Journal of Infection 88 (2024) 77–88

Contents lists available at ScienceDirect

Journal of Infection

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

Review

Persistence of post-COVID symptoms in the general population two years after SARS-CoV-2 infection: A systematic review and meta-analysis

Cesar Fernandez-de-las-Peñas [a,*], Kin Israel Notarte [b], Raymart Macasaet [c], Jacqueline Veronica Velasco [d], Jesus Alfonso Catahay [e], Abbygail Therese Ver [d], William Chung [b], Juan A. Valera-Calero [f], Marcos Navarro-Santana [f]

[a] Department of Physical Therapy, Occupational Therapy, Physical Medicine and Rehabilitation, Universidad Rey Juan Carlos, 28922 Madrid, Spain
[b] Department of Pathology, Johns Hopkins University School of Medicine, Baltimore, MD 21205, USA
[c] Department of Medicine, Monmouth Medical Center, Long Branch, NJ 07740, USA
[d] Faculty of Medicine and Surgery, University of Santo Tomas, Manila 1008, Philippines
[e] Department of Medicine, Saint Peter's University Hospital, New Brunswick, NJ 08901, USA
[f] Department of Radiology, Rehabilitation and Physiotherapy, Universidad Complutense de Madrid (UCM), Madrid, Spain

ARTICLE INFO

Article history:
Accepted 8 December 2023
Available online 13 December 2023

Keywords:
Post-COVID
Symptoms
Fatigue
Meta-analysis
Prevalence
Years

SUMMARY

Objective: This meta-analysis investigated the prevalence of post-COVID symptoms two-years after SARS-CoV-2 infection.
Methods: Electronic literature searches on PubMed, MEDLINE, CINAHL, EMBASE, Web of Science databases, and on medRxiv/bioRxiv preprint servers were conducted up to October 1, 2023. Studies reporting data on post-COVID symptoms at two-years after infection were included. Methodological quality was assessed using the Newcastle-Ottawa Scale. Random-effects models were used for meta-analytical pooled prevalence of each symptom.
Results: From 742 studies identified, twelve met inclusion criteria. The sample included 7912 COVID-19 survivors (50.7% female; age: 59.5, SD: 16.3). Post-COVID symptoms were assessed at a follow-up of 722.9 (SD: 51.5) days after. The overall methodological quality of studies was moderate (mean: 6/10, SD: 1.2 points). The most prevalent post-COVID symptoms two-years after SARS-CoV-2 infection were fatigue (28.0%, 95%CI 12.0–47.0), cognitive impairments (27.6%, 95%CI 12.6–45.8), and pain (8.4%, 95%CI 4.9–12.8). Psychological disturbances such as anxiety (13.4%, 95%CI 6.3–22.5) and depressive (18.0%, 95%CI 4.8–36.7) levels as well as sleep problems (20.9%, 95%CI 5.25–43.25) were also prevalent. Pooled data showed high heterogeneity ($I^2 \geq 75\%$).
Conclusion: This meta-analysis shows the presence of post-COVID symptoms in 30% of patients two-years after COVID-19. Fatigue, cognitive disorders, and pain were the most prevalent post-COVID symptoms. Psychological disturbances as well as sleep problems were still present two-years after COVID-19.

Introduction

The world has grappled with a devastating crisis triggered by the global spread of the coronavirus disease COVID-19 caused by the Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2). In the three years since the pandemic's inception, the continuous emergence of multiple SARS-CoV-2 variants has sustained its unrelenting spread, leading to an astonishing 768 million confirmed cases and almost 7 million associated fatalities worldwide.[1] While substantial efforts are being made to better understand the disease pathophysiology and the management of acute cases, a growing concern is the prevalence of long-lasting symptoms. The presence of symptoms following an acute SARS-CoV-2 infection has been called long-COVID[2] or post-COVID-19 condition.[3] Although there are different definitions, post-COVID-19 condition is defined as follows: "Post-COVID-19 condition occurs in people with a history of probable or confirmed SARS-CoV-2 infection, usually three months from the onset of COVID-19 with symptoms that last for at least two months and cannot be explained by an alternative medical diagnosis."[3]

* Correspondence to: Facultad de Ciencias de la Salud, Universidad Rey Juan Carlos, Avenida de Atenas s/n, 28922 Alcorcón, Madrid, Spain.
E-mail address: cesar.fernandez@urjc.es (C. Fernandez-de-las-Peñas).

https://doi.org/10.1016/j.jinf.2023.12.004

More than 100 post-COVID symptoms have been described at the beginning of the pandemic.[4] Several reviews and meta-analyses investigating the prevalence of post-COVID symptoms have been published; however, most of them included follow-up periods less than six months after SARS-CoV-2 infection.[5–10] Thus, the Global Burden of Disease Long COVID study which included 1.2 million subjects who experienced an acute symptomatic SARS-CoV-2 infection, reported that 51% of COVID-19 survivors suffered from at least one post-COVID symptom the first three months after infection and that to up to 15.1% of subjects still experienced symptoms 12 months after.[11]

With increasing evidence three years after the pandemic, a small number of meta-analyses have included studies with follow-up periods up to one-year after the infection.[12,13] A recent meta-analysis reported that 41.7% of COVID-19 survivors still experienced neurological, physical, or psychological post-COVID sequelae two-years after.[14] This meta-analysis found that fatigue (27.4%), sleep disorders (25.1%), and dyspnea (10.1%) were the post-COVID symptoms more prevalent 2-years after an acute SARS-CoV-2 infection.[14] However, this review included studies investigating post-COVID symptoms not associated with tissue damage and post-COVID sequalae associated with tissue damage.[14] Additionally, this review also pooled post-COVID data of vulnerable populations, e.g., individuals with pulmonary tuberculosis, which could lead to an overestimation of prevalence in specific symptoms.

Therefore, the objective of this study is to conduct a systematic review and meta-analysis of prevalent post-COVID symptoms in the general population two-years after a SARS-CoV-2 infection.

Methods

A systematic review and meta-analysis investigating the prevalence of post-COVID symptoms two-years after an acute SARS-CoV-2 infection according to the 2020 Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) statement was conducted.[15] The review was prospectively registered in Open Science Framework (OSF) database (https://osf.io/jwz7b).

Literature search

Electronic literature searches on PubMed, MEDLINE, CINAHL, EMBASE, Web of Science databases, and on medRxiv/bioRxiv preprint servers were conducted for published studies until October 1, 2023 by two different authors using the following terms: “long-COVID” OR “post-acute COVID-19 syndrome” OR “post-COVID-19 condition” OR “post-COVID symptom” AND “incidence” OR “prevalence” OR “outcomes” AND “two years” OR “2 years” OR “2-year.” Reference list of the published papers was also screened to identify other studies. Table 1 details the combinations of these search terms using Boolean operators on each database.

Selection criteria

The inclusion and exclusion criteria were described according to the Population, Intervention, Comparison and Outcome (PICO) principle:

Population: Adults (no vulnerable populations) with probable or confirmed infection by SARS-CoV-2. Subjects included both hospitalized and non-hospitalized patients from the general population.

Intervention: Not applicable.

Comparison: Not applicable.

Outcome: Collection of post-COVID symptoms developed after an acute SARS-CoV-2 infection by personal, telephone or electronic interview at a follow-up period closed to two-years after the infection. All post-COVID symptoms e.g., fatigue, dyspnea, pain, brain fog, skin rashes, memory loss, palpitations, cough, anxiety, depression, or sleep problems were considered. All studies were included independently of the definition used for post-COVID-19 condition. Studies monitoring changes in immunological, serological or radiological outcomes without assessing post-COVID symptoms were excluded. In addition, studies investigating post-COVID sequela e.g., organ damage or lung volumes, and not post-COVID symptomatology were also excluded.

Table 1
Database formulas during literature search.

PubMed Search Formula
#1 "post-acute COVID-19 syndrome" [MeSH Terms] OR "long-COVID" [All Fields] OR "long-COVID symptoms" [All Fields] OR "long hauler" [All Fields] OR "post-COVID-19" [All Fields] OR "post-acute COVID-19 symptoms" [All Fields] OR "COVID-19 sequelae" [All Fields]
#2 "epidemiology"[All Fields] OR "prevalence"[All Fields] OR "incidence"[All Fields] OR "outcome"[All Fields]
#3 (("two"[All Fields] AND "years"[All Fields]) OR ("2"[All Fields] AND "years"[All Fields]) OR "two-year"[All Fields])
#4 #1 AND #2 AND #3
Medline / CINAHL (via EBSCO) Search Formula
#1 (post-acute COVID-19 syndrome) OR (long-COVID) OR (long-COVID symptoms) OR (long hauler) OR (post-COVID-19) OR (post-acute COVID-19 symptoms) OR (COVID-19 sequelae)
#2 (incidence) OR (prevalence) OR (outcomes)
#3 (two years) OR (2 years) OR (2-year)
#4 #1 AND #2 AND #3
EMBASE Search Formula
(post-acute COVID-19 syndrome) OR (long-COVID) OR (long-COVID symptoms) OR (long hauler) OR (post-COVID-19) OR (post-acute COVID-19 symptoms) OR (COVID-19 sequelae) AND (incidence) OR (prevalence) OR (outcomes) AND (two years) OR (2 years) OR (2-year)

Screening process, study selection and data extraction

Observational cohorts and case-control studies where a cohort of COVID-19 survivors, either hospitalized or non-hospitalized, were reassessed for the presence of post-COVID symptoms in a follow-up period closed to two-years. Research letters and correspondences were included if they reported new data. Case studies, case series, editorials and opinion articles without data were excluded. Only human studies and full-text English language papers were considered.

The title and abstract of publications identified during the database search were screened by two independent authors. Duplicates were removed, abstracts were evaluated, and eligible articles were identified. Full text of articles were analyzed by the same two authors. Data extracted included authors, country, design, sample size, setting, age, long-COVID definition, and post-COVID symptoms at two-years after infection. Both authors needed to reach a consensus on study selection and data extraction. Disagreements at any stage of the screening process were resolved by a third independent author.

Methodological quality and risk of bias

The Newcastle-Ottawa Scale (NOS), a nine-star rating system evaluating the risk of bias and methodological quality of observational (case-control and cohort) studies, was used.[16] In cohort studies, the NOS evaluates the following items: case selection (i.e., cohort representativeness, selection of non-exposed cohort, case definition, outcome), comparability (i.e., proper control for age, sex, other factors, between-group comparisons) and exposure (i.e., outcome assessment, enough and adequate follow-up). In case-control studies, NOS items are adapted. For instance, case selection item includes adequate case definition and control selection. Thus, the methodological quality of longitudinal cohort studies or case-control studies is classified as: high quality (7-9 stars), moderate quality (5-6 starts), or low quality (< 4 stars). In cross-sectional cohort studies, a

maximum of 3 stars can be awarded: good quality (3 stars), fair quality (2 stars), or poor quality (one star). Methodological quality was evaluated by two independent authors. If there was a disagreement, a third author arbitrated the final decision.

Data synthesis and analysis

To synthesize the presence of post-COVID symptoms two-years after an acute infection, random-effects meta-analyses were performed using MetaXL software to estimate their pooled data with 95% confidence intervals (CIs) (https://www.epigear.com/index_files/metaxl.html). For quantitative data (e.g., age, days at hospital), overall means and standard deviations (SD) were calculated. When data was reported as median and interquartile range (IQR), mean and SD were calculated as described by Luo et al.[17] When necessary, data were estimated from graphs. The researchers used a random-effects model because potential heterogeneity was expected. Sample size-weighted mean scores for each study reporting data alongside 95%CI were calculated in addition to any potential meta-analytical summary effect on the pooled prevalence data for each post-COVID symptom. An $I^2 \geq 75\%$ was considered to indicate serious heterogeneity. Thus, publication bias was assessed using funnel plots with Egger weighted regression test, when a sufficient number of studies ($n \geq 10$) investigating the same post-COVID symptom was available. Grouping by hospitalization status and by gender was not possible due to the lack of data.

Results

Study selection

The electronic search identified 742 papers for review. After removing duplicates (n = 45) and papers including follow-ups shorter than two-years (n = 678), 19 papers remained. Five were excluded after abstract examination, leaving 14 articles for full-text analysis. One paper[18] was excluded since the title and abstract stated two-years but the follow-up was shorter than one-year, and another study was excluded because the data cannot be extracted.[19] Thus, 12 studies were finally included (Fig. 1).[20–31] Seven studies were conducted in European countries such as France,[26] Sweden,[25] Spain,[23] Switzerland,[21] Faroe Islands,[29] Italy,[30] and Germany.[31] Four studies were conducted in China[20,22,24,28] and one was conducted in the United States of America.[27]

Sample characteristics

The features of the sample of the included studies are summarized in Table 2. Five studies included hospitalized cohorts[20,22,24,25,28] while two studies included a cohort of non-hospitalized patients.[26,31] Two studies had two separated cohorts of hospitalized and non-hospitalized patients[23,27] in the study and the three studies mixed non-hospitalized patients with a small proportion of hospitalized patients.[21,29,30]

Most studies (n = 9) collected data by telephone interview.[20,22–27,29,30] Data collection in the remaining studies were conducted by face-to-face interview,[28] by electronical questionnaire,[21] and by postal questionnaire.[31] Although post-COVID symptoms were self-reported in all studies,[20–31] some patient-reported outcome measures (PROM) were used for collecting specific symptoms in a small number of studies. The Hospital Anxiety and Depression Scale (HADS) was used to determine anxiety and depressive levels while the Generalized Anxiety Disorder seven-item (GAD-7) scale was used to for anxiety levels alone.[24,28] Other PROM used were the Pittsburgh Sleep Quality Index (PSQI) for sleep quality,[23] British Medical Research Council for dyspnea,[24,25,28] and Checklist Individual Strength (CIS) for fatigue.[20]

Pooled calculations were conducted for the total sample because a small number of studies included only either hospitalized or non-hospitalized cohorts while others included mixed. The total sample included 7, 912 COVID-19 survivors (50.7% female; age: 59.5, SD: 16.3 years). Post-COVID symptoms were assessed at a mean follow-up period of 722.9 (SD 51.5) days after the infection. Up to 54% (95CI 30.65%-76.45%) of the sample exhibited at least one previous medical comorbidity. Hypertension (33.95%, 95%CI 25.95%-41.2%) and obesity (22.35%, 95%CI 10.65%-36.8%) were the most prevalent. The mean length of hospital stay in the hospitalized group was 14.5 days (SD 8.8) and 235 patients (3.2%) required ICU admission (mean stay: 21.2, SD: 19.4 days) (Table 3).

Methodological quality

The overall methodological quality of the studies was moderate (mean: 6, SD: 1.2 points). Three studies[22,23,28] were of high methodological quality (≥7/9 stars), eight studies[21,24–27,29–31] were of moderate quality (5-6 starts) and one[20] was of poor quality (3 stars). No disagreement between authors was observed. Table 4 summarizes the Newcastle-Ottawa Scale scores for each study and a summary of every item.

Prevalence of post-COVID symptoms two-years after

Overall, the most prevalent post-COVID symptoms two-years after an acute SARS-CoV-2 infection were fatigue (28.0%, 95% CI 12.0 to 47.0, 11 studies, Fig. 2A), cognitive problems (27.6%, 95%CI 12.6 to 45.8, 6 studies, Fig. 2B), and pain symptoms (8.4%, 95%CI 4.9 to 12.8, 11 studies, Fig. 3). In addition, psychological problems such as anxiety (13.4%, 95%CI 6.3 to 22.5, 7 studies) and depressive (18.0%, 95%CI 4.8 to 36.7, 4 studies) levels as well as sleep problems (20.9%, 95%CI 5.25 to 43.25, 4 studies) also exhibited higher pooled prevalence rates (Fig. 4). All pooled data showed high heterogeneity ($I^2 \geq 75\%$).

Post-COVID symptoms were grouped as follows: respiratory and general symptoms, neurological symptoms, gastrointestinal symptoms, pain symptoms, dermatological symptoms, and other type of post-COVID symptomatology (Table 5). The most prevalent post-COVID respiratory and general symptoms were fatigue (28.0%), runny nose (8.2%) and dyspnea (5.7%). Neurological and cognitive post-COVID symptoms showed similar pooled prevalence rate: dizziness and vertigo (6.7%), anosmia (5.25%), and ageusia (4.85%). Stomachache was the most prevalent gastrointestinal post-COVID symptom (6.7%) while headache (8.9%) and myalgia (8.1%) were the most prevalent post-COVID pain symptoms. The pooled prevalence of hair loss as the most prevalent dermatological post-COVID symptom was 7.35% (Table 5). All pooled data showed high heterogeneity ($I^2 \geq 75\%$).

Other post-COVID symptoms, e.g., chronic constipation, flatulence, blue lips, edema, ear pain, were just assessed in one study and pooled prevalence data was not possible.

Publication bias

The number of studies in several post-COVID symptoms was too small to permit publication bias assessment. Funnel plots, calculated for post-COVID fatigue (Suppl. Fig. 1), post-COVID pain (Suppl. Fig. 2), post-COVID dyspnea (Suppl. Fig. 3) and post-COVID chest/thoracic pain (Suppl. Fig. 4) revealed asymmetry in their analyses. The Egger test revealed publication bias for post-COVID pain (*Egger's* test P-value: 0.029) and dyspnea (*Egger's* test P-value: 0.012), but not for fatigue (*Egger's* test P-value: 0.215) or chest/thoracic pain (*Egger's* test P-value: 0.520).

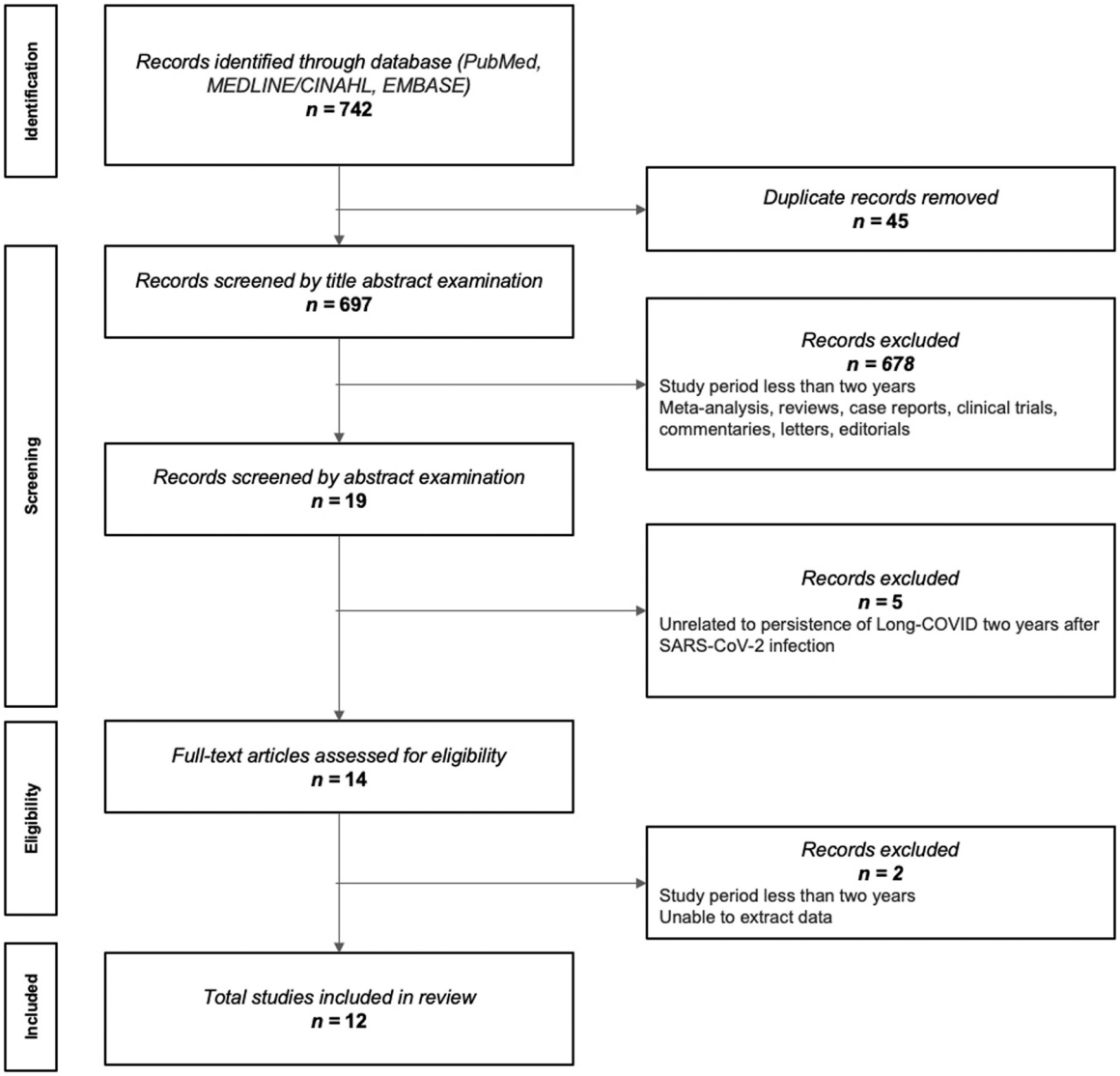

Fig. 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram.

Discussion

This meta-analysis revealed that almost 30% of subjects who had been infected by SARS-CoV-2 experienced post-COVID symptoms two-years after. Fatigue, cognitive disorders and pain were the most prevalent post-COVID symptoms within the general population two-years after. Additionally, COVID-19 survivors also reported the presence of anxiety and depression, as well as sleep problems, up to 15% and 25%, respectively.

Findings: Post-COVID symptoms

This research found that fatigue and cognitive impairments were the most frequent post-COVID symptoms two-years after infection with prevalence rates close to 28%. This agrees with Rahmati et al. who also reported fatigue (27.4%) as the most prevalent post-COVID symptom at a follow-up period of two-years.[14] This research also found that the prevalence rate of overall cognitive impairments upon analysis of memory problems and brain fog (around 20%) was higher than Rahmati et al.'s paper which reported memory loss and brain fog prevalence rates of 5.1% and 8.1%, respectively.[14] The third most prevalent post-COVID symptom was pain (8%). Post-COVID headache (8.9%) and myalgia (8.1%) were the most prevalent pain conditions. The pooled prevalence of post-COVID headache, anosmia or ageusia two-years after the infection were similar in both meta-analyses.

Some discrepancies in some symptoms were noted. An explanation to this is, first, the number of studies in this meta-analysis is higher than that of Rahmati et al.[14] Second, some post-COVID symptoms in different studies included in Rahmati et al.[14] were combined, e.g., mixed altered taste and smell. This research did not include combined data in the meta-analytic calculation. Third, different collection procedures were employed, e.g., self-reported symptoms and PROMs, which have led to different prevalence rates. Finally, Rahmati et al.[14] included also post-COVID sequelae (i.e., changes in respiratory volumes) associated with e.g. lung damage.

Previous meta-analyses reported prevalence rates ranging from 10% to 50% of most post-COVID symptoms during the first year after infection.[5–13] When analyzing current evidence, it seems that the prevalence of post-COVID symptomatology decreases with time.[5–14] Thus, a decreased tendency is observed in most, but not all, post-COVID symptoms during the following years after SARS-CoV-2 acute infection.[32,33] A recent meta-analysis identified that fatigue, sleep problems, dyspnea, and anxiety were the most prevalent post-COVID symptoms the first three months after SARS-CoV-2 infection. Meanwhile, post-COVID fatigue, dyspnea, sleep disorders, and depression were those most prevalent six

Table 2
Characteristics of the included studies investigating post-COVID symptoms at two-years follow up.

Study	Country	Sample (M/F)	Setting	Age Mean (SD)	Follow-up (days) Median (IQR)	Post-COVID symptoms
Ballouz et al., 2023[21]	Switzerland	1734 (846/888)	NH, H (4%)	With SARS-COV-2: 50 IQR 35-66 No SARS-COV-2: 65 IQR 45-72	730	Fatigue, dyspnea, cough, gastrointestinal problems, myalgia, joint pain, altered taste or smell, hair loss, chest/thoracic pain, skin rashes, cognitive problems, palpitation/tachycardia, dizziness/vertigo, ocular problems, headache, sleep problems
Fernández-de-las-Peñas et al., 2022[23]	Spain	360 H/308 NH (323/345)	H NH	60.7 (16.1) 56.7 (14.7)	724 712	Fatigue, dyspnea, anosmia, ageusia, hair loss, pain, diarrhea, skin rashes, cognitive problems, palpitation/tachycardia, ocular problems, sore throat
Helmsdal et al., 2022[29]	Faroe Islands	170 (77/93)	NH, H (2.4%)	40 (19.4)	657 IQR 587-697	Fatigue, dyspnea, headache, myalgia, joint pain, anosmia, nausea/vomiting, ageusia, skin rashes, cough, expectoration, runny nose, sore throat, diarrhea
Huang et al., 2022[28]	China	1192 (641/551)	H	57 IQR 48-65	685 IQR 675-698	Fatigue, headache, dizziness/vertigo, myalgia, joint pain, ageusia, anosmia, skin rashes, hair loss, chest/thoracic pain, sore throat, palpitation/tachycardia, nausea/vomiting, anxiety, depression, sleep difficulties
Li et al., 2022[24]	China	155 (81/74)	H	43 IQR 34-55	697 IQR 680-717	Fatigue, dyspnea, headache, ageusia, dizziness/vertigo, gastrointestinal problems, myalgia, chest/thoracic pain, sleep difficulties
Kirchberger et al., 2023[31]	Germany	304 (127/177)	NH	53 IQR 41-61	780 IQR 615-816	Fatigue, myalgia, headache, concentration problems, cough, cognitive problems, ageusia, anosmia, diarrhea, stomach ache, runny nose, dizziness/vertigo, sore throat, palpitation/tachycardia, chest/thoracic pain, hair loss, skin rashes, depression, anxiety nausea/vomiting, sleep problem,
Millet et al., 2022[27]	United States	91 H/82 NH (85/87)	H NH	55.7 (155) 47.5 (13.5)	730	Fatigue, dyspnea, headache, ageusia, anosmia, dizziness/vertigo, cognitive problems, stomach ache, skin rashes, cough, chest/thoracic pain, sore throat, runny nose, palpitation/tachycardia, diarrhea, nausea/vomiting, anxiety, depression
Peghin et al., 2023[30]	Italy	230 (107/123)	NH, H	54.7	839	Fatigue, dyspnea, anosmia, cough, gastrointestinal problems, headache, chest/thoracic pain, ocular problems, hair loss
Wahlgren et al., 2023[25]	Sweden	165 (104/61)	H	61 (13)	730	Cognitive problems, headache, dizziness/vertigo, depression, anxiety
Wambeke et al., 2023[26]	France	45 (17/28)	NH	49.6 (11.2)	687	Fatigue, dyspnea, ageusia, anosmia, pain, sore throat, cognitive problems, anxiety
Yang et al., 2022[22]	China	1864 (926/938)	H	58.5 IQR 49-68	730 IQR 719-743	Fatigue, dyspnea, dizziness/vertigo, expectoration, myalgia, ageusia, anosmia, cough, dyspnea, chest/thoracic pain, sore throat, palpitation/tachycardia, vomiting, anxiety
Zhang et al., 2023[20]	China	1212 (586/626)	H	68 (64-72)	736 IQR 720-762	Fatigue, dyspnea, myalgia, cough, sore throat, headache, dizziness/vertigo, nausea/vomiting, hair loss, palpitation/tachycardia, expectoration, chest/thoracic pain, diarrhea, anxiety

H: Hospitalized; NH: Non-hospitalized; M: Male; F: Female; SD: standard deviation; IQR: Interquartile range.

Table 3
Pooled demographic and clinical data of the total sample (n = 7912).

	Total (n = 7912)
Age, mean (SD), years	59.5 (16.3) n = 7054 - 12 studies
Gender, female/male, n (%)	2823 (50.7%)/2741 (49.3%) 8 studies
Medical co-morbidities	
1 or more comorbidities	54.0% (30.65; 76.45) n = 1767/4747 I^2 = 99.3% - 5 studies
Hypertension	33.95% (25.95; 41.2) n = 1248/3669 I^2 = 94.1% - 6 studies
Obesity	22.35% (10.65; 36.8) n = 209/1173 I^2 = 96.9% - 5 studies
Diabetes	9.4% (5.4; 14.3) n = 744/6032 I^2 = 96.9% - 9 studies
Heart Disease	6.6% (4.4; 9.2) n = 613/6865 I^2 = 91.4% - 10 studies
COPD	3.5% (1.6; 5.9) n = 197/6501 I^2 = 95.1% - 8 studies
Cancer	3.0% (1.85; 4.4) n = 172/5738 I^2 = 86.2% - 6 studies
Kidney disease	2.2% (0.93; 3.93) n = 135/5615 I^2 = 87.6% - 6 studies
Stay at the hospital, mean (SD), days	14.5 (8.8) n = 4975 - 7 studies
ICU admission	
Yes/No, n (%)	235/7208 (3.2%) n = 8 studies
Stay at ICU, mean (SD), days	21.2 (19.4) n = 125 - 3 studies
Follow up, mean (SD), days	722.9 (51.5) n = 7912 - 12 studies

COPD: Chronic Obstructive Pulmonary Disease; ICU: Intensive Care Unit; SD: Standard Deviation.

months after.[34] The prevalence tendency of long-lasting symptoms during the following years after SARS-CoV-2 infection can be different symptom-by-symptom as there is evidence suggesting a fluctuating trajectory of post-COVID symptomatology.[35]

Most published meta-analyses have reported fatigue and cognitive problems as the most prevalent post-COVID symptom throughout the first year after an acute SARS-CoV-2 infection.[5–14] This research found that different pain conditions, e.g., headache and myalgia, are also prevalent. This plethora of post-COVID symptoms can be explained by several mechanisms attributed to SARS-CoV-2 such as viral persistence, long-lasting inflammation, autoimmunity, reactivation of latent infections, alteration in gut microbiota, microvascular thrombosis or others.[36]

Independently if different etiopathogenic mechanisms are involved for each post-COVID symptom, evidence supports that long-lasting symptoms are still present two-years after SARS-CoV-2 acute infection.

Findings: Post-COVID psychological-associated symptoms

Psychological symptomatology has raised a worldwide health care concern[37] as the COVID-19 outbreak provoked a deleterious impact on mental health in the general population.[38] This meta-analysis found that around 20% of COVID-19 survivors also exhibit symptoms of anxiety, depression, and sleep problems two-years after the infection. The prevalence rates of anxiety and depressive symptomatology in this meta-analysis (13.4% and 18% respectively) were higher than prevalence rates observed by Rahmati et al. (anxiety 9%, depression 6.6%).[14] On the other hand, the prevalence rate

Table 4
Methodological quality (Newcastle-Ottawa Scale - NOS) of cohort studies included in the review.

Study	Selection				Comparability		Outcome				
	Representative of the exposed cohort	Selection of nonexposed cohort	Ascertainment of exposure	Outcome of interest	Main Factor	Additional factor	Assessment of outcomes	Sufficient follow-up	Adequacy of follow-up	Total score
Ballouz et al., 2023[21]	★	★	★	★				★	★	6/9
Fernández-de-las-Peñas et al., 2022[23]	★	★	★	★			★	★	★	7/9
Helmsdal et al., 2022[29]	★	★	★	★				★	★	6/9
Huang et al., 2022[28]	★	★	★	★	★	★		★	★	8/9
Li et al., 2022[24]	★	★	★	★				★	★	6/9
Kirchberger et al., 2023[31]	★	★	★	★				★	★	6/9
Millet et al., 2022[27]	★	★		★				★	★	5/9
Peghin et al., 2023[30]	★	★	★	★				★	★	6/9
Van Wambeke et al., 2023[26]	★	★		★			★	★	★	6/9
Wahlgren et al., 2023[25]	★	★	★	★				★	★	6/9
Yang et al., 2022[22]	★	★	★	★			★	★	★	7/9
Zhang et al., 2023[20]				★				★	★	3/9

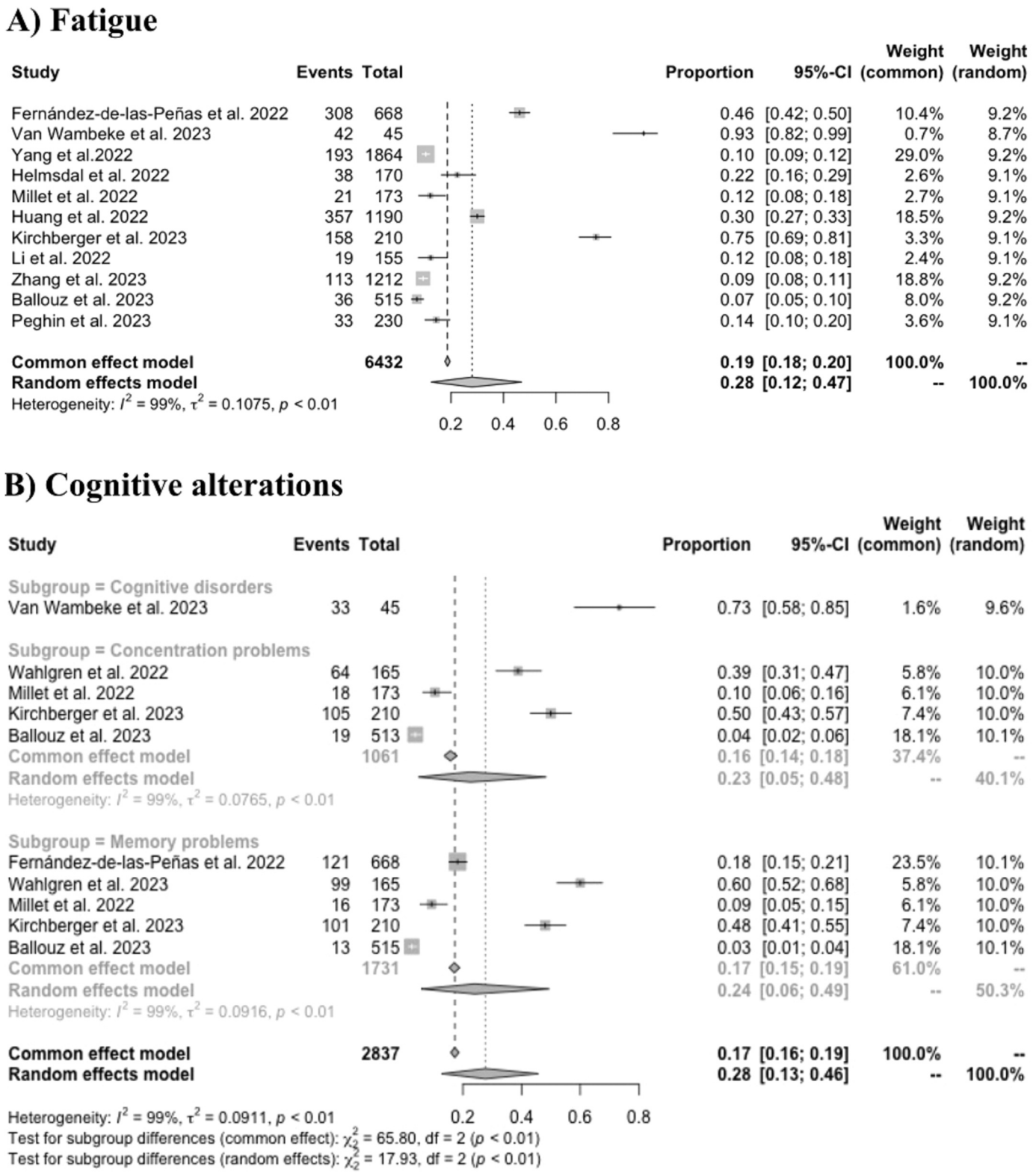

Fig. 2. Meta-analysis of prevalence of post-COVID fatigue (A) and post-COVID cognitive alterations (B) two-years after acute SARS-CoV-2 infection.

of sleep problems in this meta-analysis (20.9%) was slightly inferior to that identified by Rahmati et al. (25.1%).[14]

These heterogeneous prevalence rates of psychological symptoms are a result of differences in study designs (cross-sectional vs. longitudinal), populations (hospitalized vs. non-hospitalized cohort) or collection procedures (self-reported or use of specific PROMs). For instance, anxiety and depressive levels were self-reported in most studies and evaluated with some specific PROMs such the HADS or the GAD-7. Since these PROMs use different cut-off scores for identifying anxiety and depressive levels or sleep problems, different prevalence rates can be expected. Contrary to what is seen in biological post-COVID symptoms, previous and current data would

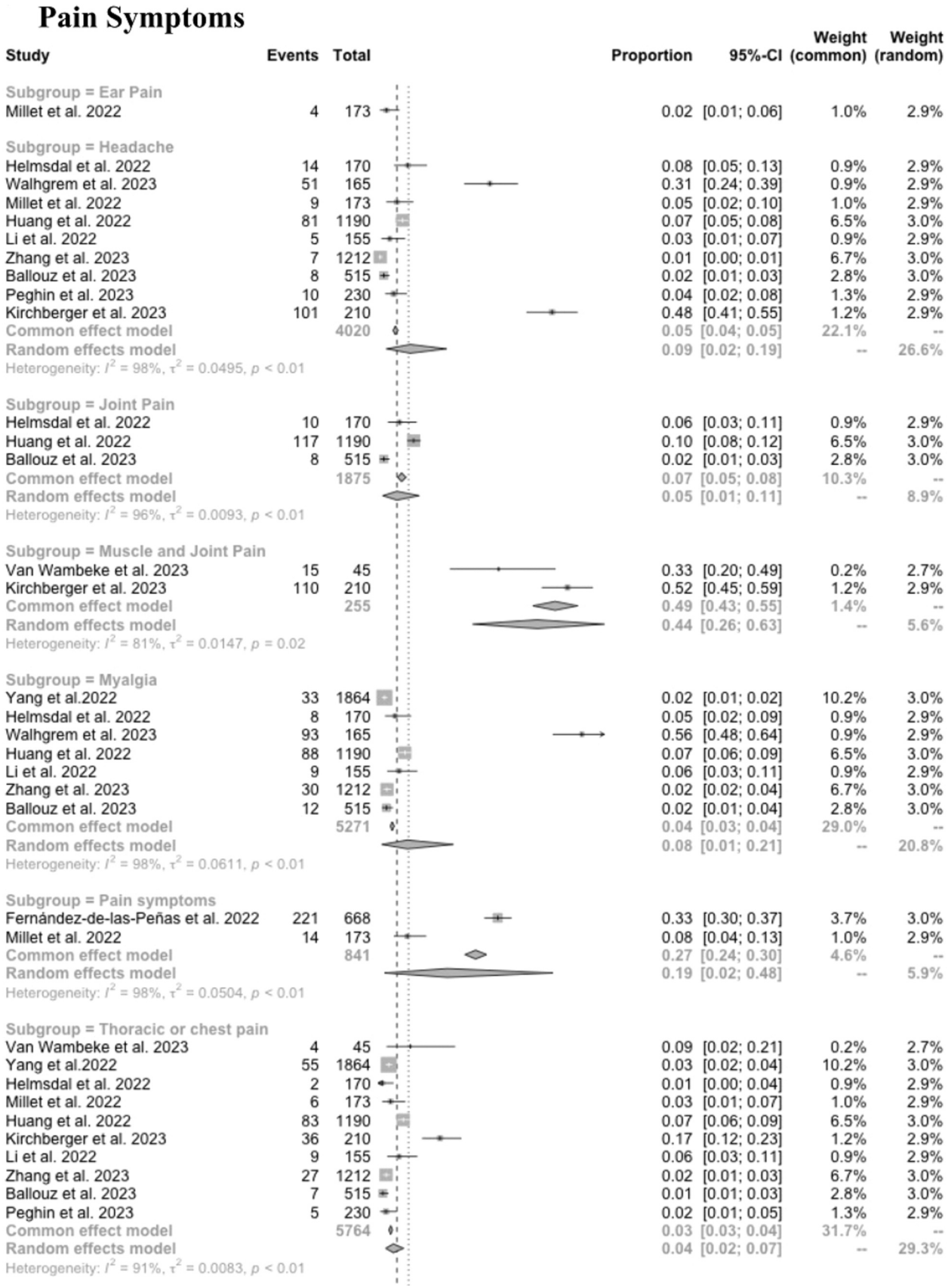

Fig. 3. Meta-analysis of prevalence of post-COVID pain symptoms two-years after acute SARS-CoV-2 infection.

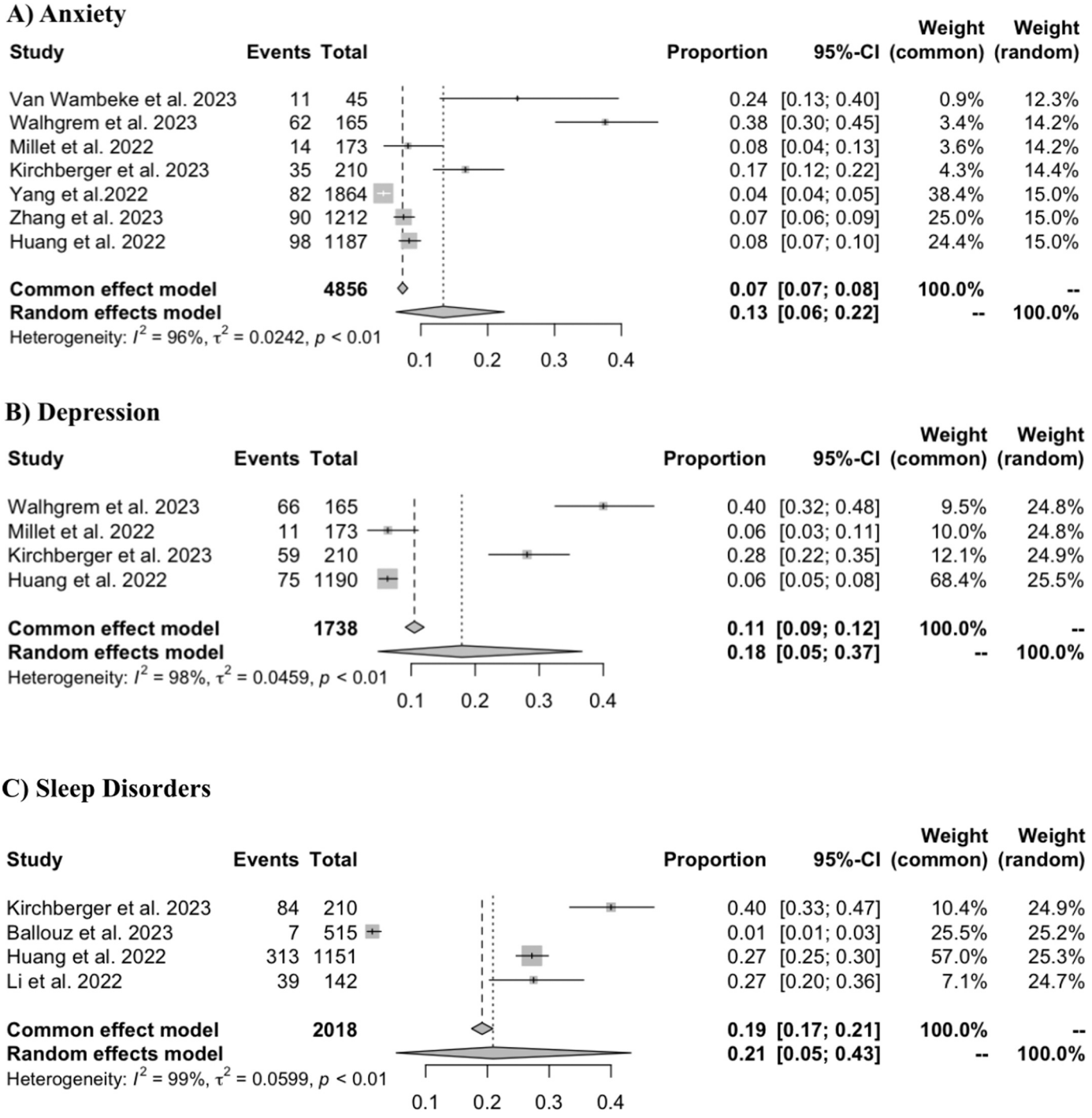

Fig. 4. Meta-analysis of prevalence of anxiety (A), depressive symptoms (B) and sleep problems (C) two-years after acute SARS-CoV-2 infection.

suggest that the prevalence of psychological symptoms, as well as sleep problems, are overall stable but can also slightly decrease with time.[39]

Anxiety, depressive levels, and poor sleep are not directly attributed to SARS-CoV-2 biology or trophism as other symptoms (e.g., fatigue, ageusia, dyspnea, anosmia, brain fog) are but can still promote biological post-COVID symptoms.[40] For instance, the presence of depressive symptoms the first month after an acute SARS-CoV-2 infection strongly predicts the presence of post-COVID fatigue one-year after.[41] Similarly, the presence of sleep disorders is associated with worse quality of life in individuals with post-COVID-19 condition.[42] This association can be explained by shared mechanisms of anxiety, depression, and poor sleep with other biological post-COVID symptoms such as fatigue or cognitive impairments.[43,44] Thus, the presence of anxiety, depression, and poor sleep could be psychological stressors that leads to the perpetuation of other post-COVID symptoms.

Limitations

This research is not without limitations. First, there was heterogeneity in most calculations, particularly due to differences in studies sample and wide variations in reported prevalence data. Due to this, a meta-regression was not possible. Second, the small number

Table 5
Pooled mean (95% confidence interval) pooled prevalence of post-COVID symptoms two-years after an acute SARS-CoV-2 infection.

Respiratory and General Symptoms	
Fatigue	**28.0% (12.0; 47.0)**
I^2	99.0%
Event/Total	1318/6432
Studies	11
Dyspnea	**9.4% (4.25; 16.35)**
I^2	96.4%
Event/Total	314/5452
Studies	11
Runny Nose	**8.2% (0.0; 31.5)**
I^2	98.2%
Event/Total	73/553
Studies	3
Sore Throat	**5.9% (1.2; 13.65)**
I^2	97.7%
Event/Total	186/3833
Studies	6
Cough	**4.0% (1.0; 8.6)**
I^2	94.8%
Event/Total	144/4544
Studies	8
Expectoration	**1.5% (1.0; 2.0)**
I^2	17.1%
Event/Total	51/3246
Studies	3
Neurological and Cognitive Symptoms	
Cognitive Alterations	**27.6% (12.6; 45.8%)**
I^2	98.7%
Event/Total	589/2837
Studies	6
Ageusia	**4.85% (1.1; 10.8)**
I^2	95.79%
Event/Total	110 /3823
Studies	8
Anosmia	**5.25% (1.25; 11.55)**
I^2	97.1%
Event/Total	160/3623
Studies	6
Dizziness or Vertigo	**6.7% (1.7; 14.5)**
I^2	98.4%
Event/Total	267/5484
Studies	8
Gastrointestinal Symptoms	
Pooled Gastrointestinal Problems	**4.5% (1.85; 8.2)**
I^2	96.9%
Event/Total	305/8958
Studies	9
Diarrhea	**2.65% (0.01; 8.75)**
I^2	NA
Event/Total	55/2433
Studies	5
Nausea or Vomiting	**1.35% (0.2; 3.3)**
I^2	92.4%
Event/Total	49/4167
Studies	6
Stomach Pain	**6.35% (0.00; 21.95)**
I^2	95.2%
Event/Total	31/383
Studies	2
Pain Symptoms	
Pooled Pain Symptoms	**8.4% (4.9; 12.8)**
I^2	98.1%
Event/Total	1292/18,199
Studies	11
Chest/Thoracic Pain	**4.25% (2.0; 7.1)**
I^2	91.5%
Event/Total	234/5764
Studies	10
Joint Pain	**5.2% (1.3; 11.4%)**
I^2	96.2%
Event/Total	135/1875
Studies	3
Headache	**8.9% (2.3; 19.0)**
I^2	98.3%
Event/Total	286 /4020
Studies	9
Myalgia	**8.1% (0.99; 20.9%)**
I^2	98.3%
Event/Total	273/5271
Studies	7
Dermatological symptoms	
Hair Loss	**7.35% (3.2; 13.05)**
I^2	95.6%
Event/Total	247/2813
Studies	5
Skin Rashes	**2.45% (0.90; 4.65)**
I^2	82.9%
Event/Total	78/2926
Studies	6
Other type of post-COVID symptom	
Ocular problems	**7.7% (3.0; 14.2)**
I^2	95.8%
Event/Total	151/2198
Studies	7
Palpitations or Tachycardia	**4.15% (0.5; 10.93)**
I^2	98.6%
Event/Total	231/5832
Studies	7
Psychological Symptoms	
Sleep problems	**20.9% (5.25; 43.25)**
I^2	99.1%
Event/Total	443/2018
Studies	4
Anxiety	**13.4% (6.3; 22.5)**
I^2	96.2%
Event/Total	392/4856
Studies	7
Depression Symptoms	**18.0% (4.8; 36.7)**
I^2	98.1%
Event/Total	211/1738
Studies	4

of studies in several post-COVID symptoms did not permit pooling data which limits the generalizability of the result. Some studies mixed cohorts of hospitalized and non-hospitalized patients, and some studies neither separated data by gender nor provided data about patients requiring ICU admission. No conclusion on these subgroups was achieved due to this limitation. Third, 75% (n = 9/12) of studies collected data by telephone and most symptoms were self-reported. Hence, there is risk of reporting bias due to recall inaccuracy. Future studies could use the "Long COVID Symptom and Impact Tool," which has been found to be a reliable instrument for monitoring post-COVID symptoms.[45] Lastly, due to the follow-up period of two-years, most study included participants infected during the earlier waves of the pandemic related to the historical strains, and infected with other variants such as Alpha and Delta. No current long-term data for the Omicron variant, the most extended and dominant variant, is available. In such a scenario, most studies did not control vaccination status, vaccine types, potential reinfections or use of antiviral drugs during the acute COVID-19 phase. Future population studies considering identified limitations in the current study are needed.

Conclusion

This meta-analysis revealed that almost 30% of subjects who had been infected by SARS-CoV-2 experienced post-COVID symptoms two-years after an acute SARS-CoV-2 infection. Fatigue, cognitive impairments, and pain were the most prevalent post-COVID symptoms two-years after. Additionally, COVID-19 survivors also reported the presence of anxiety and depression, as well as sleep problems, up to 15% and 25%, respectively. Population-based studies using

homogeneous collection procedures are needed to further determine the prevalence of post-COVID symptomatology.

Role of the funding source

The project was supported by the LONG-COVID-EXP-CM, a grant associated to the Fondo Europeo De Desarrollo Regional - Recursos REACT-UE del Programa Operativo de Madrid 2014-2020, en la línea de actuación de proyectos de I+D+i en materia de respuesta a COVID 19. The sponsor had no role in the design, collection, management, analysis, or interpretation of the data, draft, review, or approval of the manuscript or its content. The authors were responsible for the decision to submit the manuscript for publication, and the sponsor did not participate in this decision.

Author contributions

All the authors cited in the manuscript had substantial contributions to the concept and design, the execution of the work, or the analysis and interpretation of data; drafting or revising the manuscript and have read and approved the final version of the paper. *C Fernández-de-las-Peñas*: conceptualization, visualization, methodology, validation, data curation, writing-original draft, writing-review and editing. *Kin Israel Notarte*: conceptualization, visualization, methodology, validation, data curation, writing-original draft, writing-review and editing. *Raymart Macasaet*: methodology, validation, writing-original draft, writing-review and editing. *Jacqueline Veronica Velasco*: methodology, validation, data curation, writing-original draft, writing-review and editing. *Jesus Alfonso Catahay*: methodology, data curation, writing-original draft, writing-review and editing. *Abbygail Therese Ver:* methodology, data curation, writing-original draft, writing-review and editing. *William Chung:* methodology, validation, writing-original draft, writing-review and editing. *Juan A Valera-Calero:* data curation, writing-original draft, writing-review and editing. *Marcos Navarro-Santana:* methodology, validation, data curation, writing-original draft, writing-review and editing.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.jinf.2023.12.004.

References

1. World Health Organization (WHO) Coronavirus (COVID-19) Dashboard 2023. https://covid19.who.int/. Accessed: 1 September 2023.
2. Fernández-de-Las-Peñas C. *Long COVID: Current definition. Infection* 2022;**50**:285–6. https://doi.org/10.1007/s15010-021-01696-5
3. Soriano JB, Murthy S, Marshall JC, Relan P, Diaz JV, WHO Clinical Case Definition Working Group on Post-COVID-19 Condition. *A clinical case definition of post-COVID-19 condition by a Delphi consensus. Lancet Infect Dis* 2022;**22**:e102–7. https://doi.org/10.1016/S1473-3099(21)00703-9
4. Hayes LD, Ingram J, Sculthorpe NF. *More than 100 persistent symptoms of SARS-CoV-2 (long COVID): A scoping review. Front Med (Lausanne)* 2021;**8**:750378. https://doi.org/10.3389/fmed.2021.750378
5. Lopez-Leon S, Wegman-Ostrosky T, Perelman C, Sepulveda R, Rebolledo PA, Cuapio A, et al. *More than 50 long-term effects of COVID-19: A systematic review and meta-analysis. Sci Rep* 2021;**11**:16144. https://doi.org/10.1038/s41598-021-95565-8
6. Nasserie T, Hittle M, Goodman SN. *Assessment of the frequency and variety of persistent symptoms among patients with COVID-19. JAMA Netw Open* 2021;**4**:e2111417. https://doi.org/10.1001/jamanetworkopen.2021.11417
7. Di Gennaro F, Belati A, Tulone O, Diella L, Fiore Bavaro D, Bonica R, et al. *Incidence of long COVID-19 in people with previous SARS-Cov2 infection: A systematic review and meta-analysis of 120,970 patients. Intern Emerg Med* 2023;**18**:1573–81. https://doi.org/10.1007/s11739-022-03164-w
8. O'Mahoney LL, Routen A, Gillies C, Ekezie W, Welford A, Zhang A, et al. *The prevalence and long-term health effects of long Covid among hospitalised and non-hospitalised populations: A systematic review and meta-analysis. EClinicalMedicine* 2023;**55**:101762. https://doi.org/10.1016/j.eclinm.2022.101762
9. Chen C, Haupert SR, Zimmermann L, Shi X, Fritsche LG, Mukherjee B. *Global prevalence of post-coronavirus disease 2019 (COVID-19) condition or long COVID: A meta-analysis and systematic review. J Infect Dis* 2022;**226**:1593–607. https://doi.org/10.1093/infdis/jiac136
10. Fernández-de-las-Peñas C, Palacios-Ceña D, Gómez-Mayordomo V, Florencio LL, Cuadrado ML, Plaza-Manzano G, et al. *Prevalence of post-COVID-19 symptoms in hospitalized and non-hospitalized COVID-19 survivors: A systematic review and meta-analysis. Eur J Intern Med* 2021;**92**:55–70. https://doi.org/10.1016/j.ejim.2021.06.009
11. Wulf Hanson S, Abbafati C, Aerts JG, Al-Aly Z, Ashbaugh C, Ballouz T, et al. *Estimated global proportions of individuals with persistent fatigue, cognitive, and respiratory symptom clusters following symptomatic COVID-19 in 2020 and 2021. JAMA* 2022;**328**:1604–15. https://doi.org/10.1001/jama.2022.18931
12. Alkodaymi MS, Omrani OA, Fawzy NA, Shaar BA, Almamlouk R, Riaz M, et al. *Prevalence of post-acute COVID-19 syndrome symptoms at different follow-up periods: A systematic review and meta-analysis. Clin Microbiol Infect* 2022;**28**:657–66. https://doi.org/10.1016/j.cmi.2022.01.014
13. Han Q, Zheng B, Daines L, Sheikh A. *Long-term sequelae of COVID-19: A systematic review and meta-analysis of one-year follow-up studies on Post-COVID symptoms. Pathogens* 2022;**11**:269. https://doi.org/10.3390/pathogens11020269
14. Rahmati M, Udeh R, Yon DK, Lee SW, Dolja-Gore X, McEVoy M, et al. *A systematic review and meta-analysis of long-term sequelae of COVID-19 2–year after SARS-CoV-2 infection: A call to action for neurological, physical, and psychological sciences. J Med Virol* 2023;**95**:e28852. https://doi.org/10.1002/jmv.28852
15. Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. *The PRISMA 2020 statement: An updated guideline for reporting systematic reviews. BMJ* 2021;**372**:n71. https://doi.org/10.1136/bmj.n71
16. Wells G, Tugwell P, O'Connell D, Welch V, Peterson J, Shea B, et al. The Newcastle-Ottawa Scale (NOS) for assessing the quality if nonrandomized studies in meta-analyses; 2015.
17. Luo D, Wan X, Liu J, Tong T. *Optimally estimating the sample mean from the sample size, median, mid-range, and/or mid-quartile range. Stat Methods Med Res* 2018;**27**:1785–805. https://doi.org/10.1177/0962280216669183
18. Servier C, Porcher R, Pane I, Ravaud P, Tran V-T. *Trajectories of the evolution of post-COVID-19 condition, up to two years after symptoms onset. Int J Infect Dis* 2023;**133**:67–74. https://doi.org/10.1016/j.ijid.2023.05.007
19. da Silva NS, de Araújo NK, dos Santos KA, de Souza KSC, de Araújo JNG, Cruz MS, et al. *Post-Covid condition and clinic characteristics associated with SARS-CoV-2 infection: A 2-year follow-up to Brazilian cases. Sci Rep* 2023;**13**:13973. https://doi.org/10.1038/s41598-023-40586-8
20. Zhang Y, Han Z, Dai Y, Liu Y, Wang Q, Cheng L, et al. *Symptom burden among older COVID-19 survivors two years after hospital discharge. Aging Dis* 2023;**14**:2238–48. https://doi.org/10.14336/AD.2023.0304
21. Ballouz T, Menges D, Anagnostopoulos A, Domenghino A, Aschmann HE, Frei A, et al. *Recovery and symptom trajectories up to two years after SARS-CoV-2 infection: Population based, longitudinal cohort study. BMJ* 2023;**381**:e074425. https://doi.org/10.1136/bmj-2022-074425
22. Yang X, Hou C, Shen Y, Zhang M, Zhang K, Wang F, et al. *Two-year health outcomes in hospitalized COVID-19 survivors in China. JAMA Netw Open* 2022;**5**:e2231790. https://doi.org/10.1001/jamanetworkopen.2022.31790
23. Fernández-de-las-Peñas C, Rodríguez-Jiménez J, Cancela-Cilleruelo I, Guerrero-Peral A, Martín-Guerrero JD, García-Azorín D, et al. *Post–COVID-19 symptoms 2 years after SARS-CoV-2 infection among hospitalized vs nonhospitalized patients. JAMA Netw Open* 2022;**5**:e2242106. https://doi.org/10.1001/jamanetworkopen.2022.42106
24. Li D, Liao X, Liu Z, Ma Z, Dong J, Zheng G, et al. *Healthy outcomes of patients with COVID-19 two years after the infection: A prospective cohort study. Emerg Microbes Infect* 2022;**11**:2680–8. https://doi.org/10.1080/22221751.2022.2133639
25. Wahlgren C, Forsberg G, Divanoglou A, Östholm Balkhed Å, Niward K, Berg S, et al. *Two-year follow-up of patients with post-COVID-19 condition in Sweden: A prospective cohort study. Lancet Reg Health - Eur* 2023;**28**:100595. https://doi.org/10.1016/j.lanepe.2023.100595
26. Van Wambeke E, Bezler C, Kasprowicz A-M, Charles A-L, Andres E, Geny B. *Two-years follow-up of symptoms and return to work in complex post-COVID-19 patients. J Clin Med* 2023;**12**:741. https://doi.org/10.3390/jcm12030741
27. Millet C, Narvaneni S, Roman S, Horani G, Chaudhry S, Michael P, et al. *Symptoms persist in patients two years after COVID-19 infection: A prospective follow-up study. Clin Microbiol Infect* 2022;**28**:1505–7. https://doi.org/10.1016/j.cmi.2022.06.008
28. Huang L, Li X, Gu X, Zhang H, Ren L, Guo L, et al. *Health outcomes in people 2 years after surviving hospitalisation with COVID-19: A longitudinal cohort study. Lancet Respir Med* 2022;**10**:863–76. https://doi.org/10.1016/S2213-2600(22)00126-6
29. Helmsdal G, Hanusson KD, Kristiansen MF, Foldbo BM, Danielsen ME, Steig B á, et al. *Long COVID in the long run—23-month follow-up study of persistent symptoms. Open Forum Infect Dis* 2022;**9**:ofac270. https://doi.org/10.1093/ofid/ofac270
30. Peghin M, De Martino M, Palese A, Chiappinotto S, Fonda F, Gerussi V, et al. *Post-COVID-19 syndrome 2 years after the first wave: The role of humoral response, vaccination and reinfection. Open Forum Infect Dis* 2023;**10**:ofad364. https://doi.org/10.1093/ofid/ofad364

31. Kirchberger I, Meisinger C, Warm TD, Hyhlik-Dürr A, Linseisen J, Goßlau Y. *Post-COVID-19 syndrome in non-hospitalized individuals: Healthcare situation 2 years after SARS-CoV-2 infection. Viruses* 2023;**15**:1326. https://doi.org/10.3390/v15061326
32. Fernández-de-las-Peñas C, Cancela-Cilleruelo I, Rodríguez-Jiménez J, Fuensalida-Novo S, Martín-Guerrero JD, Pellicer-Valero OJ, et al. *Trajectory of post-COVID self-reported fatigue and dyspnoea in individuals who had been hospitalized by COVID-19: The LONG-COVID-EXP multicenter study. Biomedicines* 2023;**11**:1863. https://doi.org/10.3390/biomedicines11071863
33. Tran V-T, Porcher R, Pane I, Ravaud P. *Course of post COVID-19 disease symptoms over time in the ComPaRe long COVID prospective e-cohort. Nat Commun* 2022;**13**:1812. https://doi.org/10.1038/s41467-022-29513-z
34. Kuodi P, Gorelik Y, Gausi B, Bernstine T, Edelstein M. *Characterization of post-COVID syndromes by symptom cluster and time period up to 12 months post-infection: A systematic review and meta-analysis. Int J Infect Dis* 2023;**134**:1–7. https://doi.org/10.1016/j.ijid.2023.05.003
35. Fernández-de-las-Peñas C. *Are patients exhibiting post-coronavirus disease (COVID) symptoms at 12 months the same at 5 or 9 months? The fluctuating nature of post-COVID. Clin Infect Dis* 2022;**75**. https://doi.org/10.1093/cid/ciac007
36. Castanares-Zapatero D, Chalon P, Kohn L, Dauvrin M, Detollenaere J, Maertens de Noordhout C, et al. *Pathophysiology and mechanism of long COVID: A comprehensive review. Ann Med* 2022;**54**:1473–87. https://doi.org/10.1080/07853890.2022.2076901
37. Xiang Y-T, Yang Y, Li W, Zhang L, Zhang Q, Cheung T, et al. *Timely mental health care for the 2019 novel coronavirus outbreak is urgently needed. Lancet Psychiatry* 2020;**7**:228–9. https://doi.org/10.1016/S2215-0366(20)30046-8
38. Pierce M, Hope H, Ford T, Hatch S, Hotopf M, John A, et al. *Mental health before and during the COVID-19 pandemic: A longitudinal probability sample survey of the UK population. Lancet Psychiatry* 2020;**7**:883–92. https://doi.org/10.1016/S2215-0366(20)30308-4
39. Johnson SU, Amundsen OM, Johnson MS, Hoffart A, Halsøy Ø, Skjerdingstad N, et al. *Psychiatric symptoms in COVID-19-positive individuals in the general population: Trajectories of depression, anxiety, and insomnia. Psychiatry Res* 2022;**317**:114806. https://doi.org/10.1016/j.psychres.2022.114806
40. Lemogne C, Ranque B. *Rôle des facteurs psychologiques dans l'affection post-COVID-19. Bull Acad Natl Med* 2023;**207**:954–60. https://doi.org/10.1016/j.banm.2023.05.001
41. Mazza MG, Palladini M, Villa G, De Lorenzo R, Rovere Querini P, Benedetti F. *Prevalence, trajectory over time, and risk factor of post-COVID-19 fatigue. J Psychiatr Res* 2022;**155**:112–9. https://doi.org/10.1016/j.jpsychires.2022.08.008
42. Malik P, Patel K, Pinto C, Jaiswal R, Tirupathi R, Pillai S, et al. *Post-acute COVID-19 syndrome (PCS) and health-related quality of life (HRQoL)—A systematic review and meta-analysis. J Med Virol* 2022;**94**:253–62. https://doi.org/10.1002/jmv.27309
43. Liu S-T, Lin S-C, Chang JP-C, Yang K-J, Chu C-S, Yang C-C, et al. *The clinical observation of inflammation theory for depression: The initiative of the Formosa Long COVID Multicenter Study (FOCuS. Clin Psychopharmacol Neurosci* 2023;**21**:10–8. https://doi.org/10.9758/cpn.2023.21.1.10
44. Mazza MG, Palladini M, Poletti S, Benedetti F. *Post-COVID-19 depressive symptoms: Epidemiology, pathophysiology, and pharmacological treatment. CNS Drugs* 2022;**36**:681–702. https://doi.org/10.1007/s40263-022-00931-3
45. Tran V-T, Riveros C, Clepier B, Desvarieux M, Collet C, Yordanov Y, et al. *Development and validation of the long coronavirus disease (COVID) symptom and impact tools: A set of patient-reported instruments constructed from patients' lived experience. Clin Infect Dis* 2022;**74**:278–87. https://doi.org/10.1093/cid/ciab352