BMJ Mental Health

Systematic review of interventions for mental health, cognition and psychological well-being in long COVID

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► Additional supplemental material is published online only. To view, please visit the journal online (https://doi.org/10.1136/bmjment-2024-301133).

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Received 1 May 2024
Accepted 13 September 2024

To cite: Hawke LD, Nguyen ATP, Wang W, *et al*. *BMJ Ment Health* 2024;**27**:1–11.

ABSTRACT

Aims This systematic review aims to identify and synthesise the publicly available research testing treatments for mental health, cognition and psychological well-being in long COVID.

Methods The following databases and repositories were searched in October–November 2023: Medline, Embase, APA PsycINFO, Cumulative Index to Nursing and Allied Health Literature, China National Knowledge Internet, WANFANG Data, Web of Science's Preprint Citation Index, The Cochrane Central Register of Controlled Trials, Clinicaltrials.gov and the WHO International Clinical Trials Registry Platform. Articles were selected if they described participants with long COVID symptoms at least 4 weeks after SAR-CoV-19 infection, reported primary outcomes on mental health, cognition and/or psychological well-being, and were available with at least an English-language summary. The Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines for systematic reviews were followed.

Results Thirty-three documents representing 31 studies were included. Seven tested psychosocial interventions, five pharmaceutical interventions, three natural supplement interventions, nine neurocognitive interventions, two physical rehabilitation interventions and five integrated interventions. While some promising findings emerged from randomised controlled trials, many studies were uncontrolled; a high risk of bias and insufficient reporting were also frequent.

Conclusions The published literature on treatments for mental health, cognition and psychological well-being in long COVID show that the interventions are highly heterogeneous and findings are inconclusive to date. Continued scientific effort is required to improve the evidence base. Regular literature syntheses will be required to update and educate clinicians, scientists, interventionists and the long COVID community.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Long COVID presents as persistent, debilitating physical and psychological symptoms after COVID-19 infection; however, the literature on long COVID psychological treatments lacks an up-to-date synthesis.

WHAT THIS STUDY ADDS

⇒ Our systematic review shows that the publicly available research on interventions for mental health, cognition and psychological well-being in long COVID is limited in number and quality, with minimal studies demonstrating efficacy overtime.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ Rigorous testing of integrated treatments for long COVID is needed, with consideration of the multisystemic nature of this condition.
⇒ Ongoing literature synthesis and knowledge translation are recommended to inform clinicians and patients of appropriate treatment approaches.

INTRODUCTION

Although acute infection with SARS-CoV-2 can be mild and time limited, with recovery over days or weeks, a subset of patients experience long-term symptoms, which can persist for months or years after the acute infection.[1] This is referred to as long COVID or post-COVID-19 condition, among other terms.[2] WHO defines long COVID as 'the continuation or development of new symptoms three months after the initial SARS-CoV-2 infection, with these symptoms lasting for at least 2 months with no other explanation'.[2] Long COVID is associated with a wide range of enduring symptoms that appear to be similar to other postviral syndromes,[3] and which can have substantial impacts on patient well-being.[4]

The prevalence of long COVID appears to be around 13.9% among adults who experience an acute SARS-CoV-2 infection.[5] However, long COVID can affect patients with SARS-CoV-2 regardless of hospitalisation status or the severity of initial infection.[6] Symptoms of long COVID appear to be multisystemic and include neuropsychiatric symptoms. Some of the most common symptoms include fatigue, dyspnoea, 'brain fog' or cognitive dysfunction, headache, attention problems.[3] Mental health symptoms and conditions are associated with long COVID, including generalised anxiety, depression, sleep disturbance and post-traumatic stress disorder.[3] Substantial impacts on mental health, well-being and coping with the challenges of everyday life have been noted by patients.[4]

Clinical practice guidelines for long COVID call for integrated and multidisciplinary care.[1] Long COVID management requires multilevel and collaborative healthcare pathways including medical,

specialist and community care.[1] Also key to collaboration are a clear delineation of responsibilities, continuity of care and navigational support.[7] Patients with long COVID have called for integrated care pathways that span the full spectrum of services and include mental healthcare.[8] People with long COVID are a vulnerable population as they struggle with the unknowns of this condition and seek help in potential treatments that may or may not be effective.

We conducted a systematic review of registered trials examining treatments for mental health and related constructs among individuals with long COVID .[9 10] While a range of research was under way at the time, the results have yet to be synthesised. In 2022, the interventions focusing on mental health were mapped as per scoping review methodology; as is standard, the scoping review was considered a precursor to the systematic review, given the early state of the literature. It was found that the research that had been completed in 2022 was limited, diverse, of variable quality and in urgent need of further advancement. Given the novelty of long COVID, the rapid pace of the literature and the expressed need of people living with long COVID to understand effective treatment options, frequent literature synthesis updates are required. As the literature matures, a systematic review is now feasible.

Objectives

This systematic review synthesises the literature on publicly available interventions for mental health, cognition and psychological well-being among individuals with long COVID. We aim to synthesise (1) the outcomes of these interventions and (2) the design and quality of the trials.

METHODS

This systematic review was conducted in compliance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (see Supplemental File 2).[11] It adheres to a published protocol (masked). Lived experience engagement is reported using the Guidance for Reporting Involvement of Patients and the Public[12] short checklist (table 1).

Table 2 Inclusion and exclusion criteria for the literature search process

Inclusion criteria	Exclusion criteria
Recruited patients with long COVID symptoms at least 4 weeks after a confirmed or suspected infection of SAR-CoV-19	Participants without long COVID
Any interventions reporting a primary aim or primary outcomes focusing on mental health, cognition or psychological well-being	Primary aim or primary outcomes were not mental health, cognition and psychological well-being (eg, physical health or biomarker outcomes)
Published articles or abstracts, manuscripts under review, unreviewed preprints or unpublished summaries	Animal trials, treatment guidelines, trial protocols, critical reviews or opinion papers
Reports written in any language, with an attempt to obtain an English-language summary for full inclusion	Trials conducted prior to the COVID-19 pandemic (ie, before 2020)
Participants from any age group or sociodemographic population	
Trials conducted in any country, beginning in 2020 or later	

Eligibility criteria

Inclusion and exclusion criteria are listed in table 2. Following the problem/population, intervention, comparison and outcome (PICO)[13] framework, our review focuses on clinical trials with individuals with long COVID (population), investigating any type of treatment (intervention), with or without a comparison group (comparison) and reporting as primary outcomes patients' mental health, cognition and psychological well-being in relation to long COVID (outcomes). We focused on these primary outcomes to ensure that the literature reviewed had a substantial focus on mental health, cognition and psychological well-being, rather than including the extensive interventions aiming to improve a physical health metric such as a respiratory variable, for which an exploratory analysis of mental health was conducted.

To be considered long COVID, the studies had to include patients who were experiencing persisting symptoms at least

Table 1 Guidance for Reporting Involvement of Patients and the Public reporting checklist for lived experience engagement in research

Section and topic	Description
(1) Aim	This review is part of a larger project that included lived experience voices to help guide research on mental health in long COVID. The aim of engagement as part of the current systematic review was to ensure that the information sought from the literature and the reporting of the results was consistent with the needs and priorities of individuals living with the condition.
(2) Methods	From the full project engagement team, two lived experience panel members joined the systematic review subproject. After a year of ongoing meetings on the full project, they attended four review-specific meetings with the research lead and a research staff and reviewed and critically appraised the manuscript. Topics of discussion included the overarching study outline, search term selection, items for data extraction, and a review of findings and interpretations, with a constant focus on gaps, additions and novel insights. They reviewed the manuscript and are coauthors on it.
(3) Study results	Advisors made useful suggestions at each stage of the consultation. Examples include the addition of the search term 'brain fog', addition of the data extraction about the timeframe of recruitment and amount of time participants had long COVID, discussion of the slow pace of research and the hope that people with long COVID can still hold for treatments, a focus on the importance of these results to the long COVID community and an emphasis on the importance of continuing to do this work in the future. They also emphasised the importance of contextualising mental health challenges in long COVID, noting that if mental health is not addressed sensitively, it can undermine individuals' experiences, stigmatise them and block pathways to accessing healthcare and improving their health.
(4) Discussion and conclusions	The engaged advisors were able to make concrete, relevant contributions to this systematic review. By ensuring that the patient voices are embedded throughout the review, we were able to maintain a focus on the importance of the findings to people living with long COVID. The review became more relevant to their experience and to the experience of other people in the long COVID community. The advisors who were engaged expressed that they felt valued, appreciated the opportunity to contribute and considered it important that their perspectives were taken into account.
(5) Reflections/Critical perspective	Lived experience engagement was a highly valuable endeavour in the conduct of this review. The engaged advisors made interesting and important contributions to the review, from the search design stage to manuscript writing. Lived experience engagement in systematic reviews is an appropriate and valuable process.

4 weeks after the onset of suspected or confirmed COVID-19 infection. Clinical trials could be conducted in any country, with any age group and sociodemographic characteristics, in any language. The search was conducted in both English and Chinese given the spoken languages of the authors.

Literature retrieval

A health sciences librarian (TR) developed a comprehensive search strategy with the research team. The librarian conducted the searches on 30 October 2023 in Medline, Embase, APA PsycINFO, Cumulative Index to Nursing and Allied Health Literature, Web of Science's Preprint Citation Index, The Cochrane Central Register of Controlled Trials, Clinicaltrials.gov and the WHO International Clinical Trials Registry Platform. A team member with a Chinese background (DX) translated the search strategy for Chinese databases and ran the searches in China National Knowledge Internet and WANFANG Data databases on 6 November 2023. All search strategies are included in the online supplemental materials (online supplemental files 2 and 3).

Considering the fast-moving literature on long COVID, search strategies were tested and refined iteratively between the protocol's publication in September 2022 and the review in October 2023. Database-specific subject headings, and keywords in natural language, and advanced search operators were used to operationalise and optimise two concepts: (1) long COVID, (2) mental health, cognition, psychological well-being. The long COVID cluster was based on the University of Alberta Library's long COVID search filter,[14] updated to reflect new variants and terminology as of 30 October 2023. These two concepts were combined using Boolean operators and then limited to clinical trials using the Canadian Agency for Drugs and Technologies in Health's search filter for all clinical trial types.[15]

To supplement the main searches, a hand search of reference lists and Google Scholar was conducted, along with searches of titles and authors of registered trials identified in our previous systematic review and scoping review.[9 10] For articles written in languages other than English, French or Chinese, a research staff contacted the corresponding authors for English summaries.

Study screening and selection

The English-language database searches yielded 1927 records. An additional 18 records were discovered by hand searching and contacting authors. All records were uploaded into Covidence software. After the removal of duplicates, 1433 unique articles were screened at the title and abstract level by two independent reviewers, and 87 full texts were screened by the same reviewers. The Chinese-language searches generated 1307 records. After the removal of duplicates, 929 records were screened by two independent reviewers at the title/abstract level and 23 at the full-text level. No studies from the Chinese-language searches met the criteria for inclusion in the review. In total, 33 documents representing 31 studies were included in the current review. See the PRISMA flow chart in figure 1.

Data extraction

Data were extracted from the 33 documents (31 studies) into an Excel spreadsheet by one research staff, and later verified by a second team member. Any uncertainty or conflict was discussed and resolved with the research lead.

Data synthesis

Data are summarised in tables 3 and 4 and in online supplemental tables 1 and 2 and narratively synthesised in the 'Results' section.

Risk of bias assessment

Quality assessment was conducted by two research staff independently. The Cochrane Risk of Bias 2.0 tool was used to evaluate randomised controlled trials (RCTs) (n=11) on five domains: randomisation, protocol deviation, missing data, outcome measurement and selection of reported results.[16] We applied the Joanna Briggs Institute (JBI) Critical Appraisal Tools Checklist for Case Series to both the case series and single-arm trials since the definition and criteria were applicable to these studies.[17] Case studies with n=1 were assessed with the JBI Checklist for Case Reports.[18] Results of the quality assessment are reported in online supplemental tables 2–4. The appraisal process was supported by continuing discussion with the lead researcher to resolve any conflict. Meta-analyses were not conducted due to the heterogeneity of the interventions tested across a wide range of observed outcomes.

RESULTS

Thirty-three articles were identified (figure 1) that tested interventions using psychosocial approaches,[19–25] neurocognitive rehabilitation,[26–35] natural supplements,[36–38] pharmaceutical treatments,[39–43] physical rehabilitation[44 45] or integrated approaches.[46–51] There were 11 RCTs, as well as 2 controlled trials that were not randomised, 10 uncontrolled trials, 7 case studies or series and 1 qualitative study. The studies had been conducted across four continents, with recruitment of a total of 2477 participants in the early pandemic. Table 3 provides an overview of the studies and table 4 provides a descriptive summary. Detailed results are provided in online supplemental table 1 for uncontrolled trials and online supplemental table 2 for controlled trials. Across the studies, the quantitative primary outcome measures were established, validated psychometric tools.

Psychosocial interventions

Seven studies examined psychosocial interventions, including cognitive processing therapy,[19] cognitive-behavioural therapy,[20 23] acceptance and commitment therapy,[22] virtual reality,[24] forest bathing[21] and a digital peer support intervention with positive psychology approaches.[25] They were a mix of in-person and virtual treatments, with doses ranging from 1 to 12 sessions. Two were RCTs,[22 24] one with a randomised waitlist control group,[22] and one waitlist controlled.[21] The others were single-armed trials and case studies.

An RCT on acceptance and commitment therapy found differences between the treatment and control groups at post-treatment for resilience and components of quality of life (QoL) favouring the treatment group. However, pretest scores were not controlled for, limiting the interpretation of the findings.[22] In another RCT of a virtual reality treatment, a significantly smaller number of people in the treatment group reported psychological distress, post-traumatic stress disorder and anxiety at post-treatment compared with the control group.[24]

A repeated waitlist controlled trial did not report on the control period, but showed significant prepost effects on anxiety, rumination and social connection.[21] In an uncontrolled treatment feasibility trial, significant prepost differences emerged for self-efficacy, helplessness, acceptance and perceived benefit, but

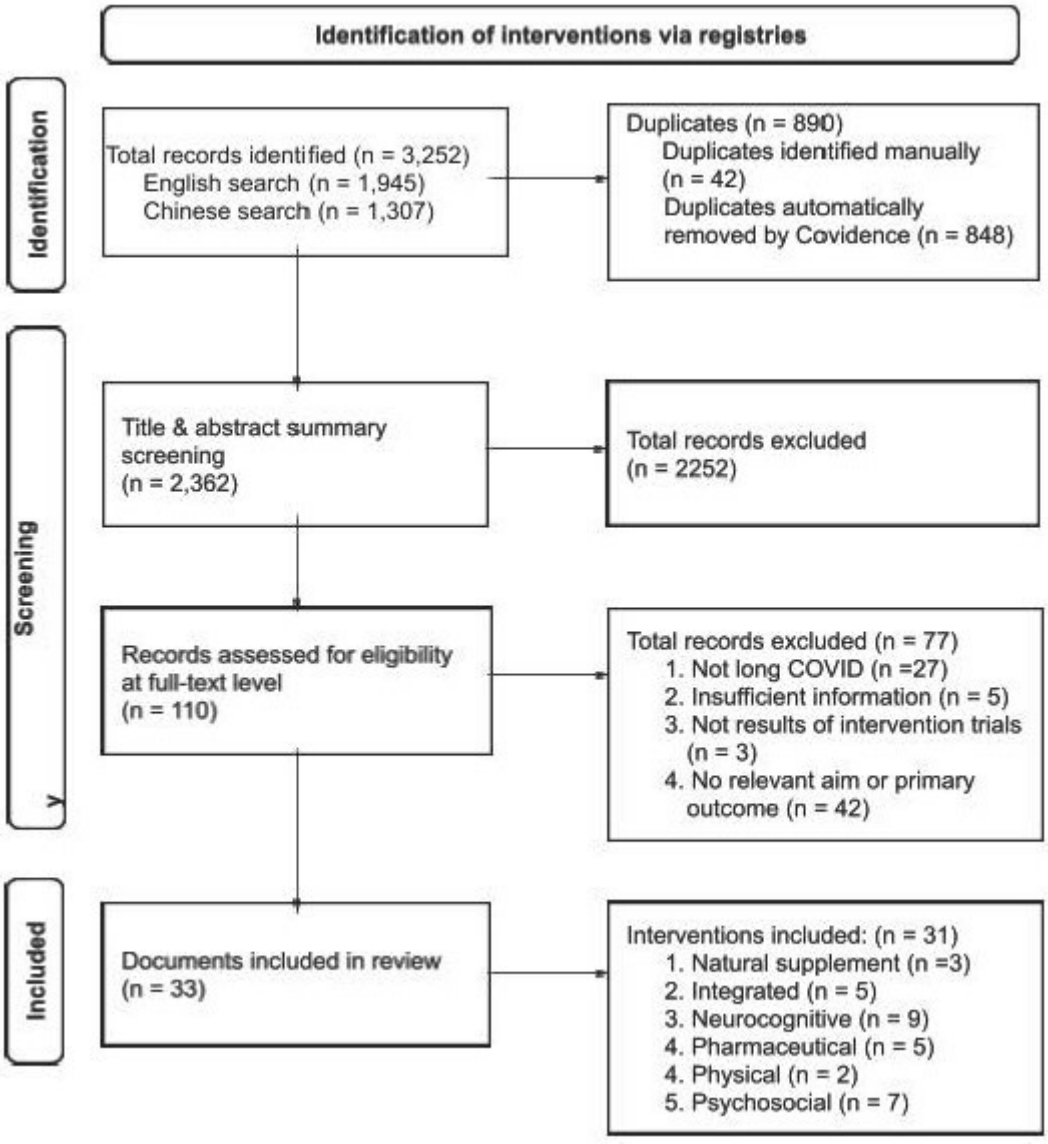

Figure 1 The Preferred Reporting Items for Systematic Reviews and Meta-Analyses flow diagram for study selection.

not for mental health symptoms.[20] In another uncontrolled trial, significant prepost differences emerged for mental well-being and self-efficacy, but not loneliness[25]; however, these cannot be associated with the treatment in the absence of a control group. Two case studies with cognitive processing therapy[19] and cognitive-behavioural therapy[23] reported reductions in PTSD,[19] depression and anxiety[23] and an increase in QoL[23] and daily functional improvements.[19 23]

Pharmaceutical interventions

Five studies of pharmaceutical treatments[39–43] included one RCT,[41] as well as single-armed trials[39 40 42] and a case study.[43] Treatment duration ranged from one time to daily for 2 months. The RCT, which examined an 8-week treatment with the antidepressant vortioxetine, showed a significant group by time interaction on depression and health-related QoL, with improvements over and above those in the control group.[41] However, no significant group by time interaction was found for cognitive functions, despite significant prepost improvements. Findings from the single-armed trials showed significant prepost improvements across a wide range of variables with the use of selected pharmaceutical products[39 40 42]; however, change over time cannot be definitively associated with a treatment effect due to the lack of a control group. In a case study, a single peripheral administration of etanercept was associated with improved cognition and reduced depression after 24 hours and 29 days.[43]

Natural supplements

Three studies investigated the effectiveness of therapeutic natural supplements.[36–38] A placebo-controlled RCT examined a hemp-deprived product with traces of tetrahydrocannabinol and cannabinoids.[38] The authors did not report on group by time interaction effects; a significant prepost difference was only found for anxiety among the mental health, cognition and psychosocial variables examined. An RCT on an adaptogen formulation showed no significant group by time effects on cognitive and emotional symptoms, despite significant prepost improvements.[37] A multi-armed trial was conducted of a treatment with palmitoylethanolamide and lutein, which are described to have anti-inflammatory and neuroprotective benefits.[36] While significant prepost results suggest the possibility of

Table 3 Overview of selected studies

Variable	N	%
Intervention type		
Psychosocial interventions	7	23
Pharmaceutical interventions	5	16
Natural supplement interventions	3	10
Neurocognitive interventions	9	29
Physical rehabilitation	2	6
Integrated interventions	5	16
Allocation		
Case studies/series	7	23
Uncontrolled trials	10	32
Randomised controlled trials	11	35
Non-randomised controlled trials	2	6
Qualitative studies	1	3
Delivery format		
In person	16	52
Virtual	5	16
Hybrid	3	10
Self-administered	7	23
Location		
Asia	1	3
Europe	21	68
Middle East	3	10
North America	4	13
South America	2	6
Recruitment start date		
2020	4	13
2021	11	35
2022	5	16
Not reported	11	35
Primary outcome		
Mental health	18	58
Cognition	17	55
Psychological well-being	12	39

treatment effectiveness in reducing mental clouding, this cannot be definitively concluded without a control group.

Neurocognitive interventions

Nine studies (representing 10 records) examined neurocognitive interventions.[26–35] Intervention length ranged from 10 days to 4 months. Three studies were RCTs.[28 29 34]

Diverse treatments using neuromodulation were explored, including electroencephalogram neurofeedback[30 32] and brain stimulation techniques such as cranial electrical stimulation,[29] transcranial direct/alternating current stimulation[33 34] and repetitive transcranial magnetic stimulation.[31] Three studies combined brain stimulation with cognitive training[26 35] or mindfulness meditation.[28] One study combined brain stimulation with eye stimulation.[33]

An RCT combining brain stimulation and mindfulness showed significant group by time interactions in several cognitive and psychological domains, although changes in other domains were not significant.[28] An RCT of high-definition transcranial direct current stimulation found significant group by time interactions for cognitive fatigue, psychosocial fatigue, anxiety and QoL.[34] An RCT of cranial electrical stimulation reported significant prepost improvements depression, but not anxiety, and no information was provided on the group by time interaction.[29] A study with a non-randomised controlled group found significant prepost improvements in both the treatment and control groups across cognition and mental health. Although they did not statistically examine treatment interaction effects, the effect sizes were larger in the treatment group than in the control group for some variables.[27] Two studies presented significant prepost improvements in variables such as cognitive functions, anxiety and depression, but without control groups to confirm treatment effects.[31 32] Participants in case studies reported positive outcomes over time for cognition, emotions, daily functioning and independent living.[26 30 33 35]

Physical rehabilitation

Two studies investigated five sessions per week of hyperbaric oxygen therapy, at 90 min of 100% oxygen at two atmosphere absolute.[44 45] An RCT consisting of 40 sessions in 4 months with a sham control group[45] demonstrated the effectiveness of hyperbaric oxygen therapy on total cognitive and psychological distress scores, with significant group by time interactions[45]; no significant group by time interaction was found for emotional limitations, emotional well-being or social functioning. A case study of a 60 session regimen reported prepost improvements in various neurocognitive domains.[44]

Integrated interventions

Five studies (representing six reports) described integrated interventions.[46–51] These included diet and nutrition, self-management, meditation, cognitive training and rehabilitation. Treatment duration ranged from 4 weeks to 6 months. One RCT examined a rehabilitation mobile app promoting QoL.[50 51] Analyses of change scores indicated no significant differences across a range of mental health, cognition and well-being-related variables in the context of low treatment adherence. A 6-month follow-up report in preprint form shows continued non-significance. For the other RCT, the authors reported significant improvement in the mental health composite score.[48] Among the uncontrolled single-arm trials with prepost metrics, studies suggested improvements over time.[46 47] A qualitative study found that integrated cognitive psychoeducational training contributed to the development of an insightful understanding of long COVID symptoms and helped participants manage their daily living and work.[49]

Quality assessment

Overall, five RCTs were rated as low risk, three as high risk and two as having some concerns. Almost all case series and single-arm trials presented clear details on inclusion criteria, outcome measurements and clinical information of the samples. However, none of the case series and single-arm trials reported whether there was consecutive or complete inclusion of participants. Most were missing details on ethnicity and education and did not report on adverse events or study location demographic descriptions. Three out of five case studies (n=1) did not report on whether there were any adverse events during treatment. Most of the case studies reported sufficient information on the patient's clinical profile and the study protocol.

DISCUSSION

This systematic review synthesised the evidence on interventions for mental health, cognition and psychological well-being in patients with long COVID. Results reveal a highly heterogeneous literature, a range of treatment modalities and study designs of various levels of rigour. While significant improvements were

Table 4 Study description

Study	Intervention summary	Control intervention	Country	Design and sample size: treatment n (control n)	Time since COVID-19	Treatment dose/ duration	Relevant outcomes	Treatment results
Psychosocial interventions								
Bogucki and Sawchuk[19]	Cognitive processing therapy to help identify, evaluate and restructure distorted cognitions with a focus on safety, trust, power, esteem and intimacy	n/a	USA	Case study: 1 (n/a)	>5 months	Twelve weekly individual sessions	PTSD, depression, anxiety, subjective report	Prepost reduction in PTSD symptoms and subjective functional improvement
Huth *et al*[20]	Cognitive behavioural therapy: goal setting, psychoeducation, stress reduction, attention and cognitive readjustment, management of physical activity	n/a	Germany	Single-arm trial: 64 (n/a)	M=62.45 (SD=27.67) weeks (13.29–121.14 weeks)	Eight 60 min weekly sessions	Somatic symptom distress, depression, anxiety, self-efficacy, illness-related cognitions	Significant prepost reduction in helplessness; increase in acceptance, self-efficacy, perceived benefit of the intervention only
McEwan *et al*[21]	Online forest bathing: mindfulness with a slow walk in nature, with online group meetings	Repeated waitlist	UK	Repeated waitlist trial: 22 (n/a)	Months and years	Four 60 min, weekly group sessions	Anxiety, rumination, social connection	Significant prepost improvement in anxiety, rumination, social connection
Nikrah *et al*[22]	Acceptance and commitment therapy: to develop psychological flexibility, decision-making capacity	Waitlist	Iran	RCT: 15 (15)	At least 30 days	Seven 90 min weekly sessions	Resilience, health-related QoL	Group×time interaction not provided. May show increase in resilience, and overall health-related QoL
Skilbeck[23]	Cognitive behavioural therapy: self-management focus with psychoeducation, acceptance, goal setting and activity pacing	n/a	UK	Case study: 1 (n/a)	8 months	Twelve 60 min individual sessions	QoL, depression, anxiety, subjective report	May show improvement (p values not provided) in QoL, depression and anxiety. Subjective treatment acceptability and improvement in daily life
Vlake *et al*[24]	ICU-specific virtual reality intervention: use of virtual reality to describe ICU procedures and treatments	No treatment	The Netherlands	RCT, open label: 45 (44)	3 months	One time, 14 min session	Psychological distress, PTSD symptoms health-related QoL	Group×time interaction not provided. Significant improvement in PTSD symptoms at 3-month follow-up. Significantly fewer people with probable anxiety at 1-month follow-up
Wright *et al*[25]	The HOPE programme for long COVID: digital peer support intervention with positive psychology approaches	n/a	UK	Single-arm trial: 47 (n/a)	M=377.3 (SD=171.8) days	Eight weekly sessions	Positive mental well-being, self-efficacy, loneliness	Significant prepost improvement in positive mental well-being and self-efficacy only
Pharmaceutical interventions								
Bogolepova *et al*[39]	Cholytilin (choline alfoscerate) or MexiB 6	n/a	Russia	Single-arm trial: 50, 50 (n/a)	5.4 months	Group 1: MexiB 6: 3 tablets daily Group 2: Cholytilin: 3 daily capsules (1200 mg)	Cognition, anxiety, depression	Significant prepost improvement in cognitive functions, anxiety and depression for both treatment groups
Esin *et al*[40]	Anvifen: GABAergic nootropic drug	n/a	Russia	Single-armed trial: 92 (n/a)	12 weeks	500 mg, 3 times daily (21 days)	Anxiety, depression, cognition, health-related QoL—psychological component	Significant prepost improvement in cognitive functions, psychological component of health-related QoL, anxiety and depression

Continued

Table 4 Continued

Study	Intervention summary	Control intervention	Country	Design and sample size: treatment n (control n)	Time since COVID-19	Treatment dose/ duration	Relevant outcomes	Treatment results
MacIntyre *et al*[41]	Vortioxetine: antidepressant	Placebo	Canada	RCT, double blind: 75 (74)	3 months after acute COVID-19 infection	5–20 mg/day (8 weeks)	Cognition, depression, health-related QoL	No significant group×time interaction for cognition. Significant group × time interaction for depression and health-related QoL
Putilina *et al*[42]	Cortexin	n/a	Russia	Single-arm trial: 979 (n/a)	12 weeks or longer	10 mg/day or 20 mg/ day for 10 days	Mental state and attention	Significant prepost improvement in mental state and attention
Tobinick *et al*[43]	Etanercept	n/a	USA	Case study: 1 (n/a)	12 months	One time 25 mg dose, perispinal administration	Cognition, depression	Improvement in cognition and depression post-treatment
Natural supplement interventions								
De Luca *et al*[36]	Oral supplement containing palmitoylethanolamide and lutein, with olfactory training	n/a	Italy	Multi-arm trial: Group 1: 43 Group 2: 16 Group 3: 10 (n/a)*	6 months or more	Palmitoylethanolamide 700 mg, luteolin 70 mg, one dose daily for 90 days	Mental clouding	Significant prepost reduction in mental clouding between baseline and 3 months for participants as a whole and one subgroup
Karosanidze *et al*[37]	Chisan/ADAPT-232: fixed combination of adaptogens Rhodiola, Eleutherococcus and Schisandra	Placebo	Georgia	RCT, quadruple blind: 50 (50)	30 days	30 mL, two doses daily for 14 days	Cognition, anxiety, depression	No significant group×time interaction. Significant prepost improvement in attention/memory, anxiety and depression
Young *et al*[38]	Endourage, formula C: hemp-derived, cannabidiol-rich supplement with trace of tetrahydrocannabinol	Placebo	USA	RCT, single blind: 12 (11)	4 weeks and above	Starting at 0.25 mL, one dose daily for 28 days	QoL components	Group×time interaction not provided. Significant prepost improvement in QoL—emotional distress anxiety only
Neurocognitive interventions								
Cavendish *et al*[26] Vidal *et al*[35]	Transcranial direct current stimulation and cognitive training: non-invasive brain stimulation and online cognitive training	n/a	Brazil	Case series: 4 (n/a)	2–4 months	20 daily 20 minute sessions+cognitive training	Cognition, depression, emotional symptoms	May show decreases in cognitive, depressive and emotional symptoms (p values not provided)
García-Molina *et al*[27]	Outpatient neuropsychology rehabilitation programme: personalised cognitive training plan	No treatment	Spain	Controlled trial without randomisation: 91 (32)	M=7.7 (SD=3.45) months	Individualised 60 min weekly sessions (8 weeks)	Cognition, anxiety, depression	Group×time interaction not provided. Significant prepost differences in several cognitive functions, anxiety and depression
Hausswirth *et al*[28]	The Rebalance Programme: non-invasive cognitive stimulation and guided mindfulness training with sound therapy and light stimulations	Healthy control and long COVID control, no treatment	France	RCT: 17 (17, 15)	4 weeks or several months	Ten 30 min sessions within 4 weeks	Cognition, mood, anxiety, depression, perceived stress, mental fatigue	Significant group×time interaction in mental fatigue, anxiety, depression, mood disturbance and on several cognitive domains
Leitl *et al*[29]	Cranial electrical stimulation: non-invasive brain stimulation as adjunct to pulmonary rehabilitation	Sham treatment	Germany	RCT: 40 total	10±5 months	Daily 60 min sessions (3 weeks)	Anxiety, depression	Group×time interaction not provided. Significant prepost reduction in depression, but not anxiety
Łuckoś *et al*[30]	EEG neurofeedback: neurofeedback with goal-oriented cognitive training	n/a	Poland	Case study: 1 (n/a)	≥6 months	Twice weekly (15 weeks)	Cognition, subjective report	May show improvement in cognitive functions. Subjective report of independence and return to work

Continued

Table 4 Continued

Study	Intervention summary	Control intervention	Country	Design and sample size: treatment n (control n)	Time since COVID-19	Treatment dose/ duration	Relevant outcomes	Treatment results
Noda *et al*[31]	Transcranial magnetic stimulation: repetitive transcranial magnetic stimulation and intermittent theta burst stimulation with MagPro R30 TMS device with the Cool-B70 coil	n/a	Japan	Single-arm trial: 23 (n/a)	M=48.6 (SD=30.2) weeks	20 daily sessions	Depression, difficulty with activities of daily living, cognitions	Significant prepost improvement of depression, and difficulty with activities of daily living and cognitive functions with large effect sizes
Orendáčová *et al*[32]	Neurofeedback: a neuromodulation method using EEG signals	n/a	Czech Republic	Single-arm trial: 10 (n/a)	3–19 months (median 12 months)	Five 25–45 min sessions (2 weeks)	Anxiety, depression	Significant prepost reduction in anxiety and depression 1 week after treatment
Sabel *et al*[33]	Transcranial alternating current stimulation: non-invasive brain stimulation with neuromodulation device and psychological counselling	n/a	Germany	Case series: 2 (n/a)	Patient 1: 7 months Patient 2: 9 months	Daily 30–45 min sessions (10 and 13 days)	Cognition, subjective report	Prepost improvement in cognitive measures. Subjective improvement in cognition and daily activities
Santana *et al*[34]	High-definition transcranial direct current stimulation: non-invasive brain stimulation with low amplitude sustained current targeting specific brain regions	Sham treatment	Brazil	RCT, triple blind: 35 (35)	3–12 months	Ten 30 min sessions, twice a week	Cognitive and psychosocial fatigue, anxiety, health-related QoL	Significant group×time interaction in cognitive and psychosocial fatigue, anxiety and health-related QoL
Physical rehabilitation								
Bhaiyat *et al*[44]	Hyperbaric oxygen therapy: exposure to 100% oxygen at 2 atmosphere absolute in a chamber	n/a	United Arab Emirates	Case study: 1 (n/a)	3 months	Sixty 90 min sessions, 5 times a week	Cognition	Prepost improvement in memory and other cognitive domains
Zilberman-Itskovich *et al*[45]	Hyperbaric oxygen therapy: exposure to 100% oxygen by mask at 2 atmosphere absolute in a chamber	Sham treatment	Israel	RCT, double blind: 37 (36)	At least 3 months	Forty 90 min sessions, 5 times a week	Cognition, health-related QoL, psychological distress	Significant group×time interaction in total cognition and psychological distress only
Integrated interventions								
Brough *et al*[46]	Psychoeducation and mind-body interventions: educational sessions about COVID-19 and long COVID experiences, strength and conditioning, memory, yoga, qigong, nutrition, meditation, mindfulness, aromatherapy	n/a	UK	Single-arm trial: 22 (n/a)	2 months	Four or six weekly group sessions	Well-being	May show improvement (p values not reported) in well-being. Qualitative reports of satisfaction and usefulness
Compagno *et al*[47]	Multidisciplinary rehabilitation programme: physical training, cognitive behavioural therapy, eye movement desensitisation and reprocessing therapy	n/a	Italy	Single-arm trial: 30 (n/a)	M=3 months (range 1–6 months)	Three 90 min physical training sessions, four psychological sessions	Health-related QoL—mental domain, anxiety, depression	Significant prepost improvements in health-related QoL—mental domain, depression, anxiety
Raunkiae *et al*[49]	Rehabilitation for long-term cognitive effects of COVID-19: needs assessment, neurocognitive screening, cognitive training, compensatory tools, energy conservation, psychoeducation, daily activity management	n/a	Denmark	Qualitative: 12 (n/a)	M=233 (SD=102) days (139–412 days)	5-day residential, 12 weeks at home, 2 follow-up residential	Individual interview	Qualitative reports of improved understanding of their illness, improved daily activity management and coping with working life

Continued

Table 4 Continued

Study	Intervention summary	Control intervention	Country	Design and sample size: treatment n (control n)	Time since COVID-19	Treatment dose/ duration	Relevant outcomes	Treatment results
Philip *et al*[48]	English National Opera Breathe programme: breathing retraining through singing techniques and lullabies	TAU	UK	RCT, single blind: 74 (76)	Treatment: M=330 (SD=124) days. Control: M=311 (SD=130) days	Six weekly 60 min sessions	Health-related QoL	Group×time interaction not provided
Samper-Pardo *et al*[50]	ReCOVERY Mobile app: nutrition, rest and sleep, physical exercises, breathing, cognitive exercises, community participation	TAU	Spain	RCT, open label: 52 (48)	M=16.12 (SD=6.34) months	Three motivational sessions, rehabilitation app (12 weeks)	Health-related QoL, cognition, emotional well-being, social support, self-efficacy	No significant group×time interactions
Samper-Pardo *et al*[51]	ReCOVERY Mobile app: nutrition, rest and sleep, physical exercises, breathing, cognitive exercises, community participation	TAU	Spain	RCT, open label: 52 (48)	M=16.12 (SD=6.34) months	Three motivational sessions, rehabilitation app (24 weeks)	Health-related QoL, cognition, emotional well-being, social support, self-efficacy	No significant group×time interaction

*Group 1: supplement+olfactory training; group 2: supplement only; group 3: supplement+previous olfactory training.
EEG, electroencephalographic; n/a, not available; PTSD, post-traumatic stress disorder; QoL, quality of life; RCT, randomised controlled trial; TAU, treatment as usual.

found among participants for some variables in most studies over time, much of the research is lacking the control group necessary to confirm the impact of the intervention, and it is important to note that this body of literature therefore does not demonstrate efficacy. Based on quality assessments, the quality of the emerging evidence raises significant concern.

As a whole, participants showed improvements over time across the body of research, across a range of metrics. This confirms that individuals with long COVID improve in their mental health, cognition and well-being over time, which is encouraging. Since the improvements were also seen in control groups, such improvement could be independent of treatment[52] and may vary based on the amount of time the individuals have had long COVID. Caution is required when interpreting treatment effects without a control group. Definitively establishing the size of the effect of the temporal improvement, with rigorous methods and generalisable results, would help mitigate this challenge.

Among the trials with control groups, some found significant treatment effects on some variables, while others did not. A pharmacological treatment (vortioxetine) achieved effects on QoL and depression,[41] both of which are substantially affected in long COVID.[4] Forms of brain stimulation achieved treatment effects across depression, anxiety and cognitive domains.[28 34] While professional bodies and patients alike advocate for integrated interventions as the best practice for long COVID,[1 8] only a limited number of such interventions have been rigorously tested. This is an important area for future research. To confirm the safety and efficacy of interventions, interventionists should consider evaluating integrated treatment models that incorporate the promising neurocognitive interventions and test them within well-designed RCTs to inform clinical practice. Existing integrated models of care for analogous conditions should be considered.

In our quality assessment, only five RCTs met the 'low risk' threshold, while many case series and single-arm trials lacked demographic and inclusion information.[10] Given that long COVID has only a newly emerging treatment evidence base, our scoping review suggested that some of the research to date is of lower than ideal quality. It is possible that in the rush to generate evidence, certain research quality standards were sometimes overlooked. While the sense of urgency is real, it is important to balance urgency with quality standards. Some individuals living with long COVID may be desperate for effective treatments and may be vulnerable to unproven treatments, amplifying the need to generate high-quality evidence to support effective treatment pathways.

Long COVID is still a new clinical entity. Research is a slow process, with long timelines from protocol development to publication, and even longer delays before the implementation in clinical practice. However, rapid research is not always conducive to the highest high-quality outputs. In just over 4 years since COVID-19 manifested, 33 articles have been published on interventions for mental health, cognition and psychological well-being in long COVID. None were indexed in the Chinese-language databases, representing a gap in the Chinese-language literature. Despite quality gaps, this still represents a considerable effort to respond to a public health emergency. Many more studies are likely on the cusp of publication, providing hope for people living with long COVID. Frequent literature synthesis endeavours will be required, such as a living evidence synthesis. Additionally, the timing of infection and the COVID-19 variant contracted, before or after vaccination, may impact long COVID trajectories and treatment responses.

Limitations should be kept in mind. Notably, the systematic search was conducted in late 2023 and any articles published after the search date were not included. For pragmatic reasons, some articles were excluded due to language limitations after attempting to acquire English-language summaries. Imposing a different definition of long COVID (eg, 12 weeks) would have influenced the articles included in some cases. Meta-analyses could not be conducted due to intervention diversity and study limitations. Most of the registered trials included in our systematic review[9] (masked reference) were at the end-of-grant knowledge translation stage, and investigators had not yet released the results for review.

In sum, limited high-quality research to date has tested interventions for mental health, cognition and psychological well-being in long COVID. The published research shows clinical and statistical heterogeneity and inconsistent findings. Minimal literature has been published on studies rigorously designed to demonstrate efficacy above and beyond the effect of time. Nevertheless, some promising findings provide hope for improvements over time. Ongoing research with appropriate methodologies is required to continue to build this small but emerging evidence base. As per treatment recommendations, integrated interventions should be tested, specifically those that leverage long COVID interventions showing preliminary promise, along with efficacious interventions for analogous conditions. Ongoing and regular literature syntheses are required to update and educate clinicians, scientists, interventionists and the long COVID community.

Acknowledgements We thank Wuraola Dada-Phillips and Weitao Bao for support in the manuscript selection process. We further thank Sheng Chen for the statistical support.

Contributors LDH obtained funding, designed the review protocol, oversaw the screening and data extraction, synthesised the data and drafted the manuscript. ATPN contributed to the article selection process, conducted the data extraction, contributed to the data synthesis and writing and contributed to drafting the manuscript, and edited and approved the final version. DX contributed to the study design and the article selection process, and edited and approved the final version. TR contributed to the design of the review, designed the library database search and edited and approved the final manuscript. SD and SG supported the study design, literature search, data extraction and data synthesis, and edited and approved the manuscript. All other authors, WW, EEB, CFS, DRT, GS, SLR, DC, contributed to the study design and the data synthesis, and edited and approved the manuscript. LH is guarantor.

Funding The study received funding from the Canadian Institutes of Health Research (Funding #: WI1-179893).

Disclaimer The funder had no involvement in the review process, manuscript writing or publishing decisions.

Competing interests DC has received grant for research from Servier, Boehringer Ingelheim; travel support and honoraria for talks and consultancy from Servier, Seqirus, Lundbeck. He is a founder of the Optimal Health Programme (OHP), and holds 50% of the intellectual property for the programme; and is part owner of Clarity Healthcare. He does not knowingly have stocks or shares in any pharmaceutical company. Other authors have no conflict of interest to declare.

Patient consent for publication Not applicable.

Ethics approval Not applicable.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement All data relevant to the study are included in the article or uploaded as supplementary information.

Author note Transparency declaration: The lead author (LDH) affirms that the manuscript is an honest, accurate and transparent account of the study being reported; that no important aspects of the study have been omitted and that any discrepancies from the study as originally registered have been explained.

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