



# Measuring Fatigue in Multiple Sclerosis: A Rapid Review

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## Abstract

**Background** Fatigue is one of the most prevalent and debilitating symptoms of multiple sclerosis (MS), as people with MS describe it. It has a complex pathogenesis and often precedes the clinical symptoms of MS and potentially indicates disease progression. Given its prevalence, impact, and intricate connections to disease pathology, accurate measurement is crucial to manage and study fatigue in people with MS; however, current measurements often lack content validity. A mismatch between key aspects of fatigue and existing fatigue scales will limit these scales' ability to capture the full scope of MS-related fatigue. We aimed to examine the current evidence on MS-related fatigue to define key aspects of fatigue in the literature and compare them with the scales used to measure MS-related fatigue.

**Methods** This integrated rapid review (PROSPERO registration: CRD42024505743) synthesised evidence on MS-related fatigue domains and their representation in validated scales. A systematic search was conducted on January 24, 2024, across three electronic databases: PubMed, Scopus, and ProQuest with no restriction on publication date. Eligible studies included those reporting on fatigue domains, signs and symptoms in people with MS and those on validated fatigue scales in MS. The quality of the included studies was assessed using the Mixed Methods Assessment Tool. Data was synthesised with meta-aggregation of the fatigue domains, signs, and symptoms and mapping them against the items from validated fatigue scales.

**Results** We identified 7089 articles and included 85 studies (quantitative: 65; qualitative: 9; mixed methods: 8); 54 investigated fatigue domains, five reported fatigue scale development, and 26 focused on both. The review included 34,984 participants (9814 male; 25,126 female) with a mean age of 47.43 years (range 36–55.4). A total of 791 items related to fatigue domains, signs, symptoms, and experiences were extracted and categorised into three key areas: fatigue triggers, domains, and impacts. We identified eight fatigue triggers (physical, cognitive, psychological, social, medical, lifestyle, temporal, and environmental), five fatigue domains (general, physical, cognitive, psychosocial, and social), and five areas of fatigue impact (global, physical, cognitive, psychological, and social impacts of fatigue). Twenty-nine scales, tests, measures, and indices that measure MS-related fatigue were identified. Nineteen of these were validated by self-reported fatigue scales. The scales fully covered the domains of MS-related fatigue. However, the identified scales did not fully capture medical and lifestyle triggers, as well as psychological and global impacts. Additionally, no single scale fully encompassed all three aspects of fatigue and their corresponding subcategories.

**Conclusion** This review demonstrates the importance of integrating the subjective experiences of people with MS into research to ensure that the multidimensional aspects of MS-related fatigue, together with these people's values, needs, and preferences, are captured and used to develop useful, comprehensive, and meaningful tools designed to measure MS-related fatigue. In addition, this clearer discernment of the triggers, domains, and impacts of MS-related fatigue is critical in the clinic and research. Better tools will enable a better understanding of the underlying mechanisms, as well as tracking and managing fatigue.

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## Key Points

Eight fatigue triggers (physical, cognitive, psychological, social, medical, lifestyle, temporal, and environmental), five fatigue domains (general, physical, cognitive, psychosocial, and social), and five areas of fatigue impact (global, physical, cognitive, psychological, and social impacts of fatigue) were recognised from the 85 included studies.

Twenty-nine scales, tests, measures, and indexes that measure MS-related fatigue were identified, nineteen of which were validated by self-reported fatigue scales.

The scales fully cover the domains of MS-related fatigue.

However, they did not cover MS-related fatigue triggers, including physical, cognitive, medical, and lifestyle triggers, and they only partially covered the psychological and global impacts of MS-related fatigue.

## 1 Introduction

Multiple sclerosis (MS) is a chronic neurologic condition characterised by immune-mediated neuronal and myelin damage in the brain and the spinal cord, with a growing global burden, disproportionately affecting adults during their peak working years. Incident cases of MS increased by 41.8% globally between 1990 and 2019, with 1.16 million disability-adjusted life years (DALYs) attributed to MS in 2019 alone [1]. The disease exhibits a peak in incidence around age 30–39 years, and a peak in DALY burden around 50–59 years, highlighting its impact on working young and middle-aged adults. Due to its localisation in the brain and the spinal cord, MS presents with a broad spectrum of neurologic and non-neurologic symptoms. Common symptoms include sensory disturbances (e.g., numbness, tingling), motor impairments (e.g., weakness, spasticity, gait difficulties), and visual problems (e.g., blurred or double vision). Non-neurologic symptoms include fatigue, pain, anxiety, and depressive symptoms. These non-neurologic symptoms can emerge early in the disease course and may substantially affect daily functioning, irrespective of physical or neurological symptoms.

Fatigue is one of the most commonly reported symptoms of MS, with a prevalence of 37% to 80% [2, 3]. It is increasingly being recognised not merely as a by-product of MS, but as an intrinsic and primary symptom, given its high prevalence, underlying mechanisms, and complex interaction

with MS pathophysiology. Fatigue is also described as one of the most debilitating symptoms and a significant contributor to decreased quality of life [4, 5]. The aetiology of MS-related fatigue is complex and multifaceted, including psychological, cognitive, neurological, immunological, and environmental [6]. Some evidence further suggests that fatigue may precede other clinical manifestations of MS, and the worsening of fatigue may indicate progression of MS [7, 8]. One of the widely accepted definitions of fatigue defines MS-related fatigue as “a subjective lack of physical and/or mental energy that is perceived by the individual or caregiver to interfere with usual and desired activities” [9]. This person-centred definition captures the multidimensional nature of fatigue and highlights the need for measurement tools that accurately capture it.

Variability in the reported prevalence of MS-related fatigue may reflect differences in manifestation for different people and different types of MS. It may also reflect variation in tools used to measure MS-related fatigue. Currently, MS-related fatigue is measured using patient-reported outcome measures (PROMs), some of which are widely used, including the Fatigue Severity Scale (FSS), the Modified Fatigue Impact Scale (MFIS), the Fatigue Symptoms and Impacts Questionnaire (FSIQ-RMS), and the Neurological Fatigue Index–MS (NFI-MS). The FSS, one of the earliest tools developed, focuses on the functional impact of fatigue. In contrast, more recent tools, such as the FSIQ-RMS, incorporate patient-derived conceptualisations of fatigue into item development [10]. However, a recent systematic review has found that most fatigue PROMs used in MS do not fully satisfy the content validity standards [11]. Common deficiencies include unclear construct definitions, limited use of guiding conceptual frameworks, and inadequate consumer involvement during the item development. In contrast, a systematic review of qualitative studies described the experiences of fatigue in people with MS as comprising two major dimensions of MS-related fatigue: biopsychosocial experiences of fatigue and factors that influence fatigue [12]. This misalignment between the two reviews raises concerns about the adequacy of existing PROMs in capturing the complex and multidimensional nature of MS-related fatigue.

Given its prevalence, impact, and intricate connections to disease pathology, it is crucial to measure, follow-up, manage, and study fatigue in people with MS. However, the elements of fatigue, hereby referred to as domains, impacts, experiences, and measures of fatigue reported in the current literature, are not well defined, and an integrated review addressing these aspects is lacking. Understanding these aspects of fatigue is vital for conceptualising, defining, and accurately measuring MS-related fatigue [13]. This integrated rapid review aimed to examine the current evidence on MS-related fatigue to define and

integrate fatigue experiences with the domains and scales used to measure it.

## 2 Methods

We performed an integrated rapid review of the literature in accordance with the principles recommended by the WHO and Cochrane [14, 15]. We selected an integrative review method for its ability to synthesise evidence from diverse literature and disciplines, evaluate the current body of work, and identify knowledge gaps [16]. The rapid review approach was chosen for its streamlined, time-efficient process while maintaining the rigour of a systematic review. This review is registered with PROSPERO (PROSPERO ID: CRD42024505743).

### 2.1 Search Strategy and Selection Criteria

The search terms were developed to ensure reproducibility and increase transparency following the PICOS framework (Population/Intervention/Comparison/Outcomes/Study Design) [17]. Between January 14th and January 24th, 2024, the search terms were developed in collaboration with four health services researchers (three with clinical backgrounds in nursing and medicine: TN, AP, JD, NC). This was followed by a consultation with four people with MS (ME, KC, JDr, VF) and a neurologist (GH). An information specialist or librarian was not involved in the design or execution of the search strategy.

Search terms were combined using Boolean operators ‘AND’ and ‘OR’. Preliminary searches were undertaken to inform and refine the final search strategy and determine outcomes. The final search terms were: (‘multiple sclerosis’ OR ‘clinically isolated syndrome’) AND (lassitude OR weary OR wear\* OR tired\* OR fatigue\*) AND ((domains OR signs OR symptoms OR experience) OR (evaluation OR assess\* OR diagnos\* OR follow-up OR track OR scale\* OR measure\* OR survey OR tool OR instrument OR questionnaire OR interview OR ‘focus group’)). The final searches were conducted by a team member (TN) on the following three electronic databases with structured search capabilities (inclusion of Boolean operators) that are health-focused on January 24, 2024: PubMed, Scopus, and ProQuest.

### 2.2 Data Screening

A parallel screening process was conducted to identify (1) key fatigue domains in MS (Stream 1: Domains) and (2) key validated fatigue scales (Stream 2: Scales), as shown

in Fig. 1. Studies that met the inclusion criteria in Table 1, which were developed using the PICOS framework, were included. The screening criteria were refined through a team discussion (TN, AP, NC, JD), and preliminary screening of five available studies was conducted during protocol development.

The search results were imported into Covidence, an internet-based software that facilitated collaboration between reviewers [18]. The screening process included

1. Title and abstract screening with partial double review on a random 50 papers (1.2%) by TN with either JD, AP, or NC.
2. Full-text screening with partial double review on a random 10 full texts (2.7%) by TN with either JD, AP, or NC.
3. Any disagreements were resolved by consensus between the two reviewers (100%), and reasons for exclusion were noted.

### 2.3 Data Extraction

After screening, the authorship team designed, reviewed, and piloted a data extraction tool. In the piloting process, two independent reviewers (TN and AP) extracted data independently and in duplicates from five studies each and compared their results to establish agreement and validity of the tool. One reviewer (TN) conducted a complete data extraction. Any disagreements were resolved through discussion until a consensus was reached (TN, AP, JD, NC). Due to time restrictions, missing data was not collected by contacting relevant authors.

The data extraction tool contained the following items:

1. General information: Reference, year, title, location.
2. Sample information: MS type, sample size, mean age (total, female and male), sex (number and percentage), education (total education years stratified by gender), disease duration (stratified by MS types), diagnostic criteria or inclusion criteria.
3. Outcome: Signs, symptoms, domains, components and subcomponents, experience of fatigue and validated fatigue scales.
4. Study design: Study designs, tools, scales, assessments, questionnaires, and surveys are used to measure the outcomes and the validation type and results.

### 2.4 Quality Assessment

The Mixed Methods Appraisal Tool (MMAT) was used to assess the quality of the studies [19]. The MMAT is designed to appraise a range of study types, including qualitative

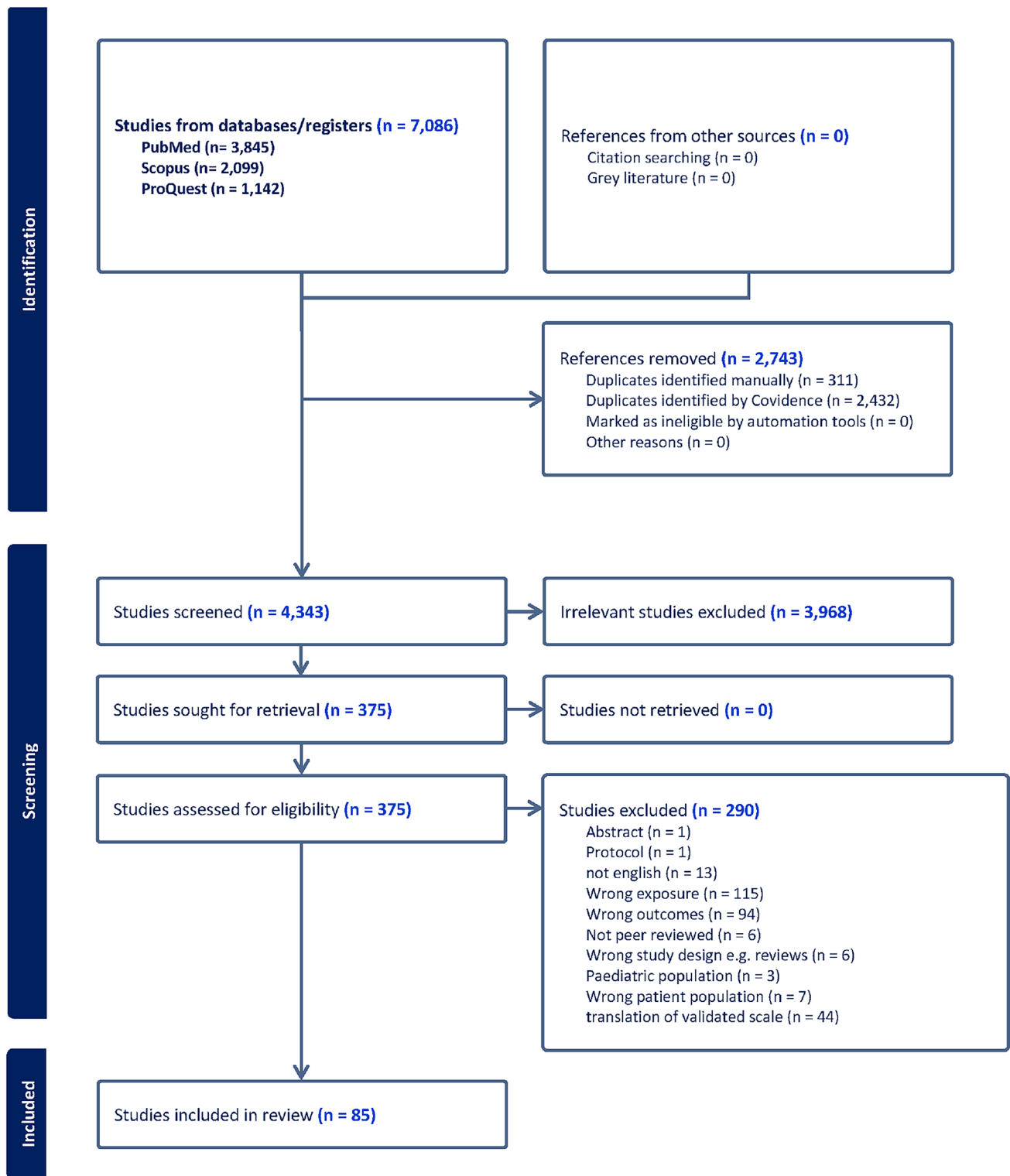


Fig. 1 PRISMA screening flow chart. The figure shows the identification, screening, and inclusion stages along with details

**Table 1** Eligibility criteria (PICOS) for key fatigue domains and validated scales

PICOS	Inclusion criteria	Exclusion criteria
Population	Studies on people with multiple sclerosis or clinically isolated syndrome Human adult population	Studies on other diseases Paediatric or animal studies
Intervention	Studies looking at fatigue OR lassitude OR weariness OR tiredness OR exhaustion	Studies investigating symptoms other than fatigue
Comparison	All studies with or without a comparison group	N/A
<i>Outcome</i>		
Domains	Studies investigating domains, signs, symptoms, experience of fatigue	Studies investigating outcomes not mentioned in the inclusion criteria
Validated MS-related fatigue scales	Studies reporting on validation and development of fatigue scale	Studies investigating outcomes not mentioned in the inclusion criteria
<i>Settings or study design</i>		
Domains	Both empirical and non-empirical studies that investigate domains, signs, symptoms, and experience of fatigue by evaluating, assessing, measuring, tracking, following up, with either questionnaires, tools, scales, surveys, interviews, or focus groups	Research abstracts, reviews, and systematic reviews
Validated MS-related fatigue scales	Empirical studies, randomised clinical trials, surveys, and mixed-method studies	Qualitative studies, research abstracts, scientific presentations, editorial, commentary, thesis
Others	English studies	Studies in languages other than English

MS multiple sclerosis

research, randomised controlled trials, non-randomised studies, quantitative descriptive studies, and mixed methods studies. Each study is appraised against the five methodological criteria tailored to the study type. In line with MMAT guidance, no overall score or cut-off values were calculated; instead, individual criteria were used to inform a qualitative judgement of the study. Two reviewers (TN and AP) partially double-appraised the included studies (five random studies), and one reviewer (TN) completed the appraisal. Any discrepancies were resolved through discussion until a consensus was reached among the three reviewers (TN, JD, AP).

## 2.5 Protocol Amendment and Aim Development

The protocol for this study was developed in January and was revised in June 2025. The revision included the addition of a formal review aim, based on the original research question, “What are the key domains of fatigue in MS and key validated fatigue scales?”. The review aim was refined to “examine the current evidence on MS-related fatigue to define and integrate fatigue experiences with the domains and scales used to measure it.” This refinement remains consistent with the final search terms and inclusion criteria. The PROSPERO record (CRD42024505743) has been amended to reflect this clarification.

## 2.6 Data Analysis

Data analysis was guided by the Cochrane updated recommendations for rapid reviews [14]. The results component included a descriptive analysis of the included studies and an assessment of the quality of the evidence. Following this, in accordance with the guideline of the Joanna Briggs Institute [20], an inductive meta-aggregation approach was used to analyse the extracted data on fatigue experience, signs, and symptoms (Stream 1: Domains). No pre-existing framework was applied; rather, fatigue aspects were coded inductively based on the reported content in the studies to allow the themes to emerge from the data, grounded in the evidence reported in the included studies.

Themes were derived through iterative coding and synthesis over several sessions involving researchers (TN, JD, NC), a neurologist (GH), a data scientist (RB), and four people with MS (ME, KC, JDr, VF). For qualitative studies, findings were qualited [20]. For example, if fatigue was induced by physical exertion and muscle fibres were measured, it was coded as muscle fatigue and grouped under a broader theme, physical fatigue, and into fatigue domains.

Three in-depth team discussions were held to review, refine, and finalise the themes, including ascertainment, confirmation, and at times additions to and amendments to the key aspects and their sub-categories by our lived experience team members (ME, KC, JDr, VF) and four researchers (TN, AP, JD, NC) until consensus was reached. The final key aspects of MS-related fatigue and their subcategories were

then mapped against the items within the identified, validated fatigue scales in Stream 2, allowing for a comparison of coverage across scales by the same research team.

### 3 Results

The review identified 7089 articles and included 85 studies (quantitative: 68; qualitative: 9; mixed methods: 8). Of those, 52 investigated fatigue domains, five developed fatigue scales, and 28 focused on both (Fig. 1). The review included 34,984 participants (range 9–9324, 9814 males; 25,126 females, gender missing: 44) with a mean age of 47.43 years (range 36–55.4). The sample range of the included studies varied based on the type of study, with 9–101 for qualitative studies; 44–3057 for mixed methods; and 13–9324 for quantitative studies (Supplementary Table 1, see electronic supplementary material [ESM]). The mean MS duration was 11.50 years (range 4–21.78).

The studies on fatigue domains included cross-sectional ( $n = 25$ ) [21–45], non-randomised experimental ( $n = 9$ ) [42, 46–54], qualitative ( $n = 9$ ) [55–63], cohort ( $n = 4$ ) [64–68], mixed methods ( $n = 3$ ) [4, 69, 70], randomised cross-over ( $n = 1$ ) [71], and randomised controlled trials ( $n = 1$ ) [72] (Fig. 2). The studies focusing on scales consisted of cohort studies ( $n = 2$ ) [73, 74], cross-sectional studies ( $n = 1$ ) [75], a diagnostic test accuracy study ( $n = 1$ ) and a mixed methods study ( $n = 1$ ) [76] (Supplementary Table 1, see ESM). The studies on both included diagnostic test accuracy studies ( $n = 13$ ) [77–88], cross-sectional studies ( $n = 6$ ) [89–94], mixed methods ( $n = 4$ ) [95–98], cohort studies ( $n = 2$ ) [8, 99], and non-randomised experimental studies ( $n = 1$ ) [100].

Twenty-seven fatigue domain studies (MS vs control:  $n = 17$  [24, 25, 28, 29, 31, 34, 36, 40, 42, 43, 46, 48–51, 53, 59]; fatigued versus non-fatigued:  $n = 7$  [26, 37, 45, 47, 54, 67, 72]; both comparisons:  $n = 3$  [52, 64, 65]), one scale development study (MS vs control [73]) and 15 studies focusing on both domains and scales had control groups (MS vs control:  $n = 9$  [78, 83, 85, 88, 93, 95, 98, 100]; fatigued

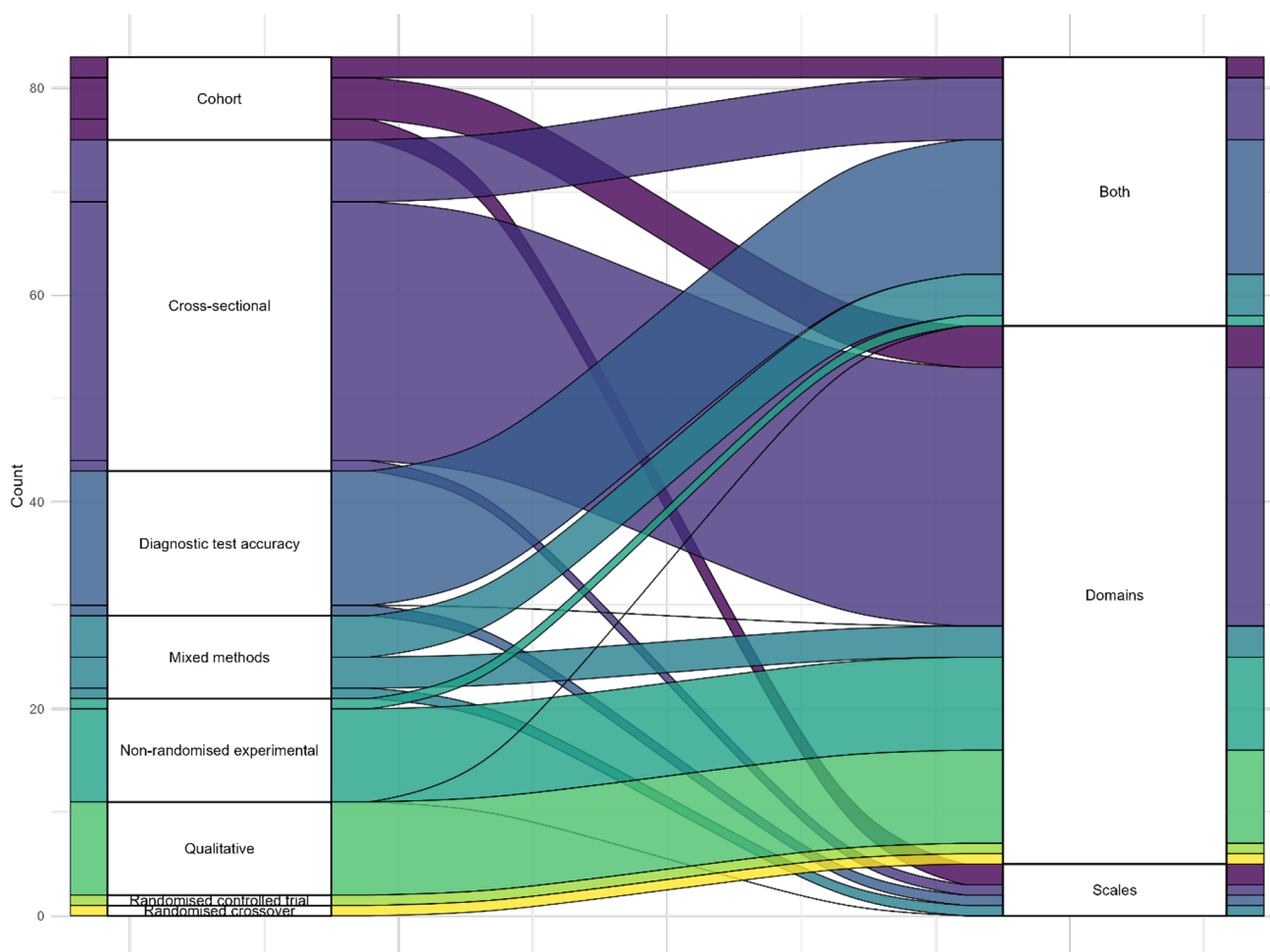


Fig. 2 A Sankey diagram illustrating study designs and items investigated in the included studies

vs non-fatigued:  $n = 5$  [8, 77, 79, 90, 97]; both comparisons:  $n = 1$  [92]).

### 3.1 Quality Assessment

Based on the MMAT, the majority of the included studies ( $n = 66$ , 77.6%) had low bias in at least three of the five methodological criteria (Supplementary Table 2, see ESM). One or more items were rated as “Cannot tell” in 51 studies (65.9%), most commonly due to insufficient reporting on sample representativeness or the appropriateness of the measurement tool. Two studies (2.4%) had three or more unclear biases. Five studies (5.9%) were judged to have a high risk of bias in at least one domain. These included one qualitative study, three quantitative descriptive studies, and one mixed methods study. Despite the methodological limitations, all included studies were retained to ensure a comprehensive synthesis of the available evidence. However, studies with high or unclear risk of bias were interpreted with caution in the analysis and discussion.

### 3.2 Fatigue Domains

A total of 791 items were extracted across fatigue domains, signs, symptoms, and experiences. These items were categorised into three key areas: fatigue triggers, domains, and impacts, reflecting the progression of the fatigue experience from triggers to the fatigued state and the impacts.

Items fitting the description of factors that were linked to the initiation or onset of fatigue in people with MS were categorised as fatigue triggers. Examples of these triggers included heat, physical exertion (physical activity with repetitions or involving the affected muscles), and noise. The items categorised as fatigue triggers were meta-aggregated into the following categories of fatigue triggers: (1) physical triggers—physical exertion; (2) cognitive triggers—cognitive load; (3) psychological triggers—stress; (4) social triggers—social activity; (5) medical triggers—MS symptoms, comorbidity; (6) lifestyle triggers—nutrition, sleep, alcohol; (7) temporal triggers—progression of day; and (8) environmental triggers—temperature (Table 2).

Items defining the body and physiological functions that are fatigued during the experience of MS-related fatigue were categorised as fatigue domains. Examples of these domains included “my muscles feel weak” and “my mind is tired”. The items included in the fatigue domain were meta-aggregated into the following domains: (1) general fatigue—“I have no energy”; (2) physical fatigue—“my muscles are tired”; (3) cognitive fatigue—“my mind is slow”; (4) psychosocial fatigue—“I feel mentally tired”; (5) social fatigue—“I am less motivated for social activity”. The domain items were further meta-aggregated into subdomains (Table 3).

Lastly, items that described what or how things had changed due to fatigue were listed as fatigue impacts. For example, items such as ‘I need to limit my activity’, or ‘I need to rest’ were included in fatigue impacts (Table 4). These were meta-aggregated into the following categories of fatigue impacts that followed the statement, “because of fatigue...”: (1) global impacts—“I feel a lack of energy”; (2) physical impacts—“I have to pace my activity”; (3) cognitive impacts—“I have difficulty paying attention”; (4) psychological impacts—“I am less able to provide emotional support”, and (5) social impacts—“I have had to reduce my workload”.

### 3.3 Fatigue Scales and Comparison

The review identified 29 validated measurement tools for MS-related fatigue across 31 studies (Table 4). These consisted of 24 scales (including five shorter versions) [74, 76–85, 89, 90, 91–94, 95–99, 101, 102], three indices [73, 75, 88], a test [77], and a system [100].

The fatigue triggers, domains, and impacts identified in the extracted data were matched to the fatigue domains identified in the validated scales (Fig. 3 and Tables 2, 3, 4, 5, and 6). Most tools provided limited coverage of fatigue triggers, with only a few partially covering physical (FSS, NFI-MS), temporal (NFI-MS), cognitive (Vanderbilt Fatigue Scale for Adults [VFS-A]), or environmental (Fatigue Scale for Motor and Cognitive Functions [FSMC], VFS-A) triggers. Lifestyle and medical triggers were not covered by any tool.

Coverage of fatigue domains was more consistent, with several scales addressing physical, cognitive, psychological, and social domains. Each subcategory of fatigue domains was addressed by at least one of the tools. Fatigue impacts were more frequently assessed than triggers; however, the current scales partially covered psychological and global impacts, with some subcategories not being addressed. Few tools comprehensively addressed all categories and subcategories of impacts. Importantly, no single tool comprehensively captured all three overarching aspects of fatigue and their subcategories.

## 4 Discussion

This integrated rapid review identified three key aspects of MS-related fatigue: triggers, domains (bodily manifestations or symptoms and signs of fatigue), and impacts. Our findings revealed a notable misalignment between the key aspects of fatigue and the constructs captured by current scales. The identified scales do not fully capture medical and lifestyle triggers, as well as psychological and global impacts. Importantly, no single scale comprehensively assessed all three aspects and their subcategories of

**Table 2** A detailed table of fatigue triggers

Fatigue triggers	Example of extracted items from fatigue domain studies		Items from validated scales	
	Quantitative study	Qualitative study	Scale names	Scale items
Physical triggers	Exercise and or exertion were precipitating factors [33]	Anecdotal factors of fatigue—physical exertion [61, 63]	The Neurological Fatigue Index (NFI-MS) [97]	I soon become weak after physical effort
Cognitive triggers	Slower responses were seen as cognitive task progressed in pwMS fatigue [68]	NA	Fatigue Scale for Motor and Cognitive Functions (FSMC) [98]	When I concentrate for a long time, I get exhausted sooner than other people of my age
Psychological triggers	NA	Antecedent factors of fatigue—stress, worry [61].	Fatigue Scale for Motor and Cognitive Functions (FSMC) [98]	When faced with stressful situations, I now find that I get physically exhausted quicker than I used to
Social triggers	NA	Social cause for fatigue (work situation, home situation, life too busy, childhood) [44]	Fatigue Scale for Motor and Cognitive Functions (FSMC) [98]	The demands of my work exhaust me mentally more quickly than they used to
Medical triggers	76% said fatigue makes other disease symptoms worse [85]	The exacerbation of symptoms with increasing fatigue [61]	Vanderbilt Fatigue Scale for Adults (VFS-A) [93]	I get headaches after taking part in group conversations
Lifestyle triggers	Antecedent factors of fatigue: alcohol, poor nutrition, sleep [61]	Fatigue increased with insomnia [67]	NA	NA
Temporal triggers	Real-time fatigue increased throughout the day [82]	NA	NA	NA
Environmental triggers	NA	When I'm tired if I take a cold shower, I get better [79]	The Neurological Fatigue Index (NFI-MS) [97]	By the end of the day I'm shattered
			F-2-MS scale Fatiguability [79]	When I'm tired if I take a cold shower, I get better
			Fatigue Scale for Motor and Cognitive Functions (FSMC) [98]	When it is hot, my main feeling is one of extreme physical weakness and lack of energy

This table includes examples of data items extracted from studies on fatigue domains, categorised as fatigue triggers. These examples are compared to the items measuring fatigue triggers from validated scales identified through the review

NA not applicable, *pwMS* people living with multiple sclerosis

**Table 3** A detailed table of fatigue domains

Fatigue domains		Example of extracted items from fatigue domain studies		Items from validated scales	
Fatigue subdomains	Quantitative study	Qualitative study	Scale names	Scale items	
Physical fatigue	Musculoskeletal fatigue (e.g. low muscle strength, slow motor nerve conduction, low motor neuron recruitment, low muscle activation)	Decay of maximal force in muscles during exercise [73] Slower motor nerve conduction and lower motor neurons recruited in MS patients [43] Fatigue group's muscle activation during maximal effort is less than that of healthy individuals [52]	Cannot walk or move further [58]	Fatigue impact scale [69] Chalder Fatigue Questionnaire [78]	My muscles feel much weaker than they should Do you have less strength in your muscles?
	Sensory fatigue (e.g. low vision, lower listening ability)	Worsening of sensation or vision after physical exertion [71] Listening fatigue is a problem in my life [93]	NA	Vanderbilt Fatigue Scale for Adults (VFS-A) [93]	Listening fatigue is a problem in my life
	Physical fitness (e.g. weakness, lower physical endurance)	Higher fatigue group perceived the exercise as strenuous (Rating of Perceived Exertion) [52]	Physically weak and physically drained [63]	Checklist Individual scale (20 items) [39]	Physically I feel in a good shape
Cognitive fatigue	Attention and focus (e.g. alertness, attention/concentration)	pwMS fatigue had lower scores on concentration problems [44]	Difficulties in remembering and concentrating [57]	Fatigue Rating Scale (FRS) [32]	Do you have difficulty concentrating?
	Memory and thoughts (e.g. memory, organising thoughts, thinking)	Memory variability mediated the residual cognition fatigue in pwMS [51]	To think clearly and solve complex problems was very difficult	PROMIS-Fatigue MS [91]	How often did your fatigue make you more forgetful?
	Communication (e.g. communication and understanding communication)	It takes A LOT of mental effort to understand what people are saying [93]	Difficult to communicate clearly [63]	Fatigue Rating Scale (FRS) [32] Fatigue Scale for Motor and Cognitive Functions (FSMC) [98]	Do you find it more difficult to find the correct word? When I am experiencing episodes of exhaustion, certain words simply escape me
Decision making	When I am experiencing episodes of exhaustion, I am incapable of making decisions [98]	Difficult to think clearly and solve complex problems was very difficult [58]	The Fatigue Impact Scale for Daily Use (D-FIS) [90] Modified Fatigue Impact Scale (MFIS) [87]	Because of fatigue, I find it difficult to make decisions I have had difficulty making decisions	
Speed (e.g. reaction time)	Slower responses were seen as cognitive task progressed in pwMS fatigue [68]	Slowed thinking [58]	The Fatigue Impact Scale for Daily Use (D-FIS) [90]	Because of fatigue, I feel slowed down in my thinking	

Table 3 (continued)

Fatigue domains	Fatigue subdomains	Example of extracted items from fatigue domain studies		Items from validated scales	
		Quantitative study	Qualitative study	Scale names	Scale items
Psychological fatigue	Emotional wellness (e.g. moody, irritable, overwhelmed)	65% of MFIS was explained by "x" and mental component of EP59 QoL scale [52]	Developing a sense of being emotionally overwhelmed [59]	Fatigue Impact Scale (FIS) [69]	I am more irritable and more easily angered
	Emotional support (e.g. provision of emotional support)	NA	NA	Fatigue Impact Scale (FIS) [69]	I am not able to provide adequate emotional support
	Loss of motivation	NA	NA	Swedish Occupational Fatigue Inventory [81]	I feel lack of concern (0–10)
Social fatigue	Social motivation	Social motivation [96]	NA	Fatigue Impact Scale (FIS) [69]	I am less motivated...social activities
	Social activity	pwMS fatigue had lower scores on social interactions [63]	NA	PROMIS Fatigue (MS) 8a [93]	How often were you too tired to enjoy life?
General fatigue	Lack of energy	69.2% described fatigue as fatigability [48]	Having no more emotional energy or nothing to give [59]	Fatigue Rating Scale (FRS) [32]	Are you lacking in energy?

This table includes examples of data items extracted from studies on fatigue domains, categorised into fatigue domains. These examples are compared to the items measuring fatigue domains from validated scales identified through the review

MFIS Modified Fatigue Impact Scale, NA not applicable, pwMS people with multiple sclerosis, QoL quality of life

**Table 4** A detailed table of fatigue impacts

Fatigue impacts	Example of extracted items from fatigue domain studies		Items from validated scales		
	Fatigue subcategories	Quantitative study	Qualitative study	Scale names	Scale items
Physical impacts	Need to cope or reduce physical fitness (e.g. need to reduce, top, pace, limit physical activities)	NA	Activity limitation [56] A feeling of saving strength and needing to rest [60]	Fatigue impacts Scale (FIS) [69]	I have to be careful about pacing my physical activities
	Reduced ability to undertake activities (e.g. cannot finish physical tasks)	Walk test performance lower in pwMS [100]	Exhausted at minimal activity [70]	Fatigue impacts Scale (FIS) [69]	I am less able to complete tasks that require physical effort
	Changed physiology or physical feeling (e.g. physical discomfort, changed function)	NA	Changed physical functioning [63]	NA	NA
Cognitive impacts	Impacts on communication	NA	Difficult to communicate clearly [63]	The Fatigue Symptoms and Impacts Questionnaire-RMS (FSIQ-RMS) [95]	Communicating clearly (scale 1-11)
	Impacts on memory	Memory test performance lower in pwMS [100]	Forgetful [63]	PROMIS-Fatigue MS [91]	How often did your fatigue make you more forgetful?
	Impacts on thinking and learning	NA	Because of my episodes of exhaustion, I now find it more difficult to learn new things than I used to [98]	Fatigue Scale for Motor and Cognitive Functions (FSMC) [98]	Because of my episodes of exhaustion, I now find it more difficult to learn new things than I used to
Impacts on attention/focus	Impacts on attention/focus	NA	Loss of concentration [63]	Modified Fatigue Impact Scale (MFIS) [87]	I have had difficulty paying attention for long periods of time
	Impacts on decision making	Subjective cognitive fatigue was higher for processing speed (PS) tasks compared with working memory (WM) tasks, increased across time, and was notably higher in the MS group compared with the healthy control group [53]	I have had difficulty making decisions [87]	Modified Fatigue Impact Scale (MFIS) [87]	I have had difficulty making decisions
	Impact on cognitive motivation	NA	Because of my episodes of exhaustion, I now feel less like doing things which require concentration [98]	Fatigue Scale for Motor and Cognitive Functions (FSMC) [98]	Because of my episodes of exhaustion, I now feel less like doing things which require concentration

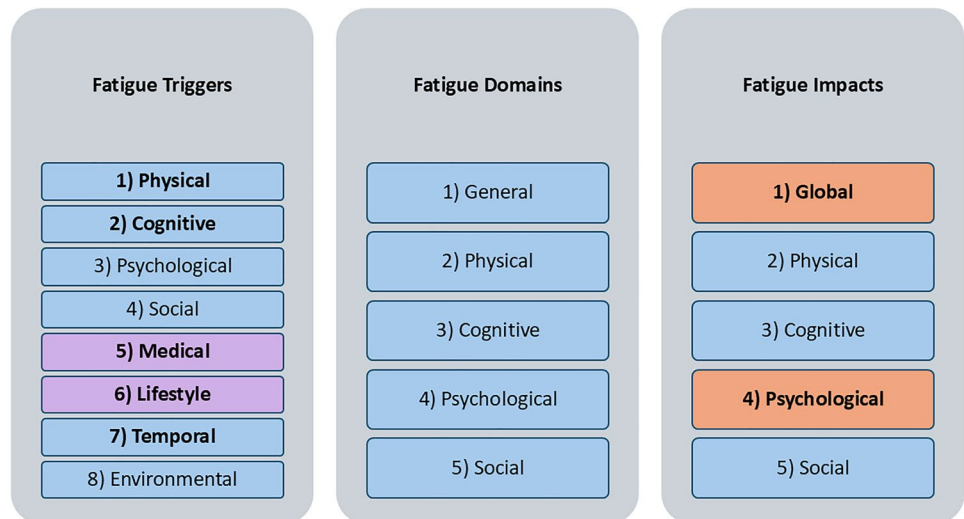
Table 4 (continued)

Fatigue impacts	Fatigue subcategories	Example of extracted items from fatigue domain studies		Items from validated scales	
		Quantitative study	Qualitative study	Scale names	Scale items
Psychological impacts	Emotional wellness	People who reported being more depressed tended to report more severe fatigue [103]	I am more irritable and more easily angered [69]	Fatigue Impact Scale (FIS) [69]	I am more irritable and more easily angered
			NA	PROMIS Fatigue (MS) &a [93]	How much were you bothered by your fatigue on average?
	Emotional support	NA	NA	Fatigue Impact Scale (FIS) [69]	I am not able to provide adequate emotional support
Social impacts	Coping emotionally	NA	Some of the respondents described the activation of a fighting spirit [58]	NA	NA
		NA	Trying to accept and take into account [57]	F-2-MS scale [79]	I have lost interest in doing activities that I used to do before
	Social motivation	Social motivation [96]	NA	Fatigue Impact Scale (FIS) [69]	I am less motivated...social activities
Global impacts	Social activity	pwMS fatigue had lower scores on social interactions [63]	NA	PROMIS Fatigue (MS) &a [93]	How often were you too tired to enjoy life?
	Impact on general energy (e.g. lack of energy, difficulty finishing things)	NA	Lack of energy to maintain former activities and roles [57]	Fatigue Rating Scale (FRS) [32]	Are you lacking in energy?
	Prevention/coping strategies (e.g. creating meaningful activities, planning, managing temperature)	NA	Trying to manage practical solutions, conserving energy [57]	NA	NA

This table includes examples of data items extracted from studies on fatigue domains, categorised into fatigue impacts. These examples are compared to the items measuring fatigue impacts from validated scales identified through the review

NA not applicable, *pwMS* people with multiple sclerosis

**Fig. 3** Fatigue triggers, domains, and impacts as covered by the validated fatigue scales identified in the review. Blue colour-coded labels indicate full coverage, brown is partial, and violet is not covered by identified validated scales



**Table 5** Fatigue scales. The table contains index, measures, tests, and self-reported scales of fatigue identified through the review

N	Scale name	Scale description
1.	Fatigue index (decay of maximal force during exercise)	An index calculated based on physical tests
2.	PROMIS Fatigue (MS) 8a	Self-reported fatigue scale
3.	Fatigue Severity Scale (FSS)	Self-reported fatigue scale
4.	Modified Fatigue Impact Scale (MFIS)	Self-reported fatigue scale
5.	Fatigue index	Fatigue index calculated based on physical tests
6.	The Fatigue Symptoms and Impacts Questionnaire – RMS (FSIQ-RMS)	Self-reported fatigue scale
7.	Cognitive fatigability assessment test (cFAST)	A test based on the results of cognitive tasks
8.	The Fatigue Impact Scale for Daily Use (D-FIS)	Self-reported fatigue scale
9.	Chalder Fatigue Questionnaire (CFQ)	Self-reported fatigue scale
10.	Functional Assessment of Chronic Illness Therapy Fatigue Version (FACIT-F)	Self-reported fatigue scale
11.	F-2-MS scale	Self-reported fatigue scale
12.	Fatigue Impact Scale (FIS)	Self-reported fatigue scale
13.	MS Symptom and Impact Diary (MSSID)	Self-reported scale that contains fatigue items
14.	Vanderbilt Fatigue Scales for Adults	Self-reported fatigue scale
15.	Swedish Occupational Fatigue Inventory	Self-reported fatigue scale
16.	Fatigue Severity Scale – 7 items (FSS-7)	A short version of a previous self-reported fatigue scale
17.	Real-Time Digital Fatigue Scores (RDFSs)	Self-reported fatigue scale
18.	Visual analogue scale for fatigue (VAS-F)	Self-reported fatigue scale
19.	Electronic Visual Analogue Scale for Fatigue (eVAS-F)	An electronic version of a previous self-reported fatigue scale
20.	Fatigue Severity Scale (FSS)	Self-reported fatigue scale
21.	PS fatigue subscale (PSF)	Self-reported fatigue scale
22.	Unidimensional Fatigue Scale (UFS)	Self-reported fatigue scale
23.	The Modified Fatigue Impact Scale – 5 items (MFIS-5)	A short version of a previous self-reported fatigue scale
24.	FSS-9 and FSS-5	A short version of a previous self-reported fatigue scale
25.	The Neurological Fatigue Index (NFI-MS)	Self-reported fatigue scale
26.	Fatigue Scale for Motor and Cognitive Functions (FSMC)	Self-reported fatigue scale
27.	The Fatigue Performance Scale	Self-reported fatigue scale
28.	Fatigue index or Kliniken Schmieder (FKS)	An index calculated based on physical tests
29.	FAtigue MONitoring System (FAMOS)	A system that measures fatigue based on accelerometer results

**Table 6** Matrix of fatigue aspects and their coverage by the identified scales

Scale name	Fatigue triggers					Fatigue domains					Fatigue impacts							
	Physical	Cognitive	Psychological	Social	Medical	Lifestyle	Temporal	Environmental	Physical	Cognitive	Psychological	Social	General	Physical	Cognitive	Psychological	Social	Global
Fatigue index (decay of maximal force during exercise)	-	-	-	-	-	-	-	-	-	+	-	-	-	-	-	-	-	-
PROMIS Fatigue (MS) 8a	-	-	-	-	-	-	-	-	+	-	-	-	-	-	+	+	+	+
Fatigue Severity Scale (FSS)	-	-	-	-	+	-	-	-	+	-	-	-	-	+	+	-	-	+
Modified Fatigue Impact Scale (MFIS)	-	-	-	-	-	-	-	-	-	+	+	+	+	-	+	+	+	+
Fatigue index	-	-	-	-	-	-	-	-	-	+	-	-	-	-	-	-	-	-
The Fatigue Symptoms and Impacts Questionnaire-RMS (FSIQ-RMS)	-	-	-	-	-	-	-	-	+	+	+	+	+	-	+	+	+	+
Cognitive fatigability assessment test (cFAST)	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	+	-	-
The Fatigue Impact Scale for Daily Use (D-FIS)	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-

Table 6 (continued)

Scale name	Fatigue triggers				Fatigue domains							Fatigue impacts						
	Physical	Cognitive	Psychological	Social	Medical	Lifestyle	Temporal	Environmental	Physical	Cognitive	Psychological	Social	General	Physical	Cognitive	Psychological	Social	Global
Chalder Fatigue Questionnaire (CFQ)	-	-	-	-	-	-	-	-	+	+	+	-	-	-	-	-	+	+
Functional Assessment of Chronic Illness Therapy fatigue version (FACIT-F)	-	-	-	-	-	-	-	-	+	-	-	-	+	-	-	-	+	+
F-2-MS scale	-	-	-	-	-	-	+	-	+	+	+	-	-	+	+	+	-	+
Fatigue Impact Scale (FIS)	-	-	-	-	-	-	-	-	-	+	+	+	+	-	+	+	+	+
MS Symptom and Impact Diary (MSSID)	-	-	-	-	-	-	-	-	+	+	+	+	-	-	-	-	-	+
Vanderbilt Fatigue Scales for Adults	-	-	-	-	-	-	-	+	-	+	-	+	-	-	+	+	-	+
Swedish Occupational Fatigue Inventory	-	-	-	-	-	-	-	-	+	-	-	-	-	+	+	-	-	+
Fatigue Severity Scale 7 items (FSS-7)	-	-	-	-	-	-	-	-	-	+	+	+	+	-	+	+	-	+

Table 6 (continued)

Scale name	Fatigue triggers					Fatigue domains					Fatigue impacts							
	Physical	Cognitive	Psychological	Social	Medical	Lifestyle	Temporal	Environmental	Physical	Cognitive	Psychological	Social	General	Physical	Cognitive	Psychological	Social	Global
Real-Time Digital Fatigue Scores (RDFSs)	-	-	-	-	+	-	-	-	-	-	-	-	-	-	-	-	-	-
Visual analogue scale for fatigue (VAS-F)	-	-	-	-	-	-	-	-	+	+	-	-	-	+	+	-	-	-
Electronic Visual Analogue Scale for Fatigue (eVAS-F)	-	-	-	-	-	-	-	-	+	+	+	-	-	+	+	-	-	-
Fatigue Severity Scale (FSS)	+	-	-	-	-	-	-	-	+	-	-	-	-	+	+	-	-	+
PS fatigue subscale (PSF)	NF	NF	NF	NF	NF	NF	NF	NF	NF	NF	NF	NF	NF	NF	NF	NF	NF	NF
Unidimensional Fatigue Scale (UFS)	-	-	-	-	-	-	-	-	+	+	+	+	+	+	+	+	-	+
The Modified Fatigue Impact Scale – 5 items (MFIS-5)	-	-	-	-	-	-	-	-	-	+	+	-	-	-	+	+	-	-
FSS-9 and FSS-5	+	-	-	-	-	-	-	-	+	-	-	-	-	+	-	-	-	+
The Neurological Fatigue Index (NFLMS)	+	-	-	-	-	-	+	-	+	+	-	-	-	+	-	+	-	+

Table 6 (continued)

Scale name	Fatigue triggers					Fatigue domains					Fatigue impacts							
	Physical	Cognitive	Psychological	Social	Medical	Lifestyle	Temporal	Environmental	Physical	Cognitive	Psychological	Social	General	Physical	Cognitive	Psychological	Social	Global
Fatigue Scale for Motor and Cognitive Functions (FSMC)	-	+	+	+	-	-	+		-					-	+	+	-	+
The Fatigue Performance Scale	NF	NF	NF	NF	NF	NF	NF	NF	NF	NF	NF	NF	NF	NF	NF	NF	NF	NF
Fatigue index or Kliniken Schmieder (FKS)	-	-	-	-	-	-	-	-	-	+	-	-	-	-	-	-	-	-
Fatigue Monitoring System (FAMOS)	-	-	-	-	-	-	-	-	-	+	-	-	-	-	-	-	-	-

+ covered, - not covered, NF not found

MS-related fatigue, underscoring a critical gap in measuring MS-related fatigue.

These misalignments are partially conceptual. Most fatigue scales predominantly adopt a symptom- and outcome-oriented approach, in which fatigue severity and functional impacts are prioritised, and the triggers or the full impact are often overlooked. The limited attention to triggers and psychological impacts restricts the clinical utility in identifying fatigue drivers and supporting personalised fatigue management [104]. Methodologically, this review identified a limited integration of lived experience or consumer involvement in scale development, with five studies focusing on scales using mixed methods. This aligns with a recent systematic review, which found that widely used scales such as MFIS and FSMC lack evidence in responsiveness to change and have limited content validity despite demonstrating good internal consistency (Cronbach's  $\alpha$  typically  $>0.85$ ) and overall psychometric robustness [105].

In addition, we identified that none of the scales included in the review captures the full aspect of fatigue. This limitation has direct implications for intervention studies, particularly in disease-modifying therapies (DMTs). This has been highlighted by Le et al. (2024) [106], who noted that fatigue-related outcomes are underrepresented due to a mismatch between the constructs measured by the existing tools and the fatigue experiences prioritised by people with MS. When fatigue is included, the tools fail to capture meaningful fatigue outcomes due to this mismatch. Together with the present findings, this evidence suggests a critical and clinically relevant gap between clinical methodologies and the multifaceted aspects of fatigue. Addressing this gap will require a more nuanced and responsive assessment, one that is consumer-informed, comprehensive, and capable of capturing the full range of fatigue aspects and their subparts.

This review offers a novel contribution by integrating qualitative and quantitative findings to identify key aspects of MS-related fatigue and systematically mapping these against existing validated fatigue scales. While prior reviews have explored consumer perspectives of fatigue and measurement tools separately [11, 12], this review advances the field by triangulating multiple types of evidence to evaluate alignment between key identified aspects of fatigue (derived from different kinds of studies) and current measurement scales used in MS. In doing so, it may serve as a foundation for the future development of more comprehensive and patient-informed fatigue assessment tools in MS. The importance of precise and responsive measurement tools is further underscored by recent findings from Petracca et al. (2024) [107], which demonstrate that telerehabilitation and onsite rehabilitation significantly reduce fatigue and improve quality of life for people with MS.

#### 4.1 Clinical Relevance, Broader Impact and Implications for Future Research

A comprehensive fatigue assessment tool could enhance clinical practice by supporting the identification of modifiable factors and enabling personalised fatigue management. In addition to this, a more comprehensive assessment of fatigue, particularly its triggers, may enable insights into disease mechanisms, inform stratification in clinical trials, and may guide public health interventions aimed at mitigating long-term disability and burden associated with MS.

The expected impact would be twofold: (1) a methodology to assess fatigue that is suitable, robust, valid, and acceptable to people with MS and (2) more effective fatigue management strategies based on individuals' fatigue profiles. To achieve such tools, future research should adopt or integrate an active involvement of people with MS and lived experience experts in all stages of the tool or scale development to ensure that the full spectrum of fatigue aspects is reflected. For this, we recommend using co-design methods. This approach will enable the direct involvement of people with MS in planning, item generation, prioritisation, content validation, and testing. One such example is the Fatigue Symptoms and Impacts Questionnaire-Relapsing-Remitting Multiple Sclerosis (FSIQ-RRMS). However, it does not capture the full complexity of MS-related fatigue, likely due to the limited scope of experiential evidence available at the time of its development. Future PROMs should build upon such efforts by integrating the expanded conceptual understanding of fatigue emerging from recent experience-focused research.

#### 4.2 Limitations

We recognise that limitations include fewer databases, partial screening, data extraction, and quality assessment processes of the rapid review. In addition, only English language publications were considered, which may have excluded relevant studies that have addressed culturally adapted tools. The methodological limitations of the rapid review may have led to the exclusion of relevant studies compared with a systematic review, and the potential lack of inclusion of experiences of different MS subtypes. Another significant limitation pertains to the measurement of fatigue itself. Fatigue rarely occurs in isolation in people with MS, often coexisting with conditions like depression or sleep abnormalities [108, 109]. Some studies included in the study did not account for the potential effects of these substantial comorbidities, which could influence the findings.

## 5 Conclusion

This review underlines that MS-related fatigue is multidimensional, and aspects are not fully covered through the existing tools. A clear, comprehensive, and meaningful measurement of fatigue, however, is essential not only to guide treatment decisions but also to enable people with MS to communicate their lived experiences. It is, therefore, integral to embed this lived experience into the design of suitable and robust tools to ensure that the tools capture the triggers, domains, and impacts of MS-related fatigue, making it accessible and usable for people with MS, researchers, and clinicians.

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**Conflict of Interest** The present study’s authors are part of a broader team that has received funding from the International Progressive MS Alliance.

**Data Availability** Data sharing does not apply to this article as no new data were created or analysed in this study. However, the data are available from the corresponding author upon reasonable request.

**Author Contributions** Tergel Namsrai – Conceptualisation (support), data curation (lead), formal analysis (equal), visualisation, methodology (equal), project administration (support), software, writing – original draft preparation (lead), writing – editing. Anne Parkinson – Conceptualisation (support), funding acquisition (equal), formal analysis (equal), methodology (equal), project administration (lead). Richard Burns – Conceptualisation (support), funding acquisition (equal), formal analysis (support). Geoffrey Herkes – Conceptualisation (support), funding acquisition (equal), formal analysis (support). Mark Elisha – Conceptualisation (support), formal analysis (support), writing – reviewing and editing (support). Katrina Chisholm – Conceptualisation (support), formal analysis (support), writing – reviewing and editing (support). Janet Drew – Conceptualisation (support), formal analysis (support), writing – reviewing and editing (support). Vanessa Fanning – Conceptualisation (support), funding acquisition (equal), formal analysis (support), writing – reviewing and editing (support). Anne Bruestle – Conceptualisation (support), funding acquisition (lead), visualisation, writing – reviewing and editing (support). Hanna Suominen – Conceptualisation (support), funding acquisition (equal), writing – reviewing and editing (support). Nicolas Cherbuin – Conceptualisation (equal lead), formal analysis (support), funding acquisition (equal), writing – reviewing and editing, supervision (equal). Jane Desborough – Conceptualisation (equal lead), formal analysis (equal), funding acquisition (equal), methodology (equal), writing – review-

ing and editing (lead), supervision (equal). Note: Some authors who contributed to the conceptualisation of this review were involved in the broader project design during grant development, prior to the registration of the rapid review protocol on PROSPERO.

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## References

1. Qian Z, et al. Global, regional, and national burden of multiple sclerosis from 1990 to 2019: Findings of global burden of disease study 2019. *Front Public Health*. 2023;11:1073278.
2. Rooney S, et al. Prevalence of fatigue and its association with clinical features in progressive and non-progressive forms of Multiple Sclerosis. *Multiple Scler Relat Disord*. 2019;28:276–82.
3. Oliva Ramirez A, et al. Prevalence and burden of multiple sclerosis-related fatigue: a systematic literature review. *BMC Neurol*. 2021;21(1):468.
4. Penner I-K, et al. Exploring the impact of fatigue in progressive multiple sclerosis: a mixed-methods analysis. *Multiple Scler Relat Disord*. 2020;43:102207.
5. Nourbakhsh B, Julian L, Waubant E. Fatigue and depression predict quality of life in patients with early multiple sclerosis: a longitudinal study. *Eur J Neurol*. 2016;23(9):1482–6.
6. Penner I-K, Paul F. Fatigue as a symptom or comorbidity of neurological diseases. *Nat Rev Neurol*. 2017;13(11):662–75.
7. Disanto G, et al. Prodromal symptoms of multiple sclerosis in primary care. *Ann Neurol*. 2018;83(6):1162–73.
8. Salter A, et al. Severity and worsening of fatigue among individuals with multiple sclerosis. *Mult Scler J Exp Transl Clin*. 2023;9(2):20552173231167080.
9. Guidelines, M.S.C.f.C.P. Fatigue and multiple sclerosis: evidence-based management strategies for fatigue in multiple sclerosis. Washington, DC: Paralyzed Veterans of America; 1998.
10. Regier DA, et al. Valuation of health and nonhealth outcomes from next-generation sequencing: approaches, challenges, and solutions. *Value Health*. 2018;21(9):1043–7.
11. Close J, et al. Measuring fatigue in multiple sclerosis: there may be trouble ahead. *Neurol Ther*. 2023;12(5):1649–68.
12. Newton G, Griffith A, Soundy A. The experience of fatigue in neurological patients with Multiple Sclerosis: a thematic synthesis. *Physiotherapy*. 2020;107:306–16.
13. Henschke A, et al. Personalizing medicine and technologies to address the experiences and needs of people with multiple sclerosis. *J Person Med*. 2021;11(8):791
14. Garritty C, et al. Updated recommendations for the cochrane rapid review methods guidance for rapid reviews of effectiveness. *BMJ*. 2024;384:e076335.
15. Tricco AC, Langlois EV, Straus SE. Rapid reviews to strengthen health policy and systems: a practical guide. Geneva: World Health Organization; 2017.

16. Kutcher AM, LeBaron VT. A simple guide for completing an integrative review using an example article. *J Prof Nurs.* 2022;40:13–9.
17. Methley AM, et al. PICO, PICOS and SPIDER: a comparison study of specificity and sensitivity in three search tools for qualitative systematic reviews. *BMC Health Serv Res.* 2014;14(1):579.
18. Veritas Health Innovation. Covidence systematic review software. [www.covidence.org](http://www.covidence.org).
19. Hong QN, Gonzalez-Reyes A, Pluye P. Improving the usefulness of a tool for appraising the quality of qualitative, quantitative and mixed methods studies, the Mixed Methods Appraisal Tool (MMAT). *J Eval Clin Pract.* 2018;24(3):459–67.
20. Aromataris E, Lockwood C, Porritt K, Pilla B, Jordan Z, editors. JBI manual for evidence synthesis. JBI; 2024.
21. Beckerman H, et al. Fatigue profiles in patients with multiple sclerosis are based on severity of fatigue and not on dimensions of fatigue. *Sci Rep.* 2020;10(1):4167.
22. Berard JA, Smith AM, Walker LAS. Predictive models of cognitive fatigue in multiple sclerosis. *Arch Clin Neuropsychol.* 2019;34(1):31–8.
23. Cehelyk EK, et al. Uncovering the association between fatigue and fatigability in multiple sclerosis using cognitive control. *Multiple Scler Relat Disord.* 2019;27:269–75.
24. Chen MH, et al. Cognitive fatigue is associated with altered functional connectivity in interoceptive and reward pathways in multiple sclerosis. *Diagnostics (Basel).* 2020;10(11):930.
25. Chipchase SY, Lincoln NB, Radford KA. Measuring fatigue in people with multiple sclerosis. *Disabil Rehabil.* 2003;25(14):778–84.
26. Coates KD, et al. Multiple sclerosis-related fatigue: the role of impaired corticospinal responses and heightened exercise fatigability. *J Neurophysiol.* 2020;124(4):1131–43.
27. Cook KF, et al. Creating meaningful cut-scores for Neuro-QOL measures of fatigue, physical functioning, and sleep disturbance using standard setting with patients and providers. *Qual Life Res.* 2015;24(3):575–89.
28. DeLuca J, et al. Neural correlates of cognitive fatigue in multiple sclerosis using functional MRI. *J Neurol Sci.* 2008;270(1–2):28–39.
29. Drebing D, et al. Association between fatigue and motor exertion in patients with multiple sclerosis—a prospective study. *Front Neurol.* 2020;11:208.
30. Flachenecker P, et al. Fatigue in multiple sclerosis: a comparison of different rating scales and correlation to clinical parameters: clinical and laboratory research. *Multiple Scler.* 2002;8(6):523–6.
31. Flensner G, et al. Fatigue in relation to perceived health: people with multiple sclerosis compared with people in the general population. *Scand J Caring Sci.* 2008;22(3):391–400.
32. Ford H, Trigwell P, Johnson M. The nature of fatigue in multiple sclerosis. *J Psychosom Res.* 1998;45(1):33–8.
33. Freal JE, Kraft GH, Coryell JK. Symptomatic fatigue in multiple sclerosis. *Arch Phys Med Rehabil.* 1984;65(3):135–8.
34. Genova HM, et al. Examination of cognitive fatigue in multiple sclerosis using functional magnetic resonance imaging and diffusion tensor imaging. *PLoS ONE.* 2013;8(11): e78811.
35. Greim B, Benecke R, Zetl UK. Qualitative and quantitative assessment of fatigue in multiple sclerosis (MS). *J Neurol.* 2007;254 Suppl 2:ii58–64.
36. Guillemin C, et al. The complex interplay between trait fatigue and cognition in multiple sclerosis. *Psychol Belg.* 2022;62(1):108–22.
37. Hadjimichael O, Vollmer T, Oleen-Burkey M. Fatigue characteristics in multiple sclerosis: the North American Research Committee on Multiple Sclerosis (NARCOMS) survey. *Health Qual Life Outcomes.* 2008;6:100.
38. Hameau S, et al. Relationship between neuromuscular and perceived fatigue and locomotor performance in patients with multiple sclerosis. *Eur J Phys Rehabil Med.* 2017;53(6):833–40.
39. Heine M, et al. Real-time assessment of fatigue in patients with multiple sclerosis: how does it relate to commonly used self-report fatigue questionnaires? *Arch Phys Med Rehabil.* 2016;97(11):1887–1894.e1.
40. Marchesi O, et al. Fatigue in multiple sclerosis patients with different clinical phenotypes: a clinical and magnetic resonance imaging study. *Eur J Neurol.* 2020;27(12):2549–60.
41. Moore H, et al. Fatigue in multiple sclerosis: a UK MS-register based study. *Multiple Scler Relat Disord.* 2022;64: 103954.
42. Schwid SR, et al. Cognitive fatigue during a test requiring sustained attention: a pilot study. *Multiple Scler.* 2003;9(5):503–8.
43. Steens A, et al. Fatigue perceived by multiple sclerosis patients is associated with muscle fatigue. *Neurorehabil Neural Repair.* 2012;26(1):48–57.
44. Vercoulen JH, et al. The measurement of fatigue in patients with multiple sclerosis. A multidimensional comparison with patients with chronic fatigue syndrome and healthy subjects. *Arch Neurol.* 1996;53(7):642–9.
45. Weinges-Evers N, et al. Correlation of self-assessed fatigue and alertness in multiple sclerosis: clinical and laboratory research. *Multiple Scler.* 2010;16(9):1134–40.
46. Claros-Salinas D, et al. Induction of cognitive fatigue in MS patients through cognitive and physical load. *Neuropsychol Rehabil.* 2013;23(2):182–201.
47. Hu M, et al. Perceived fatigue and cognitive performance change in multiple sclerosis: Uncovering predictors beyond baseline fatigue. *Multiple Scler Relat Disord.* 2019;32:46–53.
48. Iriarte J, de Castro P. Correlation between symptom fatigue and muscular fatigue in multiple sclerosis. *Eur J Neurol.* 1998;5(6):579–85.
49. Jacobs JB, et al. A model-based study of internuclear ophthalmoparesis and ocular-motor fatigue in multiple sclerosis. *Prog Brain Res.* 2019;249:329–44.
50. Morrow SA, Rosehart H, Johnson AM. Diagnosis and quantification of cognitive fatigue in multiple sclerosis. *Cogn Behav Neurol.* 2015;28(1):27–32.
51. Riegler KE, et al. Perceived fatigue impact and cognitive variability in multiple sclerosis. *J Int Neuropsychol Soc.* 2022;28(3):281–91.
52. Royer N, et al. A comprehensive evaluation of multiple sclerosis-related fatigue with a special focus on fatigability. *Med Sci Sports Exerc.* 2023;55(11):2002–13.
53. Sandry J, et al. Subjective cognitive fatigue in multiple sclerosis depends on task length. *Front Neurol.* 2014;5:214.
54. Zangemeister WH, et al. Oculomotor fatigue and neuropsychological assessments mirror multiple sclerosis fatigue. *J Eye Mov Res.* 2020. <https://doi.org/10.16910/jemr.13.4.6>.
55. Cook KF, et al. Multiple sclerosis and fatigue: understanding the patient's needs. *Phys Med Rehabil Clin N Am.* 2013;24(4):653–61.
56. Cowan CK, Pierson JM, Leggat SG. Psychosocial aspects of the lived experience of multiple sclerosis: personal perspectives. *Disabil Rehabil.* 2020;42(3):349–59.
57. Eilertsen G, et al. Similarities and differences in the experience of fatigue among people living with fibromyalgia, multiple sclerosis, ankylosing spondylitis and stroke. *J Clin Nurs.* 2015;24(13–14):2023–34.
58. Flensner G, Ek AC, Söderhamn O. Lived experience of MS-related fatigue—a phenomenological interview study. *Int J Nurs Stud.* 2003;40(7):707–17.
59. Kratz AL, et al. Development of a person-centered conceptual model of perceived fatigability. *Qual Life Res.* 2019;28(5):1337–47.

60. Lexell J, Olsson M, Soderberg S. The meaning of fatigue for women with multiple sclerosis. *J Adv Nurs*. 2005;49(1):7–15.
61. Stufbergen AK, Rogers S. The experience of fatigue and strategies of self-care among persons with multiple sclerosis. *Appl Nurs Res*. 1997;10(1):2–10.
62. Turpin M, et al. Understanding and living with multiple sclerosis fatigue. *Br J Occup Ther*. 2018;81(2):82–9.
63. Watson C, et al. Results from patient interviews on fatigue in progressive multiple sclerosis and evaluation of fatigue patient-reported outcome (PRO) instruments. *Neurol Ther*. 2022;11(2):725–39.
64. Ferreira M, et al. Using endogenous saccades to characterize fatigue in multiple sclerosis. *Mult Scler Relat Disord*. 2017;14:16–22.
65. Finke C, et al. Dynamics of saccade parameters in multiple sclerosis patients with fatigue. *J Neurol*. 2012;259(12):2656–63.
66. Grothe M, et al. The seasonal fluctuation of fatigue in multiple sclerosis. *Front Neurol*. 2022;13: 900792.
67. Lerdal A, et al. A prospective study of patterns of fatigue in multiple sclerosis. *Eur J Neurol*. 2007;14(12):1338–43.
68. Sander C, et al. Capturing fatigue parameters: the impact of vagal processing in multiple sclerosis related cognitive fatigue. *Mult Scler Relat Disord*. 2019;32:13–8.
69. Hobart J, et al. Achieving valid patient-reported outcomes measurement: a lesson from fatigue in multiple sclerosis. *Mult Scler*. 2013;19(13):1773–83.
70. Mills RJ, Young CA. A medical definition of fatigue in multiple sclerosis. *QJM*. 2008;101(1):49–60.
71. Karpatkin H, et al. Increases in fatigue do not change spasticity scores in persons with multiple sclerosis. *Neurodegener Dis Manag*. 2018;8(3):143–50.
72. Romani A, et al. Fatigue in multiple sclerosis: multidimensional assessment and response to symptomatic treatment. *Multiple Scler*. 2004;10(4):462–8.
73. Djaldetti R, et al. Fatigue in multiple sclerosis compared with chronic fatigue syndrome: a quantitative assessment. *Neurology*. 1996;46(3):632–5.
74. Kamudoni P, et al. A comparison of the measurement properties of the PROMIS Fatigue (MS) 8a against legacy fatigue questionnaires. *Multiple Scler Relat Disord*. 2022;66: 104048.
75. Surakka J, et al. Assessment of muscle strength and motor fatigue with a knee dynamometer in subjects with multiple sclerosis: a new fatigue index. *Clin Rehabil*. 2004;18(6):652–9.
76. Kamudoni P, et al. Standardizing fatigue measurement in multiple sclerosis: the validity, responsiveness and score interpretation of the PROMIS SF v1.0—fatigue (MS) 8a. *Multiple Scler Relat Disord*. 2021;54:103117.
77. Barrios L, et al. Cognitive fatigability assessment test (cFAST): Development of a new instrument to assess cognitive fatigability and pilot study on its association to perceived fatigue in multiple sclerosis. *Digit Health*. 2022;8:20552076221117740.
78. Chilcot J, et al. The Chalder Fatigue Questionnaire is a valid and reliable measure of perceived fatigue severity in multiple sclerosis. *Multiple Scler*. 2016;22(5):677–84.
79. Delgado-Álvarez A, et al. Validation of two new scales for the assessment of fatigue in Multiple Sclerosis: F-2-MS and FACIT-F. *Multiple Scler Relat Disord*. 2022;63: 103826.
80. Johansson S, et al. Can the Fatigue Severity Scale 7-item version be used across different patient populations as a generic fatigue measure—a comparative study using a Rasch model approach. *Health Qual Life Outcomes*. 2014;12:24.
81. Johansson S, et al. The Swedish occupational fatigue inventory in people with multiple sclerosis. *J Rehabil Med*. 2008;40(9):737–43.
82. Kim E, et al. Novel method for measurement of fatigue in multiple sclerosis: real-Time Digital Fatigue Score. *J Rehabil Res Dev*. 2010;47(5):477–84.
83. Kos D, et al. A rapid screening tool for fatigue impact in multiple sclerosis. *BMC Neurol*. 2006;6:27.
84. Kos D, et al. Electronic visual analogue scales for pain, fatigue, anxiety and quality of life in people with multiple sclerosis using smartphone and tablet: a reliability and feasibility study. *Clin Rehabil*. 2017;31(9):1215–25.
85. Krupp LB, et al. The fatigue severity scale: application to patients with multiple sclerosis and systemic lupus erythematosus. *Arch Neurol*. 1989;46(10):1121–3.
86. Meca-Lallana V, et al. Assessing fatigue in multiple sclerosis: psychometric properties of the five-item Modified Fatigue Impact Scale (MFIS-5). *Multiple Scler J Exp Transl Clin*. 2019;5(4):2055217319887987.
87. Mills RJ, et al. Rasch analysis of the Modified Fatigue Impact Scale (MFIS) in multiple sclerosis. *J Neurol Neurosurg Psychiatry*. 2010;81(9):1049–51.
88. Sehle A, et al. Objective assessment of motor fatigue in multiple sclerosis: the Fatigue index Kliniken Schmieder (FKS). *J Neurol*. 2014;261(9):1752–62.
89. Azoulay M, et al. A novel disease specific scale to characterize the symptoms and impacts of fatigue in US adults with relapsing multiple sclerosis: a real-world study. *Multiple Scler Relat Disord*. 2022;59: 103637.
90. Benito-León J, et al. Impact of fatigue in multiple sclerosis: the Fatigue Impact Scale for Daily Use (D-FIS): clinical and laboratory research. *Multiple Scler*. 2007;13(5):645–51.
91. Cook KF, et al. A PROMIS fatigue short form for use by individuals who have multiple sclerosis. *Qual Life Res*. 2012;21(6):1021–30.
92. Fisk JD, et al. Measuring the functional impact of fatigue: initial validation of the fatigue impact scale. *Clin Infect Dis*. 1994;18:S79–83.
93. Hornsby BWY, et al. Development and validation of the Vanderbilt Fatigue Scale for Adults (VFS-A). *Psychol Assess*. 2021;33(8):777.
94. Mills R, et al. Rasch analysis of the Fatigue Severity Scale in multiple sclerosis. *Multiple Scler*. 2009;15(1):81–7.
95. Hudgens S, et al. Development and validation of the FSIQ-RMS: a new patient-reported questionnaire to assess symptoms and impacts of fatigue in relapsing multiple sclerosis. *Value Health*. 2019;22(4):453–66.
96. Meads DM, et al. The development and validation of the Unidimensional Fatigue Impact Scale (U-FIS). *Mult Scler*. 2009;15(10):1228–38.
97. Mills RJ, et al. Development of a patient reported outcome scale for fatigue in multiple sclerosis: the Neurological Fatigue Index (NFI-MS). *Health Qual Life Outcomes*. 2010;8:22.
98. Penner IK, et al. The fatigue scale for motor and cognitive functions (FSMC): validation of a new instrument to assess multiple sclerosis-related fatigue: clinical and laboratory research. *Multiple Scler*. 2009;15(12):1509–17.
99. Greenhalgh J, et al. The MS Symptom and Impact Diary (MSSID): psychometric evaluation of a new instrument to measure the day to day impact of multiple sclerosis. *J Neurol Neurosurg Psychiatry*. 2004;75(4):577–82.
100. Yu F, et al. Fatigued patients with multiple sclerosis can be discriminated from healthy controls by the recordings of a newly developed measurement system (FAMOS): a pilot study. *Disabil Rehabil Assist Technol*. 2013;8(1):77–83.
101. Learmonth YC, et al. Psychometric properties of the Fatigue Severity Scale and the Modified Fatigue Impact Scale. *J Neurol Sci*. 2013;331(1–2):102–7.

102. Marrie RA, et al. Validation of the NARCOMS Registry: fatigue assessment: Clinical and Laboratory Research. *Multiple Scler*. 2005;11(5):583–4.
103. Schwartz CE, Coulthard-Morris L, Zeng Q. Psychosocial correlates of fatigue in multiple sclerosis. *Arch Phys Med Rehabil*. 1996;77(2):165–70.
104. Desborough J, Brunoro C, Parkinson A, Chisholm K, Elisha M, Lueck C, Drew J, Fanning, V, Cook M, Suominen H, Bruestle A, Tricoli A, Henschke A, Phillips C. 2020, “It struck at the heart of who I thought I was”: A meta-synthesis of the qualitative literature examining the experiences of people with multiple sclerosis, *Health Expectations*, 23 (5), 1007-1027
105. Sellitto G, et al. Outcome measures for physical fatigue in individuals with multiple sclerosis: a systematic review. *Expert Rev Pharmacoecon Outcomes Res*. 2021;21(4):625–46.
106. Le HH, Stocks SJ, Ait-Tihyaty M. A systematic literature review of the measurement of patient-reported fatigue in studies of disease modifying therapies for multiple sclerosis. *Multiple Scler Relat Disord*. 2024;91: 105846.
107. Petracca M, et al. Telerehabilitation and onsite rehabilitation effectively improve quality of life, fatigue, balance, and cognition in people with multiple sclerosis: an interventional study. *Front Neurol*. 2024;15:1394867.
108. Kaminska M, et al. Sleep disorders and fatigue in multiple sclerosis: evidence for association and interaction. *J Neurol Sci*. 2011;302(1–2):7–13.
109. Tarasiuk J, et al. Co-occurrence of fatigue and depression in people with multiple sclerosis: a mini-review. *Front Neurol*. 2022;12:817256.

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