Long COVID and post-infective fatigue syndrome – a review.

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Key points (40 words)

- Fatigue after COVID-19 is common, but generally resolves over months, like other post-infective fatigue states
- Post-COVID fatigue results from end-organ injury, mental health conditions, or idiopathic post-COVID fatigue
- Post-COVID fatigue should be assessed with validated questionnaires, interviews, and protocolized investigations

Abstract (175 words)

Fatigue is a dominant feature of both acute and convalescent COVID-19 (sometimes termed 'long-COVID'), with up to 46% of patients reporting fatigue lasting weeks to months. The investigators of the international Collaborative on Fatigue Following Infection (COFFI) conducted a systematic review of post-COVID fatigue, a narrative review on fatigue after other infections and made recommendations for clinical and research approaches to assessment of fatigue following COVID-19.

In the majority of COVID-19 cohort studies, persistent fatigue was reported by a significant minority of patients, ranging from 13-33% at 16-20 weeks post symptom onset. Data from the prospective cohort studies in COFFI and others, indicate that fatigue is also a prevalent outcome from many acute systemic infections notably infectious mononucleosis, with a case rate for clinically-significant post-infective fatigue after exclusion of recognized medical and psychiatric causes, of 10-35% at 6 months.

To better characterize post-COVID fatigue, the COFFI investigators recommend: application of validated screening questionnaires for case detection, standardized interviews encompassing fatigue, mood, and other symptoms, and investigative approaches to identify end-organ damage and mental health conditions.

Introduction

Emerging data suggest that some patients fail to fully recover following acute COVID-19 infection. Patients who report symptoms persisting for weeks or months after the acute illness have been termed "long haulers", or as having "long-COVID"[1]. Although a case definition of “long-COVID” has not been established, fatigue is a dominant feature, along with other symptoms reminiscent of the acute infection. The condition has gained attention from the media, the public, as well as the scientific and medical communities[2].

The term ‘fatigue’ has diverse meanings, including that experienced by people as part of daily living (‘physiological’ or ‘everyday’ fatigue), or in disease (e.g., anemia) (‘pathological fatigue’). The fatigue state may be objectively measurable as a reduction in the efficiency of force generation recorded on physical examination as weakness (as in myopathy), or it may be a purely subjective sensation (i.e., fatigue as a symptom). Importantly also, when patients complain of fatigue, they may actually be referring to weakness, dyspnea, difficulties in concentration, somnolence, or low mood. Hence, careful delineation of the nature of the symptom complaint(s) is key in both clinical and research settings. The subjective experience of fatigue (as with pain) is automatically interpreted in light of other concomitant brain processes, such as perceptions, emotions, and cognitions[3].

Evolutionarily, fatigue might be considered as a homeostatic alarm directed towards energy preservation[3], which is well exemplified in the acute sickness response to a wide range of pathogens. This response features a stereotyped collection of physiological, behavioral, and psychological manifestations including fever, fatigue, hypersomnia, musculoskeletal pain, anorexia, mood disturbance, and cognitive impairment[4]. Persistence of one or more of these symptoms for weeks or months beyond the acute phase of infection is common[5]. In this context, patients describe the persistent fatigue as having both ‘physical’ components (loss of energy, and a feeling of heaviness), and ‘mental’ components (a feeling of brain fog). Another characteristic feature is that relatively minor physical or cognitive activity triggers a prolonged exacerbation of the fatigue and other symptoms[6].

When fatigue persists for six months or more, it is termed 'chronic'[7]. When thorough clinical assessments and investigations do not reveal alternative explanations for chronic fatigue, and if other typical symptoms such as musculoskeletal pain and cognitive difficulties are present, a diagnosis of chronic fatigue syndrome (CFS), or more specifically, post-infective fatigue syndrome (PIFS), may be considered[5, 7].

The investigators of the international Collaborative on Fatigue Following Infection (COFFI) [5], have sought to provide guidance on these complexities of fatigue following COVID-19 infection by: conducting a systematic review on the emerging data on the epidemiology of fatigue following COVID-19 infection; and comparing the literature regarding fatigue after other infections through a narrative review. Recommendations for clinical and research approaches to assessment of fatigue following COVID-19 are provided.

Fatigue after COVID-19 - a systematic review

A meta-analysis of studies in acute COVID-19 infection revealed an overall prevalence of fatigue of 23% (95% CI 15–33%)[8]. The current review focused on persistent fatigue following acute COVID-19 infection, defined here as 21 days or greater post symptom onset. The review aimed to describe the incidence, natural history, and predictors of such post-COVID fatigue.

Methods

References were identified through searches of PubMed for articles published from January 2020 to January 2021, using terms "fatigue", "malaise" or "tired", and "COVID-19" or "COVID19" or "SARS-CoV-2". Additional articles were identified by searching reference lists and citations of included articles. In addition, MedRxiv (a preprint server for health sciences) was also searched using terms "fatigue", "tired", "persistent symptoms" and "COVID-19" to identify relevant pre-publication manuscripts. Prospective cohort studies and cross-sectional studies were included, provided that they: specifically reported the rates of fatigue in the convalescent phase after confirmed acute COVID-19 infection, included a minimum of 10 participants, and were written in English. Almost all studies

used those who had completed follow-up as the denominator for symptom prevalence rates. Accordingly, data were extracted from each study to re-calculate the proportion of patients reporting fatigue using all eligible COVID-19 confirmed subjects as the modified denominator (including those who refused, were lost to follow-up, or died).

Results

Study and patient characteristics

The search until January 2021 yielded 914 articles from PubMed, an additional 208 records identified through MedRxiv, and six additional papers through reference lists and citations. A total of 1117 records were screened by title and abstract, and 154 articles were subjected to full text review. The reasons for exclusion of these full-text articles (n=133) are outlined in the PRISMA flowchart (Supplementary Figure 1). The final list of included articles (n=21) described three prospective studies[9-11], and 18 cross-sectional studies[12-29]. The sample sizes ranged from 33–4,182 participants (median n=131, total n=7,639), with an age range between 32–71 years (median 50 years), of whom 52% were male (median 52%; range: 28-70%). Most studies (15 of 21) only included patients who had been admitted to hospital[11-18, 20, 21, 23, 25, 26, 28, 29], with the remaining six studies including a mixture of hospitalized and non-hospitalized patients[9, 10, 19, 22, 24, 27]. Ten studies included patients who were admitted to ICU[12-15, 19, 22, 24-26, 28], and three specifically excluded ICU patients[17, 20, 21]. To ensure consistent reporting of observation periods, 'time since symptom onset' was used as the anchor point. If the authors only provided the time since hospitalization or the time since discharge, it was assumed that subjects were symptomatic for seven days before hospitalization, and the duration of hospitalization was taken as the median reported for each study.

Prevalence of fatigue

The average period of observation across all studies was 82 days since symptom onset (range: 27-199 days). To date, only a single study has conducted follow up beyond 129 days [29]. Three prospective

cohort studies assessed rates of fatigue from symptom onset[11], through to 60 days post symptom onset[9, 10]. In the acute phase, the peak fatigue rates in these studies ranged from 8%[11]-29%[10] (Figure 1). At 4 weeks post-symptom onset, rates of fatigue ranged from 9%[10]-49%[9]. A trend of resolution was evident within the individual cohorts with falling rates of fatigue reported at 8 weeks (4%[10]-35%[9]) after symptom onset. When the modified denominator was considered including all eligible subjects with confirmed COVID-19 infection, the recalculated rates of fatigue were lower, ranging from 7%[11]-29%[10] in the acute phase; 9%[10]–25%[9] at week 4; and 4%[10]-18%[9] at week 8. None of these prospective cohort studies collected data beyond 8 weeks.

The 18 cross-sectional studies[12-20] assessed fatigue at various time windows ranging from 4 weeks to 28 weeks post symptom onset. The median proportion of patients reporting fatigue were: 50% at 4-7 weeks[17, 23, 24, 28]; 53% at 8-11 weeks[13, 15, 21, 22, 26], 40% at 12-15 weeks[12, 18, 19]; 28% at 16-20 weeks[14, 16, 20, 25, 27], and 34% at 28 weeks from symptom onset[29]. When the rates of fatigue were recalculated using the more inclusive denominator, the median rates were: 23% at 4-7 weeks[17, 23, 24, 28], 42% at 8-11 weeks[13, 15, 21, 22, 26], 26% at 12-15 weeks [12, 18, 19], 23% between weeks 16–20 weeks[14, 16, 20, 25, 27], and 32% at 28-weeks from symptom onset . The ranges of fatigue prevalence from each time window are reported in Figure 2[29]. In several studies, patients reported additional symptoms such as dyspnea[12-16, 24-26, 28], and/or cognitive difficulties[14, 15, 18, 29] at similar, but somewhat lower rates than fatigue.

Functional impact and predictors of long COVID

In three studies which measured the functional impact of persistent symptoms, there was evidence of associated disability with 40%[15], 31%[19], and 9-15%[14, 25] of patients unable to return to work, at 2-,3- and 4-months post-symptom onset respectively. Although no studies were sufficiently powered to run multivariable-regression analysis, exploratory analyses found that severity of illness as measured by hospitalization[9], ICU[24], duration of stay in hospital[20], duration of viral shedding[20], and dyspnea during hospitalization[9, 20] were associated with fatigue at follow-up.

Critique

It should be noted that almost all studies (20 of the 21) were likely to be influenced by ascertainment bias (as not all of those with confirmed COVID-19 and eligible were included in the reported denominators)[30]. As expected, the rates of fatigue reported from cross-sectional studies were higher than those from prospective studies, which is likely to reflect the greater selection bias in those who remain unwell electing to respond to cross-sectional surveys. Further bias was introduced by studies which excluded those who were severely unwell [9, 14, 17, 21]. By contrast, the largest study was an observational cohort of a subset of individuals (n=4182) utilizing the COVID Symptom Study online app, which has been taken up by several million individuals in the UK and USA [10]. Although a convenient method of assessment, computer literacy may have restricted the participating population, and this cohort had unusually high number of female participants (72%), whereas epidemiological studies show no gender difference in the prevalence of acute COVID-19 infection[31].

The measurement of fatigue was generally poorly described, with most studies providing little detail on the instrumentation used. Most studies used either only a "customized questionnaire"[9, 11, 13, 21, 24-26, 28, 29], "telephone interview"[12, 15, 16, 20], "medical records"[14], or a mobile phone application[10], with no further details provided. Only five studies administered validated multi-item fatigue questionnaires, using the Chalder Fatigue scale[17, 19], the Fatigue Severity Scale[18], the Somatic and Psychological HEalth Report (SPHERE)[22], the Fatigue Impact Scale[27], or the PROMIS Scale-Global Health[23].

Multiple studies have identified significant long term complications of severe acute COVID-19 infection and the associated hospitalization, including pulmonary, cardiac, neurological, and psychiatric conditions - many of which may manifest with the complaint of persistent fatigue.[32, 33] In the follow-up studies reviewed here which identified persistent fatigue, very few conducted systematic clinical or laboratory assessments to consider these possibilities, with those doing so including a full blood count[11, 12, 21], chest x-ray[12, 26], chest CT[11, 17, 25], or lung function

tests[21, 25]. Only one study described cardiac investigations (e.g., electrocardiography or echocardiography) to screen for cardiac pathology[21]. Mental health status and social supports were only assessed in one study[28].

Summary

From this review, it is clear that fatigue is a dominant complaint in "long COVID" and that larger prospective studies with longer follow-up, using more comprehensive and well validated methods for the assessment of fatigue and related conditions, are needed. Previous studies of fatigue after other infections may help guide the choice of measures.

Post-infective fatigue states after other infections – a narrative review

Fatigue is a very common symptom in primary care where it is generally short-lived and attributable to infective illnesses or minor psychiatric disorders[34]. Several acute infections are also a well-established trigger for the onset of chronic fatigue.

Methods

In addition to consideration of data from the COFFI cohorts, a narrative review was conducted searching PubMed for prospective cohort, observational, or case-control studies which followed individuals from acute infection for chronic fatigue.

Results

Fifteen studies were identified following from several different viral, bacterial or protozoal pathogens, including *Epstein-Barr virus* (EBV), *Dengue virus*, *Chikungunya virus, Ebola virus, Coxiella burnetii* (the causative agent of Q fever), and *Giardia lamblia*. These studies documented a prevalent complaint of post-infective fatigue persisting in disabling degree for six months or more in 10-35% of adolescents or adults (see Supplementary Table 1 for cohort summaries and references). In all of these studies multi-item validated questionnaires were used to characterize the fatigue state. In six studies, a case definition for chronic fatigue syndrome was applied at six months which necessitated a clinical

assessment including a medical history, physical examination, mental health assessment, and laboratory investigations leading to a designation of PIFS, after exclusion of other medical or psychiatric conditions (Supplementary Table 1)[7]. By contrast, a prospective case-control cohort study in general practice found that patients presenting with minor symptomatic infections, such as common colds, did not experience an increased likelihood of developing chronic fatigue[35].

Predictors of PIFS

A systematic review of biological, psychological and social predictors of chronic fatigue or PIFS six months after onset in the prospective cohort studies, revealed that clinical and laboratory features indicative of the severity of the acute infection were the most consistent predictors, including: the presence of markers of the host immune response, including biochemical hepatitis; self-reported severity of acute illness, and of fatigue in particular; and associated functional impairment such as the number of days in bed or days off school. In addition, there was some evidence across studies for self-reported anxiety, perceived stress, neuroticism, negative beliefs about the acute illness, and pre-morbid distress, as risk factors[36]. A notable exception to the latter was the sole prospective cohort which collected data prior to the acute illness to characterize mental health and personality characteristics[37]. This study followed US college students (n=4501) for asymptomatic seroconversion or symptomatic acute EBV, revealed a case rate for PIFS of 23% at six months and showed that premorbid psychological factors did not predict PIFS[37]. Nested case-control studies from the prospective cohorts have investigated subjects with well characterized PIFS and matched control subjects who recovered uneventfully from the same acute infection, and have not found evidence of ongoing replication of the pathogen beyond several weeks (although persistent detection of nucleic acids is recognized); or of a consistent pattern of ongoing immune activation[38-42].

Summary

Taken together these findings from post-infective cohorts show that: fatigue is a common and sometimes disabling symptom after a diverse range of infections; the natural history of persistent fatigue is often of slow resolution over months or longer; the severity of the acute illness, psychological status at baseline, and the cognitive and behavioral responses to the acute illness predict PIFS; and that structured medical and psychiatric assessments of those with self-reported chronic fatigue will identify a subset with explanatory diagnoses such as residual long injury.

Discussion

Clinical and research approaches to the assessment of post-infective fatigue

In combination, the limitations of the studies in COVID-19 and the evidence from studies in other post-infective cohorts argue that a validated case definition for chronic fatigue after COVID-19 infection is needed for both clinical and research purposes. In line with current definitions of post-infective fatigue[5], we suggest that the label *post-COVID fatigue* should be applied when the fatigue is: a dominant symptom; chronic; disabling to an extent that it interrupts all or a majority of normal activities (such as work/school attendance, social activities, etc.); persistent for 6 months or more (3 months in children/adolescents); and emerged during confirmed acute COVID-19 (i.e., with a positive SARS-CoV-2 test), without symptom-free interval since onset.

If a case of post-COVID fatigue is identified, a search for underlying diagnoses should be initiated, including for: end-organ sequelae of the acute COVID-19 illness and hospitalization; mental health conditions precipitated or exacerbated by COVID-19; and other (non-COVID-related) premorbid or intercurrent disorders of which fatigue is a feature. We recommend a structured diagnostic work-up (see Supplementary Tables 2 & 3 for summaries of instruments and references). In both clinical and research settings, brief screening questionnaires to characterize the fatigue state, such as the Chalder Fatigue Scale or the SPHERE (Supplementary Table 2), provide a systematic approach to identify 'clinically-significant' fatigue, in line with the disease-specific recommendations from the National Institute of Neurological Disorders and Stroke Common Data Elements. As the symptom of fatigue is

often part of a multi-symptom cluster, it is appropriate to include other validated questionnaires to screen for: related physical symptoms (such as the SPHERE), and mental health (such as the Patient Health Questionnaire-9, or the Hospital Anxiety and Depression Scale (Supplementary Table 2). Screening for other relevant symptom domains may also be undertaken with validated instruments to assess pain and sleep quality. Clinically-significant fatigue is usually taken to be associated with disability, and so concurrent assessment of functional status using an instrument such as the SF-36 is strongly recommended (Supplementary Table 2).

As both medical and mental health conditions may manifest with fatigue, or co-occur with a post-infective fatigue state, for research purposes in particular, the validated, clinician-administered, semi-structured diagnostic interview schedules for fatigue states (Structured Clinical Interview for Neurasthenia, SCIN)[6], and psychiatric disorders (Composite International Diagnostic Interview, CIDI), offer an ideal approach to further assessment. In addition, if screening questionnaires raise of the possibility of sleep disturbance as a contributor, the Structured Diagnostic Interview for Sleep patterns and Disorders may be utilized (Supplementary Table 3).

In clinical practice, patients with persistent fatigue after COVID, should have a careful history to elucidate the nature of the symptoms, the timing of onset, and their impact on functional status; as well as a physical examination with particular emphasis on respiratory, cardiac, and neurological findings. This clinical assessment should include review of pre-morbid and intercurrent mental health with a particular emphasis on depression, anxiety, and post-traumatic stress disorder. In addition, a restricted list of laboratory tests should be ordered, such as a full blood count, kidney, liver, and thyroid function tests, C-reactive protein, blood glucose, ferritin, B-type natriuretic peptide, as well as a chest x-ray[43]. Additional investigations or specialist referral may be considered if the history or examination raises concerns. Children and adolescents with post-COVID fatigue should be referred to a pediatric service for assessment.

For those cases in whom this process does not reveal an explanatory condition, we recommend making a diagnosis of *idiopathic post-COVID fatigue.* These patients may satisfy diagnostic criteria for PIFS – that is a post-infective fatigue syndrome following COVID-19[7]. In terms of clinical care, provision of such a diagnosis is a key starting point for reassurance of a generally self-limiting natural history and supportive care[44]. For research purposes, we recommend that additional symptoms and co-morbid conditions are well charted, enabling statistical analyses that control for these factors.

Pathophysiology

As the pathophysiology of PIFS remains unresolved, a biopsychosocial approach to conceptualizing research approaches to idiopathic post-COVID fatigue is recommended, incorporating predisposing, precipitating, and perpetuating factors. Predisposing factors in PIFS may include genetic[45], as well as psychosocial vulnerabilities[46]. COVID-19 is the precipitating factor, but may well act in concert with other concomitant triggers, such as distressing life events (e.g., death of a relative from COVID-19, loss of employment)[47]. Perpetuating factors may include the advent of sleep disturbance,[48] autonomic dysfunction with sympathetic predominance[49], endocrine disturbance with hypothalamus-pituitary-adrenal (HPA) axis attenuation[50], reactive mood disorder such as depression or anxiety[51], as well as abnormal illness beliefs and behavioral changes such as activity patterns which are boom-bust or avoidant[52], resulting in a complex set of determinants of illness and disability[36]. It is likely that idiopathic post-COVID fatigue will have comparable pathophysiology to PIFS. For research investigations of the predictors or associations of post-COVID fatigue, large sample sizes and stratification by the multiple contributory variables are recommended, and careful matching by, or controlling for, these variables in case-control designs.

Conclusion

Although there are many unknowns to be resolved about long COVID for both clinical and research contexts, the lessons learnt from several decades of investigation of fatigue states after other

312 infections highlight the need the careful clinical characterization, protocolized investigations and a
313 broad bio-psychosocial approach.
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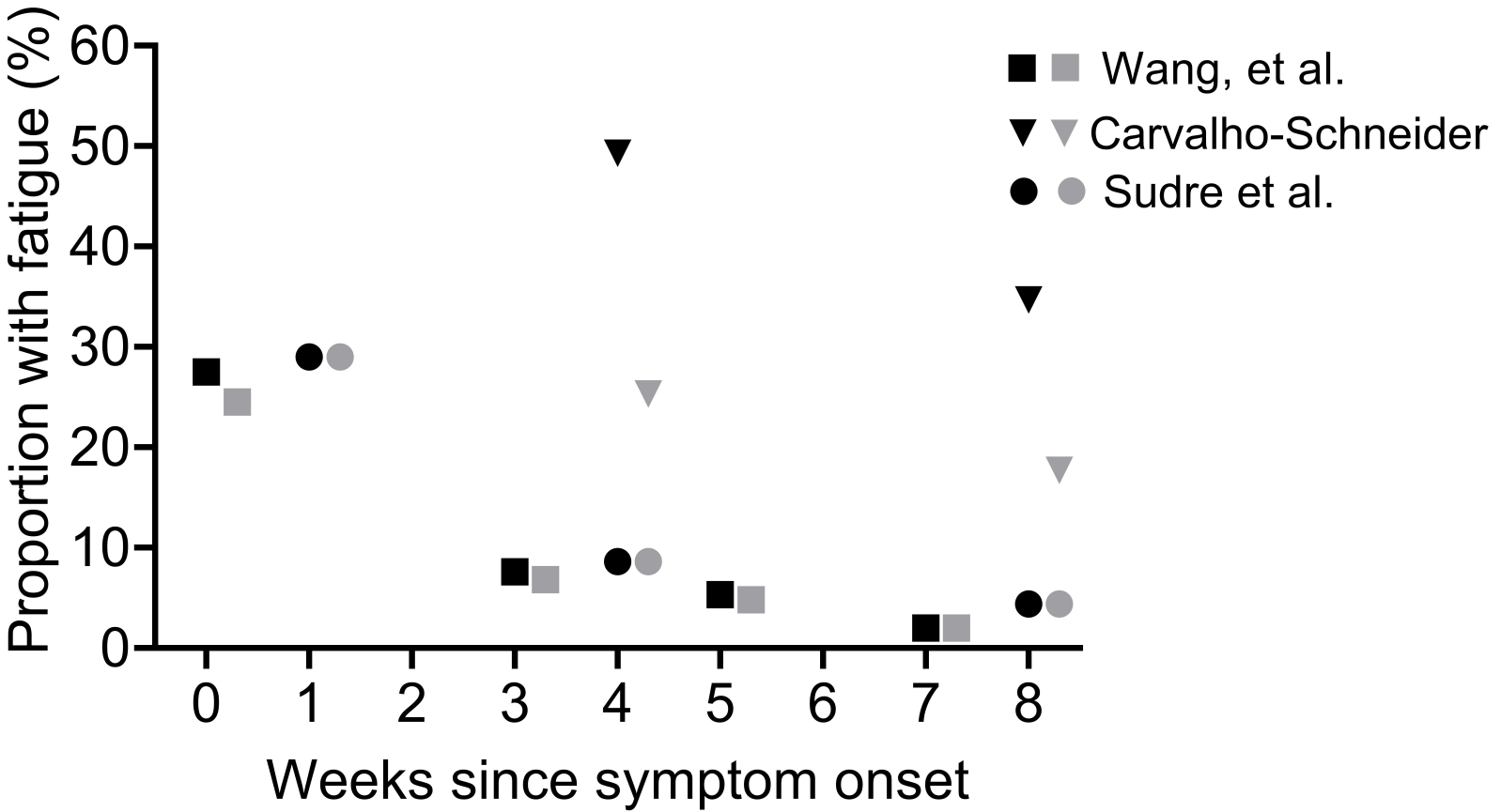
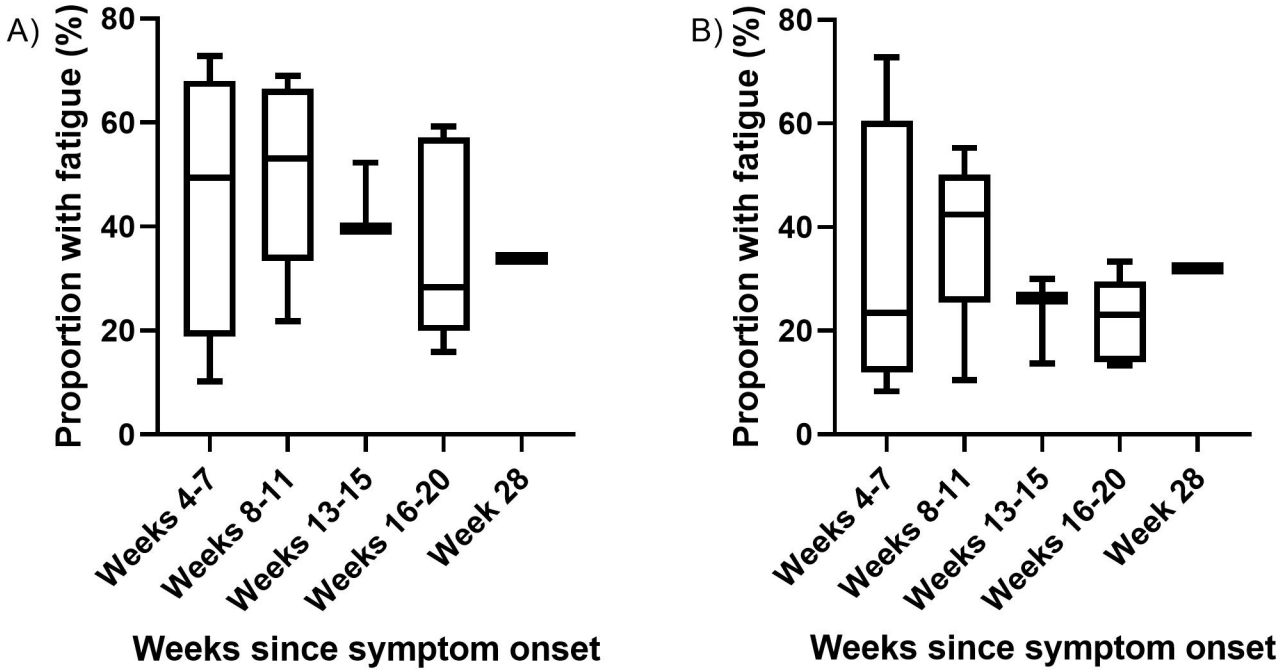
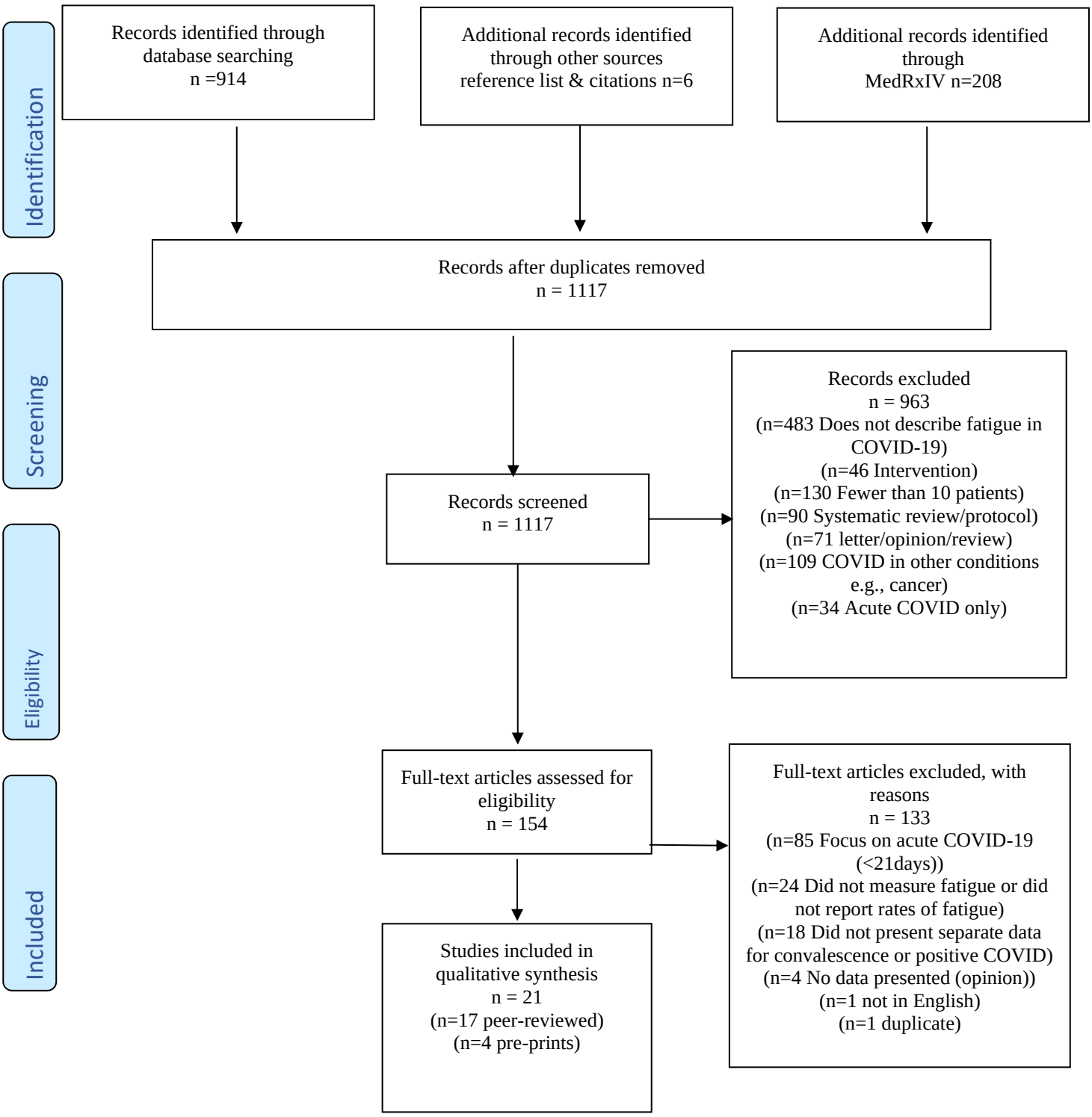
Figure legends.

Figure 1: Prevalence of fatigue in COVID-19 from prospective studies. Black symbols refer to the original rate reported by each study. Grey symbols refer to rate recalculated with all eligible individuals included in the denominator.

Figure 2: Prevalence of fatigue in COVID-19 from cross-sectional studies. The box extends from the 25th to 75th percentiles, the line represents the median, the whiskers show the minimum and maximum. Week 28 is represented by a single study. Panel A shows the original rates reported by the included studies. The proportion of patients reporting fatigue were: 10%-73% at 4-7 weeks[17, 23, 24, 28]; 22%-69% at 8-11 weeks[13, 15, 21, 22, 26], 39%-52.3% at 12-15 weeks[12, 18, 19]; 16%-59% at 16-20 weeks[14, 16, 20, 25, 27] and 34% at 28 weeks from symptom onset[29]. Panel B shows these rates recalculated with all eligible individuals included in the denominator: 8%-24% at 4-7 weeks[17, 23, 24, 28], 10%-55% at 8-11 weeks[13, 15, 21, 22, 26], 14%–26% at 12-15 weeks [12, 18, 19], 13%-33% between weeks 16–20 weeks[14, 16, 20, 25, 27] and 32% at 28-weeks from symptom onset (Figure 2)[29]


Proportion with fatigue (%)
60
50
40
30
20
10
0
0
1
2
3
4
5
6
7
8
Weeks since symptom onset
Wang, et al.
Carvalho-Schneider
Sudre et al.


A)
Proportion with fatigue (%)
80
60
40
20
0
Weeks 4-7
Weeks 8-11
Weeks 13-15
Weeks 16-20
Week 28
Weeks since symptom onset
B)
Proportion with fatigue (%)
80
60
40
20
0
Weeks 4-7
Weeks 8-11
Weeks 13-15
Weeks 16-20
Week 28
Weeks since symptom onset



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

Supplementary Table 1: Summary of cohort studies evaluating post-infective fatigue.

Study	Triggering infection or illness	Participants (n=eligible / n=followed-up, % female, mean age, setting, country)	Study design	Chronic fatigue and related measure(s) – Questionnaires (Q) Interviews (I)	Outcome timepoints	Case rate of chronic fatigue (CF) or post-infective fatigue syndrome (PIFS) caseness	Baseline predictors of chronic fatigue (CF) or post-infective fatigue syndrome (PIFS) caseness at 6 months	Alternative diagnoses identified at 6 month clinical and laboratory assessment for PIFS
Buchwald et al, 2000[1]	EBV	n=150 / n=144, 53% 21 years Health maintenance organisation - mixed primary, secondary, tertiary care USA	Prospective cohort	Q: checklist of IM symptoms, SF-36, SCL-90, List of Threatening Experiences, Perceived Social Support Inventory, I: DIS	2 months, 6 months	CF: 38% at 2 months; 12% at 6 months	CF: female gender; greater premorbid life events, greater social support	NA
Candy et al, 2003[2]	EBV	n=139 / n=71, 60% 23 years Six general practices and a student healthcare centre, UK	Prospective cohort	Q: Chalder Fatigue Scale, GHQ, SF-36, Illness Perceptions Questionnaire	3 months, 6 months, 12 months	CF: 47% at 3 months; 40% at 6 months; 38% at 12 months	CF: female gender, illness perceptions	NA
Cope et al, 1996[3]	Presumed viral illness	n=64 cases with CF; (n=64 non-infective controls) 78% 30 years primary care UK	Case-control	Q: Symptom Interpretation Questionnaire, GHQ, Beck depression Inventory, Spielberger State and Trait Anxiety Inventory, Multi-dimensional Health Locus of Control, Ways of Coping Questionnaire I: Semi-structured clinical interview for fatigue, CIS	6 months	PIFS: 35% at 6 months	PIFS: premorbid fatigue, sick certification, psychological attributional style	Yes (but no details of other diagnoses available)
Duvignaud et al, 2018[4]	Chikungunya	n=440 / n=362 (cases were required to report fatigue at onset) 62% Adolescents and adults Population level Reunion Island	Prospective case-control	I: Telephone interview	15-36 months post onset (mean = 24 months)	CF: 39%	CF: Female gender, age>60, severe acute illness	NA
Hanevik et al, 2014[5]	Giardia	n=1252 / n=817 67% 38 years Population Norway	Prospective case-control	Q: Chalder Fatigue Scale	3 years 6 years	CF: 46% at 3 years; 31% at 6 years	NA	NA
Hickie et al, 2006[6]	EBV, Ross River Virus, Q fever	n=430 / n=253 43% 34 years Primary care	Prospective cohort	Q: SPHERE, Brief Disability Questionnaire, Eysenck Personality Inventory	3 months, 6 months, 12 months	CF: 27% at 3 months; 12% at 6 months; 9% at 12 months PIFS: 11% at 6 months	Severe acute illness	Yes - Q fever endocarditis (n=1)

Study	Triggering infection or illness	Participants (n=eligible / n=followed-up, % female, mean age, setting, country)	Study design	Chronic fatigue and related measure(s) – Questionnaires (Q) Interviews (I)	Outcome timepoints	Case rate of chronic fatigue (CF) or post-infective fatigue syndrome (PIFS) caseness	Baseline predictors of chronic fatigue (CF) or post-infective fatigue syndrome (PIFS) caseness at 6 months	Alternative diagnoses identified at 6 month clinical and laboratory assessment for PIFS
		Australia		I: Semi-structured clinical interview (CIDI)				
Hotopf et al, 1996[7]	Aseptic meningitis	n=255 / n = 83 cases, (n=76 viral illness controls) 64% female 32 years Specialist hospital UK	Prospective case-control	Q: Chalder Fatigue Scale, Beck Depression inventory, GHQ, SF-36	6-24 months post onset (mean = 18 months)	CF: 25%	Premorbid psychiatric disorder; prolonged convalescence	NA
Jason et al, 2020[8]	IM	n=4703 / n=4501 61% 19 years University USA	Prospective cohort	Q: Fatigue Severity Scale, COPE scale, Perceived Stress Scale, Beck Depression Inventory, Beck Anxiety Inventory, SF-36. I: Medical and psychiatric examination	Baseline (pre-IM), at IM diagnosis, 6 months	PIFS: 23% at 6 months	Severe acute illness, cytokine levels	Yes (but no details of other diagnoses available)
Katz et al, 2009[9]	IM	n=301 90% Adolescent -age NA Primary / secondary care USA	Prospective cohort	Q: Chalder Fatigue Scale I: Semi-structured clinical interview	6 months, 12 months, 24 months	PIFS: 13% at 6 months, 7% at 12 months, 4% at 24 months	Female gender	Yes – transverse myelitis, depression, anorexia nervosa (n=1 for each)
Lowe et al, 2014[10]	STEC	n=608 / n=389 69% 46 years Regional hospitals Germany	Prospective cohort	Q: Chalder Fatigue Scale, Patient Health Questionnaire-9, Generalised Anxiety Disorder Scale, Post-traumatic Stress Diagnostic Scale, SF-12 I: Structured Clinical Interview for DSM-IV (SCID)	6 months	CF: 43% at 6 months	Severe acute illness, pre-existing chronic condition	NA
Moss-Morris et al 2011[11]	IM	n=440 / n=246 62% 29 years Primary care New Zealand	Prospective case-control	Q: Fatigue (in house), HADS, IPQ, BRIQ	3 months 6 months	CF: 9% at 3 months; 7% at six months	Female gender, younger age, prolonged convalescence, perfectionism, anxiety, depression, emotional representations	NA
Pedersen et al, 2019[12]	EBV	n=200 / n=195 65% 17 years Primary care Norway	Prospective case-control	Q: Chalder Fatigue Scale, HADS, IPQ, CAPS, Functional Disability Inventory, PedsQL	6 months	CF: 46% PIFS: 14%	CRP, step count, sensory sensitivity score, pain severity, cognitive performance, anxiety	Yes (but no details of other diagnoses available)
Seet et al, 2007[13]	Dengue	n=163 / n=127 44%	Cross-sectional	Q: Fatigue Questionnaire I: Telephone interview	2 months	CF: 24 % at 2 months	CF: older age, female gender, severe illness	NA

Study	Triggering infection or illness	Participants (n=eligible / n=followed-up, % female, mean age, setting, country)	Study design	Chronic fatigue and related measure(s) – Questionnaires (Q) Interviews (I)	Outcome timepoints	Case rate of chronic fatigue (CF) or post-infective fatigue syndrome (PIFS) caseness	Baseline predictors of chronic fatigue (CF) or post-infective fatigue syndrome (PIFS) caseness at 6 months	Alternative diagnoses identified at 6 month clinical and laboratory assessment for PIFS
		36 years Specialist hospital Singapore						
Sneller et al, 2019[14]	Ebola	n= 966 / n=869 antibody positive cases (and n=2350 antibody negative controls) Population Liberia	Prospective case-control	I: Structured clinical interview including single item report of fatigue	6 months, 12 months	CF: 18% at 18 months (versus 6% in controls)	NA	NA
White et al, 2001[15]	IM	n=469 / n=250 (including those with confirmed EBV: n=101) and various other diagnoses including URTI Primary / secondary care UK	Prospective cohort	I: Semi-structured clinical interview	6 months	PIFS: 10% of the confirmed EBV group	PIFS: positive Monospot test; lower physical fitness	Yes (but no details of other diagnoses available)

BRIQ: Behavioural Responses to Illness Questionnaire; CRP: C reactive protein; CAPS: Children and Adolescents Perfectionism Scale; CIDI: Composite International Diagnostic Interview; CIS: Clinical Interview Schedule for mental health; DIS: National Institute of Mental Health Diagnostic Interview Schedule; EBV: Epstein-Barr virus; GHQ: General Health Questionnaire; HADS: Hospital Anxiety and Depression Scale; IPQ-R: Illness Perception Questionnaire; IM: Infectious mono; Illness Perception Questionnaire; NA: Not Applicable; PedsQL: Paediatric Quality of Life Inventory; SCID: Structured Clinical Interview for DSM-IV; SPHERE: Somatic and Psychological HEalth Report; SF-36: Medical outcomes survey – short form; SF-12: 12-Item Short Form Health Survey; SCL-90: Symptom Checklist-90; STEC: Shiga toxin - producing Escherichia coli O104; URTI: Upper Respiratory Tract Infection

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Supplementary Table 2: Suggested list of questionnaires for investigation of persistent fatigue & symptoms after COVID-19

Questionnaire	Symptom Domain	Comment *(Caseness for clinically-significant disorder in the relevant domain - if applicable)*	Relevant references
Somatic and Psychological Health Report (SPHERE)	Fatigue	SPHERE: 34-item instrument assessing a range of physical and psychological symptoms that commonly accompany fatigue. Screens for caseness for both fatigue and mood disorder in medical and psychiatric settings. *Fatigue caseness (SOMA): ≥3 indicates 'clinically-significant'* *Mood disturbance caseness (PSYCH) ≥2 indicates 'clinically-significant'*	Hickie IB, Davenport TA, Hadzi-Pavlovic D, Koschera A, Naismith SL, Scott EM, et al. Development of a simple screening tool for common mental disorders in general practice. *Med J Aust* 2001;175(Suppl.):S10–7.
Chalder Fatigue Scale		Chalder fatigue scale: 11-item instrument with 4-choice format measure fatigue severity. Provides scores for mental and physical fatigue. *≥4 (bimodal scoring) indicates 'severe fatigue'.*	Chalder T, Berelowitz G, Pawlikowska T, Watts L, Wessely S, Wright D, et al. Development of a fatigue scale. *J Psychosom Res* 1993;37:147–53.
Checklist Individual Strength (CIS)		CIS: 20-item inventory with four subscales: fatigue severity, concentration, reduced motivation, and activity. Fatigue severity measures general and physical fatigue. *The fatigue severity subscale >36 indicates severe fatigue.*	Bultmann U, de Vries M, Beurskens AJ, Bleijenberg G, Vercoulen JH, Kant IJ. Measurement of prolonged fatigue in the working population: determination of a cut-off point for the Checklist Individual Strength. *J Occup Health Psychol* 2000;5:411–6.
PedsQL-Multidimensional Fatigue Scale		PedsQL-MFS: 18-item, includes three subscales: general fatigue (six items), sleep/rest fatigue (six items), and cognitive fatigue (six items). Each item has a Likert-type response scale, with higher scores indicating fewer fatigue symptoms.	Worm-Smeitink M, Gielissen M, Bloot L, van Laarhoven HWM, van Engelen BGM, van Riel P, Bleijenberg G, Nikolaus S, Knoop H. The assessment of fatigue: Psychometric qualities and norms for the Checklist individual strength. *J Psychosom Res*. 2017; 98:40-46. Varni JW, Burwinkle TM, Katz ER, Meeske K, Dickinson, P. The PedsQL in pediatric cancer: reliability and validity of the Pediatric Quality of Life Inventory Generic Core Scales, Multidimensional Fatigue Scale, and Cancer Module. *Cancer* 2002, 94(7), 2090-106.
Fatigue Severity Scale (FSS)		FSS: 9-item on 7-point scale measuring severity of fatigue and affects the person's activities. *A score of > 4 indicates problematic fatigue.*	Krupp LB, LaRocca NG, et al. The fatigue severity scale. Application to patients with multiple sclerosis and systemic lupus erythematosus. *Arch Neurol* 1989; 46(10): 1121-3.
PEM items from DePaul Symptom Questionnaire (DSQ)	Post-exertional malaise (PEM)	DSQ: Five items from the DSQ to assess frequency and severity of the common post-exertional exacerbation of symptoms (PEM) over 6 months.	Jason, L.; Jessen, T.; Porter, N.; Boulton, A.; Gloria-Njoku, M.; Friedberg, F. Examining Types of Fatigue among Individuals with ME/CFS. *Disabil. Stud Q*. 2009. Cotler J, Holtzman C, et al. A Brief Questionnaire to Assess Post-Exertional Malaise. *Diagnostics (Basel, Switzerland)* 2018; 8(3): 66.
Fatigue and Energy Scale (FES)		FES: A 6 item questionnaire which records the current fatigue state (i.e., "right now") and its severity in two dimensions (physical and mental fatigue).	Keech A, Sandler CX, Vollmer-Conna U, Cvejic E, Lloyd AR, & Barry, BK. (2015). Capturing the post-exertional exacerbation of fatigue following physical and cognitive challenge in patients with chronic fatigue syndrome. *J Psychosomatic Research*, *79*(6), 537–549.
Pittsburgh Sleep Quality Index (PSQI)	Sleep disturbance	PSQI: A 19-item questionnaire evaluating sleep quality and disturbances over the past month. A total score (0-21) is calculated from 7 component scores (subjective sleep quality, sleep latency, sleep duration, habitual sleep	Buysse DJ, Reynolds 3rd CF, Monk TH, Berman SR, Kupfer DJ. The Pittsburgh Sleep Quality Index: a new instrument for psychiatric practice and research. *Psychiatry Res* 1989;28:193–213.

Questionnaire	Symptom Domain	Comment *(Caseness for clinically-significant disorder in the relevant domain - if applicable)*	Relevant references
Sleep Assessment Questionnaire (SAQ)		efficiency, sleep disturbances, use of sleeping medication, and daytime dysfunction). *Total score > 5 suggests poor sleep quality.* SAQ (proprietary): A 17-item instrument measuring 7 factors intended to screen for sleep disorders: insomnia/hypersomnia, restlessness, sleep schedule, excessive daytime sleeping, sleep apnoea, restless leg/motility, and non-restorative sleep.	Unger ER, Nisenbaum R, Moldofsky H, et al. Sleep assessment in a population-based study of chronic fatigue syndrome. *BMC Neurol*. 2004;4:6.
McGill Pain Questionnaire (MPQ)	Pain	MPQ: For characterisation of pain states and their severity. Available in short and long form. The four components include: (1) a human figure drawing to indicate the location of pain; (2) a series of 78 adjectives to describe patient experience; (3) questions about prior pain experience, pain location, and the use of pain medication; and (4) a pain intensity index. The short form does not assess areas of bodily involvement.	Melzack R. The McGill Pain Questionnaire: major properties and scoring methods. *Pain* 1975;1:277–99.
Brief Pain Inventory (BPI)		BPI: Assesses the severity and impact of pain on daily function, location of pain, pain medications and amount of pain relief in the past 24 hours or the past week.	Cleeland CS. Measurement of pain by subjective report. In: Chapman CR, Loeser JD, editors. *Advances in Pain Research and Therapy*, Volume 12: Issues in Pain Measurement. New York: Raven Press; 1989. pp. 391-403.
Hospital Anxiety and Depression Symptoms (HADS)	Mental health (anxiety/depression)	HADS (proprietary): 14-item questionnaire measuring anxiety and depression in hospital and community settings. Detects presence and severity of mood disorders. *For both scales ≥ 8 indicates caseness for anxiety or depression. 8–10 Mild, 11–14 Moderate, 15–21 Severe.*	Zigmond AS, Snaith RP. The hospital anxiety and depression scale. *Acta Psychiatr Scand* 1983; 67(6): 361-70.
Patient Health Questionnaire-9 (PHQ9)		PHQ-9: 9 item questionnaire to assess the severity of depression. *Depression severity: 0-4 none, 5-9 mild, 10-14 moderate, 15-19 moderately severe, 20-27 severe*	Kroenke K, Spitzer RL, Williams JB. The PHQ-9: validity of a brief depression severity measure. *J Gen Intern Med*. 2001 16(9):606-13.
Generalised Anxiety Disorder Assessment (GAD-7)		GAD-7: 7-item anxiety questionnaire to assess the severity of anxiety. *Anxiety severity: 5-9 mild, 10-14 moderate, >15 severe.*	Spitzer RL, Kroenke K, Williams JB, Löwe B. A brief measure for assessing generalized anxiety disorder: the GAD-7. Arch Intern Med. 2006 22;166(10):1092-7.
General Health Questionnaire (GHQ)		GHQ (proprietary): 28-item questionnaire for screening minor psychiatric disorders in the general population. Assesses the individual's current state and asks if that differs from their usual state. Suitable from adolescence upwards (not children).	Goldberg D, Willaims P. A user's guide to the General Health Questionnaire. Windsor, UK: NFER-Nelson Publishing Company, Pty., Ltd.; 1998.
Depression Anxiety Stress Scale 21 (DASS21)		DASS21: 21-item designed to measure the emotional states of depression, anxiety and stress (7 items per scale).	Lovibond SH. & Lovibond, PF (1995). Manual for the Depression Anxiety & Stress Scales. (2nd Ed.) Sydney: Psychology Foundation.
Beck Depression Inventory (BDI)		BDI: 21-item questionnaire measuring depressive symptomatology Higher scores indicate more depression.	Beck AT, Steer RA, Brown GK. Manual for the Beck Depression Inventory-II 1996; San Antonio, TX: Psychological Corporation.
Beck Anxiety Inventory (BAI)		BAI: 21-item self-report instrument measuring anxiety. Higher scores indicate more anxiety.	Beck AT, Epstein N, et al. An inventory for measuring clinical anxiety: psychometric properties. *J Consult Clin Psychol* 1988; 56(6): 893-7.

Questionnaire	Symptom Domain	Comment *(Caseness for clinically-significant disorder in the relevant domain - if applicable)*	Relevant references
Medical Outcomes Survey Short Form-36 (SF-36)	Functional impairment	SF-36: 36-item measure of physical health, mental health and quality of life. Measures the effects of the illness on physical activity, social activity, usual role activities, bodily pain, general mental health, vitality, and general health perceptions over the previous 4 weeks.	Ware Jr JE, Sherbourne CD. The MOS 36-item Short-Form Health Survey (SF-36). Conceptual framework and item selection. *Med Care* 1992;30:473–83.
Sickness Impact Profile (SIP)		SIP: measures functional disability in different areas of daily functioning. Has 12 subscales: 12 categories including sleep and rest, eating, work, home management, recreation and pastimes, ambulation, mobility, body care and movement, social interaction, alertness behaviour, emotional behaviour, and communication.	Bergner M, Bobbitt RA, Carter WB. Gilson BS: the Sickness Impact Profile. Development and final revision of a health status measure. *Med Care* 1981;19:787–805.
Brief Disability Questionnaire (BDQ)		BDQ: 8-item, assessing disability in everyday activities. Measure physical disability and 'mental-health' disability. Score 8 – 13 = moderate disability, 14-22 severe disability. Asks individuals to estimate how many days over the prior few weeks they were unable to carry out their usual role and how many days they spent in bed.	Von Korff M, Ustun TB, Ormel J, Kaplan I, Simon GE. Self-report disability in an international primary care study of psychological illness. *J Clin Epidemiol* 1996;49:297-303.
PedsQL - PedsQLTM Generic Core Scales		PedsQL: 23 items to measure functional impairment in children aged 2–18.	Varni JW, Seid M,Kurtin PS. The PedQLTM 4.0: reliability and validity of the Pediatric Quality of Life Inventory Version 4.0 Generic Core Scales in healthy and patient populations. *Med Care* 2001;39:800–12.
Illness Perception Questionnaire (IPQ)	Psychological domains	IPQ: Measures individuals expectations of their illness. Has five scales which assess *identity* (the symptoms the patient associates with the illness), *cause* (personal ideas about aetiology), *timeline* (perceived duration of illness), *consequences* (expected effects and outcome and *cure control* (how the individual controls or recovers from the illness).	Weinman J, Petrie KJ, et al. The illness perception questionnaire: A new method for assessing the cognitive representation of illness. *Psychology & Health* 1996; 11(3): 431-45.
Positive and Negative Affect Schedule (PANAS)		PANAS: 20-item to measure positive affect (10-items) and negative affect (10-items negative affect)	Watson D, Clark LA, Tellegen A. Development and validation of brief measures of positive and negative affect: the PANAS scales. J Pers Soc Psychol. 1988;54(6):1063-70.
Behavioural Responses to Illness Questionnaire (BRIQ)		BRIQ: 13-item questionnaire measuring illness-related behaviours: 1) *all-or-nothing* behaviour and 2) *limiting behaviour* (excessive rest).	Spence M, Moss-Morris R, Chalder T. The Behavioural Responses to Illness Questionnaire (BRIQ): a new predictive measure of medically unexplained symptoms following acute infection. *Psychol Med*. 2005 35(4):583-93.
Coping Orientation to Problems Experienced (COPE) Scale		COPE Scale**:** 28-item questionnaire assessing how people cope with stress, includes problem-focused and emotion-focused scales.	Carver CS, Scheier MF, Weintraub JK. Assessing coping strategies: a theoretically based approach. *J Pers Soc Psychol* 1986;56(2):267-283.

Supplementary Table 3: Suggested list of structured interviews, clinical and laboratory assessments for the investigation of persistent fatigue & symptoms after COVID-19.

Assessment or Investigation	Domain (*COVID-19 specific elements)	Comment	Relevant references
Medical assessment	Thorough medical history and physical examination including functional status, signs of respiratory impairment or heart failure*, pulse oximetry*.	Characterize the fatigue state (e.g., fatigue, weakness, somnolence, dyspnea), identify pre-morbid, concurrent, or *de novo* contributors to the fatigue state.	Wilson J, Morgan S, Magin PJ, van Driel ML. Fatigue–a rational approach to investigation. *Aust Fam Physician* 2014; 43: 457–461. Greenhalgh T, Knight M, A'Court C, Buxton M, & Husain L. Management of post-acute covid-19 in primary care. *The BMJ.* 2020 370. Sandler, C. X., & Lloyd, A. R. Chronic fatigue syndrome: progress and possibilities. *Medical Journal of Australia.* 2020 *212*(9), 428–433. National Institute for Health and Care Excellence. COVID-19 rapid guideline: managing the long-term effects of COVID-19. 2020. World Health Organization. Global COVID-19 Clinical Platform Case Report Form (CRF) for Post COVID condition (Post COVID-19 CRF). 2021.
Mental health assessment	Thorough history and current mental state examination.	Characterize the fatigue state (e.g., anxiety, sleep disturbance, motivation loss). Identify pre-morbid, concurrent, or *de novo* contributors to the fatigue state.	Stadje, R., Dornieden, K., Baum, E. et al. The differential diagnosis of tiredness: a systematic review. *BMC Fam Pract* 2016 17, 147. Kroenke K, Wood DR, Mangelsdorff AD, Meier NJ, Powell JB. Chronic Fatigue in Primary Care: Prevalence, Patient Characteristics, and Outcome. JAMA. 1988;260(7):929–934. Griffith JP, Zarrouf FA. A systematic review of chronic fatigue syndrome: don't assume it's depression. Prim Care Companion J Clin Psychiatry 2008; 10: 120–128. World Health Organization. Clinical management of COVID-19: interim guidance. 2020.† National Institute for Health and Care Excellence. COVID-19 rapid guideline: managing the long-term effects of COVID-19. 2020. World Health Organization. Global COVID-19 Clinical Platform Case Report Form (CRF) for Post COVID condition (Post COVID-19 CRF). 2021.

Blood tests	Full blood count, urea, electrolytes and creatinine levels, liver, and thyroid function tests, C-reactive protein levels or erythrocyte sedimentation rate, and fasting blood glucose, D-dimer,* brain natriuretic peptides,* ferritin*.	Investigations to identify potential causes of chronic fatigue.	Fukuda K, Straus SE, et al. The chronic fatigue syndrome: a comprehensive approach to its definition and study. International Chronic Fatigue Syndrome Study Group. *Ann Intern Med* 1994; 121(12): 953-9. Wilson J, Morgan S, Magin PJ, van Driel ML. Fatigue–a rational approach to investigation. *Aust Fam Physician* 2014; 43: 457–461. BMJ. BMJ Best Practice Coronovairus disease 2019 (COVID-19). 2020.† National Institute for Health and Care Excellence. COVID-19 rapid guideline: managing the long-term effects of COVID-19. 2020. Shah S, Shah K, Patel SB, et al. Elevated D-dimer levels are associated with increased risk of mortality in COVID-19: a systematic review and meta-analysis. *Cardiol Rev*. 2020;28(6):295-302. † Aboughdir M, et al. Prognostic value of cardiovascular biomarkers in COVID-19: a review. *Viruses*. 2020 11;12(5).† World Health Organization. Global COVID-19 Clinical Platform Case Report Form (CRF) for Post COVID condition (Post COVID-19 CRF). 2021.
Imaging and other investigations	Chest x-ray, chest CT*, 12-lead ECG*, echocardiogram*, neuroimaging (MRI)*	Investigations to identify potential causes of ongoing fatigue and/or end organ sequelae of COVID-19.	National Institute for Health and Care Excellence. COVID-19 rapid guideline: managing the long-term effects of COVID-19. 2020. Marshall, J. C., et al. A minimal common outcome measure set for COVID-19 clinical research. *Lancet Infect Dis* 2020 20: e192–e197. Almqvist J, et al. Neurological manifestations of coronavirus infections - a systematic review. *Ann Clin Transl Neurol*. 2020;7(10):2057-2071.. Castro RA, Frishman WH. Thrombotic complications of COVID-19 infection: a review. *Cardiol Rev* 2021; 29(1): 43-7. Ojo AS, Balogun SA, Williams OT, Ojo OS. Pulmonary fibrosis in COVID-19 survivors: predictive factors and risk reduction strategies. *Pulm Med* 2020: 6175964.

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	Cognitive performance: Cambridge Neuropsychological Test Automated Battery (CANTAB)	CANTAB (proprietary): Includes tests of memory, attention, and executive function and is administered via a touch-sensitive computer screen. The CANTAB allows a decomposition of complex tasks commonly used in clinical assessment into their cognitive components. Tests include versions of the Wisconsin Card-Sorting Test, the Tower of London, and the Delayed Matching-to-Sample Test. Is non-verbal and largely language and culture independent.	Sahakian BJ, Owen AM. Computerized assessment in neuropsychiatry using CANTAB: discussion paper. *J R Soc Med* 1992;85:399– 402.
	Cognitive Function Index (CFI)	CFI: Measurement of cognitive performance. Assessment includes the California Verbal Leaning Test, the Rey-Osterrieth Complex Figure Test, the computerized NES continuous performance test, the Trail Making Test A and B, the grooved pegboard test, and the WAIS-III Vocabulary and Digit Span subtests. Eight factors were identified including: verbal learning and memory, visual learning and memory, focused attention, simple information processing, sustained attention, general verbal ability, complex information processing, and fine motor speed.	Brimacombe M, Lange G, et al. Cognitive Function Index for Patients with Chronic Fatigue Syndrome. *J Of Chronic Fatigue Syndrome* 2004; 12(4): 3-23.
Interviews	**Domain**	**Comment**	Relevant reference
Semi-structured Clinical Interview for Neurasthenia (SCIN)	Fatigue and related symptoms	Publicly available semi-structured clinical interview that assesses various aspects of fatigue (e.g., ‘‘fatigue’’ (including physical and mental fatigability), ‘‘pain symptoms’’, ‘‘neurocognitive difficulties’’, ‘‘sleep problems’’ and ‘‘mood disturbance’’. Captures patterns of occurrence of symptoms & degree to which each symptom causes functional impairment.	Bennett, B et al. Characterization of Fatigue States in Medicine and Psychiatry by Structured Interview. Psychosomatic Medicine, 76(5), 379–388.
Composite International Diagnostic Instrument (CIDI)	Mood disturbance	CIDI: A computerized structured interview for assessment of mental disorders. Measures prevalence, severity, determines burden of mental health disorders. Supported by the World Health Organization (WHO), the CIDI has been widely used in large epidemiologic studies and therefore allows for national comparisons of psychiatric prevalence rate. Can be administered by trained lay interviewers.	Andrews G, Peters L. The psychometric properties of the Composite International Diagnostic Interview. Soc Psychiatry Psychiatr Epidemiol 1998;33:80–8. Robins LN, et al. The Composite International Diagnostic Interview. An epidemiologic Instrument suitable for use in conjunction with different diagnostic systems and in different cultures. Arch Gen Psychiatry. 1988 Dec;45(12):1069-77.
Structured Clinical Interview for DSM-IV Axis I (SCID)		SCID: A semi-structured interview guide for major mental health disorders. Must be administered by trained interviewers.	Spitzer RL, Williams JB, Gibbon M, First MB. The Structured Clinical Interview for DSM-III-R (SCID). I. History, rationale, and description. Arch Gen Psychiatry 1992;49:624–9.

Diagnostic Interview Schedule (DIS)		DIS: A structured diagnostic interview designed to assess specific symptoms, chronology, duration and associated impairments. Can be administered by trained lay interviewers.	Diagnostic Interview Schedule. Arch Gen Psychiatry 1982; 39(12): 1442-5.
Structured Diagnostic Interview for Sleep patterns and disorders (DISP)	Sleep	Publicly available structured interview that screens for a range of sleep disorders (delayed sleep phase, hypersomnia, insomnia, narcolepsy with cataplexy, period limb movement disorder, restless legs syndrome, rapid eye movement sleep behavior disorder, sleep apnea) and clinical impact (symptom course, impairment, severity and treatment). Can be administered by trained lay interviewers.	Merikangas KR, et al. The structured diagnostic interview for sleep patterns and disorders: rationale and initial evaluation. *Sleep Med.* 2014;15(5):530-5.

* COVID-19 specific elements

† This reference is regarding the management of acute COVID-19. The relevance for persistent COVID-19 symptoms is uncertain.