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Review Article

Fatigue and cognitive impairment in Post-COVID-19 Syndrome: A systematic review and meta-analysis

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ABSTRACT

Importance: COVID-19 is associated with clinically significant symptoms despite resolution of the acute infection (i.e., post-COVID-19 syndrome). Fatigue and cognitive impairment are amongst the most common and debilitating symptoms of post-COVID-19 syndrome.

Objective: To quantify the proportion of individuals experiencing fatigue and cognitive impairment 12 or more weeks following COVID-19 diagnosis, and to characterize the inflammatory correlates and functional consequences of post-COVID-19 syndrome.

Data sources: Systematic searches were conducted without language restrictions from database inception to June 8, 2021 on PubMed/MEDLINE, The Cochrane Library, PsycInfo, Embase, Web of Science, Google/Google Scholar, and select reference lists.

Study selection: Primary research articles which evaluated individuals at least 12 weeks after confirmed COVID-19 diagnosis and specifically reported on fatigue, cognitive impairment, inflammatory parameters, and/or functional outcomes were selected.

Data extraction & synthesis: Two reviewers independently extracted published summary data and assessed methodological quality and risk of bias. A meta-analysis of proportions was conducted to pool Freeman-Tukey double arcsine transformed proportions using the random-effects restricted maximum-likelihood model.

Main outcomes & measures: The co-primary outcomes were the proportions of individuals reporting fatigue and cognitive impairment, respectively, 12 or more weeks following COVID-19 infection. The secondary outcomes were inflammatory correlates and functional consequences associated with post-COVID-19 syndrome.

Abbreviation: PCS, Post-COVID-19 syndrome.

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Results: The literature search yielded 10,979 studies, and 81 studies were selected for inclusion. The fatigue meta-analysis comprised 68 studies, the cognitive impairment meta-analysis comprised 43 studies, and 48 studies were included in the narrative synthesis. Meta-analysis revealed that the proportion of individuals experiencing fatigue 12 or more weeks following COVID-19 diagnosis was 0.32 (95% CI, 0.27, 0.37; $p < 0.001$; n = 25,268; $I^2 = 99.1\%$). The proportion of individuals exhibiting cognitive impairment was 0.22 (95% CI, 0.17, 0.28; $p < 0.001$; n = 13,232; $I^2 = 98.0$). Moreover, narrative synthesis revealed elevations in proinflammatory markers and considerable functional impairment in a subset of individuals.
Conclusions & relevance: A significant proportion of individuals experience persistent fatigue and/or cognitive impairment following resolution of acute COVID-19. The frequency and debilitating nature of the foregoing symptoms provides the impetus to characterize the underlying neurobiological substrates and how to best treat these phenomena.
Study registration: PROSPERO (CRD42021256965).

1. Introduction

The global confirmed case count of coronavirus disease 2019 (COVID-19) surpassed 275 million as of December 2021 (Coronavirus disease (COVID-19), 2021). The actual case positive rate, however, is estimated to be much higher with multiple models predicting the actual number to be 10 (3 to 24) times greater than the number of confirmed cases (Wu et al., 2020; Havers et al., 2020; Aizenman, 2021). In keeping with this view, a projection of over 2.75 billion people may have been infected by COVID-19.

>30% of individuals affected by COVID-19 (Tenforde et al., 2020), including asymptomatic cases (Huang et al., 2021), and approximately 80% of patients hospitalized for COVID-19[7] may experience post-COVID sequelae. Fatigue and cognitive impairment, along with other enduring neuropsychiatric (e.g., depression) (Renaud-Charest et al., 2021) and physical (e.g., dyspnea) manifestations, comprise 'post-acute sequelae of SARS-CoV-2′ (i.e., symptoms persisting for at least 4 weeks following infection) (Nalbandian et al., 2021), colloquially referred to as 'long COVID' (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7992371/). The National Institute for Health and Care Excellence (NICE) defines 'post-COVID-19 syndrome' (PCS) as a constellation of symptoms which develop during or following COVID-19 infection, persist for >12 weeks, and are not sufficiently explained by alternative diagnoses (https://www.nice.org.uk/guidance/ng188). Towards the aim of identifying a common nomenclature in case definition, the World Health Organization (WHO) has recently proposed the moniker 'post COVID-19 condition' (https://www.who.int/publications/i/item/WHO-2019-nCoV-Post_COVID-19_condition-Clinical_case_definition-2021.1). Post COVID-19 condition is defined as persistent symptoms usually occurring 3 months from onset in individuals with past confirmed or probable SARS-CoV-2 infection and persisting for at least 2 months which cannot be explained by an alternative diagnosis (hq) WH. A clinical case definition of post COVID-19 condition by a Delphi consensus, 6 October, 2021).

Research efforts into PCS were originated by online patient advocacy groups, who have reported substantial detriments to quality of life and daily functioning as a consequence of persistent symptoms, lack of formal diagnosis, and effective established treatments (Siegelman, 2020; Rubin, 2020). Fatigue and cognitive impairment have been consistently reported to be some of the most common and debilitating features of PCS (Davis et al., 2020; Marshall, 2020; Report: What does COVID-19 recovery actually look like, 2020). Chronic fatigue (Sabes-Figuera et al., 2010) and cognitive impairment (Winston, 2020; Xu et al., 2017) constitute a significant global economic burden, respectively. Unlike other common symptoms of PCS including dyspnea and depression, there are no established and effective treatments for post-viral fatigue and cognitive impairment, as well as related conditions such as Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS). The global incidence of COVID-19 infection and the potential economic burden and quality of life diminution provide the impetus for identifying neurobiological substrates subserving PCS-related fatigue and cognitive impairment, associated factors and determinants, as well as safe and effective treatments. Herein, we sought to determine the proportion of individuals exhibiting fatigue and cognitive impairment 12 or more weeks following COVID-19 diagnosis, including amongst age, sex, and clinical subgroups. We additionally aimed to characterize the inflammatory correlates and functional consequences of PCS.

2. Methods

2.1. Data Sources and searches

The protocol pertaining to this systematic review and meta-analysis was registered on PROSPERO (CRD42021256965). This study followed the Meta-analysis of Observational Studies in Epidemiology (MOOSE) reporting guidelines (Stroup et al., 2000). In accordance with the 2020 Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines (Page et al., 2020), a systematic search was conducted on PubMed/MEDLINE, Cochrane Library, PsycInfo, EMBASE, and Web of Science from database inception to June 8, 2021. The search string implemented was: "long covid" OR "persistent covid" OR "post covid" OR "post-acute sequelae of SARS-CoV-2 PASC" OR "enduring COVID-19 sequelae" OR "long-haul covid" OR "long-tail covid". We manually searched the references of relevant articles, as well as Google Scholar/Google, for additional studies. No language or publication date restrictions were imposed.

Titles and abstracts were independently screened by two review authors (FC and SL) using the Covidence platform. (Better systematic review management, 2020) Articles identified as potentially relevant by at least one reviewer were retrieved, and duplicates were removed. Full text-articles were independently screened by two reviewers (FC and SL), with discrepancies resolved through discussion. Authors of potentially eligible studies were contacted to provide clarification and/or supplementary data where necessary.

2.2. Study selection

We sought articles reporting on the incidence of any primary outcome (i.e., fatigue or cognitive impairment) and/or secondary outcome (i.e., inflammatory markers or functional outcomes/quality of life measures), as defined in Table 1, in individuals with confirmed COVID-19 12 or more weeks following diagnosis. At the outset, we planned to determine the secondary outcomes solely for fatigue and cognitive impairment in PCS. However, due to the paucity of data concerning the foregoing, we subsequently included inflammatory correlates and functional outcomes associated with PCS more broadly. Inclusion criteria were established prior to article review and were as follows:

1. Complete summary estimates (i.e., exact proportions) pertaining to at least one primary outcome, and/or qualitative or quantitative data pertaining to at least one secondary outcome, as defined in Table 1,

Table 1
Definition of study variables.

PRIMARY OUTCOMES	Objective Ascertainment	Subjective Ascertainment
Fatigue (asthenia)	Fatigue ascertained via any validated tool (e.g., FACIT fatigue scale, FSS), or clinical diagnosis of CFS/EM.	Self-report or non-validated measure of fatigue, tiredness/low energy, muscular fatigue/muscular weakness (myasthenia), malaise.
Cognitive Impairment	Cognitive impairment ascertained via any validated tool for performance-based cognitive function (e.g., MoCA, TICS, SCIP), or clinical diagnosis of cognitive impairment.	Self-report or non-validated measure of cognitive impairment/'brain fog', mental slowness, deficits in attention, executive, processing, memory, learning, articulation, and/or psychomotor coordination.
SECONDARY OUTCOMES		
Inflammatory Parameters	Abnormal levels of circulating or intracellular cytokines, CRP, D-dimer, and/or procalcitonin, in accordance with thresholds determined by study investigators, or relative to control group or established standard.	N/A
Functional Outcomes/ Quality of Life	Functional impairment (including activity, occupational, and social limitations) (Ustün and Kennedy, 2009) ascertained via any validated tool for quality of life or functional outcomes (e.g., EQ-5D, mRS).	Self-report or non-validated assessment of functional impairment (including activity, occupational, and social limitations), as well as general vitality/quality of life (Ustün and Kennedy, 2009).

Acronyms: FACIT: Functional Assessment of Chronic Illness Therapy, FSS: Fatigue Severity Scale, CFS/EM: chronic fatigue syndrome/myalgic encephalomyelitis, MoCA: Montreal Cognitive Assessment, TICS: Telephone interview for cognitive status, SCIP: Screen for Cognitive Impairment for Psychiatry CRP: C-reactive peptide, D-dimer: domain dimer, N/A: not applicable, EQ-5D: European Quality of Life 5 Dimension Scale, mRS: modified Rankin Scale.

for individuals previously diagnosed with COVID-19 of any age, sex, or ethnicity.
2. Median or mean follow-up time of at least 12 weeks (84 days) since COVID-19 diagnosis, to serve as a proxy for time since infection, in accordance with the NICE definition of PCS. If the index date was hospital admission or discharge, resolution of acute illness, or onset of symptoms, it was assumed that these events occurred either concurrently or subsequent to diagnosis.
3. COVID-19 (any severity) ascertained according to laboratory testing, diagnostic code linkage, and/or clinical diagnosis.
4. Primary research.
5. Presentation as full-text article (including preprints).

Exclusion criteria were:

1. Incomplete or inexact quantitative data (i.e., no exact proportions provided for primary outcomes).
2. Outcomes precede exposure (i.e., it is stated that fatigue, cognitive impairment, inflammation, and/or functional impairment were present prior to COVID-19 infection, and/or did not markedly increase in severity following COVID-19 infection at 12 or more weeks follow-up).
3. Study solely reports new symptoms arising following resolution of acute COVID-19 (i.e., not persisting since diagnosis).
4. Outcomes of interest reported solely in the general population, or in persons without a confirmed prior COVID-19 diagnosis.
5. Median/mean follow-up time of <12 weeks (84 days) since COVID-19 infection or diagnosis.
6. COVID-19 is not verified by laboratory testing or ICD-10 linkage, or is not clinically diagnosed.
7. Post-mortem study of COVID-19 patients.
8. Case series, or any study design wherein participants are selected for inclusion based on the presence of PCS symptoms (i.e., outcomes of interest).
9. Unpublished study, abstract, case report, study with a sample size of <10 persons, or protocol.
10. Non-primary research.

2.3. Data extraction

Published summary data from included articles were independently extracted by two reviewers (FC and SL) using a piloted data extraction form, then corroborated, with discrepancies resolved through discussion. Information to be extracted was established a priori and included study characteristics, participant characteristics and subgroups, sample size and source, modes of ascertainment, follow-up period, exact proportions (including subgroup-specific data where available) pertaining to primary or secondary outcomes, qualitative data pertaining to secondary outcomes, and factors reportedly associated with PCS across individual analyses.

2.4. Quality assessment

Methodological quality and risk of bias was assessed using the Newcastle-Ottawa Scale (NOS) (Stang, 2010), modified for applicable cohort and case-control studies, as well as adapted for cross-sectional studies. Studies wherein the design was unclear were assessed according to the prospective cohort NOS. Cohort studies were penalized for failing to include a non-exposed cohort. All component studies were independently rated by two reviewers (FC and LMWL) and results were corroborated, with discrepancies resolved through discussion. Modified NOSs and methodological quality rankings for each study type are provided (supplementary material).

2.5. Data synthesis and analysis

A meta-analysis of proportions was conducted using R version 4.1.0 (R Foundation for Statistical Computing). An α level of 0.05 was chosen to indicate statistical significance. In anticipation of marked heterogeneity, the *meta::metaprop* function (Balduzzi et al., 2019) was used to pool proportions, indicated as the number of cases exhibiting fatigue or cognitive impairment (events) divided by the size of the sample (observations), via the random-effects restricted maximum-likelihood model (REML) (Kenward and Roger, 1997; Miller, 1978). Where one study reported multiple proportions qualifying as a primary outcome measure (e.g., concentration impairment and memory impairment, which can both be subsumed under cognitive impairment), only the largest proportion was included to prevent data duplication or skewing of true effect size. Where studies provided data for multiple qualifying follow-up periods, the earliest follow-up was used in the main analyses. Single proportions were transformed via the Freeman-Tukey Double arcsine method to stabilize variances (Miller, 1978), Clopper-Pearson 95% confidence intervals (CIs) were calculated for individual studies, and Wald 95% CIs were calculated for pooled proportions. Forest plots for each primary outcome were created via the *meta::forest* function. Random effects subgroup analyses, established a priori, for sex, COVID-19 hospitalization status, age group (children vs adults, defined as median/mean age <18 and ≥18 years, respectively), follow-up duration (<6 months vs ≥6 months), and mode of ascertainment (objective vs subjective) were conducted using the *byvar* argument, assuming separate estimates of between-study variance for each subgroup. Study populations were classified as comprising hospitalized populations if

≥80% of the participants had been hospitalized for COVID-19 (and vice versa for outpatients). Post hoc sensitivity analyses according to NOS quality rating groupings, as well as by study design, were undertaken. Statistically significant differences in inter-group effect sizes were calculated via the Wald-type $\chi 2$ test.

Heterogeneity was quantified using the I^2 statistic, where the cut-offs 30.0%, 50.0%, and 75.0% denote moderate, substantial, and considerable heterogeneity, respectively, as recommended by GRADE (Grading of Recommendations, Assessment, Development and Evaluations) criteria and the Cochrane Handbook's interpretation of heterogeneity scores (Deeks et al., 2008; Schünemann et al., 2019). The Egger regression intercept test and the Begg and Mazumdar rank correlation test, as well as visual inspection of funnel plots for asymmetry, were used to assess publication bias via the *meta::metabias* and *meta::funnel* functions, respectively. Qualitative analysis via narrative synthesis was performed for secondary outcomes, which were not sufficiently homogenous to meta-analyze.

3. Results

3.1. Search results

The literature search yielded 10,979 studies. Following the removal of duplicates, 5965 studies were screened by title and abstract, producing 229 eligible studies. 148 studies were further excluded following full-text screening. Details of study selection are provided in Fig. 1. In total, 81 studies were included in the review: 56 prospective cohort studies, 14 cross-sectional studies, 10 retrospective cohort studies, and 1 retrospective case-control study. Component studies are grouped by design in the supplementary material. The quantitative synthesis primarily evaluating the effect of COVID-19 exposure on fatigue (i.e., fatigue meta-analysis) included 68 studies, whereas the quantitative

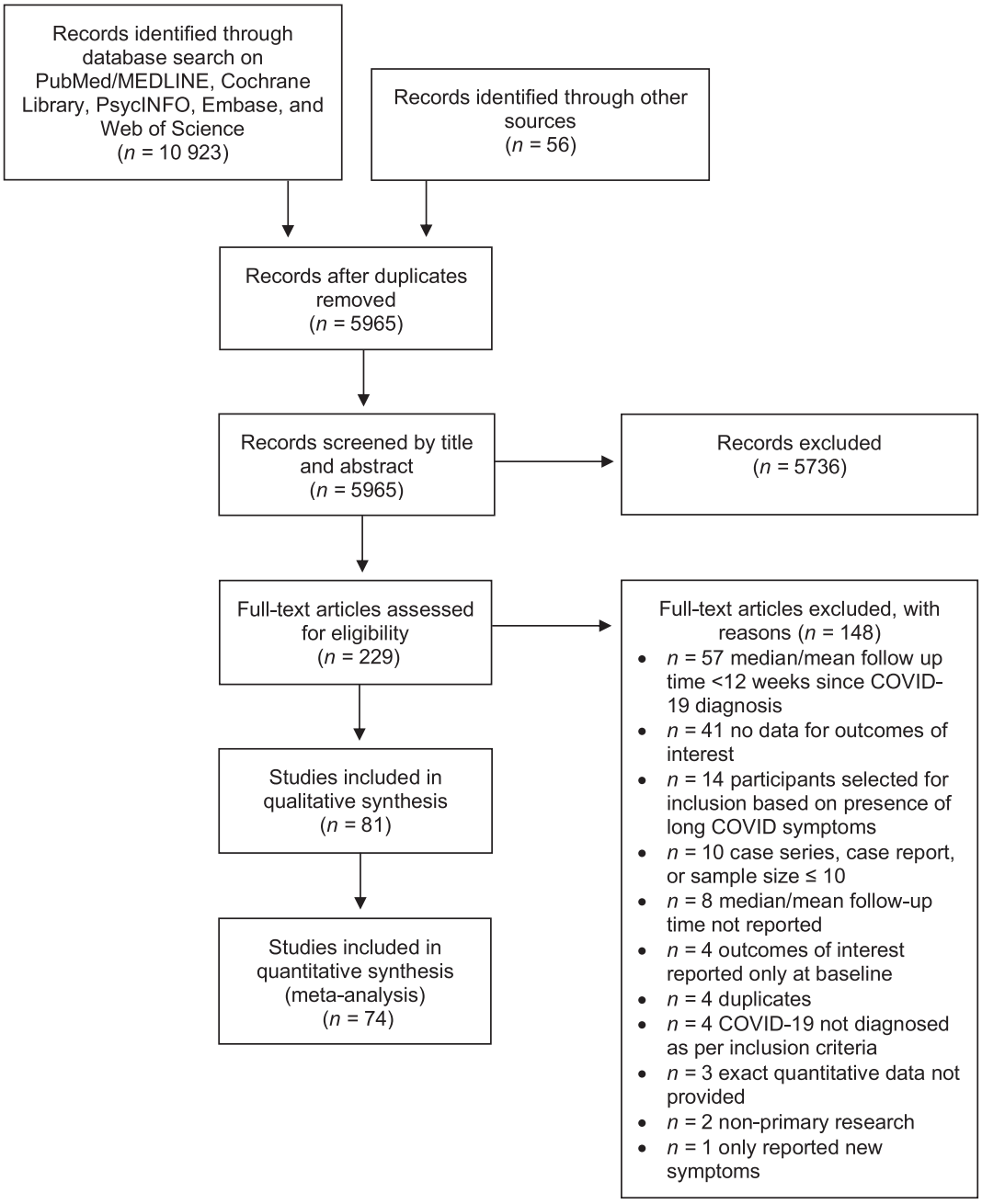

Fig. 1. Flow diagram of study selection.

Table 2
Characteristics and results of studies (n = 81) examining individuals with confirmed COVID-19 12 or more weeks following diagnosis.

Study	Country	Study Design	Sample Source	Sample Characteristics	Follow-up Duration	Ascertainment of COVID-19	Ascertainment of Outcomes	Results	Factors Associated with persistent symptoms
Abdallah et al., 2021	Canada	Prospective Cohort	The Ottawa Hospital	*N* = 63 (including 25 previously hospitalized cases and 38 previously non-hospitalized cases) ● Age Range: ≥18 ● Mean Age*:59.1 ± 13.5 ● Mean Age**: 42.2 ± 12.9 ● Sex (%F/%M)*: 36.0/64.0 ● Sex (%F/%M)**: 47.4/52.6 *pertains to hospitalized cohort**pertains to non-hospitalized cohort	Mean 119.9 ± 16.2 days following first positive test for hospitalized patients, and mean 129 ± 16.5 days for non-hospitalized patients	RT-PCR	Subjective self-report via clinical follow-up	● 71.4% (45/63) reported fatigue (72% [18/25] hospitalized and 71.1% [27/38] non-hospitalized)	
Amin-Chowdhury et al., 2021[a]	England	Prospective Cohort	Public Health England (ESCAPE study)	*N* = 140 (clinical and non-clinical healthcare workers) ● Age Range: ≥20 ● Median Age*: 41 (31–52) ● Sex* (%F/%M): 71.3/28.7	Median 7.5 (7.1–7.8) months following COVID-19 diagnosis	Serologyand RT-PCR	Subjective self-report via online questionnaire	● 39.3% (55/140) of cases reported fatigue/tiredness after exertion ● 35.0% (49/140) of cases reported forgetfulness ● 27.9% (39/140) of cases reported confusion/brain fog/trouble focusing attention ● 20.7% (29/140) of cases reported short-term memory loss ● 15.7% (22/140) of cases reported trouble trying to form words	● Female sex was associated with unusual fatigue and forgetfulness ● Having underlying comorbidities was associated with unusual fatigue and confusion
Arnold et al., 2020	United Kingdom	Prospective Cohort	Diagnostic and Severity markers of COVID-19 to Enable Rapid triage (DISCOVER) study (Bristol)	*N* = 110 (all previously hospitalized cases) ● Age Range: ≥18 ● Median Age*: 47 (32–61) ● Median Age**: 57 (48–67) ● Median Age***: 62 (54–71) ● Sex*(%F/%M): 38.2/61.8 *mild cases**moderate cases***severe cases	Median 90 (80–97) days following onset of symptoms	RT-PCR or clinico-radiological diagnosis	Objective assessment via laboratory testing (inflammatory parameters), SF-36 (quality of life), as well as subjective self-report via questionnaire	● 39% (43/110) reported fatigue ● SF-36 scores demonstrated a reduction in reported health status across all domains as compared with age-matched population norms ● 1.8% (2/110) exhibited CRP levels > 10 mg/L	● Physical SF-36 scores were significantly lower in patients with severe COVID-19 compared with mild/moderate
Augustin et al., 2021	Germany	Prospective Cohort	University Hospital Cologne (recruited through public media)	*N* = 353 ● Age Range: age* ≥18 ● Median Age*: 43 (31–54)	Median 6.8 (6–8) months following onset of symptoms	RT-PCR	Subjective self-report via systematic questionnaires and evaluation by physician	● 14.7% (52/353) of individuals reported fatigue	● Anosmia and diarrhea during acute COVID-19, as well as a lower baseline level of SARS-CoV-2 IgG, were

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Table 2 (*continued*)

Study	Country	Study Design	Sample Source	Sample Characteristics	Follow-up Duration	Ascertainment of COVID-19	Ascertainment of Outcomes	Results	Factors Associated with persistent symptoms
				● Sex* (%F/%M): 53.5/46.5 *pertains to initial cohort of 958 COVID-19 convalescent individuals, which were not all followed up					associated with higher risk of developing long-term symptoms ● Male sex was associated with a lower risk of post-COVID syndrome ● Female patients and individuals with a prior diagnosis of depression or anxiety had a higher risk of suffering from fatigue
Breton et al., 2021	USA	Retrospective Cohort	Residents of greater New York City Tristate Region	$N = 41$ cases (including 8 previously hospitalized) ● Age Range: 24–73 ● Median Age: 45 ● Sex (%F/%M): 36.6/63.4	Mean 6.1 months following COVID-19 infection	RT-PCR	Objective assessment via laboratory testing (flow cytometry; intracellular cytokine staining)	● Antigen-specific CD4 + T cells expressing IL-2, IFN-γ, and TNF-α were markedly increased in COVID-19–recovered individuals as compared with healthy donors	
Buonsenso et al., 2021	Italy	Cross-sectional	Fondazione Policlinico Universitario Agostino Gemelli (part of ISARIC)	$N = 68$ children (including 6 previously hospitalized and 3 in pediatric ICU) ● Age Range: ≤18 ● Mean Age: 11 ± 4.4 ● Sex (%F/%M): 48.1/51.9	Mean 162.5 ± 113.7 days following diagnosis	RT-PCR	Subjective self-report via phone interview or outpatient assessment	● 13.2% (9/68) of individuals reported more fatigue compared to before COVID-19 diagnosis ● 11.8% (8/68) of individuals reported lack of concentration	
Cirulli et al., 2020[a]	USA	Prospective Cohort	Helix DNA Discovery Project and the Healthy NevadaProject	$N = 357$ (including 9 previously hospitalized cases) ● Age Range*: ≥18 ● Median Age*: 56 ● Sex* (%F/%M): 64.1/35.9 *pertains to entire cohort, including both COVID-19 positive and negative	90 days following onset of symptoms	Laboratory test	Subjective self-report via online questionnaires	● 7.96% (9/113) reported fatigue ● 7.50% (9/120) reported decreased alertness ● 8.20% (10/122) reported memory loss ● 12.61% (15/119) reported difficulty concentrating	● Initial dyspnea and a large number of initial symptoms were associated with long COVID symptoms after 30 days ● Individuals who were more ill at the onset of symptoms are at higher risk of long-term symptoms ● There was an association of between anxiety disorders and autoimmune/rheumatologic disorders and long-term symptoms ● Female patients were more likely to have long-term symptoms
Darley et al., 2021[a]	Australia	Prospective Cohort	St. Vincent's Hospital Sydney (ADAPT study)	$N = 99$ ● Age Range: ≥18	Median 240 (227–256) days following infection	RT-PCR	Objective assessment via SPHERE-34 (fatigue, cognitive function)	● 23% (15/65) reported fatigue	● Female sex and hospitalization for acute COVID-19 were

(*continued on next page*)

Table 2 (*continued*)

Study	Country	Study Design	Sample Source	Sample Characteristics	Follow-up Duration	Ascertainment of COVID-19	Ascertainment of Outcomes	Results	Factors Associated with persistent symptoms
				● Median Age: 47 (35–58) ● Sex (%F/%M): 39/61				● 27% (26/97) reported poor memory a good part of, or most of the time ● 33% (32/97) patients reported poor concentration a good part of, or most of the time ● 18% (17/97) patients reported feeling lost for words a good part of, or most of the time	independently associated with persistent symptoms at 8-months
Elkan et al., 2021[a]	Israel	Retrospective Case-control	Shamir (Assaf Harofeh) Medical Center	$N = 66$ (all previously hospitalized cases) ● Age Range: ≥18 ● Median Age: 58.5 (49.8–68.3) ● Sex (%F/%M): 56.1/43.9	Median 9 (6–9) months following discharge	RT-PCR	Objective assessment via RAND-36 (quality of life), as well as subjective self-report	● 50% (33/66) reported fatigue ● ~17% reported memory impairment and concentration impairment *(exact proportion not provided)* ● RAND-36 emotional role median score: 100 (0–100) ● RAND-36 social functioning median score: 87.5 (50–100) ● RAND-36 vitality median score: 57.5 (30–76.2)	● A greater proportion of patients with more severe acute disease reported persistent symptoms
Evans et al., 2021[a]	United Kingdom	Prospective Cohort	53 National Health Service hospitals (PHOSP-COVID study)	$N = 1077$ (all previously hospitalized cases) ● Age Range: ≥18 ● Mean Age: 58 ± 13 ● Sex (%F/%M): 35.7/64.3	Median 159 (120–189) days following discharge	RT-PCR or clinician-diagnosed	Objective assessment via FACIT (fatigue), MoCA (cognitive function), EQ-5D-5L, WG-SS (quality of life and functioning), laboratory testing (serology), and subjective self-report via research visit and clinical follow-up questionnaire	● 56.2% (429/763), reported significantly worse fatigue compared to pre-COVID-19 (mean FACIT score 16.8 ± 13.2) ● 16.9% (150/888) reported cognitive impairment, operationalized as a MoCA score < 23 ● 11.2% (90/804) exhibited persistent systemic inflammation (CRP > 10 mg/L) ● 13.1% (97/738) exhibited elevated D-dimer levels (≥500 ng/ml) ● 19.3% (124/641) experienced a health-related change in their occupational status	● Female sex, middle-age, white ethnicity, two or more comorbidities, and more severe acute illness were associated with failure to recover (persistent symptoms)

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Table 2 (*continued*)

Study	Country	Study Design	Sample Source	Sample Characteristics	Follow-up Duration	Ascertainment of COVID-19	Ascertainment of Outcomes	Results	Factors Associated with persistent symptoms
								● Mean EQ5D-5L VAS changed from 81 ± 17 (pre-COVID-19) to 72 ± 20 (post-COVID-19) ● 1/5 of the population reached the threshold for a new disability with at least one domain coded as "a lot of difficulty" or "cannot do it all" on the WG-SS	
Evlice et al., 2021	Turkey	Retrospective Cohort	Hospital in Turkey	*N* = 266 (all previously hospitalized cases, including 11 in ICU) ● Age Range: ≥18 ● Mean Age: 56.96 ± 16.62 ● Sex (%F/%M): 51.5/48.5	Mean 99.80 ± 26.16 days following discharge	RT-PCR or CT	Subjective self-report via telephone survey	● 4.9% (13/266) reported fatigue	● Persistent symptoms were observed at a higher rate in cases with comorbidity ● Statistically significant relationship between high admission CRP level and presence of persistent symptoms
Fernández-de-Las-Peñas (1) et al., 2021	Spain	Retrospective Cohort	Four public hospitals in Madrid	*N* = 1142 (all previously hospitalized cases) ● Age Range: N/A ● Mean Age: 61 ± 17 ● Sex (%F/%M): 47.5/52.5	Mean 7.0 ± 0.6 months following discharge	RT-PCR	Subjective self-report via systematic telephone interview conducted by trained researchers	● 60.8% (695/1142) reported fatigue ● 19.0% (217/1142) reported memory loss ● 9.6% (110/1142) reported brain fog ● 8.1% (93/1142) reported attention disorders	● Women reported fatigue more frequently than men ● Female sex, number of days at hospital, previous comorbidities, and number of symptoms at hospital admission were associated with more long COVID symptoms
Fernández-de-Las-Peñas (2) et al., 2021	Spain	Retrospective Cohort	Three public hospitals in Madrid	*N* = 1950 (all previously hospitalized cases, including 129 in the ICU) ● Age Range: N/A ● Mean Age: 61 ± 16 ● Sex (%F/%M): 46.9/53.1	Mean 11.2 ± 0.5 months after hospital discharge	RT-PCR and radiological findings	Self-report via systematic telephone interview conducted by trained healthcare professionals	● 61.4% (1206/1950) reported fatigue ● 16% (6/38) reported no longer being able to participate in a sport or recreational activity because of their ongoing symptoms	
Ferrucci et al., 2021	Italy	Prospective Cohort	Non-intensive COVID units of the ASST Santi Paolo e Carlo hospitals	*N* = 38 (all previously hospitalized cases in non-intensive wards) ● Age Range: 22–74 ● Mean Age: 53.45 ± 12.64 ● Sex (%F/%M): 28.9/71.1	Mean 4.43 ± 1.22 months following discharge	RT-PCR	Objectively assessed via MoCA (cognitive function), BRB-NT (neurological battery of tests for cognition), SSD (fatigue)	● 50% (15/30) reported a moderate to severe increase in fatigability ● 60.5% (23/38) obtained scores below Italian normative cut-offs in at least one task of the BRB-NT [exhibited cognitive abnormalities] ● 42% (16/38) demonstrated slowing	● Females more frequently reported a subjective decline in cognitive performance following hospitalization ● Participants aged ≥ 55 obtained lower scores in all measures of verbal memory,

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Table 2 (*continued*)

Study	Country	Study Design	Sample Source	Sample Characteristics	Follow-up Duration	Ascertainment of COVID-19	Ascertainment of Outcomes	Results	Factors Associated with persistent symptoms
								of cognitive processing speed, as evidenced by low SDMT scores ● 20% (8/38) demonstrated long-term verbal and spatial memory dysfunctions ● 26.7% (8/30) reported a moderate to severe increase in forgetfulness and lack of concentration ● 23.3% (7/30) reported a moderate to severe increase in time needed to perform tasks such as reading/writing documents ● 20% (6/30) reported moderate to severe difficulties in learning new skills or procedures	when compared to those aged < 55 ● ARDS at hospitalization was associated with worse verbal memory performance and worse delayed verbal recall performance
Fortini et al., 2021	Italy	Prospective Cohort	San Giovanni di Dio Hospital	$N = 59$ (all previously hospitalized cases in non-intensive ward) ● Age Range: N/A ● Mean Age: 68.2 ± 12.8 ● Sex (%F/%M): 47.5/52.5	Median 123 (116–145) days following discharge	RT-PCR	Objective assessment via laboratory testing (inflammatory parameters), as well as subjective self-report via self-administered questionnaire	● 42.4% (25/59) reported fatigue ● 13.6% (8/59) reported confusion ● 32.2% (19/59) exhibited elevated D-dimer levels ● 32.2% (19.59) exhibited elevated IL-6 levels	● No significant correlation between the values of inflammatory parameters and patient-reported symptoms was detected by the multivariable logistic regression analysis
Froidure et al., 2021	Belgium	Prospective Cohort	Hospital in Belgium	$N = 126$ patients (all previously hospitalized and/or ICU cases) ● Age Range: N/A ● Median Age: 60 (53–68) ● Sex (%F/%M): 59/41	Median 95 (86–107) days following infection	RT-PCR and lung HRTC or chest X-ray	Subjective self-report via clinical assessment	● 25% (32/126) reported ongoing fatigue	
Frontera et al., 2021	USA	Prospective Cohort	Four NYC area hospitals	$N = 382$ (all previously hospitalized cases including 196 neurologic cases, 67 of which were admitted to the ICU, and 186 cases without neurological disorders during hospitalization, 54 of which were admitted to the ICU)	Median 6.7 (6.5–6.8) months following onset of symptoms	RT-PCR	Objective assessment via MoCA (cognitive function), Barthel index (functional impairment), as well as subjective self-report via telephone questionnaire	● 36.0% (98/272) reported worse than average fatigue, operationalized as T-score > 50 ● 49.3% (106/215) exhibited cognitive impairment, operationalized as MoCA score < 18	● Patients diagnosed with new neurological complications during hospitalization for COVID-19 had a 2-fold increased odds of worse 6-month functional outcome (as measured by the modified Rankin Score)

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Study	Country	Study Design	Sample Source	Sample Characteristics	Follow-up Duration	Ascertainment of COVID-19	Ascertainment of Outcomes	Results	Factors Associated with persistent symptoms
				● Age Range*: ≥18 ● Median Age*: 68 (55–77) ● Sex* (%F/%M): 65/35 ● Age Range**: ≥18 ● Median Age**: 69 (57–78) ● Sex** (%F/%M): 65/35 *neurologic COVID-19 cohort**non-neurologic COVID-19 cohort				● 52.6% (81/154) of those who were working premorbidly were able to return to work ● 44.11% (134/304) could not independently perform some basic activities of daily living, operationalized as Barthel index < 100	
García-Abellán et al., 2021[a]	Spain	Prospective Cohort	Hospital General Universitario de Elche	$N = 116$ (all previously hospitalized cases, including 15 previously admitted to ICU) ● Age Range: N/A ● Median Age*: 66 (57–76) ● Sex* (%F/%M): 50/50 *pertains to patients reporting symptoms at 6-month follow-up	6 months following discharge	RT-PCR and serology	Objective assessment via laboratory testing (immunological parameters), and subjective self-report via CSQ (fatigue) during clinical visit	● 10.3% (12/116) reported fatigue ● Median serum IL-6: 3 (1.8–5.1) pg/mL ● Median serum CRP: 1 (0.4–5.1) mg/L ● Median serum D-dimer: 0.4 (0.2–0.7) mcg/mL	● Patients with the highest CSQ scores showed lower CRP levels on admission and weaker initial antibody response ● Female sex predicted persistent symptoms ● Post-COVID syndrome was associated with additional distinctive innate and adaptive immune traits, consisting of a weaker initial inflammatory response, evidenced by lower baseline levels of CRP and ferritin ● Patients with mid-term lasting symptoms [follow up at 2 months] showed persistent residual inflammation
Garrigues et al., 2020	France	Retrospective Cohort	Beaujon Hospital, COVID-19 Unit	$N = 120$ (all previously hospitalized cases, including 24 in ICU that underwent mechanical ventilation) ● Age Range: N/A ● Mean Age: 63.2 ± 15.7 ● Sex (%F/%M): 37.5/62.5	Mean 110.9 days ± 11.1 following hospital admission	RT-PCR and/or chest CT	Objective assessment via EQ-5D-5L (quality of life), as well as subjective self-report via telephone questionnaire conducted by trained physicians	● 55.0% (66/120) reported fatigue ● 34.2% (41/120) reported loss of memory ● 26.7% (32/120) reported attention disorders ● 67.9% (38/56) of those who worked before hospitalization returned to work ● 71.8 % (28/39) of those who practiced sport regularly before hospitalization resumed sport	

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Study	Country	Study Design	Sample Source	Sample Characteristics	Follow-up Duration	Ascertainment of COVID-19	Ascertainment of Outcomes	Results	Factors Associated with persistent symptoms
								● EQ-VAS mean score of 70.3 ± 21.5, and EQ-5D index mean score of 0.86 ± 0.20	
Ghosn et al., 2021	France	Prospective Cohort	Institut National de la Santé Et de la Recherche Médicale	*N* = 1137 (all previously hospitalized cases, including 288 in ICU) ● Age Range: N/A ● Median Age: 61 (51–71) ● Sex (%F/%M): 37/63	3 and 6 (median 194 [188–205] days) months following hospital admission	RT-PCR	Subjective self-report via physician visit	● 57% (538/944) reported fatigue at month 3 ● 38% (404/1063) reported fatigue at month 6 ● 29% (125/431) of those who had a professional occupation had not returned to work at 6 months	● Presence of 3 + symptoms at 6-month follow-up was associated with female sex and having 3 + symptoms at admission
González et al., 2021	Spain	Prospective Cohort	Hospital Universitary Arnau de Vilanova	*N* = 62 (all previously ICU cases) ● Age Range: ≥18 ● Median Age: 60 (48–65) ● Sex (%F/%M): 25.8/74.2	3 months following discharge	RT-PCR	Objective assessment via SF-12 (quality of life), as well as subjective self-report	● 29.5% (16/62) reported muscular fatigue ● SF-12 Physical score median: 45.9 (36.1–54.4) ● SF-12 Mental score median: 55.8 (40.6–58.0) ● SF-12 showed mean scores that were substantially lower than those of healthy people, those with other chronic diseases, and healthy Spanish people	
González-Hermosillo et al., 2021	Mexico	Prospective Cohort	Instituto Nacional de Cardiología Ignacio Chávez	*N* = 130 (all previously hospitalized cases) ● Age Range: ≥18 ● Mean Age: 51 ± 14 ● Sex (%F/%M): 36.4/63.6	3 and 6 (mean 270 ± 32 days) months following discharge	RT-PCR	Subjective self-report via telephone questionnaire based on ME/CFS International Consensus Criteria	● 53% (69/130) reported fatigue that did not exist before COVID-19 at 3-month follow-up (40.5% [28/130] females reported fatigue compared to 27.8% [17/130] without fatigue) ● 46.9% (61/130) reported fatigue that did not exist before COVID-19 at 6-month follow-up ● 23% (30/130) reported concentration impairment that did not exist before	● Patients with fatigue at 3-month follow-up were older compared with those without fatigue, and had a longer length of hospital stay ● Age 40–50 years old was associated with fatigue ● There was a significantly higher prevalence of persisting symptoms in those with fatigue

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Study	Country	Study Design	Sample Source	Sample Characteristics	Follow-up Duration	Ascertainment of COVID-19	Ascertainment of Outcomes	Results	Factors Associated with persistent symptoms
								COVID-19 at 3-month follow-up ● 45.4% (59/130) reported short-term memory loss that did not exist before COVID-19 at 3-month follow-up	
Havervall et al., 2021	Sweden	Prospective Cohort	Danderyd Hospital	$N = 1395$ health care professionals (mild cases, *hospitalization status not specified*) ● Age Range: ≥18 ● Median Age: 43 (33–52) ● Sex (%F/%M): 83/17	8 months following onset of symptoms	Serology	Objective assessment via Sheehan Disability Scale (functional outcomes), as well as subjective self-report via smartphone app questionnaire	● 6.8% (22/323) reported fatigue after 4 months, and 4.0% (13/323) reported fatigue after 8 months ● 1.9% (6/323) reported concentration impairment after 4 months, and 0.6% (2/323) reported concentration impairment after 8 months ● 1.2% (4/323) reported memory impairment after 4 months, and 0.3% (1/323) reported memory impairment after 8 months ● 8% reported that long-term symptoms moderately to markedly disrupted work life ● 15% reported that long-term symptoms moderately to markedly disrupted social life ● 12% long-term symptoms moderately to markedly disrupted home life ● 11% long-term symptoms moderately to markedly disruption in any Sheehan Disability Scale category	
Huang et al., 2021	China	Ambidirectional Cohort	Jin Yin-tan Hospital	$N = 1733$ patients (all previously hospitalized cases, including 76 previously admitted to ICU)	Median 186 (175–199) days following onset of symptoms	Laboratory testing	Objective assessment viaEQ-5D-3L (quality of life), as well as subjective self-report via questionnaire	● 63% (1038/1655) reported fatigue/muscle weakness ● Median quality of life score was 80/100 (70–90), with 7%	● Increased age and severity of acute disease were positively associated with fatigue and muscle weakness

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Study	Country	Study Design	Sample Source	Sample Characteristics	Follow-up Duration	Ascertainment of COVID-19	Ascertainment of Outcomes	Results	Factors Associated with persistent symptoms
				● Age Range: ≥18 ● Median Age: 57.0 (47.0–65.0) ● Sex (%F/%M): 48/52				(113/1622) reporting mobility problems, 1% (11/1622) reporting personal care problems, 2% (25/1611) reporting problems with usual activity, and 27% (431/1616) reporting pain or discomfort	● Women reported a higher percentage of symptoms at follow-up
Jacobson et al., 2021	USA	Prospective Cohort	Patients from enrolled clinical trials at Stanford University	$N = 118$ participants (including 22 previously hospitalized cases, of which 11 were previously admitted to ICU) ● Age Range: N/A ● Mean Age: 43.3 ± 14.4 ● Sex (%F/%M): 46.6/53.4	Mean 119.3 ± 33.0 days following diagnosis	RT-PCR	Objective assessment via WPAI (functional outcomes), as well as subjective self-report via questionnaire	● 30.5% (36/118) reported fatigue overall, including 36.4% (8/22) of previously hospitalized patients and 29.2% (28/96) of non-hospitalized patients ● 17.0% (20/118) reported memory problems overall, including 22.7% (5/22) of previously hospitalized patients and 15.6% (15/96) of non-hospitalized patients ● 68.47% (80/117) overall reported being employed, including 72.7% (16/22) of previously hospitalized patients and 67.4% (64/95) of non-hospitalized patients ● 11.5% (9/78) overall reported missed work due to health, including 13.3% (2/15) of previously hospitalized patients and 11.1% (7/63) of non-hospitalized patients ● 38.9% (28/72) overall reported any work impairment due to health, including 58.3% (7/12) of previously hospitalized patients and 35.0% (21/60) of	● Older age and hospitalization were associated with higher odds of any activity impairment ● Presence of fatigue was associated with long-term activity impairment (in multivariate analysis)

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Study	Country	Study Design	Sample Source	Sample Characteristics	Follow-up Duration	Ascertainment of COVID-19	Ascertainment of Outcomes	Results	Factors Associated with persistent symptoms
								non-hospitalized patients ● 50.9% (54/106) overall reported any activity impairment due to health, including 73.7% (14/19) of previously hospitalized patients and 46.0% (40/87) of non-hospitalized patients	
Johnsen et al., 2021	Denmark	Cross-sectional	Copenhagen University Hospital at Bispebjerg	$N = 57$ (34 previously hospitalized cases and 34 non-hospitalized cases) ● Age Range: N/A ● Mean Age: 51 ± 13 ● Sex (%F/%M): 51/49	3 months following discharge/resolution of acute disease	RT-PCR	Objective assessment via WPAI, PCFS (functional outcomes), EQ-5D-5L (quality of life), and CFQ, SCIP-D, and TMT-B (cognitive function)	● 58% (26/45) demonstrated clinically significant cognitive impairment (66% [19/29] of previously hospitalized, 44% [8/19] non-hospitalized) ● Median EQ-VAS: 70 (55,81) ● Percent work time missed due to health: 0 (0,24) ● Percent impairment while working due to health: 20 (9, 45) ● Percent overall work impairment due to health: 23 (6, 66) ● Percent activity impairment due to health: 30 (10,60)	
Kashif et al., 2021[a]	Pakistan	Prospective Cohort	Hameed Latif Hospital	$N = 242$ (including hospitalized cases and non-hospitalized cases who sought healthcare at hospital) ● Age Range: 18–65 ● Mean Age: 35.64 ± 12.57 ● Sex (%F/%M): 30.6/69.4	3 months following discharge or onset of symptoms	RT-PCR	Subjective self-report via telephone interview	● 41.7% (101/242) reported fatigue	● Prolonged symptoms months after recovery from mild COVID-19 were associated with female sex
Klein et al., 2021	Israel	Retrospective Cohort	Israeli residents recruited through social media and word of mouth	$N = 103$ (all mild symptomatic cases; asymptomatic excluded, *hospitalization status not specified*) ● Age Range: ≥18 ● Mean Age: 35 ± 12 ● Sex (%F/%M): 40/60	6 months following onset of symptoms	RT-PCR	Subjective self-report via telephone questionnaire	● 22% (23/103) reported fatigue ● 6% (6/103) reported memory disorders ● 1% (1/103) reported concentration disorders	

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Study	Country	Study Design	Sample Source	Sample Characteristics	Follow-up Duration	Ascertainment of COVID-19	Ascertainment of Outcomes	Results	Factors Associated with persistent symptoms
Latronico et al., 2021[a]	Italy	Prospective Cohort	3 ICUs of the Spedali Civili University Hospital	$N = 55$ (all cases which were previously admitted to ICU with ARDS) ● Age Range: ≥18 ● Median Age: 59 (54–64) ● Sex*(%F/%M): 17/83 *pertains to a larger cohort of 163 admitted to ICU, which were not all followed up	3 and 6 months following discharge	RT-PCR	Objective assessment via FSS (fatigue), PICS, MoCA (cognitive function), SF-36 (quality of life), Barthel Index (functional outcomes)	● 36% (20/55) reported severe fatigue, operationalized as FSS score 36 + at 3 months ● 36% (16/45) reported severe fatigue, operationalized as FSS score 36 + at 6 months ● 22% (12/55) exhibited mild-severe cognitive impairment according to MoCA at 3 months ● 26% (10/38) exhibited mild cognitive impairment according to MoCA at 6 months ● 33% (18/55) of patients exhibited mild role limitations according to SF-36 ● 65% (36/55) had returned to work with the same pre-COVID-19 employment status, 5% (3/55) with worsening employment status (fewer hours worked per week), and 32% (18/55) had not returned to work ● 5% (3/55) reported significant derangement in social function, operationalized as > 2 SD on SF-36 domain at 3 months, and 3% (1/36) at 6 months	
Leth et al., 2021	Denmark	Prospective Cohort	Department of Infectious Diseases, Aarhus University Hospital	$N = 49$ (all previously hospitalized cases, including 6 previously admitted to ICU) ● Age Range: ≥18 ● Median Age: 58 (48–73) ● Sex (%F/%M): 57/43	Median 128 (98–148) days following discharge	RT-PCR	Objective assessment via OMC (cognitive function), as well as subjective self-report via in person or telephonequestionnaire	● 63% (31/49) reported fatigue ● 45% (22/49) reported difficulty concentrating ● 11% (4/38) demonstrated impaired cognitive function, operationalized as an OMC score of ≤ 24	● Significantly reduced OR of challenged concentration if the patient was a current or previous smoker

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Study	Country	Study Design	Sample Source	Sample Characteristics	Follow-up Duration	Ascertainment of COVID-19	Ascertainment of Outcomes	Results	Factors Associated with persistent symptoms
Liang et al., 2020	China	Prospective Cohort	Wuhan Union Hospital	$N = 76$ (all previously hospitalized, including 65 healthcare worker cases, and 7 previously admitted to ICU) ● Age Range: 24–76 ● Mean Age: 41.3 ± 13.8 ● Sex (%F/%M): 72.4/27.6	3 months following discharge	RT-PCR	Subjective self-report via questionnaire	● 59% (45/76) reported fatigue	● Serum troponin-I levels during acute illness showed high correlation with fatigue after hospital discharge
Liyanage-Don et al., 2021	USA	Prospective Cohort	2 Columbia University Hospitals	$N = 153$ (all previously hospitalized cases) ● Age Range: ≥18 ● Mean Age: 54.5 ± 16.7 ● Sex (%F/%M): 39.9/60.1	Median 3.7 (2.6–5.7) months following discharge	RT-PCR	Subjective self-report via online or telephone questionnaire	● 20.3% (31/153) reported fatigue	● Patients with PTSD and/or depression were more likely to report fatigue
Logue et al., 2021	USA	Prospective Cohort	University of Washington	$N = 177$ (145 previously outpatient cases, 16 previously hospitalized) ● Age Range: 18–94 ● Mean Age: 48.0 ● Sex (%F/%M): 57.1/42.9	Median 169 (range 31–300) days following onset of acute COVID-19	RT-PCR	Subjective self-report via electronic questionnaire	● 13.6% (24/177) reported fatigue ● 2.3% (4/177) reported brain fog ● 29.9% (53/177) reported worsened health-related quality of life compared with baseline measurements	
Mattioli et al., 2021	Italy	Prospective Cohort	Unit of Occupational Health, General University Hospital of Brescia	$N = 150$ (120 healthcare workers cases, including 2 with previous respiratory failure requiring hospitalization) and 30 healthcare worker healthy controls) ● Age Range: N/A ● Median Age*: 47.86 (26–65) ● Sex* (%F/%M): 75/25 *pertains to cases	4 months following first COVID-19 diagnosis	RT-PCR	Objective assessment via MMSE (cognitive function), as well as subjective self-report via clinical diagnostic assessment (including questionnaire)	● 15% (18/120) reported fatigue ● 11.6% (14/120) reported attention difficulties ● 6.6% (8/120) reported memory difficulties ● MMSE results were normal in both cases (median 29; 27–30), and controls (median 29; 28–30), operationalized as MMSE scores 24+	
Mazza et al., 2021	Italy	Prospective Cohort	IRCCS San Raffaele Hospital	$N = 226$ (including 177 hospitalized cases and 49 cases treated at home) ● Age Range: 26–87 ● Mean Age: 58.5 ± 12.8 ● Sex (%F/%M): 34/66	Mean 90.1 ± 13.4 days following discharge	RT-PCR	Objective assessment via BACS (cognitive function), as well as subjective self-report via questionnaire	● 8% (11/130) scored poorly in the domain of verbal memory (10% [7/70] males; 9% [4/44] females) ● 30% (39/130) scored poorly in the domain of verbal fluency (32% [22/130] males; 33% [17/130] females)	● Baseline systemic inflammation predicted cognitive impairment at follow-up

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Study	Country	Study Design	Sample Source	Sample Characteristics	Follow-up Duration	Ascertainment of COVID-19	Ascertainment of Outcomes	Results	Factors Associated with persistent symptoms
								● 24% (30/126) scored poorly in the domain of working memory (15% [11/73] males; 37% [19/51] females) ● 33% (43/130) scored poorly in the domain of attention and Information processing (38% [29/76] males; 27% [14/52] females) ● 55% (72/130) scored poorly in the domain of psychomotor coordination (59% [43/73] males; 56% [29/52] females) ● 46% (60/130) scored poorly in the domain of executive functions (46% [32/70] males; 56% [28/50] females)	
Mei et al., 2021	China	Prospective Cohort	Wuhan No.1 Hospital, Wuchang Hospital, Zhongshang Hospital, and Hubei Province Hospital	$N = 3,677$ (all previously hospitalized cases) ● Age Range: 10–98 ● Median Age: 59 (47–68) ● Sex (%F/%M): 54.1/45.9	Median 144 (135–157) days following discharge	RT-PCR	Subjective self-report during clinical follow-up	● 1.5% (55/3677) reported fatigue ● 1.7% (64/3677) reported reduction in physical strength ● 1.3% (49/3677) reported headache/dizziness/poor memory ● 0.03% (1/3677) reported confusion	● The majority of deaths during follow-up were male ● The risk of the development of physical abnormalities was independent of age and sex ● The incidence of post-COVID-19 sequelae of elderly COVID-19 survivors (age $\geq$ 60 years) was slightly increased compared to that of young survivors (age $<$ 60)
Menges et al., 2021[a]	Switzerland	Cross-sectional	General Population of Zurich (Zurich SARS-CoV-2 Cohort Study)	$N = 431$ (including 81 previously hospitalized cases, of which 10 were in ICU, and 350 non-hospitalized cases) ● Age Range: $\geq$18 ● Median Age: 47 (33–58) ● Sex (%F/%M): 49.7/50.3	Median 220 (181–232) days following diagnosis	RT-PCR	Objective assessment via FAS (fatigue), EQ-5D-5L (quality of life), as well as subjective self-report via online survey conducted via REDcap	● 54.7% (233/426) reported fatigue measured by FAS (59.2% [125/211] of females and 50.2% [108/215] males; 55.9% [195/349] non-hospitalized and 49.4% [38/77] hospitalized) ● Median FAS score: 22 (19–25) ● 53% (225/431) reported problems in	● Younger individuals and females more frequently reported symptoms of fatigue ● A higher proportion of female participants and initially hospitalized individuals reported not having fully recovered ● Severe to very severe acute symptoms and the presence of co-morbidities were

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Study	Country	Study Design	Sample Source	Sample Characteristics	Follow-up Duration	Ascertainment of COVID-19	Ascertainment of Outcomes	Results	Factors Associated with persistent symptoms
								at least one EQ-5D-5L dimension ● 0.5% (2/430) reported problems with self-care ● 10.5% (45/230) reported problems with daily activity ● Median EQ-5D-5L: 0.89 (0.85–1.00)	associated with non-recovery
Miskowiak et al., 2021	Denmark	Prospective Cohort	Bispebjerg Hospital (IMPACT-COVID study)	$N = 129$ (29 previously hospitalized cases, and 100 matched healthy controls) ● Age Range: N/A ● Mean Age (SD): 56.2 ± 10.6 ● Sex (%F/%M): 41/59	3–4 months following hospital discharge	RT-PCR and serology	Objective assessment via SCIP-D, TMT-B, and CFQ (cognitive function), and EQ-5D-5L (quality of life), as well as subjective self-report via questionnaire	● 65% (19/29) of patients exhibited clinically-significant cognitive impairment, operationalized as SCIP total scores ≥ 0.5 SD below the demographically adjusted predicted scores ● 83% (19/23) of patients reported subjective cognitive difficulties in daily life, operationalized as CFQ scores ≥ 43, and subjective cognitive complaints (CFQ Total scores) correlated significantly with objectively measured global cognitive impairments ● 0% reported work time missed due to health (absenteeism) ● 10% reported impairment while working due to health (presenteeism) ● 10% reported overall work impairment due to health ● 20% reported activity impairment due to health	● More global cognitive impairment and executive dysfunction both correlated with greater disability within EQ-5D 'usual activity' and 'anxiety and depression ● Greater objective cognitive impairments were associated with more subjective cognitive difficulties, absenteeism, and poorer quality of life ● Poorer pulmonary function and more respiratory symptoms after recovery were associated with more cognitive impairments
Miyazato et al., 2021	Japan	Cross-sectional	Disease Control and Prevention Center and National Center for Global Health and Medicine	$N = 63$ (all previously hospitalized cases) ● Age Range: N/A ● Mean Age: 48.1 ± 18.5 ● Sex (%F/%M): 33.3/66.7	Mean 129 ± 21 days following onset of symptoms	RT-PCR	Subjective self-report via structured telephone interview conducted by the investigators	● 9.5% (6/63) reported fatigue which was not chronic before onset of COVID-19	

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Study	Country	Study Design	Sample Source	Sample Characteristics	Follow-up Duration	Ascertainment of COVID-19	Ascertainment of Outcomes	Results	Factors Associated with persistent symptoms
Morin et al., 2021	France	Prospective Cohort	Bicêtre Hospital (Paris-Saclay University hospitals)	$N = 478$ (all previously hospitalized cases, including 142 previously admitted to ICU) ● Age Range: ≥18 ● Mean Age: 60.9 ± 16 ● Sex (%F/%M): 42.1/57.9	Median 113 (94–128) days following discharge	RT-PCR and/or CT scan	Objective assessment via Q3PC, MoCA, d-2R (cognitive function), MFI (fatigue) during in-clinic/ambulatory assessment, as well as subjective self-report via telephone questionnaire	● 31.1% (134/431) reported fatigue ● 17.5% (73/416) reported memory difficulties ● 10.1% (42/415) reported mental slowness ● 10.0% (41/412) reported concentration problems ● 20.7% (86/416) reported at least 1 cognitive symptom ● During ambulatory assessment, 49.7% (79/159) reported a cognitive complaint (impaired McNair score), and 38.4% (61/159) reported cognitive impairment (impaired MoCA or d-2R scores)	
Munblit et al., 2021[a]	Russia	Prospective Cohort	Sechenov University Hospital Network	$N = 2649$ (all previously hospitalized cases) ● Age Range: ≥18 ● Median Age: 56 (46–66) ● Sex (%F/%M): 51.1/49.9	Median 217.5 (200.4–235.5) days following discharge	RT-PCR or clinically diagnosed	Objective assessment via EQ-5D-5L (quality of life), as well as subjective self-report via telephone interview performed by medical students using	● 21.2% (551/2599) reported fatigue ● 9.1% (237/2597) reported forgetfulness ● Participants reported lower scores (poorer health state) at follow up (median 80 [65–90]) compared to pre-COVID (median 85 [70–95]), $p < 0.001$) ● Significant worsening of health was found across all symptom categories, whereas no statistically significant reduction in health state was found among patients reporting no symptoms	● Female sex was associated with chronic fatigue
O'Keefe et al., 2021[a]	USA	Cross-sectional	Emory Healthcare's Virtual Outpatient Management Clinic (VOMC)	$N = 198$ participants discharged from outpatient telemedicine program for COVID-19 (including 35 previously hospitalized cases) ● Age Range: 18–84	Median 119 (range 26–220) days following diagnosis	RT-PCR	Subjective self-report via e-mail survey	● 21.2% (42/198) reported fatigue 90–220 days after the acute COVID-19 phase ● 13.6% (27/198) reported mental fog 90–220 days after the acute COVID-19 phase	● Moderate to severe acute COVID-19, female sex, and middle age were highly associated with persistent symptoms

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Study	Country	Study Design	Sample Source	Sample Characteristics	Follow-up Duration	Ascertainment of COVID-19	Ascertainment of Outcomes	Results	Factors Associated with persistent symptoms
				● Median Age: 44 ± 14 ● Sex (%F/%M): 74.2/25.8					
Ong et al., 2021	Singapore	Prospective Cohort	4 public hospitals in Singapore	● *N* = 199 (175 prior cases, all of which were previously hospitalized, and 24 healthy controls) ● Age Range: N/A ● Median Age: 44 ● Sex (%F/%M): 24.6/75.4	Median 181 (103–191) days following discharge	RT-PCR	Objective assessed via immunoassay (inflammatory parameters), as well as subjective self-report	● 1.7% (2/120) reported fatigue at 180 days follow-up ● 0.8% (1/120) reported memory loss at 180 days follow-up ● Patients exhibited elevated levels of MIP-1β, SDF-1α, eotaxin, IL-12p70, SCF, IL-1B, IL-17A, BDNF, and VEGF, and had systemic cytokine profiles distinct from healthy controls regardless of severity of initial illness ● The levels of inflammation-associated IL-6, IP-10, IL-18, and MCP-1 significantly decreased from day 90 to 180	● Age > 65 years, non-Chinese ethnicity, and severity of acute infection were associated with increased likelihood of persistent symptoms ● There were no significant differences in the levels of immune mediators between patients with different [acute] disease severity
Orrù et al., 2021	Italy	Cross-sectional	Individuals living in Italy (recruited through the web)	*N* = 152 (*hospitalization status not specified*) ● Age Range: ≥18 ● Mean age: N/A ● Sex* (%F/%M): 82.05/17.95 *pertains to a larger dataset of 507, which do not all follow our inclusion criteria	At least 3 months following positive test	RT-PCR	Objective assessment via EQ-5D-3L (quality of life), as well as subjective self-report via online survey	● 74.34% (113/152) reported fatigue ● 48.68% (74/152) reported cognitive impairment ● 10.53% (16/152) reported moderate-serious problems with self-care ● 68.42% (104/152) reported moderate-serious problems with daily activities	
Osmanov et al., 2021[a]	Russia	Prospective Cohort	Z.A. Bashlyaeva Children's Municipal Clinical Hospital	*N* = 518 children (all previously hospitalized cases) ● Age Range: ≤18 ● Median Age: 10.4 (3–15.2) ● Sex (%F/%M): 52.1/47.9	Median 256 (223–271) days following discharge	RT-PCR	Subjective self-report via telephone surveyconducted by medical students	● 10.7% (53/518) reported fatigue ● scores on wellness scale for children with 2 + persistent symptoms significantly declined when compared to before COVID-19 onset (from 90 [80–95] to 70 ([60–80]) ● Scores on wellness scale for children with 1 persistent symptom	● Older age group and pre-existent allergic disease were associated with persistent symptoms

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Study	Country	Study Design	Sample Source	Sample Characteristics	Follow-up Duration	Ascertainment of COVID-19	Ascertainment of Outcomes	Results	Factors Associated with persistent symptoms
								significantly declined when compared to before COVID-19 onset (from 90 [80–100]) to 82.5 [70–93.8])	
Peghin et al., 2021	Italy	Prospective Cohort	Udine Hospital	$N = 599$ (442 outpatient cases, 157 previously hospitalized, including 23 in ICU) ● Age Range: 18–94 ● Mean Age: 53 ± 15.8 ● Sex (%F/%M): 53.4/46.6	Median 191 (172–204) days following onset of acute COVID-19	Nucleic acid amplification tests and/or clinical diagnosis	Subjective self-report via telephone questionnaire administered by trained nurses	● 13.1% (78/599) reported fatigue	● Female sex, a proportional increase in the number of symptoms at onset of COVID-19, and ICU admission were independent risk factors for post-COVID-19 syndrome ● Persistence of fatigue was significantly associated with disease severity at onset
Pereira et al., 2021	United Kingdom	Prospective Cohort	Hospital in North West London	$N = 38$ hospital staff (35 symptomatic and 3 asymptomatic cases, all not requiring hospitalization) ● Age Range: 23–67 ● Mean Age: 43 ● Sex (%F/%M): 84/16	7–8 months following symptom onset	RT-PCR	Subjective self-report via questionnaire based on NICE guidelines	● 57% (22/38) reported fatigue ● 24% (9/38) reported difficulty concentrating ● 16% (6/38) reported no longer being able to participate in a sport or recreational activity due to their ongoing symptoms	● Those who experienced more symptoms during the acute phase were more likely to experience persistent symptoms
Petersen et al., 2021	Faroe Islands	Prospective Cohort	The Faroese Hospital System	$N = 180$ (all outpatient cases) ● Age Range: 0–93 ● Mean Age: 39.9 ± 19.4 ● Sex (%F/%M): 54.4/45.6	Mean 125 ± 17 days following symptom onset	RT-PCR	Objective assessment via fatigue impact scale (fatigue)	● 23.9% (43/180) reported fatigue ● fatigue impact scale score mean score: 1.2 ± 1.0	● Symptoms persisted significantly more frequently in Individuals aged 50–66 years when compared with the youngest group (0–17 years) ● Symptoms seemed to be more persistent with increasing age
Pilotto et al., 2021[a]	Italy	Prospective Cohort	Spedali Civili Brescia Hospital	$N = 165$ (all previously hospitalized non-neurological cases) ● Age Range: N/A ● Mean Age: 64.8 ± 12.6 ● Sex (%F/%M): 30.3/69.7	6 months following hospitalization	RT-PCR	Objective assessment via MoCA (cognitive function), as well as subjective self-report via clinical follow-up checklist	● 33.9% (56/165) reported fatigue ● 31.5% (52/165) reported memory/concentration complaints ● 16.2% (17/105) exhibited cognitive impairment [assessed via MoCA during neurological examination]	● Patients with moderate/severe COVID-19 reported higher number of symptoms at follow-up ● Premorbid comorbidities, age at admission, and severity of COVID-19 were predictors of total number of

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Study	Country	Study Design	Sample Source	Sample Characteristics	Follow-up Duration	Ascertainment of COVID-19	Ascertainment of Outcomes	Results	Factors Associated with persistent symptoms
									symptoms reported at follow-up
Qu et al., 2021	China	Prospective Cohort	6 Hospitals in Anhui Province and Hubei Province	$N = 540$ (all previously hospitalized cases) ● Age Range: 10–99 ● Median Age: 47.5 (37.0–57.0) ● Sex (%F/%M): 50/50	3 months following discharge	RT-PCR	Objective assessment via SF-36 (quality of life), as well as subjective self-report via electronic survey form	● 29.4% (159/540) reported fatigue ● 15.4% (83/540) had poor physical component summary scores ● 32.6% (176/540) had poor mental component summary scores ● except for the general health dimension, scores on all other dimensions of SF-36 were significantly lower than Chinese norm ● female patients presented with significantly lower scores of all dimensions of SF-36	● Female sex, older age, and the presence of physical symptoms after discharge [including fatigue] were risk factors for health-related quality of life scores ● Female patients presented with significantly lower scores of all dimensions of SF-36
Rass et al., 2021	Austria	Prospective Cohort	Department of Internal Medicine II, Medical University of Innsbruck, Zams, and Muenster	$N = 135$ (31 cases previously admitted to ICU, 72 previously admitted to ward, 32 previously received mild outpatient care) ● Age Range: 19–87 ● Median Age: 56 (48–68) ● Sex (%F/%M): 39/61	Median 102 (91–110) days following onset of symptoms	RT-PCR	Objective assessment via MoCA (cognitive function), SF-36-v2 (quality of life), GOSE and mRS (functional outcome), as well as subjective self-report via clinical follow-up	● 27% (35/130) reported persistent fatigue (50% [15/30] ICU, 17% [12/71] with ward COVID-19, and 26% [8/31] with outpatient COVID-19) ● 25% (30/120) reported forgetfulness, trouble concentrating, or difficulty thinking (26% [7/27] ICU, 24% [16/67] with ward COVID-19, and 29% [7/32] with outpatient COVID-19) ● 23% (29/126) scored below 26 on the MoCA (29% [8/28] ICU, 20% [20/67] with ward COVID-19, and 3% [1/32] with outpatient COVID-19) ● Median MoCA score: 28 (26–29) (28 [25–28]) ICU, 28 [25–29] for ward COVID-19, and 29 [28–30] for outpatient COVID-19)	● Fatigue was more frequent in patients with sleep disturbances and in those with newly diagnosed neurological diseases

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Study	Country	Study Design	Sample Source	Sample Characteristics	Follow-up Duration	Ascertainment of COVID-19	Ascertainment of Outcomes	Results	Factors Associated with persistent symptoms
								● 31% (28/90) exhibited an impaired SF-36 score (43% [9/21] ICU, 31% [16/52] with ward COVID-19, and 17% [3/18] with outpatient COVID-19) ● Median GOSE: 8 (7–8) ● Median mRS: 1 (0–1)	
Rauch et al., 2021[a]	Germany	Prospective Cohort	*Life&Covid* Online Cohort Study (Ludwig-Maximilians-Universität)	$N = 127$ (including 116 outpatient cases and 11 inpatients) ● Age Range: ≥18 ● Median Age: N/A ● Sex (%F/%M): 68.5/31.5	6 months following infection	RT-PCR or Serology	Subjective self-report via e-mail survey	● 25% (32/127) reported fatigue (28% [24/87] females; 20% [8/40] males) ● 16% (20/127) reported difficulties in concentration	● At least one symptom, exertional dyspnea, and fatigue were reported more often after severe acute illness
Romero-Duarte et al., 2021	Spain	Retrospective Cohort	Four hospitals in Spain	$N = 797$ (all previously hospitalized cases, including 81 previously admitted to ICU) ● Age Range: N/A ● Mean Age: 63.0 ± 14.4 ● Sex (%F/%M): 46.3/53.7	6 months following discharge	RT-PCR	Subjective self-report via questionnaire	● 22.1% (176/797) reported fatigue (18.9% [81/428] males; 25.7% [95/369] females)	
Savarraj et al., 2021[a]	USA	Prospective Cohort	University of Texas Health Science Center	$N = 48$ (all previously hospitalized cases) ● Age Range: N/A ● Mean Age: 50 ± 17 ● Sex (%F/%M): 48/52	3 months following discharge	RT-PCR	Objective assessment via mRS (functional outcomes), BNST (cognitive function), FSS (fatigue)	● 42% (19/45) exhibited fatigue symptoms, operationalized as FSS cutoff of ≥ 4 ● 12% (5/43) exhibited cognitive deficits, operationalized as BNST cutoff of ≤ 8 ● 21% (10/48) scored poorly in terms of functional outcome, operationalized as mRS cutoff of ≥ 3	● People with long-term symptoms were significantly older ● The persistence of long-term symptoms was not associated with the severity of acute COVID-19 symptoms ● Subjects with mild course of hospitalization had a high incidence of symptoms, especially fatigue
Say et al., 2021	Australia	Prospective Cohort	Royal Children's Hospital	$N = 151$ children (including 54 asymptomatic, 91 mostly mild symptomatic cases, and 14 previously hospitalized) ● Age Range: ≤18 ● Median Age: 3 (1–8) ● Sex (%F/%M): 47/53	3–6 months following diagnosis	RT-PCR	Subjective self-report via follow-up clinic proforma	● 2% (3/151) reported fatigue	● All children that had post-acute COVID-19 symptoms had symptomatic acute COVID-19
Shang et al., 2021	China	Prospective Cohort	Zhongnan Hospital of Wuhan University, No. 7 Hospital of	$N = 796$ (all previously hospitalized cases,	6 months following discharge	RT-PCR	Subjective self-report via telephone interview	● 25.3% (201/796) reported fatigue (21.3% [86/392]	● Female sex was associated with

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Study	Country	Study Design	Sample Source	Sample Characteristics	Follow-up Duration	Ascertainment of COVID-19	Ascertainment of Outcomes	Results	Factors Associated with persistent symptoms
			Wuhan, Leishenshan Hospital	including 38 in ICU) ● Age Range: ≤18 ● Median Age: 62.0 (51.0–69.0) ● Sex (%F/%M): 49.2/50.8				males; 29.3% [115/404] females)	reporting > 1 persistent symptom
Shendy et al., 2021	Egypt	Prospective Cohort	Ministry of Health and Population	*N* = 81 (11 previously hospitalized cases, 70 non-hospitalized cases) ● Age Range: 25–40 ● Mean Age: 34.03 ± 4.9 ● Sex (%F/%M): 68/32	3–5 months following recovery from COVID-19	RT-PCR	Objective assessment via MFIS (fatigue)	● 64.2% (52/81) exhibited fatigue (72.7% [8/11] hospitalized; 62.9% [44/70] non-hospitalized), operationalized as MFIS total score ≤ 38	
Shuwa et al., 2021	United Kingdom	Prospective Cohort	Coronavirus Immune Response and Clinical Outcomes (CIRCO) study based at 4 hospitals in greater Manchester	*N* = 83 (all previously hospitalized cases) ● Age Range: N/A ● Median Age: 60 (51.0–66.5) ● Sex (%F/%M): 38.6/61.4	Median 158 (116.5–184.5) days following hospital admission	RT-PCR or clinical diagnosis	Objective assessment via cell culture and flow cytometry (immune parameters)	● Moderate to severe patients demonstrated an elevation in cytokine-producing T cells (except for TNF-α + CD8 + T cells) and increased production of cytokines ● No significant differences in the frequency of TNF-α + B cells were observed	● No significant increase in IFNγ + CD4 + T cells was seen when stratifying patients for fatigue ● Increased production of type 1 cytokines in convalescent patients was associated with COVID-19 disease severity, (apart from for IFNγ + CD4 + T cells) ● The convalescent group defined by the highest proportions of CD8 + T cells and type 1 cytokine production was enriched in patients with a poorer outcome at follow-up
Simani et al., 2021	Iran	Prospective Cohort	University-affiliated hospital of Tehran	*N* = 120 (all previously hospitalized, including 9 in ICU) ● Age Range: N/A ● Mean Age: 54.62 ± 16.94 ● Sex (%F/%M): 33.3/66.7	6 months following COVID-19 infection	RT-PCR or CT	Objective assessment via previously validated questionnaire based on Fukuda guidelines for CFS/EM (fatigue)	● 17.5% (21/120) exhibited various fatigue levels ● 14.2% (17/120) qualified for CFS criteria	● Female sex was associated with an increased risk of CFS/ME before adjustment
Skala et al., 2021	Czech Republic	Prospective Cohort	Hradec Kralove District	*N* = 102 (including 15 previously hospitalized cases and 87 outpatient cases) ● Age Range: 10–98 ● Mean Age: 46.7 ● Sex (%F/%M): 54/46	3 months following COVID-19 diagnosis	RT-PCR	Objective assessment via laboratory testing (inflammatory parameters), as well as subjective self-report via questionnaires administered by physician	● 21.6% (22/102) reported fatigue ● 4.9% (5/102) reported memory impairment ● 10.8% (11/102) exhibited CRP elevation	

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Study	Country	Study Design	Sample Source	Sample Characteristics	Follow-up Duration	Ascertainment of COVID-19	Ascertainment of Outcomes	Results	Factors Associated with persistent symptoms
Soldati et al., 2021	Brazil	Prospective Cohort	ICU unit, Complexo Hospitalar de Niterói	$N = 23$ (all previously admitted to ICU) ● Age Range: N/A ● Mean Age: 53.6 ± 11.7 ● Sex (%F/%M): 21.8/78.2	Median 83 (37–115) days following discharge	RT-PCR	Objective assessment viaTICS (cognitive function), EuroQol (quality of life)	● 9.8% (10/102) exhibited D-dimer elevation ● 13% (3/23) exhibited cognitive impairment, operationalized as TICS score 21–25 ● Mean EuroQol score: 71.9 ± 27.5 ● Patients with mild cognitive impairment had lower EuroQol scores (median 50) compared to patients with ambiguous and with normal cognitive performance (median 85), however this difference was not statistically significant ($p = 0.062$)	
Sonnweber et al., 2021	Austria	Prospective Cohort	Department of Internal Medicine II, Medical University of Innsbruck, and two additional medical centres in Zams and Münster (CovILD study)	$N = 134$ (including 109 previously hospitalized, of which 29 were previously admitted to ICU) ● Age Range: 19–87 ● Mean Age: 57 ± 14 ● Sex (%F/%M): 43/57	Mean 103 ± 21 days following diagnosis	RT-PCR	Objective assessment via laboratory testing (serology)	● 12% (16/134) exhibited elevated CRP levels (mean: 0.3 ± 0.6 mg/dL) ● 6% (8/134) exhibited elevated IL-6 levels (mean: 3.0 ± 2.5 mg/dL) ● 9% (12/134) exhibited elevated procalcitonin levels (mean: 0.07 ± 0.02) ● 27% (36/134) exhibited elevated D-dimer (mean: 564 ± 804 μg/L)	● Severity of acute COVID-19, age, sex, cardiovascular diseases, pulmonary diseases, diabetes mellitus type 2 and malignancy were related to patient recovery
Soraas et al., 2021[a]	Norway	Prospective Cohort	Conducted online in Norway	$N = 588$ (all previously non-hospitalized cases) ● Age Range: ≥18 ● Mean Age: 48 ● Sex (%F/%M): 57/43	Mean 248 ± 18 days from baseline (mean 15.9 ± 9 days from testing to baseline)	RT-PCR	Objective assessment via RAND-36 (quality of life), as well as subjective self-report via online questionnaire	● 31% (183/588) reported feeling fatigued in the 3 weeks before 8-month follow-up ● 11.5% (68/588) reported memory problems in the 3 weeks before 8-month follow-up ● 13% (74/588) reported problems concentrating and thinking in the 3 weeks before 8-month follow-up ● 42% (246/588) reported worsening of	

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Study	Country	Study Design	Sample Source	Sample Characteristics	Follow-up Duration	Ascertainment of COVID-19	Ascertainment of Outcomes	Results	Factors Associated with persistent symptoms
								health compared to one year ago ● 20% (119/588) reported that physical health has limited work or other activities in the past 4 weeks ● 13% (78/588) reported that pain has limited activities mildly or worse in the past 4 weeks	
Stavem et al., 2021	Norway	Cross-sectional	Akershus University Hospital (Ahus) and Østfold Hospital	$N = 458$ (all non-hospitalized cases) ● Age Range: ≥18 ● Mean Age: 49.5 ± 15.3 ● Sex (%F/%M): 56/44	Median 117.5 (105–135) days following first COVID-19 symptom	RT-PCR	Objective assessment via CFQ-11 and RAND-36 (fatigue) administered via web or post	● 46% (211/458) reported fatigue ● Mean CFQ-11 bimodal score: 3.9 ± 3.7 ● Mean RAND-36 energy/fatigue scale score: 56.8 ± 23.9	● Female sex, previous depression, higher BMI, single/divorced/widowed, short time since symptom debut, high symptom load and, confusion during acute COVID-19 were associated with higher multivariable odds of fatigue
Suárez-Robles et al., 2020	Spain	Cross-sectional	Hospital Clínico San Carlos	$N = 134$ (all previously hospitalized, including 2 previously admitted to ICU) ● Age Range: N/A ● Mean Age: 58.53 ± 18.53 ● Sex (%F/%M): 53.7/46.3	90 days following discharge	RT-PCR	Subjective self-report via telephone structured interview	● 54.5% (73/134) reported fatigue ● 18.7% (25/134) reported general malaise	
Sykes et al., 2021	UK	Prospective Cohort	Hull University Teaching Hospitals NHS Trust	$N = 134$ (all previously hospitalized, including 27 previously admitted to ICU) ● Age Range: 25–89 ● Mean Age: 59.6 ± 14 ● Sex (%F/%M): 34.3/65.7	Median 113 (range 46–167) days following discharge	RT-PCR	Objective assessment via EQ-5D-5L (quality of life), as well as subjective self-report via standardised clinical assessment by a specialist nurse and/or physiotherapist	● 39.6% (53/134) reported extreme fatigue (30.7% [27/88] males; 56.5% [26/46] females) ● 25.4% (34/134) reported an attention deficit (20.5% [18/88] males; 34.8% [16/46] females) ● 37.3% (50/134) reported memory impairment (27.3% [24/88] males; 56.5% [26/46] females) ● 9.7% (13/134) reported cognitive impairment (5.7% -[5/88] males; 17.4% [8/46] females)	● Females were significantly more likely to report residual symptoms including fatigue

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Study	Country	Study Design	Sample Source	Sample Characteristics	Follow-up Duration	Ascertainment of COVID-19	Ascertainment of Outcomes	Results	Factors Associated with persistent symptoms
								● EQ-5D-5L mean: 0.657 (0.30) ● CRP levels were within normal range in 84% (54/64) of patients (median: 2.9 (0.2–33) mg/L)	
Taboada (1) et al., 2020	Spain	Prospective Cohort	Seven hospitals located in northwestern Spain	$N = 91$ (all cases previously admitted to ICU) ● Age Range: N/A ● Mean Age: 65.5 ± 10.4 ● Sex (%F/%M): 35.2/64.8	6 months following ICU treatment	RT-PCR	Objectively assessed via EQ-5D-3L (quality of life) and PCFS (functional outcomes), as well as subjective self-report via structured interview conducted by trained research coordinators	● 37% (34/91) reported asthenia ● 67% (61/91) exhibited a decrease in the quality of life, including 56% (51/91) experiencing mobility problems, 37% (34/91) experiencing problems with usual activities, and 13% (12/91) experiencing problems with self-care ● 63% (57/91) reported a decreased functional status; 38% (35/91) had lowered two grades in the PCFS, 45% (41/91) described persistent functional limitations (operationalized as grades 2–4 in the PCFS)	● Advanced age, male sex, need for mechanical ventilation during ICU stay, duration of mechanical ventilation, length of ICU stay, and length of hospital stay were associated with a decreased quality of life and/or functional status
Taboada (2) et al., 2021	Spain	Cross-sectional	University Hospital of Santiago	$N = 183$ (all previously hospitalized cases, including 32 to ICU) ● Age Range: N/A ● Mean Age*: 65.9 ± 14.1 ● Sex* (%F/%M): 40.5/59.5 *pertains to all who were admitted to hospital at index, including those who are not included in follow-up	6 months following hospitalization	RT-PCR	Objective assessment via PCFS (functional status), as well as subjective self-reportvia surveys conducted by trained study investigators	● 47.5% (87/183) patients exhibited decreased functional status, operationalized as PCFS grades 2–4	● Female sex, age, length of hospital stay, mechanical ventilation, and ICU admission were associated with limitations in functional status
Tawfik et al., 2021	Egypt	Retrospective Cohort	Ain-Shams University and Ministry of Health and Population hospitals	$N = 120$ healthcare workers (including 18 previously hospitalized) ● Age Range: 23–62 ● Mean Age: 33.7 ± 7.29 ● Sex (%F/%M): 58/42	3 months following COVID-19 infection	RT-PCR and CT	Subjective self-report via questionnaire	● 35.0% (42/120) reported fatigue ● 3.3% (4/120) reported memory and attention problems	● Age ≥ 35 years was associated with development of persistent symptoms

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Study	Country	Study Design	Sample Source	Sample Characteristics	Follow-up Duration	Ascertainment of COVID-19	Ascertainment of Outcomes	Results	Factors Associated with persistent symptoms
Todt et al., 2021	Brazil	Prospective Cohort	Hospital Municipal Dr. Moyses Deutsch	$N = 251$ patients (all previously hospitalized, including 42 in ICU) ● Age Range: ≥18 ● Mean Age: 53.6 ± 14.9 ● Sex (%F/%M): 40.2/59.8	3 months following discharge	RT-PCR	Objective assessment viaEQ-5D-3L (quality of life)	● Overall worsening of EQ-5D-3L single summary index compared to before the onset of COVID-19 symptoms (medians: 0.80 [0.74–1.0] vs. 1.0 [0.80–1.0]) ● 7.4% (18/251) reported problems with self-care (EQ-5D-3L levels 2 or 3) ● 15.6% (38/251) reported problems with usual activities (EQ-5D-3L levels 2 or 3)	● Worsening of health status in usual activities was higher among females ● Participants with worsening of health status were predominantly female, more frequently had required mechanical ventilation and intensive care, and had longer length of hospital stay than participants without worsening of health status ● Poorer health status prior to admission was associated with more significant decline in health status ● Factors associated with self-care impairment: age, hypertension, number of comorbidities, intensive care, new onset hemodialysis, and length of hospital stay ● Factors associated with impairment in usual activities: age, heart failure, number of comorbidities, new onset hemodialysis, and length of hospital stay
Valiente-De Santis et al., 2020[a]	Spain	Prospective Cohort	Outpatients' office of Regional University Hospital of Málaga	$N = 108$ (all outpatient cases; both symptomatic and asymptomatic, including 30 healthcare workers) ● Age Range: N/A ● Mean Age: 55.4 ± 15.4 ● Sex (%F/%M): 55.6/44.4	12 weeks following acute COVID-19	Serology	Subjective self-report via telephone survey	● 44.9% (48/107) reported asthenia ● 1.9% (2/108) reported loss of memory ● 1.9% (2/108) reported difficulty concentrating ● CRP > 2.9 mg/dL was detected in 24.5% (25/108) ● D-dimer > 500 ng/mL was detected in 31.4% (32/108) ● IL-6 > 40 pg/mL was detected in 3.9% (4/108)	● Being a health-care worker was associated with symptom persistence, while age ≥ 65 years was protective

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Study	Country	Study Design	Sample Source	Sample Characteristics	Follow-up Duration	Ascertainment of COVID-19	Ascertainment of Outcomes	Results	Factors Associated with persistent symptoms
van den Borst et al., 2020	The Netherlands	Prospective Cohort	Radboud University Medical Center (POSTCOVER study)	$N = 124$ (all previously hospitalized cases) ● Age Range: N/A ● Mean Age: 59 ± 14 ● Sex (%F/%M): 40/60	Mean 13.0 ± 2.2 weeks following onset of symptoms	RT-PCR or clinically diagnosed	Objective assessment via laboratory testing (serological parameters), TICS, CFQ (cognitive function), SF-36 and NCSI (quality of life, fatigue)	● 69% (86/124) reported fatigue ● 64% (79/124) reported functional impairments in daily life ● 36% (45/124) exhibited abnormal scores on all mental and cognitive status questionnaires ● 15% (19/124) exhibited abnormal cognitive status, operationalized as TICS score < 34 ● 17% (21/124) exhibited self-reported cognitive impairment, operationalized as CFQ > 43 ● scores on all domains of the SF-36 were lowered, especially on the domains functioning, energy/fatigue, and general health. ● median CRP (1 (1–3) mg/L) and D-dimer (500 (500–500) ng/ml) were at normal levels in all participants ● 72% (89/124) reported impaired general quality of life	
Van Veenendaal et al., 2021[a]	The Netherlands	Prospective Cohort	University Medical Center Groningen, ICU (COFICS)	$N = 60$ (all previously admitted cases to ICU) [50 at 6 months] ● Age Range: N/A ● Median Age: 62.5 (55.3–68.0) ● Sex (%F/%M): 32/68	6 months following ICU discharge	RT-PCR	Objective assessment via SF-20 (quality of life), FAD-GF6+ (social functioning), as well as subjective self-report via telephone questionnaire conducted by research nurses (at 3 months), and mail questionnaire (at 6 months)	● 24% (12/50) reported fatigue at 6-month follow-up ● 14% (7/50) reported cognitive problems ● Role activities were impaired in ICU-survivors with a median of 0 (IQR 0–0) ● Social functioning scored a median of 80.0 (IQR 60.0–100.0) ● 33% (10/30) of pre-ICU employed persons were too ill to return to work, and employment rate was	

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Study	Country	Study Design	Sample Source	Sample Characteristics	Follow-up Duration	Ascertainment of COVID-19	Ascertainment of Outcomes	Results	Factors Associated with persistent symptoms
								decreased for the vast majority of patients; 90% did not reach their pre-ICU employment level	
Venturelli et al., 2021	Italy	Prospective Cohort	Papa Giovanni XXIII Hospital	$N = 767$ (all previously hospitalized cases, including 66 in ICU) ● Age Range: 20–92 ● Mean Age: 63 ± 13.6 ● Sex (%F/%M): 32.9/67.1	Median 105 (84–127) days following onset of symptoms	RT-PCR or Serology	Objective assessment via laboratory testing (serology), MoCA (cognitive function), Barthel index (functional impairment), and Brief Fatigue inventory (fatigue), as well as subjective self-report via questionnaire	● 70.3% (539/767) reported mild to severe asthenia, according to the Brief Fatigue Inventory ● 44.1% (334/767) reported new-onset fatigue, according to the Brief Fatigue inventory ● 24.3% (186/767) self-reported asthenia ● 0.7% (2/304) exhibited a pathologic MoCA score of 0 ● 22.7% (69/304) reported cognitive impairment symptoms ● 16% (121/767) were no longer independent, according to the Barthel index scale results ● Mean D-dimer: 700 ± 1021 ng/ml (22% [163/743] exhibited 500–999, 12% [89/743] exhibited 1000–1999, 5% [37/743] exhibited >=2000); above upper limit in 38% of cases ● Mean CRP: 0.36 ± 0.85 mg/dL (7% [53/759] exhibited values > 1.0)	● Women were more symptomatic than men, with fatigue reported almost twice as frequently
Walle-Hansen et al., 2021	Norway	Retrospective Cohort	Four general hospitals in South-Eastern Norway	$N = 106$ (all previously hospitalized cases, including 28 in ICU) ● Age range: 60–96 ● Mean age: 74.3 ± 8.5 ● Sex (%F/%M): 43/57	6 months following hospitalization	RT-PCR	Objective assessment via MoCA (cognitive function), and EQ 5D-5L (quality of life)	● 43% (46/106) displayed a negative change in cognitive function, according to MoCA ● 54% (111/206) reported decrease of 7 + points in quality of life (mean change from baseline: −11.5 ± 14.2)	● The mean sum scores of MoCA were lower in the oldest age group, indicating lower cognitive and physical function in older compared to younger participants

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Table 2 (*continued*)

Study	Country	Study Design	Sample Source	Sample Characteristics	Follow-up Duration	Ascertainment of COVID-19	Ascertainment of Outcomes	Results	Factors Associated with persistent symptoms
								● 35% (37/106) reported decline in mobility and ability to perform daily activities ● 17% (18/106) reported decline in ability to self-care ● 11% (12/106) reported major change in usual activities	
Wong et al., 2020	Canada	Prospective Cohort	Post-COVID-19 Respiratory Clinic in Vancouver	$N = 78$ (all previously hospitalized cases) ● Age range: ≥18 ● Mean age: 62 ± 16 ● Sex (%F/%M): 36/64	Median 13 (11–14) weeks following onset of symptoms	Laboratory test	Objective assessment via EQ-5D-5L (quality of life)	● 51% (40/78) exhibited quality of life impairment, operationalized as at least a moderate problem in one or more EQ-5D-5L dimensions	
Woo et al., 2020	United Kingdom	Cross-sectional	University Medical Centre Hamburg-Eppendorf	$N = 28$ (11 previously hospitalized cases, 6 previously outpatient cases, 1 case receiving no medical care, and 10 healthy controls) ● Age Range: 17–71 ● Mean Age: 42.2 ± 14.3 ● Sex (%F/%M): 57.9/42.1	Median 85 (range 20–105) days following recovery	RT-PCR	Objective assessment via TICS-M (cognitive function), as well as subjective self-report via questionnaire	● 16.7% (3/18) reported fatigue ● Cases scored median 24.17 (range: 13–40) on the fatigue assessment scale compared to healthy controls median 18.1 (range: 18–19) ● 50% (9/18) reported attention deficits ● 44.4% (8/18) reported concentration deficits ● 44.4% (8/18) reported short-term memory deficits ● 27.8% (5/18) reported trouble in finding words ● 5.6% (1/18) reported incoherent thoughts ● Cases scored a TICS-M mean of 38.83 (range: 31–46) compared to healthy controls mean of 45.8 (range, 43–50)	● Neurocognitive deficits after recovery from COVID-19 were independent from fatigue and mood alterations and may therefore might be different from the classical post-viral syndrome
Xiong et. al., 2020	China	Prospective cohort	Renmin Hospital of Wuhan University	$N = 722$ (538 previously hospitalized cases, and	Median 97 (95–102) days following discharge	COVID-19 diagnosis according to WHO interim guidance	Subjective self-report via telephone survey	● 28.3% (152/538) reported physical decline or fatigue	● Physical decline/fatigue was more common in female

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Table 2 (*continued*)

Study	Country	Study Design	Sample Source	Sample Characteristics	Follow-up Duration	Ascertainment of COVID-19	Ascertainment of Outcomes	Results	Factors Associated with persistent symptoms
				184 healthy controls) ● Age range: 20–80 ● Median age: 52 (41–62) ● Sex (%F/%M): 30.3/69.7			conducted by three experienced clinicians	(34% [52/152] males; 66% [100/152] females)	than male subjects, and in those aged 41–60
Zhao et al., 2020	China	Retrospective cohort	3 Tertiary Hospitals in Henan Province	$N = 55$ (all previously hospitalized cases) ● Age Range: ≥18 ● Mean Age: 47.74 ± 15.49 ● Sex (%F/%M): 41.82/58.18	3 months following discharge	RT-PCR	Self-report via clinical follow-up	● 16.4% (9/55) reported fatigue	
Zhou et al., 2021	China	Cross-sectional	4 Hospitals in Wuhan	$N = 72$ (55 cases, including 16 asymptomatic, and 17 healthy controls) ● Age Range*: N/A ● Median Age*: 60 (57–64) ● Sex* (%F/%M): 57.9/42.1 ● Age Range**: N/A ● Median Age**: 56.50 (52.3–63.0) ● Sex** (%F/%M): 75/25 ● Age Range***: N/A ● Median Age***: 57 (52.8–62.0) ● Sex*** (%F/%M): 56.2/43.8 *severe cohort**mild cohort***asymptomatic cohort	Mean 139.79 ± 7.41 days following illness onset for severe cohort, mean 133.75 ± 9.64 days following illness onset for mild cohort	RT-PCR or serology	Objective assessment via mesoscale-discovery (MSD) multiplexed immunoassay (immunological parameters)	● D-dimer median level in severe cohort: 0.34 (0.28–0.51) μg/ml (vs. healthy controls: 0.29 [0.29–0.38] μg/ml]) ● D-dimer median level in moderate cohort: 0.38 (0.29–0.46) μg/ml (vs. healthy controls: 0.29 [0.29–0.38] μg/ml]) ● D-dimer median level in asymptomatic cohort: 0.32 (0.25–0.46) μg/ml (vs. healthy controls: 0.29 [0.29–0.38] μg/ml]) ● CRP median level in severe cohort: 1.30 (0.46–3.74) mg/L (vs. healthy controls: 0.42 [0.11–1.23] mg/L]) ● CRP median level in moderate cohort: 0.63 (0.29–1.50) mg/L (vs. healthy controls: 0.42 [0.11–1.23] mg/L]) ● CRP median level in asymptomatic cohort: 1.06 (0.56–1.50) mg/L (vs. healthy controls: 0.42 [0.11–1.23] mg/L]) ● CRP and D-dimer levels were not	● Cytokines such as TNF-α were correlated with abnormal clinical features

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Table 2 (*continued*)

Study	Country	Study Design	Sample Source	Sample Characteristics	Follow-up Duration	Ascertainment of COVID-19	Ascertainment of Outcomes	Results	Factors Associated with persistent symptoms
								significantly elevated compared to healthy control levels ($p > 0.05$) ● Significant increases in SAA, TNF-α, and IL-1RA in severe cohort (class 1,2,3 cytokines upregulated in cases) ● Higher than normal levels of IL-17A and IL-17D in severe cohort ● No difference across all cohorts in IL-1α and IL-1β ● Normal levels of IL-6 and IL-10 across all groups ● IL-7 was decreased in severe cohort	

Proportions are reported as cases/total study sample size. 'Cases' refers to previous confirmed COVID-19 cases. Medians are reported as median (interquartile range), if the interquartile range was provided, or unless otherwise specified. Means are reported as mean ± standard deviation, if the standard deviation was provided. 'Previously hospitalized'/'admitted to ICU' refers to COVID-19 treatment. 'Admission' and 'discharge' refer to COVID-19 inpatient treatment. 'Infection' refers to infection with SARS-CoV-2. Ages are given in years. '%F/%M' refers to percentage of study sample which is female/percentage of study sample which is male.

Acronyms: COVID-19: Coronavirus disease 2019, SARS-CoV-2: Severe acute respiratory syndrome coronavirus 2, ICU: Intensive care unit, USA: United States of America, RT-PCR: Reverse transcription polymerase chain reaction, ESCAPE: Evaluation Study of Congestive Heart Failure and Pulmonary Artery Catheterization Effectiveness, DISCOVER: Diagnostic and Severity Markers of COVID-19 to Enable Rapid Triage, ISARIC: International Severe Acute Respiratory and Emerging Infection Consortium, SF-36: 36-Item Short Form Survey, CRP: C-reactive protein, IgG: Immunoglobulin G, CD4+: Cluster of differentiation 4+, CD8+: Cluster of differentiation 8+, IL-2: Interleukin-2, IFN-γ: Interferon gamma, TNF-α: Tumor necrosis factor alpha, ADAPT: Australians' Drug Use: Adapting to Pandemic Threats, SPHERE-34: 34-Item Somatic and Psychological Health Report, RAND-36: Rand 36-Item Health Survey, PHOSP-COVID: Post-hospitalization COVID-19 study, IQR: Interquartile range, FACIT: Functional Assessment of Chronic Illness Therapy, CFS/ME: Chronic Fatigue Syndrome/Myalgic Encephalomyelitis, MoCA: Montreal Cognitive Assessment, EuroQol: European Quality of Life Scale, EQ-VAS: EuroQol visual analog scale, EQ-5D-5L: EuroQol-5 Dimension-5 levels, EQ-5D-3L: EuroQol-5-Dimension-3 levels, EQ-5D-5L VAS: EuroQol-5 Dimension-5 levels visual analog scale, WG-SS: Washington Group Short Set on Functioning, CT: Computerized tomography, BRB-NT: Brief Repeatable Battery of Neuropsychological Tests, SSD: Subjective Scale of Damage, SDMT: Symbol Digit Modalities Test, ARDS: Acute respiratory distress syndrome, IL-6: Interleukin-6, NYC: New York City, CSQ: COVID-19 Symptom Questionnaire, SF-12: 12-Item Short Form Survey, SF-23: 23-Item Short Form Survey, ME/CFS: Myalgic encephalomyelitis/chronic fatigue syndrome, WPAI: Work Productivity and Activity Impairment Questionnaire, PCFS: Post-COVID-19 Functional Status, CFQ: Cognitive Failures Questionnaire, HRTC: High Resolution Computed Tomography, SCIP-D: Screen for Cognitive Impairment in Psychiatry, TMT-B: Trail Making Test Part B, FSS: Fatigue Severity Scale, PICS: Post-intensive care syndrome, SF-35: 35-Item Short Form Survey, SD: Standard deviation, OMC: Orientation-Memory-Concentration Test, OR: Odds ratio, PTSD: Post-traumatic stress disorder, MMSE: Mini-Mental State Examination, BACS: Brief Assessment of Cognition in Schizophrenia, REDCap: Research Electronic Data Capture, FAS: Fatigue Assessment Scale, Q3PC: questionnaire of cognitive complaints, d-2R: D2 Test of Attention, MFI: Multidimensional fatigue inventory, WHO CRF: World Health Organization's Post COVID Case Report form, MIP-1β: Macrophage inflammatory protein-1 beta, SDF-1α: Stromal Cell Derived Factor 1 alpha, IL-12p70: Interleukin-12p70, SCF: Stem cell factor, IL-17A: Interleukin-17A, BDNF: Brain-derived neurotrophic factor, VEGF: Vascular endothelial growth factor, IP-10: Interferon-inducible protein 10, IL-18: Interleukin-18, MCP-1: Monocyte chemoattractant protein-1, ELISA: Enzyme-linked immunosorbent assay, GOSE: Glasgow Outcome Scale-Extended, mRS: Modified Rankin Scale, BNST: Brief neurocognitive screening test, MFIS: Modified Fatigue Impact Scale, CIRCO: Coronavirus Immune Response and Clinical Outcome, TICS: Telephone interview for cognitive status, CFQ-11: Chalder Fatigue Scale 11, BMI: Body mass index, POSTCOVER: Post-COVID-19 Recovery Study, SF-20: 20-Item Short Form Survey, FAD-GF6+: McMaster Family Assessment Device-General Functioning subscale, MSD: Mesoscale-discovery multiplexed immunoassay.

[a] This article is a pre-print as of June 8, 2021.

synthesis primarily evaluating the effect of COVID-19 exposure on cognition (i.e., cognitive impairment meta-analysis) included 43 studies. 48 studies were qualitatively analyzed via narrative synthesis, including 7 which were excluded from quantitative analyses (Breton et al., 2021; Shuwa et al., 2021; Sonnweber et al., 2021; Taboada et al., 2021; Todt et al., 2021; Wong et al., 2020; Zhou et al., 2021).

3.2. Study characteristics

Ten studies analyzed data from Italy, nine from Spain, eight from the US, seven from China, six from the UK, three from Denmark, France, and Norway, respectively, two from Australia, Austria, Brazil, Canada, Egypt, Germany, Israel, Russia, and the Netherlands, respectively, and one from Belgium, the Czech Republic, England, Faroe Islands, Iran, Japan, Mexico, Pakistan, Singapore, Sweden, Switzerland, and Turkey, respectively. Sample sizes ranged from 23 to 2649, and median or mean follow-up periods ranged from 2.8 to 11.2 months. Six study authors provided confirmation regarding mode of ascertainment of COVID-19 (Ghosn et al., 2021; Say et al., 2021; Pilotto et al., 2021; Liyanage-Don et al., 2021; Miyazato et al., 2020; González et al., 2021), and one author (Fernández-de-las-Peñas et al., 2021; Fernández-de-Las-Peñas et al., 2021) confirmed that there was no sample duplication amongst two component studies, as well as advised the exclusion of a third study on the basis of possible duplication. Table 2 provides detailed characteristics and summaries of applicable findings for all 81 component studies.

3.3. Methodological quality and risk of bias

Taken together, the NOS rating of the component studies was moderate, evidenced by mean scores of 6.0 out of 9.0 for prospective/ambidirectional cohort studies, 4.1 out of 6.0 for retrospective cohort studies, and 5.6 out of 9.0 for cross-sectional studies. Common methodological limitations were the failure to include a non-exposed group in cohort studies, failure to ascertain whether outcomes were present prior to COVID-19 infection, and a lack of sample size justification in cross-sectional studies. NOS scores within each category for all component studies organised by design are included (Table S1 in the supplementary material).

We conducted sensitivity analyses a posteriori to compare pooled proportions across high, moderate, and low NOS-ranked studies. Studies of moderate NOS rank reported higher proportions of individuals exhibiting cognitive impairment when compared to low and high NOS-ranked studies ($p = 0.035$; Table 3). However, the proportion of individuals experiencing fatigue did not significantly differ across NOS ranking categories ($p = 0.885$; Table 3).

3.4. Synthesis of results

Meta-analyses of the two primary outcomes indicated that 32% of individuals experienced fatigue and 22% of individuals exhibited cognitive impairment 12 or more weeks following COVID-19 diagnosis. Furthermore, 13 of 14 studies examining inflammatory parameters reported elevations in proinflammatory markers (i.e., proinflammatory cytokines, C-reactive peptide, D-dimer, and procalcitonin) in a subset of patients. All studies investigating functional outcomes reported marked functional impairment in a sample subset.

3.4.1. Fatigue Meta-Analysis

The pooled proportion of individuals experiencing fatigue amongst COVID-19 patients 12 or more weeks following diagnosis was 0.32 (95% CI, 0.27, 0.37; $p < 0.001$; $n = 25{,}268$; Fig. 2). A larger proportion of females reported fatigue as compared to males, but the inter-subgroup difference was not statistically significant (0.46 of females vs 0.30 of males; $p_{subgroup} = 0.067$; Table 3). Subgroup analysis for age category revealed that a significantly greater proportion of adults experienced fatigue as compared to children (0.32 of adults vs 0.07 of children; $p_{subgroup} < 0.001$; Table 3). Moreover, studies which objectively assessed fatigue reported significantly greater proportions of individuals experiencing fatigue as compared to subjective modes of ascertainment (0.45 when assessed objectively vs 0.29 when assessed subjectively; $p_{subgroup} = 0.006$; Table 3). However, there was no statistically significant difference in the proportion of persons reporting fatigue between hospitalized and non-hospitalized respondents (0.36 hospitalized vs 0.44 non-hospitalized; $p_{subgroup} = 0.185$; Table 3). Likewise, there was no significant difference in the proportions of persons experiencing fatigue at <6 months follow-up since COVID-19 diagnosis compared to ≥6 months (0.33 when <6 months vs 0.31 when ≥ 6 months; $p_{subgroup} = 0.755$; Table 3). Sensitivity analyses revealed that stratifying studies by design produced statistically significant differences in effect size, although the effect sizes between prospective cohort, retrospective cohort, cross-sectional studies (i.e., the 3 most common study designs) did not significantly differ.

3.4.2. Cognitive Impairment Meta-Analysis

The pooled proportion of individuals exhibiting cognitive impairment amongst COVID-19 patients 12 or more weeks following diagnosis was 0.22 (95% CI, 0.17, 0.28; $p < 0.001$; $n = 13{,}232$; Fig. 3). There was a non-significant trend towards a greater proportion of females than males who exhibited cognitive impairment, (0.56 of females vs 0.36 of males; $p_{subgroup} = 0.063$; Table 3), however, the subgroup proportion for females was not statistically significant (0.56; 95% CI, 0.46, 0.66; $p = 0.960$; Table 3). Only one study reported on cognitive impairment in children (Buonsenso et al., 2021), thus, significant differences between child and adult subgroups were not determined ($p_{subgroup} = 0.182$; Table 3). Studies which objectively assessed cognitive impairment reported significantly greater proportions of individuals with cognitive impairment as compared to those employing subjective modes of ascertainment (0.36 objectively assessed vs 0.18 subjectively assessed; $p_{subgroup} = 0.002$; Table 3). There was no statistically significant difference between hospitalized and non-hospitalized subgroup proportions reporting post-COVID cognitive impairment (0.30 hospitalized vs 0.20 non-hospitalized; $p_{subgroup} = 0.096$; Table 3). Likewise, there was no significant difference in the proportions reporting cognitive impairment at <6 and ≥6 months follow-up (0.22 when <6 months vs 0.21 when ≥6 months; $p_{subgroup} = 0.794$; Table 3). Unlike for fatigue, stratifying studies by design did not produce any statistically significant differences in effect sizes ($p_{subgroup} = 0.366$; Table 3).

3.4.3. Heterogeneity

The fatigue ($I^2 = 99.1\%$) and cognitive impairment ($I^2 = 98.0\%$) meta-analyses exhibited considerable heterogeneity. Select subgroup analyses resulted in a reduction of heterogeneity (Table 3).

3.4.4. Publication Bias

Visual inspection of funnel plot asymmetry for the fatigue meta-analysis did not suggest the presence of publication bias (Supplementary, Fig. S1), and neither the Egger regression intercept test (intercept = 0.538; SE = 0.061; $p = 0.390$) nor the Begg and Mazumdar rank correlation test ($p = 0.857$) were statistically significant. Conversely, visual inspection of funnel plot asymmetry for the cognitive impairment meta-analysis suggested the presence of publication bias (Supplementary, Fig. S2); the Egger regression intercept test was statistically significant (intercept = 0.187; SE = 0.040; $p < 0.001$), whereas the Begg and Mazumdar rank correlation test was not significant ($p = 0.818$).

3.4.5. Inflammatory Parameters

14 studies investigated peripheral inflammatory parameters in COVID-19 patients 12 or more weeks following diagnosis (Zhou et al., 2021; Breton et al., 2021; Shuwa et al., 2021; Sonnweber et al., 2021; Arnold et al., 2021; Fortini et al., 2021; García-Abellán et al., 2021; Ong et al., 2021; PHOSP-COVID Collaborative Group et al., 2021; Skala et al.,

Table 3
Subgroup and sensitivity analyses for the primary outcomes.

	No. of Studies	Proportion	95% CI	*p*	I^2	Q	$p_{subgroup}$ (χ2 test)
FATIGUE							
Sex							
Females	7	0.46	(0.32, 0.60)	<0.01	96.0%	3.36	0.067
Males	7	0.30	(0.22, 0.39)	<0.01	92.6%		
Age Group[a]							
Adults (≥18 years)	65	0.32	(0.26, 0.37)	<0.001	98.3%	13.83	**<0.001**
Children (<18 years)	3	0.07	(0.03, 0.16)	<0.01	78.5%		
COVID-19 Hospitalization Status							
Hospitalized	45	0.36	(0.30, 0.43)	<0.001	99.4%	1.76	0.185
Non-Hospitalized	10	0.44	(0.34, 0.55)	<0.01	92.9%		
Follow-up Duration							
<6 Months	46	0.33	(0.26, 0.39)	<0.001	99.1%	0.10	0.755
≥6 Months	26	0.31	(0.24, 0.37)	<0.001	99.0%		
Mode of Ascertainment[b]							
Subjective	55	0.29	(0.24, 0.35)	<0.001	99.2%	7.56	**0.006**
Objective	13	0.45	(0.35, 0.55)	<0.01	96.4%		
NOS Rating Category							
High	24	0.28	(0.20, 0.37)	<0.001	98.9%	0.59	0.750
Moderate	27	0.32	(0.25, 0.40)	<0.01	96.6%		
Low	17	0.30	(0.17, 0.46)	<0.01	98.4%		
Study Design							
Prospective Cohort	48	0.28	(0.22, 0.34)	<0.001	97.6%	94.84	**< 0.001**
Retrospective Cohort	8	0.31	(0.17, 0.49)	<0.01	98.7%		
Cross-sectional	10	0.36	(0.21, 0.53)	<0.01	97.1%		
Ambidirectional Cohort	1	0.63	(0.60, 0.65)	N/A	N/A		
Retrospective Case-control	1	0.50	(0.38, 0.62)	N/A	N/A		
COGNITIVE IMPAIRMENT							
Sex							
Females	2	0.56	(0.46, 0.66)	0.960	0.0%	3.46	0.063
Males	2	0.36	(0.19, 0.55)	0.020	82.5%		
Age Group[a]							
Adults (≥18 years)	42	0.19	(0.14, 0.26)	<0.01	97.0%	1.77	0.182
Children (<18 years)	1	0.12	(0.06, 0.22)	N/A	N/A		
COVID-19 Hospitalization Status							
Hospitalized	24	0.30	(0.22, 0.38)	<0.01	96.7%	2.77	0.096
Non-Hospitalized	5	0.20	(0.12, 0.29)	<0.01	70.8%		
Follow-up Duration							
<6 Months	31	0.22	(0.15, 0.30)	<0.001	98.2%	0.07	0.794
≥6 Months	14	0.21	(0.13, 0.30)	<0.01	97.3%		
Mode of Ascertainment[b]							
Subjective	31	0.18	(0.12, 0.24)	<0.01	97.9%	9.97	**0.002**
Objective	12	0.36	(0.27, 0.46)	<0.01	94.9%		
NOS Rating Category							
High	12	0.18	(0.10, 0.29)	<0.01	95.7%	10.95	**0.004**
Moderate	17	0.32	(0.21, 0.44)	<0.01	92.6%		
Low	14	0.10	(0.05, 0.18)	<0.01	97.4%		
Study Design							
Prospective Cohort	31	0.18	(0.12, 0.26)	<0.01	97.4%	2.01	0.366
Retrospective Cohort	5	0.16	(0.06, 0.35)	<0.01	92.5%		
Cross-sectional	7	0.26	(0.16, 0.44)	<0.01	92.9%		

Acronyms: NOS: Newcastle-Ottawa Scale, N/A: not applicable.
Statistically significant subgroup effect sizes, ascertained as $p_{subgroup}$ (χ2 test) <0.05, are bolded.
[a] Studies categorized by age group depending on mean or median age.
[b] Refers to ascertainment of outcomes (see Table 1).

2021; Sykes et al., 2021; Santis et al., 2020; van den Borst et al., 2020; Venturelli et al., 2021). Of those which quantified intracellular cytokine levels, Breton et al. reported marked increases in the numbers of CD4+ T cells expressing the inflammatory cytokines interleukin (IL)-2, interferon (IFN)-γ, and tumor necrosis factor (TNF)-α in individuals with prior COVID-19 as compared with healthy donors (Breton et al., 2021). Ong et al. reported that previously-hospitalized patients exhibited elevated levels of proinflammatory cytokines, including but not limited to macrophage inflammatory protein 1β, IL-1β, and IL-17A (Ong et al., 2021). Ong et al. additionally reported that concentrations of the proinflammatory factors IL-1β, IL-17A, IL-12p70, stem cell factor (SCF), and MIP-1β were significantly higher in prior COVID-19 patients compared to healthy controls, regardless of acute phase severity (Ong et al., 2021). Moreover, Shuwa et al. determined that patients with prior moderate to severe acute illness demonstrated an elevation in most cytokine-producing T cells, as well as increased production of cytokines, whereas no significant differences in the frequency of TNF-α+ B cells were observed (Shuwa et al., 2021). Zhou et al. reported significant increases in serum amyloid A, TNF-α, and IL-1RA in the severe COVID-19 cohort, higher than normal levels of IL-17A and IL-17D, and decreased IL-7 (Zhou et al., 2021). Between 3.9% and 32.2% of post-COVID individuals exhibited elevated IL-6 levels (Sonnweber et al., 2021; Fortini et al., 2021; Santis et al., 2020), and García-Abellán et al. reported a median serum IL-6 level of 3 pg/mL (García-Abellán et al., 2021), which exceeds the standard reference value of ≤ 1.8 pg/mL (IL6 - Clinical: Interleukin 6, 2021). Breton et al. similarly reported that post-COVID patients exhibited systemic cytokine profiles distinct from uninfected controls (Breton et al., 2021), whereas Zhou *et al.* reported normal levels of IL-6 and IL-10 across all groups (Zhou et al., 2021).

Between 1.8% and 24.5% of patients exhibited elevated CRP levels (Sonnweber et al., 2021; Arnold et al., 2021; PHOSP-COVID Collaborative Group et al., 2021; Skala et al., 2021; Santis et al., 2020),

operationalized as >10 mg/L or >2.9 mg/dL. Median CRP levels ranged between 0.6 and 2.9 mg/L (Zhou et al., 2021; García-Abellán et al., 2021; Sykes et al., 2021; van den Borst et al., 2020). Moreover, 9.8% to 38.0% of patients exhibited elevated levels of D-dimer (i.e., ≥500 ng/mL) (Sonnweber et al., 2021; Fortini et al., 2021; PHOSP-COVID Collaborative Group et al., 2021; Skala et al., 2021; Santis et al., 2020; Venturelli et al., 2021). Conversely, Zhou et al. reported that CRP and D-dimer levels were not significantly elevated in their post-COVID sample compared to healthy controls ($p > 0.05$), but that cytokines such as TNF-α were correlated with abnormal clinical features (Zhou et al., 2021). In addition, Sonnweber et al. reported elevated procalcitonin levels in 9.0% of patients (mean 0.07) (Sonnweber et al., 2021).

Taken together, 13 of 14 studies (all except van den Borst et al.) (van den Borst et al., 2020) examining inflammatory parameters report elevation in at least one measure of inflammation in a subset of patients or across the whole post-COVID sample (as a median/mean, compared to healthy controls or standard reference values). It should be noted that nine of 14 studies reported both the presence of proinflammatory markers as well as persistent fatigue and/or cognitive impairment within their sample (Fortini et al., 2021; García-Abellán et al., 2021; Ong et al., 2021; PHOSP-COVID Collaborative Group et al., 2021; Skala et al., 2021; Sykes et al., 2021; Santis et al., 2020), and several studies noted an association between elevation in measures of inflammation and PCS symptoms (PHOSP-COVID Collaborative Group et al., 2021; Skala et al., 2021; Sykes et al., 2021).

3.4.6. Functional Outcomes/Quality of Life

34 studies investigated functional outcomes, frequently subsumed under quality of life (QOL) measures, in COVID-19 patients 12 or more weeks following diagnosis (Huang et al., 2021; Ghosn et al., 2021; González et al., 2021; Fernández-de-Las-Peñas et al., 2021; Arnold et al., 2021; PHOSP-COVID Collaborative Group et al., 2021; Sykes et al., 2021; van den Borst et al., 2020; Venturelli et al., 2021; Taboada et al., 2021; Todt et al., 2021; Wong et al., 2020; Elkan et al., 2021; Frontera et al., 2021; Garrigues et al., 2020; Havervall et al., 2021; Jacobson et al., 2021; Johnsen et al., 2021; Latronico et al., 2020; Logue et al., 2021; Menges et al., 2021; Miskowiak et al., 2021; Munblit et al., 2021; Orrù et al., 2021; Osmanov et al., 2021; Pereira et al., 2021; Qu et al., 2021; Rass et al., 2021; Savarraj et al., 2020; Soldati et al., 2021; Soraas et al., 2021). Nine studies measured QOL using the European Quality of Life 5 dimension 5 levels (EQ-5D-5L) scale (Wong et al., 2020; PHOSP-COVID Collaborative Group et al., 2021; Garrigues et al., 2020; Johnsen et al., 2021; Miskowiak et al., 2021; Munblit et al., 2021), four used the EQ-5D-3L scale, (Huang et al., 2021; Todt et al., 2021; Orrù et al., 2021; Taboada et al., 2021) seven used the 36-Item Short Form Survey (SF-36/RAND-36) (Arnold et al., 2021; van den Borst et al., 2020; Elkan et al., 2021; Latronico et al., 2020; Qu et al., 2021; Rass et al., 2021; Soraas et al., 2021), three used the Barthel Index (Venturelli et al., 2021; Frontera et al., 2021; Latronico et al., 2020), 11 used another scale (Taboada et al., 2021; González et al., 2021; PHOSP-COVID Collaborative Group et al., 2021; van den Borst et al., 2020; Havervall et al., 2021; Jacobson et al., 2021; Osmanov et al., 2021; Pereira et al., 2021; Rass et al., 2021; Savarraj et al., 2020; Soldati et al., 2021), and three via self-report (Ghosn et al., 2021; Fernández-de-Las-Peñas et al., 2021; Logue et al., 2021). with some studies implementing multiple assessment tools. All studies demonstrated functional impairment or reduction in at least one QOL dimension (in up to 72% of patients) (van den Borst et al., 2020) compared to regional norms, uninfected controls, or pre-COVID status, and four studies reported decrements across all QOL dimensions in their post-COVID sample (González et al., 2021; Arnold et al., 2021; van den Borst et al., 2020; Munblit et al., 2021).

Functional impairment post-COVID was exhibited by 21% to 63% of individuals (Taboada et al., 2021; Savarraj et al., 2020; Taboada et al., 2021); activity impairment (including difficulties with performing daily tasks, self-care, and mobility) in 1.0% to 68.4% (Huang et al., 2021; Todt et al., 2021; Frontera et al., 2021; Menges et al., 2021; Miskowiak et al., 2021; Orrù et al., 2021; Havervall et al., 2021; Jacobson et al., 2021; Johnsen et al., 2021; Soraas et al., 2021; Walle-Hansen et al., 2021; Taboada et al., 2021), social impairment in 5% to 15% (Elkan et al., 2021; Havervall et al., 2021; Latronico et al., 2020; Van Veenendaal et al., 2021), and 16.0% to 28.2% reportedly unable to partake in a sport/recreational activity (Fernández-de-Las-Peñas et al., 2021; Garrigues et al., 2020; Pereira et al., 2021). One in five previously hospitalized persons reached the threshold for an additional disability on the Washington Group Short Set on Functioning (WG-SS) scale (PHOSP-COVID Collaborative Group et al., 2021). Moreover, between 29.0% and 47.4% of those who were employed premorbidly were not able to return to work (Ghosn et al., 2021; Frontera et al., 2021; Garrigues et al., 2020; Jacobson et al., 2021; Latronico et al., 2020), 5% to 90% were unable to reach their pre-COVID employment level (PHOSP-COVID Collaborative Group et al., 2021; Latronico et al., 2020; Van Veenendaal et al., 2021), and between 8.0% and 38.9% reported disruption in work life (Havervall et al., 2021; Jacobson et al., 2021; Miskowiak et al., 2021; Soraas et al., 2021). Comprehensive results, including mean and median scores on QOL scales where reported, are available in Table 2. EQ-5D population norms are provided elsewhere (Szende et al., 2013).

3.4.7. Reported Factors Associated With Post-COVID-19 Syndrome

Overall, 53 of out 81 studies reported factors associated with increased incidence of PCS symptoms according to their respective analyses. Female sex was associated with an increased risk of developing PCS symptoms (including fatigue and cognitive impairment, in some instances), a greater number of persistent symptoms, or decrements in QOL dimensions in 24 studies (Taboada et al., 2021; Todt et al., 2021; Ghosn et al., 2021; Fernández-de-las-Peñas et al., 2021; García-Abellán et al., 2021; PHOSP-COVID Collaborative Group et al., 2021; Sykes et al., 2021; Venturelli et al., 2021; Menges et al., 2021; Munblit et al., 2021; Qu et al., 2021; Amin-Chowdhury et al., 2021; Augustin et al., 2021; Cirulli et al., 2020; Darley et al., 2021; Ferrucci et al., 2021; Kashif et al., 2021; O'Keefe et al., 2021; Peghin et al., 2021; Shang et al., 2021; Simani et al., 2021; Stavem et al., 2021; Xiong et al., 2021), while male sex predicted decreased functional status/QOL in one study (Taboada et al., 2021).

Increased age was associated with more reports of PCS symptoms or QOL diminution in 14 studies (Huang et al., 2021; Sonnweber et al., 2021; Todt et al., 2021; Ong et al., 2021; Jacobson et al., 2021; Qu et al., 2021; Savarraj et al., 2020; Walle-Hansen et al., 2021; Ferrucci et al., 2021; Xiong et al., 2021; González-Hermosillo et al., 2021; Petersen et al., 2021; Tawfik et al., 2021;18(3):em291.; Mei et al., 2021), whereas Menges et al. noted that younger individuals more frequently reported fatigue (Menges et al., 2021), and Valiente-De Santis et al. reported that age ≥65 years was protective against COVID-19 symptom persistence (Santis et al., 2020). Pre-existing comorbidities were associated with PCS symptoms or QOL decrements in 9 studies (Sonnweber et al., 2021; Todt et al., 2021; Fernández-de-las-Peñas et al., 2021; PHOSP-COVID Collaborative Group et al., 2021; Menges et al., 2021; Osmanov et al., 2021; Amin-Chowdhury et al., 2021; Stavem et al., 2021; Evlice et al., 2021). Furthermore, greater severity of acute disease, hospitalization, or increased length of hospital stay were associated with PCS symptoms or QOL decrements in 19 studies (Huang et al., 2021; Pilotto et al., 2021; Fernández-de-las-Peñas et al., 2021; Arnold et al., 2021; Ong et al., 2021; Taboada et al., 2021; Todt et al., 2021; Elkan et al., 2021; Jacobson et al., 2021; Menges et al., 2021; Taboada et al., 2021; Darley et al., 2021; Ferrucci et al., 2021; O'Keefe et al., 2021; Peghin et al., 2021; González-Hermosillo et al., 2021; Rauch et al., 2021). Interestingly, Jacobson et al. reported that the presence of fatigue was associated with long-term activity impairment (Jacobson et al., 2021), Miskowiak et al. reported that greater global cognitive impairment and executive dysfunction both correlated with greater difficulty within the EQ-5D 'usual activity' and 'anxiety and depression' domains (Miskowiak et al., 2021), and Soldati et al. reported that patients with mild cognitive impairment tended to have a low QOL score (Soldati et al., 2021).

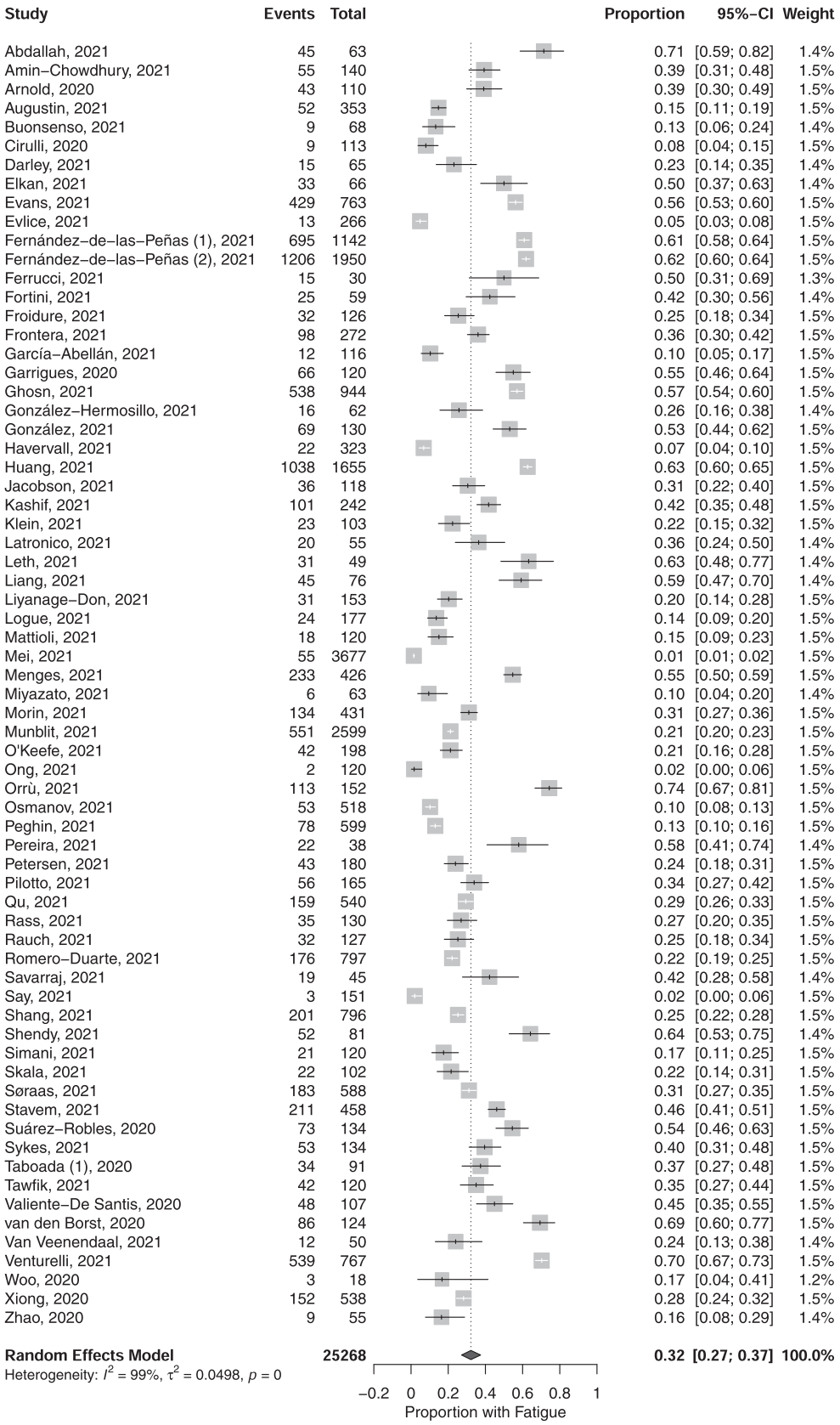

Fig. 2. Pooled proportions of individuals experiencing fatigue 12 or more weeks following COVID-19 diagnosis.

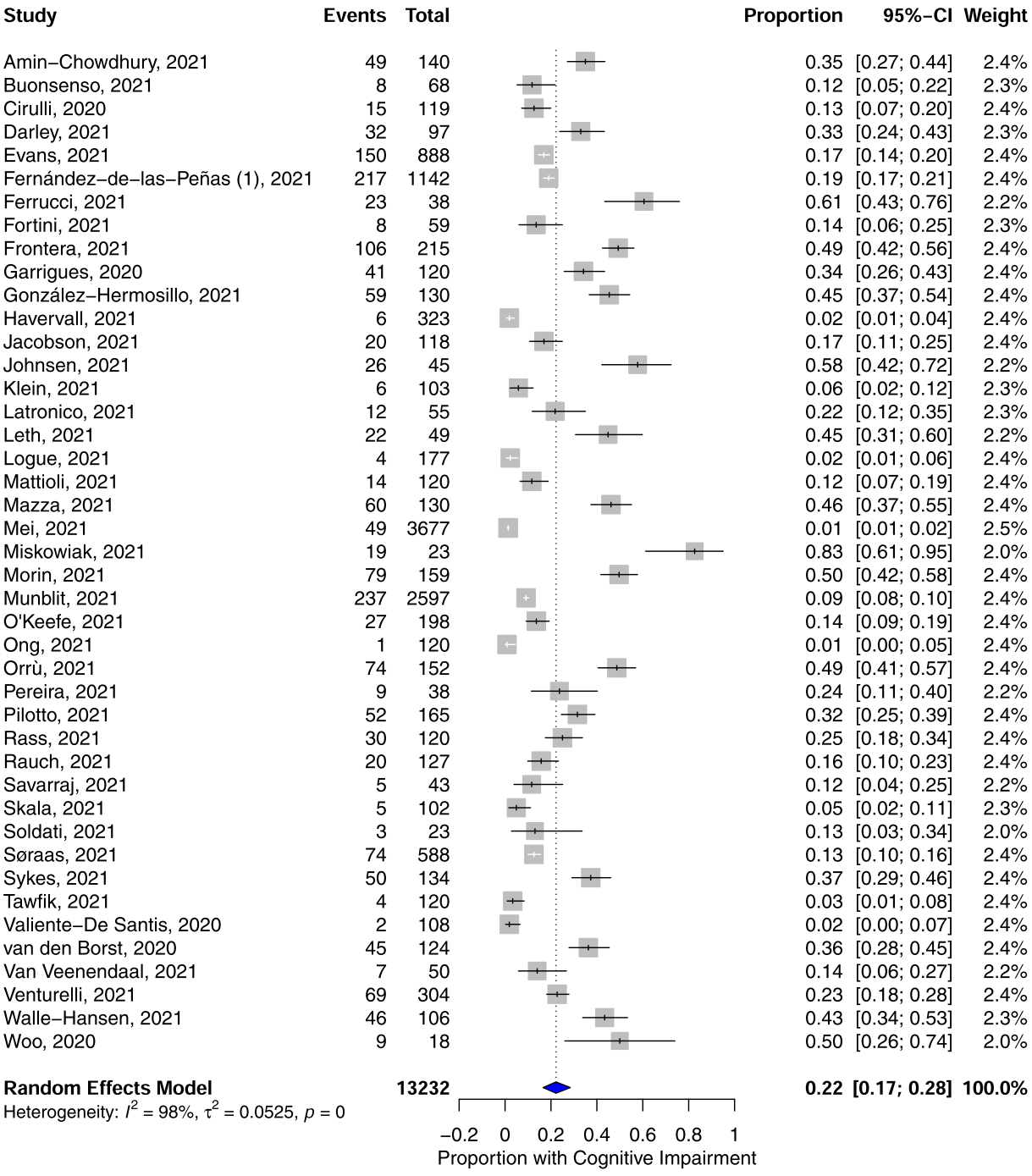

Fig. 3. Pooled proportions of individuals exhibiting cognitive impairment 12 or more weeks following COVID-19 diagnosis.

Moreover, Woo et al. reported that persistent neurocognitive deficits were independent from fatigue and mood alterations, and may thus differ from the classical post-viral syndrome (Woo et al., 2020). Table 2 details all factors reportedly associated with PCS symptoms across individual component studies.

4. Discussion

Herein we identified that approximately a third of individuals experienced persistent fatigue and over a fifth of individuals exhibited cognitive impairment 12 or more weeks following confirmed COVID-19 diagnosis. Similar incidences of fatigue and cognitive impairment, respectively, were observed amongst hospitalized and non-hospitalized populations. Furthermore, in contradistinction to other persistent symptoms which may be self-limiting (e.g., anosmia) (Hopkins et al., 2020), fatigue and cognitive impairment appear to endure and may potentially worsen over time in susceptible individuals (Jason et al., 2021), as evidenced by similar proportions of affected individuals at <6 and ≥ 6 months follow-up. A lower incidence of fatigue and cognitive impairment, respectively, were identified amongst children as compared to adults. Moreover, we established that persistent inflammation was consistently reported in a subset of patients, and that symptoms of PCS (including fatigue and cognitive impairment) are associated with marked functional impairment. Frequently reported factors associated with a greater incidence of PCS symptoms amongst component studies included female sex, older age, greater severity of acute illness, and pre-existing comorbidities.

Fatigue and cognitive impairment in PCS comprise a form of post-infectious fatigue syndrome, and exhibit phenotypic similarity to ME/CFS, which is often precipitated by an infectious agent (Taboada et al., 2021). Similar incidence rates of fatigue, as well as decreased QOL measures, have been reported in the aftermath of previous coronavirus epidemics, including severe acute respiratory syndrome coronavirus (SARS) and Middle East respiratory syndrome coronavirus (MERS) (Lam et al., 2009; Rogers et al., 2020). Furthermore, PCS shares overlapping symptoms with the encephalitis lethargica epidemic (von Economo's encephalitis) of the 1920 s (e.g., fatigue, cognitive impairment, headache), which was hypothesized to be causally related to the 1918 Spanish influenza pandemic (Hoffman and Vilensky, 2017).

There are multiple mechanisms whereby SARS-CoV-2 infection can engender or exacerbate persistent fatigue and/or cognitive impairment. Neurological dysfunction can ensue due to non-mutually exclusive factors including but not limited to direct viral encephalitis, neuroinflammation (including damage to blood–brain barrier integrity) (Nalbandian et al., 2021; Lam et al., 2009; Rogers et al., 2020), hypoxia, and cerebrovascular disease (Nalbandian et al., 2021; Komaroff and Lipkin, 2021; Higgins et al., 2021). Multiple studies have identified neuroanatomical alterations and neurodegeneration (Douaud et al., 2021), cerebral microvascular injury (Lee et al., 2021), and metabolic aberrations (including hypometabolism in areas associated with motivation, such as the dorsolateral prefrontal cortex) (Guedj et al., 2021) in the brains of COVID-19 patients.

It is also recognized that systemic sequelae including endothelial dysfunction (Libby and Lüscher, 2020), hyperinflammation, autoimmunity, latent viral reactivation (Oronsky et al., 2021), multi-organ pathology, and autonomic nervous system dysfunction can interact with the foregoing in a synergistic manner (Yong, 2021). The causal relationship between specific pro-inflammatory cytokines, mood symptoms, and cognitive decline is firmly established (Sartori et al., 2012; Rosenblat et al., 2014). We report that a subset of individuals consistently exhibited markers of inflammation following the resolution of acute COVID-19 infection, suggesting hyperinflammation is an amenable cause of fatigue and/or cognitive impairment in PCS. Indeed, other post-infectious syndromes (e.g., post-infectious encephalitis) (Sonneville et al., 2009) have been previously associated with elevations in inflammatory parameters.

Several non-mutually exclusive hypotheses regarding the pathogenesis of PCS would suggest that anti-inflammatory pharmacologic approaches may be of some utility in select patients. Moreover, psychotropic medications (e.g., selective serotonin reuptake inhibitors) (Gałecki et al., 2018) may modulate pro-inflammatory cytokine levels, and possibly exert salutary effects on mood and cognition in COVID-19 survivors (Heckenberg et al., 2018). In addition to pharmacologic strategies, disparate psychosocial treatments (e.g., cognitive remediation) may also be effective in treating symptoms of PCS. There is also the need to determine whether the type and frequency of vaccines (i.e., boosters) influence the risk for incident, persistent and/or severity of PCS. Reports of breakthrough infections in persons previously receiving a full vaccination schedule invites the need for characterization of risk in that subset of individuals. Moreover, the influence of both medical and psychiatric comorbidity on the risk for PCS, notably cognitive impairment, as well as the moderating influence of social, economic, and spatial determinants of health should be evaluated.

5. Limitations

The results presented herein should be interpreted within the context of several limitations. First, component studies were observational, therefore causal relationships cannot be inferred. Second, the majority of studies did not ascertain whether outcomes were present prior to COVID-19 infection (i.e., period prevalence rather than incidence), although this is a limitation accounted for by the NOS. Thus, we cannot exclude the possibility that fatigue and cognitive impairment preceded SARS-CoV-2 infection (although infection may have exacerbated symptoms). Third, as most component studies were based on hospitalized individuals, the results may not be representative for the majority of individuals affected by COVID-19. Furthermore, it is firmly established that the incidence of depressive and anxious symptoms in the general population has increased since the pandemic onset (Xiong et al., 2020); fatigue and cognitive impairment may be consequences of chronic stress and/or depression resulting from social and economic challenges of COVID-19, rather than a result of infection, in a proportion of PCS patients. It is also noteworthy that social consequences may be exacerbated for infected individuals. The majority of cohort studies failed to include a non-exposed control group, providing no basis for comparison (see Table S1 in supplementary material).

With respect to selection bias, there is an overrepresentation of hospitalized cases in the analyses herein, and a subset of reports may be attributable to post-intensive care syndrome, comorbid conditions, and/or medications (Heckenberg et al., 2018). Conversely, PCS patients not receiving healthcare for their symptoms are underrepresented. Moreover, fatigue and cognitive impairment may be secondary to other sequelae of SARS-CoV-2 infection, including but not limited to major depressive disorder (Taquet et al., 2021). Another limitation in most studies of objective cognitive functions was the use of dementia screening tools (e.g., MoCA, TICS) that have limited sensitivity to cognitive decline in younger populations and may thus have led to underestimation of cognitive impairments (McIntyre et al., 2019). Future studies would thus be recommended to apply more sensitive tools devoid of ceiling effects, for example the Screen for Cognitive Impairment for Psychiatry (SCIP) (Miskowiak et al., 2021; Miskowiak et al., 2017) and THINC-integrated tool (THINC-it) (McIntyre et al., 2020; McIntyre et al., 2017; McIntyre et al., 2013).

Another methodological limitation is the considerable level of heterogeneity exhibited in both meta-analyses, which may be attributable to variation in methods of data collection and sample characteristics amongst component studies. For example, the various subjective and objective assessment tools utilized differential scales (e.g., dichotomous Yes/No vs. Likert), providing varying levels of granularity. Stratifying studies by design, mode of ascertainment, and quality did not markedly reduce heterogeneity (Table 3). We also included preprints (Table 2), which have not undergone peer review.

6. Conclusion

In this systematic review and meta-analysis of 81 studies, we established that approximatelt a third of the included individuals experienced persistent fatigue and over a fifth of individuals exhibited cognitive impairment 12 or more weeks following COVID-19 diagnosis. Furthermore, a subset of individuals exhibited markers of systemic inflammation, and PCS was associated with marked levels of functional impairment. Limited evidence suggested a possible association between elevated pro-inflammatory markers and fatigue or cognitive impairment in PCS. Future research should endeavour to identify the underlying mechanisms, develop standardized diagnostic criteria, and establish therapies to prevent and treat fatigue and cognitive impairment in PCS patients.

Author contributions

RSM and FC conceptualized and designed study. FC and SL conducted literature search, study selection, and data extraction. FC and LMWL conducted quality and bias assessment of component studies. FC and YL conducted statistical analyses. FC interpreted statistical results, conducted qualitative analysis, and wrote the first draft of the manuscript with input from RSM, KWM, and MV. All authors provided critical review for important intellectual content, and approved the final version of the manuscript.

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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. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.bbi.2021.12.020.

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