


SYSTEMATIC REVIEW UPDATE

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A systematic review and meta-analysis of long COVID symptoms

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Abstract

Background Ongoing symptoms or the development of new symptoms following a SARS-CoV-2 diagnosis has caused a complex clinical problem known as “long COVID” (LC). This has introduced further pressure on global healthcare systems as there appears to be a need for ongoing clinical management of these patients. LC personifies heterogeneous symptoms at varying frequencies. The most complex symptoms appear to be driven by the neurology and neuropsychiatry spheres.

Methods A systematic protocol was developed, peer reviewed, and published in PROSPERO. The systematic review included publications from the 1st of December 2019–30th June 2021 published in English. Multiple electronic databases were used. The dataset has been analyzed using a random-effects model and a subgroup analysis based on geographical location. Prevalence and 95% confidence intervals (CIs) were established based on the data identified.

Results Of the 302 studies, 49 met the inclusion criteria, although 36 studies were included in the meta-analysis. The 36 studies had a collective sample size of 11,598 LC patients. 18 of the 36 studies were designed as cohorts and the remainder were cross-sectional. Symptoms of mental health, gastrointestinal, cardiopulmonary, neurological, and pain were reported.

Conclusions The quality that differentiates this meta-analysis is that they are cohort and cross-sectional studies with follow-up. It is evident that there is limited knowledge available of LC and current clinical management strategies may be suboptimal as a result. Clinical practice improvements will require more comprehensive clinical research, enabling effective evidence-based approaches to better support patients.

Keywords Long COVID, Pain, Neuropsychiatry, Neurology, Autonomic dysfunction, Gastrointestinal

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Introduction

Global experience with a rapidly evolving and advanced strain of the coronavirus have led to over a million deaths since January 2020. The first case of SARS-CoV-2 was reported in China around December 2019. Healthcare systems have been under immense pressure to support both SARS-CoV-2 patients and survivors who continue to demonstrate various symptomatology which appear to impact the overall quality of life and wellbeing. A report from the Center for Disease Control and Prevention (CDC) in the USA reported that patients recovered from SARS-CoV-2 have continuous symptoms of shortness of breath, fatigue, brain fog, cough, chest pain, stomach pain and headache. Bin Cao and colleagues reported that these complications appear to last for at least 6 months thus far [1]. Similarly, Carfi and colleagues reported 87.4% of the survivors suffered from a variety of symptoms at post-60 days since the original SARS-CoV-2 diagnosis [2].

As SARS-CoV-2 survivors continue to share their experiences, clinical researchers hypothesize the continuation of complex symptomatology for a longer period of time than initially anticipated [3]. As a result, several independent authorities have developed long COVID guidelines, although the consensus continues to change with the changing evidence base from data gathered from patients. Therefore, a universally accepted Long COVID definition is yet to be elaborated, although a general overview is available. One such important guideline set is from the National Institute for Health and Care Excellence (NICE), which stipulates “*Long COVID*’ (LC) is commonly used to describe symptoms that continue or develop after acute SARS-CoV-2 diagnosis post-4 weeks” [4]. The current research landscape exploring LC is also limited due to the varying reports of symptoms identified in clinical datasets that demonstrates it to be a ‘*moving target*’ and it is challenging clinical researchers to guide clinicians on the most optimal steps to pursue when managing the clinical care of these patients. The World Health Organization’s (WHO) Novel Coronavirus Pneumonia Emergency Response Epidemiology Team describes LC as a *complex course of illness*. Therefore, pandemic policymaking itself requires evidence-based clinical research along with patient-reported outcomes and clinician experiences to be reported in an effective manner to channel a more holistic approach to optimise long-term clinical management. A key component appears to be the difference in LC symptoms between men and women, as reported by Mathew et al., who demonstrate that these observations are vital to understand, and that at present this is based particularly on clinician experience with limited pathophysiological and aetiology [5].

In this study, we conducted a meta-analysis of peer-reviewed and published data using a systematic approach to better understand LC from a neurological and neuropsychiatry perspective.

Methods

A systematic methodology was developed, peer reviewed, and published in PROSPERO (CRD42021235351). The primary aim of this systematic review was to determine the prevalence of LC symptomatology pertaining to neuropsychiatry, neurology, and pain. The secondary aim was to determine any other infrequently reported symptoms that may influence neuropsychiatry and/or neurology and/or pain diagnosis following LC. The Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) was used to report this study.

The published PROSPERO protocol in its current state is reflective of a wide study for long COVID as such, our response to your query that this manuscript answers one of the 4 objectives listed in PROSPERO. Furthermore, at the time we conducted this review we did not have much other than symptomatology and we therefore intend to extend this to a more robust output with our next manuscript which will be an extension of the original. The second manuscript will also cover the remainder of the aims listed in the PROSPERO protocol.

Search strategy

Multiple databases of Embase, Pubmed, Science Direct, and ProQuest were used with multiple MeSH terms such as nervous system diseases, autonomic central nervous system diseases, autonomic diseases, autonomic nervous system disorders, disorders of the autonomic nervous system, autonomic nervous system diseases, peripheral autonomic nervous system diseases, autonomic peripheral nervous system diseases, parasympathetic nervous system diseases, sympathetic nervous system diseases, headaches, migraine, headache after mental exertion, exertional headache, tension headache, cluster headache, intra cranial hypertension, temporal headache, retro-orbital headache, cervicogenic headache, chronic pain, fibromyalgia, back pain, erythromelalgia, endometriosis, intercostal neuralgia, leg pain, neuropathic pain, chronic pelvic pain, sciatica, muscle fatigue, metal fatigue, cognition, apathy, sleep arousal, sleep deprivation, sleep initiation and maintenance, anxiety, depression emotional lability.

All studies and surveys were included in the Preliminary R1 round. The reviews and meta-analysis identified were scrutinized for references that can be included in our meta-analysis. A final set was arrived at looking at the possible relevance of the studies comprising of 302

studies. This was analyzed as per PRISMA diagram in Fig. 1 in the “Results” section.

Eligibility criteria

In this meta-analysis, we looked at persistent symptoms in COVID patients, including cohort and cross-sectional studies. All studies included were reported in English.

Data extraction and synthesis

Screening and data extraction were performed by four independent reviewers. Any disagreements were discussed and reached a consensus by two reviewers. To

fully investigate the impact of LC on the physical health of survivors, we grouped all reported symptoms into five main categories: general symptoms (which includes pain and other infrequently reported symptoms), neurological, mental disorders, cardiopulmonary, and obstetric problems.

Data extractions were made via studies that included SARS-CoV-2 survivors that had either been hospitalized or treated as outpatients. Therefore, these patients had a confirmed positive test for SARS-CoV-2 in addition to relevant symptoms. All studies that did not report on follow-up data were excluded. For studies that reported

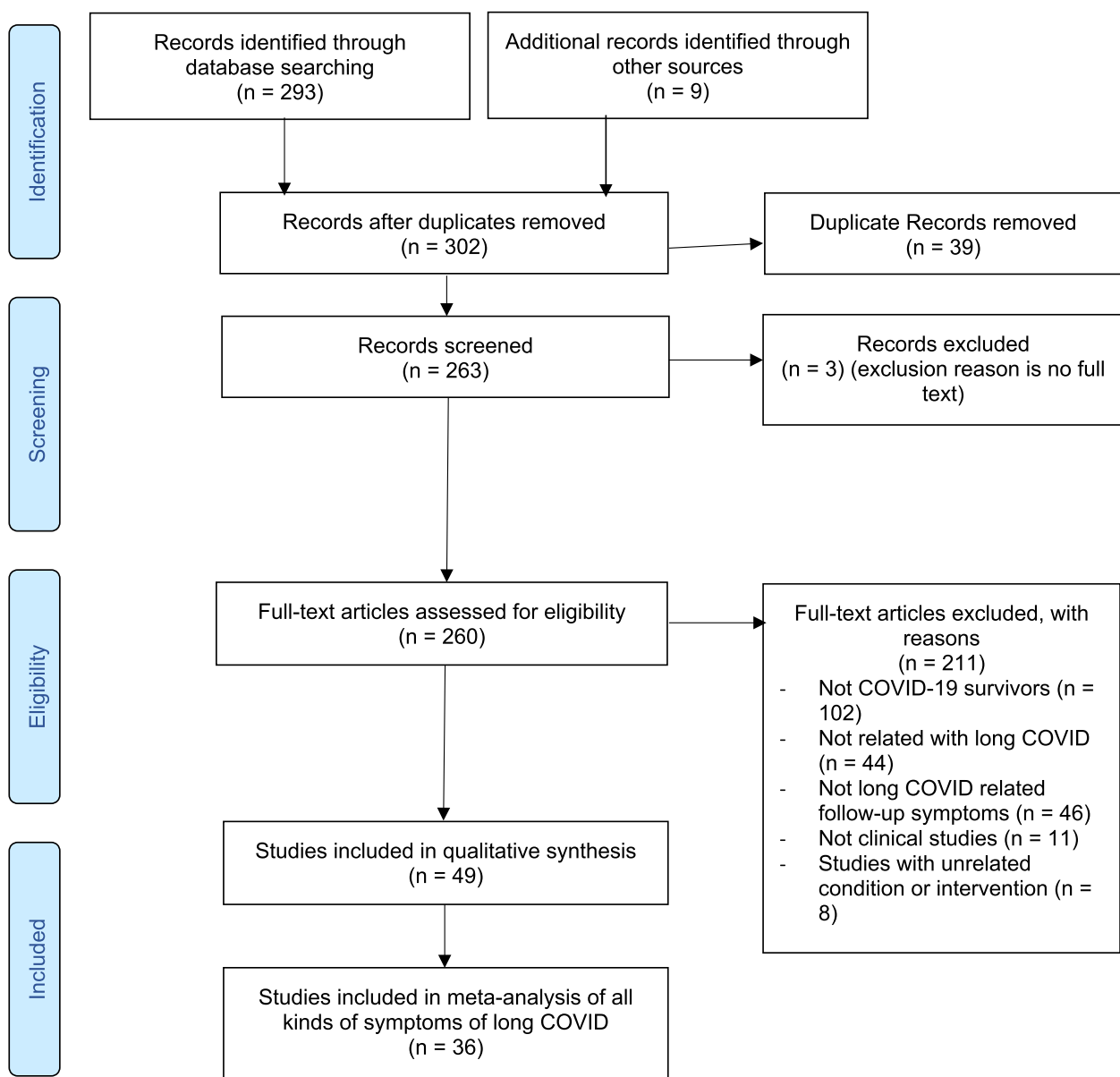


Fig. 1 PRISMA flow diagram

Table 1 Risk of bias quality assessment

	Selection (S)				Comparability (C)		Exposure/ Outcome (E/O)			Sub Total assessment				Quality Assessment
	1	2	3	4	1a	1b	1	2	3	S ⁺	C ^{&}	E/O ^{&}	Conclusion	NOS
Akter et al	*	NO	*	*	*	*	*	*	*	Good	Good	Good	Good	7
Huang et al	*	NO	*	*	NO	*	*	*	*	Good	Good	Good	Good	6
Humphreys et al	*	NO	*	NO	*	NO	NO	*	*	Fair	Good	Good	Fair	5
Simani et al	*	NO	*	*	NO	*	*	*	*	Good	Good	Good	Good	6
Taylor et al	*	NO	*	*	NO	*	*	*	*	Fair	Good	Fair	Fair	6
Felipe et al	NO	NO	*	*	*	*	*	*	*	Fair	Good	Good	Good	6
Hopkins et al	*	NO	*	*	*	*	*	*	*	Good	Good	Good	Good	7
Petersen et al	*	NO	*	*	*	*	*	*	*	Good	Good	Good	Good	7
Iqbal et al	*	*	*	*	*	*	*	*	*	Good	Good	Good	Good	8
Poncet-Megemont et al	*	*	*	*	*	*	*	*	*	Good	Good	Good	Good	8
Trevisan et al	*	*	*	*	*	*	*	*	*	Good	Good	Good	Good	7
Klein et al	*	NO	*	NO	*	NO	*	NO	NO	Fair	Good	Poor	Poor	4
Munro et al	*	NO	NO	*	NO	NO	*	NO	NO	Fair	Poor	Fair	Poor	4
Chopra et al	*	NO	*	*	NO	NO	*	NO	NO	Good	Poor	Fair	Fair	5
Putri et al	*	NO	*	*	*	*	*	*	*	Good	Good	Good	Good	7
Liu et al	*	NO	*	*	*	*	*	NO	NO	Good	Good	Fair	Good	6
Tenforde et al	*	*	*	*	*	*	*	*	*	Good	Good	Good	Good	8
Sykes et al	*	NO	*	*	*	*	*	*	*	Good	Good	Good	Good	6
Townsend et al	*	NO	*	*	NO	*	*	*	*	Good	Fair	Good	Good	7
Writing Committee for the COMEBAC study group, 2021 [6]	*	NO	*	*	*	*	*	NO	NO	Good	Good	Fair	Fair	5
Augustin et al	*	NO	*	*	*	*	*	*	*	Good	Good	Good	Good	6
Duncan et al	*	NO	*	NO	*	*	*	NO	NO	Fair	Good	Fair	Fair	4
Osikamaiya et al	*	NO	*	*	*	*	*	*	*	Good	Good	Good	Good	6
Orrù et al	*	*	*	*	*	*	*	*	*	Good	Good	Good	Good	7
Pujari et al	*	NO	*	NO	*	*	*	*	*	Fair	Good	Good	Good	6
Frontera et al	*	*	*	*	*	*	*	*	*	Good	Good	Good	Good	7
Holmes et al	*	*	*	*	*	*	*	*	*	Good	Good	Good	Good	7
Townsend et al	*	NO	*	NO	*	*	*	NO	NO	Fair	Good	Fair	Fair	4
Estiri et al	*	NO	*	*	*	*	*	NO	NO	Good	Good	Fair	Fair	5
Chevinsky et al	*	NO	*	*	*	*	*	NO	*	Good	Good	Good	Good	6
Pereira et al	*	NO	*	*	*	*	*	NO	NO	Good	Good	Fair	Fair	6
Romero-Duarte et al	*	NO	*	*	*	NO	*	NO	NO	Good	Fair	Fair	Fair	5
Graham et al	*	NO	*	*	*	*	*	*	*	Good	Good	Good	Good	7
Trinkmann et al	*	*	*	*	*	*	*	*	*	Good	Good	Good	Good	7
Nguyen et al	*	NO	*	*	*	NO	*	NO	NO	Good	Fair	Fair	Fair	5
Vrillon et al	*	NO	*	*	*	*	*	*	*	Good	Good	Good	Good	7
Modi et al	*	NO	*	*	*	NO	*	NO	NO	Good	Fair	Fair	Fair	4
Pasquini et al	*	NO	*	*	*	*	*	NO	NO	Good	Good	Fair	Good	5
Boscolo-Rizzo et al	*	NO	NO	*	*	*	*	NO	NO	Fair	Good	Fair	Fair	5
Capelli et al	*	NO	*	*	NO	*	*	NO	NO	Good	Fair	Fair	Fair	4
Yvonne et al	*	*	*	*	*	*	*	*	*	Good	Good	Good	Good	7
Raman et al	*	*	*	*	*	*	*	*	*	Good	Good	Good	Good	7
Swapna Mandal et al	*	*	*	*	*	*	*	*	*	Good	Good	Good	Good	6
Woo et al	*	NO	*	*	*	*	*	*	*	Good	Good	Good	Good	6
Puntmann et al	*	NO	*	*	*	NO	*	*	*	Good	Fair	Good	Good	5
Bellan et al	*	*	*	*	*	*	*	*	*	Good	Good	Good	Good	7
Stavem et al	*	NO	*	*	*	*	*	*	*	Good	Good	Good	Good	6
Malek et al	*	NO	*	*	NO	*	*	NO	NO	Good	Fair	Fair	Fair	5
Printza et al	*	NO	*	NO	*	*	*	NO	NO	Fair	Good	Fair	Fair	4

Table 2 Characteristics of studies included in meta-analysis

First author	Publication year	Study type	Sample size	Country	Percent of women	Ethnicity	Follow-up time, months	p value
Akter	2020	Cross-sectional study	734	Bangladesh	24%	/	1	/
Huang	2021	Cohort study	1733	China	48%	/	5	/
Humphreys	2021	Qualitative study	18	UK	50%	55.6% White 16.7% White other 16.7% Asian 5.6% Black 5.6% Mixed	1	/
Simani	2021	Cross-sectional study	120	Iran	33.3%	/	6	/
Taylor	2021	Qualitative study	13	UK	84.6%	84.6% White British	/	/
Felipe	2020	Cross-sectional study	46	Brazil	54.3%	/	4	/
Hopkins	2020	Cohort study	382	UK	74.6%	/	1	Loss of smell $p < 0.001$
Petersen	2020	Cohort study	180	Faroe Islands	54.4%	/	4	/
Iqbal	2021	Cross-sectional study	158	Pakistan	55.1%	/	1	/
Poncet-Megemont	2020	Cohort study	139	France	62.6%	/	1	/
Trevisan	2021	Observational study	1618	Italy, Spain, and Norway	55%	/	6	/
Klein	2021	Cohort study	103	Israel	37.9%	/	6	/
Munro	2020	Cross-sectional study	138	UK	12.5%	/	/	/
Chopra	2020	Cohort study	488	USA	/	51.6% Black 37.3% White 11.1% other/ unknown Or 4.4% Hispanic 86.7% Non-Hispanic 9.3% Unknown	2	/
Putri	2021	Survey	109	Taiwan	44.95%	100% Asian	0.25	/
Liu	2020	Cross-sectional study	675	China	53%	/	1	/
Tenforde	2020	Cross-sectional study	292	USA	52%	34.8% White, non-Hispanic 17% Black, non-Hispanic 36.3% Hispanic 11.9% other	0.5	$p = 0.01$
Sykes	2021	Cross-sectional study	134	UK	34.3%	91% White 1.5% Black 6% Asian 1.5% Mixed/ other	4	/
Townsend	2021	Cohort study	40	Ireland	90%	/	5	/
Writing Committee for the COMEBAC Study Group, 2021 [6]	2021	Cohort study	478	France	42.1%	/	4	/
Augustin	2021	Cohort study	353	Germany	53.5%	/	7	/

Table 2 (continued)

First author	Publication year	Study type	Sample size	Country	Percent of women	Ethnicity	Follow-up time, months	p value
Duncan	2021	Survey	NA	Scotland	/	/	/	/
Osikomaiya	2021	Cohort study	274	Nigeria	33.9%	/	0.5	/
Orrù	2021	Cross-sectional study	152	Italy	/	/	3+	Insomnia $p < 0.05$ quality of life $p < 0.05$
Pujari	2021	Cross-sectional study	94	India	26.6%	/	0.5	/
Frontera	2021	Prospective study	382	USA	35%	Hispanic 15%/22% Non-Hispanic 62%/59% Prefer not to answer 23%/19%	6	/
Holmes	2021	Cohort study	27	Australia	/	/	6	/
Townsend	2020	Longitudinal study	111	Ireland	63%	/	3	/
Estiri	2021	Cohort study	57,622	USA	/	/	3–6, 6–9	/
Chevinsky	2021	Cohort study	148,892	USA	57%	40.9% White 25.2% Black 2.4% Asian 21% Hispanic 10.6% Others	1–4	/
Pereira	2021	Cohort study	38	UK	84%	BAME group 37%	7	/
Romero-Duarte Á	2021	Cross-sectional study	797	Spain	46.3%	/	6	/
Graham	2021	Cohort study	50	USA	66%	88% White, 4% Black or African American, 4% Asian, 0% American Indian or Alaskan Native, 4% Other Or Hispanic or Latino 12% Not Hispanic or Latino 88%	4	/
Trinkmann	2021	Cross-sectional study	246	Germany	56.1%	/	2	$p < 0.01$
Nguyen	2021	Cohort study	125	France	55.2%	/	7	/
Vrillon	2021	Cohort study	125	France	58.4%	/	0.7	/
Modi	2021	Qualitative study	131	USA	47%	71% White(non-Hispanic) 7% White (Hispanic) 8% Black 2% Asian 1% American Indian 8% Multiracial 4% other (Hispanic)	6	/
Pasquini	2021	Cross-sectional study	26	Italy	65.4%	/	4	/

Table 2 (continued)

First author	Publication year	Study type	Sample size	Country	Percent of women	Ethnicity	Follow-up time, months	p value
Boscolo-Rizzo	2021	Cohort study	183	Italy	54.6%	/	6	/
Capelli	2021	Cohort study	55	Italy	64%	/	8	/
Yvonne	2020	Cross-sectional study	2113	Netherlands and Belgium	85%	/	2	$p < 0.001$
Raman	2021	Cohort study	58	UK	41.4%	BAME group 22.4%	2	$p < 0.0001$ to 0.044
Swapna Mandal	2020	Cross-sectional study	384	UK	38%	38.8% British Caucasian 17.1% Other Caucasian 6.5% British Asian 10.3% Other Asian 6.8% Black British 7.6% Other black 13.9% Other ethnicity	2	$p < 0.0001$ for all symptoms
Marcel S. Woo	2020	Cross-sectional study	18	Germany	57.9%	/	3	/
Puntmann	2020	Cohort study	100	France	47%	/	2.5	/
Bellan	2021	Cohort study	238	Italy	59.7%	/	4	/
Stavem	2020	Cross-sectional study	451	Norway	56%	/	3	$p < 0.001$
Małek	2021	Cohort study	26	Poland	81%	/	1.5	/
Printza	2020	Cross-sectional study	90	Greece	41.1%	/	1	/

P value (°) P value < 0.05 represents a significant improvement in symptoms at follow-up time compared to onset

on a control and patient group, only the patient data was extracted and used. A data extraction sheet specific to the clinical question of this study was developed. This Excel spreadsheet included study type, sample size, country, characteristics, information, outcomes, duration of symptoms, and prevalence.

Risk of bias assessment

A quality assessment was performed using the Newcastle–Ottawa Scale (NOS) (Table 1) to critically appraise the literature included within the systematic review using common variables. Methodological quality and risk of bias was assessed by independent reviewers according to the NOS, which has validity for use in cohort studies [7] and the adapted version [8] for cross-sectional studies. The scale consists of eight items with three quality parameters: (i) selection, (ii) comparability, and (iii) outcome. We scored the quality of the studies (poor, fair, and good) by allocating stars to each domain as stated below:

- A *poor* quality score was allocated 0 or 1 star(s) in selection, 0 stars in comparability, and 0 or 1 star(s) in the outcomes domain
- A *fair* quality score was awarded, 2 stars in selection, 1 or 2 stars in comparability, and 2 or 3 stars in outcomes.
- A *good* quality score was awarded, 3 or 4 stars in selection, 1 or 2 in comparability, and 2 or 3 stars in outcomes [7].

Data analysis

A random-effects model with an inverse variance method was used for the meta-analysis and the heterogeneity was assessed by I^2 . A subgroup analysis was conducted in terms of study geographical location on the symptoms that were reported in more than 10 studies. Sensitivity analysis was used to test the robustness of the results. Funnel plots and Egger's tests for symptoms with more than 10 studies would

be analyzed to detect publication bias. All data analysis will be carried out using R and STATA 15.

Results

Of the 302 studies identified, 49 met the inclusion criteria. 36 studies were included in the final meta-analysis. This was reported within the PRISMA document as demonstrated in Fig. 1.

The 36 studies included comprised of a total sample size of 11,598 people. Of the 36, 50% were cohort studies and the remainder cross-sectional. The longest follow-up time among the 36 studies was 8 months, although the most common follow-up time was 4 months. The 36 studies covered multiple geographical locations, where 19 countries reported five primary classifications of symptomatology of general clinical, neurological, neuropsychiatry, and cardiopulmonary. Primary clinical features within these categories included fatigue, cognitive impairment, joint pain, anxiety, and depression. These appear to align with the present understanding of LC symptomatology. Study-based characteristics and outcomes are demonstrated in Table 2.

Meta-analysis

The meta-analysis included 36 studies, which are summarized in Fig. 2.

Categorization

General symptoms

General symptoms included those associated with pain (such as general pain, muscle or joint pain, and mobility dysfunction), fatigue, fever, hair fall, skin rash, and weight loss. The pooled prevalence of the general problem was 14.4% with a 95%CI of 11.63% to 17.81%. A forest plot for general symptoms is shown in Fig. 3.

Fatigue was the most frequently reported symptom within the general problem category. Twenty-one of the 36 studies reported fatigue symptoms and the pooled prevalence of fatigue was 29.2% with a 95%CI of 21.59% to 39.45%. Muscle pain was the second most prevalent symptom reported among the 13 studies, which led to a pooled prevalence of 13.30% with a 95%CI of 7.48% to 23.67%. However, the prevalence rate of muscle pain is not as high as some of the other symptoms associated within the generalized category.

The pooled prevalence of joint pain and hair fall were 28.25% (95%CI 14.76% to 54.05%) and 20.29% (95%CI 10.56% to 38.98%) respectively. It appears that the prevalence of these two symptoms were high, but only a few studies mentioned these in comparison to those reporting fatigue and muscle pain. Therefore, it is worth standardizing these variables across all studies to manage a better understanding of the clinical relevance.

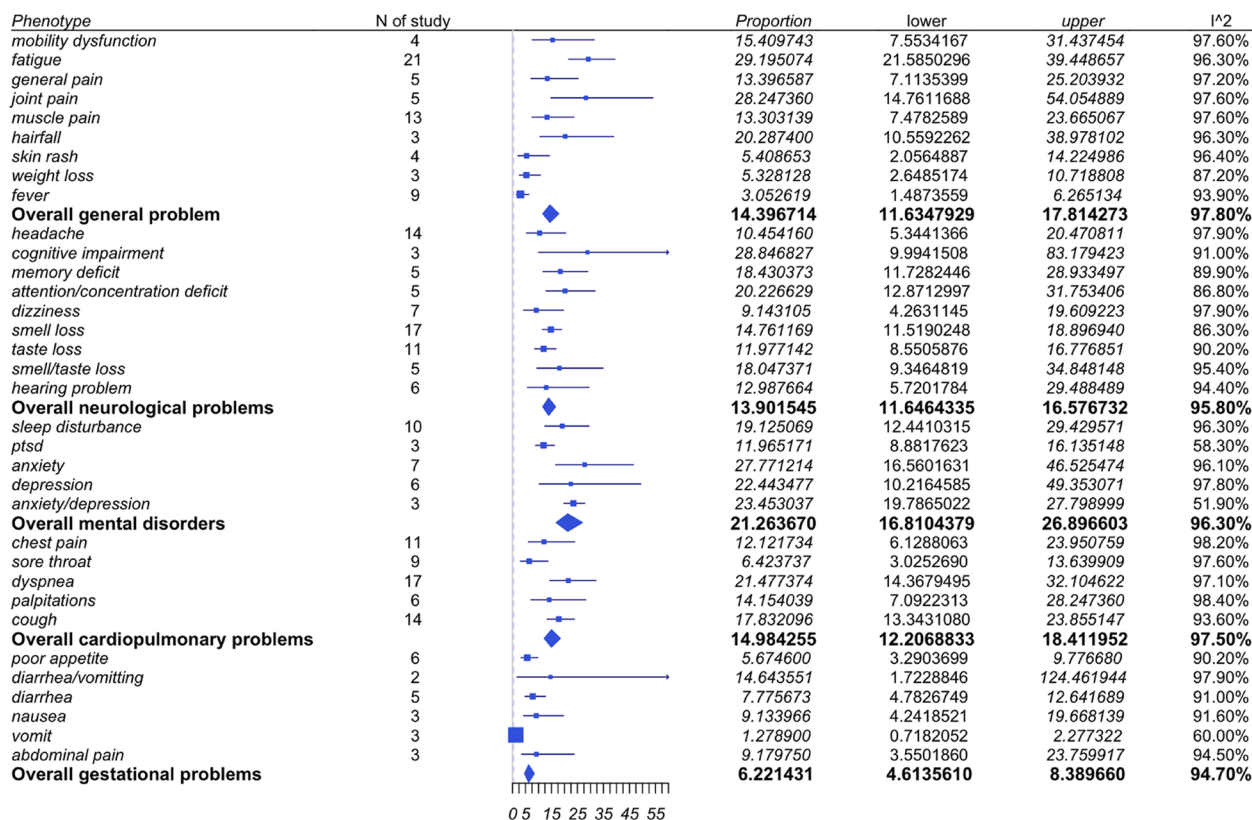


Fig. 2 Summary of studies included in meta-analysis

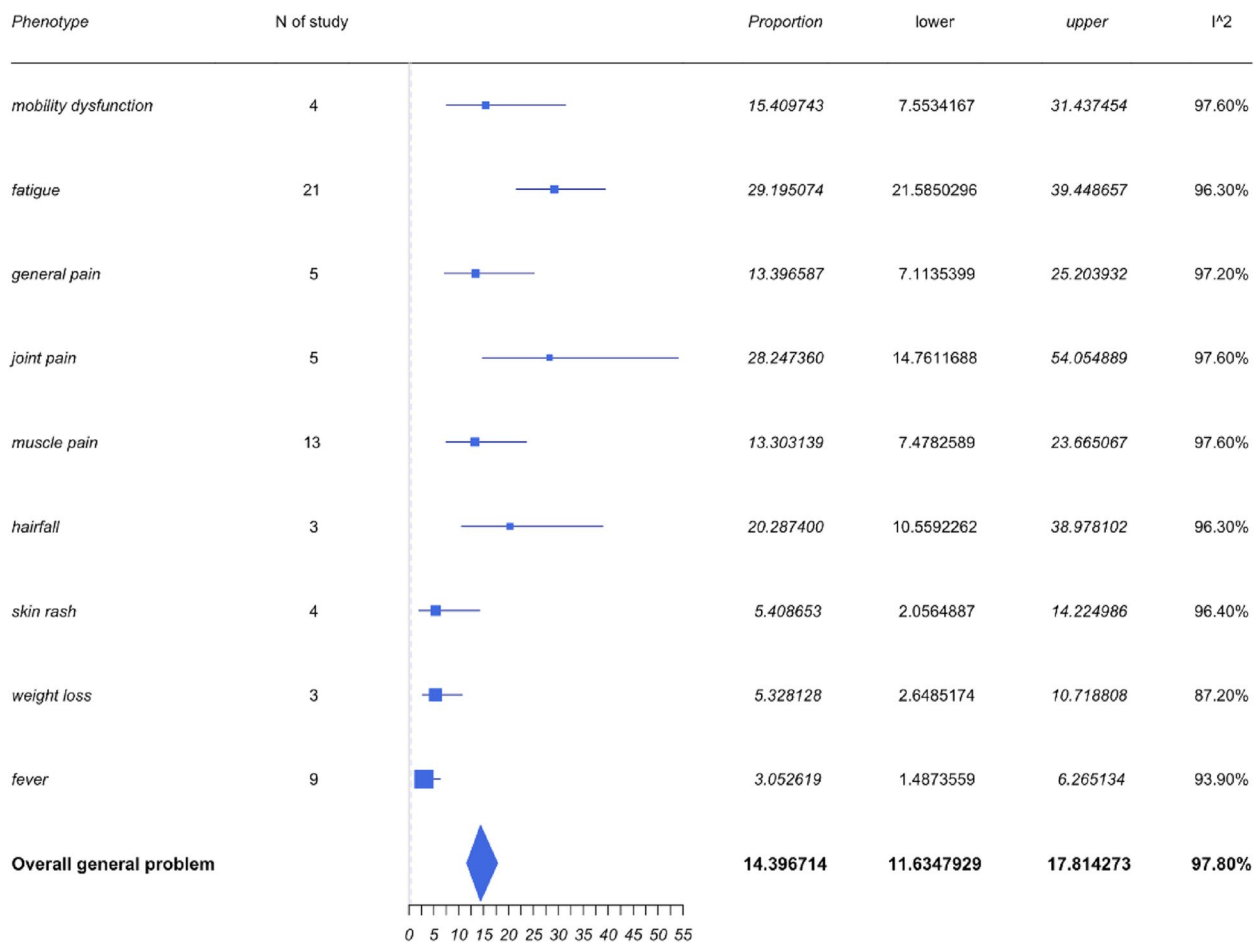


Fig. 3 Forest plots for general symptoms

Neurological symptoms

The neurological symptoms included headache, cognitive impairment, and loss of smell, taste, and hearing. As shown in Fig. 4, the most frequently reported neurological problems were loss of smell and taste, and headache. The pooled prevalence for loss of smell or taste and both taste and smell as well as headaches were 14.76%, 11.98%, 18.05%, and 10.45% respectively. However, the most prevalent neurological symptom reported appears to be cognitive impairment with a pooled prevalence of 28.85% with a 95%CI of 9.99% to 83.18%. The 95% CI is wide, and the identified heterogeneity based on I^2 was 91%. Despite the high heterogeneity, only 3 studies mentioned the symptoms of cognitive impairment. Further studies and improved sampling would be required to demonstrate a more precise statistical conclusion in regard to cognitive impairment and LC.

Mental health symptoms

Four symptoms, and mental health (MH) symptoms including depression, anxiety, PTSD, and sleep

disturbances, were reported within the neuropsychiatry category. The pooled results can be found in Fig. 5. The collective prevalence of MH symptoms was 21.26% (95%CI 16.81 to 26.9%), while each symptom independently also demonstrated a high prevalence. Anxiety prevalence was identified to be 27.77% with a 95%CI of 16.56 to 46.53%, while the prevalence of depression was 22.44% (95%CI 10.22 to 49.35%). The pooled prevalence of studies reporting patients with both anxiety and depression was 23.45% (95%CI 19.79 to 27.8%). The prevalence of sleep disturbance was identified to be 19.13% with a 95%CI of 12.44 to 29.43%. This is an important facet to demonstrate given that there is a large number of studies demonstrating depression and anxiety to be the most commonly reported MH outcomes among SARS-CoV-2 patients.

Cardiopulmonary symptoms

LC patients demonstrated cardiopulmonary symptoms with 5 commonly reported issues of chest pain, sore throat, dyspnea, palpitations, and cough. As can be seen from

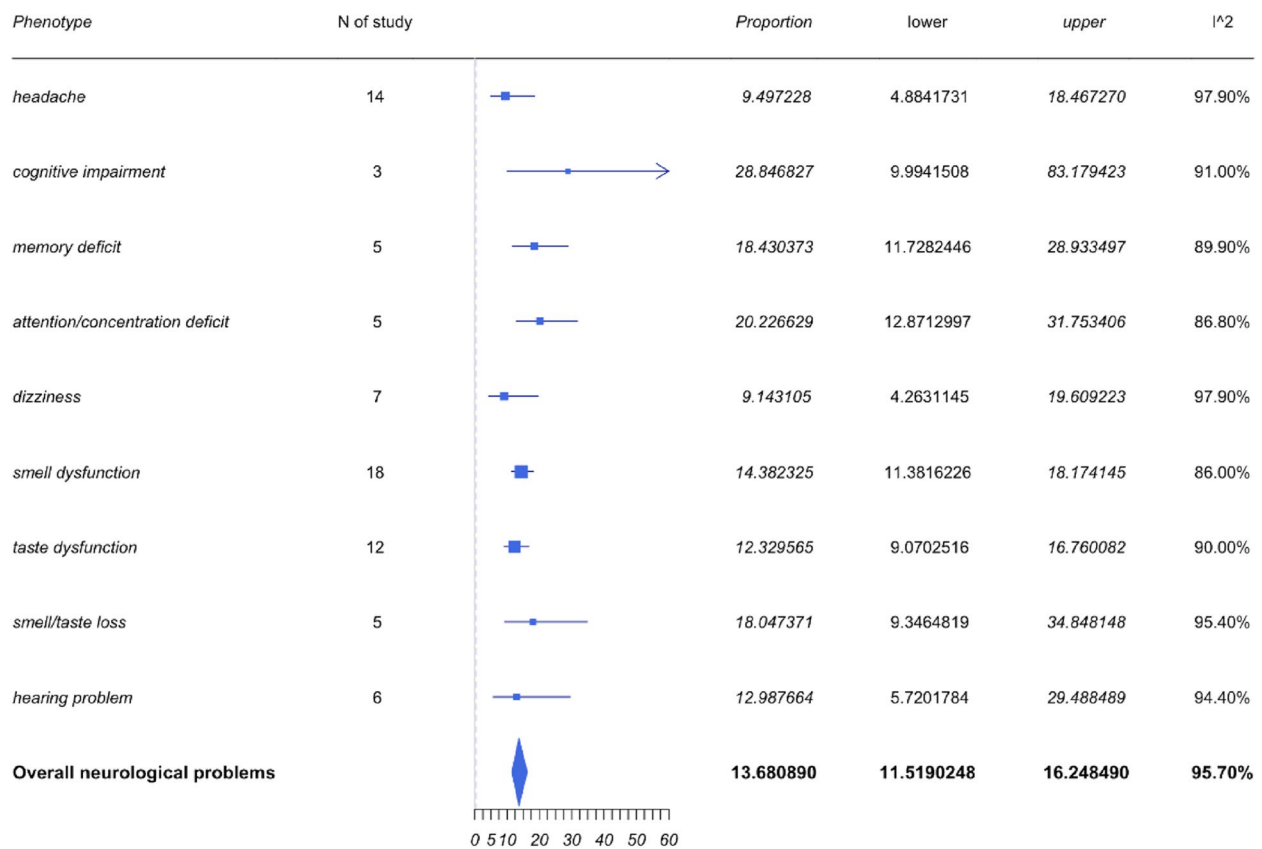


Fig. 4 Forest plots for neurological symptoms

Fig. 6, dyspnea appeared to have the highest prevalence with 17 of 36 studies reporting it as a primary end point. The pooled prevalence was therefore 21.48% with a 95%CI of 14.37 to 21.2%. Cough was the second most commonly reported symptom across 14 of 36 studies. The pooled prevalence was 17.83% with a 95%CI of 13.34 to 23.86%.

Gastrointestinal symptoms

The overall prevalence of gastrointestinal problems, as shown in Fig. 7, was 6.22% with a 95%CI of 4.61 to 8.39% and is comparatively minimal to the other categorical symptoms identified. Commonly reported symptoms reported in this category were poor appetite, diarrhea and emesis, diarrhea or emesis, nausea, and abdominal pain. Diarrhea and emesis had the highest prevalence of 14.64% with a 95%CI of 1.72 to 24.46%. Studies about diarrhea/emesis were too small. Only two studies mentioned diarrhea and emesis, which also indicated a high heterogeneity with an $I^2=97.9\%$.

Subgroup analysis

A subgroup analysis was conducted based on geographical regions correlated with the 8 symptoms of fatigue, headache, cough, loss of smell and taste, dyspnoea, chest, and muscle pain (see Fig. 8).

High prevalence of each symptom was reported by the studies from North America (mainly USA), followed by the Middle East and Australia. Most of the symptoms had a lower prevalence in Africa and Asia. Due to the small number of studies in the subgroup, the conclusions may have bias; for this reason, data from one subgroup was of concern to us. Ten studies from Europe reported dyspnoea in this subgroup and the pooled prevalence of this subgroup was 30.87% with 95%CI of 20.18 to 41.55%, which was the second highest prevalence among different regions. This suggested that dyspnoea was a highly prevalent symptom in European countries and should be addressed by the healthcare system to improve post-discharge care.

Funnel plots of the eight symptoms identified were reported in Fig. 9. It is apparent, based on the funnel plots, there is the presence of high heterogeneity. Many studies were outside the scope of 95% CI, so it was difficult to intuitively detect the bias. Therefore, Egger’s test was used to determine publication bias.

Sensitivity analysis

Many studies were outside the 95% confidence interval as demonstrated within the funnel plots, which could

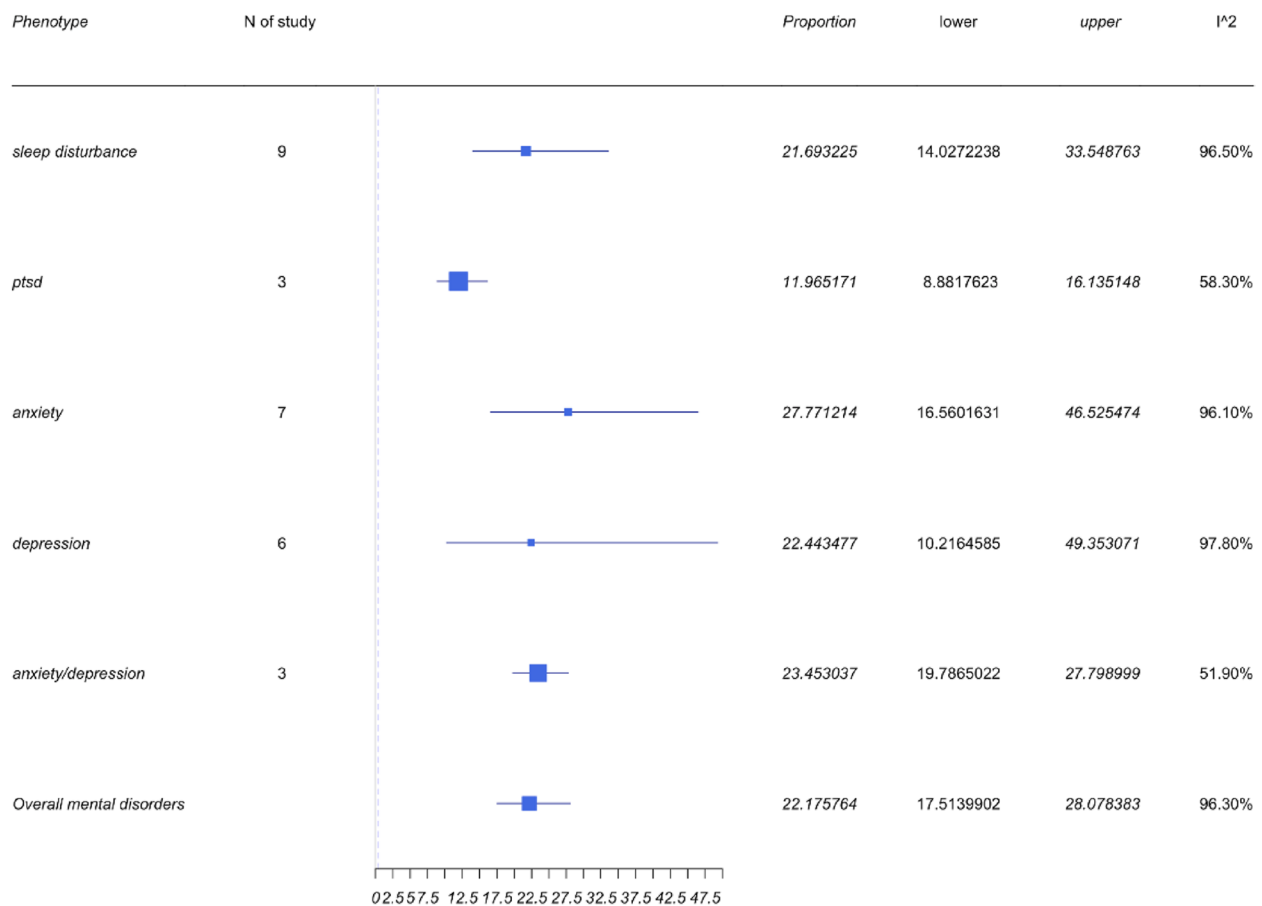


Fig. 5 Forest plots for mental health symptoms

impact the overall conclusions of this study. Therefore, a sensitivity analysis was conducted to determine the consensus of the overall conclusion of the study. A Copas selection model was used [9, 10] to adjust the pooled prevalence, as demonstrated in Table 3.

In Table 3, the proportion of selected studies varied, and the changes in the *P* value of the residual selection bias are depicted in Fig. 10 (1–8). The Copas model (CSM) was used to determine bias within studies based on *P* values exceeding 0.1. The proportion of studies used within the CSM are listed within Table 3. It is evident the CSM selected 49.55% studies with headache as a symptom, while the remaining 50.45% indicated a significant standard error, demonstrating poor quality and high heterogeneity, thus were excluded.

The result from the CSM was compared to a random effects model (REM), indicating *P* values exceeding 0.05, which demonstrates a lack of statistical significance. Therefore, the results of this study are consistent and provide robust conclusions.

Publication bias

Egger’s test was used to determine publication bias. The *P* values were calculated based on Egger’s test.

As shown in Table 4, studies reporting symptoms of headache and dyspnea have significant bias, with *P* values of 0.022 and 0.007 respectively. Therefore, the pooled prevalence of headache and dyspnea were 9.5% and 21.48%. In Fig. 9(2) and (3), the prevalence of headache and dyspnea may have been underestimated, and more studies should be found to further confirm the conclusions.

Limitations

There are strengths and weaknesses to our study given that comparing patients with maximum symptoms risks bias reporting. Studies that reported on neuropsychiatry symptoms of depression and anxiety, for example, did not demonstrate a clinical diagnosis. The identified and reported features cannot be deemed to

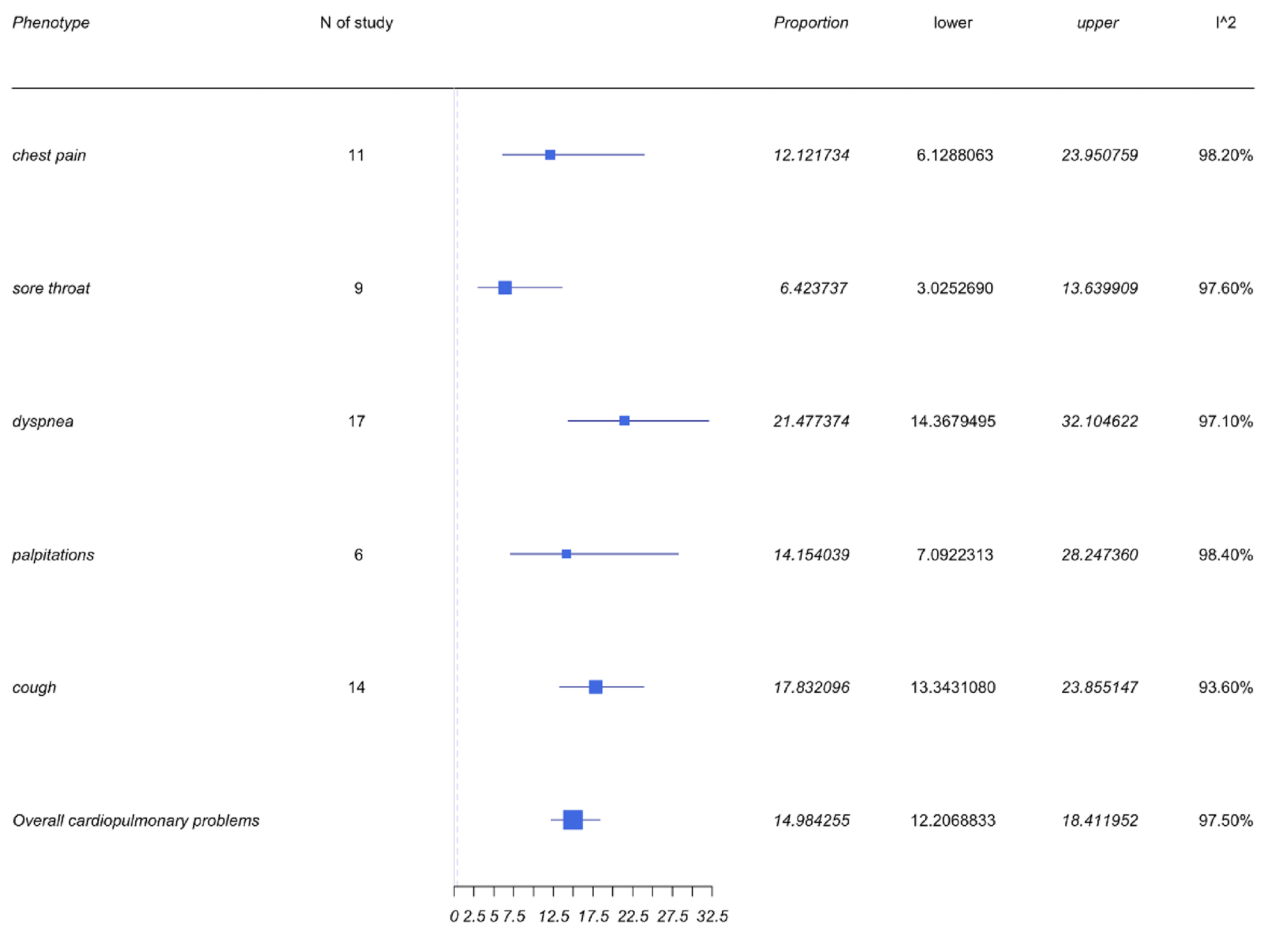


Fig. 6 Forest plots for cardiopulmonary symptoms

be LC as these patients could have underlying conditions that may not have been reported. Patients who may have had critical respiratory illness, for example, may have been part of these studies, but this data was not captured within the original peer-reviewed publications. This would influence the analysis conducted within our study; therefore, an underrepresentation and/or overrepresentation of some of these symptoms is a point to consider.

Discussion

This meta-analysis demonstrates the most recent studies identified with possible long COVID symptoms. The pooled data indicate both self-reported and clinically reported symptoms. This initial step is vital to design and develop comprehensive research in the future, especially since SARS-CoV-2 appears to be reporting a varying degree of symptoms.

The evidence identified demonstrates that long COVID appears to have multiple symptoms, without clear aetiology similar to fibromyalgia and chronic fatigue syndrome. The aforementioned conditions also have an association with postviral illness which appear to last longer than previously anticipated. As a result, healthcare systems endeavour challenges with draining resources and souring costs in addition to wellbeing concerns for staff. Another direct result of long COVID disease will be the added burden on waiting times for patients requiring other clinical care and elective procedures created by the pandemic.

The population prevalence of long COVID identified here could be used to determine symptom-based models to evaluate the requirement for healthcare system resources, and possible disease sequelae which may require care. Presently, instituting effective therapies is based upon present clinical knowledge than

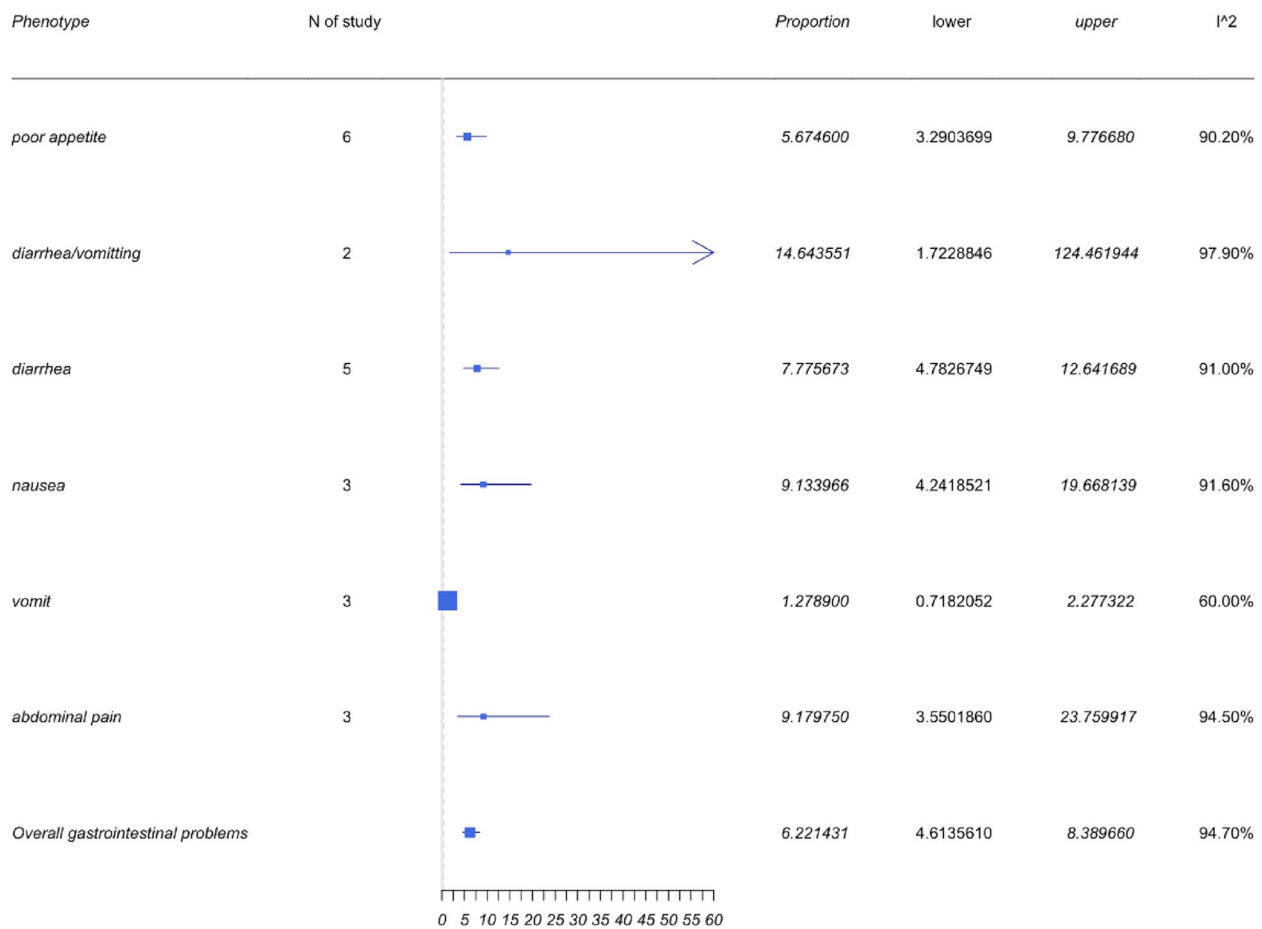


Fig. 7 Forest plots for gastrointestinal symptoms

evidence-based practices. Repurposing drugs is another common theme among clinicians, and these raise concerns around long COVID potentially becoming a chronic condition in the near future, especially for patients who had significant issues with COVID. With a growing number of variants of SARS-Cov-2 virus, this further exacerbates the present unknowns of managing these patients in an optimal manner. However, this meta-analysis does provide an opportunity to plan early intervention strategies and target therapies in the future.

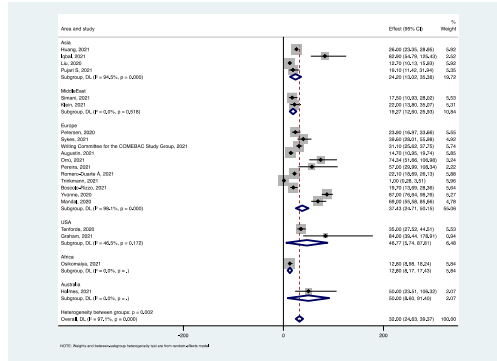
As it is an evolving pathology, further studies are being reported and published swiftly, which has its own challenges. Therefore, to consistently report the latest evidence, there is a requirement for a *living systematic review and meta-analysis* as well as better methodologies should be developed. It is interesting to note that developed countries appear to have a higher incidence of long COVID based on the geographical data identified within this study. There is a possibility of over- and under

reporting, as well as validation of self-reported data. The lack of accurate validated measurements for reported long COVID symptoms similar to other fundamental clinical measures such as blood pressure and temperature causes further problems.

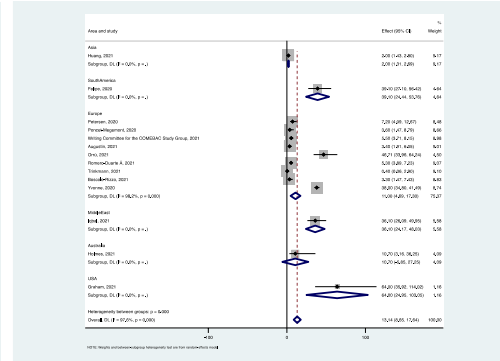
In addition to these factors, ethical and moral implications to patients, the public, and healthcare professionals continue to augment debates as the pandemic has forced all stakeholders to rethink access to healthcare and treatment.

It is evident from this study that there are post-COVID symptoms that patients continue to report. It might be beneficial to reduce the severity of the disease. A useful method to reduce these of course would be to increase the vaccination program outputs globally. With mass migration also attributed to the spread of COVID-19, an important facet to consider would be to understand the barriers and potential issues around vaccine acceptability, especially for those returning to work or their education in countries of residence.

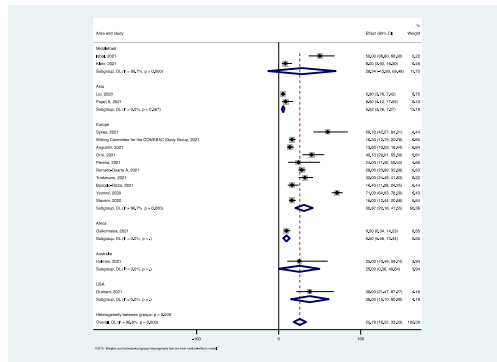
(1) Fatigue



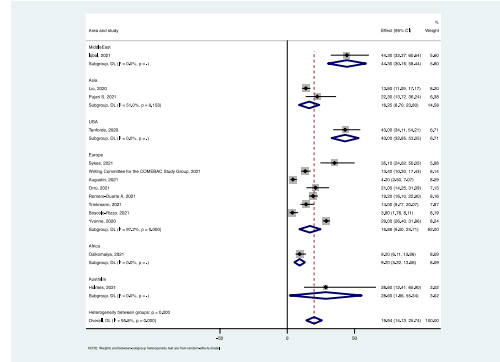
(2) Headache



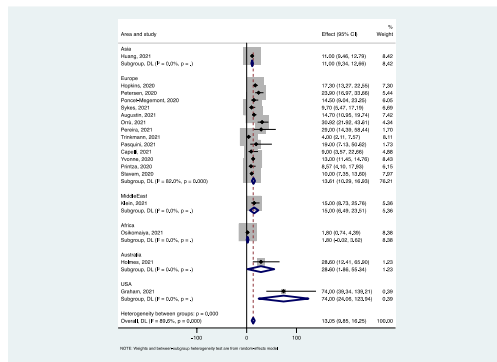
(3) Dyspnea



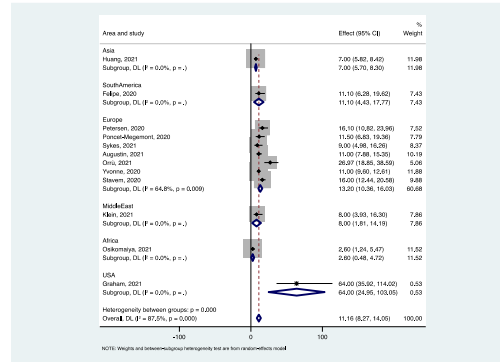
(4) Cough



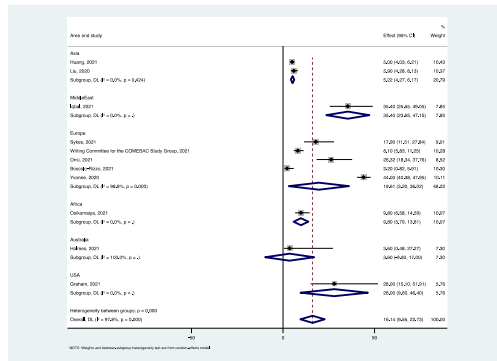
(5) Smell dysfunction



(6) Taste dysfunction



(7) Chest pain



(8) Muscle pain

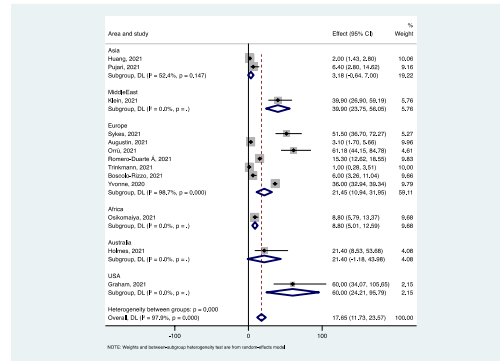
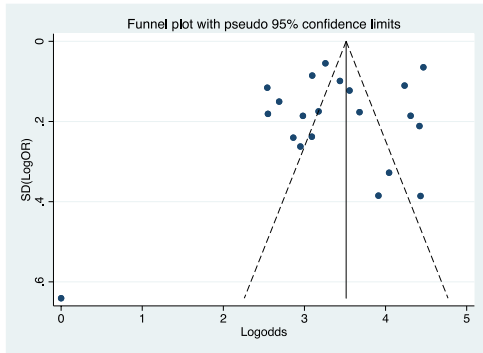
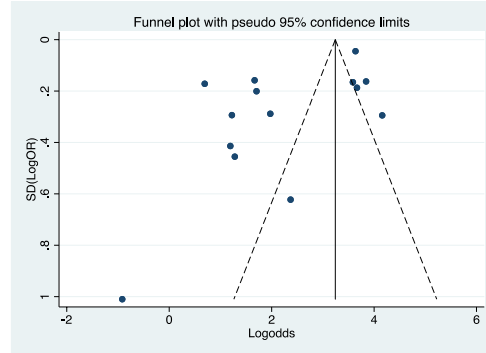


Fig. 8 Forest plots of subgroup analysis

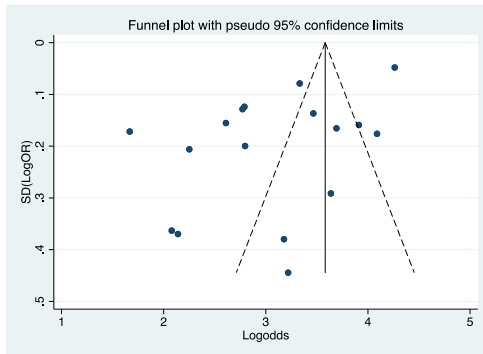
(1) Fatigue



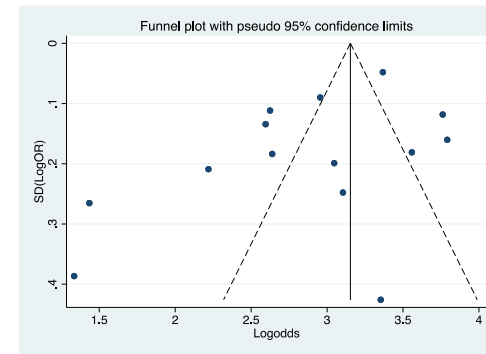
(2) Headache



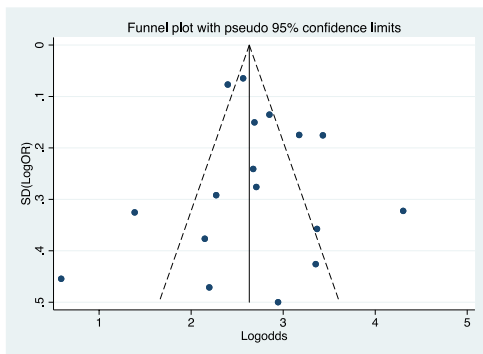
(3) Dyspnea



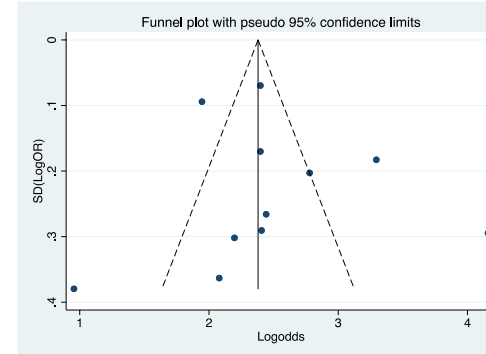
(4) Cough



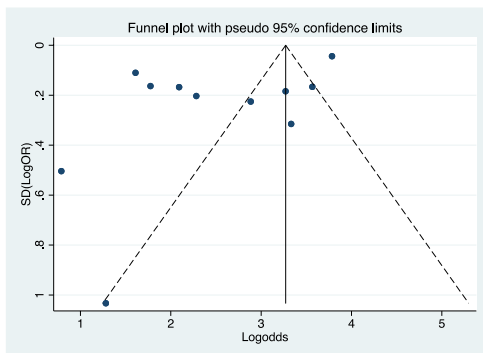
(5) Smell dysfunction



(6) Taste dysfunction



(7) Chest pain



(8) Muscle pain

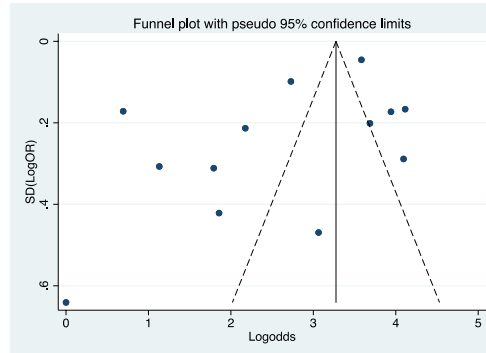


Fig. 9 Funnel plots of eight symptoms (reported in more than 10 studies)

Table 3 Summarized results of sensitivity analysis

Phenotype	N of study	Model	Probability of publishing study with largest standard error	Proportion(%)	Lower(%)	Upper(%)	p value for differences between two conclusions
Headache	14	Copas selection model	49.55%	13.4637	10.0332	18.0672	0.1135
		Random effects model		9.4972	4.8842	18.4673	
Smell dysfunction	18	Copas selection model	100.00%	14.1682	10.1188	19.8380	0.5006
		Random effects model		14.3823	11.3816	18.1741	
Taste dysfunction	12	Copas selection model	100.00%	12.2338	8.2962	18.0402	0.5495
		Random effects model		12.3296	9.0703	16.7601	
Chest pain	11	Copas selection model	100.00%	12.4236	7.2232	21.3681	0.103
		Random effects model		12.1217	6.1288	23.9508	
Dyspnea	17	Copas selection model	100.00%	21.5591	15.1515	30.6797	0.1819
		Random effects model		21.4774	14.368	32.1046	
Cough	14	Copas selection model	91.11%	18.176	12.8109	25.7852	0.1238
		Random effects model		17.8321	13.3431	23.8551	
Fatigue	21	Copas selection model	92.46%	29.1951	21.5850	39.4487	0.1478
		Random effects model		28.9161	20.3158	41.1531	
Muscle pain	13	Copas selection model	67.65%	15.6426	9.1963	26.6103	0.1038
		Random effects model		13.3031	7.4783	23.6651	

The COVAX Facility is an international collaborative effort shared between the Coalition for Epidemic Preparedness Innovations (CEPI), the Global Alliance for Vaccines and immunizations (GAVI), the World Health Organization, supporting governments and international organizations [11]. The COVAX Facility is meant to facilitate the development and production of diagnostics, therapeutics, and vaccines to combat the COVID-19 pandemic and to make them accessible to LMIC governments [12, 13]. The COVAX Facility does not have a legal entity, therefore cannot enter into binding agreements, and relies upon agreements between its constituent partners (e.g., GAVI, WHO) procuring government, and the vaccine manufacturers [14]. Therefore, the law of contract governs access to vaccines, data related to vaccine procurement and distribution, and related matters.

Similarly, sharing of data to better assess the mental and physical health sequelae has been hampered by the lack of an international coordinating mechanism to do so or a uniform set of guidelines that governments, public health officials, private companies, and others may use to share such data [15]. As a result, COVID data related to incidence, disease burden, and long COVID as well as a potential disease sequelae may not be fully understood by the global healthcare community. This is a particular

a problem for assessing both COVID and long COVID syndrome impact on differing ethnicities, age groups, and overall health status. Even within academic and clinical research, only open access publications provide insight into evidence.

The justification of resources being reallocated to non-life-threatening sequelae of long COVID could be a contentious topic. This further raises legal implications for policymakers.

The research on nociplastic and immunological explanations for pain symptoms could throw more light in future on the development of pain with long COVID. Genetic studies may also throw some light into the development of long-standing chronic pain or even long COVID, although this requires bio-sampling at a high frequency. The role of nutritional status and activity levels also needs to be established and its association with long COVID needs further study.

Conclusions

A key finding of this study is that the speed at which SARS-CoV-2 research is being conducted has meant epistemic authority consolidates around particular clinical areas. Therefore, it is vital to synthesise the evidence without any background noise. However, as demonstrated in this study, the gathering of LC data

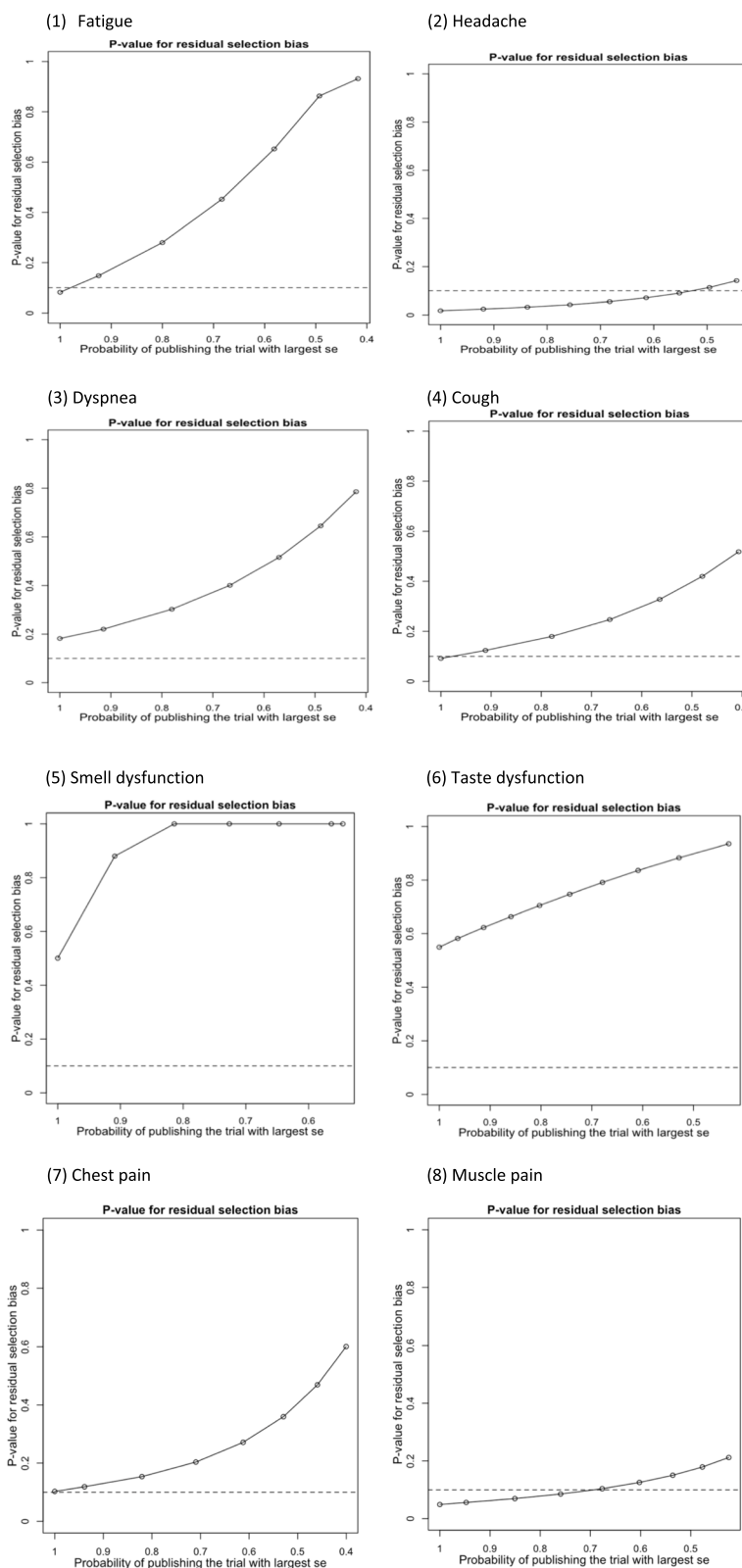


Fig. 10 P values for residual selection bias

Table 4 Summarized *P* values of Egger's tests for symptoms with more than 10 studies

Phenotype	Number of studies	<i>P</i> value of Egger's test
General problems		
Fatigue	21	0.14
Muscle pain	13	0.093
Neurological problems		
Smell loss	18	0.616
Taste loss	12	0.517
Headache	14	0.022*
Cardiopulmonary problems		
Chest pain	11	0.048
Dyspnea	17	0.007*
Cough	14	0.085

* $p < 0.05$ indicates significance

has been limited. The identified data could be associated with autonomic dysfunction, although to confirm this, further investigations would be required. Mapping LC outcomes would be a long-term commitment; therefore, future systematic reviews and meta-analysis should be reported in a *living* format, combining both clinical and research data to allow a more comprehensive synthesis of evidence with a view to using surveillance data.

Abbreviations

CI	Confidence interval
CSM	Copas selection model
GAVI	Global Alliance for Vaccines and Immunizations
LC	Long COVID
MH	Mental health
NOS	Newcastle-Ottawa Scale
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analysis
REM	Random effects model
WHO	World Health Organization

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Authors' contributions

PP and GD developed study design and GD wrote the first draft of the manuscript. AN conducted database searches and study selection and data extraction. YZ, JQS, and GD performed statistical analyses and contributed to the "Results" section. AN, AS, GD, YE, YZ, DK, VR, SR, SH, KE, JQS, and PP critically reviewed and revised the manuscript. All authors read and approved the final version of the manuscript.

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Availability of data and materials

All data used within this study have been publicly available. The authors will consider sharing the dataset gathered upon request.

Declarations

Ethics approval and consent to participate

Not applicable

Consent for publication

Not applicable

Competing interests

PP has received a research grant from Novo Nordisk, and the other, educational from Queen Mary University of London, from John Wiley & Sons, and other from Otsuka, outside the submitted work. SR reports research funding associated with other studies from Janssen, Otsuka, and Lundbeck. AS reports funding associated with other projects from Medtronic. GD reports research funding associated with NIHR RCF. VR reports funding associated with other studies from the Medical Research Council. This research is based on evidence gathered systematically and has not been influenced unduly by expertise. All other authors declare that they have no competing interests.

The views expressed are those of the authors and not necessarily those of the NHS, the National Institute for Health Research, Department of Health and Social Care or Academic institutions.

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