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Fatigue outcomes following COVID-19: a systematic review and meta-analysis

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ABSTRACT

Objectives Fatigue is a pervasive clinical symptom in coronaviruses and may continue beyond the acute phase, lasting for several months or years. This systematic review and meta-analysis aimed to incorporate the current evidence for postinfection fatigue among survivors of SARS-CoV-2 and investigate associated factors.

Methods Embase, PsyINFO, Medline, CINAHL, CDSR, Open Grey, BioRxiv and MedRxiv were systematically searched from January 2019 to December 2021. Eligible records included all study designs in English. Outcomes were fatigue or vitality in adults with a confirmed diagnosis of SARS-CoV-2 measured at >30 days post infection. Non-confirmed cases were excluded. JBI risk of bias was assessed by three reviewers. Random effects model was used for the pooled proportion with 95% CIs. A mixed effects meta-regression of 35 prospective articles calculated change in fatigue overtime. Subgroup analyses explored specific group characteristics of study methodology. Heterogeneity was assessed using Cochran's Q and I^2 statistic. Egger's tests for publication bias.

Results Database searches returned 14 262 records. Following deduplication and screening, 178 records were identified. 147 (n=48 466 participants) were included for the meta-analyses. Pooled prevalence was 41% (95% CI: 37% to 45%, k=147, I^2=98%). Fatigue significantly reduced over time (−0.057, 95% CI: −107 to −0.008, k=35, I^2=99.3%, p=0.05). A higher proportion of fatigue was found in studies using a valid scale (51%, 95% CI: 43% to 58%, k=36, I^2=96.2%, p=0.004). No significant difference was found for fatigue by study design (p=0.272). Egger's test indicated publication bias for all analyses except valid scales. Quality assessments indicated 4% at low risk of bias, 78% at moderate risk and 18% at high risk. Frequently reported associations were female gender, age, physical functioning, breathlessness and psychological distress.

Conclusion This study revealed that a significant proportion of survivors experienced fatigue following SARS-CoV-2 and their fatigue reduced overtime. Non-modifiable factors and psychological morbidity may contribute to ongoing fatigue and impede recovery.

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STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ This review and meta-analysis was conducted using a significant sample size from a comprehensive search of the literature, including only confirmed cases.
⇒ Substantial unexplained heterogeneity between studies limits generalisability of our findings.
⇒ Only one reviewer screened and extracted the data from each study leaving the potential for missing articles and selection errors.
⇒ Outcome measures of fatigue were unvalidated in the majority of studies, limiting confidence in our estimates.
⇒ Total point prevalence was likely impacted by the predominance of hospitalised patients with potentially more severe disease.

INTRODUCTION

Fatigue may be characterised as tiredness or exhaustion as a result of physical or mental exertion or as a result of an illness or disease. The experience of fatigue is common and is usually short-lived but, for a small number of people, it can become long-lasting, associated with a number of impairments in daily living and quality of life.[1] It is one of the most common presenting symptoms of coronaviruses.[2] The current pandemic has also revealed a considerable burden of lasting symptoms,[3–12] with approximately one in four people experiencing fatigue by one estimate.[13] Systematic reviews indicate a pooled prevalence of post-COVID-19 fatigue to vary among 45%,[14] 52%[15] and 64%.[16] In previous epidemics, fatigue was enduring. In a follow-up of 90 SARS survivors 30 months post illness, for instance, 1 study found significantly lower vitality scores compared with Hong Kong population norms.[17] A small study of Middle East respiratory syndrome patients revealed that 32.7% had clinically relevant chronic fatigue, according to their Fatigue Severity Scale (FSS) scores, at 18 months' follow-up.[18] Likewise, for a considerable number of patients with COVID-19, tiredness symptoms extend beyond 3 months and represent a larger burden of postinfection symptomology.[19–41] A large study of 1142 hospitalised patients found that 61% had fatigue 7 months post COVID-19.[42] Similarly, those who perceived themselves as

experiencing 'poor recovery' had lower vitality on the 15D instrument, compared with those making a 'full recovery' (p<0.001) 1 year post illness.[43]

More severe disease, associated with being hospitalised or intensive care unit (ICU) admission, has been related to postillness fatigue.[44–51] In a small cohort of 55 people, 30 days post discharge for COVID-19, each additional day of hospitalisation increased fatigue by 1.2.[52] Apart from hospitalised patients, among non-hospitalised or those treated for milder disease, fatigue is persistent.[53–61] In 359 patients, 63.4% reported significant fatigue up to 12 months post infection and were more likely than admitted patients to require referral for fatigue symptomology.[62]

Determinants of postillness fatigue include female gender[63–66] and older age, although the latter relationship was not consistent. Being over 50 years was associated with fatigue severity in some studies,[52 67 68] but not in others.[69 70] Exercise impairments are a common feature of post-COVID-19 sequelae.[71–77] Poorer performance on the 6 min walk test (6MWT) was associated with fatigue and lower vitality at 6 months despite no concomitant impairments in pulmonary functions.[78] Indeed, impairments in lung functions have not thus far fully explained worse fatigue in COVID-19.[78–81] Nevertheless, patients often report persistent dyspnoea, which was consistently related to their fatigue,[82–85] suggestive of multidimensional functional consequences. For instance, quality of life,[86] functional status[87] and an increased risk for postinfection healthcare needs[88] were all related to fatigue.

Anxiety, post-traumatic stress and depressive symptoms are prevalent in survivors of respiratory viral infections.[85 89–94] A meta-analysis of 36 COVID-19 articles found high rates of anxiety (29%) and depressive symptoms (23%) 4–12 weeks post illness.[95] The relationship between mental health outcomes and fatigue is consistent among convalescing patients with COVID-19. Depressive symptoms, for example, were associated with lower vitality[96] and fatigue.[79 97] In a retrospective study of 55 patients, baseline anxiety was related to higher fatigue 30 days after hospitalisation.[52] Moreover, these relationships can be present at 12 months' follow-up. Mazza *et al*[98] found depression (r=0.56, q=0.05) and post-traumatic stress disorder (PTSD) (r=0.52, q=0.05) were related to fatigue severity in 402 post-COVID-19 patients. Neuropsychiatric symptoms, comprising anxiety, mood swings, irritability and depression and others, predicted chronic fatigue 9 months later for those with mild/moderate disease (p=0.01).[99]

Summary and aims

For the majority of patients, acute fatigue diminishes during the course of a virus, but current evidence suggests some experience longer lasting symptoms, and these affect functional and psychological recovery. Meta-analyses have focused on postacute sequelae of COVID-19 or clusters of symptoms, and therefore fewer studies have investigated solely fatigue outcomes. Moreover, a proportion of these reviews were narrative in design, which did not provide a pooled estimate for fatigue. Furthermore, fatigue is reported as the most prominent factor of post-infection symptomology indicative of its importance in understanding recovery. Therefore, the objectives of this systematic review were to (a) investigate the prevalence of persistent fatigue among survivors of COVID-19, (b) integrate the findings by conducting a meta-analysis and (c) investigate current evidence for factors associated with fatigue outcomes in this context.

METHODS

Search strategy

The protocol and PICO framework for this study (online supplemental file 1) was developed using the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA).[100] Embase, PsyINFO, Medline, CINAHL, Cochrane Database of Systematic Reviews, Open Grey, MedRxiv and BioRxiv were systematically searched from January 2019 to 31 December 2021. Search terms: severe acute respiratory syndrome or severe acute respiratory adj2 syndrome or coronavirus or corona virus or corona adj1 virus or COVID-19 or COVID-19 or SARS-CoV-2 or SARS-CoV or SARSCOV2 or SARSCOV-2 or nCoV-2 or 2019-nCoV or nCoV19 or nCoV2 or COVID-19 or COVID-19 or covid and 'chronic fatigue' or fatigue or tired* or exhaust* or quality adj2 life or QoL or health related quality) adj2 life or HRQoL. We incorporated 'health-related quality of life' into our search terms in order to capture 'vitality', which we used as proxy for fatigue. Reference lists of the review studies were manually searched for additional articles. Full search protocols for each database are available in online supplemental file 2. Duplicate references were removed electronically and imported into Rayyan[101] for screening and inclusion decisions.

Inclusion and exclusion criteria

Included were original articles with primary data, published in English between January 2019 and December 2021. Adult patients (≧18 years) must have had a diagnosis of SARS-CoV-2 confirmed by RT-PCR, IgM/IgG serology or clinical assessment (eg, X-ray, CT scan of the chest). 'Probable' or self-reported cases were excluded. All study designs were incorporated except qualitative and case reports. Main outcomes were fatigue/vitality reported as 'postdischarge', 'posthospitalisation', 'postacute', 'postillness' or 'postonset'. Outcomes were included if measured at a median/mean time of >30 days post infection as defined. All associations with fatigue/vitality were included if reported/quantified (eg, anxiety, dyspnoea). We excluded pandemic fatigue (defined as 'worn out' by pandemic warnings, government safety instructions, media coverage or compliance requirements), healthcare worker fatigue in the context of their work (eg, burnout, compassion fatigue), comorbid physical disease or pregnant populations. We excluded 'muscle fatigue', 'leg fatigue' and fatigue combined with 'malaise' or 'muscle weakness'. Protocols, vaccination studies,

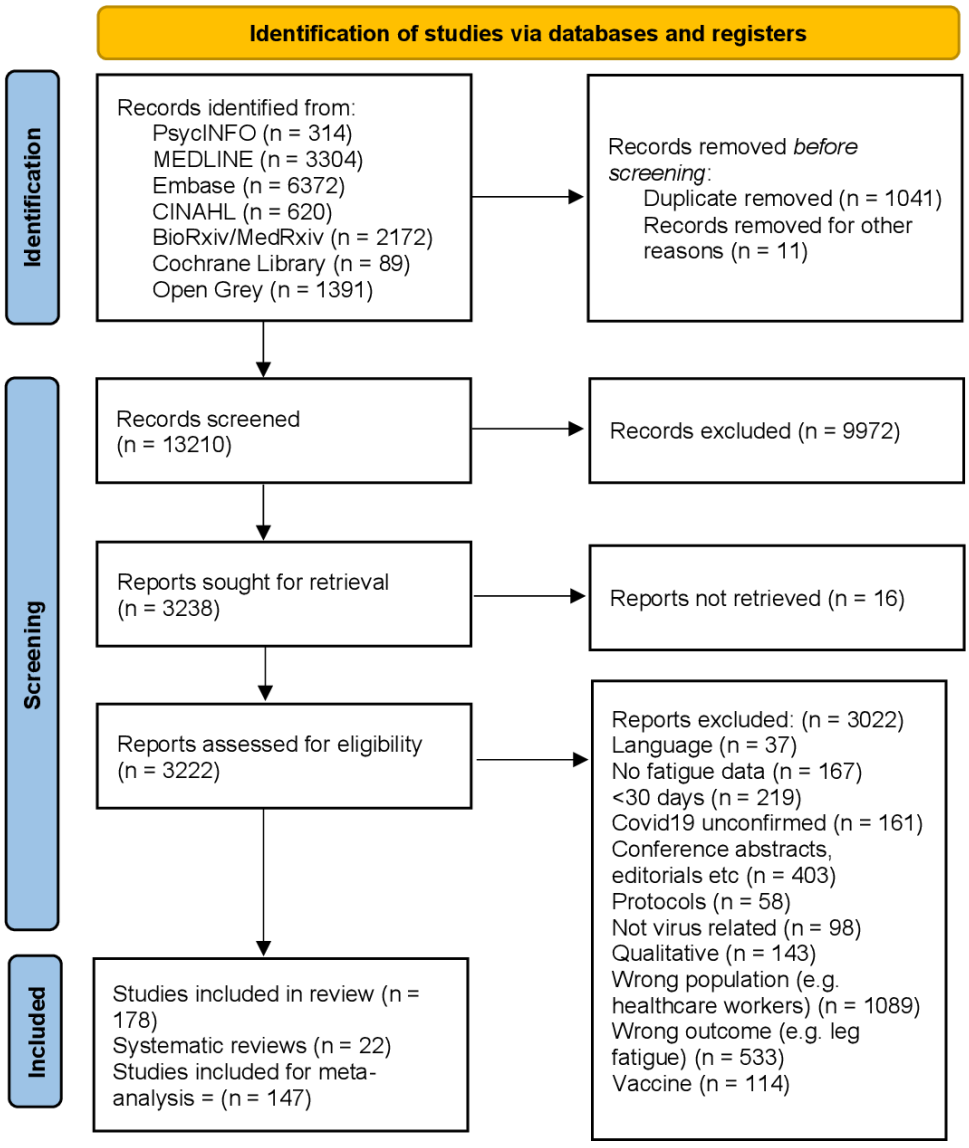

Figure 1 Preferred Reporting Items for Systematic Review and Meta-Analysis 2020 flow diagram.

newspaper articles, conference papers, commentaries, opinions or editorials were also omitted.

Data extraction

Titles and abstracts were screened by one reviewer (KP-W). Full texts were screened by KP-W. A data spreadsheet was created to record extracted data from the included studies. Spreadsheet variables were citation, population, sample size, control group, location, virus type and diagnostic method, follow-up period, study design, inclusion/exclusion criteria, objectives, outcome variable of interest (eg, fatigue, vitality), associated variables (eg, PTSD, dyspnoea), scales/measures employed, results, power calculation (Y/N). The senior researcher (TC) reviewed 10% of the final included studies. Discrepancies were resolved via discussion and consensus. A PRISMA flow diagram is available in figure 1.

Quality assessments

Risk of bias was assessed by the JBI Critical Appraisal Tools.[102] Items related to bias included 'Were confounding factors identified?', which demanded a 'yes', 'no', 'unclear' or 'not applicable'. An overall assessment was made by assigning a grade of low quality, moderate quality or good quality. Three researchers (KP-W, OS and TC) independently graded 73%, 14% and 13% each of the total articles and, for the purposes of inter-rater estimation, researchers graded the same 10% of the articles. Inter-rater agreement was assessed by Fleiss' kappa, which indicated moderate agreement (k=0.534, p=0.004).

Statistical analysis

We computed pooled mean prevalence for fatigue outcomes with 95% CIs using a random effects model as high heterogeneity was anticipated. A number of studies investigated fatigue across multiple time points. Therefore, in order to maintain the independence of observations for the pooled prevalence, we selected 1 time point with accompanying prevalence from each study using 1 of the 3 methods: (a) fatigue reported at the stated mean/median time of the follow-up assessment, for example,

127 days post illness, (b) fatigue at the 3-month follow-up (being the mode for all 147 studies) or (c) for studies investigating fatigue>4 months, we selected the shortest time point. Studies with missing data were excluded from analyses. Where studies investigated both 'fatigue' and chronic fatigue syndrome (CFS) outcomes, we incorporated the 'fatigue' data only. This was because a confirmed diagnosis of CFS could not be established. To determine the trend for fatigue, 35 prospective studies, with available data for >2 follow-up times, were included in a meta-regression using the mixed effects framework for meta-analyses developed by Sera *et al*.[103] Meta-regression coefficients were estimated using a restricted maximum likelihood estimator. To determine the proportion of fatigued participants by study design, and to increase the power, we categorised studies into two categories: 'cross-sectional' and 'prospective'. The latter included longitudinal and retrospective designs. The cross-sectional category comprised the remaining designs. Two categories were used to investigate proportions for 'ongoing symptomatic COVID-19' (1–3 months) and 'post-COVID-19 syndrome' (>3 months) following The National Institute for Health and Care Excellence guidelines (nice.org.uk). The robustness of the main pooled prevalence was checked by controlling for the presence of outliers. Studies with 95% CIs falling outside the 95% CI of the total pooled effect were defined as 'outliers'. Sensitivity analysis was performed on the mean pooled prevalence by excluding high risk of bias studies and unpublished studies. To investigate the proportion of fatigued by scale, two categories were used: (a) studies with a valid fatigue scale and (b) studies without a valid fatigue scale. Meta-analyses were conducted using R Studio, V.1.3.1073[104] using packages meta, metafor, dmetar, metareg, mixmeta and irr. Heterogeneity was assessed using Cochran Q statistic. We obtained the I^2 statistic with the degree of heterogeneity categorised as 'not important' (0%–40%), 'moderate' (30%–60%), 'substantial' (50%–90%) and 'considerable' (75%–100%).[105] We conducted Egger's tests and produced funnel plots to explore potential publication bias for all proportional analyses. For 'vitality' outcomes, lack of comparable controls and missing data precluded a means difference analysis.

Patient and public involvement

No patient was involved in this study.

RESULTS

Search results

A total of 14262 articles were identified using the database search protocols. Following the removal of duplicates, 13210 articles remained for title and abstract screening. Of these, a total of 3222 were selected for full-text screening producing a final total of 178 studies and 22 systematic reviews. We identified 147 as eligible for a quantitative analysis. A summary of the 147 included articles is available in online supplemental table 1. The studies are tabulated according to categorical and continuous fatigue outcome measures. Summary table of systematic reviews is available in online supplemental file 3.

Study characteristics

A total of 178 articles comprising 48466 participants and 22 systematic reviews were included.[13–16 91 95 106–121] A total of 14 (8%) were preprints, 30 (17%) used a fatigue scale and 27 (15%) used a validated measure with a fatigue item(s). A total of 13 (7%) used the 'vitality' subscale of the 36-Item Short Form Survey (SF-36) and 108 (61%) employed a questionnaire, interview or health records. The most common countries were Italy with 25 studies and the USA with 23 studies. The UK had 19 studies and China had 14 studies. Spain had 12 and France had 9 studies. Germany had eight studies and Switzerland had seven studies. The Netherlands and Turkey had six studies each and India had five studies. Iran had four studies. Bangladesh, Denmark, Egypt and Pakistan had three studies each. Brazil, Chile, Israel, Mexico, Norway and Sweden all had two studies. Austria, Australia, Belgium, Canada, Colombia, Finland, Ireland, Hungary, Japan, Lithuania, Mexico, Nepal, Poland, Russia, Saudi Arabia and Zambia each had one study. There were 80 prospective and 11 retrospective cohort deigns. Six longitudinal studies, 29 cross-sectional, 8 case–controls, 5 case series, 36 cohorts, 3 randomised-controlled trials and 22 systematic reviews. The most frequent follow-up times were 3 months (46 studies), 6 months (22 studies), 1 month (20 studies), 12 months (12 studies) and 2 months (12 studies). All other time points had <8 studies. JBI quality assessments resulted in most studies receiving a moderate rating. Full ratings are available in online supplemental file 4. In summary, 32 were assigned a 'high' risk of bias, 139 received a 'moderate' risk assessment and only 7 were considered 'low' risk. Lower grades were assigned for selection bias, lack of adequate control groups, small samples, study design and methodological bias (employment of unvalidated/unreliable scales).

Meta-analyses

A total of 48466 participants were included for the meta-analysis of proportions using a random effects model. A pooled prevalence from 147 studies was found to be 41% (95% CI: 37% to 45%, I^2=98%). A forest plot of this analysis is available in figure 2. Fatigue was present between 1 month and 1 year post infection with a median time of 3 months (IQR=2–6). An Egger's test was conducted to assess possible publication bias for our proportional analysis. The results indicated funnel plot asymmetry (bias=3.35, p=0.001) (online supplemental file 5).

To explore potential origins of heterogeneity and to test the robustness of our pooled prevalence, outliers were controlled for. A 1% difference was found once n=84 outlier studies were removed; 42% (95% CI: 40% to 45%, I^2=67%), although heterogeneity was reduced to 'substantial'. Given the range of postinfection assessment periods, the effect of time on fatigue was investigated by a linear

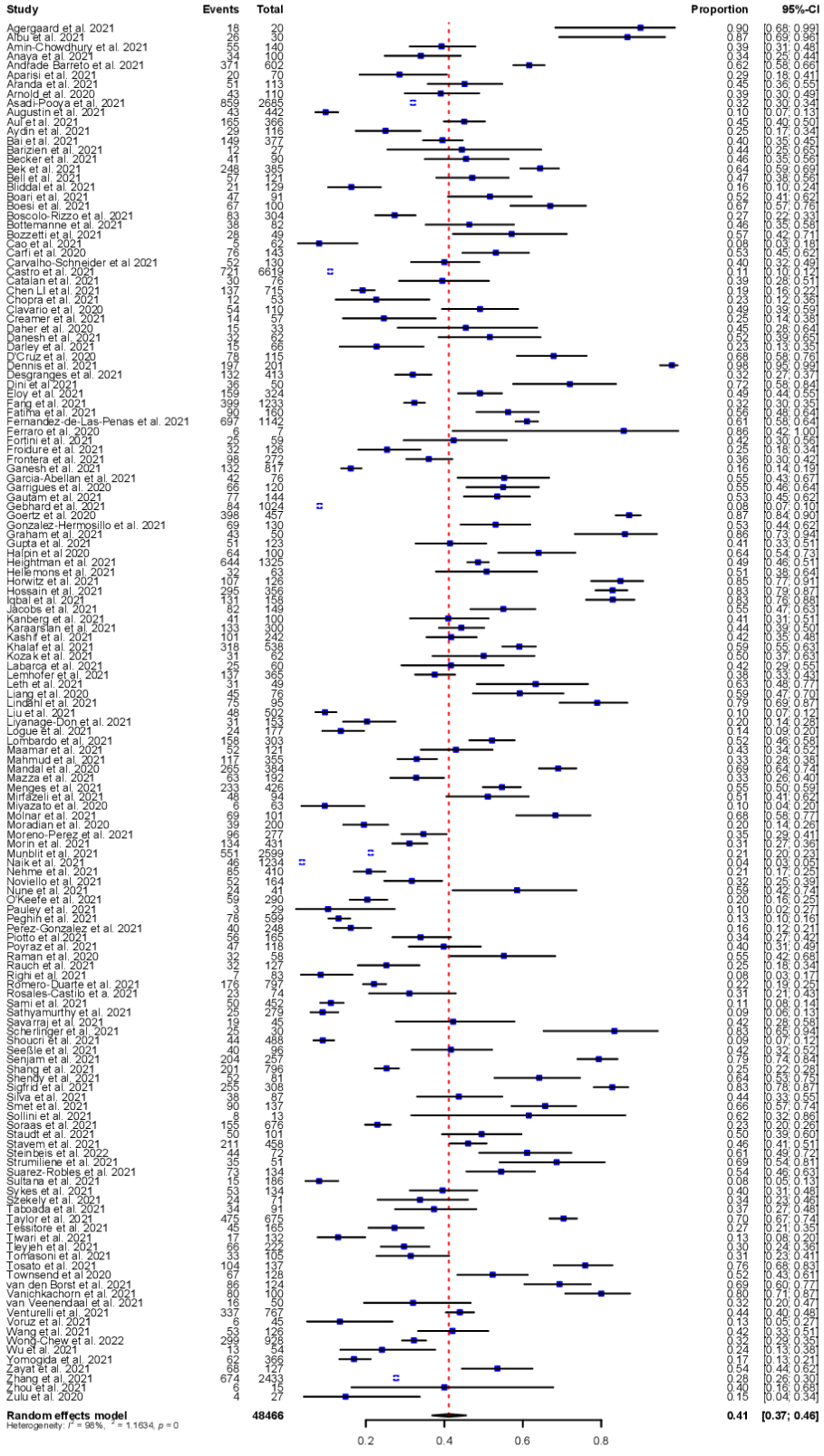

Figure 2 Forest plot for proportion of fatigued.

Table 1 Results of linear mixed-effect meta-regression of time and hospitalisation

Parameter	Estimate	SE	AIC	P value	95% CI	
					Lower	Upper
Months	−0.0577	0.0252	501.933	0.05	−0.1070	−0.0084
Hospitalisation	−0.0871	0.1088	–	0.445	−0.3013	0.1326
Months: hospitalised	0.0324	0.0674	505.680	0.630	−0.0997	0.1645

AIC, Akaike information criterion.

mixed effects model meta-regression. The outcome variable was the proportion of individuals reporting fatigue, with 'months' (number of months since infection) and 'hospitalisation' (whether someone was hospitalised) as predictors. A total of 35 studies with available fatigue data and multiple time points (≥2 follow-ups) were included. We found an effect of time, with the proportion of fatigued participants decreasing by 5.7% per month (95% CI: 1% to 10%, p=0.05). There was no effect of hospitalisation and no interaction between hospitalisation and time (table 1).

We conducted two subgroup analyses to explore the origins of heterogeneity arising from study methodology and investigate between group differences. No significant difference in fatigue was found between n=67 cross-sectional studies (44%, CI: 38% to 50%, I^2=97.6%) and n=80 prospective studies (39%, CI: 33% to 45%, I^2=98%), p=0.272.

A higher proportion of fatigued participants was found in n=36 studies using a scale (51%, 95% CI: 43% to 58%, I^2=96.2%) compared with n=111 studies using an unvalidated questionnaire (38%, 95% CI: 33% to 43%, I^2=98%), p=0.004. To assess fatigue occurring at (a) 1–3 months ('ongoing symptomatic COVID-19') and (b) >3 months ('post-COVID-19 syndrome'), two random effects subgroup analyses were conducted. Between 1 and 3 months, the proportion of fatigued was 41% (95% CI: 36% to 47%, k=86, I^2=98.3%). At >3 months, the proportion was 41% (95% CI: 34% to 48%, k=61, I^2=97.4%). Sensitivity analysis was performed by excluding n=30 quality assessments (graded 'low') and removing unpublished results from the main analysis (n=8). Results found the pooled prevalence to be 40% (95% CI: 36% to 45%, I^2=98.3%) and 41% (95% CI: 37% to 46%, k=139, I^2=98%), respectively, indicating little impact on the main results. Egger's tests indicated publication bias for both time categories and sensitivity. Plots are available in online supplemental files 6–15.

Factors associated with fatigue

Not all studies investigated or reported factors associated with fatigue. For some, the available data for each risk factor were too few to conduct a quantified analysis. Studies also used diverse outcome measures or non-validated scales. In addition, some risk factors were reported but not accompanied by quantified data making comparisons between studies problematic. Consequently, reported associations were arranged in tabular form illustrating the direction of the association with fatigue (table 2). A positive symbol (+) indicated a positive association, a negative symbol (−) indicated a negative association and a zero (0) indicated no significant association between the investigated variable and fatigue.[122] The follow up time point in the prospective cohort designs is shown in brackets. Where a risk factor was examined with another (eg, ICU admission with age), one set of results was included. Full details of the associations are available in online supplemental file 16.

Non-modifiable factors

Older age was reported in 30 studies with mixed results. A total of 6 reported an association with or an increased likelihood of fatigue (OR=1.02) in participants>50.[52 66–68 123 124] Two reported higher fatigue in >60 year olds[125] and >40 year olds.[83] Some, however, reported that younger age related to fatigue[126–129] or no difference in fatigue severity between <65 and >65 year olds.[130] The remaining 17 studies did not find a relationship to fatigue.[69 70 79 80 84 85 96 98 99 131–138] However, studies reporting non-significant results had small-to-modest sample sizes and were therefore potentially underpowered. Gender was investigated by 46 studies. A total of 30 studies reported a significant association with fatigue. More women were fatigued,[42 52 63–66 68 96 98 99 123 125 128 130 133 136 139–152] they (54.3%) reported more severe/moderate fatigue than men (29.6%)[86 129] and had significantly lower vitality scores (M=81.80) compared with men (M=83.25).[124] However, 16 used an unvalidated instrument potentially affecting results. Those finding no significant difference[70 79 80 83 84 131 132 135 137 138 153 154] had small sample sizes and only three used a fatigue scale.

Physical factors

The key physical factors associated with fatigue were dyspnoea, pulmonary functions, exercise capacity, comorbidities and ICU admission. An association between breathlessness and fatigue was found in three studies[79 84 85] and those with fatigue had a higher prevalence of breathlessness in four other studies.[82 83 129 155] At 3–6 months post infection, two did not find a relationship,[80 96] suggestive of improvements over time. Staudt *et al* (2021) found that 'respiratory symptoms' on the St George's Respiratory Questionnaire (SGRQ) were related to fatigue in multivariate analyses at 10 months post infection (OR=1.06,

Table 2 Variables associated with fatigue

Factor	Cross-sectional bivariate	Multivariate	Prospective cohort bivariate	Multivariate
PTSD↑	+ +		+ +	
Anxiety symptoms↑	+ 0 +	+	+	0
Depression↑	+ + + + + +	+ +	+ (0^{6} +^{12})	+ 0
Psychiatric morbidity↑			+	
Physical comorbidities	0 0 0	+ +	0 0	+ + + + + + +
Psychological distress			0	
Somatisation			+	0
Pulmonary functions	+ 0 0	0		0
Pneumonia (CXR)		+		
Disease severity↑	+ 0 -+0 0 0 0	+	+ 0 + 0 0 0 + 0 0 0 0 + ++0 0	0 0
Age↑	0–0 + - 0 0 -	-+0 0 0 + 0 0	0 0+0 0 0 0–0	+ 0 – + 0 +
ICU admission	0 0 + + ++0	0 0 +	+ 0 + +	
Female gender	+ + - 0 ++0 + ++0 + + ++0 + + + +	+ + ++0	++0 + 0 ++0 + 0 + ++0	+ +++0 0 +
Ethnicity	0 0	0		
Marital status			0	
Rural/urban habitat			0	
Occupation type			0	
BMI/obesity/weight↑	0 ++0	0 0+0	0 0 0	0
Returned to work	+	+	0	
Employed				+
Retired				–
Exercise capacity <	+ + - -		0	0 0
Intubated/IMV	+		- (-^{3} +^{6}) 0	+
Serum troponin-1			+	
Nucleic acid test (>14 days, 46–69 years old)	+	+		
Reduction of serum NfL levels			0	
Blood (eg, lymphocytes10^{9}/L, IgG)	0 + -	+	0	0
SpO_2				0 0
Gut microbiota	+			
% predicted VO_2			0	
Mean consecutive difference in extensor digitorum communis	+			
Alcohol consumption	0	0		
Smoking history	0 0 0	0 0		0 0
Length of stay >	0+0 0	+	0 +	
Hospital readmission				+
Education↑	0	0		
Physical health↓	0 +			+
Pain	+		+	
Post functional status/daily functioning↓	+ + + +			
Frailty↑			+	
Resilience↓	–			
Sleep (quality and quantity)	+ + +		+ 0	

Continued

Table 2 Continued

Factor	Cross-sectional bivariate	Multivariate	Prospective cohort bivariate	Multivariate
Steroid treatment	0 0			
Days since onset >	0	+		
Cognitive problems↑	+ + +		+	
Breathlessness/dyspnoea/ hyperventilation↑	+ 0 +	+ 0	+ +	+ +
Post-COVID-19 functioning↓			+	+

BMI, body mass index; CXR, X-ray of the chest; ICU, intensive care unit; IgG, immunoglobulin G; NfL, serum neurofilament light chain; PTSD, post-traumatic stress disorder; SpO2, oxygen saturation; VO2, maximal oxygen consumption.

p=0.05). However, only two used a dyspnoea scale or a fatigue scale. All had small sample sizes, therefore potentially underpowered. Pulmonary functions were reported in five studies. Forced expiratory volume in one second (FEV_1) related to higher vitality in 1 (r=0.0.23, p<0.05),[78] but non-significant in the others.[79 80 155] These studies assessed survivors≥3 months, suggesting results are indicative of functional improvements overtime. Exercise capacity was generally poor in survivors[156] and seven studies examined its relationship with fatigue, with mixed results. Better exercise performance was associated with vitality (r=0.526, p<0.001),[78] but not with 4 m gait speed test[85] or 6MWT.[79] Two others found improved fatigue following a physical rehabilitation programme.[97 157] At 3 months post infection, fatigue was cited as the reason for halting a cardiopulmonary performance test or limiting exercise in three studies.[158–160] Myopathy was associated with fatigue in another small study of 20 people[161] suggestive of poor conditioning contributing to limited capacity. Generally, fatigue had an inverse relationship with exercise capacity in the early months. Where the relationship remained beyond 3 months,[78] patients were overweight/obese, which possibly affected performance. Also, all studies had small sample sizes limiting generalisability.

Physical comorbidities such as hypertension, asthma and diabetes were related to fatigue in nine studies.[52 63 68 126 128 136 146 148 162] Four found no relationship.[132 133 137 147] A large study of 4755 participants found hypertension increased the likelihood (OR=1.27, p=0.05) of persistent fatigue>6 months.[148] Yomogida *et al*[68] reported that having at least one comorbidity increased the risk for fatigue (OR=4.39, p<0.001). Moreover, worse physical health was related to fatigue (OR=10.48)[65 163 164] implying general poorer functioning among survivors.[165]

For those admitted to ICU, some experienced high fatigue (eight studies),[83 129 131] and lower vitality,[166 167] or had an increased likelihood for fatigue (OR=4.63).[52 128 168] Four studies found no association between ICU admission and worse fatigue or vitality.[42 169–171] Patients who received mechanical ventilation had lower vitality (M=50, 95% CI: 44 to 57) than a sex-matched and age-matched group (M=68, 95% CI: 67 to 69).[172] Similarly, more intubated patients had fatigue (38.1%) than non-intubated (29.9%).[173] One study found the proportion of fatigued participants was higher in the ward group (74%) compared with ICU (33%).[143] Disease severity also had an inconsistent impact on fatigue, with most studies finding no association with severe acute disease or fatigue prevalence in severity categories.[80 86 93 130 136 137 153 174–180] Six studies found a significant association with critical illness or a significantly higher proportion of fatigued in severe illness.[123 135 145 181–183] Two studies found a relationship between severity of acute illness and vitality,[184 185] although both had small samples and were single-centre designs. Interestingly, moderately severe COVID-19 related to fatigue (OR=2.1) in one study.[186] Even after a longer hospital stay, the relationship with fatigue was inconsistent with two finding significance,[52 124] while four did not.[69 98 137 149] Taken together, these results indicate an uncertain contribution of critical illness to fatigue, although the non-significant results chiefly occurred>6 months. However, the classification of disease severity varied between studies and countries making comparisons difficult.

Psychological factors

A relationship with anxiety was found up to 6 months post infection in three studies.[52 83 149] The fatigued had higher anxiety (56.3%) compared with non-fatigued (24.6%, p<0.001).[83 149] In contrast, no significant interaction between anxiety and fatigue at 1 month related to later fatigue.[187] Similar results were found for depression. Previous depression was associated with lower vitality (−12.05, p=0.005) in one study[96] and a higher proportion of fatigued had depressive symptoms in four other studies (p=0.004).[83 90 155 188] Other studies found consistently moderate positive correlations (r=0.470).[98 171 189] or increased fatigue scores (b=0.89, p=0.05) in those with depressive symptoms.[52] The relationship continued up until 12 months.[79 98] Four studies found that those with PTSD symptoms were fatigued[90 129] and PTSD was associated with fatigue at 6 and 12 months after infection.[98] Barizien *et al*[132] found higher scores on the PTSD Checklist for Diagnostic and Statistical Manual of Mental Disorders (DSM-5) in those with fatigue (M=31, IQR=18) compared with those without fatigue (M=18, IQR=19, p<0.001). Generalisability of these results, however, is likely limited

due to modest sample sizes and single-centre designs. In addition, only three studies used a valid fatigue scale.

DISCUSSION

This review investigated the prevalence of persistent fatigue in survivors who had a confirmed diagnosis of SARS-CoV-2, using a mean of >30 days post infection. We found a considerable proportion of patients continued to experience fatigue up to 12 months after their initial illness, which was associated with some non-modifiable factors including female gender, age and modifiable factors such as anxiety, depression and post-traumatic stress. Our findings support other research indicating that fatigue is an important symptom in persistent postacute sequelae.[14 112 150 190–196] Rates of fatigue may depend on when it was measured and, in this respect, we found overall rates of fatigue decreased by 6% per month. Fatigue did not differ by hospitalisation status, indicating that the contribution of severe disease was not related to fatigue recovery for most people. This is consistent with previous reviews, which did not find support for the effects of critical illness on fatigue outcomes.[117 197] Respiratory impairments, a key clinical indicator, were associated with worse vitality post recovery (r=0.290, p=0.026),[78] although at 10 months, FEV_1 was not associated[79] implying that, as lung function improved, fatigue diminished. Indeed, rehabilitation aimed at improving functioning by incorporating aerobic exercises, improved vitality scores.[97 167 198] Some survivors, however, continued to experience dyspnoea, which was associated with their fatigue,[83–85] despite normal pulmonary tests.[80 159] Similarly, reduced exercise capacity, as a result of critical illness, is thought to contribute to reduced HRQoL and fatigue outcomes in recovered patients.[199] However, our review did not find a consistent relationship between exercise performance and worse fatigue in those who had more severe disease. It is possible that these limitations are related to diminished muscle function[199] and deconditioning. Rehabilitation programmes have led to improved vitality[157 198] and lower fatigue.[97 157] A 9-week telerehabilitation study of 115 participants, incorporating 2/3 aerobic exercises per week to improve physical capacity, reported significantly increased vitality scores from pre=40.7(SD=21.7) to post=58.5(SD=21.2), p=0.001.[167] While deconditioning could explain fatigue, persistent fatigue may be related to other variables including psychological factors.

Depression and anxiety were found to be correlated with fatigue in our review.[52 171] Moreover, these relationships were found some distance from the initial infection.[98 155] In a prospective study of 402 participants using a fatigue scale, Mazza *et al* found that both anxiety (r=0.48) and PTSD (r=0.52) were moderately correlated with fatigue at 12 months, post illness. These findings accord with critical illness studies[200] and systematic reviews suggesting that symptoms of depression, anxiety, PTSD and fatigue persist long after discharge.[197] For COVID-19, we cannot be certain of the longevity of psychological factors or their relationship to fatigue because the body of evidence is too small, but current literature indicates the relationship remains up to 6 months.[83 132] This fits with previous COVID-19 research indicating those with chronic fatigue were more likely to have psychiatric morbidity 4 years following SARS infection.[201] Similarly, those with psychiatric illness reported higher fatigue than those without (p<0.05) in survivors of SARS.[202]

Theoretical implications

The associations of fatigue persistence were multidimensional. Factors such as dyspnoea and comorbidities (eg, hypertension) were likely risk factors for fatigue in the shorter term, whereas psychological factors appeared more likely to be associated with fatigue longer term. The psychological risk factors could have been related to adverse effects of the pandemic as well as infection.[203 204] Taken together, these factors, alongside other mechanisms such as skeletal muscle deficits,[205] could lead to poorer global functioning and lower engagement in activities or exercise. Lower scores on objective walking tests and reduced physical functioning were associated with fatigue in some studies. We have summarised diagrammatically the factors associated with post-COVID-19 fatigue (see figure 3).

Practical implications

Our review suggests post-COVID-19 fatigue is complex, affecting multiple domains of physical and psychological well-being. While there were small improvements in fatigue over time, our review indicates that fatigue remains a significant problem for patients beyond their anticipated recovery time.[206] Pulmonary rehabilitation programmes have shown promise.[97 167 198] Our results also suggest that psychological interventions may benefit some survivors. Given fatigue is one of a number of post-COVID-19 symptoms,[207–210] an integrated management approach has been suggested.[211] Care pathways should identify those most at risk for long-term symptoms such as women and older people with comorbidities.

Future directions

Few studies have examined correlates between fatigue, physical and pulmonary functioning, psychological and social functioning in hospitalised and outpatients. Some research focuses on symptom 'clusters' or 'post-COVID-19 syndrome'[212–215] limiting understanding of fatigue processes specifically. Future studies should interrogate risk factors further to help inform the development of clinical interventions to address persistent fatigue. Furthermore, fatigue is the principal symptom for postillness patients, but there is little research into what mechanisms may ameliorate distress resulting from infection, and thus protect against long symptoms. Severity of the illness, for instance, was not conclusive in our study and nor was length of hospital stay, pointing to the importance of individual differences.

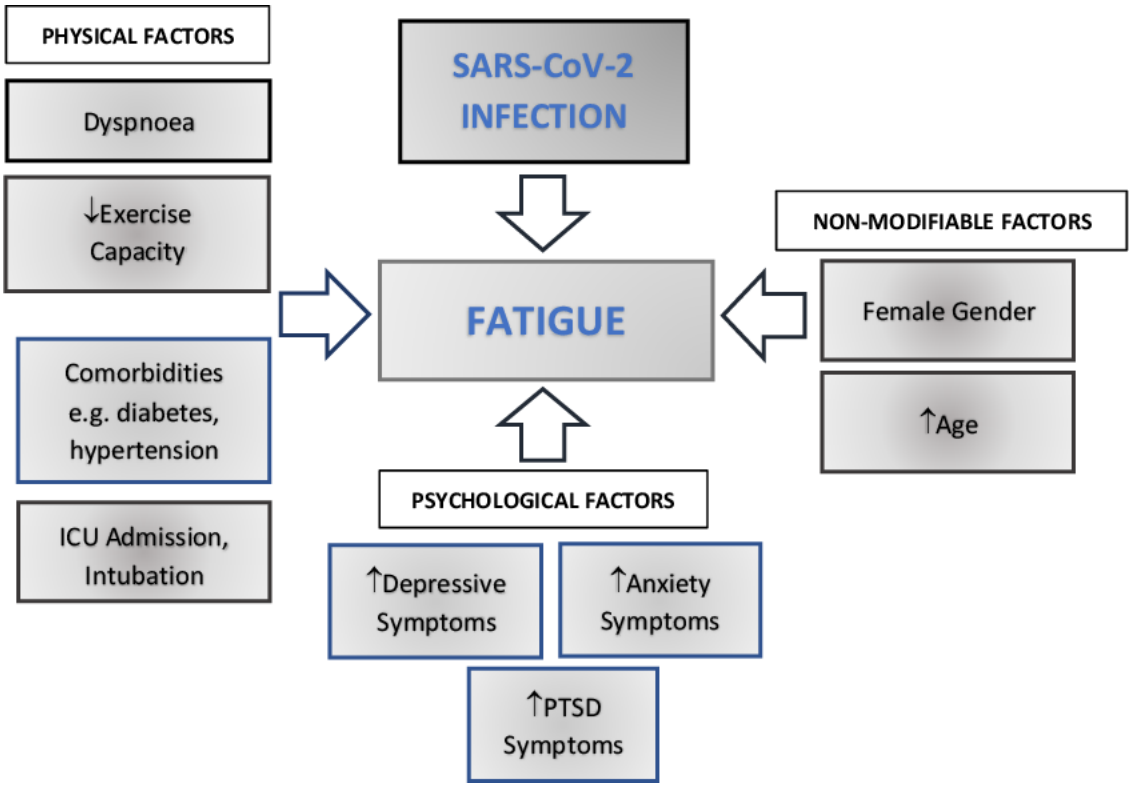

Figure 3 Diagram of post-COVID-19 fatigue findings. ICU, intensive care unit.

Limitations

The generalisability of our results should be applied with caution due to a number of limitations. First, we found considerable, unexplained between-study heterogeneity. Measurement error was not found to explain the inconsistency. However, diverse tools were used to measure fatigue in different populations. Non-validated questionnaires were unlikely to capture fatigue dimensions accurately given most only had 1–2 fatigue-related items. Moreover, scoring and cut-offs were under-reported, contributing to variability. Included studies could not adequately exclude 'pandemic-related fatigue' in their selections or definitions. Therefore, we recognise that our results could not completely exclude such fatigue and its potential influence on participants in the included studies. Some studies used particular populations, including older age or only those admitted to ICU, meaning they were not representative. Furthermore, our sample comprised primarily of hospitalised patients with potentially more severe disease. This was complicated by different admission and discharge protocols across countries, with some admitting all confirmed patients regardless of disease severity. This could explain why there was no difference between hospitalised and non-hospitalised survivors. We also encountered missing data, which reduced the reliability of our results. Moreover, Egger's tests suggested all but one analyses were asymmetric representing a high likelihood of publication bias. Small study effects were likely to affect precision. Larger studies, with more precise CIs, are likely to be a more reliable indicator of fatigue proportions. Moreover, sample bias probably occurred due to recruitment from single-centre post-COVID-19 clinics[216–218] for persistent symptoms and therefore could be expected to have higher fatigue than controls or population norms. Different admission and discharge protocols and lung function reference ranges vary between countries.[219] Our results, therefore, should be viewed with this in mind. Methodologically, our study had only one reviewer for screening and data extraction, and we did not contact authors for missing data meaning our study was at higher risk for excluding relevant data. Other limitations include the inclusion of non-peer reviewed articles and those limited to English. For the meta-analysis, given the multiple assessment times, we incorporated one median follow-up time obtained from each study, which may not denote actual fatigue prevalence. Despite these limitations, we incorporated a substantial sample size likely to be a reasonable estimate of fatigue in this population.

CONCLUSION

This large review provides a broad illustration of fatigue outcomes and complements the body of information for persistent symptoms in those recovering from COVID-19. We report that fatigue decreases over time, but recovery pathways are potentially impeded by a number of risk factors, independent of disease severity or hospitalisation. Our study indicates the

need for long-term clinical and psychological rehabilitation support for survivors of COVID-19.

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