

Supplementary File 1. PRISMA-P Protocol

TITLE: PRISMA-P Protocol for a Systematic Review: Fatigue outcomes following COVID-19: A systematic review and meta-analysis

REGISTRATION: PROSPERO 2020 CRD42020201247

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AMENDMENTS: Protocol amendments will be tracked, dated and numbered. The responsibility for tracking and registering changes to the protocol will be held by the 1st Reviewer with prior agreement and approval from the Senior

Reviewer. Final authorisation for any changes to the protocol will be from the Senior Reviewer.

A summary of changes table (Table 1, Appendix A.) will be utilised to track changes and record authorisations. An explanation and rationale for the amendments will be recorded in Table 2 (Appendix A.)

FUNDING:

No specific funding has been obtained for this review.

This protocol was developed and designed in collaboration between all stated authors.

RATIONALE:

Fatigue is a commonplace presenting symptom for a number of infectious diseases, including coronaviruses. Studies reporting fatigue in the current COVID-19 epidemic suggest a fatigue prevalence of between 18% in children to 100% in emergency department patients [1] during the acute phase. Fatigue has been implicated in increasing the risk for ICU care in some patients presenting with COVID-19, with a risk ratio of between 1.24 and 1.52. [2] Further, it is an emerging symptom associated with chronic stress among healthy populations during forced lockdown conditions, who reported increased somatic symptomology such as sleepiness, insomnia, headaches, digestive disturbances and fatigue compared to before lockdown conditions. [3]

Apart from acute clinical symptoms, fatigue may continue post-recovery or have a sudden onset following an acute viral infection. The current pandemic has revealed a considerable burden of lasting symptoms with approximately 1 in 4 people experiencing fatigue by one estimate. [4] Studies also indicate fatigue as one of the primary persistent symptoms. Systematic reviews indicate a pooled-prevalence of post-COVID-19 fatigue to vary between 45%, [5] 52% [6] and 64%. [7] For a considerable number of COVID-19 patients, fatigue symptoms extend beyond 3 months and represent the largest burden of post-infection symptomology. [8,9] This accords with evidence for post-viral fatigue in previous coronavirus outbreaks. One study investigating recovered SARS patients, found that 64% suffered continuing fatigue 3

months post-discharge and 60% experienced continuing fatigue at 12 months. [10] Another Hong Kong study reported 40.3% of recovered patients had chronic fatigue 4 years after contracting SARS and around 27% met the criteria for chronic fatigue syndrome.

Factors associated with post-illness fatigue include disease severity at the acute stage, which is more likely to require critical care or hospitalisation. [11–14] Physical factors have also been implicated in some studies. Reduced exercise capacity, for instance, is common in recovered patients even at 6 months post-infection and has been related to lower vitality. This is despite no concurrent impairments in pulmonary functions. [15] Although pulmonary functions are weakly related to fatigue, dyspnoea remains a problem for recovered patients, with studies indicating a positive correlation with fatigue. Other determinants include female gender, [16–19] and older age, particularly over 50 years old [20–22] have been related to worse fatigue following a COVID-19 infection. Psychological factors include anxiety, post-traumatic stress and depressive symptoms, which are frequent in survivors of respiratory viral infections, [23–25] have a consistent relationship with higher fatigue. Depression and PTSD, for instance, were related to fatigue severity in 402 post-Covid patients. [26]

Current systematic reviews and meta-analyses support fatigue as a primary symptom during COVID-19 recovery, which may persist for several months post-infection. Given the potential to affect recovery, this review will add to the current body of knowledge in both prevalence and associations to potentially aid in developing interventions for fatigue outcomes following the current coronavirus pandemic. The overall aim is to investigate the prevalence of long-term fatigue outcomes in survivors of COVID-19.

This systematic review will comply with the PRISMA-P guidelines (Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocol. [27]

OBJECTIVES: The objective of this review are: (a) to examine the prevalence of continuing/persistent fatigue among recovered patients, (b) to explore

potential explanatory variables associated with fatigue outcomes where data is available (e.g. psychological, physical and sociodemographic). The study objectives will utilise a PICO framework (Appendix B.)

METHODS:

Eligibility Criteria

- Original articles available in English;
- Studies with primary data;
- Studies reporting fatigue using a valid fatigue measure (e.g. Chalder Fatigue Questionnaire), the 'vitality' subscale of the SF-36 or SF-12 instruments or studies using a clinical interview, checklist or questionnaire with a fatigue item(s);
- Studies investigating fatigue occurring ≥ 30 days after the acute phase/hospitalisation or post-infection as defined in each article. Fatigue defined as 'post-discharge', 'post-hospitalisation', 'post-acute', 'post-illness' or 'post-onset' must have been measured at a median/mean time of ≥ 30 days.
- Patient populations with a diagnosis of SARS-CoV-2 (COVID-19) confirmed by RT-PCR, IgM/IgG serology or clinical assessment (e.g. CT scan, chest X-ray);
- Adults ≥ 18 years old;
- Letters containing primary data;
- Any study design including cohort, case-control, cross-sectional, randomised control trials, meta-analysis.

Exclusion criteria

- Pandemic fatigue (defined as 'worn out' by pandemic warnings, or by government safety instructions, or with media coverage, or with compliance requirements');
- 'Muscle fatigue', 'leg fatigue' and fatigue data combined with 'malaise' or 'muscle weakness';
- Fatigue associated with physical disorders (e.g. thyroiditis, Parkinson's disease, cancer);
- Pregnant participants; children and adolescents < 18 years old;

- Fatigue measured or reported as a clinical symptom during the ‘acute phase’ (defined as the period of hospitalisation or fatigue occurring < 30 days post-infection);
- Participants without a confirmed diagnosis of COVID-19 (i.e. participants who self-report a diagnosis), or studies including ‘probable’ cases;
- Fatigue among healthcare workers, which arising in the context of their work (e.g. burnout, compassion fatigue);
- Newspaper articles, conference papers/abstracts, editorials, opinions, background articles;
- Clinical or treatment procedures or protocols,
- Case reports and qualitative studies;
- COVID-19 vaccination studies, animals;
- Absence of outcome data (i.e. not quantified or reported in text).

Information sources:

PsycINFO, MEDLINE, EMBASE, CINAHL, OpenGrey, Cochrane Database of Systematic Reviews.

Search Strategy:

The search strategy will be piloted and amended where appropriate to select the most appropriate studies. An example of the search strategy is available in Appendix C. The search strategy language will be amended according to each database requirements.

Study Records:

The following data will be extracted and recorded in a spreadsheet: author(s), title, population and participant numbers, follow-up period, control/comparator, location, study inclusion/exclusion criteria, study design, study objectives, outcomes of interest, associations with fatigue, scales/instruments employed, results, effect size and power calculation (Y/N). In addition, the quality of each study (see Risk of Bias) will be indicated. A separate database will be compiled detailing the studies that will be fully-screened but excluded, together with the rationalisation for the exclusion.

Selection Process:

The 1st reviewer will conduct the initial search in the selected databases for relevant studies. The senior reviewer will review a proportion of the identified studies based on the inclusion and exclusion criteria. The senior reviewer will independently audit the selected studies and review the data extraction spreadsheet. Agreement for the final included studies for any meta-analysis and narrative review will be in collaboration. Disagreements will be settled through consensus and agreement. A PRISMA flow chart will be used to record the number of records collected, number of fully-screened records, number of records excluded, studies identified through reference lists and total number of records for inclusion in any meta-analysis.

Data items/collection:

The variables for the data to be recorded will include the following and will be entered into a data extraction spreadsheet:

- citation details
- target population & location (survivors, region/country),
- study eligibility criteria,
- population characteristics (sample size, socio-demographics)
- outcomes under study (fatigue, vitality),
- how the outcomes were measured (Chalder Fatigue Scale), [28]
vitality scale of the SF-36/SF-12, including the definition of clinical outcomes for a scale, cut-off points, upper/lower scores, explanation of whether a high or low score is favourable,
- study variables (e.g. PTSD, depressive symptoms, exercise capacity),
- metrics (e.g. changes in fatigue),
- timing of outcome measurements (e.g. assessments at 6-week intervals),
- mean and standard deviations for each group,
- comparator group,
- effect size,
- time (baseline data and follow-up times e.g. 1 month, 3 months),
- study design and setting (e.g. hospital, outpatients, population),

- study methods (single, multicentre, parallel, cluster)

For randomised control trials:

- Intervention or comparator descriptions (e.g. drug type, control group, placebo group),
- Doses, times and frequencies, length of intervention,
- How an intervention was assessed, length of exposure, cumulative exposure,
- Integrity of the intervention (the degree to which the procedures were implemented as stated/planned),
- Post-intervention metrics (e.g. changes in fatigue, pre-post-test),
- Randomisation procedures,
- Adverse effects,

Results

- Number of participants in each stated group (including number of patients lost, withdrawn, lost to follow-up or excluded with reasons),
- Summary data for each group, each outcome and each time point (means and standard deviations for continuous data, OR for dichotomous data),
- Between-group estimates measuring effect of the intervention on the outcome (e.g. OR, RR, mean differences) and their confidence intervals
- Confounders measured.

In the event of incomplete data regarding the exposures or outcomes, effect sizes or other important data, reviewers will request this information from the authors. Where there is no response, the missing data will be calculated according to [29] or the paper will be excluded.

Risk of bias:

Risk of bias (RoB) assessment will be conducted for each included study using the relevant JBI tool. [30] The RoB will be conducted independently by three researchers. The assessments (e.g. good, moderate, poor) will be reported. A

selection of reviews will be independently cross-checked by all 3 researchers to establish reliability of the assessments. Methods to summarise the RoB assessments for all the studies and a description of these assessments will be incorporated into the data synthesis (i.e. sensitivity analyses) and their potential influence on the findings will be discussed.

Data synthesis

This systematic review will employ a quantitative approach and provide a summary pooled estimate of the risk for fatigue, combining the results of all the studies where appropriate. Where 3 or more studies can be combined based on the same outcome measure, a meta-analysis will be performed. Where there are less than 3 studies identified for the same outcome, the effect sizes will be described in text. For the meta-analysis, we will compute odds ratios (OR) for binary outcomes to estimate the risk of fatigue relative to the exposure virus and target population (survivors), with 95% confidence intervals as an overall synthesised measure of effect size. For continuous outcomes, standardised mean differences for the combined effect size will be computed. Data from all studies will included in the analysis. Additional statistical tests may be conducted dependent upon data availability (e.g. fatigue outcome relative to gender, socioeconomic status, pre-existing psychiatric conditions etc).

It is expected that there will be considerable heterogeneity in study types and outcome measures, therefore it is expected that a random effects model will be performed for the meta-analysis to provide an estimate of the mean effect size for the included studies. The random effects model is expected to allow for wider heterogeneity and take account of the estimated between-study weight differences. To assess between-study-heterogeneity a Cochran's Q will be performed and the effect of heterogeneity will be quantified using the I^2 statistical-test. A value of 50% or greater for the I^2 will be considered as indicative of greater variability. A value of greater than 75% will be considered as considerable variability. Statistical measures of effect will be extracted from the included studies for calculating pooled effect sizes of the association between an included influenza virus and fatigue outcomes.

Effect sizes, 95% confidence intervals and statistical significance will be presented by quantitative and graphical representations (i.e. forest plots). Statistical significance will be set at $p < 0.05$ (2-tailed) for all analyses. Sensitivity analysis will be conducted utilising the RoB assessments across all the studies. For example, excluding low grade studies, studies with declared conflicts of interest. A funnel plot will be performed to assess publication bias.

Meta-bias(es)

In order to assess publication bias, funnel plots (observed for 10+ studies included in the meta-analysis) with an Egger test [31] to test asymmetry at alpha level 0.1 will be conducted.

Confidence in cumulative evidence

GRADE (Grading of Recommendations, Assessment, Development and Evaluation working group methodology) will be used to assess the quality of evidence for all outcomes. The quality of evidence will be assessed for risk of bias, consistency, directness, precision and publication bias. Quality will be judged as high (further research is very unlikely to change our confidence in the estimate of effect), moderate (further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate), low (further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate) or very low (very uncertain about the estimate of effect)

Reporting standards

The reporting of this systematic review will be in compliance with the PRISMA guidelines (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) [32].

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Appendix A

Table 1. SUMMARY OF CHANGES TABLE

<i>Document</i>	<i>Protocol Version Number</i>	<i>Date</i>	<i>Authorisation</i>
Amendment No. 1			
Amendment No. 2			
Amendment No. 3			
Amendment No. 4			
<i>Current Protocol</i>	<i>Final</i>	<i>12.12.22</i>	<i>TC</i>
Original	1.01	04.08.20	

Table 2. AMENDMENT RATIONALE

<i>Section Number/Heading</i>	<i>Description of Amendment</i>	<i>Rationale Summary</i>

Appendix BPICOS

Patient/Population	Exposure	Comparison	Outcome
Adults	COVID19 diagnosis	Where applicable	Fatigue
Patients	SARS-CoV-2	Healthy controls	Fatigue
Survivors	COVID-19	Non-treatment	Vitality
Outpatients	n-CoV-2	Treatment as usual	Low energy
Inpatients	2019-nCoV2		Chronic fatigue
	Coronavirus		Tiredness
	Socio-demographics		Exhaustion
	COVID-19 severity		Asthenia
	ICU admission		General fatigue
	Ventilation status		Lethargy
	Anxiety symptoms		
	Depressive symptoms		
	PTSD symptoms		
	Stress/distress		
	Sleep		
	Quality of life		
	Physical functioning		
	BMI		
	Clinical factors (lung function, serology, CT scans)		
	Comorbidities		

Appendix CExample Search Strategy

	Database	Search
	PSYCINFO	
1		("severe acute respiratory syndrome" or "severe acute respiratory adj2 syndrome").mp
2		exp coronavirus/ or "corona virus".mp. or "corona adj1 virus".mp.
3		(COVID-19 or COVID19 or SARS-CoV-2 or SARS-CoV* or SARSCOV2 or SARSCOV-2 or nCoV-2 or 2019-nCoV* or nCoV19* or nCoV2).mp.
4		(covid19 or covid-19 or covid*).mp.
5		1 OR 2 OR 3 OR 4
6		chronic fatigue*. mp
7		(fatigue or tired*).mp [mesh word]. or exhaust*.tw.
8		(((((quality adj2 life) or QoL or health related quality) adj2 life) or HRQoL).tw.
9		6 OR 7 OR 8
10		(5 and 9) not cancer not child* not adolescent* not vaccin* not burnout not HIV Limit 10 to up="20190101-2021"