

The fatigue enigma: towards an integrative theoretical framework across clinical conditions.

DAVIES, Jennifer L <<http://orcid.org/0000-0001-7635-4815>>, DAWES, Helen <<http://orcid.org/0000-0002-2933-5213>>, PREATONI, Ezio <<http://orcid.org/0000-0001-5383-7072>>, EDWARDS, Deborah <<http://orcid.org/0000-0003-1885-9297>>, THOMAS, Bethan <<http://orcid.org/0009-0002-0294-6839>>, JONES, Rhiannon <<http://orcid.org/0009-0009-0792-2060>>, NOCIVELLI, Brittany <<http://orcid.org/0000-0002-7303-3159>>, DENTON, Rhys <<http://orcid.org/0009-0008-2816-1881>>, DALTON, Caroline <<http://orcid.org/0000-0002-1404-873X>> and BUSSE MORRIS, Monica <<http://orcid.org/0000-0002-5331-5909>>

Available from Sheffield Hallam University Research Archive (SHURA) at:

<https://shura.shu.ac.uk/37577/>

This document is the Accepted Version [AM]

Citation:

DAVIES, Jennifer L, DAWES, Helen, PREATONI, Ezio, EDWARDS, Deborah, THOMAS, Bethan, JONES, Rhiannon, NOCIVELLI, Brittany, DENTON, Rhys, DALTON, Caroline and BUSSE MORRIS, Monica (2026). The fatigue enigma: towards an integrative theoretical framework across clinical conditions. *Fatigue: Biomedicine, Health & Behavior*, 1-14. [Article]

Copyright and re-use policy

See <http://shura.shu.ac.uk/information.html>

The Fatigue Enigma: Towards an Integrative Theoretical Framework Across Clinical Conditions

Jennifer L Davies^{1*}, Helen Dawes², Ezio Preatoni³, Deborah Edwards⁴, Bethan Thomas¹, Rhiannon Jones⁵, Brittany Nocivelli⁶, Rhys Denton⁶, Caroline Dalton⁷, Monica Busse Morris^{6,8}, on behalf of the GW4 Fatigue Community[†]

¹ School of Healthcare Sciences, Cardiff University, Cardiff, UK

² NIHR Exeter, Biomedical Research Centre, Medical School, University of Exeter, Exeter UK

³ Department for Health, University of Bath, Bath, UK

⁴ The Wales Centre for Evidence Based Care, School of Healthcare Sciences, Cardiff University, Cardiff, UK

⁵ School of Medicine, Cardiff University, Cardiff, UK

⁶ Centre for Trials Research, School of Medicine, Cardiff University, Cardiff, UK

⁷ Advanced Wellbeing Research Centre, Sheffield Hallam **University**, Sheffield UK

⁸ Faculty of Nursing, Midwifery and Palliative Care, Kings College London, London, UK

*Corresponding author: Jennifer L Davies; DaviesJ@Cardiff.ac.uk

ORCID IDs

Jennifer L Davies 0000-0001-7635-4815

Helen Dawes 0000-0002-2933-5213

Ezio Preatoni 0000-0001-5383-7072

Deborah Edwards 0000-0003-1885-9297

Bethan Thomas 0009-0002-0294-6839

Rhiannon Jones 0009-0009-0792-2060

Brittany Nocivelli 0000-0002-7303-3159

Rhys Denton 0009-0008-2816-1881

Caroline Dalton 0000-0002-1404-873X

Monica Busse Morris 0000-0002-5331-5909

Biographical notes

Jennifer L. Davies

Dr Jennifer Davies is a Senior Lecturer at the School of Healthcare Sciences, Cardiff University. Her research focuses on the neural and muscular control of human movement, with particular interest in how sensory information, motor coordination, and muscle activity are affected by factors such as stress, anxiety, and fatigue. She leads interdisciplinary work exploring the mechanisms underlying physical fatigue in both health and disease, integrating approaches from movement neuroscience and rehabilitation science.

Helen Dawes

Professor Helen Dawes is a rehabilitation scientist and physiotherapist at the University of Exeter and Co-Director of the Rehabilitation Theme within the NIHR Exeter Biomedical Research Centre. Her research investigates the mechanisms and management of fatigue and its cognitive and physical correlates across neurological, post-viral, and chronic conditions. She leads translational research aimed at improving rehabilitation outcomes and interventions for individuals experiencing fatigue.

Ezio Preatoni

Dr Ezio Preatoni is Senior Lecturer in Biomechanics at the University of Bath. His research lies at the intersection of human movement science, biomechanics, and sensor technology, with a focus on understanding how fatigue influences coordination, variability, and performance in sport and health contexts. His work contributes to developing novel approaches to quantify fatigue and to optimise recovery and performance in physically demanding settings.

Deborah Edwards

Dr Deborah Edwards is Principal Research Fellow at the Wales Centre for Evidence Based Care, Cardiff University. Her expertise lies in evidence synthesis and methodological development to support the design and implementation of complex healthcare interventions. She contributes to advancing understanding of fatigue through systematic evaluation of evidence.

Bethan Thomas

Bethan Thomas is a doctoral researcher at Cardiff University. Her work focuses on the mechanisms underlying fatigue in long-term health conditions and explores physiological, sensory, and cognitive aspects of fatigue, with the aim of contributing to a better understanding of how fatigue develops and persists, and how it may be mitigated through targeted interventions. She worked as a research assistant within the GW4 network studying fatigue in people with multiple long-term conditions, from which is work is based.

Rhiannon Jones

Rhiannon Jones was a student at the School of Medicine, Cardiff University at the time of this work and is now a foundation doctor within Hywel Dda Health Board. She worked as a research assistant within the GW4 network studying fatigue in people with multiple long-term conditions, from which is work is based.

Brittany Nocivelli

Brittany Nocivelli was a doctoral researcher at the time of this work and is currently a Research Associate in the Centre for Adult Social Care and DECIPHer centres in the School of Social Sciences at Cardiff University. She works to improve research inclusivity of

underserved, vulnerable populations and the development of interventions to empower underrepresented populations to participate in research. She worked as a research assistant within the GW4 network studying fatigue in people with multiple long-term conditions, from which is work is based.

Rhys Denton

Rhys Denton is a Research Manager at Centre for Trials Research in the School of Medicine at Cardiff University. He worked as a research assistant within the GW4 network studying fatigue in people with multiple long-term conditions, from which this work is based. His interests lie in research accessibility and he contributes his lived experience of fatigue as a researcher and as a public contributor.

Caroline Dalton

Dr Dalton is Reader in Neuroscience and Genetics and Theme Lead for Living Well with Chronic Disease at the Advanced Wellbeing Research Centre at Sheffield Hallam University. Her research spans Long COVID and ME/CFS, physical-activity interventions, symptom monitoring, wearable devices and fatigue. She has authored intensive-longitudinal studies exploring within-person predictors of physical activity and fatigue in Long COVID, advancing understanding of symptom-activity dynamics.

Monica Busse Morris

Professor Busse-Morris is a physiotherapist and clinical trials methodologist, specialising in mobility, lifestyle interventions and rehabilitation in complex chronic disease. She led major interventional trials in Long COVID, including a self-management support intervention (LISTEN trial) that reported significant reductions in fatigue impact. Her work bridges mechanism, mobility and rehabilitation strategy in fatigue-bearing conditions.

Abstract

Background: Fatigue is a complex phenomenon that presents persistent challenges for research and clinical care across multiple conditions. **Objective:** To explore development of an integrative theoretical framework linking lived experience, underlying mechanisms, and the design and evaluation of interventions. **Methods:** We conducted systematic scoping reviews to identify (i) systematic and narrative reviews of mechanisms or pathways of fatigue across clinical conditions, and (ii) systematic reviews and recent randomised controlled trials of interventions addressing fatigue. These reviews informed four consensus workshops with researchers, clinicians, and individuals with lived experience of fatigue that examined: (1) the meaning and evaluation of fatigue across conditions; (2) mechanisms and pathways; (3) evidence for outcomes and novel interventions; and (4) consensus development and program theory generation. **Key findings:** We present a summary of the discussions across the workshops and highlight the challenges that remain in evaluating the utility of an integrative theoretical framework. Substantial conceptual ambiguity was identified in how fatigue is defined and how mechanisms, pathways, and interventions are categorised. Inconsistent terminology, measurement approaches, and theoretical specification limit synthesis across conditions, and the current evidence base remains insufficiently articulated to support a coherent cross-condition account. **Conclusion:** Critical gaps remain in the use of common language, outcome measures, and theory-informed approaches to intervention development. Addressing these foundational limitations is necessary to determine whether an integrative framework for fatigue can be constructed, and whether this may support knowledge translation across diagnostic boundaries and hypothesis-driven research that is responsive to stakeholder priorities and delivers meaningful clinical benefit.

Introduction

Fatigue is commonly reported by individuals with a wide range of conditions, including neurologic, musculoskeletal, immunologic, endocrinologic, cardiorespiratory, gastroenterologic, reproductive, psychiatric, hematologic, metabolic, or infectious disorders, and cancer [1-5]. It affects functioning and quality of life, and the impact is even greater in individuals with multiple (more than one) long-term conditions [6,7]. Globally, one third of adults are now living with multiple long-term clinical conditions [8,9]. This poses a specific challenge to patients, clinicians and health systems, as clinical guidelines for the treatment of fatigue are typically targeted to a single condition [10-13].

Several interrelated biological systems are implicated in the mechanisms and experience of fatigue symptoms, requiring multidisciplinary working and communication across professions and disciplines. Emergent theories suggest that fatigue may be better conceptualised as a symptom prevalent across multiple chronic medical conditions, rather than a disease-specific symptom [14]. However, challenges and barriers to this approach are not insignificant [15] not least because fatigue itself is hard to characterise, with a multiple definitions and overlapping constructs [16-19]. In everyday usage, the English term “fatigue” can encompass a broad range of phenomena, including exhaustion, tiredness, reduced motivation, and performance decline. Other languages may distinguish more explicitly between experiential tiredness and exercise-related performance decrement. Such linguistic and conceptual variability complicates attempts to share knowledge across conditions where fatigue is prevalent.

The severity and impact of fatigue (defined here as the experience reported by the individual) and fatigability (defined here as measurable physiological, neural, or functional indicators) are key overarching constructs, yet these are not synonymous and may not co-vary. Fatigue as a reported symptom and fatigue as an observable sign require explicit differentiation, particularly when integrating findings from acute experimental paradigms and chronic clinical populations. Temporal characteristics add further complexity: acute fatigue, often short-lived and adaptive, differs in its functional role and biological correlates from chronic fatigue, which may persist beyond adaptive timeframes and become disabling. There is no established core outcome set for defining or measuring fatigue and fatigability across conditions, professions and disciplines [20]. The resulting heterogeneity in definitions, constructs, and outcome measures hinder the synthesis of research findings across conditions and may limit progress in this important area.

We conducted a series of consensus workshops with experts in the field, including researchers, clinicians, and individuals living with fatigue (experts by experience). These workshops were informed by systematic scoping reviews of the literature on fatigue. By combining evidence synthesis with expert perspectives, we aimed to evaluate the feasibility of developing an integrative framework for understanding fatigue as a cross-disciplinary and transdiagnostic phenomenon, while explicitly recognising its heterogeneity across contexts and conditions. Our objective was to evaluate the feasibility of generating a theoretically grounded account of this complex and ‘wicked’ problem that could link individualised lived experience, research into relevant mechanisms or pathways, and the design and evaluation of interventions. Such an account may provide a basis for translation of knowledge across clinical and diagnostic boundaries and for advancing hypothesis-driven research. Here, we present a summary of the evaluations and discussions that took place across the four consensus workshops, and the challenges that remain in moving towards an integrative theoretical framework of fatigue across clinical conditions.

Methods

Rapid scoping reviews

Two rapid scoping reviews were performed to inform the consensus workshops. The objectives of the reviews were to identify (1) systematic and narrative reviews of mechanisms or pathways of fatigue across any clinical condition and (2) systematic reviews and recent randomised controlled trials (RCTs) of interventions addressing fatigue across any clinical condition. These were addressed through two separate systematic literature searches. The Population, Concept and Context (PCC) framework was used to inform the eligibility criteria [21], as detailed in Table 1. For objective 2, the search for RCTs was restricted to the two calendar years immediately preceding the workshops as we were interested specifically in exploring contemporary interventions for fatigue.

[Insert Table 1 here]

Three databases were searched on the OVID platform: Medline, Embase and PsycINFO. For both searches, terms were mapped to the concepts of fatigue and chronic health condition. For (1), the concept of fatigue was combined with mechanism or pathway. For (2), the concept of fatigue was combined with intervention and either RCT or review. Full search strategies are shown in Supplementary Material 1.

The retrieved citations were collated, and duplicates were removed in EndNote version 20. Citations were then transferred into the web tool Rayyan™ for screening. One reviewer (BT, BN or RJ) screened titles and abstracts using the inclusion criteria described in Table 1 and all decisions were checked by a second reviewer (DE). Data from the full texts of eligible articles were extracted directly into Excel by one reviewer (BT, BN, RJ or RD) and checked by a second reviewer (DE). The manually extracted data included author(s), year of publication, study type (systematic review, narrative review, RCT), and study population(s). For systematic reviews and RCTs, study title was also extracted. Systematic reviews returned in search (1) were uploaded into NVivo software (Lumivero, Denver, CO, USA) and the mechanism(s) studied were highlighted and coded by one reviewer (BT, BN, RJ or RD) and checked by a second reviewer (DE). All studies (systematic reviews and RCTs) returned in search (2) were uploaded into NVivo software and the details of the interventions were highlighted and interventions then coded by one reviewer (BT, BN, RJ or RD) and checked by a second reviewer (DE). This coding was then recorded with the extracted study data. For interventions, it was also recorded whether the intervention was designed based on a model or theoretical framework (if this information was available).

Consensus workshops

An online launch event was held in July 2023 to advertise the workshops and attract interest (for details see Supplementary Material 2). This was followed by four online workshops between November 2023 and March 2024. Thirty-eight individuals participated across the four workshops, including seven individuals with lived experience of chronic fatigue. Those individuals that have consented to be named are listed in Supplementary Material 3. All workshops were facilitated and visually summarised by Scarlet Design Ltd. (Cardiff, Wales).

The first workshop (November 1, 2023) focused on what fatigue means to people with lived experience of different conditions and how it can be evaluated, with discussions about indicators of chronic fatigue that are important to consider in research across conditions. The second workshop (November 30, 2023) focused on mechanisms/pathways of fatigue, with discussions on mechanisms important to consider in research. These workshops were informed by results from the first aim of the rapid scoping review (to identify systematic and narrative reviews of mechanisms or pathways of fatigue across any clinical condition). The third workshop (January 18, 2024) focused on evidence for outcomes and novel interventions for fatigue, with five contemporary interventions [22-26] that were identified by the second aim of the rapid scoping review (to identify systematic reviews and recent RCTs of interventions addressing fatigue across any clinical condition) discussed in breakout rooms. The discussion rooms were focused on the theoretical/mechanistic underpinning for the interventions. The fourth workshop (March 13, 2024) was focused on deriving a consensus on identified issues and generating a program theory for cross condition fatigue.

Workshops 1 and 2 included presentations from invited speakers (Supplementary Material 2). All workshops included semi-structured breakout rooms, each moderated by one of the core project team (JD, MB, HD, RD, CD), and semi-structured full-group discussions moderated by Scarlet Design Ltd. The full-group discussions were recorded and transcribed for the purposes of exploring emergent themes.

Recognising the importance of a theory or systems perspective to inform complex intervention research, the overarching themes emerging from the discussions were extracted and summarised in relation to the updated Medical Research Council (MRC) framework for developing and evaluating complex interventions [27]. The mapping of the discussion themes to the MRC framework (with particular reference to interventions, mechanisms of action of those interventions, stakeholder perspectives in relation to those interventions, and key uncertainties as precursors to efficacy or effectiveness evaluations) has informed the findings presented here.

Results

Scoping Review

Mechanisms: We identified 43 systematic reviews and 90 narrative reviews of mechanisms or pathways of fatigue. These covered 71 different clinical conditions (Supplementary Material 4). Cancer and multiple sclerosis were the most common conditions, with mechanisms of cancer-related fatigue considered in 40 of the 259 reviews (15%) and mechanisms of fatigue in people living with multiple sclerosis considered in 34 (13%; Supplementary Figure 1). Most clinical conditions (51 out of 71; 72%) were considered in only one or two reviews of mechanisms or pathways of fatigue (Supplementary Material 4). Inflammatory processes and psychological factors were the most studied mechanisms, covered in 23 (53%) of systematic reviews each, followed by sleep (42%) and immune system (40%) (Supplementary Figure 2). The extracted data is available on the Open Science Framework (<https://osf.io/zdtw2/files>). These findings were used to inform workshops 1 and 2.

Interventions: We identified 36 randomised controlled trials of interventions for fatigue (published between January 2022 and December 2023) and 120 systematic reviews of interventions for fatigue (published between January 2001 and December 2023). Cancer

was the most studied condition, with interventions for cancer-related fatigue considered in 60% of the identified studies (93 out of 156; Supplementary Figure 3). Most interventions were non-pharmacological, with exercise or movement, psychological and behavioural interventions the most common (Supplementary Figure 4). The overlap between the clinical conditions in which mechanisms were studied and the clinical conditions in which interventions were studied is shown in Supplementary Figure 5. The extracted data is available on the Open Science Framework (<https://osf.io/zdtw2/files>). These findings were used to inform workshop 3.

Key Discussion Areas

In workshop 1, individuals with lived experience of chronic fatigue and a range of different clinical conditions spoke about what fatigue meant to them, their experiences of communicating about their fatigue with clinicians and other individuals in their lives, the varying techniques used to track symptoms (mobile phone/computer applications, paper diary), the frustration with limitations of existing approaches to symptom tracking and reporting, the complexity of multiple conditions, and their own personal responses to sleep (Figure 1). The subsequent discussions on the experience of living with chronic fatigue covered themes of individuality, domains of experience, sleep, use of pacing/budgeting strategies, measurement burden, timescale of measurement, and relation of measurements to mechanisms (Table 2).

In workshop 2, discussions on the mechanisms and pathways of fatigue covered the importance of consistency in defining and measuring fatigue, integration of biological systems, learning from non-pathological fatigue, animal models, and across clinical conditions, biological/genetic markers and 'hidden' fatigue (Table 3).

In workshop 3, discussions on novel interventions for fatigue covered intervention content, intervention classification, theoretical approach, and outcome measures (Table 4). The MRC framework identifies six core elements that should be considered in the development and evaluation of complex interventions – context (the circumstances in which the intervention is developed, evaluated and implemented), programme theory (how the intervention (and specific components thereof) is expected to achieve its effect), stakeholders (different views and perspectives of service users and implementers), key uncertainties, intervention refinement, and economic considerations [27]. When aligned to this framework, the discussion themes highlighted areas that should be improved to move the field, namely: improved reporting of circumstances (contexts) relevant to the intervention, better understanding of mechanisms of actions to inform programme theory, clear communication of how stakeholder perspectives have been considered in relation to interventions, and rationale for selected outcome measures (in relation to the intervention components, programme theories or mechanisms of actions) as precursors to efficacy or effectiveness evaluations.

The discussions across all consensus workshops highlighted a perception of inconsistency in the way fatigue is defined, operationalised and measured across mechanistic and intervention research. To further explore this, we used Elicit AI (<https://elicit.com/>) to extract the definitions and measures of fatigue used across all 199 systematic reviews and RCTs identified in the scoping review. This data is available on the Open Science Framework (<https://osf.io/zdtw2/files>).

[Insert Figure 1 here]

[Insert Table 2 here]

[Insert Table 3 here]

[Insert Table 4 here]

Discussion

Across both the rapid scoping review and the consensus workshops, substantial conceptual variability emerged in how fatigue is defined and how mechanisms, pathways and interventions are classified within research and clinical settings. Our findings highlight the absence of a coherent structure that links lived experience of fatigue, underlying mechanisms, and the design and evaluation of interventions for fatigue across clinical conditions. An integrative framework could provide a structured basis for comparing findings across contexts, clarifying theoretical assumptions, and informing the development and evaluation of interventions, and thus support cumulative progress in the field. However, the current evidence base remains fragmented and is insufficient to support a fully theoretically grounded account. Rather than rendering such a framework unattainable, our results clarify the conceptual and methodological work required to advance a structured understanding of fatigue across conditions. By making explicit the variability in definitions, constructs and classification approaches evident in the current literature, this work provides a necessary foundation for determining whether and how meaningful cross-condition comparison may be achieved.

The scoping review highlighted substantial inconsistency across mechanistic and intervention research in the way fatigue is defined, operationalised and measured. This conceptual variability is consistent with guidance from the International Society for Quality of Life Research (ISOQOL), which emphasises the importance of explicit construct specification in patient-reported outcome research [28]. ISOQOL distinguishes between fatigue as a subjective, self-reported experience and related constructs such as performance decrement or fatigability and highlights the need to clarify temporal characteristics and contextual relevance when selecting outcome measures. Such distinctions are particularly important in fatigue research, where the term is used to encompass phenomena ranging from acute physiological tiredness to persistent, disabling symptoms across chronic conditions. The absence of consistent specification regarding whether fatigue is conceptualised as a symptom, a sign, acute or chronic, physical or cognitive, contributes to the fragmentation identified in the present work. Greater clarity and consistency in construct specification are essential to reduce fragmentation and enable more coherent communication across research communities.

Mechanisms and pathways are investigated using varied conceptualisations of fatigue, limiting the extent to which findings can be meaningfully compared or transferred across contexts. In intervention studies, insufficient description of development processes, theoretical underpinnings (if any), the components of the intervention (and any control) and intended mechanisms of action, make it difficult to compare across studies. This lack of detail of how interventions are theorised to influence fatigue makes it challenging to classify approaches, evaluate the potential for an intervention to be tested in a different clinical

condition or context, address further avenues of potential research along related or linked pathways, and creates barriers for synthesising findings through meta-analyses.

From a theoretical standpoint, many interventions for complex, chronic fatigue remain limited by gaps in understanding of context and by limited consideration of programme theory [27]. The process of intervention development should be transparent and theory-driven and importantly informed by the views of those with lived experience of fatigue, e.g., [29,30].

It is clear from our review that stakeholder involvement represents a further area of under-specification. Outcome measures and the frequency with which they are measured should be selected with care and coproduced with patients so as not to oversample or impose unnecessary burden, and to allow the lived experience to be integrated into the research. We found that reporting rarely details how stakeholder engagement informed the understanding of inputs, activities, outputs and outcomes. Without explicit integration of lived experience into intervention design and evaluation, efforts to construct an integrative framework remain incomplete.

Studies that test an intervention should detail the development of the intervention, the theoretical approach on which the intervention is based, the components of the intervention and control, and the mechanisms that the intervention is targeting [30]. We found that interventions that targeted fatigue were not sufficiently described to be able to understand the clinical contexts in which they were most suited or effective. Without this contextual clarity, it is difficult to assess the conditions under which interventions work, difficult to generalise findings across settings, and difficult to integrate into an integrative framework.

Mechanistic rationales for how interventions are expected to influence fatigue are also seldom articulated within intervention studies. Links between targeted biological pathways and overarching programme theories are seldom reported or discussed, and there is limited integration of insights from animal models of fatigue, human models of non-pathological fatigue, and human studies of pathological fatigue across clinical conditions. This fragmentation weakens the theoretical coherence necessary to evaluate the potential for cross-condition integration.

The conceptualisation of fatigue as a whole-person experience influenced by multiple interacting systems also resonates with theoretical developments in stress research. Early formulations of stress as a non-specific adaptive response to diverse internal and external demands [31], and subsequent work in psychoneuroimmunology [32,33] and allostatic load [34], illustrate how broad constructs can evolve through interdisciplinary integration and increasing biological specification. While fatigue and stress are not synonymous, these developments provide a potentially informative parallel for future theoretical work in fatigue, particularly in considering how cumulative physiological and psychosocial demands may contribute to persistent symptoms.

The current level of conceptual and methodological specification within the literature limits the extent to which the feasibility of a theoretically grounded cross-condition framework of fatigue can be meaningfully evaluated. Progress toward such evaluation will depend on strengthening conceptual coherence and improving the transparency with which mechanisms, context, and intervention development are described. Addressing these gaps is a necessary step toward determining whether and how an integrative framework linking lived experience, biological mechanisms, and intervention design can be developed.

Conclusion

Our aim here was to identify opportunities for translating knowledge across clinical and diagnostic boundaries. The evidence-based workshops highlighted critical gaps in common language, common outcome measures, and theoretically informed approaches to intervention development that impede advancement towards a theoretically grounded, cross-condition account of fatigue. Addressing these gaps is not merely descriptive; it would provide a foundation for determining whether and how an integrative framework linking lived experience, biological mechanisms, and intervention design can be developed.

Progress in this area will require greater consensus on what fatigue is, what fatigue is not, and which validated measures should be used to measure it. Such efforts must be informed by authentic stakeholder involvement to ensure that theoretical refinement remains grounded in lived experience. In parallel, consensus on common or unique biological and genetic markers of fatigue would facilitate performance of large-scale clustering studies to identify fatigue phenotypes/trajectories independent of clinical condition. These advances would support more precise, hypothesis-driven research and strengthen efforts to translate findings across clinical conditions, including among individuals with multiple clinical conditions.

Funding statement

This work was funded by a Building Communities award from GW4 to JD, HD, DE and MBM (<https://gw4.ac.uk/community/gw4-community-studying-fatigue-in-people-with-multiple-long-term-conditions/>).

Acknowledgement

†The GW4 Fatigue community consisted of researchers, clinicians, and individuals with lived experience of fatigue who attended one or more or four online workshops held between November 2023 and March 2024. Those who consented to be named are listed in Supplementary Material 3.

Disclosure statement

The authors declare no competing interests. The GW4 Fatigue Community contributed to the workshops as described in the methods; individual members of this community who consented to be named are listed in the Appendix. Members of the community were not involved in decisions regarding manuscript submission and have not submitted individual disclosure statements.

Data availability statement

Data relating to the literature reviews are available on the Open Science Framework <https://osf.io/zdtw2/files>

Figure 1

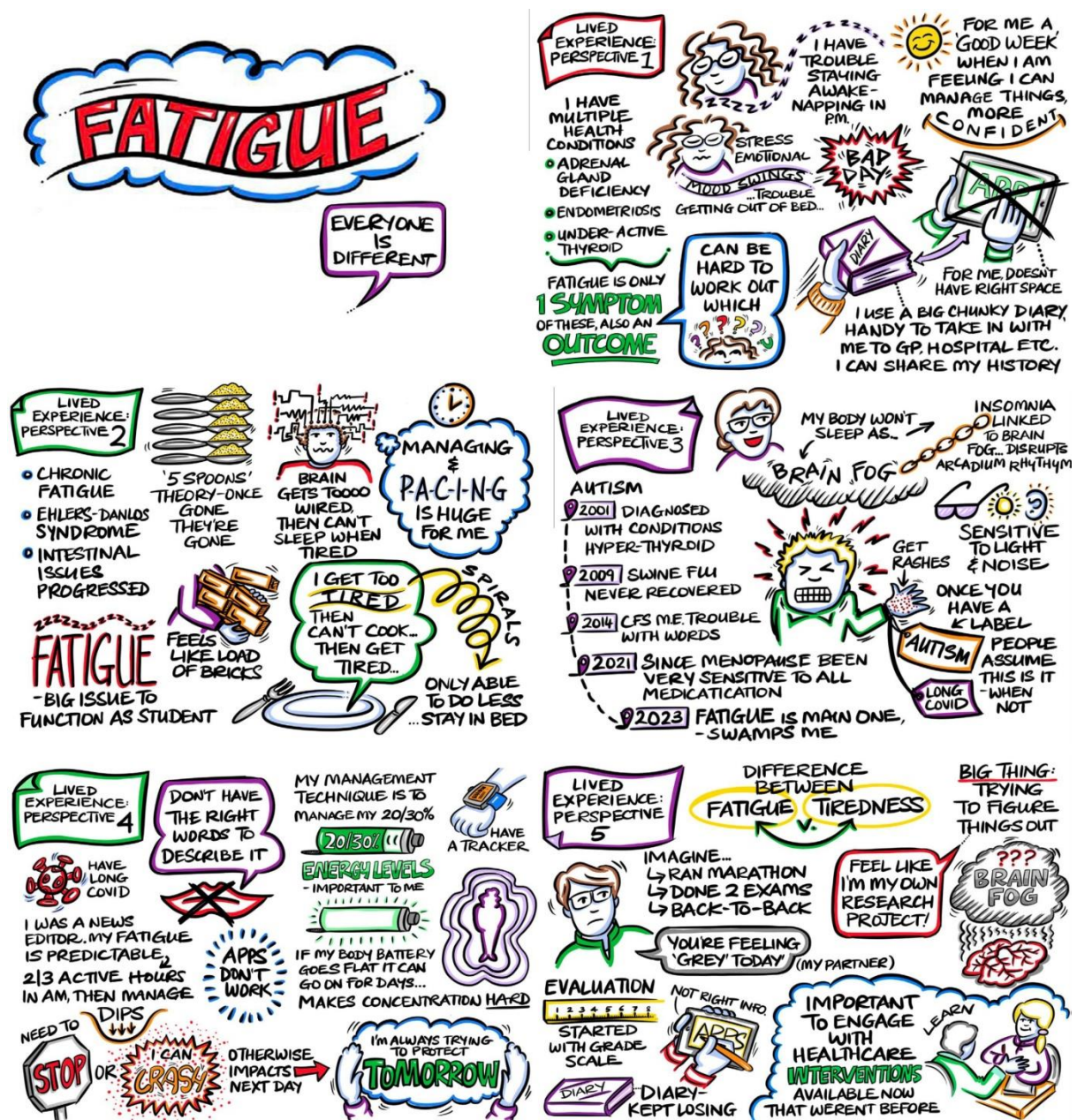
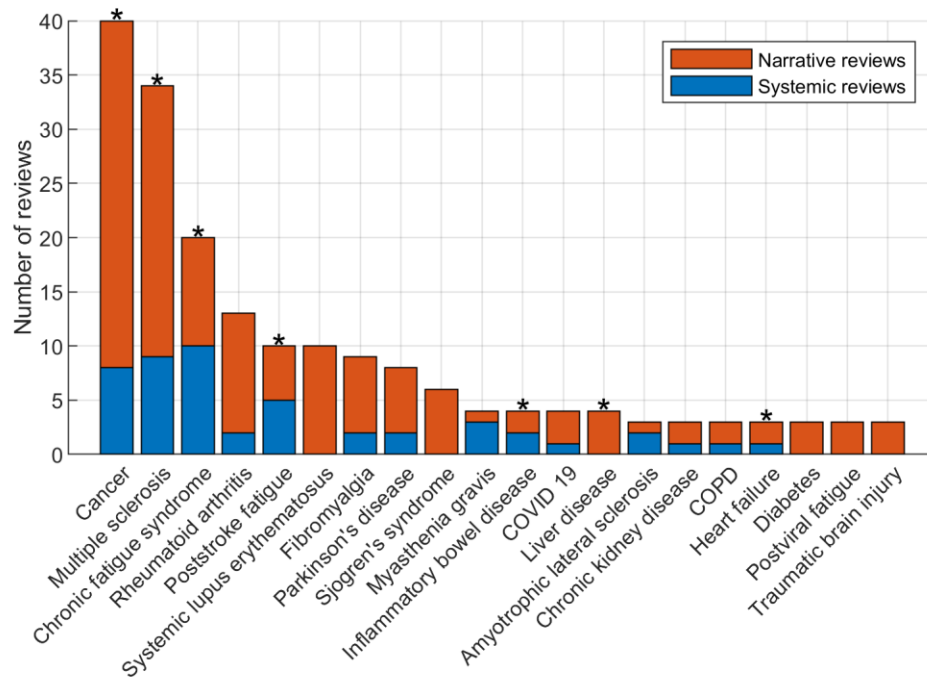


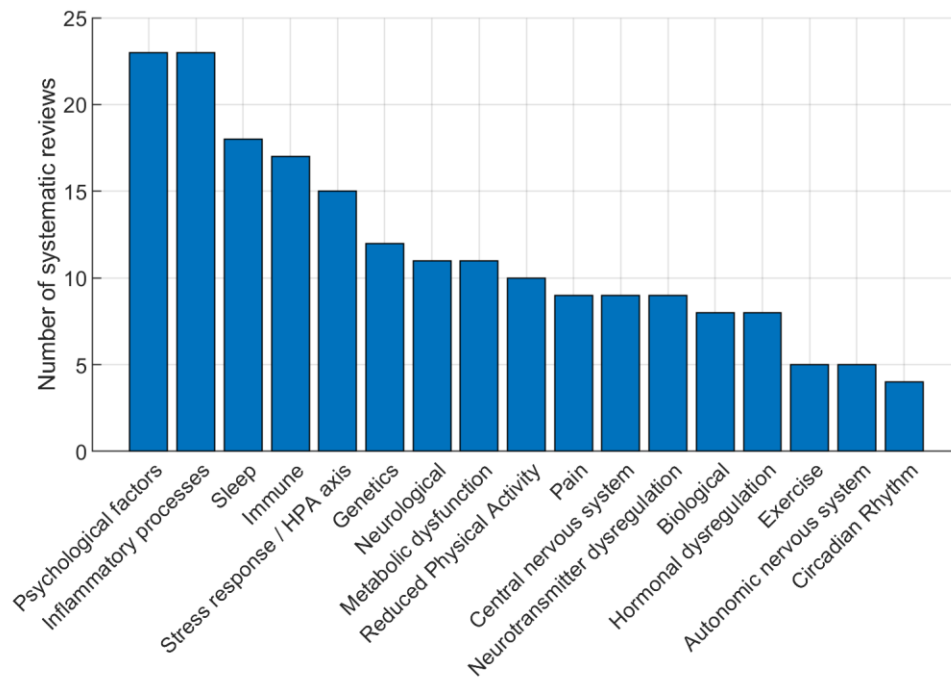
Figure 1. Illustrations of perspectives of chronic fatigue from individuals with lived experience.

Supplementary Figure 1



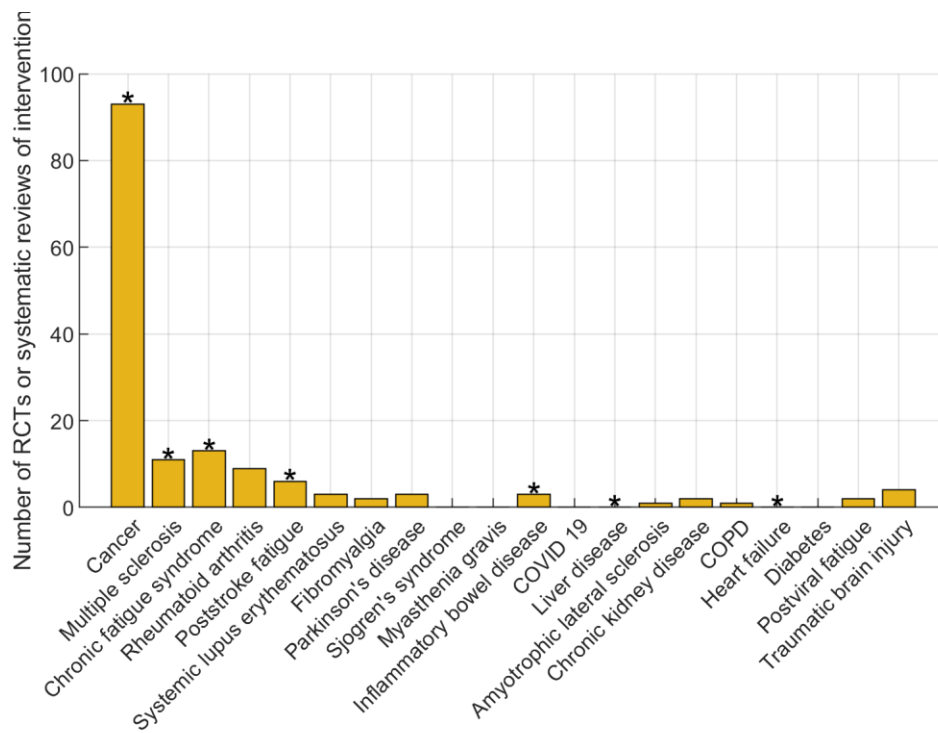
Supplementary Figure 1. Clinical conditions covered by more than two reviews of mechanisms or pathways of fatigue. Clinical conditions covered by only one or two reviews were excluded for clarity of presentation but are included in Supplementary Material. Asterisks indicate conditions for which fatigue is included in the James Lind Alliance Top 10 Research Priorities.

Supplementary Figure 2



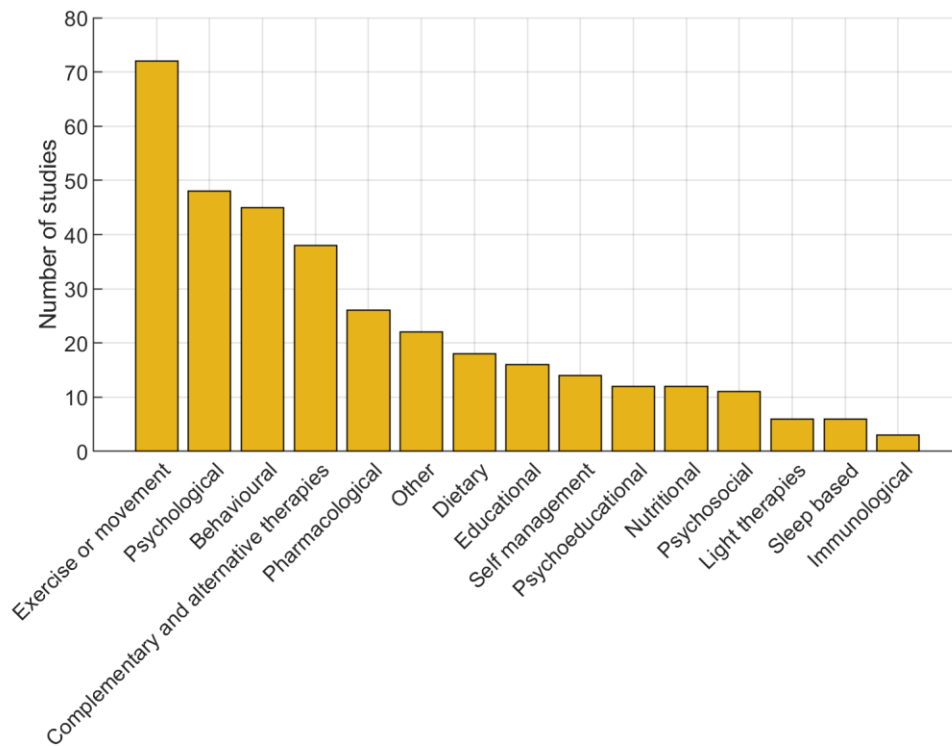
Supplementary Figure 2. Mechanisms considered in systematic reviews of mechanisms or pathways of fatigue.

Supplementary Figure 3



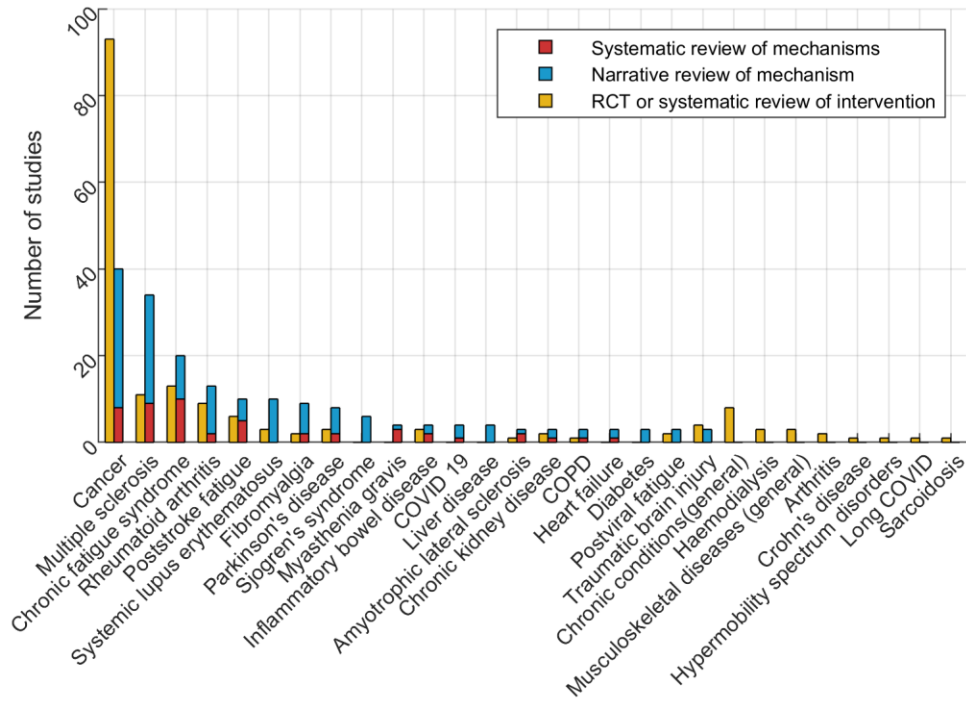
Supplementary Figure 3. Clinical conditions covered by randomised controlled trials and systematic reviews of interventions for fatigue. Asterisks indicate conditions for which fatigue is included in the James Lind Alliance Top 10 Research Priorities.

Supplementary Figure 4



Supplementary Figure 4. Types of interventions covered by randomised controlled trials and systematic reviews of interventions for fatigue

Supplementary Figure 5



Supplementary Figure 5. The overlap between the clinical conditions in which mechanisms are studied and in which interventions are studied.

Supplementary Material 1. Literature search strategies.

Search 1: Mechanisms

Database: APA PsycINFO

Search conducted 10th July 2023

	Search terms	Results
1	fatigu*.ti.	9244
2	post exertion malaise.ti.	1
3	1 or 2	9244
4	mechanism*.tw.	326329
5	patho*.tw.	161180
6	pathway*.tw.	104497
7	4 or 5 or 6	526416
8	3 and 7	1158
9	limit 8 to (human and English language)	983

Database: Ovid MEDLINE(R) ALL

Search conducted 10th July 2023

	Search terms	Results
1	fatigu*.ti.	33761
2	post exertion malaise.ti.	1
3	1 or 2	33761
4	mechanism*.tw.	2721138
5	patho*.tw.	2213515
6	pathway*.tw.	1423210
7	4 or 5 or 6	5364352
8	3 and 7	4082
9	limit 8 to (human and English language)	3141

Embase

Search not conducted due to the volume of literature retrieved from Medline and PsycINFO

Search 2a: Interventions – Randomised controlled trials

Database: APA PsycINFO

Search conducted 20th December 2023

	Search terms	Results
1	Fatigu*.ti.	9640
2	Post exertional malaise.ti	9
3	1 or 2	9464
4	intervention*.ti.	89623
5	exp randomized controlled trial/	1536
6	random*.ab.	241457
7	Placebo.ab.	43613
8	trial.ab.	115480
9	groups.ab.	569282
10	5 or 6 or 7 or 8 or 9 or 10	822930
11	exp animals/ not humans.sh.	379604
12	10 not 11	766515
13	review.ti.	186741
14	3 and 4 and 12	109
15	limit 14 to yr="2022 -Current"	13

Database: Ovid MEDLINE(R) ALL
 Search conducted 20th December 2023

	Search terms	Results
1	Fatigu*.ti.	34830
2	Post exertional malaise.ti	41
3	1 or 2	34845
4	intervention*.ti.	207345
5	exp randomized controlled trial/	606830
6	controlled clinical trial/	95490
7	random*.ab.	1432266
8	Placebo.ab.	244153
9	trial.ab.	677774
10	groups.ab.	2612435
11	5 or 6 or 7 or 8 or 9 or 10	4042535
12	exp animals/ not humans.sh.	5179577
13	11 not 12	3504143
14	3 and 4 and 13	355
15	limit 14 to yr="2022 -Current"	105

Database: Embase
 Search conducted 20th December 2023

	Search terms	Results
1	Fatigu*.ti.	41937
2	Post exertional malaise.ti	53
3	1 or 2	41959
4	intervention*.ti.	272940
5	exp randomized controlled trial/	802653
6	controlled clinical trial/	471802
7	random*.ab.	2023055
8	Placebo.ab.	368579
9	trial.ab,	998790
10	groups.ab.	3662440
11	5 or 6 or 7 or 8 or 9 or 10	5650274
12	exp animals/ not humans.sh.	31162001
13	11 not 12	629826
14	review.ti.	823488
15	3 and 4 and 13	15
16	limit 14 to yr="2022 -Current"	1

Search 2b: Interventions – Systematic reviews

	Search terms	Results
1	Fatigu*.ti.	9640
2	Post exertional malaise.ti	9
3	1 or 2	9464
4	intervention*.ti.	89623
5	exp randomized controlled trial/	1536
6	random*.ab.	241457
7	Placebo.ab.	43613
8	trial.ab.	115480
9	groups.ab.	569282
10	5 or 6 or 7 or 8 or 9 or 10	822930
11	exp animals/ not humans.sh.	379604

12	10 not 11	766515
13	review.ti.	181389
16	3 and 4 and 13	43

Database: Ovid MEDLINE(R) ALL
Search conducted 20th December 2023

	Search terms	Results
1	Fatigu*.ti.	34830
2	Post exertional malaise.ti	41
3	1 or 2	34845
4	intervention*.ti.	207345
5	exp randomized controlled trial/	606830
6	controlled clinical trial/	95490
7	random*.ab.	1432266
8	Placebo.ab.	244153
9	trial.ab.	677774
10	groups.ab.	2612435
11	5 or 6 or 7 or 8 or 9 or 10	4042535
12	exp animals/ not humans.sh.	5179577
13	11 not 12	3504143
14	Review.ti.	725165
17	3 and 4 and 14	157

Database: Embase
Search conducted 20th December 2023

	Search terms	Results
1	Fatigu*.ti.	41937
2	Post exertional malaise.ti	53
3	1 or 2	41959
4	intervention*.ti.	272940
5	exp randomized controlled trial/	802653
6	controlled clinical trial/	471802
7	random*.ab.	2023055
8	Placebo.ab.	368579
9	trial.ab,	998790
10	groups.ab.	3662440
11	5 or 6 or 7 or 8 or 9 or 10	5650274
12	exp animals/ not humans.sh.	31162001
13	11 not 12	629826
14	review.ti.	823488
15	3 and 4 and 16	15

Supplementary Material 2. Invited speakers at online workshops.

The launch event included a keynote from Professor Roger Enoka (University of Colorado Boulder, USA) titled *Distinguishing between fatigue and fatiguability*, alongside four additional presentations: Professor Chris Burton (University of Sheffield, UK), *Ecological momentary assessment in fatigue*; Dr Caroline Dalton (Sheffield Hallam University, UK), *Monitoring symptoms and activities in fatigue*; Professor Helen Dawes (University of Exeter, UK), *Attend to fatigue*; and Professor Nancy Mayo (McGill University, Canada), *Fatigue: Measuring a multidimensional construct*.

The first workshop (November 1, 2023) focused on what fatigue means and how it can be evaluated and involved two invited presentations: Dr Fiona Leggat (St George's, University of London) presented learnings from the LISTEN trial [35] about how individuals living with long COVID described their fatigue. Drs Nicola Harman and Susanna Dodd (University of Liverpool and COMET [Core Outcome Measures in Effective Trials] initiative) spoke about the development of core outcome sets. Five invited individuals with lived experience of chronic fatigue shared how they monitor their fatigue levels and/or how they would describe 'good' and 'bad' days (corresponding to days with minimal fatigue and severe fatigue, respectively).

The second workshop (November 30, 2023) focused on mechanisms/pathways of fatigue and involved four invited presentations: Professor Simon Jones (Cardiff University) presented on interleukin-6, Dr Rachel Sumner (Cardiff Metropolitan University) presented on stress hormones, Dr Penny Lewis (Cardiff University) presented on sleep, and Dr Jennifer Davies (Cardiff University) presented on the sensory and motor systems.

Supplementary Material 3. Members of the GW4 fatigue community who participated in one or more of the four workshops as an attendee and agreed to be named in this report.

Aaron Greenhouse-Tucknott, Cognitive Neuroimaging Unit, Institut National de la Santé et de la Recherche Médicale, Commissariat à l'Energie Atomique et aux énergies alternatives, Centre national de la recherche scientifique, Université Paris-Saclay, France

Bethan Thomas, School of Healthcare Sciences, Cardiff University, UK

Brittany Nocivelli, Centre for Trials Research, School of Medicine, Cardiff University, UK

Christopher Russell, Vivisco Limited, UK

Caroline Dalton, Advanced Wellbeing Research Centre, Sheffield Hallam University, UK

Claire Nollett, Centre for Trials Research, Cardiff University, UK

Deborah Edwards, The Wales Centre for Evidence Based Care, School of Healthcare Sciences, Cardiff University, UK

Diana Robinson

Ezio Preatoni, Department for Health, University of Bath, UK

Fiona Leggat, School of Health and Medical Sciences, City St Georges, University of London, UK

Gemma Brownbill, School of Sport, Exercise and Health Sciences, Loughborough University, UK

Helen Dawes, NIHR Exeter Biomedical Research Centre, Medical School, University of Exeter, UK

Jennifer L Davies, School of Healthcare Sciences, Cardiff University, UK

Joanna Rutkowska-Wheeldon, Cardiff and Vale University Health Board, Cardiff, UK.

John Derek Franklin, Kleijnen Systematic Reviews Limited, UK

Kate Button, School of Healthcare Sciences, Cardiff University, UK

Katrina Burchell, Pernicious Anaemia Society, UK

Monica Busse Morris, Faculty of Nursing, Midwifery and Palliative Care, Kings College London, UK; and Centre for Trials Research, School of Medicine, Cardiff University, UK

Nick Courtier, School of Healthcare Sciences, Cardiff University, UK

Paulo C. R. Santos, IDOR / Pioneer Science Initiative, Rio de Janeiro, Rio de Janeiro, Brazil; Department of Computer Science and Applied Mathematics, Weizmann Institute of Science, Rehovot, Israel; and Center of Advanced Technologies in Rehabilitation, Sheba Medical Center, Ramat Gan, Israel.

Pavlos E. Evangelidis, Public Health and Sport Science, University of Exeter, UK

Rachael Pattinson, School of Dentistry, Cardiff University, UK

Rhiannon Jones, School of Medicine, Cardiff University, UK

Rhys Denton, Centre for Trials Research, School of Medicine, Cardiff University, UK

Samit Chakrabarty, School of Biomedical Sciences, University of Leeds, UK

Timothy Pickles, Centre for Trials Research, Cardiff University, UK

Willow Holloway, Disability Wales, UK; Autistic UK; Fair Treatment for the Women of Wales, UK; and The Autistic Women's Empowerment Project, UK

Supplementary Material 4. Conditions covered in systematic and narrative reviews of mechanisms of fatigue.

Condition	Number of systematic reviews	Number of narrative reviews	Total number of reviews
Cancer	8	32	40
Multiple sclerosis	9	25	34
Chronic fatigue syndrome	10	10	20
Rheumatoid arthritis	2	11	13
Systemic lupus erythematosus	0	10	10
Poststroke fatigue	5	5	10
Fibromyalgia	2	7	9
Parkinson's disease	2	6	8
Sjogren's syndrome	0	6	6
Liver disease	0	4	4
COVID	1	3	4
Inflammatory bowel disease	2	2	4
Myasthenia gravis	3	1	4
Diabetes	0	3	3
Postviral fatigue	0	3	3
Traumatic brain injury	0	3	3
Chronic kidney disease	1	2	3
COPD	1	2	3
Heart failure	1	2	3
Amyotrophic lateral sclerosis	2	1	3
Cardiovascular disorders	0	2	2
Neuromuscular disorder	0	2	2
Primary biliary cholangitis	0	2	2
Long COVID	1	1	2
Neurological disorders	1	1	2
Osteoarthritis	1	1	2
Brain injury	2	0	2
Charcot-Marie-tooth disease	2	0	2
Guillain-Barre syndrome	2	0	2
Muscular dystrophy	2	0	2
Postpolio syndrome	2	0	2
Systemic exertion intolerance disease	2	0	2
Anaemia	0	1	1
Ankylosing spondylitis	0	1	1
Autoimmune conditions	0	1	1
Chronic disease	0	1	1
Chronic inflammatory diseases	0	1	1
Coeliac disease	0	1	1
Cryopyrin-associated periodic syndrome	0	1	1
Depression	0	1	1
Dystonia	0	1	1
Essential tremor	0	1	1

Functional movement disorders	0	1	1
HIV	0	1	1
Idiopathic inflammatory myopathies	0	1	1
Infections	0	1	1
Inflammatory Arthritis	0	1	1
Malnutrition	0	1	1
Myocardial infarction	0	1	1
Neuromyelitis optica spectrum disorder	0	1	1
Parkinsonian syndromes	0	1	1
Post orthostatic tachycardia	0	1	1
Psoriasis	0	1	1
Psoriatic arthritis	0	1	1
Renal failure	0	1	1
Rheumatic disease	0	1	1
Scleroderma	0	1	1
Sick building syndrome	0	1	1
Silicone breast implants syndrome	0	1	1
Spondylarthritis	0	1	1
Thyroid disease	0	1	1
Chronic inflammatory demyelinating polyneuropathy	1	0	1
Congenital myasthenic syndromes	1	0	1
Facioscapulohumeral dystrophy	1	0	1
Glycogenosis	1	0	1
Immune neuropathy	1	0	1
Inflammatory myopathies	1	0	1
Lipid storage myopathies	1	0	1
Lyme disease	1	0	1
Metabolic myopathy	1	0	1
Mitochondrial myopathy	1	0	1
Muscle channelopathies	1	0	1
Myotonic dystrophy	1	0	1
Poliomyelitis	1	0	1
Primary mitochondrial diseases	1	0	1
Primary systemic vasculitis	1	0	1
Spinal muscular atrophy	1	0	1
Spino-bulbar muscular atrophy	1	0	1
Systemic sclerosis	1	0	1
Viral infections	1	0	1

References

1. Walker S, Goodfellow H, Pookarnjanamorakot P, et al. Impact of fatigue as the primary determinant of functional limitations among patients with post-COVID-19 syndrome: a cross-sectional observational study. *BMJ Open*. 2023 Jun 7;13(6):e069217.
2. Chen K, Fan Y, Hu R, et al. Impact of depression, fatigue and disability on quality of life in Chinese patients with multiple sclerosis. *Stress Health*. 2013 Apr;29(2):108-12.
3. Elbers RG, van Wegen EE, Verhoef J, et al. Impact of fatigue on health-related quality of life in patients with Parkinson's disease: a prospective study. *Clin Rehabil*. 2014 Mar;28(3):300-11.
4. Breslin E, van der Schans C, Breukink S, et al. Perception of fatigue and quality of life in patients with COPD. *Chest*. 1998 Oct;114(4):958-64.
5. Park NH, Kang YE, Yoon JH, et al. Comparative study for fatigue prevalence in subjects with diseases: a systematic review and meta-analysis. *Sci Rep*. 2024 Oct 7;14(1):23348.
6. Davis JM, 3rd, Myasoedova E, Gunderson TM, et al. Multimorbidity and Fatigue in Rheumatoid Arthritis: A Cross-Sectional Study of a Population-Based Cohort. *Rheumatol Ther*. 2020 Dec;7(4):979-991.
7. Goertz YMJ, Braamse AMJ, Spruit MA, et al. Fatigue in patients with chronic disease: results from the population-based Lifelines Cohort Study. *Sci Rep*. 2021 Oct 25;11(1):20977.
8. Chowdhury SR, Chandra Das D, Sunna TC, et al. Global and regional prevalence of multimorbidity in the adult population in community settings: a systematic review and meta-analysis. *EClinicalMedicine*. 2023 Mar;57:101860.
9. Ho IS, Azcoaga-Lorenzo A, Akbari A, et al. Variation in the estimated prevalence of multimorbidity: systematic review and meta-analysis of 193 international studies. *BMJ Open*. 2022 Apr 29;12(4):e057017.
10. NICE. Myalgic encephalomyelitis (or encephalopathy)/chronic fatigue syndrome: diagnosis and management 2021 [21/09/2024]. Available from: <https://www.nice.org.uk/guidance/ng206/chapter/Recommendations>
11. NICE. Multiple sclerosis in adults: management 2022 [21/09/2024]. Available from: <https://www.nice.org.uk/guidance/ng220/chapter/Recommendations#ms-symptom-management-and-rehabilitation>
12. NICE. Stroke rehabilitation in adults 2023 [21/09/2024]. Available from: <https://www.nice.org.uk/guidance/ng236/chapter/Recommendations#fatigue>
13. NICE. Advanced breast cancer: diagnosis and treatment 2009 [updated 16/8/2017;21/09/2024]. Available from: <https://www.nice.org.uk/guidance/cg81/chapter/Recommendations>
14. Menting J, Tack CJ, Bleijenberg G, et al. Is fatigue a disease-specific or generic symptom in chronic medical conditions? *Health Psychol*. 2018 Jun;37(6):530-543.
15. Rudroff T. Revealing the Complexity of Fatigue: A Review of the Persistent Challenges and Promises of Artificial Intelligence. *Brain Sci*. 2024 Feb 19;14(2).
16. Skau S, Sundberg K, Kuhn HG. A Proposal for a Unifying Set of Definitions of Fatigue. *Front Psychol*. 2021;12:739764.
17. Kluger BM, Krupp LB, Enoka RM. Fatigue and fatigability in neurologic illnesses: proposal for a unified taxonomy. *Neurology*. 2013 Jan 22;80(4):409-16.
18. Pattyn N, Van Cutsem J, Dessy E, et al. Bridging Exercise Science, Cognitive Psychology, and Medical Practice: Is "Cognitive Fatigue" a Remake of "The Emperor's New Clothes"? *Front Psychol*. 2018;9:1246.
19. Davies K, Dures E, Ng WF. Fatigue in inflammatory rheumatic diseases: current knowledge and areas for future research. *Nat Rev Rheumatol*. 2021 Nov;17(11):651-664.

20. Billones R, Liwang JK, Butler K, et al. Dissecting the fatigue experience: A scoping review of fatigue definitions, dimensions, and measures in non-oncologic medical conditions. *Brain Behav Immun Health*. 2021 Aug;15:100266.
21. Peters MDJ, Marnie C, Tricco AC, et al. Updated methodological guidance for the conduct of scoping reviews. *JBI Evid Implement*. 2021 Mar;19(1):3-10.
22. Bachmair EM, Martin K, Aucott L, et al. Remotely delivered cognitive behavioural and personalised exercise interventions for fatigue severity and impact in inflammatory rheumatic diseases (LIFT): a multicentre, randomised, controlled, open-label, parallel-group trial. *Lancet Rheumatol*. 2022 Aug;4(8):e534-e545.
23. Butler M, D'Angelo S, Ahn H, et al. A Series of Personalized Virtual Light Therapy Interventions for Fatigue: Feasibility Randomized Crossover Trial for N-of-1 Treatment. *JMIR Form Res*. 2023 Sep 18;7:e45510.
24. Carrasco-Querol N, Gonzalez Serra G, Bueno Hernandez N, et al. Effectiveness and health benefits of a nutritional, chronobiological and physical exercise primary care intervention in fibromyalgia and chronic fatigue syndrome: SYNCHRONIZE + mixed-methods study protocol. *Medicine (Baltimore)*. 2023 Apr 25;102(17):e33637.
25. Duarte C, Spilker RLF, Paiva C, et al. MITIG.RA: study protocol of a tailored psychological intervention for managing fatigue in rheumatoid arthritis randomized controlled trial. *Trials*. 2023 Oct 6;24(1):651.
26. Vroegindeweij A, Swart JF, Houtveen J, et al. Identifying disrupted biological factors and patient-tailored interventions for chronic fatigue in adolescents and young adults with Q-Fever Fatigue Syndrome, Chronic Fatigue Syndrome and Juvenile Idiopathic Arthritis (QFS-study): study protocol for a randomized controlled trial with single-subject experimental case series design. *Trials*. 2022 Aug 19;23(1):683.
27. Skivington K, Matthews L, Simpson SA, et al. A new framework for developing and evaluating complex interventions: update of Medical Research Council guidance. *BMJ*. 2021 Sep 30;374:n2061.
28. Reeve BB, Wyrwich KW, Wu AW, et al. ISOQOL recommends minimum standards for patient-reported outcome measures used in patient-centered outcomes and comparative effectiveness research. *Qual Life Res*. 2013 Oct;22(8):1889-905.
29. Duncan E, O'Cathain A, Rousseau N, et al. Guidance for reporting intervention development studies in health research (GUIDED): an evidence-based consensus study. *BMJ Open*. 2020 Apr 8;10(4):e033516.
30. Hoffmann TC, Glasziou PP, Boutron I, et al. Better reporting of interventions: template for intervention description and replication (TIDieR) checklist and guide. *BMJ*. 2014 Mar 7;348:g1687.
31. Selye H. Stress and the general adaptation syndrome. *Br Med J*. 1950 Jun 17;1(4667):1383-92.
32. Haykin H, Rolls A. The neuroimmune response during stress: A physiological perspective. *Immunity*. 2021 Sep 14;54(9):1933-1947.
33. Seyidoglu N, Aydin C. Insight of the Recent Perspectives from Psychoneuroimmunology: Stress, Nutrition and Life Quality. In: Rezaei N, Yazdanpanah N, editors. *PsychoNeuroImmunity: Volume 1: Integration of Psychology, Neurology, and Immunology*. Cham: Springer Nature Switzerland; 2024. p. 331-353.
34. McEwen BS, Stellar E. Stress and the individual. Mechanisms leading to disease. *Arch Intern Med*. 1993 Sep 27;153(18):2093-101.
35. Potter C, Leggat F, Lowe R, et al. Effectiveness and cost-effectiveness of a personalised self-management intervention for living with long COVID: protocol for the LISTEN randomised controlled trial. *Trials*. 2023 Feb 1;24(1):75.