Including people with fatigue: a systematic review and meta-analysis of physical activity after cancer treatment

Rosie Twomey^{1,2}, Samuel Yeung³, James G. Wrightson⁴, Lillian Sung⁵, Paula D. Robinson⁶, Guillaume Y. Millet^{3,7,8}, S. Nicole Culos-Reed^{3,9,10}

¹Ohlson Research Initiative, Arnie Charbonneau Cancer Institute, Cumming School of Medicine, University of Calgary, Calgary, AB, Canada; ²O'Brien Institute of Public Health, Cumming School of Medicine, University of Calgary, Calgary, AB, Canada; ³Faculty of Kinesiology, University of Calgary, Calgary, AB, Canada; ⁴Department of Clinical Neurosciences, University of Calgary and Alberta Children's Hospital, Calgary, AB, Canada; ⁵Pediatric Oncology Group of Ontario, Toronto, ON, Canada; ⁶Division on Haematology/Oncology, The Hospital for Sick Children, Toronto, ON, Canada; ⁷Univ Lyon, UJM Saint-Etienne, Inter-university Laboratory of Human Movement Biology, EA 7424, F-42023, Saint-Etienne, France; ⁸Institut Universitaire de France; ⁹Department of Oncology, Cumming School of Medicine, Calgary, AB, Canada; ¹⁰Department of Psychosocial Resources, Tom Baker Cancer Centre, Alberta Health Services, Calgary, AB, Canada

Corresponding author:

Rosie Twomey, Ph.D.

Rosemary.Twomey@ucalgary.ca

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Abstract

Background: Physical activity is recommended for the management of cancer-related fatigue (CRF), yet the evidence is primarily based on interventions delivered during cancer treatment, with no eligibility criterion for fatigue. There is a need to examine the quantity and quality of the existing literature on physical activity for clinically-relevant CRF that continues after cancer treatment (post-cancer fatigue). The objective of this systematic review was to summarize and evaluate the effect of physical activity on post-cancer fatigue in adults, using randomized trials where fatigue was an eligibility criterion. **Methods:** Studies were included if they: included adult participants with a cancer diagnosis who had completed initial cancer treatments (e.g., surgery, chemotherapy and/or radiation therapy); explicitly stated that fatigue was a participant eligibility/inclusion criterion, regardless of how this was described or assessed; involved a physical activity intervention of any type, intensity, frequency, or duration; measured fatigue as a primary or secondary outcome. Electronic databases (Ovid MEDLINE(R), Ovid MEDLINE(R) and In-Process & Other Non-Indexed Citations, Embase, PsycINFO, Cochrane Database of Systematic Reviews, and CINAHL) were last searched on October 13, 2020. Risk of bias was assessed using the Cochrane Collaboration's tool for randomized trials. Study characteristics were synthesized and a random-effects meta-analysis for the severity of fatigue across different scales at the end of the intervention was conducted. **Results:** A total of 1035 participants were randomized across 19 studies. We estimate that less than 10% of the randomized trials of physical activity for CRF include people with post-cancer fatigue. The effect of physical activity on post-cancer fatigue was modest and variable (Hedge's g -0.40; $p = 0.010$; 95% prediction intervals -1.41 to 0.62). **Discussion:** Most studies had an unknown or high risk of bias, there was substantial heterogeneity between trials and evidence for the effect of physical activity on post-cancer fatigue was graded as low quality. Including people with clinically relevant fatigue is a priority for future research in cancer survivorship. Additional transparently reported randomized clinical trials are needed to better understand the benefits of physical activity for post-cancer fatigue. **Funding:** N/A. **Registration:** PROSPERO (CRD42019136492). **Keywords:** exercise; cancer rehabilitation; chronic fatigue; post-cancer fatigue; survivorship

Introduction

Fatigue, characterized by a sensation of tiredness, weariness, or exhaustion, is a common and debilitating symptom associated with cancer or cancer treatment. Cancer-related fatigue (CRF) is a distressing, persistent sense of physical, emotional, and/or cognitive tiredness or exhaustion that is not proportional to recent activity and interferes with usual functioning [1]. CRF differs from fatigue experienced by healthy individuals because it is non-transient and less likely to be relieved by rest. Most people undergoing cancer therapy will experience CRF (e.g. ~85% during chemotherapy [2]). Although estimates of prevalence after treatment (with curative intent) vary depending on the definition and measurement of CRF, many people will experience an improvement in CRF over time once treatment is completed. However, although CRF can resolve within the first few months after treatment, for approximately 25% of people, it will continue for months or years [3–5]. The terms ‘post-cancer fatigue’ and ‘chronic CRF’ are used to describe CRF that continues for months or years after treatment (≥ 3 months is one criteria used [6–8]). For the purpose of this review, we will use the term ‘post-cancer fatigue’ to describe CRF that is clinically-relevant (i.e. moderate to severe) and continues post-cancer-treatment. Post-cancer fatigue can result in a reduction in health-related quality of life [9], increased utilization of healthcare resources [10,11], difficulties returning to work, and a reduced capability to work [12,13].

Physical activity is recommended for the management of CRF, both during and after cancer treatment [14]. This is based on evidence from more than 170 randomized trials to date [15], and there have been multiple systematic reviews on the topic in the past decade [15–19]. However, the majority of physical activity interventions are delivered during treatment, with <25% delivered after treatment completion [15]. Furthermore, relatively few randomized trials involving physical activity interventions include fatigue as an eligibility criterion [15]; thus, CRF may not be present or may only be mild at baseline. Therefore, there are relatively few studies investigating the benefits of exercise for post-cancer fatigue. We recently reported that some people with post-cancer fatigue experience post-exertional malaise (worsening of symptoms) after exercise [8]. This highlights the need to monitor tolerance of exercise and symptom exacerbation in future exercise interventions involving people with post-cancer fatigue. There is a need to examine the quantity and quality of the existing literature on physical activity for post-cancer fatigue. The objective of this systematic review was to summarize and evaluate the effect of physical activity on post-cancer fatigue in adults, using randomized trials where fatigue was an eligibility criterion.

Methods

The protocol was registered using PROSPERO (CRD42019136492; www.crd.york.ac.uk/prospere; Supplementary File 1). The Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) statement was followed for reporting [20]. For transparency, all supplementary material, data and code is openly available at: <https://osf.io/dnvsq/>.

Search Strategy

We updated the search used in a previous systematic review [15], in collaboration with co-authors of that review (LS, PDR, NCR). In the previous review, the search was conducted from 1980 to May 11, 2017. In order to identify studies indexed since May 11, 2017, we performed a new search and replicated the previous search strategy. We searched for eligible trials from 2016 to October 13, 2020, using identical search terms in the following electronic databases: Ovid MEDLINE(R), Ovid MEDLINE(R) and In-Process & Other Non-Indexed Citations, Embase, PsycINFO, Cochrane Database of Systematic Reviews, and CINAHL. The search strategy is included in Supplementary File 2.

Inclusion/Exclusion Criteria

Inclusion and exclusion criteria were defined *a priori*. Records were included if they were a full-text publication, published in English and included a randomized or quasi-randomized trial with a parallel-group design. Records were excluded if they were a study protocol, abstract or thesis. The participants had to be adults (aged ≥ 18 or described as adults) with a cancer diagnosis, who had completed initial cancer treatments (e.g., surgery, chemotherapy and/or radiation therapy). Studies had to explicitly state that fatigue was a participant eligibility/inclusion criterion, regardless of how this was described or assessed. Studies had to involve a physical activity intervention. As previously reported by Oberoi et al. [15], eligible interventions included physical activity of any type, intensity, frequency, or duration used for the management of fatigue. Physical activity was defined as any bodily movement produced by skeletal muscles, which results in energy expenditure above resting (basal) levels [21]. This included physical activity interventions categorized using the American College of Sports Medicine [21]: (i) aerobic – includes brisk walking, running, cycling, climbing stairs, working out in a gym using a treadmill, stationary bike or elliptical machine, water aerobics, aerobic dance and hiking; (ii) neuromotor – includes yoga, tai chi and qigong; (iii) resistance – includes use of free weights and dumbbells, machines with stacked weights or pneumatic resistance,

elastic tubing and resistance bands; and (iv) flexibility – includes ballistic stretches, dynamic stretching, and static stretching. Single-joint physiotherapy interventions were excluded, and cognitive behavioural therapy was excluded unless physical activity was a major focus of the intervention. Among trials comparing two different types of physical activities, either the aerobic or the activity of lower intensity was chosen as the experimental arm (with the consensus of RT, SY and JGW). As previously detailed by Oberoi et al. [15], eligible control group types included: (i) usual care or waitlist control; (ii) physical activity when studies compared two different types of physical activities such as aerobic versus resistance; (iii) non-physical activity, active control (not usual care or waitlist control) such as psychological, pharmacological or mind and body interventions; and (iv) combination (physical activity and non-physical activity, active control). Studies were included if they measured fatigue as a primary or secondary outcome. The primary difference between the present review and the previous review [15] is that the present review excluded studies if they did not include fatigue as an eligibility/inclusion criterion and if the physical activity intervention was delivered during chemotherapy or radiation therapy. We screened the 170 studies included in the previous review for eligibility in the present review according to these additional criteria (Figure 1).

Data Extraction

Search results were stored and de-duplicated in Zotero, an open-source reference management software (<https://www.zotero.org/>). Following de-duplication, screening of the references retrieved in the literature search was performed in a systematic review software (Rayaan [22]). The titles and abstracts were independently screened for eligibility by two researchers (SY, RT), blinded to the other's decisions during this initial process. Any publication considered potentially eligible by either reviewer was retrieved in full and assessed for eligibility. After this process, the inclusion of studies in this meta-analysis was determined by the agreement of both reviewers. Discrepancies between the two reviewers were resolved by consensus and adjudication by a third reviewer (JGW). Data were extracted in duplicate by two reviewers (SY and RT), and any discrepancies were resolved by consensus and adjudication by a third reviewer (JGW). Where multiple records reported on the same trial, only one record was included (that which reported on fatigue as an outcome pre versus post-intervention). Extracted variables are presented in Tables 1-3 and Supplementary File 3.

Risk of Bias

The risk of bias was assessed using the Cochrane Collaboration's tool for randomized trials [23]. RT and JGW graded each risk of bias parameter as high risk, low risk, or unclear risk based on recommendations for judging the risk of bias [23]. The approach evaluates sequence generation and allocation concealment (selection bias), blinding of participants and personnel (performance bias), blinding of outcome assessors (outcome bias), incomplete outcome data (attrition bias), selective reporting (reporting bias) and other bias. For attrition bias, we judged studies to be at high risk when more than 30% of data were missing for the post-intervention (short-term) follow-up. For reporting bias, one reviewer (RT) checked for a major discrepancy between the registered and published outcomes of these trials and decisions were reviewed by a second reviewer (JGW). A major discrepancy was defined if the registered and published primary outcomes (or fatigue outcome, if fatigue was not specified as a primary outcome) were different or assessed at a different time point, according to specific criteria described in Chen et al. [24]. The other bias category was used for baseline differences, reporting of adherence to interventions and contamination between groups. Effects may be underestimated if participants in the physical activity intervention do not adhere and if participants in the control group increase physical activity due to involvement in the study (and this may or may not be reported). We considered studies with <70% adherence to have a high risk of other bias. We did not restrict the meta-analysis to only studies that were judged as having a low risk of bias because we anticipated that few would be included. The Grades of Recommendation, Assessment, Development and Evaluation (GRADE) system was used, which classifies the quality of evidence as one of four levels: high, moderate, low, and very low [25]. Because there can be challenges with blinding, adherence and contamination in PA studies in clinical populations even if they are well designed, we did not downgrade based on this alone. Instead, we downgraded by one level if other bias (e.g. selection or attrition bias) were apparent.

Meta-Analysis

A meta-analysis for the severity of fatigue across different scales at the end of the intervention was conducted. For two trials that contained three arms (two eligible physical activity groups versus a control group) [26,27], a single pairwise comparison was created by combining data from both groups using methods recommended in the Cochrane Handbook for Systematic Reviews of Interventions [28]. Data were analyzed for the first time-point following completion of the intervention to maximize the data available and due to heterogeneity in the timing of follow-up. The meta-analysis was performed using an open-source add-on for meta-analysis (the metafor package [29]) in the statistical software environment of R [30]. For

analyses across different fatigue scales, data were synthesized using the standardized mean difference (SMD), i.e. Hedges' g , after rescaling such that higher scores reflect more fatigue. Because we anticipated heterogeneity between studies, a random-effects model was used (Hartung-Knapp-Sidik-Jonkman method [31]). Cochran's Q and the I^2 statistic were used to evaluate heterogeneity (the latter using Cochrane's rough guide to interpretation [23]). Although not a measure of absolute heterogeneity, the I^2 describes the percentage of variability in the point estimates that is due to heterogeneity rather than sampling error [23].

Results

The flow diagram of study identification and selection is presented in Figure 1. The database search identified 10,044 citations, of which 6301 were removed as duplicates, including 29 citations that were duplicated with Oberoi et al. [15] (due to a planned overlap in search dates). From the 3743 records (Supplementary File 4), we evaluated 67 full texts. Five studies met the eligibility criteria and were included in this systematic review [5,7,27,32,33]. One study required adjudication with a third reviewer [34]. That study investigated two weeks of physiotherapy for patients admitted to a palliative care service and was excluded due to the severity of the disease and high risk of deterioration in the general condition of the participants during the study period [34]. We included 16 records from Oberoi et al. for full-text evaluation based on collaboration with the authors of this review [15], and excluded two. We contacted the authors of three studies to confirm eligibility regarding treatment completion [35–37], and these were subsequently included. Therefore, a total of 19 studies were eligible for this review and were included (Figure 1). Of these 19 studies, 12 were described by the authors as pilot studies or as assessing feasibility [26,32,35–43].

Estimated Proportion of Studies with Fatigue as an Eligibility Criterion

Of the 3743 citations from our updated search, we estimate (based mainly on abstract screening alone) that approximately 92 would have met the original eligibility criteria of Oberoi et al. [15] (Supplementary File 5). This provides an estimate of the proportion of studies that included fatigue as an eligibility criterion versus the total number that used a physical activity intervention for the management of fatigue. Adding 92 to the 169 studies (in adults) included Oberoi et al. [15] gives a total of 261 studies. Therefore, we estimate that 7% (i.e. 19 of 261) of all randomized studies on physical activity for the management of CRF included fatigue as an eligibility criterion after cancer treatment.

Participant Characteristics

A total of 1035 participants were randomized across 19 studies, and the pooled loss to attrition was $19 \pm 13\%$ (mean $\pm$ SD). Of 19 studies, 12 [26,27,32,33,38–45] were conducted in people with breast cancer, and four [5,7,46,47] included >1 type but were conducted primarily in people diagnosed with breast cancer. One study included people with gynaecological cancer [37], and one did not report the cancer type [35]. Treatment received was primarily multimodal (Table 1) and was not reported in three studies [35,39,46]. The time since treatment completion ranged from 9 days to >3 years. A minimum time since treatment was specified in 10/19 of studies [5,7,27,38,42–46] and ranged from ≥ 4 weeks to ≥ 3 years. Five studies specified that people receiving ongoing/long-term hormonal therapy were eligible [7,36,38,39,42].

Figure 1. Flow diagram. The search strategy used in Oberoi et al. [15] was replicated and the search was updated to include recent records (May, 2017-October, 2020). The search resulted in 67 full text articles that were assessed for eligibility. Of the $n=170$ articles included in Oberoi et al [15], the authors identified $n=16$ that were potentially eligible for the present review given our additional eligibility criteria. Therefore, a total of $n=83$ full text articles were assessed for eligibility and $n=19$ were included in the present review. *Including 29 duplicates with Oberoi et al. [15] **Chemotherapy/primarily chemotherapy.

Table 1. Study details and measurement of fatigue

Author, year, & country	Cancer Type	Age	Total Randomized	Loss to Attrition	Treatment Received	Primary Outcome	Fatigue outcome (if not primary)	MCID (as reported)	Individual improvement/ Deterioration
Abrahams et al. 2019 Netherlands	>1 type	45±12	n=141	28%	Surgery, CT, RT, HT, TT	CIS-fatigue	-	Reliable change index ≥1.96	51% in intervention & 46% in control improved
Bennett et al. 2007 New Zealand	>1 type: Breast 77%	≥18	n=56	16%	NR	Self-reported physical activity	Schwartz Cancer Fatigue Scale	NR	NR
Bower et al. 2012 USA	Breast	40-64	n=31	6%	RT, CT, HT	Fatigue Symptom Inventory	SF-36 Vitality scale	Reliable change index 22.7	NR: Mean improvement in SF-36 of 23.9 in intervention
Campo et al. 2013 USA	Prostate	≥55	n=40	28%	Surgery, RT, CT, ADT	FACIT-F	-	3	69% in Qigong & 38 % in stretching improved; 12% & 30% deteriorated
Cantarero-Villanueva et al. 2013 Spain	Breast	25-65	n=68	10%	NR	Piper Fatigue Scale	-	2.5 points	NR
Donnelly et al. 2011 UK	Gynaeco-logical	≥18	n=33	3%	Surgery + CT, RT	MFSI-SF & FACIT-F	-	3 (FACIT-F)	NR: Mean score improved by >MCID
Galantino et al. 2003 USA	Breast	40-59	NR (n=11)	NR	CT or RT	Six-minute walk test & body mass index	Brief Fatigue Inventory	NR	75% of participants improved (both groups)
Heim et al. 2007 Germany	Breast	Range: 31-70	n=90	30%	Surgery, CT or RT, or HT	NS	Multidimensional Fatigue Inventory	NR	NR
Kim et al. 2020 Korea	Breast	20-69	n=50	4%	Surgery, CT, RT, HT, TT	NS	Piper Fatigue Scale (revised)	NR	NR
Kröz et al. 2017 Germany	Breast	18-75	n=126*	33%	Surgery, CT, RT, HT	Composite measure (PSQI & CFS-D)	Cancer Fatigue Scale (CFS-D)	NR	NR
Larkey et al. 2015 USA	Breast	40-75	n=101	14%	CT, RT	Fatigue Symptom Inventory	-	3	NR: Mean score improved by 2.5 points to 2.1 (<3 considered not fatigued)
Mayo et al. 2014 Canada	>1 type	Adults	n=26	42%	NR	FACIT-F & Fatigue Symptom Inventory	-	3-4 (FACIT-F)	55% in intervention & 25% in control improved; 25% & 45% deteriorated
Pagola et al. 2020 Spain	Breast	18-65	n=23	0%	Surgery, CT, RT, HT	PERFORM questionnaire	-	3.5	NR: Mean change scores above the MCID in both groups
Payne et al. 2008 USA	Breast	≥55	n=20	10%	Postmenopausal women receiving HT	NS	Piper Revised Fatigue Scale	NR	NR
Prinsen et al. 2013 Netherlands	>1 type: Breast 35%, Head & neck 24%	18-65	n=64	42%	Curative (surgery, CT, RT, IT, &/or HT)	NS	CIS-fatigue	NR	NR
Rogers et al. 2014 Canada	Breast	30-70	n=46	9%	Surgery, CT, RT, HT	NS	FSI & PROMIS fatigue	NR	58% had worse fatigue intensity & 37% had worse fatigue interference (FSI), though only 16% deteriorated on the PROMIS
Sandler et al. 2017 Australia	>1 type: Breast (89%) & Colon	≥18	n=46	15%	Surgery, CT, RT, HT, TT	Somatic fatigue subscale of SPHERE	-	Improvement >1SD	32% of intervention & 8% of control improved; n=2 in control deteriorated
Stan et al. 2016 USA	Breast	20-75	n=34	32%	Surgery, CT, RT, HT	Feasibility & MFSI-SF	-	NR	NR
Yuen et al. 2007 USA	Breast	Range: 32-78	n=29	24%	Surgery, CT, RT	NS	Piper Fatigue Scale	NR	n=2 had worse fatigue after intervention

Loss to attrition was calculated for the first post-intervention time-point. CIS-fatigue, fatigue severity subscale of the Checklist Individual Strength; CT, chemotherapy; FACIT-F, Functional Assessment of Chronic Illness Therapy-Fatigue; HT, hormonal therapy; IT, immunotherapy; MCID, minimal clinically important difference; MFSI-SF, Multidimensional Fatigue Syndrome Inventory-Short Form; NR, not reported; NS, not specified; PROMIS, Patient-Reported Outcomes Measurement Information System; RT, radiotherapy; TT, targeted therapy. *Total allocated.

Fatigue as an Eligibility Criterion

Across studies, there was variability in how fatigue as an eligibility criterion was assessed (Table 2). Sandler et al. [7] used an empirically derived somatic symptom subscale of the Somatic and Psychological Health Report (SPHERE) [48], where a score of ≥ 3 has been validated to designate disabling/prolonged fatigue states [49]. Two studies [5,47] used the fatigue severity subscale of the Checklist Individual Strength [50] and a cut-point of ≥ 35 , developed for use in people with chronic fatigue syndrome and also recommended for CRF [51]. Cantarero-Villanueva et al. [39] used the revised Piper Fatigue Scale [52]; the origin of the cut-point used was not stated (Table 2). Campo et al. [36] used the National Cancer Institute Common Terminology Criteria for Adverse Events [53] to qualify fatigue not relieved by rest, limiting instrumental or self-care activities of daily living. However, a score >20 on a 0-100 general fatigue grading scale was also accepted. Pagola et al. [32] used the Perform questionnaire and a cut point of <45 that was not justified by the authors but may have been based on the mean score of patients not undergoing any kind of treatment [54]. Nearly half of the studies ($n=9$) used a 0-10 numerical rating scale (NRS) or visual analogue scale (Table 2) as an eligibility criterion for fatigue. Six of these used a threshold score of ≥ 4 (Table 2) as recommended for routine CRF screening [55,56]. Kröz et al. [27] supplemented the rating with the Cancer Fatigue Scale (CFS-D) [57,58], and we were unable to determine the origin of the cut-point used, though other cut-points were available [59]. Rogers et al. used a 0-10 scale for average fatigue over the past week [42] but also accepted a rating of sleep dysfunction. The authors noted that this method was not selected based on validity/clinical judgement, but to avoid overly restrictive inclusion criteria that would have impeded their ability to recruit within a time frame limited by budgetary constraints. Payne et al. also used a score of ≥ 3 and specified three components (rating of usual fatigue, frequency and interference) [41]. In a lenient use of a 0-10 NRS, Donnelley et al. included participants if they scored ≥ 1 [37].

Table 2. Fatigue as an eligibility criterion

Study	Time Since Treatment	Questionnaire	Cut-point used	Other details or descriptions
Abrahams et al. [60]	Minimal 1 year	CIS-fatigue [50]	≥35 [51]	“severe fatigue”
Bennett et al. [46]	≥6 months	NR	NR	“fatigued”
Bower et al. [38]	≥6 months since local & adjuvant therapy (except HT)	SF-36 vitality scale [61]	≤50	“and self-report that fatigue was a consequence of cancer or cancer therapy” The SF-36 consists of four items that assess how much of the time (from “none of the time” to “all of the time”) an individual “felt full of pep,” “had a lot of energy,” “felt worn out,” and “felt tired” during the past four weeks.
Campo et al. [36]	NS: Median of ~5 years since diagnosis [#] Current HT: 48%	NCI CTCAE [53], or a 0-100 general fatigue grading	≥1 or >20, respectively	“Significant fatigue” - NCI CTCAE ≥1 = fatigue not relieved by rest, limiting instrumental or self-care activities of daily living [53] - General fatigue grading: “fatigue currently and in the past week”
Cantarero-Villanueva et al. [39]	Finished treatment in the previous 18 months (except HT)	Piper Fatigue Scale	>3	Responses to this scale are based on “the fatigue you are experiencing now”.
Donnelly et al. [37]	Undergoing treatment or post therapy & within 3 years of diagnosis (mean months = ~9±9 months)	0-10 numerical rating scale	1-10	“mild to severe fatigue”
Galantino et al. [40]	Had undergone adjuvant treatment in the past year	NR	-	“suffering from self-reported fatigue”
Heim et al. [44]	>6 weeks since surgery, RT or CT	0-10 linear analogue scale	≥4	-
Kim et al. [33]	NS: Completed CT & RT ≥6 months and <5 years from enrolment	“More than 4 out of 10”	≥4	“experienced greater than moderate fatigue”
Kröz et al. [27]	≥36 months since surgery, CT or RT & <45 months since diagnosis	Fatigue Numerical Scale & Cancer Fatigue Scale (CFS-D) [57,58]	≥4 & ≥24, respectively	“diagnosis of chronic CRF for >6 months” CFS-D: Responses to this scale are based on “current state”
Larkey et al. [45]	6 months to 5 years (since surgery, CT, RT)	SF-36 vitality scale [61]	≤50	-
Mayo et al. [35]	NR (during & after rehabilitation) [#]	0-10 visual analogue scale	≥4	“moderate to severe fatigue”
Pagola et al. [32]	≤5 years since treatment	Perform questionnaire [32]	<45	-
Payne et al. [41]	NR	0-10 scale	≥3	Participants were asked: How do you rate your usual rate of fatigue (0 = no fatigue & 10 =extreme fatigue)? How frequently do you feel that level of fatigue? To what extent does your fatigue interfere with usual activities of daily living?
Prinsen [47]	Completed curative treatment <1 year earlier	CIS-fatigue [50]	≥35 [51]	“severe fatigue”
Rogers et al. [42]	≥4 weeks after primary (except HT), >8 weeks after surgery	0-10 Likert scale or 0–3 Likert scale	≥3 or ≥1, respectively	0-10: average fatigue over past week 0-3: sleep dysfunction
Sandler et al. [7]	3-12 months (except HT)	Somatic fatigue subscale of SPHERE [48]	≥3	SPHERE asks about the prevalence of symptoms over the “past few weeks” and has a conservative scoring algorithm where “never” or “some of the time” are both designated as 0. A score of ≥3 has been validated to designate disabling/prolonged fatigue states [49].
Stan et al. [43]	4-12 months post-surgery, ≥2 months post RT/CT	0-10 single numeric analogue scale	≥4	-
Yuen et al. [26]	Completion of RT &/or CT (range: 9 days to 35 months)	0-10 numeric rating scale	≥4	-

CIS-fatigue, fatigue severity subscale of the Checklist Individual Strength; CT, chemotherapy; NCI CTCAE, National Cancer Institute Common Terminology Criteria for Adverse Events; NR, not reported; NS, not specified; PSQI, Pittsburgh Sleep Quality Index; HT, hormonal therapy; RT, radiotherapy; SPHERE, Somatic and Psychological HEalth Report; [#]authors confirmed treatment completion.

Measuring and Monitoring Fatigue

Overall, 13 different scales were used across the 19 studies (Table 1), indicating that there was no consensus on the measurement of CRF before and after a physical activity intervention. Only 11 studies specified that fatigue was a primary outcome. Five studies did not specify a primary outcome in the paper (Table 1). Only two studies used the same tool for both the screening for and measurement of fatigue [32,60]. Three studies used more than one fatigue scale to measure fatigue as an outcome [37,38,45].

Six studies specified the minimal clinically important difference (MCID) in fatigue in the methods [7,32,35,37,39,60], though only of these four reported on this in the results/discussion [7,32,37,60]. Three further studies considered the MCID [36,38,45], and the remainder ($n=10$), did not (Table 1). Six studies considered improvement or deterioration of fatigue on an individual level [7,26,35,36,42,60] (Table 1). Despite relatively small sample sizes (ranging from 5-42 participants in the intervention arm), no study plotted individual trajectories from pre- to post-intervention.

Characteristics of the Intervention

The characteristics of the interventions are presented in Table 3. Half the interventions were categorized as aerobic, four included a combination of resistance and aerobic exercise, three were neuromotor, and one was resistance only. Several interventions were multimodal, including behavioural support alongside physical activity. More than half of the interventions were 12-weeks long, and the others ranged from 6-24 weeks. Most of the interventions were home-based, some were fully or partially supervised, there was variation in exercise frequency and duration, and when exercise intensity was reported, it was mainly low to moderate and monitored using heart rate or rating of perceived exertion. Several studies did not include details regarding exercise progressions (Table 3) or adherence (Supplementary File 3) and only six studies described any adverse events [27,32,38,39,43,45]. Therefore, most studies did not include the minimum data set considered necessary to report exercise interventions [62].

Table 3. Intervention characteristics

Author	ACSM Category	Intervention Description	Duration (weeks)	Supervision/ Delivery	Frequency (per week)	Intensity	Time (min)	Progression	Comparator /Control	Monitoring of fatigue
Abrahams et al. [60]	Aerobic	Graded exercise therapy (GET)	~12	Non-supervised PA, 6±2 GET sessions (a component of CBT)	14	Low	3-120 min	Graded increases in duration by 1 min, up to 60 min twice daily	Other components of CBT	NS: likely discussed in sessions with therapists as part of GET
Bennett et al. [46]	Aerobic	Motivational interviewing for physical activity	24	Non-supervised, initial in-person session & 3 phone calls	Goal = most days	Moderate	Goal = 30	NR	Usual care	NS: participants asked about adverse events or problems during each call
Bower et al. [38]	Neuromotor	Iyengar yoga classes	12	Supervised, groups of 4-6	2	NR	90	Postures progressed from simpler to more challenging	Health educations classes	NR
Campo et al. [36]	Neuromotor	Qigong (eccentric focus)	12	Supervised classes & home-based (DVD)	2 classes	Somewhat strong (RPE 0-10 of ~4)	60	Progression to more time performing standing movements	Non-aerobic stretching	NR
Cantarero-Villanueva et al. [39]	Aerobic	Deepwater aquatic exercise	8	Supervised, groups of 10-12	3	Moderate	60	NR	Usual care	NS: discomfort or low-intensity pain/stiffness after an exercise session was reported
Donnelly et al. [37]	Aerobic & Resistance	Walking & strengthening exercises	12	Home-based, initial in-person consultation & weekly calls	Goal = at least 5	Moderate (RPE 6-20 of 12-13)	30	NS: Physical activity levels discussed weekly	Usual care	NR
Galantino et al. [40]	Aerobic	Walking (video & written instructions)	6	3 supervised group sessions & home-based with weekly calls	Goal = at least 3	Monitored (RPE & HR), NR	60	NR	Tai Chi	A weekly journal inquired about the nature of fatigue before & after exercise
Heim et al. [44]	Aerobic & Resistance	Strength exercises & walking (demonstrations & brochure)	NR	During an in-patient complex rehabilitation program	Aerobic: 2 RT: 3	NR	30	NR	Complex rehabilitation (usual care)	NR
Kim et al. [33]	Aerobic & Resistance	Exercise adherence program based on social capital	12	Supervised groups of 3-6 for 8 sessions & home-based	1 (6 weeks) 2 (6 weeks)	Low-High	NR	NR	Written information on exercise	NS: Exercise journal provided
Kröz et al. [27]	Aerobic	Aerobic training	10	8 trainer-led sessions complemented by home-based training	3-5	Monitored, NR	30-45	Performance adjustments based on HR	Multimodal therapy	NS: Subjective health complaints reported were recorded & graded
Larkey et al. [45]	Neuromotor	Qigong/Tai Chi Easy	12	Both supervised & home-based	Goal = 5	Low	30-60	NR	Sham Qigong	NR
Mayo et al. [35]	Aerobic	Individualised walking program	8	Non-supervised (pedometer & weekly calls)	Daily (steps per day)	NR	NR (steps per day)	Based on rating of fatigue (10% weekly ↑ or ↓)	Usual care (rehabilitation program)	Weekly calls to ascertain level of fatigue
Pagola et al. [32]	Aerobic & Resistance	High-intensity aerobic & resistance exercise	16	Supervised	2	RPE 0-10, Aerobic: 7-8 RT: 6-7	75	Aerobic: based on RPE 7-8/10 RT: Increase in sets	RT & non-supervised moderate aerobic exercise	NS: Number of RT exercises depended on perceived fatigue
Payne et al. [41]	Aerobic	Walking exercise intervention	14	Non-supervised & home-based	2	Moderate	20	NR	Usual care	NR
Prinsen [47]	Aerobic	CBT including a physical activity (walking or cycling)	24	Home-based physical activity (in-person CBT)	14 (2/day)	NR	5-120	From 5-10 min up to 90-120 min per day	Waitlist control	NR

Rogers et al. [42]	Aerobic & Resistance	Walking & strength training with behavioural support	12	Supervised (26 sessions) + home-based walking	Walking: 4 Resistance: 2	Moderate (48-52% HRR)	40	Walking: gradually advanced RT: advanced as tolerated at 2 wk intervals	Usual care	<i>NS</i> : Non-serious adverse events reported (e.g. modification of resistance exercise due to lymphedema)
Sandler et al. [7]	Aerobic	Combined GET/CBT	12	5 consultations with an EP & 6-8 with a psychologist (home-based GET)	Regular	Low	30	GET (graduated increases in duration to 30 min, then increase in frequency)	Education package (principles of CBT/GET)	GET & activity pacing (CBT) encourages participants to avoid exacerbations of fatigue
Stan et al. [43]	Resistance	Strengthening exercises	12	Home-based (DVD)	3-5	<i>NS</i> : 'Rapid Easy Strength Training'	20	<i>NR</i>	Yoga	<i>NS</i> : Bi-monthly phone calls to assess & document side-effects
Yuen et al. [26]	Aerobic & Resistance	Aerobic & resistance exercise	12	Home-based	3	Aerobic: RPE 6-20 of 10-13	20-40	Aerobic: <i>NR</i> Resistance: Progress in no. of circuits (from 1-3) & resistive load	Usual care	Monthly calendars to record fatigue each day (0-10 NRS). Calendars collected at 12 wks

ACSM, American College of Sports Medicine; EP, exercise physiologist; CBT, cognitive behavioural therapy; GET, graded exercise therapy, HR, heart rate; HRR, heart rate reserve; *NR*, not reported; NRS, numerical rating scale; *NS*, not specified; RPE, rating of perceived exertion.

Risk of Bias (Figure 2, Supplementary File 6)

Most studies were considered to be at low risk of selection bias related to random sequence generation (two at high risk [27,44] and three at unclear risk [35,40,41]) and allocation concealment (two at high risk [27,44] and seven at unclear risk [26,32,33,35,40,41,43]). Larkey et al. [45] used a form of ‘sham’ QiGong to blind participants, but the personnel delivering the interventions were not blinded. Some bias is inherent to exercise studies even if they are well-designed, due to the inability to blind participants. All studies except Larkey et al. were at high risk of detection bias (where the participant is the assessor for patient-reported outcomes, and knowledge of the intervention could influence the outcome). Most studies were considered to be at low risk of attrition bias, but four studies were at high risk of attrition bias due to >30% attrition and/or unequal attrition between groups [27,35,43,44,47].

Only seven studies included a reference to a trial registration [7,27,36,37,47,60,63], and Prinsen et al. also cited a study protocol [47]. However, only three studies were prospectively registered [32,47,60], and only two of these could be considered low risk of reporting bias (Figure 2). By definition [24], the comparison in the paper by Sandler et al. resulted in a discrepancy with the trial registration and was rated as high risk of reporting bias due to a difference in the primary outcome between the trial registration (an improvement in fatigue as assessed as a global score from a structured clinical interview) versus the paper (an improvement in fatigue assessed using a scale) [7]. In practical terms, both outcomes are essentially a self-report of fatigue, but the justification for the switch should have been noted in the paper. There were no further major discrepancies, but Prinsen et al. was rated as unclear risk of reporting bias because the trial registration listed numerous primary outcomes, and the primary outcome was not specified in the paper [47]. Other details for trial registrations are reported in Supplementary File 7. For the other nine studies, we were unable to find trial registrations. Five were conducted after the 2008 Declaration of Helsinki Revision regarding prospective registration as a principle of medical research. Three studies were considered to be at high risk of other bias due to baseline differences [46,47,58], and the risk was unclear in three studies [37,40,41]. Four studies were at high risk of other bias due to adherence of <70% [36,37,43,58]. Adherence was unclear or not reported in seven studies [35,40,41,44,46,47,60]. Finally, six studies were at high risk of other bias due to contamination (due to increases in physical activity in the control groups and/or due to similarities in physical activity levels between groups [7,32,37,44–46]).

Figure 2. Risk of bias summary. *Not included in the meta-analysis.

Meta-Analysis

Sixteen studies were included in the meta-analyses (data from 758 participants) [7,26,27,32,33,35,37–39,42,43,45,46,60,64]. Three studies were excluded due to a lack of data or lack of response to a request for additional data. Data from one study [44] was extracted from a figure using WebPlotDigitizer [65]. Data, code and additional details for the meta-analysis are available in Supplementary Files 8 and 9. The reduction in the severity of fatigue in the physical activity intervention compared to control was $g = -0.40$ (95% CI -0.68 to -0.11; $p = 0.010$; Figure 3). The 95% CI in this random-effects model contains highly probable values for the mean effect of physical activity. However, the 95% prediction intervals (-1.41 to 0.62; Figure 3) provide information on the range of treatment effects that are likely to be seen in other settings (future studies or when working with people with post-cancer fatigue in an exercise oncology setting) [66]. The prediction interval demonstrates that although larger effects in the direction of benefit (i.e. a decrease in fatigue) are included, it also contains values above zero, meaning that physical activity may have no effect or may lead to worse fatigue in some settings/participants (as also noted in Table 1 and in previous reviews [17]). In addition,

the Cochran's Q indicated variation across studies ($Q = 45.64, p < 0.001$) and the I^2 statistic was 67% (95% CI 44.6 to 80.50%), which may represent substantial heterogeneity [28].

Figure 3. Forest plot for standardized mean difference (SMD) effect size for post-intervention CRF. The grey squares represent the SMD, and the left and right extremes of the squares represent the corresponding 95% confidence intervals. The grey diamond represents the overall effect and the bold black line represents the prediction interval, derived from the SMD and 95% CI.

Using GRADE, the quality of the evidence (the extent of confidence that an estimate of effect is correct) was downgraded to low quality (i.e. further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate) [25]. The evidence was downgraded one point due to study limitations (high risk of bias) and one point due to inconsistent results (high heterogeneity) [25].

Exploratory sub-analysis showed that (i) removing $n=3$ studies that included physical activity in the control group (e.g. of a lower intensity) had very little influence on the primary meta-analysis ($g = -0.42$; 95% CI -0.77 to -0.08; prediction interval -1.55 to 0.70; $p = 0.020$; Supplementary File 10); (ii) the summary effect was slightly reduced and not statistically

significant in $n=8$ studies reporting change scores from pre- to post-intervention ($g = -0.34$; 95% CI -0.81 to 0.13 ; prediction interval -1.61 to 0.94 ; $p = 0.135$; Supplementary File 11) and (ii), the summary effect was reduced and not statistically significant in $n=7$ studies reporting a follow-up measurement of fatigue ($g = -0.23$; 95% CI -0.65 to 0.18 ; prediction interval -1.29 to 0.82 ; $p = 0.221$; Supplementary File 11).

Discussion

The primary objective of this review was to summarize the evidence for the effect of physical activity on CRF after cancer treatment in adults, based on randomized trials where fatigue was an eligibility criterion. We found 19 studies that met our inclusion criteria indicating that only ~7% of all randomized trials on physical activity for the management of CRF are designed to include people with fatigue after cancer treatment, and to date, most of these are pilot/feasibility trials. Most studies were at a high or unknown risk of more than one type of bias (excluding performance and detection bias), the evidence was graded as low quality, and it was rarely possible to determine if participants were experiencing a chronic fatigue state.

Fatigue as an eligibility criterion

To investigate post-cancer fatigue, a study must include participants who are experiencing CRF (a distressing, persistent sense of tiredness or exhaustion that interferes with usual functioning associated with cancer or cancer treatment [1]) that has not resolved over a prolonged period (e.g. several months). To ensure fatigue is cancer-related, alongside an evaluation of CRF onset and history, studies should exclude based on factors other than cancer/cancer therapy that may be the cause of fatigue. These include psychiatric disorders (e.g. a major depressive episode or psychosis), anemia, sleep disorders (e.g. untreated sleep apnea or restless leg syndrome), untreated hypothyroidism, autoimmune-related disorders (e.g. systemic lupus or rheumatoid arthritis) or shift work. Most studies ($n=14$) reported that they excluded participants based on a psychiatric disorder, but only half of the studies included consideration of factors that might explain CRF [7,26,27,33,37,38,42,45,47,60], rather than only exclusion criteria based on contraindications to physical activity.

Although not all included studies used the terms ‘post-cancer fatigue’ or ‘chronic CRF,’ there was good congruence between the purpose of this review and the aims of the included studies. Therefore, it is surprising that most studies did not fully consider the screening and measurement of CRF (with some exceptions, e.g. [7]). Half of all studies reported the minimum

time since treatment completion (Table 1), and half excluded participants based on other common causes of fatigue. Furthermore, there was uncertainty about the validity of most of the questionnaires and/or cut-points used as an assessment of CRF severity because it was unclear if the method was able to differentiate clinically-significant CRF from everyday tiredness. Two studies [38,45] used the vitality (energy and fatigue) scale of the 36-Item Short-Form Health Survey (SF-36) [61]. Beginning in 2000 [9], Bower et al. used the mid-point of the SF-36 to dichotomize participants into fatigued and non-fatigued groups, where >50 represents well-being, and ≤ 50 represents limitations or disability related to fatigue. The extent to which this is a valid cut-point for moderate-severe CRF is not certain (for example, an individual could answer “some of the time” for all four of the above items for a score of 42), but the cut-point has since been used in several studies and differences in, for example, proinflammatory cytokine activity between groups have been found [67].

Finally, two studies did not report the scale/method used for eligibility based on the presence of fatigue but reported that participants were included if they were “fatigued” [46] or were “suffering from self-reported fatigue” [40]. Using an arbitrary or overly lenient definition of CRF may result in the inclusion of people who have negligible or mild fatigue. However, this can be avoided because there are well-established questionnaires with validated and clinically meaningful cut-points for the assessment of CRF severity [68–70]. Half of all studies used a 0–10 NRS for fatigue, and most did not report the framing of the question or recall period (e.g. fatigue right now, average fatigue over the past week, etc.). Although a 0–10 NRS is recommended for the routine screening of CRF in clinical practice [55,56], it is not recommended as the only screening method for eligibility in a randomized trial focussed on CRF. The guidelines state that a score of ≥ 4 should be followed by a focused assessment [55,56], and this was not the case for studies using a 0–10 NRS.

In recent studies that include a physical activity intervention and explicitly focus on CRF, there is little consensus in the literature for the cut-point to evaluate fatigue - even when the most widely-recommended questionnaire is used (the FACIT-F). For example, recent studies have used a cut-point of <45 [71], which is described as arbitrary in the study that first used it [72]. Others have used a cut-point of <42 [73] or <43 [74], where 43 is the score which divided groups based on analysis of the general population versus patients with chemotherapy-induced anemia (Hgb <11.0 g/dL) [75]. Scales used to measure CRF have been reviewed elsewhere [76–78]. One framework that should be considered is the consensus-developed diagnostic

criteria, as proposed for the International Statistical Classification of Diseases and Related Health Problems, 10th revision (ICD-10) [79]. To help operationalize this without a diagnostic interview, the FACIT-F has a cut-point (<34) that correctly identifies over 90% of 'ICD-10 positive' cases and has been recommended for the 'diagnosis' of CRF [69].

Meta-analytic evidence for the effect of physical activity on post-cancer fatigue

As shown in other meta-analyses, physical activity has a beneficial effect on CRF, but the effect is small to moderate (e.g. $-0.30 - 0.49$) [15,18]. It has previously been suggested that physical activity may be most beneficial if those most in need are targeted (i.e. people with more severe or persistent CRF) [14,80]. However, in the present study, we found a similarly small-moderate (-0.40) effect to those earlier meta-analyses. One conclusion could be that the effect of physical activity on CRF is consistent and modest. However, there was substantial heterogeneity, and as we have outlined above, limitations with the definition of CRF in the included studies. Therefore, it is possible that the small effect is a result of methodological decisions made in the included studies, and our meta-analysis may involve the same problems as the previous literature. Indeed, in a quasi-experimental non-randomized study, Sheehan et al. [71] included people with moderate-severe CRF after cancer treatment (mean scores of ~ 20 on the FACIT-F). In this study, a large effect of ~ 1.33 for the effect of progressive exercise vs. health education was observed. This suggests that people with severe CRF may benefit more within a tailored and partly-supervised physical activity intervention [71]. Future well-designed studies in people with post-cancer fatigue may help confirm this finding.

Exploratory sub-analysis showed that (i) removing $n=3$ studies that included physical activity in the control group (e.g. of a lower intensity) had little influence on the primary meta-analysis ($g = -0.42$; 95% CI -0.77 to -0.08 ; prediction interval -1.55 to 0.70 ; $p = 0.020$; Supplementary File 10); (ii) the summary effect was slightly reduced and not statistically significant in $n=8$ studies reporting change scores from pre- to post-intervention ($g = -0.34$; 95% CI -0.81 to 0.13 ; prediction interval -1.61 to 0.94 ; $p = 0.135$; Supplementary File 11) and (ii), the summary effect was reduced and not statistically significant in $n=7$ studies reporting a follow-up measurement of fatigue ($g = -0.23$; 95% CI -0.65 to 0.18 ; prediction interval -1.29 to 0.82 ; $p = 0.221$; Supplementary File 12).

Monitoring of fatigue

Although it was not the primary aim of the study, we did pre-specify our interest in the monitoring of fatigue in included studies. We have recently reported that some people with post-cancer fatigue may experience post-exertional malaise [8]. Almost half of the included studies did not report any method for monitoring fatigue during the intervention. We acknowledge that these studies may have included monitoring and not reported it and that some studies instead reported the number of participants that deteriorated from pre- to post-intervention alongside the number of participants who improved (Table 1). One study did advise that some participants will not experience improvements in their fatigue with an exercise intervention (based on the findings therein) [42]. Monitoring fatigue and adjusting exercise dose/intensity to avoid symptom exacerbation is important because not doing so may increase attrition and/or lead to deflated effect sizes. We suggested that a 0-10 NRS is well suited to frequent monitoring of momentary fatigue for regular review by an exercise professional, and this could be combined with a patient diary as used in some of the included studies.

Limitations

Because physical activity was often one component of a multimodal intervention, it was not always possible to know the independent contribution of physical activity to an improvement in CRF. However, in at least one study [47], the effects of the intervention were not mediated by a change in physical activity. Thirteen studies reported raw means and standard deviations for participants with complete data (post-intervention). Only three studies included missing values carried forward (i.e. used the intention to treat analysis, which avoids overoptimistic estimates of the benefits of an intervention), and this is reflected in the sample sizes (Supplementary File 8).

We acknowledge that although fatigue at baseline is rarely an eligibility criterion in studies on physical activity for CRF, this is not synonymous with fatigue being rarely present at baseline. Most studies explicitly focussed on CRF without an eligibility criterion for fatigue, likely include a subset of participants with moderate-severe CRF. Arguably, the people most in need are those with advanced cancer with a high symptom burden. Although not a limitation per se, in our screening (Supplementary File 5), we noticed that there are very few studies on physical activity for CRF in people living with end-stage cancer. In this population, supportive care interventions and trials are challenging, and at least in the short-term, an eligibility criterion for CRF may be overly restrictive.

Recommendations for research on physical activity for post-cancer fatigue

Along with prospective trial registration and transparent reporting practices, our synthesis of the evidence on physical activity resulted in several specific recommendations for designing future trials on post-cancer fatigue:

- Fatigue severity should be clinically relevant. This could be identified using a validated cut-point on a questionnaire with known psychometric properties, e.g. <34 [69] on the FACIT-F [70,81].
- The time since fatigue onset that is used to define ‘post-cancer fatigue’ or ‘chronic CRF’ should be specified and justified.’
- Participants should be excluded based on factors other than cancer/cancer therapy that may be the cause of fatigue (e.g. psychiatric disorders).
- The primary outcome should be a questionnaire that is validated for the measurement of CRF.
- The validated MCID or the change score of interest must be pre-specified, and the number of participants improving or deteriorating must be reported using this score.
- Fatigue should be monitored during the intervention, and data on symptom exacerbation must be reported.
- The intervention should be tailored and guided by an exercise professional to monitor fidelity, support adherence and reduce attrition.
- A complete description of the intervention in line with international reporting guidelines [62,82] must be included so other researchers can replicate the intervention and build on research findings.
- The protocol and all findings must be transparently reported (using supplementary files or archives such as the Open Science Framework as needed) [83].

Conclusion

We estimate that less than 10% of the randomized trials of physical activity for CRF after cancer treatment include fatigue as an eligibility criterion. Based on limited data and substantial heterogeneity between trials, the benefit of physical activity for post-cancer fatigue is modest and variable. Additional transparently reported randomized clinical trials are needed to better understand the benefits of physical activity for post-cancer fatigue.

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Conflicts of interest/Competing interests

The authors have no conflicts of interest to disclose.

Availability of data and material

Openly available at: <https://osf.io/dnvsq/>

Contributions

RT: Conceptualization, Methodology, Investigation, Formal analysis, Data curation, Writing - original draft, Visualization, Project administration.

JGW: Conceptualization, Investigation, Formal analysis, Validation, Visualization, Writing - review and editing.

SY: Investigation, Writing - review and editing.

LS, PDR & GYM: Writing - review and editing.

SNCR: Conceptualization, Supervision, Writing - review and editing.

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