,289	
Memory loss	Fischer 2022	45/172	Memory loss	0,262	0,201	0,332	-5,981	0,000	20,04
Memory loss	Jimeno-Almazan 2022	44/72	Memory loss	0,611	0,495	0,716	1,870	0,062	19,96
Memory loss	Kim 2021	41/83	Memory loss	0,494	0,388	0,600	-0,110	0,913	19,99
Memory loss	Ladlow 2020	17/53	Memory loss	0,321	0,210	0,457	-2,550	0,011	19,89
Memory loss	Subramanian 2022	201/35705	Memory loss	0,006	0,005	0,006	-73,149	0,000	20,11
Memory loss				0,212	0,025	0,736	-1,099	0,272	
Mental confusion	Ariza 2022	67/319	Mental confusion	0,210	0,169	0,258	-9,638	0,000	25,22
Mental confusion	Fischer 2022	45/172	Mental confusion	0,262	0,201	0,332	-5,981	0,000	25,18
Mental confusion	Jimeno-Almazan 2022	40/72	Mental confusion	0,556	0,440	0,666	0,941	0,347	25,09
Mental confusion	Ladlow 2020	5/53	Mental confusion	0,094	0,040	0,207	-4,813	0,000	24,52
Mental confusion				0,251	0,024	0,822	-0,817	0,414	
Overall				0,233	0,073	0,540	-1,728	0,084	

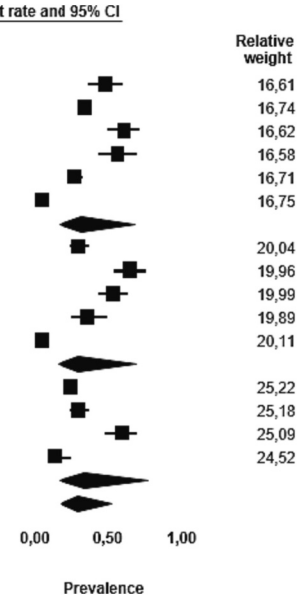

Fig. 3. Forest plot event rates of brain fog as a composite measure of cognitive symptoms.

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

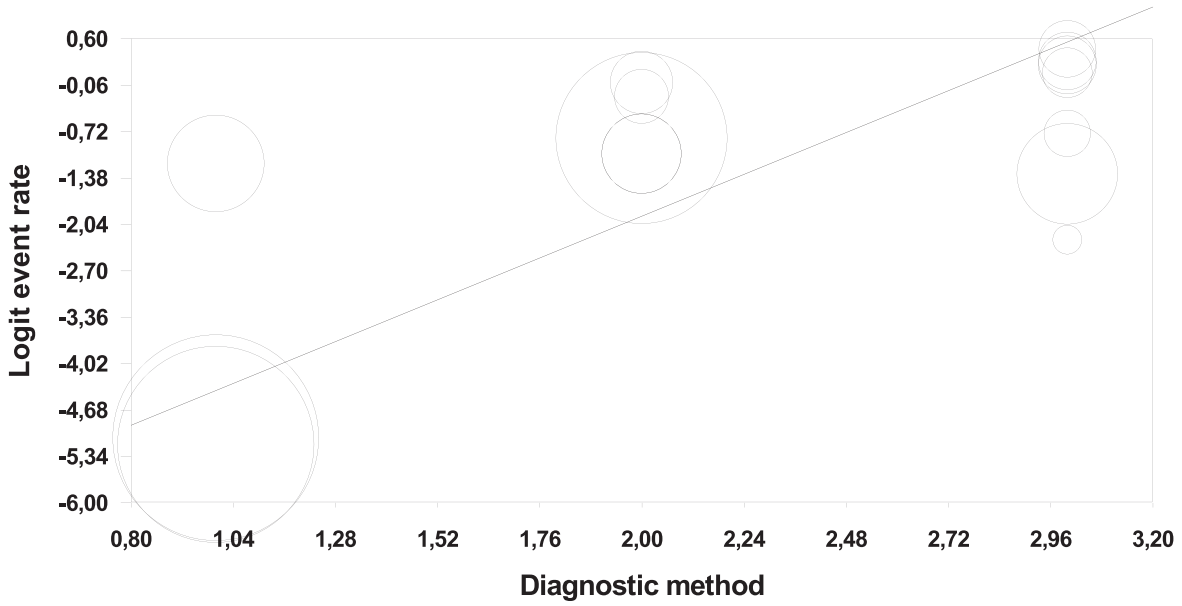

Fig. 4. Meta-regression of probability that brain fog will occur in relation to diagnostic method.
1 = routine medical file/database; 2 = non-validated questionnaire; 3 = validated instruments.
Area proportional to study weight.

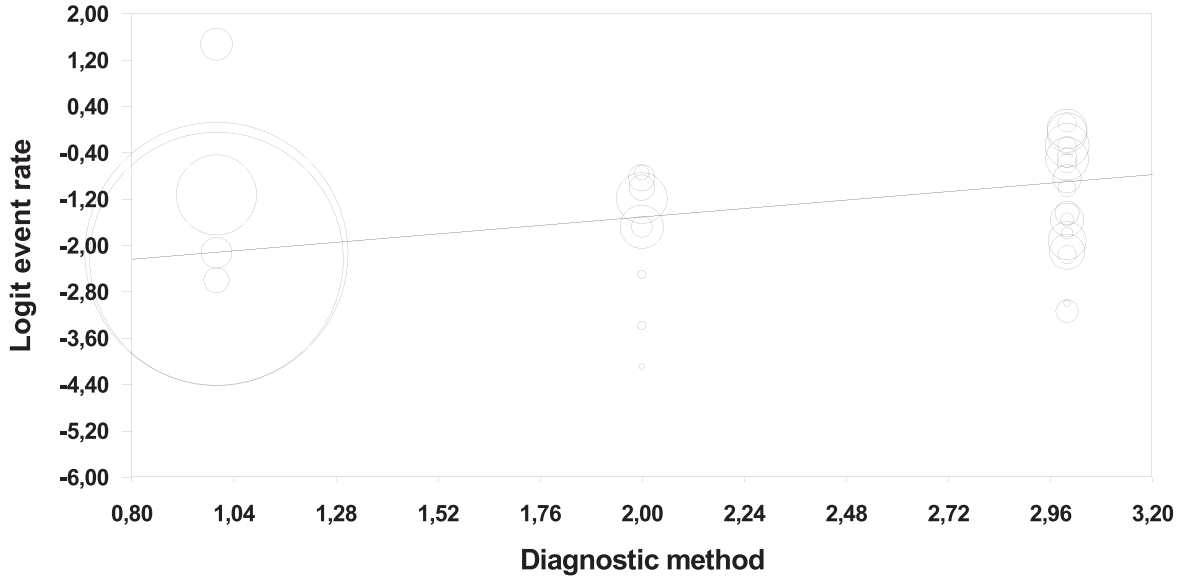

Fig. 5. Prevalence of mental health conditions association with diagnostic methods.
Area proportional to study weight.

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

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. **Jessie Shepherd:** Writing – review & editing, Data curation. **Hugh Montgomery:** Writing – review & editing, Methodology, Funding acquisition. **W. David Strain:** Writing – review & editing, Funding acquisition. **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 (SUPREMOCOL) 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 books on Psychiatry, an honorarium payment related to a lecture at the Big Questions in Neuroscience Annual meeting from Janssen UK, and has received travel and accommodation in the UK for a lecture from The Lloyd Register Foundation. CFC is an International member of the Scientific Advisory Board on the IMPACT in South Asia Research project, funded by the NIHR Global Health Program. KK is a past Chair of the Ethnicity Subgroup of the UK Scientific Advisory Group for Emergencies (SAGE) and a past Member of SAGE. KK is supported by the National Institute for Health Research (NIHR) Applied Research Collaboration East Midlands (ARC EM) and the NIHR Leicester Biomedical Research Centre (BRC). MG is part-funded by NIHR applied Research Collaboration North West Coast. HM has consulted for Astra Zeneca on covid vaccines and monoclonal therapies. HM has accepted lecture fees and conference support from Astra Zeneca relating to covid vaccines and monoclonal therapies. GYHL is a consultant and speaker for BMS/Pfizer, Boehringer Ingelheim, Daiichi-Sankyo, Anthos; no fees are received personally. DW holds an NIHR Advanced Fellowship to study hospital acquired pneumonia; this is held at University of Liverpool. CLW receives support from Applied Research Collaboration (ARCNWC): NIHR ARC NWC, PARticipation And engagement in Life and LEisure activities foLlowing stroke (PARALLEL): developing of a complex intervention: NIHR ARC NWC Mental Health Early Career Researcher Development Fellowship, NIHR HTA (EASE: Evaluating Antidepressants for emotionaliSm after strokE: A multi-centre, randomised, double-blind, placebo-controlled trial to establish the effect(s) of administration of sertraline (50 mg once daily for Six Months) in people with a recent stroke and post-stroke emotionalism; Should we use post-operative antibiotics following surgery for patients with mandible fractures? The MANTRA trial (MANdibular TRauma and Antibiotic use); Acceptability and feasibility of using the Virtual Engagement Rehabilitation Assistant (VERA) for community-based neurological rehabilitation). CLW receives support from NIHR Palliative and End of Life Care Research Partnerships for Living well and Dying Well in the last year of life for older people in rural and remote communities across the UK, and from NIHR Programme Grants for Applied Research for PREPARE: imPRoving End of life care Practice in stroke cARE. CLW is a member of Data Monitoring and Ethics Committees (Clinical and cost-effectiveness of a personalised health promotion intervention enabling independence in older people with mild frailty ('HomeHealth'): A Randomised Controlled Trial; The Metoclopramide for Avoiding Pneumonia after Stroke (MAPS-2) Trial: a single-blind, 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 Postoperative 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.

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