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REVIEW

eHealth and mHealth interventions in the treatment of fatigued cancer survivors: A systematic review and meta-analysis

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Abstract

Objectives: To (1) evaluate existing eHealth/mHealth interventions developed to help manage cancer-related fatigue (CRF); and (2) summarize the best available evidence on their effectiveness.

Methods: A comprehensive literature search of PubMed, MEDLINE, EMBASE, and the Cochrane Library up to November 2016 was conducted. Study outcomes were extracted, tabulated, and summarized. Random effects meta-analyses were conducted for the primary outcome (fatigue), and the secondary outcomes quality of life and depression, yielding pooled effect sizes (*r*), and 95% confidence intervals (CI).

Results: For eHealth interventions, our search of published papers identified 9 completed studies and 6 protocols for funded projects underway. No studies were identified for mHealth interventions that met our inclusion criteria. A meta-analysis of the 9 completed eHealth studies revealed a statistically significant beneficial effect of eHealth interventions on CRF (r = .27, 95% CI [.1109 – .4218], P < 0.01). Therapist-guided eHealth interventions were more efficacious then self-guided interventions (r = .58, 95% CI: [.3136 – .5985, P < 0.001). Small to moderate therapeutic effects were also observed for HRQoL (r = .17, 95% CI [.0384 – .3085], P < 0.05) and depression (r = .24, 95% CI [.1431 – .3334], P < 0.001).

Conclusions: eHealth interventions appear to be effective for managing fatigue in cancer survivors with CRF. Continuous development of eHealth interventions for the treatment of CRF in cancer survivors and their testing in long-term, large-scale efficacy outcome studies is encouraged. The degree to which mHealth interventions can change CRF in cancer survivors need to be assessed systematically and empirically.

KEYWORDS

cancer-related fatigue, cancer survivors, eHealth intervention, mental health, mHealth intervention, psycho-oncology, self-efficacy

1 | INTRODUCTION

Significant improvements in early cancer detection and advanced treatment options have dramatically improved disease-free survival in cancer survivors.[1] There are currently more than 15.5 million cancer survivors in the United States (almost 5% of the total US population), a number that is projected to dramatically increase by 31%, to 20.3 million, by 2026.[2] However, the consequences of cancer and its treatment, including the risk of recurrent cancer, other chronic diseases, and persistent adverse effects can significantly impact physical function and quality of life.[3] In light of this, there is growing demand for tailored aftercare resources, including supported self-management, to help survivors address individual needs and otherwise cope with the consequences of cancer.[4]

Cancer-related fatigue (CRF) is the most prevalent problem among cancer survivors.[5] It is defined as "a distressing, persistent, subjective sense of physical, emotional, and cognitive tiredness or exhaustion related to cancer or cancer treatment that is not proportional to recent activity and interferes with usual functioning, and is not relieved by sleep or rest".[6] Chronic CRF has a profound impact on the physical,

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emotional, and mental health of cancer survivors. It causes many to have problems with memory and concentration, and to suffer from listlessness, low self-esteem, and even depression.[7] Furthermore, CRF interferes with usual functioning[8] and, ultimately, can affect quality of life.[9] These adverse health outcomes persist many years beyond successful cancer treatment in a substantial number of cancer survivors.[10,11] According to the literature, 30% of patients suffer from CRF even 10 years after termination of cancer treatment.[5]

CRF is a complex and multifactorial problem that has many etiologies. Factors like pain, emotional distress, depression, sleep disturbances, anemia, and nutritional deficiencies exhibit a close relationship with the progression of CRF.[6,12,13] However, the exact mechanisms responsible for CRF are still not fully understood. Potential biological mechanisms associated with CRF onset include inflammation,[14,15] serotonin dysregulation, disruption of the hypothalamic-pituitary-adrenal axis (involving the hormone cortisol),[16] modulation of the circadian rhythm, and low parasympathetic activity.[17]

Nonpharmacological and pharmacological approaches are commonly employed to treat fatigue and its sequelae. While limited evidence exists documenting any effectiveness of psycho-stimulants in the management of CRF, nonpharmacological approaches have been widely recognized as effective. Such approaches include energy conservation, activity management,[18] optimizing restful sleep, relaxation techniques, psychosocial support, and cognitive behavioral therapy.[19] According to National Comprehensive Cancer Network (NCCN) guidelines, physical activity is the number one recommendation for managing CRF.[20] As shown by multiple studies, physical activity has the potential to change cancer survivors' post-treatment symptoms.[21,22] In addition, weight gain, including obesity, is a common complication after cancer treatment and is associated with the increased incidence of chronic conditions like cardiovascular disease, diabetes, and hypertension, as well as secondary cancers and primary cancer recurrence.[23] Up to 71% of cancer survivors are overweight or obese.[24,25] Although the NCCN guidelines highly encourage cancer survivors to maintain a healthy lifestyle—including weight management, healthy nutrition, and engaging in physical activity—it is difficult for most to achieve these healthy lifestyle goals.[26] Interestingly, several studies indicate few differences in adhering to healthy lifestyle behaviors among cancer survivors and those without a history of cancer,[27] suggesting that achieving a healthy life style is a general problem of the US population as well as other countries. Furthermore, important barriers to healthy life style changes in cancer survivors are among others, lower socioeconomic status, lower education level, restricted access to recreational facilities, and mental health problems (eg, distress, depression, fatigue).[28] As cancer survivors are generally motivated to make positive health behavior changes, further investigations of ways how to best promote adherence to life style interventions in cancer survivors are needed.

Given poor outcomes among cancer survivors with CRF, there is a growing demand for tailored interventions to promote knowledge about CRF, strengthen self-efficacy, increase physical activity, support weight management, and improve dietary behaviors. eHealth and mHealth interventions have the potential to engage patients in their health care by reaching a large population, including individuals who have limited access to appropriate health care providers in a cost-effective way, and by providing timely feedback regarding outcomes.[29] Advances in mobile technology offer a wide range of approaches to send reminders or track information via ubiquitous internet access, wireless connectivity with other devices, global positioning systems (GPS), accelometers, and other sensors.[30]

In health psychology, web-based or mobile health interventions, often referred to as eHealth interventions (health service delivered through the use of information technology, including the Internet, digital gaming, and virtual reality[24]), and mHealth interventions (health service delivered through mobile and wireless applications, including text messaging, apps, wearable devices, remote sensing, and the use of social media), respectively,[25] provide promising opportunities to access patients and engage them in their own health care. eHealth interventions developed to increase self-management and manage physical symptoms have been shown to be effective in various chronic disease populations.[31] Currently, few eHealth and mHealth interventions exist for cancer survivors with CRF.[32-34] However, with the rapid development of medical technology in health care, using eHealth/mHealth interventions to manage CRF will likely become increasingly important and could represent a helpful psychological intervention. This being said, despite the projected proliferation of eHealth/mHealth interventions to manage treatment-related symptoms in cancer survivors, it is still unclear how effective such interventions are for the treatment of CRF.

The overall objectives for this review were therefore to (1) review the evidence regarding existing eHealth/mHealth interventions for the management of CRF among cancer survivors; (2) explore the effectiveness of eHealth/mHealth interventions, also for the treatment of CRF in cancer survivors; and (3) provide recommendations and suggest future directions for the development and application of such mobile/web-based interventions.

2 | METHODS

This systematic review was conducted and reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement.[35] In accordance with these guidelines, our systematic and meta-analytic review protocol was registered with the International Prospective Register of Systematic Reviews (PROSPERO) database (PROSPERO; Registration No. CRD42016050966).

2.1 | Search strategy

A comprehensive literature search was conducted to identify scientific articles that included eHealth or mHealth interventions to manage fatigue among cancer survivors with CRF. For the purposes of this review, the term "cancer survivor" referred to any cancer patient who had completed treatment for cancer. A systematic search of electronic databases, including PubMed, MEDLINE, EMBASE, CINAHL, PsychINFO, and the Cochrane Central Register of Controlled Trials (CENTRAL; The Cochrane Library), was conducted from inception to November 2016. Search terms were used in various combinations, including the following key words: cancer, cancer survivors, CRF,

fatigue, mobile intervention, smartphone application, web-based intervention, online interventions, eHealth/mHealth interventions, telehealth, Internet-delivered, quality of life, physical activity, self-efficacy, and self-management. Medical Subject Headings (MeSH) or equivalent and text word terms were used.

2.2 | Eligibility criteria

To be considered for inclusion, articles were required to meet the following criteria:

1. Reviewed and published in English.
2. Involved adult cancer survivors (≥18 years).
3. Offered 1 or more online interventions or smartphone applications tailored to manage fatigue in cancer survivors.
4. Had fatigue as the primary outcome, measured by means of a standardized, scientifically validated and reliable psychometric instrument.
5. Had any 1 of the following study designs: randomized controlled trial (RCT), cross-sectional survey, prospective case-control or cohort study, pilot study, longitudinal observational study, or qualitative survey.

The criteria for exclusion from the review were as follows:

1. Intervention offered to a population other than cancer patients.
2. Cancer patients currently receiving treatment for their cancer.
3. Fatigue as a secondary, versus primary, outcome.
4. Pediatric cancer patients.
5. Intervention not a web-based or smartphone intervention.
6. Reporting issues (eg, only the abstract available, book chapters, systematic reviews, meta-analyses, and no data report).

2.3 | Data selection and extraction

Preliminary screening was conducted based on titles and abstracts. Full-text articles were obtained for all abstracts meeting the inclusion criteria for further evaluation and for articles that could not be rejected with certainty. The reference lists of studies meeting the eligibility criteria were screened for additional relevant studies. Two review authors (AS; VK) independently screened a full-text copy of every paper to determine its eligibility for inclusion, in accordance with the above-listed criteria. Disagreement between the 2 reviewers was resolved by discussion, and a third reviewer (CF) was involved for those papers for which agreement could not be reached. A high level of agreement was achieved among the 2 reviewers (AS and VK) with an agreement rate of 96% of the studies (366/380). The following details for each study were systematically extracted: source (eg, journal) and year of publication, country of origin, title, study design, total sample size, intervention period, characteristics of the population (age, gender, type/site of cancer), eHealth/mHealth mode, outcome measures, and results. The process of data selection is outlined in Figure 1. The evaluation of data was processed by means of qualitative descriptions. Results were summarized in tables and presented in narrative form. Continuous variables for primary (CRF) and secondary health outcomes were pooled for meta-analysis wherever means and standard deviations were either available or calculable.

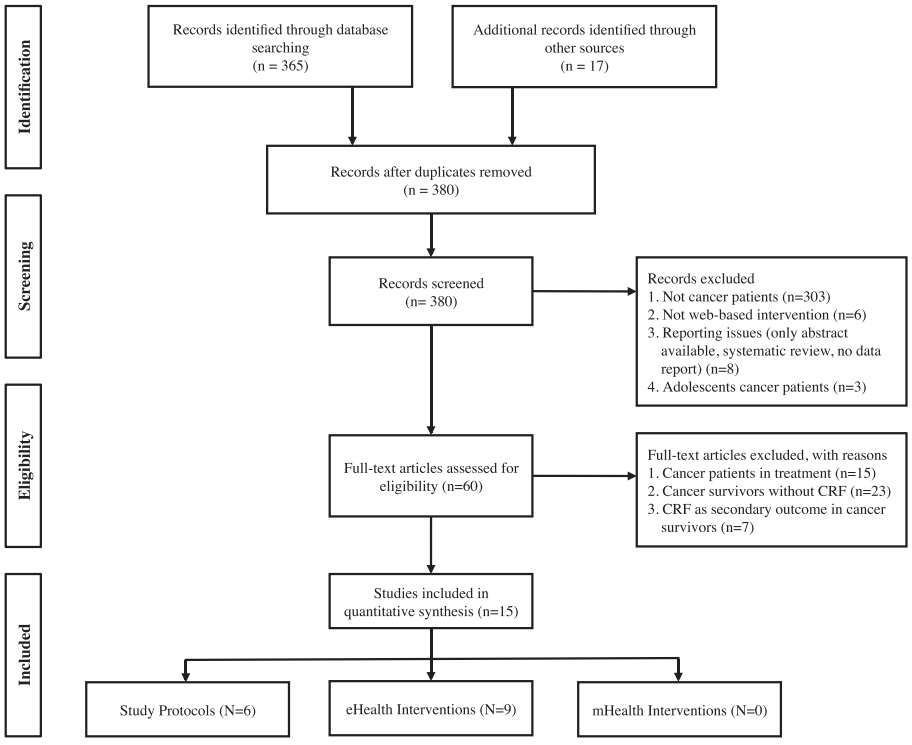

FIGURE 1 Search retrieval process

2.4 | Methodological quality assessment

The Cochrane Collaboration's tool for assessing risk of bias[36] was used to assess the methodological quality of each included study. The Cochrane Collaboration's tool is based on 7 bias domains: (1) the randomization process; (2) treatment allocation; (3) blinding of participants and personnel; (4) blinding of outcome assessors; (5) blinding of outcome data; (6) reporting of results; and (7) other sources of bias (fatigue screening prior to inclusion). A second investigator verified the extracted data. The overarching risk of bias (low risk of bias, unclear risk of bias, high risk of bias) was summarized based on the Cochrane risk of bias tool.[37]

2.5 | Statistical analysis

Fatigue was set as the major outcome of interest; secondary outcomes for meta-analysis included HRQoL and depression. Random-effects meta-analysis was used to generate pooled effect sizes (*Pearson's correlation r*) between groups (treatment vs control group) with corresponding 95% confidence intervals (CI). In addition, we tested whether the effectiveness of eHealth interventions on CRF severity was dependent upon mode of intervention (self-guided vs therapy-guided interventions). Effect sizes of 0.1, 0.3, and 0.5 are generally considered to be small, moderate, and large, respectively.[38] All statistical tests were 2-tailed, $P < 0.05$ set as the threshold for statistical significance. Between-study heterogeneity was examined by means of Cochran's *Q*-tests and the I^2 statistic. I^2 describes the percentage of total variation across studies caused by heterogeneity rather than by chance, where high values of the index ($I^2 > 50\%$) indicate the existence of significant heterogeneity.[39] Publication bias was assessed by funnel plots symmetry, as well as by Egger's linear regression test and the rank correlation test.[40,41] A meta-regression was conducted to assess whether study quality affected the reported therapeutic effect.

All statistical analyses were performed in *R* (software version 3.3.2) using the Metafor package[42] and Rstudio (version 1.0.136).

3 | RESULTS

Presentation of results will be provided in 3 sections. The first will describe study selection and characteristics. The second will outline the results of the systematic literature review, and the third will report on results of the meta-analytic comparison.

3.1 | Study selection

The literature search identified 380 potential eligible articles (Figure 1). Screening titles and abstracts resulted in 60 citations potentially meeting eligibility criteria. After completely reviewing the corresponding full-text articles, the total number of articles eligible for inclusion into the systematic review was reduced to 15. Figure 1 illustrates the main reasons for excluding articles.

3.2 | Study characteristics

Eligible studies were published between 2011 and 2016 (Table 1) and were predominantly based in the Netherlands (5 studies) and the USA (4 studies), with 3 studies orchestrated in the United Kingdom, 1 in Ireland, 1 in Korea, and 1 in Spain. Among the 9 studies that reported outcome data, 8 were randomized controlled trials (RCT), while 1 was a pilot study. An additional 6 papers described funded projects that were underway (all were study protocols for an eHealth intervention designed for fatigued cancer survivors). The mean duration of the intervention was 13.5 weeks (range 6 to 48 weeks). The mean number of participants across the 9 eligible studies was 176 (range: 18-409), of which 78% were female. The mean age of subjects was 50.4 years old (range 32 to 58). The most common cancer type was breast cancer (41%), followed by head and neck cancer (14%), hematologic cancer (9%), and thyroid cancer (8%). General characteristics of the eligible studies are summarized in Table 2.

4 | SYSTEMATIC REVIEW

4.1 | eHealth mode

The eHealth interventions used in the eligible studies were albeit heterogeneous and diverse in type and content. eHealth interventions adopted in the eligible studies included educational programs[33] and behavior change interventions, including psycho-educational modules on fatigue, anxiety, depression, diet, exercise, sleep, and social relationships,[34,47,48,52] mindfulness-based cognitive therapy,[46] and an imagery-based behavioral intervention.[50] Two studies investigated a web-based exercise intervention.[45,49]

4.2 | Primary outcome (cancer-related fatigue)

Only 9 of the 15 eligible studies assessed fatigue using a standardized, scientifically validated and reliable psychometric test instrument. A range of different outcome measures was used. In 6 studies (67%), a significant reduction in fatigue was reported for the intervention group relative to the comparison group after 9 weeks (CIS: $P < 0.01$)[46]; MFSI-SF: $P \leq 0.001$),[48] after 12 weeks (BFI: $P < 0.01$)[50]; (BFI: $P \leq 0.001$; FSS: $P \leq 0.001$)[33] and after 6 months of follow-up (R-PFS: $P < 0.01$)[45]; (CIS-fatigue severity: $P < 0.05$).[52]

4.3 | Secondary outcomes

Secondary outcomes included psychometric instruments to measure HRQoL, depression, psychological distress, sleep, pain, physical and mental functioning, and eating habits. Three out of 6 studies identified significantly improved HRQoL both 12 weeks[50] and 6 months following completion of the web-based intervention.[33,45] Six studies included at least 1 outcome measure to assess depression. A significant reduction in depression was reported at 9-week,[46] 12-week,[33] and 6-month[52] follow-up. Psychological distress was assessed in only 2 studies, with 1 study indicating a clinically relevant decrease in psychological distress at 12 weeks of follow-up.[50] Likewise, sleep behavior (sleep quality[33,50] and insomnia[34,48]) was evaluated in 4 studies, all RCTs; 3 of these 4 studies revealed any significant improvement, which was measured 9 weeks,[48] 12 weeks,[50] and 6 months[34] after the intervention. Significant improvements were also observed for pain at 6-month follow-up.[45]

TABLE 1 Summary of studies on eHealth/mHealth interventions for fatigued cancer survivors with CRF included into the systematic review

Author & Year	Title	Study design	Sample	Mode of delivery	Treatment approach	Feasibility/ acceptability/ adherence	Outcome measures	Results	Methodological limitations
Abrahams et al 2015[43] The Netherlands	A randomized controlled trial of web-based cognitive behavioral therapy for severely fatigued breast cancer survivors (CHANGE-study): study protocol	Nonblinded multicenter RCT; intervention vs care condition; baseline; 6 mo post assessment	132 fatigued BCS	eHealth intervention; therapist guided	CBT	NA	CIS, SIP, BSI, EORTC-QLQ-C30	Web-based cognitive behavioral therapy (CBT) will provide additional treatment option for fatigued BCS. Beneficial in terms of increased therapeutic capacity, increased accessibility for a larger number of patients, and time and cost saving for patients.	
Bantum et al 2014[33] USA	Surviving and thriving with cancer using a web-based health behavior change intervention: randomized controlled trial	RCT; 6 mo follow-up, control vs intervention group	303 cancer survivors (all types of cancer)	eHealth intervention; self-guided	The Chronic Disease Self-Management Program (CDSMP)	MD	BFI; WHIRS; PHQ-8; FFQ	Intervention group showed significantly greater reduction in insomnia and greater increase in physical activity. No significant group difference was found for fatigue.	Selection bias Heterogeneous sample No consideration of minorities Lack of controlling for confounding factors
Bruggeman-Everts et al 2015[29] The Netherlands	Web-based individual mindfulness-based cognitive therapy for cancer-related fatigue—a pilot study	One group; pretest-posttest design; 9-wk follow-up	257 cancer survivors (all types of cancer)	eHealth intervention; therapist guided	Mindfulness-based cognitive therapy for cancer survivors	62% adhered to intervention	CIS; HADS	Findings suggest that web-based mindful-based cognitive therapy may be effective in reducing symptoms of CRF in cancer survivors.	Lack of control group Small sample size Selective dropout Lack of controlling for confounding factors Short follow-up time
Corbett et al 2016[44] Ireland	Protocol for a pilot randomized controlled trial of an online intervention for post-treatment cancer survivors with persistent fatigue	2-armed RCT; 8-wk follow-up; intervention vs control group	80 cancer survivors (all types of cancer)	eHealth intervention; therapist guided	CBT	NA	PFS-R; QLACS	Objective: to develop a supportive resource to target representations and coping strategies of cancer survivors with CRF post-treatment.	
Foster et al 2015[45a] UK	Managing fatigue after cancer treatment: development of RESTORE, a web-based resource to support self-management	RCT; 6 + 12-wk follow-up	4 cancer survivors (all types of cancer)	eHealth intervention; self-guided	Self-management program	NA	Developing Prototype web-based intervention	The aim was to develop evidence-based and theoretically formed web-based intervention (RESTORE) designed to enhance self-efficacy of fatigued cancer survivors.	

(Continues)

TABLE 1 (Continued)

Author & Year	Title	Study design	Sample	Mode of delivery	Treatment approach	Feasibility/ acceptability/ adherence	Outcome measures	Results	Methodological limitations
Foster et al 2016[46a] UK	A web-based intervention (RESTORE) to support self-management of cancer-related fatigue following primary cancer treatment: a multicenter proof of concept randomized controlled trial	2-armed RCT; 12-wk follow-up	163 cancer survivors (all types of cancer)	eHealth intervention; self-guided	Theory-driven, evidenced-based self-management program	Intervention as feasible and acceptable	BFI, PSEFSM, SC-SES, FACT-G, PWI, PHQ-9	RESTORE was feasible and acceptable. There was evidence of higher fatigue self-efficacy post-treatment. No significant difference was found for CRF.	Selection bias Small sample size
Freeman et al 2015[47] USA	A randomized trial comparing live and telemedicine delivery of an imagery-based behavioral intervention for breast cancer survivors: reducing symptoms and barriers to care	Multicenter RCT; life- vs telemedicine delivery; baseline, 4, and 12 wk post treatment	48 BCS	eHealth intervention; therapist guided	Imaginary-based behavioral intervention	Good adherence	FACIT-F, FACIT-B, FACIT-Cog, FACIT-SP-Ex, SF-36, BSI-18, PSQI	Significant changes in CRF, cognitive dysfunction, sleep disturbances, and HRQoL. No differences between life- and telemedicine delivery.	Small sample size Lack of control group Lack of controlling of confounding variables
Galiano-Castillo et al 2016[48] Spain	Telehealth system: a randomized controlled trial evaluating the impact of an internet-based exercise intervention on quality of life, pain, muscle strength, and fatigue in breast cancer survivors	2-armed RCT; 8-wk and 6 mo-follow-up, intervention vs control group	81 BCS	eHealth intervention; therapist guided	Rehabilitative exercise program	High acceptance and adherence to intervention	PFS-R, EORTC QLQ-C30, BPI	Intervention group showed significantly improved scores for global health status, cognitive functioning and total fatigue. This program may improve adverse effects and maintain benefits in BCS.	Selection bias Small sample size
Grimmett et al 2013[49a] UK	RESTORE: an exploratory trial of an online intervention to enhance self-efficacy to manage problems associated with cancer-related fatigue following primary cancer treatment: study protocol for a randomized controlled trial	RCT; 6-wk follow-up	125 cancer survivors (all types of cancer)	eHealth intervention; self-guided	Self-management program	NA	BFI, PSEFSM, SC-SES, FACT-G, PWI, PHQ-9	Data from this study were used to refine the intervention and contribute to the design of an effectiveness trial.	

(Continues)

TABLE 1 (Continued)

Author & Year	Title	Study design	Sample	Mode of delivery	Treatment approach	Feasibility/ acceptability/ adherence	Outcome measures	Results	Methodological limitations
Rabin et al 2011[50] USA	Internet-based physical activity intervention targeting young adult cancer survivors	RCT; 12-wk follow-up; intervention vs control group	18 cancer survivors (all types of cancer)	eHealth intervention; self-guided	Physical activity program	Intervention acceptable and feasible	PAR, POMS	Nearly significant difference in fatigue subscale scores between intervention and control group. Online intervention appeared to be feasible and acceptable and seemed to be beneficial for cancer survivors.	Small sample size Lack of controlling for confounding variables No minorities included
Ritterband et al 2012[42] USA	Initial evaluation of an internet intervention to improve the sleep of cancer survivors with insomnia	RCT; 9-wk follow-up; intervention vs control	28 cancer survivors (all types of cancer)	eHealth intervention; self-guided	CBT	High acceptance and adherence to intervention	ISI; Sleep diary, MFSI-SF, HADS	Online delivered CBT intervention for insomnia resulted in significantly improved insomnia severity and general fatigue.	Small sample size Selection bias Lack of controlling variables
[b]Willems et al 2015[51b] The Netherlands	The Kanker Nazorg Wijzer (Cancer Aftercare Guide) protocol: the systematic development of a web-based computer tailored intervention providing psychosocial and lifestyle support for cancer survivors	Focus group interviews	13 cancer survivors (all types of cancer)	eHealth intervention; self-guided	Problem-solving therapy; CBT	NA	-	Article describes the systematic development of a web-based intervention for cancer survivors.	
[b]Willems et al 2016[52b] The Netherlands	Short-term effectiveness of a web-based tailored intervention for cancer survivors on quality of life, anxiety, depression, and fatigue: randomized controlled trial	Multicenter RCT; baseline, 3, and 6 mo; intervention vs control group	409 cancer survivors (all types of cancer)	eHealth intervention; self-guided	Problem-solving therapy; CBT	MD	CIS, EORTC-QLQ-C30, HADS	The intervention was effective in reducing depression and fatigue.	Selection bias Selective dropout rates Lack of controlling for confounding variables
Wolvers et al 2015[53] The Netherlands	Effectiveness, mediator, and effect predictors of internet interventions for chronic cancer-related fatigue: the design and an analysis plan of a 3-armed randomized controlled trial	3-armed RCT; baseline, 2 wk, 6 mo, and 12 mo post treatment; 2 experimental vs 1 control conditions	330 cancer survivors (all types of cancer)	eHealth intervention; therapist guided	Mindfulness-based cognitive therapy	NA	CIS, HADS, WAI,	This paper describes a Systematic trial design for studying 2 different interventions for CRF in order to get insight into effectiveness and mediators.	

(Continues)

TABLE 1 (Continued)

Author & Year	Title	Study design	Sample	Mode of delivery	Treatment approach	Feasibility/ acceptability/ adherence	Outcome measures	Results	Methodological limitations
Yun et al[52] 2012 Korea	Web-based tailored education program for disease-free cancer survivors with cancer-related fatigue: a randomized controlled trial	RCT; baseline and 12 wk post assessment; intervention vs control group	273 cancer survivors (all types of cancer)	eHealth intervention; self-guided	Transtheoretic model; CBT	MD	BFI, FSS, EORTC QLQ-C30, ECSI; MNA, MOS-SS	Intervention group showed a significant decrease in fatigue and greater decrease in HADS as well as quality of life relative to control.	Selection bias Self-report bias No waiting-list control group

Note. The color gray represents study protocols. NA = not applicable; MD = missing data.

Abbreviations outcome measures: BCS = breast cancer survivors; BFI = Brief Fatigue Inventory; CBT = Cognitive Behavioral Therapy; CS-SES = Cancer Survivors Self-efficacy Scale; CRF = Cancer-Related Fatigue; ECSI = Energy-Conservation Strategies Inventory; FACT-G = Functional Assessment of Cancer Therapy—General; FFS = Fatigue Severity Scale; FFQ = Food Frequency Questionnaire; ISI = Insomnia Severity Index; HADS = Hospital Anxiety and Depression Scale; MFSI-SF = Multidimensional Fatigue Symptom Inventory-Short-Form; MNA = Mini-Nutritional Assessment Questionnaire; MOS-SS = Medical Outcome Study-Sleep Scale; PAR = 7-day Physical Activity Recall; PFS-R = Revised Piper Fatigue Scale; PHQ-8/9 = Patient Health Questionnaire; POMS = Profile of Mood States; PSEFSM = Perceived Self-Efficacy for Fatigue Self-management; PWI = Personal Wellbeing Index; QLACS = Quality of Life in Adult Cancer Survivors; RCT = Randomized Controlled Trial, WAI = Work Ability Index; WHIRS = Women's Health Initiative Insomnia Rating Scale.

[a]Reporting the same study.

[b]Reporting the same study.

TABLE 2 Summary of characteristics of selected studies (*N* = 9)

Characteristics	*N* (%)
2000-2005	0
2006-2010	0
2011-2012	3
2013-2014	1
2015-2016	5
Study design	
RTC	8
1 group	1
2 groups	0
>2 groups	0
Intervention period (wk) (mean; range)	13.5 (6-48)
Total sample size (mean; range)	176; (18-409)
Age (mean; SD)	50.4 (7.9)
Gender (female %)	78
Type of disease (%)	
Breast cancer	41
Gynecologic cancer	5
Hematologic cancer	9
Prostate cancer	7
Lung cancer	3
Head and neck cancer	14
Thyroid cancer	8
Other	13
Years since cancer treatment completed (mean; range)	1.9 (0.2-4)

A variety of outcome measures were used to assess physical and mental functioning. Clinically meaningful differences were found for cognitive function and spiritual well-being[50] at 12-week follow-up. Nutritional status was evaluated in 2 studies, but only 1 revealed any significant change following the web-based intervention, at 12-week follow-up.[33]

4.4 | eHealth interventions

Within the systematically reviewed literature, the web continued to be the predominant mode for intervention delivery for the management of CRF. Overall, all eligible studies with published results (9/9) applied eHealth interventions. Many studies were systematically developed based upon pre-existing theoretical models, following meticulous-described study protocols and feasibility studies.[47,51,52,54,55] Each eHealth intervention was developed on the basis of a specific theory (cognitive behavioral therapy,[33,48] mindfulness-based cognitive therapy,[46] psychoeducational approach[34]) or following national guidelines for cancer survivors (National Comprehensive Cancer Network[33]; American College of Sports Medicine for cancer survivors[45]); or the intervention was systematically and theoretically designed, including feasibility trials to evaluate the intervention's usability and acceptability to patients.[52,55]

Clinically significant improvement in fatigue in the intervention versus the waiting list group was reported in 6 studies.[33,45,46,48,50,52] In some studies, the effects detected for the eHealth intervention targeting the management of fatigue were comparable to the effects documented for face-to-face treatments.[45,50,52] Maintenance of the beneficial effect on fatigue over a follow-up period of 6 months was observed in 2 studies,[45,52] while the therapeutic effect appeared to wane in another study by 12-week follow-up.[47]

4.5 | mHealth interventions

Our review identified no RCT, feasibility studies, or study protocols utilizing any mHealth intervention targeting the management of fatigue in cancer survivors with CRF.

4.6 | Adoption and adherence to usage

Most studies revealed high levels of user acceptability and feasibility of using an eHealth intervention.[45,47-49] Among the studies that indicated a dropout rate, the mean retention rate for web-based intervention use was 78.6% (range 46% to 94%).[33,34,45-47,49] Most cancer survivors were satisfied with the web-based intervention that they had been offered and would recommend it to others.[45,49] Overall, participants were most satisfied with the intervention's flexibility, easy accessibility, and interactive presentation of content.[47] They also reported an increased understanding of CRF and experienced a greater feeling of self-efficacy in fatigue management.[46]

Suggested improvements voiced by cancer survivors for web-based interventions targeting the management of CRF included providing more cancer-specific information and more personal feedback,[47] including additional face-to-face and/or telephone contact.[46]

A proportion of patients (25%) stopped using the eHealth intervention for 1 or more of the following reasons: the intervention was difficult to integrate into their daily life activities; the intervention was rated as too intensive[46,49]; older cancer survivors struggled with navigating the web-based intervention due to their low level of computer literacy.[47]

4.7 | Level of methodological quality

Results of the methodological assessment are described in Figure 2. The raters agreed on 90.5% (57 of 63 items) of the items. Studies reporting randomization and allocation without a description of procedures were rated as having *unclear* risk of bias per the Cochrane Collaboration standards.[37] Of the 9 studies included, 8 studies were randomized controlled trials (RCT) and 1 was a 1-group design. The RCTs provided insufficient information about the allocation concealment. Only 1 study attempted to blind participants and personnel. Only 3 studies specified clearly that outcome assessors were blinded. Furthermore, only 3 of the 8 studies actively screened cancer patients for fatigue prior to study enrolment. A low risk of bias was graded in 4 out of 9 studies.

4.8 | Psychometric properties of outcome measures

There was variation in the quality of the reporting and the extent to which psychometric assessments were used for outcome measures. Few studies (N = 3/9) described the psychometric properties of the outcome instruments used in the fatigued cancer survivor population with Cronbach's alpha ranging between .71 and .97. Major limitations in the eligible studies included selection bias (67%), lack of controlling for confounding variables (67%), small sample size (65%) that limited both statistical power and generalizability, and the lack of an active control group (50%) (Table 1).

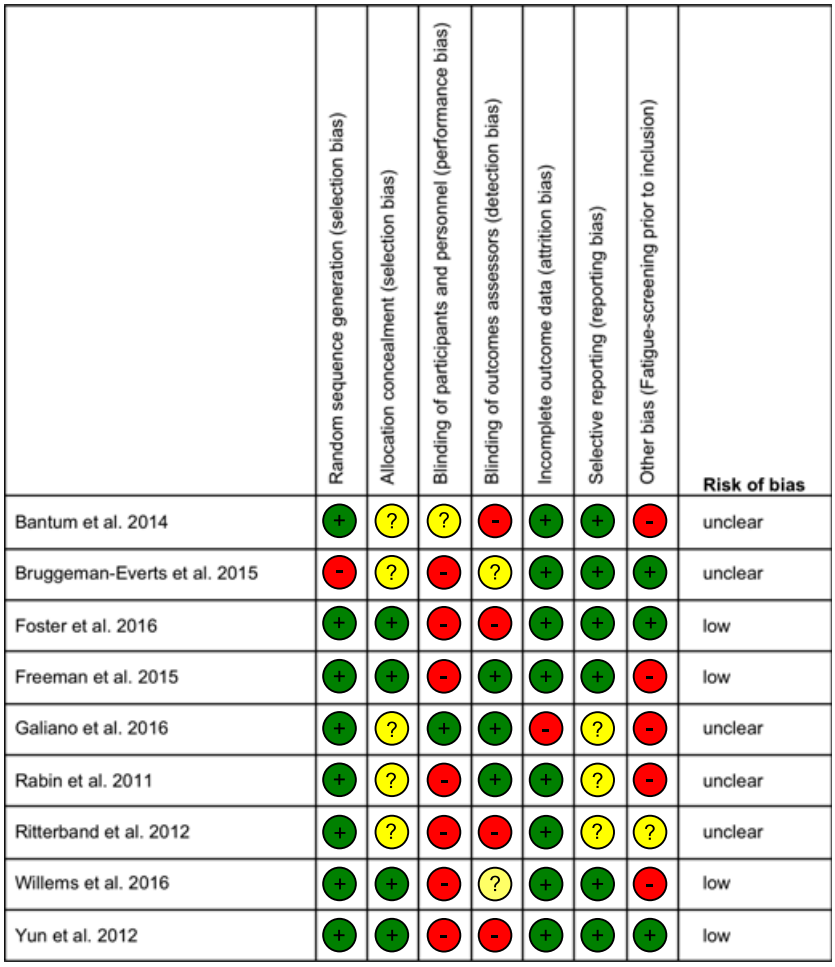

FIGURE 2 Risk of bias summary. Legend: (+) indicates low risk of bias; (?) indicates unclear risk of bias; (-) indicates high risk of bias

5 | META-ANALYSIS

Pairwise meta-analysis was conducted on the 9 completed studies, analyzing for therapeutic effects on fatigue between groups (treatment vs control group).[33,34,45-50,52] Six of these studies also were assessed to measure therapeutic effects on HRQoL,[33,45,47,48,50,52] and 6 for effects on depression.[33,34,46-48,52] The intervention's overall effect sizes for fatigue (N = 9), HRQoL (N = 6), and depression (N = 6) are shown in Figure 3. For the remaining secondary outcomes (psychological distress, pain, sleep, physical and mental functioning, eating habits), no meta-analysis could be conducted, as there were too few studies available or the outcome data were too heterogeneous to be analyzed.

5.1 | Effects of eHealth interventions on fatigue

A total of 9 studies with 1580 cancer survivors were included in our meta-analysis of eHealth interventions and fatigue. eHealth

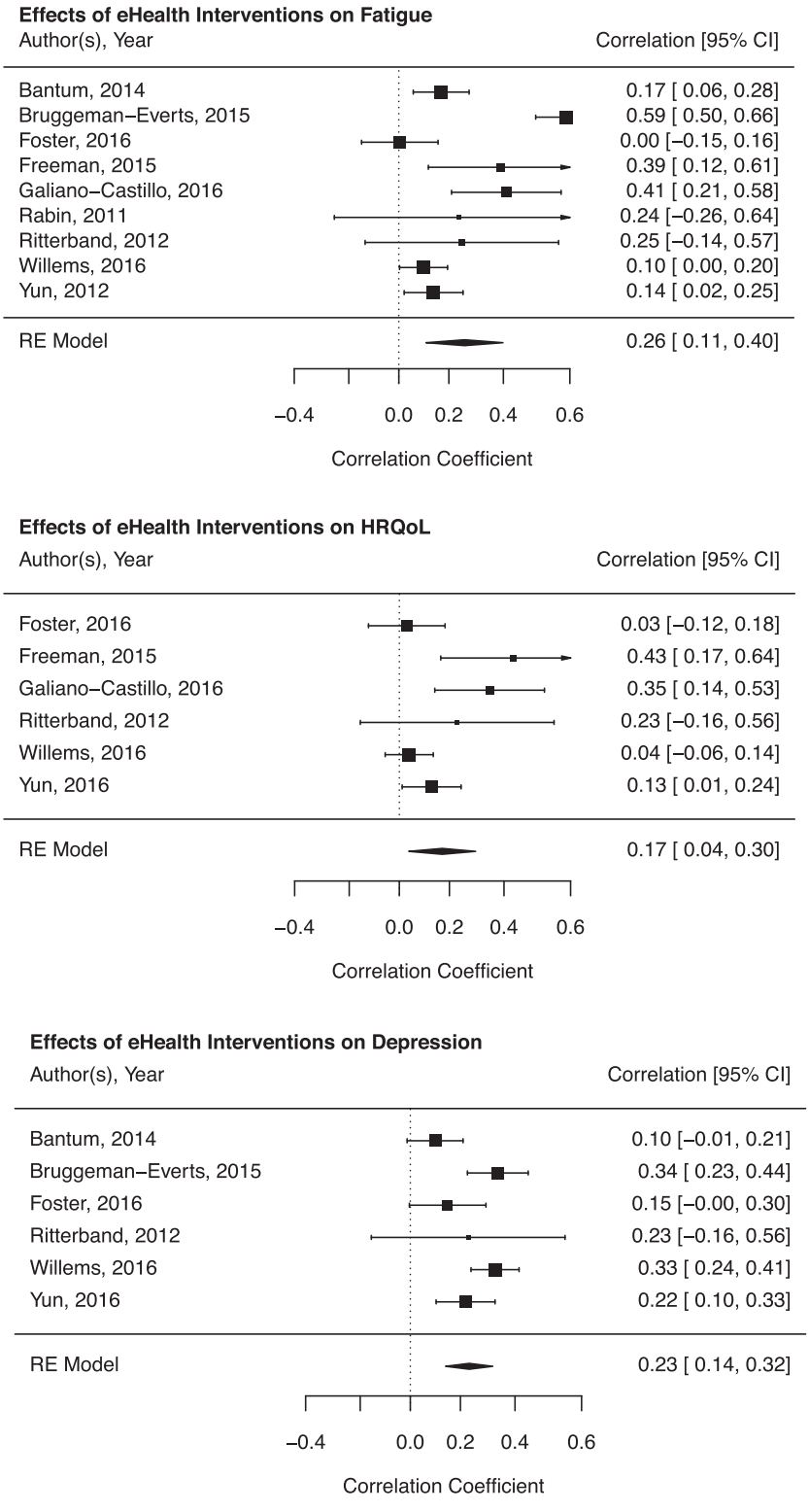

FIGURE 3 Forest plot of effects of eHealth interventions on fatigue, HRQoL, and depression. The effect sizes (*Pearson's correlation r*) and 95% confidence intervals (CIs) are reported for each study as well as the summary effect size (the polygon at the bottom). The edges of the polygon represent the 95% confidence limit. The square size refers to the statistical weight, with which the effect size entered the meta-analytic comparison. Studies with larger squares contributed more to the summary effect size

interventions were associated with statistically significant improvements in fatigue (r = .2664, 95% CI: [.1109 – .4218], P < 0.01). Within-group heterogeneity (I^2) across the studies was high (I^2 = 87.46%, P < 0.001). However, a funnel plot of the adjusted estimates was broadly symmetrical; and the Egger's regression test (P = 0.735) and rank correlation test (P = .477) were not significant, suggesting no evidence of publication bias. Meta-regression revealed no statistically significant association between study quality and therapeutic effect size (P > 0.05). We then examined whether the mode of intervention (self-guided vs therapist guided) did change the strength of the observed correlation. Analysis revealed that therapist-guided interventions were more efficacious than self-guided (r = .58; P < 0.001; CI: [.3136 – .5985) in the treatment of CRF.

5.2 | Effects of eHealth interventions on HRQoL

For HRQoL, 6 studies, representing 1002 cancer survivors, were included in meta-analysis. eHealth interventions significantly improved HRQoL (r = .1734, 95% CI: [.0384 – .3085], P < 0.05). However, a high level of overall heterogeneity was observed (I^2 = 71.82%, P < 0.01). Some degree of asymmetry in the funnel plot was observed during meta-analysis for HRQoL, suggesting a certain level of bias across the studies. The Egger's test was significant (P < 0.01), while the Rank correlation test was not. Exclusion of 1 outlier study reduced publication bias considerably (Egger's regression test P = 0.091; rank correlation test P = 0.233). Sub-analyses revealed no evidence of any moderating effect of study quality on effect size.

5.3 | Effects of eHealth interventions on depression

For depression, 6 studies (N = 1433 cancer survivors) were pooled for meta-analysis. Meta-analysis identified a positive effect of eHealth interventions on depression (r = .2383, 95% CI: [.1431 – .3334], P < 0.001). Considerable heterogeneity was noted (I^2 = 65.75%, P < 0.05). However, the funnel plot of all studies appeared to be symmetrical, and neither Egger's regression test (P = .43) nor the Rank correlation test (P = 0.82) was statistically significant, providing no evidence of publication bias in the meta-analysis. Similarly, study quality did not significantly impact therapeutic effect size.

6 | DISCUSSION

The current systematic review and meta-analysis systematically synthesize the empirical literature on eHealth and mHealth interventions for the management of fatigue in cancer survivors with CRF and evaluated their overall effectiveness. Fifteen publications, including 8 RCTs, 1 pilot study, and 6 study protocols for planned but not-yet-completed web-based interventions were included in this review. For our meta-analysis, outcome data were only available for the 9 completed studies. The small number of available RCTs illustrates how the application of eHealth/mHealth interventions in the aftercare of fatigued cancer survivors is still in its early stages. All of the eligible studies evaluated eHealth, as opposed to mHealth interventions. The RCTs varied greatly in their study methods and outcome measures, making it somewhat difficult to pool effects for meta-analysis. Moreover, the interventions were diverse in terms of type and content, and in the duration of the intervention and follow-up. All of the eligible studies were theory-based eHealth interventions, largely grounded in cognitive behavioral therapy.

Overcoming CRF is difficult, and eHealth/mHealth interventions may provide an important route by which to achieve individualized cancer survivorship plans, and, through this, successful self-management.[33] However, the patterns of usage, levels of engagement, and degree to which eHealth/mHealth interventions can change behavior all need to be assessed systematically and empirically.

6.1 | eHealth interventions

Significantly reduced fatigue levels following an eHealth intervention were observed in 6 of the 9 completed studies. The 3 remaining studies detected no significant differences in fatigue levels between the intervention and waiting list control groups.

Consistent with another meta-analyses on web-based self-management support interventions for cancer survivors,[56] the results of our meta-analysis revealed significant, small to moderate-sized effects of eHealth interventions, in terms of improving fatigue and other health outcomes. These effects were maintained over a 3-month to 6-month period. In addition, it was examined whether any differences in efficacy between self-guided versus therapist-guided interventions exist. Analysis revealed that therapy-guided eHealth interventions were more efficacious in the management of fatigue. Of note, the sample size for this analysis was small, and, thus, these results need to be interpreted with caution. Further research is required to determine exactly how the mode of intervention (therapist- vs self-guided interventions) affects the effectiveness of eHealth interventions in the management of CRF. In comparison, for live interventions, specifically multimodal exercise programs and cognitive behavioral interventions, moderate effects in the treatment of CRF were reported,[43] suggesting that life interventions are still superior to eHealth interventions. Further empirical research is clearly warranted to examine the efficacy of eHealth interventions relative to life interventions.

Most of the eHealth interventions included in this review were developed specifically for the purpose of improving fatigue in cancer survivors with CRF, which may account for their effectiveness at reducing fatigue. However, only 3 of these studies actually screened cancer survivors for fatigue prior to their enrolment.[33,46,47] This leads to the assumption that most of the cancer survivors investigated might not have suffered from moderate to severe CRF at baseline; consequently, the ability to observe substantial behavioral changes induced by the intervention might have been limited. In addition, the lack of differences between groups might reflect a lack of effectiveness of the intervention. Further, it is becoming increasingly difficult to establish appropriate control groups for mHealth and eHealth interventions, as society becomes more Internet and mobile app savvy. As such, not all studies included in this review and meta-analysis instructed their study subjects specifically to not access another treatment while completing the intervention. Such contamination of controls might easily lead to type II error, meaning that true treatment benefits of the intervention of interest are missed. In contrast, a number of

published study protocols were identified that were designed specifically to assess cancer survivors suffering from considerable fatigue.[44,53,57]

Suggestions for improvements in eHealth interventions voiced by cancer survivors included quick and easy use and access, real-time feedback that permits them to observe their progress over time, and ways to increase their motivation to engage in the intervention.

6.2 | mHealth interventions

Smartphones have emerged as an important tool for promoting communication between patients and health care providers, as well as for promoting patient engagement in their own health, for disease prevention, and for interventions affecting health behaviors.[58-62] However, only a few smartphone applications currently exist that are intended to improve the follow-up care of cancer survivors, relative to the rapidly growing market of mobile health applications. Thus, the development and adoption of smartphone applications targeted to fatigued cancer survivors are a relatively recent field of research. It is therefore not surprising that our search failed to identify any published RCT on mHealth interventions for CRF in cancer survivors. There are few published studies that have utilized smartphone applications as part of interventions aimed at altering health behaviors in a population of cancer patients or survivors. Most of this published literature has focused on interventions designed to enhance disease management—ranging from appointment reminders, to applications to aid in symptom recording to enhance subsequent patient-doctor discourse, to education regarding the patient's diagnosis and treatment[63,64]—or to promote adherence to dietary and physical activity guidelines.[65,66] Although these studies were limited by small sample sizes and short follow-up periods, the efficacy of mHealth interventions was consistently reported in terms of better management and delivery of cancer care, improved physical activity, and more healthy living.

Furthermore, there are some study protocols in the literature for planned trials that encompass mHealth interventions for cancer survivors,[67-72] suggesting that mHealth intervention studies will increase considerable over the next few years.

6.3 | Adoption and adherence to usage

Achieving adherence to healthy behaviors over time is 1 of the biggest challenges for eHealth interventions, as the dropout rate can be high.[73] Dropouts include patients lost to follow-up and patients who fail to comply with using the intervention. In the current review, however, none of the studies measured utilization over time. In contrast, in the existing literature, high user acceptability of eHealth interventions was expressed by cancer survivors with fatigue. This being said, the samples included in the eligible studies might be affected by selection bias. Cancer survivors who participated in the RCT might not be representative of cancer survivors overall, with older patients considerably under-represented, because most of the patients were recruited via the Internet. While the literature assumes that minorities use the internet as much as Caucasians, individuals lacking a high school education, and those with low household incomes (less than $20 000 per year) tend to use the internet less. Therefore, future studies should include cancer survivors who are more diverse in age, gender, and ethnicity to achieve more clinically applicable results.

6.4 | Quality assessment

The methodological quality of the studies reviewed varied. Although the average rating for methodology was good, the trials included in our review had several potential sources of bias and error. In particular, insufficient information regarding allocation concealment, and the lack of blinding participants and personnel as well as outcome assessors might have biased results. These were the most important reasons for low methodological quality scores.

In addition, we evaluated the quality of the selected studies by assessing whether or not CRF was confirmed via standardized, validated outcome measures prior to study inclusion. We found that levels of fatigue were screened prior to patient enrollment in only 3 of the 9 eligible studies. This might have substantially limited the studies' ability to detect significant improvements in fatigue with the intervention, as well as the generalizability of findings.

7 | STUDY STRENGTHS AND LIMITATIONS

This systematic review used a robust search strategy and is reported in accordance with PRISMA guidelines. Strict inclusion and exclusion criteria were applied by 2 independent authors. Nonetheless, there also were limitations that should be considered. First, difficulties exist both in defining and measuring CRF, due to its subjective nature.[74] We tried to address this problem by only including studies that used standardized, scientifically validated measures for fatigue. Second, the number of eligible studies included in the meta-analysis was small, and there was considerable heterogeneity in the outcome measures assessed. Third, the fact that only 3 studies assessed fatigue at pretreatment is a significant limitation in the literature and for this paper. Moreover, the rigor by which investigators adhere to the methodology varied and might have introduced bias. Methodological sources of bias and threat to study validity may negatively impact research translation and may hinder progress. Following principles of methodological rigor and transparent reporting practices is therefore imperative in the context of clinical studies. Fourth, the lack of comparable data between different study interventions and for different outcomes, again due to substantial heterogeneity, forced us to perform less reliable descriptive data synthesis instead of the more robust meta-analysis initially intended. For this reason, the results of our meta-analysis must be considered with caution. It is likely, however, that over the next few years, the number of published RCTs assessing eHealth and mHealth interventions among cancer survivors will increase considerably, allowing for more comprehensive and robust systematic reviews. Fifthly, publication bias—the phenomenon by which studies with significant (positive) findings are more likely to be published than those without—is always a risk with meta-analysis or any review of the literature. In our analyses, indicators of publication bias were observed by funnel plot asymmetry and significant Egger's linear regression tests for HRQoL, which was 1 of our secondary outcomes of interest. Sensitivity analyses revealed that the exclusion of 1 outlier study[50]

minimized this bias. In addition, we also excluded articles not published in English, which may have biased our results, and certainly limit their generalizability. Another issue to be considered is that, in some studies,[49] improvements were observed in both the treatment and control group, an effect that might be explained by the normal resolution of fatigue due to increasing time since treatment completion (years since treatment completed: *M* = 1.9 years; range: 0.2 years to 4 years). These limitations aside, the importance of the current meta-analysis lies in its compilation of all the data currently available which should help to improve future research in this area.

8 | IMPLICATIONS FOR FUTURE RESEARCH AND CLINICAL PRACTICE

While there has been considerable progress over the past few years in the development of eHealth interventions for the management of CRF, there is still a lack of such interventions taking advantage of mHealth technologies. Of note, the device familiarity can significantly impact the preference for eHealth interventions, which may affect the efficacy of such intervention as well as the retention rate.[75,76] Specifically, older or less educated individuals may have more difficulties in navigating interventions on a mobile device and may prefer desktop or laptop computers.[76] Thus, future research should consider providing eHealth interventions with accessibility across mobile and nonmobile devices and to familiarize and train study participants in the handling of mHealth interventions on mobile devices.

Fatigue is a common and distressing symptom among cancer survivors. Designing interventions to specifically target fatigue is of clinical significance. However, as symptoms of fatigue usually co-occur with other symptoms like pain, insomnia, and depression,[12] it would be reasonable to design and utilize eHealth and mHealth interventions that seek to target these symptoms simultaneously.

In order to assess the effectiveness of eHealth interventions in the management of CRF, we recommend including not only self-report measures but also biological markers, such as markers of proinflammatory cytokines (IL-1ra, sIL-6r, IL-6, TNF-α), salivary cortisol, or heart-rate variability.[77] Further research also is needed to determine for which cancer survivors with CRF (eg, cancer type, age, gender, ethnicity) eHealth/mHealth interventions might be most helpful at decreasing fatigue severity. Additionally, future investigations should examine the benefits of eHealth/mHealth interventions for racial/ethnic minorities or patients who have limited access to health care. Furthermore, further research is needed to evaluate patient use of and satisfaction with such interventions, as well as to identify perceived barriers and facilitators, as well as strategies to increase adherence.

Moving forward, research should focus on conducting rigorous RCT with adequately powered sample sizes, longer follow-up periods, and the inclusion of cancer survivors with at least moderately severe baseline levels of fatigue.

9 | CONCLUSIONS

This systematic review and meta-analysis has shown that eHealth interventions might be beneficial at improving fatigue and other health outcomes in cancer survivors with CRF. As such, we feel that eHealth interventions present a promising addition and complement to existing face-to-face treatments and could be useful to improve self-management among such patients. However, our review also highlights the dire need for future RCT with longer follow-up periods and larger samples so that, 1 day soon, the most effective of these interventions can be integrated into regular clinical practice. Taking into account the number of recently published study protocols for eHealth and mHealth interventions for cancer survivors, there is no doubt that the body of data will increase considerably over the next few years. We predict that eHealth/mHealth interventions will assume a major role in the future development of individualized survivorship care plans.

AUTHORS' CONTRIBUTIONS

AS carried out the background research and initial screening of titles. AS also was responsible for writing the manuscript. AS and VK independently screened full-text papers for their eligibility. VK, GT, and CF made substantial contributions to the conception and design of the project and reviewed the manuscript.

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CONFLICT OF INTEREST

The authors declare no conflict of interests.

ETHICS

No ethical approval was required as this is a systematic review and meta-analysis.

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