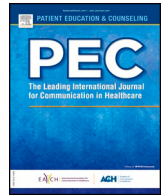




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Review article

Fatigue self-management education in persons with disease-related fatigue: A comprehensive review of the effectiveness on fatigue and quality of life

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ABSTRACT

Objectives: To systematically synthesize the effectiveness of fatigue self-management education (SME) on fatigue and quality of life (QoL) in persons with disease-related fatigue, and to describe the intervention characteristics.

Methods: We systematically reviewed the literature on SMEs in people with disease-related fatigue. We included randomized controlled trials (RCT), which aimed to improve self-management skills for fatigue in daily life. We synthesized the effectiveness and mapped the intervention characteristics.

Results: We included 26 RCTs studying samples from eight disease groups. At follow-up, 46% studies reported statistically significant improvements on fatigue and 46% on QoL. For persons with cancer 6/8 and multiple sclerosis 8/10 RCTs showed positive evidence in favor of SME. The range of effect sizes was wide (d : 0.0 -> 0.8). Delivery modalities (inpatient, outpatient, home), interactions (individual, group, remote), and duration [range (h): 1–17.5] varied.

Conclusions: The overall evidence on the effectiveness of SMEs on fatigue and QoL is limited and inconsistent. For persons with cancer and multiple sclerosis, the evidence provides a positive effect. The RCTs with medium to large effect on QoL indicate the potential benefit of SMEs.

Practical implication: Duration and peer interaction should be considered when tailoring SMEs to populations and contexts.

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1. Introduction

Disease-related fatigue (referred to as fatigue) is a common, multifactorial underlying symptom in a broad range of chronic conditions [1]. Fatigue is described as the difficulty or inability to initiate activity (subjective sense of weakness); reduced capacity to maintain activity (easy fatigability); or difficulty with concentration, memory, and emotional stability (mental fatigue) [2]. It involves complex pathophysiological and psychological processes that are still not fully understood [3].

Cancer-related fatigue (CRF) has been reported to be experienced by up to 80% of patients [4] and to be the most distressing symptom during and after treatment for cancer [5]. Severe fatigue is also highly prevalent in neurological [6,7] (e.g., multiple sclerosis) and rheumatic disorders [8] and is a common experience among persons with chronic obstructive pulmonary disease, diabetes or survivors of heart failure [9–12]. Due to the subjective nature of fatigue and the lack of specific therapies, it is often neglected or ignored by clinicians, although it is rated by patients as one of the key factors resulting in a decreased quality of life (QoL) [1]. Independent of the underlying mechanism, fatigue causes similar consequences across different disease populations. Work capacity and or the household, educational, avocational, social engagement; and self-care activities decrease. Everyday routines, habits and roles must be modified, which impairs QoL and increases disability [13].

Self-management education (SME) of patients is a common approach to deal with chronic conditions [14]. This complex intervention is a systematic learning experience combining different methods, such as the provision of information and behavior change techniques, to influence the way patients experience their condition or side effects of the illness [15]. The aim of SME is to teach patients how to cope with a condition and to enable the acquisition of helpful behaviors, habits, and routines [16]. In SME the agent of change is the person itself. SME targets the integration of new skills through higher self-efficacy and behavior change and thereby aims to reduce the impact of fatigue and to improve long-term social participation and QoL. Complex interventions such as SME are characterized by a variety of interacting intervention components [17,18]. There might be several mechanisms of action taken and the targeted outcome dimensions might differ. SMEs often allow a certain degree of flexibility and tailoring to individuals and situations in which they are carried out. The variety and the difficulty levels of behaviors required by those delivering and those receiving the intervention are high [17].

According to Lorig et al. [14], independently of the underlying disease, SME addresses medical, emotional and role management tasks. Five self-management skills (problem solving, decision making, resource utilization, forming of a patient/health care

provider partnership, and taking action) build thereby the core elements of the intervention [14]. The medical and behavioral management of fatigue focuses on symptom reduction or adherence to treatment programs (e.g., diet, sleep hygiene, or exercise) and is often part of nursing, physiotherapy or physician intervention. The emotional management mainly addresses thoughts, beliefs and behaviors related to fatigue; it is approached by cognitive behavior therapy (CBT) and sometimes combined with relaxation exercise and provided mainly by psychologists or other experts (e.g., specialized nurses). The coping with everyday tasks and duty is part of role management and is addressed by occupational therapists (OTs), who use energy conservation and management strategies, e.g., daily activity schedules, occupational balance or workload and environment adaptation. Emotional and role issues are often addressed contemporaneously and delivered by therapists from different disciplines with different practice models (e.g., nurse, psychologist, OT). While progress has been made evaluating CBT, OT or psychosocial interventions in different disease populations with fatigue [16,19–22], evaluations of the effectiveness of patient education which teaches self-management skills of persons with disease-related fatigue is lacking. What is missing is the knowledge on which intervention elements enable persons with fatigue to incorporate self-management skills into their daily routines to optimize performance, and to improve most effectively perceived fatigue and QoL. According to Plow et al. [22], this is mainly due to the complexity of the interventions (i.e. high heterogeneity of delivery modalities), the inconsistent use of labels and terminology by different disciplines and the lack of a standardized conceptual framework to describe the applied behavior change strategies. The interventions are often inconsistently described and their implementation is challenging and requires many resources [17,23]. Complex interventions like SME are difficult to evaluate because of many possible outcome dimensions, instruments and measurement time-points. Additionally, methodological biases of clinical trials (i.e. small and underpowered sample sizes, selection bias, low follow-up rate) may complicate the evaluation [17,23].

The aims of this systematic literature review were therefore to a) synthesize the effectiveness of SME to improve fatigue and QoL of persons with disease-related fatigue and b) systematically describe the intervention characteristics. The findings will inform on the possible benefits of SME and map procedures, formats and settings.

2. Materials and methods

2.1. Data sources

The present systematic literature review followed the PRISMA reporting guidelines [25]. The following databases were searched

from conception until February 3, 2021 (last search date): MEDLINE, CINAHL, PsycINFO and Scopus electronic database.

2.2. Search strategy

For search term selection, the research question was divided into persons with disease-related fatigue; patient education and its components; and QoL. These key terms were extended through synonyms (Table A1. and the detailed electronic search strategy for MEDLINE Table A2). To increase the consistency of our research results, we followed back the results from 25 systematic reviews and included all relevant studies in the initial pool of our search (table A3).

2.3. Inclusion and exclusion criteria

Articles were eligible if they met the following hierarchical inclusion criteria: (1) primary research article written in English, German, French or Italian and published in a peer-reviewed journal, (2) randomized clinical trial that provides data on effectiveness with a sample size $N \geq 30$, and (3) investigated the effect of a self-management education intervention on fatigue and QoL in people with fatigue.

2.3.1. Person-related criteria

Patients were aged > 18 years and diagnosed with any disease in which fatigue is a main symptom and is caused by the pathological processes of the disease and its treatment (e.g., cancer, multiple sclerosis, rheumatic disorders, heart failure). Fatigue severity or impact had to be assessed at baseline. We excluded studies in which only patients with a mental health disorder were eligible (e.g., depression, schizophrenia or dementia), diseases with unclear etiology due to their controversial causation theories (e.g. chronic fatigue syndrome, Gulf War veterans' illnesses) and patients with any kind of sleep disorder.

2.3.2. Intervention-related criteria

For the intervention to be classified as a SME, at least one of the following criteria had to be met [26]: (1) imparting health-related information that influences values, beliefs, attitudes and motivations, (2) achieving health or illness-related learning through knowledge acquisition, assimilation and dissemination, or (3) leading to the development of skills or lifestyle/behavior modification. The aim of the intervention had to be to improve self-management skills for disease-related fatigue and its consequences in everyday life. Therefore, interventions that aimed to reduce fatigue through exercise (e.g., fitness, yoga, relaxation, mindfulness) or companion education with other therapeutical interventions were excluded. The intervention had to be described sufficiently.

2.3.3. Outcome-related criteria

At least one self-reported QoL measurement (e.g., health-related QoL, well-being, or life satisfaction) and one fatigue assessment had to be included. We only included studies with at least 3 time points, (baseline, post intervention, follow-up) or two time points when the second time point was at least 1 month post intervention.

2.4. Study selection

Two reviewers (RH and KR) independently performed the title/abstract screening and the full-text assessment. Discrepancies were resolved by consensus. Remaining disagreements were resolved by GM.

2.5. Data extraction

The authors collaboratively developed an Excel data sheet to document and organize data from the eligible articles. From each study, RH extracted article characteristics (title, authors, year, journal), study characteristics (location, study aim, research design, sample size, outcome measures), sample characteristics (diagnosis, mean age, gender, partnership status and employment), intervention characteristics (aim, total duration, session length, frequency, delivery format, professionals involved), intervention focus (theoretical background, self-management tasks addressed and skills trained [14], and behavior change techniques (BCT) applied [27]). To improve the rating consistency of the intervention details, AW randomly rated 14 of the 26 (54%) included interventions independently, and consensus was achieved with RH by discussion if needed. RH also extracted data related to major findings on fatigue and QoL (means, SD, effect size, p-value) and recorded whether the difference between compared arms was statistically significant ($p < 0.05$) favoring the experimental arm, non-statistically significant, or statistically significant favoring the control arm. KR crosschecked all extracted data.

2.6. Data synthesis

The present systematic literature review was performed using best evidence synthesis method [24]. The results of the data extraction were synthesized by computing the mean, frequency and/or range for sample characteristics. The durations of the interventions were collapsed based on the median into short, medium and long-term interventions. The effect on QoL dimensions at post intervention and at the last reported follow-up was synthesized by computing Cohen's d with the Practical Meta-Analysis Effect Size Calculator [28] using the mean difference between the intervention and control groups (parallel arm RCT) or between pre- and post-intervention mean scores (crossover design) or p-values.

2.7. Assessment of methodological quality

We used the tool RoB_2.0 [29] to assess the risk of bias of the included studies. This tool is structured into five domains of bias: (1) bias arising from the randomization process; (2) bias due to deviations from intended interventions; (3) bias due to missing outcome data; (4) bias in measurement of the outcome; and (5) bias in selection of the reported results. Through signal questions and an algorithm, the judgments (low risk, some concern, high risk) for each risk-of-bias dimension were established, and an overall risk was identified for each included study. RH conducted the risk of bias assessment. KR crosschecked the assessment, and consensus was reached by discussion if needed.

3. Results

A total of 3182 articles were identified. After the exclusion of duplicates, 2828 titles and abstracts were screened. Of the articles retrieved for further full-text assessment, 172 were excluded (Fig. 1 and Table A4). There were large differences across the studies in terms of populations studied, intervention characteristics, outcome measures used, and follow-up periods. This precluded a statistical synthesis (meta-analysis) of the available evidence.

3.1. Characteristics of studies and study samples

The 28 articles reported on 26 RCTs (2 crossover, 24 parallel arm design) and 2 follow-ups of already included RCTs. Studies were performed between 2000 and 2019 in eight different countries on eight disease groups including multiple sclerosis [MS ($n = 10$)],

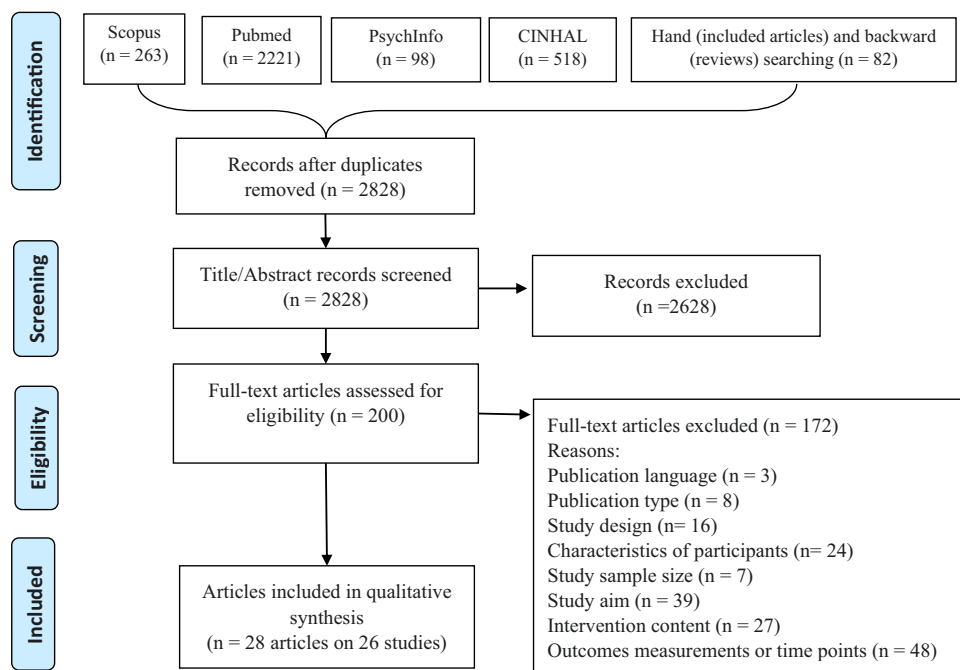


Fig. 1. Flow Diagram of literature search and article selection.

cancer (n = 8), rheumatoid arthritis [RA (n = 3)], systemic lupus erythematosus [SLE (n = 1)], heart failure [HF (n = 1)], post-polio syndrome [PPS (n = 1)], inflammatory bowel disease [IBD (n = 1)] and chronic neurological condition (n = 1), with an overall population of 3526 people. The control interventions used in these RCTs were mainly care as usual or to control for attention [30–41], alternative interventions without self-management education elements (e.g. progressive muscle relaxation) [42–44], or unspecific education through information [45–51]. Three used passive controls (waiting list) [52–55]. In two studies [43,44], the trial interventions were integrated into a multidisciplinary program. The sample size varied between 31 and 308, with a median of 113 study participants. See Table 1 for the characteristics of the pooled study population and Table 2 for the details on the study aim, sample size and experimental and control interventions for each study.

Table 1
Pooled study population characteristics for the 26 included studies.

Pooled study population: n	3526
Age (years): weighted mean (SD) / range	45.3 (7.3) / 41–65.7
Sex: female, n (range) / % (range)	2621 (25–246) / 73.3 (38–100)
Disease:	N (%)
Multiple sclerosis	1415 (51.0)
Cancer	1046 (37.7)
Rheumatoid arthritis	591 (21.3)
Systemic Lupus erythematosus	122 (4.4)
Heart failure	92 (3.3)
Chronic neurological condition	95 (3.4)
Post-polio syndrome	67 (2.4)
Inflammatory bowel disease	98 (3.5)
Partnership status:	n (%)
Living with someone	1467 (41.6)
Living alone	463 (13.1)
Not stated	1596 (45.2)
Employment:	n (%)
Employed	1060 (30.1)
Not employed	1330 (37.7)
Not stated	1137 (32.2)

Abbreviations: SD: standard deviation, n: number

3.2. Intervention characteristics

The aim of all 26 interventions was to reduce the impact of fatigue on patients' daily life through patient education and behavior changes. The intervention characteristics, the delivery modalities and the involved health professionals varied considerably between the interventions (Table 3). Seven intervention protocols [42,43,44,49,51–53] used the energy conservation and management approach based on Packer et al. [58], 7 were based on evidences and models of CBT [32,36,38,40,41,45,47]. The remaining 12 interventions were a combination of these approaches or guided by other theories. For all interventions, the active patient involvement and his/her self-management capability were core elements. The focus of the education and the issues addressed were most frequently a combination of emotional and role management tasks (12 studies, 46%)[30–32,37,38,41,45–48,50,54]. Eight studies (31%) [39,42–44,49,51–53] focused on role performance only, one (4%) [40] addressed medical and role-management tasks, while the remaining five studies (19%) [33–36,55] considered all three types of tasks. The most frequently addressed self-management skill was *taking action* (n = 25) followed by *problem solving* (n = 22) and *decision-making* (n = 21), half of the interventions taught also *using resources* (n = 9) and 11 out of 26 interventions addressed *communication with health professionals* skills too. The 26 SMEs used a different number and different combinations of the 26 BCTs [mean (SD) / median: 13 (3) / 12] described by Michie et al. [27]. *Information on the consequences of fatigue and encouragement of patients* were applied by 25 and *intention formation* by 24 out of 26 SMEs. Other frequently applied BCTs were *self-monitoring* (n = 23), *practice* (n = 19), *instruction* (n = 19), *goal setting and goal reviewing* (n = 18), while *relapse prevention* (n = 3) and *contingent rewards* (n = 2) were used rarely (Table A5).

The range of the duration [mean/IQR (h): 7.7 / 3:12] and the frequency [mean/IQR (weeks): 13.4 / 6: 18] were broad. The shortest intervention [46] had a total duration of one hour (3 sessions over 3 weeks), while the longest [51] lasted 17.5 h in total (6 × 2.5 h over 6 weeks). Out of 26 interventions, seven had a short (<4.7 h) [30,33,35,42,45,46,50], six a medium (4.7–9.4 h)[32,36,43,48,49,52]

Table 2
Study characteristics of the 26 studies reported in the 28 included articles.

First author (Publication year) Origin country, time period study conduct	Study population	General study focus/aim	Study design, center (n)	Gender [% females]	Age [mean] (SD)	Partnership status [% Living with someone]	Employment [% employed]	Sample sizes (n)	Experimental intervention	Control intervention
Given et al. [36] (2002) USA, ns	Cancer patients	To compare data from a supportive nursing intervention plus conventional care versus conventional care alone among patients undergoing chemotherapy	2 arms, parallel-groups RCT, (4)	71.7	58.2 (10.2)	77.0	22.1	113	Conventional care + supportive care intervention	Conventional Care
Yates et al. [46] (2005) Australia, 2000–2002	Cancer patients	To evaluate the efficacy of a brief targeted intervention that incorporates educative and supportive strategies to assist patients to develop knowledge and skills to engage in self-care behaviors.	2 arms, parallel-groups RCT, (3)	100.0	49.4 (9.4)	92.7	41.3	109	Psychoeducational intervention	General cancer education
Ream et al. [31] (2006) UK, ns	Cancer patients	To test a one-to-one, in person, intervention that aimed to educate and support patients in initiating self-care measures for managing fatigue during chemotherapy.	2 arms, parallel-groups RCT, (2)	44.7	56.5 (10.1)	66.0	30.1	103	Supportive intervention for fatigue	Standard care
Armes et al. [30] (2007) UK, 2001–2003	Cancer patients	To test if behaviorally oriented intervention is superior to usual care in reducing cancer related fatigue.	2 arms, parallel-groups RCT, (1)	60.0	59.0 (11.3)	85.5	ns	55	Brief, behaviorally oriented intervention	Standard care
Goedendorp et al. [40] (2010) Netherlands, 2005–2007	Cancer patients	To determine the efficacy of a brief nursing intervention or an extensive intervention aimed at fatigue based on CBT compared with usual care	3 arm, parallel-groups RCT, (6)	63.0	56.7 (10.8)	81.0	ns	220	intervention based on CBT	brief nursing intervention / care as usual
Purcell et al. [35] (2011) Australia, 2008–2009	Cancer patients	To test if providing pre-post radiotherapy fatigue education and support (RFES) reduced severity of fatigue experienced at the end and 6 weeks after radiotherapy.	factorial, 4 arms, parallel-groups RCT, (1)	47.2	58.8 (2.3)	ns	ns	53	CRF education intervention	Standard care
Reif et al. [54] (2013) Germany, 2008–2010	Cancer survivors	To evaluate a patient education program that aims at reducing perceived fatigue in cancer survivors.	2 arms, parallel-groups RCT, (10)	79.9	57.7 (10.1)	67.1	41.5	234	Self-management program for CFR	Waiting list
Foster et al. [45] (2016) UK, 2012–2013	Cancer survivors	To test the proof of concept of RESTORE, a web-based resource designed to increase self-efficacy to manage cancer related fatigue	2 arms parallel-groups RCT, (12)	76.7	57.8 (9.9)	ns	56.6	159	Web-based intervention to support self-management (RESTORE)	Leaflet
Mathiowetz et al. [53] (2005) USA, 2002–2003	Multiple sclerosis patients	To assess the short term efficacy and effectiveness of ECM on quality of life, fatigue and self-efficacy in patients with MS-related fatigue	2 arms cross over RCT, (1)	82.8	48.3 (8.4)	ns	42.0	169	Energy conservation course	Waiting list
Mathiowetz et al. [57] (2007) USA		to report the 1-year follow-up of Mathiowetz (2005)								
Finlayson [52] (2011) USA, 2007–2009	Multiple sclerosis patients	To test the effectiveness and efficacy of an teleconference	2 arms cross over RCT, (1)	79.0	56.0 (9.0)	ns	27.6	181	Teleconference- fatigue management program	Waiting list

(continued on next page)

Table 2 (continued)

First author (Publication year) Origin country, time period study conduct	Study population	General study focus/aim	Study design, center (n)	Gender [% females]	Age [mean] (SD)	Partnership status [% Living with someone]	Employment [% employed]	Sample sizes (n)	Experimental intervention	Control intervention
Thomas et al. [32] (2013) UK, 2008–2009	Multiple sclerosis patients	fatigue management program for people with MS. To evaluate the effectiveness and cost-effectiveness of FACETS when added to current local practice	2 arm, parallel-group RCT, (3)	72.6	49.0 (10.1)	71.3	35.4	164	Intervention applying cognitive behavioral + energy effectiveness techniques	Current local practice
Thomas et al. [56] (2014) UK		To report the 1-year follow-up of Thomas (2013)								
Ehde et al. [48] (2015) USA, 2011–2013	Multiple sclerosis patients	To evaluate the efficacy of a telephone-delivered SMI designed to help adults with MS effectively manage fatigue, chronic pain, and/or depression.	2 arms, parallel-groups RCT, (1)	87.1	52.2 (10.0)	61.3	88.3	163	Telephone self-management	Telephone MS education
Kos et al. [42] (2016) Belgium, 2011–2014	Multiple sclerosis patients	To evaluate the effectiveness of an individual self-management occupational therapy intervention program versus relaxation on the performance of and satisfaction with relevant daily activities in patients with MS-related fatigue.	2 arms parallel groups RCT, (1)	ns	41.0 (9.2)	ns	ns	31	Self-management occupational therapy	Progressive muscle relaxation
Blikman et al. [49] (2017) Netherlands, 2011–2014	Multiple sclerosis patients	To test the effectiveness of an individual ECM intervention on fatigue and participation in persons with primary MS-related fatigue.	2 arms parallel-groups RCT, (1)	74.4	47.1 (11.2)	ns	ns	86	Individual energy conservation management	Information only, 3 MS nurse consultations
Van den Akker et al. [41] (2017) Netherlands, 2011–2014	Multiple sclerosis patients	To assess the effectiveness of CBT in decreasing fatigue and improving societal participation in patients with multiple sclerosis compared to nurse consultations.	2 arm, parallel-groups RCT, (3)	76.0	48.5 (9.9)	73.6	40	91	Cognitive behavioral therapy	MS nurse consultation
Pöttingen et al. [55] (2018) Germany, 2014	Multiple sclerosis patients	To evaluate the efficacy of a self-guided online fatigue intervention in multiple sclerosis	2 arm, parallel-groups RCT, (1)	80.7	41.3 (10.2)	71.3	49	275	self-guided online fatigue intervention in MS (ELEVIDA)	Waiting list
Plow et al. [44] (2019) USA, ns	Multiple sclerosis patients	To compare the effectiveness of telephone-delivered interventions on fatigue, physical activity, and quality of life outcomes in adults with MS related fatigue	3 arms parallel-groups RCT,(1)	84.6	52.1 (8.4)	83.7	38.9	208	Fatigue self-management plus physical activity	Physical activity only / contact-control social support intervention
Hersche et al. [43] (2019) Switzerland, 2017–2018	Multiple sclerosis patients	To assess the feasibility and changes in outcomes of IEME compared to PMR in patients with MS related fatigue.	2 arms parallel groups RCT, (1)	66.0	51.2 (1.95)	76.6	48.9	47	Rehabilitation + energy management education	Rehabilitation + Progressive muscle relaxation
Ghahani et al. [51] (2010) Australia, 2007–2008	Patients with chronic neurological conditions	To test the effectiveness of the new online version of the fatigue self-management program.	3 arms, parallel-groups RCT, (1)	81.1	50.2 (12.3)	ns	34.7	95	Online fatigue Self-management program	Online information only(No treatment)
Zuidema et al. [34] (2019) Netherlands, 2014–2015	Rheumatoid arthritis patients	To evaluate the efficacy of a Web-based self-management enhancing program for patients with rheumatoid arthritis.	2 arms, parallel-groups RCT,(2)	65.6	ns	ns	42	157	Care as usual + Web-rheumatoid arthritis self-management	Care as usual
Hewlett et al. [47] (2011) UK, ns	Rheumatoid arthritis patients	To test group CBT fatigue self-management program vs. groups management program for patients with rheumatoid arthritis.	2 arms, parallel-groups RCT, (1)	73.8	59.2 (11.3)	ns	ns	126	CBT-group for fatigue self-management	1 h didactic group session (continued on next page)

Table 2 (continued)

First author (Publication year) Origin country, time period study conduct	Study population	General study focus/aim	Study design, center (n)	Gender [% females]	Age [mean] (SD)	Partnership status [% Living with someone]	Employment [% employed]	Sample sizes (n)	Experimental intervention	Control intervention
Hewlett et al. [37] (2019) UK, ns	Rheumatoid arthritis patients	receiving fatigue information alone in people with RA To assess impact of fatigue between a group cognitive behavior self-management course for rheumatoid arthritis fatigue compared to usual care alone	2 arms, parallel-groups RCT,(7)	79.9	ns	ns	ns	308	Reducing Arthritis Fatigue	Care as usual
Koopman et al. [38] (2016) Netherlands, 2009–2012	Patients with post-polio syndrome	To investigate the efficacy of exercise therapy andCBT in patients with post-polio syndrome on fatigue and quality of life compared to care as usual	3 arm, parallel-groups RCT, (7)	54.5	59.0 (8.1)	52.0	73.1	67	Cognitive behavioral therapy	Care as usual / Exercise therapy
Vogelaar et al. [39] (2014) Netherlands, 2010–2011	Inflammatory bowel disease patients	To assess whether solution focused therapy is more effective in improving fatigue and QoL than care as usual (CAU) in people with inflammatory bowel disease	2 arm, parallel-groups RCT, (2)	63.0	41.1 (10.3)	ns	ns	98	Solution focused therapy	Care us usual
Karlson et al. [50] (2004) USA, ns	Systemic lupus erythematosus patients	To test psycho educational intervention to improve patient self-efficacy, partner support, and problem-solving skills of the patient-partner pair to manage systemic lupus erythematosus.	2 arms, parallel-groups RCT, (2)	97.5	41.8 (11.3)	ns	ns	122	Psycho-educational Intervention in groups	Attention placebo (45 min video + monthly telephone calls)
Wang et al. [33] (2016) Taiwan, 2012	Heart failure patients	To investigate the effects of a supportive educational nursing care program on fatigue and quality of life in patients with heart failure.	2 arms, parallel-groups RCT, (1)	38.0	65.8 (0.2)	94.6	19.6	92	Supportive educational nursing	Routine nursing care

Abbreviations: CBT: cognitive behavioral therapy, MS: multiple sclerosis, RCT: randomized clinical trial, ns: not stated, CRF: cancer related fatigue, RA: rheumatoid arthritis

Table 3
Overview of intervention characteristics of the 26 studies reported in the 28 included articles.

First author / diseases	Aim of experimental intervention	Underlying approach, model, or theory	SM-tasks addressed		Problem solving	SM-skills trained		Communication health prof.	Delivery modalities		Lead of intervention	Home-work / self-training
			Medicale	Emotional		Role	Using resources		Place	Setting		
Given [36] cancer	to acquire knowledge, skills, behavioral reframing, how to manage experienced problems	CBT, supportive counseling, self-care management	✓	✓	✓	✓	✓	✓	Out	Face to face + telephone	Individual + caregiver	Nurse
Yates [46] cancer	to improve patients' knowledge and skills to perform self-care behaviors designed to minimize fatigue management through energy management	PRECEDE model of health behavior [63]	✓	✓	✓	✓	✓	✓	Out	Face to face + telephone	Individual	Nurse
Ream [31] cancer	to alter fatigue-related behavior	Energy conservation Psychobiological model [60]	✓	✓	✓	✓	✓	✓	Out	Face to face	Individual	cancer nurse ✓
Armes [30] cancer	to avoid deconditioning, dysfunctional cognitions about fatigue and to cope with the consequences of having cancer.	Fear-avoidance model of symptom management model of precipitating and perpetuating factors [66]	✓	✓	✓	✓	✓	✓	Out	Face to face	Individual	Nurse ✓
Goedendorp [40] cancer	to employ self-care behaviors designed to minimize fatigue to achieve behavior modifications and impact health-related self-efficacy	Health Belief Model	✓	✓	✓	✓	✓	✓	Out	Face to face	Individual	ns
Purcell [35] cancer	to increase participant's self-efficacy to manage CRF	Self-efficacy theory [59], CBT, evidence of fatigue management in cancer survivors	✓	✓	✓	✓	✓	✓	Out	Face to face	Group	Nurse + Psy ✓
Reif [54] cancer	to teach how to manage energy	de Vries et al. [61]	✓	✓	✓	✓	✓	✓	Out	Face to face	Group	Nurse + Psy ✓
Foster [45] cancer	to teach participants how to manage energy	Self-efficacy theory [59], CBT, evidence of fatigue management in cancer survivors	✓	✓	✓	✓	✓	✓	Home	On-line	Remote	No instructor ✓
Mathiowetz [53,57] MS	to teach participants how to manage energy	Energy conservation strategies [58]	✓	✓	✓	✓	✓	✓	Out	Face to face	Group	OT ✓
Finlayson [52] MS	to teach participants how to manage energy	Energy conservation strategies [58]	✓	✓	✓	✓	✓	✓	Home	Telephone	Group	OT ✓

(continued on next page)

Table 3 (continued)

First author / diseases	Aim of experimental intervention	Underlying approach, model, or theory	SM-tasks addressed		Role solving	SM-skills trained		Communication health prof.	Taking action	Duration and frequency: Sessions (n) x min, total duration [h], over (n) weeks	Delivery modalities		Lead of intervention	Home-work / self-training	
			Medicale	Emotional		Decision-making	Using resources				Place	Setting			Inter-action
Thomas [32,56] MS	to normalize the experience of fatigue, to use energy more effectively, to develop helpful thinking	CBT-Model, development project	✓	✓	✓	✓	✓	✓	✓	Medium: 6 x 90, [9], 6	Out	Face to face	Group	HP	✓
Ehde [48] MS	to learn, apply SM-skills	Energy conservation strategies [58], CBT	✓	✓	✓	✓	✓	✓	✓	Medium: 8 x 60, [8], 8	Home	Telephone	Individual	SW + Psy	✓
Kos [42] MS	to achieve control over performance within the limits of energy, to increase self-efficacy in fatigue management	Energy conservation strategies [58], Self-Management [14]	✓	✓	✓	✓	✓	✓	✓	Short: 3 x 60–90, [± 4], 3	Out	Face to face+ telephone	Individual	OT	✓
Blikman [49] MS	to promote attitude optimum use of the available energy	Energy conservation strategies [58]	✓	✓	✓	✓	✓	✓	✓	Medium: 12 x 45, [9], 18	Out	Face to face	Individual	OT	✓
Van den Akker [41] MS	to influence dysfunctional behavioral cognitions, behaviors and emotions that perpetuate fatigue, to learn how control and modify the factors that influence fatigue	Cognitive behavioral model of MS-fatigue [66]	✓	✓	✓	✓	✓	✓	✓	Long: 12 x 45, [9], 18	Out	Face to face	Individual	Psy	✓
Pöttgen [55] MS	to increase outcomes of fatigue impact, physical activity, and health-related quality of life.	based on evidence-based CBT principles	✓	✓	✓	✓	✓	✓	✓	Self-tailored x 30–60, [ns], 12	Home	On-line	Remote	developer team	✓
Plow [44] MS	to manage available energy and to achieve a satisfying and meaningful daily routine	Energy conservation and management strategies [58]	✓	✓	✓	✓	✓	✓	✓	10 x (ns), [ns], 12	Home	Telephone	Individual + 1x group	OT	✓
Hersche [43] MS	to learn SM of fatigue	Energy management [58], scientific evidence	✓	✓	✓	✓	✓	✓	✓	Medium: 6 x 60 + 1 x 30, [6.5], 3	In	Face to face	5x Group + 2x Individual	OT	✓
Ghahari [51] NCD	to learn SM of fatigue	Energy conservation strategies [58]	✓	✓	✓	✓	✓	✓	✓	Long: 7 x 2.5, [17.5], 7	Home	On-line	Individual + peer	OT	✓
			✓	✓	✓	✓	✓	✓	✓		Home	On-line	Remote	No instructor	✓

(continued on next page)

Table 3 (continued)

First author / diseases	Aim of experimental intervention	Underlying approach, model, or theory	SM-tasks addressed		Problem solving	SM-skills trained		Delivery modalities		Lead of intervention	Home-work / self-training			
			Medicale	Emotional		Role	Decision-making	Using resources	Communication health prof.			Taking action	Place	Setting
Zuidema [34] RA	to enhance patients' ability to self-manage their disease and thus improve their quality of life.	Theory of planned behavior [65]	✓	✓	✓	✓	✓	✓	ns (self-tailored)					
Hewlett [47] RA	to turn cognitive and behavioral changes into improved well-being	CBT, SM [14], experiences from clinicians and patients	✓	✓	✓	✓	✓	✓	Long: 6 × 120 + 1 × 60 [13], S1-6 weekly, S7 week 14	Out	Face to face	Group	Psy + OT	✓
Hewlett [37] RA	to modify factors which influence RA-fatigue and its impact	Framework for complex interventions [64] Integration of CB-approaches, theory of self-efficacy [59]	✓	✓	✓	✓	✓	✓	Long: 6 × 120 + 1 × 60 [13], S1-6 weekly, S7 week 14	Out	Face to face	Group	Nurse + OT	✓
Koopman [38] PPS	to modify the perpetuating factors of fatigue	cognitive behavioral model of MS-fatigue [66]	✓	✓	✓	✓	✓	✓	Long: Self-tailored at least 1. max. 16 × 60 [± 14], 18	Out	Face to face	Individual	Psy	✓
Vogelaar [39] IBD	to focus on the existing adequate coping abilities of patients, rather than on their problems	modified to focus on fatigue management [67]	✓	✓	✓	✓	✓	✓	Long: 6 × 90 [9], (13) last week 27	Out	Face to face	Group	Psy	
Karlson [50] SLE	to improve self-efficacy, problem-solving skills to manage SLE	Self-efficacy theory [59]	✓	✓	✓	✓	✓	✓	Short: 1 × 45 + 5 × 20, [2.75], 26	Out	+ Home	Face to face + telephone	Individual + caregiver	Nurse
Wang [33] HF	to achieving an optimal balance between restorative and restorative energy	Supportive intervention [31] Symptom model [62]	✓	✓	✓	✓	✓	✓	Short: 4 × 30, [2], 12	Out	Face to face	Individual	Nurse	✓

Abbreviation: MS: multiple sclerosis, RA: rheumatoid arthritis, SLE: systemic lupus erythematosus, NCD: neurological chronic disease, HF: Heart failure, PPS: Post-polio syndrome, IBD: Inflammatory bowel disease, CRF: cancer-related fatigue, SM: Self-management, CBT: Cognitive Behavioral therapy, BCT: Behavior Change Techniques, S: session, OT: occupational therapist, HP: Health professional, SW: Social worker, Psy: Psychologist, ✓: declared, ns: not stated

and nine a long duration (>9.4 h) [37,38–41,47,51,53,54]. The remaining three interventions were self-tailored [34,38,55], or the duration was not clearly reported [31]. The majority of the interventions were performed in an outpatient setting (17/65%), seven at home (on-line, telephone or home visit), one used a combination [50] and one [43] was performed during an inpatient period. In this sample, 42% of the interventions used an individual interaction between patient and therapist [30,31,33,35,38,40–42,46,48,49], 27% used peer groups [32,37,39,47,52–54], 19% used both forms of interaction [36,43,44,50,51] while 12% [34,45,55] did not include any communication with an health professionals or peers (remote). The interaction was mostly face-to-face (n = 15), while other modalities were by phone (n = 3), online (n = 4), or a combination of different modalities (n = 4). In summary, 9 interventions (35%) were delivered face to face with an individual interaction in an outpatient setting [30,31,33,35,38,40–42,49], while six (23%) had a face to face group interaction in an outpatient setting [32,37,39,47,53,54]. The remaining 11 (42%) protocols had other types of combinations of intervention characteristics (online and telephone interventions, group and individual interaction). The delivering professionals were mainly OTs (n = 9), nurses (n = 8) and psychologists (n = 7) after a specific training or with experience in the field. In four interventions [37,47,48,54], a pair of professionals led the sessions. In 69% (18/26) of the interventions, homework and/or self-training/monitoring was a declared part.

3.3. Effects on fatigue and quality of life

In this sample of 26 complex SMEs, the time point of assessment varied according to the intervention duration and the study design (Table 4). There were six studies with one year [34,41,49,50,56,57] and one with two year follow-up data [37]. The remaining studies had a latency of 2.5–10 months with a median of 4 months from baseline to follow-up. Fatigue impact or severity were measured through self-reported questionnaires and were the primary outcome for most of the RCTs (n = 21). Regarding the outcome fatigue, 50% of the studies [30,31,33,36,37,39,41,44,46,52–55] showed a positive effect reporting statistically significant differences ($p < 0.05$) in favor of the experimental intervention at post intervention. Out of them, seven [31,37,41,52–55] maintained the positive effect while five [32,40,47,50,51] reported positive effects only at follow-up. In summary, 8 (30%) [34,35,38,42,43,45,48,49] of the included studies showed no effect on fatigue at any of the measured time-points.

QoL was measured with multidimensional questionnaires in most studies; half of the included studies used the Short Form Health Survey (SF36). Twelve out of 26 studies (46%) showed in at least one dimension a statistically significant positive effect and eight maintained the significant difference compared to the control intervention at follow-up. In summary, 38% of the included studies showed no effect on QoL at any of the measured time-points. Five out of 26 studies (20%) [35,38,45,48,49] showed no effect for fatigue or QoL. In the subgroup of studies with people with cancer, 6 out of 8 studies; (including 80% of the pooled cancer population, n = 834) [30,31,36,40,46,54] reported a significant effect on fatigue and 5 out of 8 (59%) [30,31,36,40,54] on QoL. In the subgroup of studies with persons with MS, 6 out of 10 studies (65% of the pooled MS-population, n = 924) [32,41,44,52,53,55] showed an effect on fatigue and 7 out of 10 (68%) [32,41–43,52,53,55] on QoL. Two out of three studies including persons with RA showed a significant decrease in fatigue (73% of the pooled RA-population, n = 434) and 1 out of 3 significantly improved QoL (27%).

3.4. Risk of bias

The overall risk of bias was low for 11 (42%) studies [30,32,37,41,45,48–50,54,55]. In four studies [36,38,39,42], the

randomization process was not clear, in six studies [31,33,35,36,43,46], the analysis performed to estimate the effect of assignment was inappropriate, and for eight trials [31,34,43,44,47,51–53] less than 95% of outcome data from the randomized persons were available. In three trials [31,36,43], the bias accumulation was judged as high risk (Table 4).

3.5. Statistically significant improvements and intervention characteristics

Regarding delivery modalities, 10 out of 15 SMEs (67%) with individual [30,31,33,36,40,41,44,46,50,51], 7 out of 8 (88%) with peer group [32,37,39,47,52–54], and 1 out of 3 (33%) with a remote [55] interaction found statistically significant improvements on fatigue. The pink box in the column “group” in the outcome fatigue indicates the study of Reif et al. [54] with a sample of 234 cancer patients that found a significant improvement on fatigue. For QoL, 9 out of 15 SMEs (60%) with individual [30,31,33,36,40–42,50,51], 6 out of 8 (75%) with peer group [32,39,43,52–54], and 2 out of 3 (67%) with remote [34,55] interaction reported statistically significant improvements (Fig. 2).

Regarding the duration (Fig. 3), short SMEs (<4.7 h) showed in 4 out of 7 studies (57%) [30,33,46,50] statistically significant improvement on fatigue. SMEs with a medium duration (4.7–9.3 h) showed a statically significant improvements on fatigue in 3 out of 6 studies (50%) [32,36,52], and those with a long duration (>9.3 h) in 8 out of 9 studies (89%) [37,39–41,47,51,53,54]. Four out of 7 studies (57%) with short [30,33,42,50], 4 out of 6 (67%) with medium [32,36,43,52], and 6 out of 9 (67%) [39–41,51,53,54] with long duration reported statically significant improvements on QoL.

3.6. Effect size of fatigue self-management education on quality of life

In terms of the effect size, nine studies [35,37,40,44–59] reported a change in QoL at post intervention corresponding to no practical effect ($d < 0.2$). Of the remaining studies, nine reported a small ($d \geq 0.2$) [32–34,36,38,39,50–52], six at least a medium ($d \geq 0.5$) [30,31,41–43,55] and two also large effects ($d \geq 0.8$) [53,54] in one or more measured dimensions of QoL. At the last follow-up, 80% (n = 21) of studies reported no or a small effect. One study [57] maintained a medium effect and four [30,42,43,54] maintained or increased towards a large in at least one subscale. The dimensions, which were most often affected positively and strongly, were related to mental health (SF36: vitality, mental health, emotional functioning, and social functioning). In contrast, those related to physical health (physical functioning, role functioning, bodily pain, general health) were less often positively affected and the effect sizes were smaller (Table 5).

4. Discussion and conclusion

4.1. Discussion

In this systematic review, we provide a comprehensive overview of the effectiveness of SME on fatigue and QoL in people living with disease-related fatigue. Moreover, we summarize the most relevant information regarding the intervention characteristics and the delivery modalities of the 26 included studies, which covered eight different disease populations with MS, cancer, and RA being the main disease groups.

The overall evidence on the effectiveness of SMEs on fatigue and QoL based on the 26 included RCTs is unclear. While the data for cancer and MS are promising, the evidence for the other diseases remain limited and inconsistent. Additionally, there is a considerable risk of bias in some of the included studies. This is in line with the findings from Farraghe et al. [69] who reported a lack of robust RCTs

Table 4
Effects on fatigue and quality of life post-intervention and at follow-up, and risk of bias for the 26 studies reported in the 28 included articles.

Disease	First author	Sample analyzed (n) EG / CG1 / CG2	Time point of assessment weeks (n) from baseline	Fatigue outcome instrument	Quality of life outcome instrument	Effects on fatigue		Effects on quality of life		Risk of bias						
						PI	FUP	PI	FUP	R	D	MI	ME	S	O	
Cancer	Given [36]	53/59	10 ^a / 20	Symptom Experience Scale	Short Form Health Survey (SF36; PF, SF)	+	+	+	+	—	—	✓	✓	—	—	HR
	Yates [46]	49/48	7 (PI) / 10 / 14	Fatigue experience, fatigue-management behavior ¹	EORTC QLQ-C30	+	+	+	+	✓	—	✓	✓	✓	—	SR
	Ream [31]	43/43	4.5 / 9 / 13 (PI)	Fatigue VAS ¹	SF36 (reported only MH and VF)	+	+	+	+	✓	—	✓	✓	✓	—	HR
	Armes [30]	28/27	12 (PI) / 16 / 39	Global Fatigue (VAS-F) ¹ , Fatigue Outcome Measure (FOM), Multidimensional Fatigue Inventory (MFI)	EORTC-QLQ-C30 (PF only) + subscale Fatigue	+	+	+	+	✓	✓	✓	✓	✓	—	LR
	Goedendorp [40]	82 / 77 / 81	NA / 27	Fatigue subscale of checklist Individual Strength (CIS) ¹	EORTC QLQ-C30	NA	+	NA	+	✓	✓	✓	✓	—	—	SR
	Purcell [35]	21/24	5 (PI) / 11	Multidimensional Fatigue Inventory (MFI) ¹	EuroQual-5D (EQ-5D) + VAS	+	+	+	+	✓	—	✓	✓	✓	—	SR
	Reif [54]	120/114	6 (PI) / 31	Fatigue Assessment Questionnaire (FAQ) ¹	EORTC QLQ-C30 questionnaire	+	+	+	+	✓	✓	✓	✓	✓	—	LR
	Foster [45]	83 / 76	6 (PI) / 12	Brief Fatigue Inventory (BFI)	Personal Wellbeing Index (PWI)	+	+	+	+	✓	✓	✓	✓	✓	—	LR
	Mathiowetz [53,57]	78/91	7 (PI) / 13 / 65	Fatigue Impact scale (FIS) ¹	Short Form Health Survey (SF36)	+	+	+	+	✓	✓	✓	✓	✓	—	SR
	Finlayson [52]	94 / 96	6 (PI) / 19 / 19 / 32	Fatigue impact scale (FIS) ¹ , Fatigue severity scale (FSS)	Short Form Health Survey (SF36)	+	+	+	+	✓	✓	✓	✓	✓	—	SR
MS	Thomas [32,56]	84/80	11 (PI) / 24 / 52	Global Fatigue severity (subscale of FAI) ¹	Short Form Health Survey (SF36)	+	+	+	+	✓	✓	✓	✓	✓	—	LR
	Ehde [48]	75 / 88	10 (PI) / 26 / 52	Modified Fatigue Impact scale (MFIS) ¹	Short Form Health Survey (SF8)	+	+	+	+	✓	✓	✓	✓	✓	—	LR
	Kos [42]	17/14	3 (PI) 16	Modified fatigue impact scale (MFIS) ¹ , Fatigue Checklist Individual Strength (CIS-20R)	Short Form Health Survey (SF36)	+	+	+	+	✓	✓	✓	✓	✓	—	SR
	Blikman [49]	42 / 44	8 / 16 (PI) / 26 / 52	Checklist Individual Strength (CIS20r) ¹ , Modified Fatigue Impact scale (MFIS), Fatigue severity scale (FSS)	Short Form Health Survey (SF36)	+	+	+	+	✓	✓	✓	✓	✓	—	LR
	Van den Akker [41]	44 / 47	16 (PI) / 26 / 52	Checklist Individual Strength (CIS20r) ¹ , Fatigue severity scale (FSS), Modified Fatigue Impact scale (MFIS)	Short Form Health Survey (SF36)	+	+	+	+	✓	✓	✓	✓	✓	—	LR
	Pöttgen [55]	139 / 136	12 (PI) / 40	Chalder Fatigue Scale ¹ , Fatigue Scale for Motor and cognitive Functions (FSMC)	Hamburg Quality of Life Questionnaire for MS (HAQUAMS)	+	+	+	+	✓	✓	✓	✓	✓	—	LR
	Plow[44]	70/69/69	14 (PI) / 26	Fatigue Impact Scale (FIS) ¹	Multiple Sclerosis Impact Scale (MSIS)	+	+	+	+	✓	✓	✓	✓	✓	—	SR
	Hersche [43]	18/17	3 (PI) / 17	Modified Fatigue Impact Scale (MFIS)	Short Form Health Survey (SF36)	+	+	+	+	✓	✓	✓	✓	✓	—	HR

(continued on next page)

Table 4 (continued)

Disease	First author	Sample analyzed (n) EG / CG1 / CG2	Time point of assessment weeks (n) from baseline	Fatigue outcome instrument	Quality of life outcome instrument	Effects on fatigue		Effects on quality of life		Risk of bias							
						PI	FUP	PI	FUP	R	D	MI	ME	S	O		
NC	Ghahari [51]	34 / 28 / 33	7 (PI) / 12	Fatigue impact scale (FIS) ¹	Personal Wellbeing Index (PWI)	+	+	+	+	✓	✓	✓	✓	✓	✓	✓	SR
RA	Zuidema [34]	78 / 79	26 ¹ / 52	Level of fatigue (Numeric Rating Scales)	Short Form Health Survey (SF36)	+	+	+	+	✓	✓	✓	✓	✓	✓	✓	SR
	Hewlett[47]	65 / 62	NA ³ / 18	Multi-Dimensional Assessment of Fatigue scale (MAF) ¹	RA Quality-of-Life scale	NA	NA	NA	NA	✓	✓	✓	✓	✓	✓	✓	SR
	Hewlett[37]	157 / 158	26 ^a / 52 / 78 / 104	Bristol RA Fatigue Effect (BRAFE) ¹	Global question	+	+	+	+	✓	✓	✓	✓	✓	✓	✓	LR
PPS	Koopman [38]	23 / 23	18 (PI) / 31 / 45	Fatigue Questionnaire (CIS20-F) ¹	Short Form Health Survey (SF36)	+	+	+	+	✓	✓	✓	✓	✓	✓	✓	SR
IBD	Vogelaar [39]	49 / 49	27 (PI) / 40	Checklist Individual Strength (CIS) ¹ ; Fatigue severity scale (FSS); Modified Fatigue Impact scale (MFIS)	Short Form Health Survey (SF36)	+	+	+	+	✓	✓	✓	✓	✓	✓	✓	SR
SLE	Karlson [50]	64 / 58	26 (PI) / 52	Fatigue scale for Lupus patients	Short Form Health Survey (SF36)	+	+	+	+	✓	✓	✓	✓	✓	✓	✓	LR
HF	Wang [33]	38 / 37	4 / 8 / 12 (PI)	Piper fatigue scale (PFS) ¹	Minnesota living with heart failure questionnaire (MLHFQ)	+	+	+	+	✓	✓	✓	✓	✓	✓	✓	SR

Abbreviations: MS: multiple sclerosis, RA: rheumatoid arthritis, SLE: systemic lupus erythematosus, NCD: neurological chronic disease, HF: Heart failure, PPS: Post-polio syndrome, IBD: Inflammatory bowel disease
^a: Not immediately post intervention, ¹: primary outcome, PI: post intervention, FUP: follow-up, ✓: significant positive differences, ◊: no significant differences, NA: not applicable
Risk of bias: ◊: no risk, ◊◊: some concerns: R: Bias arising from the randomization process, D: Bias due to deviations from intended interventions, MI: Bias due to missing outcome data, ME: Bias in measurement of the outcome, S: Bias in selection of the reported result, O: Overall risk of bias, LR: low risk, SR: some risk, HR: high risk

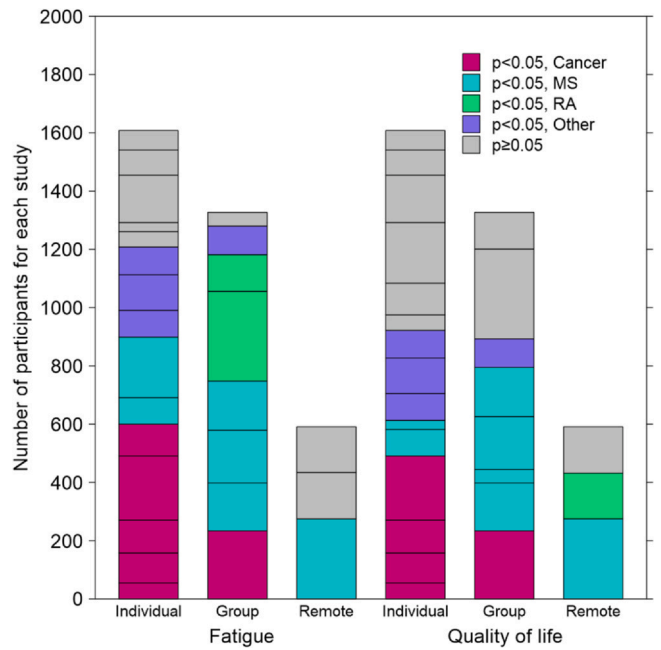


Fig. 2. Improvements in fatigue and quality of life for different delivery modalities and disease groups. Caption: Number of participants for each study with statistically significant improvement on fatigue and QoL. Studies are grouped according to delivery modalities. Abbreviations: MS: multiple sclerosis, RA: rheumatoid arthritis, p < 0.05: statistically significant p > = 0.05: not statistically significant.

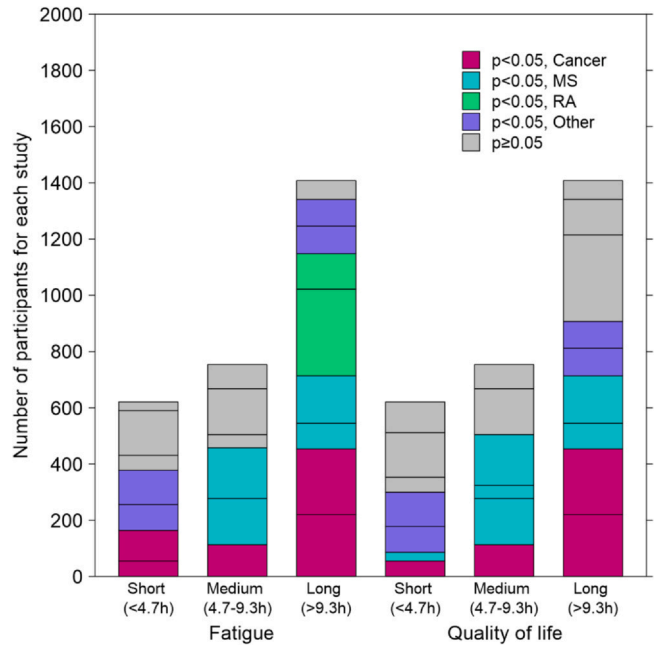


Fig. 3. Improvements in fatigue and quality of life for SMEs with different durations and disease groups. Caption: Number of participants for each study with statistically significant improvements on fatigue and QoL. Studies are grouped according to duration. Abbreviations: MS: multiple sclerosis, RA: rheumatoid arthritis, p < 0.05: statistically significant, p > 0.05: not statistically significant.

for energy management education in chronic diseases. However, only a few RCTs reported no effect at all. Considering the subgroup of 18 studies (8 with high quality) including persons with cancer (8 studies) and MS (10 studies), the evidence is moderately consistent showing positive effects in favor of SME. The proportions of studies with positive effects within these two disease populations (cancer

Table 5

Effect sizes (d) for effects on global QoL or QoL-dimensions at post intervention and follow-up for the different QoL measurements. Color key: white: no practical effect (< 0.2), orange: small (> 0.2), blue: medium (> 0.5), green: large (> 0.8) effect (according to [68]).

First author (Disease) / Quality of life measurement	Effect on quality of life dimensions or of global QoL: effect size (d)														Analysis					
	First post intervention (PI)										Last follow-up (FUP)									
	PF	RP	BP	VT	SF	RE	MH	GH	PCS	MCS	PF	RP	BP	VT		SF	RE	MH	GH	PCS
SF36 / 8																				
Kos [42] (MS)	0.25	-0.32	0.51	0.01	-0.17	-0.17	0.24	0.26	ns	ns	0.42	-0.19	1.68*	0.33	0.22	-0.17	-0.46	0.07	ns	ns
Hersche [43] (MS)	0.68	0.61	0.04	0.06	0.12	-0.28	0.59	-0.35	ns	ns	0.96*	0.69	0.52	0.17	-0.14	0.08	0.54	-0.09	ns	ns
Finlayson [52] (MS)	0.19	0.37*	0.37	0.41*	0.32*	0.26*	0.48*	0.26	ns	ns	0.27	0.39*	0.39	0.33*	0.29*	0.17	0.27*	0.19	ns	ns
Mathiowetz [53,57] (MS)	0.17	0.63*	0.18	1.14*	0.42*	0.40	0.60*	0.08	ns	ns	0.41	0.61*	0.20	0.61*	0.61*	0.23	0.44*	0.12	ns	ns
Thomas [32,56] (MS)	-0.05	0.13	0.04	0.24	-0.07	0.09	0.15	-0.06	ns	ns	0.10	0.27	-0.06	0.35*	-0.11	0.21	0.30	-0.1	ns	ns
Blikman [49] (MS)	-0.23	-0.26	-0.10	0.11	-0.04	-0.00	0.03	0.13	ns	ns	0.05	0.01	-0.30	0.10	0.04	0.19	0.06	0.10	ns	ns
Van den Akker [41] (MS)	-0.1	0.41	0.22	0.52	-0.28	0.06	0.0	-0.11	ns	ns	-0.20	-0.25	0.0	0.04	-0.3	0.01	-0.18	-0.11	ns	ns
Ehde [48] (MS)	0.04	NA	NA	NA	NA	NA	0.14	NA	NA	NA	-0.19	NA	NA	NA	NA	NA	0.05	NA	NA	NA
Zuidema [34](RA)	0.24	0.15	0.29	0.39	0.20	0.00	0.27	0.24	ns	ns	0.15	0.00	-0.10	0.34*	-0.09	-0.32	-0.01	0.00	ns	ns
Given [36] (Cancer)	NA	0.21	NA	NA	0.0	NA	NA	NA	ns	ns	NA	0.49*	NA	NA	0.41*	NA	NA	NA	ns	ns
Ream [31] (Cancer)	ns	ns	ns	0.6*	ns	ns	0.7*	ns	ns	ns	NA									
Karlson [50] (SLE)	ns	ns	ns	ns	ns	ns	ns	0.20	0.0	0.0	ns	ns	ns	ns	ns	ns	ns	ns	0.28	0.45
Koopman [38] (PPS)	ns	ns	ns	ns	ns	ns	ns	0.20	0.11	0.11	ns	ns	ns	ns	ns	ns	ns	ns	0.20	-0.3
Vogelaar [39] (IBD)	ns	ns	ns	ns	ns	ns	ns	0.29	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns	-0.1	ns
EORTC QLQ c30																				
Reif [54] (Cancer)	0.70*	0.76*	0.84*	0.78*	0.65	0.91*	0.65	0.91*	0.0	0.0	1.10*	1.10*	1.34*	1.13*	1.13*	1.01*	1.24	0.54	ns	ns
Armes [30] (Cancer)	0.56*	NA	NA	NA	NA	NA	NA	0.0	0.0	0.0	0.80*	NA	NA	NA	NA	NA	NA	NA	0.54	ns
Yates [46] (Cancer)	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns
Goedendorp [40] (Cancer)	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns
HAQUAMS																				
Pöttgen [55] (MS)	0.53	0.27	0.16	0.28	0.18	0.21	0.21	0.21	0.21	0.21	0.35	0.27	0.25	0.12	0.15	0.19	0.19	0.19	0.19	0.19
MLHFQ	Overall quality of life										Overall quality of life									
Wang [33] (HF)	0.46*										NA									
Personal wellbeing Index																				
Ghahari [51](NCD)	^a -0.19					0.36					^a -0.15					^c 0.14				
Foster [45](Cancer)	0.04										-0.06									
Multiple Sclerosis Impact Scale	Physical functioning					Mental functioning					Physical functioning					Mental functioning				
Plow [44] (MS)	0.06					0.02					-0.05					-0.31				
EQ-5D	Utility					VAS														
Purcell [35] (Cancer)	0.03					0.0					NA					NA				
Rheumatoid arthritis-QoL																				
Hewlett [47] (RA)	NA										0.05									
Global question																				
Hewlett [37] (RA)	-0.02										NS									

Abbreviations: BL: baseline, PI: post intervention, FUP: follow-up, *: statistically significant positive effect, PP: per protocol, ITT: intention to treat, ^a: mean difference between EG vs CG1, ^b mean difference between pre - post intervention, ^c mean difference between EG vs CG2

SF-36: Short Form Health Survey: Dimensions: PF: Physical Functioning, RP: Role-Physical, BP: Bodily Pain, VT: Vitality, SF: Social Functioning, RE: Role-Emotional, MH: Mental Health, GH: General Health, PCS: Physical Component Score, MCS: Mental Component Score. EORTC-QLQc30: European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-C30: Dimensions: PF: Physical functioning, RF: Role functioning, CF: Cognitive functioning, SF: Social Functioning, EF: Emotional functioning. PWI: Personal Wellbeing Index. MSIS: Multiple Sclerosis Impact Scale, EQ-5D: EuroQual-5D, VAS: Visual Analog Scale, MLHFQ: Minnesota living with heart failure questionnaire, HAQUAMS: Hamburg Quality of Life Questionnaire for MS
MS: multiple sclerosis, RA: rheumatoid arthritis, SLE: systemic lupus erythematosus, NCD: neurological chronic disease, HF: Heart failure, PPS: Post-polio syndrome, IBD: Inflammatory bowel disease

and MS) were in line with results from disease-specific systematic reviews on fatigue education [16,70]. The majority of the included studies reported at least small effects on one of the dimensions of QoL at post intervention. The large effects reported in some studies with persons with MS and cancer [30,43,54], and the capacity to significantly affect both outcomes, QoL and fatigue [31,48,52–55], or to even increase the positive impact on QoL at follow-up are remarkable.

The descriptive summary of these complex interventions highlights the heterogeneity of the intervention characteristics. The duration, the frequency and the delivery modalities were diverse but straight-forward to extract, while content-related elements were often described insufficiently and therefore less clear to categorize. The incomplete reporting of education interventions is a well-known problem [71]. According to Rudd et al., [72] this prevents not only a comprehensive evaluation but also the replication and the implementation of evidence-based educations in a real-world setting. We consider the TIDieR checklist [23] an indispensable tool to properly report complex interventions.

Our results show that long interventions (> 9.3 h distributed over several weeks) achieved more often statistically significant differences on fatigue and QoL compared to those with a short duration. The duration and in general the dosage might therefore be one of the possible discriminative characteristics for significant and larger effects. The depth and intensity of the reflection and its pertinence are decisive points when aiming for behavioral changes [73,74]. That concerns not only the total duration, the frequency and the number

of themes addressed, but is also reflected by the concrete strategies taught during sessions and homework, the supportive materials, and the applied BCT [27]. We showed that a group of BCT was an integral part of nearly all interventions (intention formation, encouragement, information), other BCTs were less often listed. Unfortunately, the descriptions of the BCT used are often imprecise or the techniques are not discussed, which does not permit further analysis of them. Our findings concerning the set of self-management skills that were taught are supported by Plow et al. [75]. The skills using resources and communicating efficiently with health professionals received less attention and time compared to the other skills. In tendency, the self-management tasks and skills and the BCT applied did not seem to have an influence on the delivery modalities of the interventions or the outcomes. Based on learning theories, the level of participant involvement during education is a key element [73,74]. The intensity of the interactions might therefore be another key element for significant outcomes and effective interventions. Treatments which include group of peers and the exchange of their experiences is clearly different to the experiences a person might have in an individual or remote interaction [74,76,77]. It is however necessary to consider the difficulty of organizing groups, which must be compatible with the conditions of the institution and the needs of the participants. The advantage of the group setting might not compensate for the logistic and organizational challenges of the implementation and performance of a group education in a real-world setting. That might be the reason why, even though they are probably not more cost-effective, the majority (including all short

interventions) of the included SEMs in this systematic review were delivered individually. To be able to identify association between effectiveness and a set of intervention characteristics (skills, tasks, durations, interactions) a meta-regression would be the methods of choice.

Another question arising is if the person- and disease-related characteristics such as age, gender, and level of education, or the disease, the time from disease on-set, and the time point of SME have an influence on the reported effects in the different studies. For example, the data on persons with cancer and MS suggest consistently a possible efficacy when compared to others diseases. The disease-related factor remains however speculation, as long as the number of high-quality RCTs for the other diseases is limited.

The pooled study population had a mean age of 45 years and was predominantly female (73%). The included publications reported the socio-demographic information of the study participants in different ways. Detailed data on compliance were missing. It would be advisable that fatigue-focused SME is accessible from the early stage of the disease, to avoid the loss of meaningful activities and to maintain life roles and a sense of control. In this case, the content and format should be adapted to guarantee a good match between the actual needs of participants with only first and/ or mild experiences with fatigue and the self-management skills trained. To investigate these aspects, it would be necessary to perform cohort studies to observe the long-term effects of the use of self-management skills on the different life roles.

In addition to the intervention characteristics discussed above, three more methodological aspects might have an influence on the effect size and the statistical significance of the results. Although we included only studies with RCT designs, there are some important differences between them. We observed that the four studies that used waiting lists as control interventions had the highest effects. This finding could support the argument that for people living with fatigue, any kind of support or attention might have some effect due to the central importance of not being left alone with the everyday problems caused by fatigue. Another aspect to consider is the time of follow-up. The implementation of behavior changes, the mastery in performing new skills and the formation of new habits is conditioned by the personal engagement and the support from the social environment, but also by the time factor. Therefore, studies with short follow-up periods might not capture this evolution and may not sufficiently take into account the fact that it takes time to integrate behavioral changes into people's routines. The third aspect involves the outcome dimensions and instruments to assess it. The targeted outcome of patient education is the acquisition of knowledge, skills and behavior to enable the person to manage fatigue rather than to reduce symptoms. Self-efficacy is an ideal proximal indicator for estimating the effectiveness of education, while the relevant endpoint from the patient's perspective is QoL. Unfortunately, self-efficacy is often not considered at all, while QoL is usually a secondary outcome; this might be the reason why several trials did not discuss the findings for QoL, and many did not report all the tested scores. For some studies, the results for QoL measured by the SF-36 were different from those of the primary outcome fatigue, but they did not modify the overall interpretation of the randomized trials [75].

In our review, there was a predominance of studies investigating SMEs in people with MS or during / after cancer treatment, while RCTs in persons with other diseases with similar experiences of fatigue burden have been less frequently performed. During the full-text screening, we however found several pilot studies and recently published study protocols for other chronic conditions (e.g. chronic obstructive pulmonary disease, traumatic brain injury); which indicates a growing attention of researchers and clinicians of the potential benefit of patient education in fatigue management.

Limitations: The overall methodological quality of the included studies was not fully satisfactory. Education interventions are complex, and the type of RCT depends on the clinical context in which they are embedded. For four disease populations (systemic lupus erythematosus, heart failure, post-polio syndrome, inflammatory bowel disease), only one article each satisfied the inclusion criteria which limits the strength of evidence and conclusions we can draw for these populations. However, in addition to the data on statistically significant differences between the SME groups and corresponding control groups, the computation of a standardized mean effect (Cohens' d) on QoL provides the whole range of effect size of the SMEs and facilitates the comparison. We excluded persons with mental health diseases. This was because emotional and psychosocial issues might be a barrier to a successful confrontation with self-management tasks and changes in routines and behavior. The review process was carried out collaboratively between the authors to ensure consensus and maintain an over-disciplinary perspective.

4.2. Conclusions

While the overall evidence on the effectiveness of SMEs on fatigue is limited and inconsistent, for cancer and MS the data show a moderate trend towards efficacy. We described a set of complex interventions including a broad variety of study populations and were able to show that fatigue is a burden that can be approached with SME. The content of the SMEs reflect the underlining theories and the delivery modalities the needs of the people and the conditions of the clinical setting in which they are implemented. Considering the subgroup of studies including persons with cancer and MS, the evidence is moderately consistent and indicates positive effects in favor of SMEs. The studies with medium and large effect size on QoL at follow-up indicate the positive potential of SMEs, and ask for methodologically rigorous research on the common characteristics of these effective interventions.

4.3. Practical implications

The results show the potential benefit of structured SMEs on fatigue and QoL for persons with disease-related fatigue and the variety of intervention elements that can be combined for tailoring SME interventions to targeted groups and contexts.

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CRediT authorship contribution statement

Ruth Hersche: Conceptualization, Methodology, Formal analysis, Investigation, Visualization, Writing – original draft, Project administration. **Katharina Roser:** Methodology, Investigation, Validation, Visualization, Writing – review & editing. **Andrea Weise:** Investigation, Validation. **Gisela Michel:** Validation, Investigation, Writing – review & editing, Supervision. **Marco Barbero:** Writing – review & editing, Supervision.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at [doi:10.1016/j.pec.2021.09.016](https://doi.org/10.1016/j.pec.2021.09.016).

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