The Effect of Exercise on Cancer-Related Cognitive Impairment and Applications for Physical Therapy: Systematic Review of Randomized Controlled Trials

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Background. Cancer-related cognitive impairment (CRCI), often called "chemo-brain" or "chemo-fog," is a common side effect among adults with cancer, which can persist well after treatment completion. Accumulating evidence demonstrates exercise can improve cognitive function in healthy older adults and adults with cognitive impairments, suggesting exercise may play a role in managing CRCI.

Purpose. The purpose was to perform a systematic review of randomized controlled trials (RCTs) to understand the effect of exercise on CRCI.

Data Sources. Relevant literature was retrieved from CINAHL, Medline (Ovid), and EMBASE.

Study Selection. Eligible articles were RCTs that prescribed aerobic, resistance, combined aerobic/resistance, or mind-body (eg, yoga or Qigong) exercise during or following cancer treatment and included cognitive function outcome measures.

Data Extraction. Descriptive information and Cohen *d* effect sizes were directly extracted or calculated for included trials.

Data Synthesis. Twenty-nine trials were included in the final analysis. A statistically significant effect of exercise on self-reported cognitive function, both during and postadjuvant treatment, was reported in 12 trials (41%) (Cohen *d* range: 0.24–1.14), most commonly using the EORTC QLQ-C30. Ten trials (34%) performed neuropsychological testing to evaluate cognitive function; however, only 3 trials in women with breast cancer reported a significant effect of exercise (Cohen *d* range: 0.41–1.47).

Limitations. Few RCTs to date have evaluated the effect of exercise on CRCI as a primary outcome. Twenty-six trials (90%) in this review evaluated CRCI as secondary analyses.

Conclusions. Evidence supporting exercise as a strategy to address CRCI is limited. Future research evaluating CRCI as a primary outcome, including self-reported and objective measures, is needed to confirm the possible role of exercise in preventing and managing cognitive impairments in adults with cancer.

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Reduced cognitive function is a commonly reported side effect of cancer and its treatment, including chemotherapy.[1,2] Specifically, cancer patients report and exhibit difficulties with learning, memory, attention, concentration, processing speed, and executive function.[3] Up to 85% of patients receiving cancer treatment have been found to report mild to severe cognitive complaints, which can last months and even years after treatment completion. Along with significantly impacting overall quality of life, cancer-related cognitive impairment (CRCI) can adversely affect activities of daily living and interpersonal relationships.[1,2] Clinicians commonly use self-report of symptoms to identify individuals with CRCI and may use standardized questionnaires or objective neuropsychological tests to monitor change over time or with an intervention. However, at this time, there is no established cut-point for CRCI using standardized, self-report questionnaires or objective neuropsychological tests.

The precise mechanisms underlying the pathophysiology of CRCI are unclear. Preclinical and clinical research supports the potential contribution of chemotherapy directly to: (1) neurotoxic effects on brain structure and function (eg, white matter damage, inhibition of neurogenesis, altered neurotransmitter levels), (2) inflammatory reactions triggering elevated levels of neurotoxic cytokines, (3) oxidative stress, and (4) alterations to central nervous system vascularization and blood flow.[3–7] However, CRCI has been linked to a variety of cancer treatments, including surgery, radiation, and hormonal therapy, in addition to chemotherapy.[8] Other prevalent side-effects of a cancer diagnosis and treatment, such as fatigue, anxiety, depression, stress, and sleep dysfunction, may moderate or mediate effects on cognitive performance and vice versa.[8,9] Demographic factors are also known to affect cognition in adults, including age, race, socioeconomic status, and education, as well as menopausal status, health status, and body mass index.[10–13] In light of the prevalence and associated individual burden of CRCI, there is a clear need for strategies to manage CRCI. Currently, no established treatment options exist to reduce the risk of CRCI or diminish its severity.[14–16] Pharmacological therapies aimed at putative mechanisms (eg, inflammation, oxidative stress, or catecholamine action) for CRCI have been tested with limited success.[14–16] Cognitive behavioral therapies and other memory training approaches (eg, teaching cognitive compensatory strategies) have also shown limited efficacy in managing CRCI.[17–19] In contrast, exercise has been established as a safe and effective therapy for the management of numerous adverse effects of cancer treatments, including fatigue, psychological distress, functional decline, and detrimental body composition changes.[20] Based on the accumulating evidence for the positive role of exercise in improving cognitive function in healthy older adults[21] and those with mild cognitive impairment or more severe neurocognitive impairment (eg, Alzheimer's disease, stroke),[22,23] there is significant interest in the potential of exercise as an effective management strategy for CRCI.

Recent observational studies in women with breast cancer who received chemotherapy have reported positive associations between cognitive function and aerobic exercise, measured by self-report,[24,25] accelerometers,[26,27] and aerobic fitness.[24,27] In a systematic review of randomized and nonrandomized rodent and human trials, an emergent benefit of exercise on CRCI was reported within a small number of interventional studies compared with usual care.[28] In particular, benefits of exercise on self-reported cognitive function in women with breast cancer were identified.[28] Since then, understanding the potential role of exercise in counteracting CRCI is a growing area of interest for the exercise oncology field, and the available literature has expanded to include additional randomized controlled trials (RCTs). Therefore, the purpose of the current systematic review is to provide a comprehensive update and summary of RCTs in humans to date that have examined the effect of exercise on CRCI in individuals with cancer. We also discuss implications of the available data for physical therapy practice and highlight future research directions.

Methods

Data Sources and Searches

This systemic review was performed in accordance with the Preferred Reporting Items of Systematic Reviews and Meta-analyses statement. A literature search was conducted using CINAHL, Medline (Ovid), and EMBASE from the earliest available year for each database (CINAHL: 1937; Medline (Ovid): 1946; EMBASE: 1947) and up to November 2018. Search strategies were predefined and created in collaboration with a trained research librarian at the University of British Columbia. Subject headings and keywords included those relating to cancer (eg, neoplasm, cancer, tumour, or malignancy), exercise (eg, exercise, physical activity, aerobic training, strength training, or mind-body exercise), and cognition (eg, cognitive function, neuropsychological tests, attention, memory) and were combined with an "AND" term. Search terms were modified according to suggestions from the different search engines and are reported in full in Appendixes 1–3. No language restrictions were placed on the search. Reference lists of eligible articles were also hand searched for additional potentially eligible trials.

Study Selection

Eligible trials had to enroll adults ≥18 years old with an early-stage cancer diagnosis (excluding brain cancer) and deliver an exercise intervention (supervised, home-based, or a combination of both) lasting 3 or more weeks. Trials were limited to RCTs that included at least 1 exercise arm. Exercise interventions had to include continuous or interval aerobic (eg, walking, cycling), resistance (eg,

weightlifting machines, free weights, body weight, band exercises), or mind-body exercise (eg, yoga, Qigong, Tai-Chi). Physical activity counseling trials with a specific focus on behavior change and therapeutic interventions (eg, physical therapy or rehabilitation exercise for limb mobility) were excluded. Trials had to assess patient-reported (eg, self-report questionnaires) or objective (eg, neuropsychological testing) measures of cognitive function. Cross-sectional studies, quasi-experimental studies, case reports, published abstracts, dissertations, reviews, and conference presentations were excluded.

Data Extraction and Quality Assessment

Two reviewers (K.Z. and E.C.) inspected the titles and abstracts of the identified articles in the search to generate 2 complete independent lists to determine eligibility. Identified articles were then obtained in full and further reviewed by 2 independent reviewers (K.Z. and E.C.) using a standard data extraction form developed by the reviewers to make a final decision regarding study inclusion. Any papers in question were resolved by consensus and input from the primary author (K.L.C.). All title, abstract, and full text screening was performed using online software (Rayyan).[29]

Risk of bias was independently evaluated for each eligible trial by 2 reviewers (K.Z. and K.A.B.) using the Cochrane Handbook at the outcome level,[30] and any discrepancies were resolved by the primary author (K.L.C.). Each parameter of bias (ie, selection, performance, detection, attrition, reporting bias, and other sources of bias) was graded as high, low, or unclear risk. Among exercise trials, masking of participants is challenging and can result in a high risk of performance bias.[31] This inevitable bias has been acknowledged by the reviewers and should not infer poor methodological quality of the trial. Attrition bias was rated as "high" if >20% of outcome data was missing. High risk of bias for other sources of bias was predefined as adherence (ie, session attendance) to the exercise intervention <75%, contamination of the control group (ie, trial identified that control group participants engaged in exercise), or significant between-group baseline differences that may have affected the outcome.[32]

Data Synthesis and Analysis

Effect sizes for each outcome measure were directly extracted from trials if reported or estimated using the Cohen *d* effect size (difference in group means divided by the pooled standard deviation). Other measures of effect size (ie, eta-squared or the Cohen *f* effect size) and t- and *F* statistics from independent t-tests and analyses of variance, respectively, were converted to Cohen *d* effect sizes. Given the limited number of eligible trials and considerable heterogeneity in participant characteristics, outcome definitions, and exercise interventions, a narrative synthesis was conducted.

Results

Trial Inclusion and Characteristics

The Preferred Reporting Items of Systematic Reviews and Meta-analyses flow diagram is depicted in Figure 1. The initial database search generated a total of 8431 articles, along with 22 additional records identified from other sources. Following duplicate removal, 6643 articles remained and 6513 were excluded upon reviewing titles and abstracts. A total of 130 articles were reviewed as full texts for a more detailed evaluation, resulting in 98 being excluded. The final analysis included 29 trials, including two 3-arm trials by Mijwel et al.[33] and Schmidt et al.[34] that each tested 2 different exercise interventions (ie, aerobic training arm and resistance training arm) compared with a control group. The characteristics and results of each arm are reported separately (Table 1). A total of 32 publications were included, as 3 trials published 2 manuscripts with separate results for different cognitive outcomes from the same intervention.[35–40]

Characteristics of all included trials, including sample, exercise intervention, and cognitive outcomes, are reported in Table 1. The majority of trials were in breast cancer (n = 14),[33,34,36,38,41–50] followed by hematological cancers (n = 7),[51–57] and prostate cancer (n = 2),[58,59] along with 6 trials in mixed groups of cancer survivors.[39,60–64] The trials were split between 15 (52%) during cancer treatment (eg, chemotherapy, radiation, stem cell transplant)[33,34,36,39,47,49–52,54,56,57,60,62] and 14 (45%) posttreatment,[38,41–46,48,53,55,58,61,63,64] including 6 trials in women receiving hormonal treatment for breast cancer.[38,41,42,45,46,48] One trial included patients both during and after treatment.[39]

Overall, 12 trials used combined aerobic and resistance training,[33,34,38,42,52,54–59,63] 7 used aerobic-only training,[36,41,48,51,60–62] 3 used resistance-only training,[47,49,53] and 7 trials used mind-body exercise (eg, yoga, Qigong).[39,43–46,50,64] The trials ranged from 3 to 52 weeks, with the majority using interventions of 12 weeks duration (n = 9).[34,36,45,47,49,55,59,62,63] Most trials (n = 20) were completely supervised, and the remaining trials were supervised with a home-based component (n = 8),[39,41,45,46,48,53,57,60] or completely home-based (n = 2).[36,38] Frequencies of the interventions were 2 to 7 days per week, with the majority of prescribed sessions being 2 days per week, (n = 10),[33,34,44,47,49,55,58,59,63,64] 3 days per week (n = 6),[38,39,42,46,53,62] or 5 days per week (n = 5).[36,54,56,57,61] Intensity of aerobic exercise was reported using heart rate maximum (n = 6),[54,55,58,59,61,51] heart rate reserve (n = 4),[41,52,62,63] rating of perceived exertion (n = 4),[33,34,48,57] or was not reported (n = 4).[36,38,42,60] Intensity of resistance exercise was reported as percent of 1 repetition maximum (n = 6),[33,34,47,49,51,56,63] rating of perceived exertion (n = 3)[53,54,57], or not reported (n = 5).[38,42,52,55,58,59] Duration of the interventions ranged from 15 to 90 minutes per session, with the majority of aerobic exercise

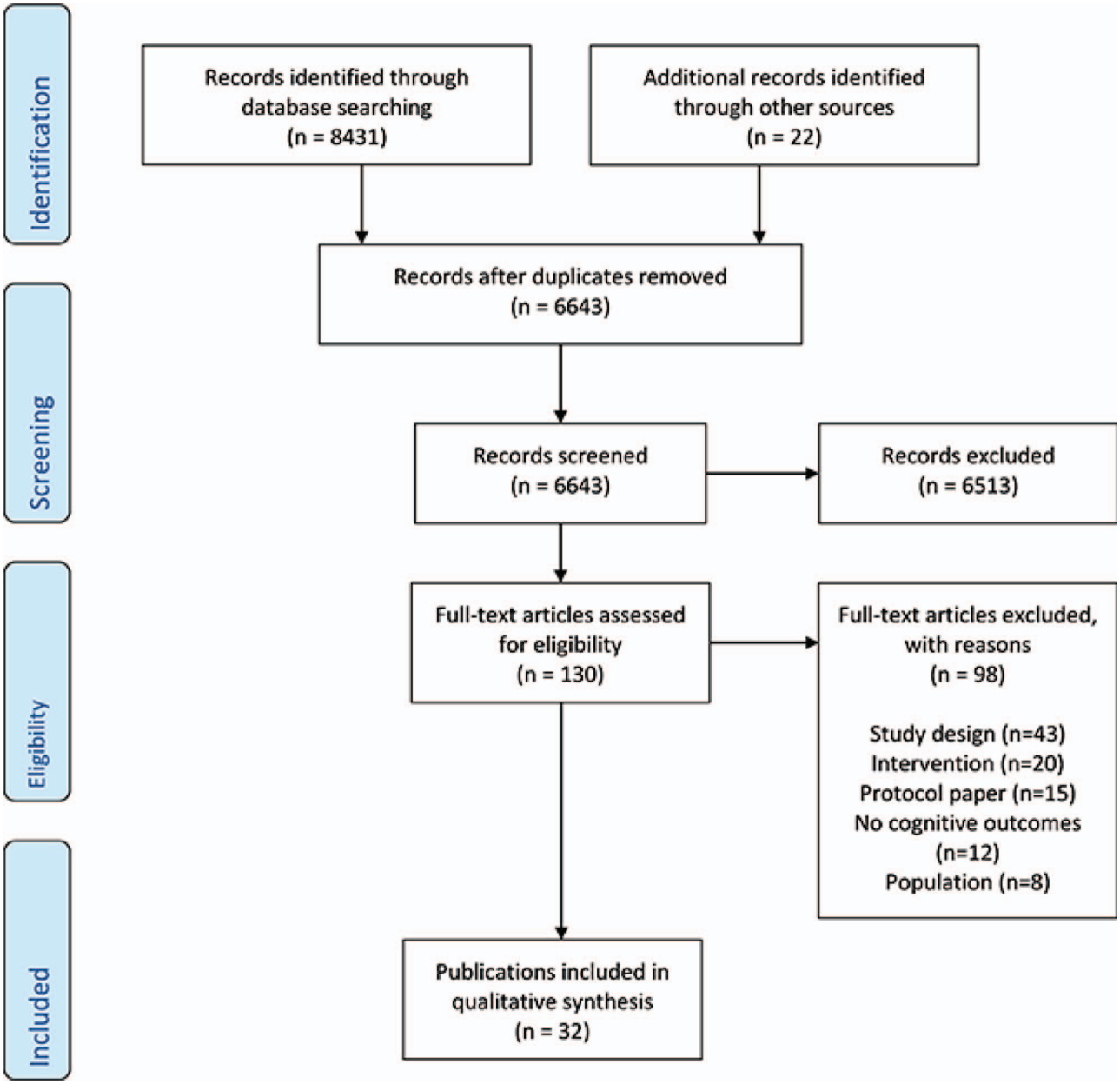

Figure 1.
Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) diagram of the literature search used.

components being 20 (n = 5)[33,51,55,56,59] or 30 (n = 6)[36,54,58,61–63] minutes and mind-body exercise more commonly ranging from 45 to 60 (n = 4)[39,45,46,50] to 70 to 75 (n = 2) minutes.[43,64] Aerobic exercise types included a combination of aerobic activities (eg, walking, cycling, elliptical) (n = 9),[33,41,51,52,57–59,63] cycling only (n = 5),[34,54,56,61,62] walking only (n = 2),[36,60] or circuit training (n = 1)[48] or were not reported (n = 1).[38] Resistance exercise types included resistance bands and body/free weights (n = 6),[52–57] machine based (n = 3),[34,47,49] or a combination of bands/body/free weights and machines (n = 3)[33,58,59], or were not reported (n = 2).[38,63] One intervention was aquatic based (n = 1)[42] and involved both aerobic (ie, cardiovascular endurance) and resistance (eg, water resistance) exercise. For mind-body exercise, interventions were yoga (n = 4),[43,44,50,64] Qigong (n = 2),[39,46] and a combination of Qigong and Tai Chi (n = 1).[45]

Table 1.
Summary of Eligible Randomized Controlled Trials That Evaluated the Effect of Exercise on Cognitive Outcome Measures[a]

Trial (First author, Year)	Population (Cancer Type)	Sample Size (n)	Treatment Type	Mode	Duration (wk)	Frequency (d/wk)	Supervised versus Home-Based	Exercise Prescription (Time & Intensity)	Type of Outcome	Outcome Measures
Aerobic exercise interventions										
During treatment										
Backman (2014)	Mixed	77	Chemotherapy	Walking	10	7	Both	SUP AER: 60 min group walk (1 x/wk) HB: 10,000 steps/d	Self-report	EORTC QLQ-C30 cognitive function
Baumann (2010)	Hematopoietic	64	HSCT	Cycling, walking, stair-climbing/ADL training	4	7	Supervised	AER: 10–20 min at 80% HRmax, 5 sets of 20 reps stair-climbing	Self-report	EORTC QLQ-C30 cognitive function
Gokal (2016, 2018)	Breast	50	Chemotherapy	Walking	12	5	Home-based	AER: 10–30 min	Self-report	Cognitive Failures Questionnaire, POMS confusion item
									Objective	WAIS-III: Digit Forwards/Backwards (working memory), Attention to Response (attention), Block Design (perceptual organization), Stroop (executive function)
Mijwel (2018)[a]	Breast	240	Chemotherapy	Cycling, elliptical, walking, jogging	16	2	Supervised	AER: 20 min moderate (RPE: 13–15) & 3 x 3 min HIIT (RPE: 16–18)	Self-report	EORTC QLQ-C30 cognitive function, PFS Cognitive/Mood subscale
Peterson (2018)[b]	Mixed	28	Mixed treatments, types NR	Cycling	12	3	Supervised	AER: 30 min at 55–65% HRR	Objective	WMS-IV: Brief Cognitive Status (general cognitive function), Logical Memory (verbal learning & memory), COWA (verbal fluency) WAIS-III: Letter/Number Sequencing & Coding (executive function), Block Design (perceptual organization), TMT A/B (processing speed)
Schmidt, T. (2015)[a]	Breast	67	Chemotherapy	Cycling	12	2	Supervised	AER: 45 min at RPE: 11–14	Self-report	EORTC QLQ-C30 cognitive function
									Objective	D2-Test of Attention

(*Continued*)

Table 1.
Continued

Trial (First author, Year)	Population (Cancer Type)	Sample Size (n)	Treatment Type	Mode	Duration (wk)	Frequency (d/wk)	Supervised versus Home-Based	Exercise Prescription (Time & Intensity)	Type of Outcome	Outcome Measures
Posttreatment										
Campbell (2018)	Breast	19	Chemotherapy, radiation; ongoing HT	Walking, cycling, elliptical	24	4	Both	SUP AER: 20–45 min at 60–80% HRR & 4 sets of HIIT (5–10 min) by wk 12	Self-report	FACT-Cog
								HB AER: 30 min	Objective	TMT A/B (processing speed), HVLT (verbal memory & learning), COWA (verbal fluency), Animal Naming (verbal fluency), Stroop (executive function)
Dimeo (2004)	Mixed	72	Surgery, chemotherapy, radiation	Cycling	3	5	Supervised	AER: 30 min at 80% HR_{max} (RPE: 13–14) (5 x 3 min wk 1, 4 x 5 min wk 2, 3 x 8 min wk 3)	Self-report	EORTC QLQ-C30 cognitive function
Saarto (2012)	Breast	573	Chemotherapy, radiation; ongoing HT	Circuit (step aerobics, walking)	52	3-4	Both	SUP & HB AER: 60 min (RPE: 11–13 to 14–16)	Self-report	EORTC QLQ-C30 cognitive function
Resistance exercise interventions										
During treatment										
Mijwel (2018)[a]	Breast	240	Chemotherapy	Machine-based, free weights, body weight	16	2	Supervised	RT: 2–3 sets of 8–12 reps at 70–80% 1-RM & 3 x 3 min HIIT (RPE: 16–18)	Self-report	EORTC QLQ-C30 cognitive function, PFS Cognitive/Mood subscale
Schmidt, M. (2015)	Breast	101	Chemotherapy, HT	Machine-based	12	2	Supervised	RT: 3 sets of 8–12 reps 60–80% 1-RM	Self-report	FAQ Cognitive Fatigue Scale, EORTC QLQ-C30 Cognitive/Mood subscale
									Objective	TMT A/B (processing speed)
Schmidt, T. (2015)[a]	Breast	67	Chemotherapy	Machine-based	12	2	Supervised	RT: 1 set of 20 reps at 50% 1-RM	Self-report	EORTC QLQ-C30 cognitive function
									Objective	D2-Test of Attention
Steindorf (2014)	Breast	155	Radiation, HT	Machine-based	12	2	Supervised	RT: 3 sets of 8–12 reps 60–80% 1-RM	Self-report	FAQ Cognitive Fatigue Scale, EORTC QLQ-C30 cognitive function
									Objective	TMT A/B (processing speed)

(*Continued*)

Table 1.
Continued

Trial (First author, Year)	Population (Cancer Type)	Sample Size (n)	Treatment Type	Mode	Duration (wk)	Frequency (d/wk)	Supervised versus Home-Based	Exercise Prescription (Time & Intensity)	Type of Outcome	Outcome Measures
Posttreatment										
Hacker (2011)	Hematopoietic	19	HSCT	Resistance bands, body weight	6	3	Both	RT: 1–2 sets of 8–10 reps (RPE: ~13)	Self-report	EORTC QLQ-C30 cognitive function
Aerobic & resistance exercise interventions										
During treatment										
Bryant (2018)	Hematopoietic	17	Induction therapy	Walking, cycling/resistance bands	4	4	Supervised	AER 5–15 min at 50–70% HRR RT: 10–20 min at 3 sets of 10 reps	Self-report	PROMIS Applied Cognition and General Cognitive Concerns
Galvao (2010)	Prostate	57	Radiation, HT	Cycling, walking, jogging/machine-based, body weight	12	2	Supervised	AER: 15–20 min at 65–80% HR_{max} (RPE: 11–13) RT: 2–4 sets of 6–12 RM	Self-report	EORTC QLQ-C30 cognitive function
Jarden (2009)	Hematopoietic	42	HSCT	Cycling/free weights	4-6	5	Supervised	AER: 15–30 min at 50–75% HR_{max} (RPE: 10–13) RT: 1–2 sets of 10–12 reps (RPE: 10–13)	Self-report	Stem Cell Transplantation Symptom cognitive cluster
Oechsle (2014)	Hematopoietic	48	Myeloablative chemotherapy	Cycling/resistance bands, body weight	3	5	Supervised	AER: 10–20 min (individualized intensity) RT: 2 sets of 16–25 reps 40–60% 1-RM	Self-report	EORTC QLQ-C30 cognitive function MFIS Cognition subscale
Wiskemann (2011)	Hematopoietic	105	ASCT	Walking, cycling, jogging/resistance bands, body weight	15	5	Both	AER: 20–40 min (RPE: 12–14) RT: 2–3 sets of 8–20 reps (RPE: 14–16)	Self-report	EORTC QLQ-C30 cognitive function, MFI mental fatigue dimension
Posttreatment										
Buffart (2015)	Prostate	100	Radiation, HT	Cycling, walking, jogging/machine-based, body weight	24	2	Supervised	AER: 20–30 min at 70–85% HR_{max} (RPE: 11–13), RT: 2–4 sets of 6–12 RM	Self-report	EORTC QLQ-C30 cognitive function
Cantarero-Villanueva (2013)	Breast	68	Chemotherapy, radiation; ongoing HT	Aquatic program	8	3	Supervised	AER: 40 min aquatic exercises, 10 min warm-up/cool-down	Self-report	PFS Cognitive/Mood subscale
Galiano-Castillo (2016, 2017)	Breast	81	Chemotherapy, radiation; ongoing HT	NR	8	3	Home-based	AER & RT: ~90 min	Self-report	EORTC QLQ-C30 cognitive function
									Objective	Auditory Consonant Trigram (short-term memory, attention), TMT A/B (processing speed)

(*Continued*)

Table 1.
Continued

Trial (First author, Year)	Population (Cancer Type)	Sample Size (n)	Treatment Type	Mode	Duration (wk)	Frequency (d/wk)	Supervised versus Home-Based	Exercise Prescription (Time & Intensity)	Type of Outcome	Outcome Measures
Knols (2011)	Hematopoietic	131	HSCT	Cycling, walking/ free weights	12	2	Supervised	AER: 20 min at 50–80% HR_{max} RT: NR	Self-report	EORTC QLQ-C30 cognitive function
Van Weert (2010)	Mixed	147	Surgery, chemotherapy, radiation	Cycling, group sports, games/ resistance (type NR)	12	2	Supervised	AER: 20–30 min at 40–80% HRR RT: 20–30 min at 30–60% 1-RM	Self-report	MFI mental fatigue dimension
Mind-body exercise interventions										
During treatment										
Vadiraja (2009)	Breast	88	Radiation	Yoga (asanas, breathing, meditation)	6	3	Supervised	50 min	Self-report	EORTC QLQ-C30 cognitive function
Posttreatment										
Culos-Reed (2006)	Breast	38	Chemotherapy, radiation	Yoga (breathing, 6–10 asanas, relaxation)	7	NR	Supervised	70 min	Self-report	POMS concentration item, Symptoms of Stress Inventory cognitive disorganization subscale
Derry (2015)	Breast	200	Surgery, chemotherapy, radiation	Yoga (breathing, floor, standing, chair & restorative poses)	24	2	Supervised	90 min	Self-report	Breast Cancer Prevention Trial cognitive problems scale
Janelsins (2016)	Mixed	328	Surgery, chemotherapy, radiation; ongoing HT	Yoga (supine, seated, standing, transitional, & restorative poses, breathing, mindfulness)	4	2	Supervised	75 min	Self-report	MDASI memory difficulty item
Larkey (2016)	Breast	87	Surgery, chemotherapy, radiation; ongoing HT	Qigong/Tai Chi	12	6-7	Both	SUP: 60 min HB: 30 min	Self-report	FACT-Cog
									Objective	WAIS-III: Digit Span (attention), Letter-Number Sequencing (working memory)
Myers (2018)[c]	Breast	50	Chemotherapy, radiation; ongoing HT	Qigong (breathing, gentle arm movements, chanting)	8	3	Both	SUP: 60 min HB: 15 min	Self-report	FACT-Cog PROMIS Applied Cognition and General Cognitive Concerns
									Objective	Rey auditory verbal learning (memory) TMT A/B (processing speed), COWA (executive function)

(*Continued*)

Table 1.
Continued

Trial (First author, Year)	Population (Cancer Type)	Sample Size (n)	Treatment Type	Mode	Duration (wk)	Frequency (d/wk)	Supervised versus Home-based	Exercise Prescription (Time & Intensity)	Type of Outcome	Outcome Measures
Mixed during and posttreatment										
Oh (2010, 2012)	Mixed	81	Chemotherapy	Qigong (standing stretching/-body movement, seated postures, meditation)	10	3	Both	SUP: 45 min HB: 30 min meditation	Self-report	FACT-Cog, EORTC QLQ-C30 cognitive function, POMS confusion item

[a]1-RM = 1 repetition maximum; ADL = activities of daily living; AER = aerobic exercise; ASCT = autologous stem cell transplantation; COWA = Controlled Oral Word Association; EORTC QLQ-C30 = European Organization for Research and Treatment of Cancer Quality of Life Questionnaire–Core 30; FACT-Cog = Functional Assessment of Cancer Therapy-Cognitive Function; FAQ = Fatigue Assessment Questionnaire; HB = home-based; HIIT = high-intensity interval training; HR = heart rate; HR_{max} = heart rate maximum; HRR = heart rate reserve; HSCT = hematopoietic stem cell transplantation; HT = hormone therapy; HVLT = Hopkins Verbal Learning Test; MDASI = MD Anderson Symptom Inventory; MFI = Multidimensional Fatigue Inventory; MFIS = Modified Fatigue Impact Scale; NR = not reported; PFS = Piper Fatigue Scale; POMS = Profile of Mood States; PROMIS = Patient-Reported Outcome Measurement Information System; RM = repetition maximum, RPE = rating of perceived exertion; RT = resistance training; Sup = supervised; TMT A/B = Trail Making Test A/B; WAIS-III = Wechsler Adult Intelligence Scale-Third Edition; WMS-IV = Wechsler Memory Scale-Fourth Edition.
[b]3-arm trial, with separate aerobic and resistance training intervention arms and a usual care control group.
[c]4-arm trial, consisting of aerobic training, cognitive training, and aerobic + cognitive training intervention arms and a usual care control group (results from the aerobic + cognitive training intervention arms are not included in this review, as the effect of cognitive training on any cognitive changes experienced could not be discounted).
[d]3-arm trial, consisting of Qigong and Gentle Exercise intervention arms and a survivorship support control group. (results from the Gentle Exercise arm are not included in this review, as the intervention (eg, stretching, flexibility) did not meet the inclusion criteria.

The majority of trials used self-reported outcome measures of cognitive complaints (n = 20, 69%), 8 trials (28%) reported on self-reported and objective neuropsychological tests,[34,35,37,41,45–47,49] and 1 trial (3%) reported only objective neuropsychological tests.[62] The most commonly used self-reported outcome measure was the cognitive function subscale European Organization for Research and Treatment of Cancer Quality of Life Questionnaire–Core 30 (EORTC QLQ-C30) (n = 17),[33,34,38,40,47–51,53,55–61] along with the Functional Assessment of Cancer Therapy–Cognitive Function questionnaire (FACT-Cog) (n = 4).[40,41,45,46] The trials that included objective tests were all in women with breast cancer, either during (n = 4)[34,35,47,49] or postadjuvant treatment (including hormonal treatment) (n = 4),[37,41,45,46] with the exception of 1 trial in mixed cancer survivors during varied types of treatments.[62] Objective tests included a number of established neuropsychological tests, including the Trail Making Test A/B (TMT A/B) (n = 6),[37,41,45,47,49,62] Stroop test (n = 2),[35,41] and Controlled Oral Word Association (COWA) (n = 3).[41,46,62] Cognitive function was the primary outcome in 3 (10%) trials, which all tested the effect of an aerobic exercise intervention relative to usual care. These trials included 2 trials in women with breast cancer either during chemotherapy[35] or posttreatment,[41] and 1 trial in individuals with mixed cancer types receiving a variety of cancer treatments.[62] Cognitive function was a secondary/exploratory outcome in the remaining 26 included trials (90%).

Bias Assessment

Risk of bias is summarized for all included trials in Figure 1 and individually for each trial in Figures 3 to 5. Overall, the majority of studies had a low risk of bias for selection bias based on adequate random sequence generation (n = 16, 55%)[33,34,38,39,42,44,48,50,51,54,55,57–59,61,64] and allocation concealment (n = 17, 59%).[33,34,38,42,44–50,51,52,55,59,61,63,64] Additionally, the majority of studies (n = 27, 93%) had a low risk of bias for detection bias based on masking of outcome assessment.[33,34,38,39,41–61,63,64] Only 1 trial (3%) had a low risk performance bias by masking study personnel and participants to a Qigong or sham Qigong group[45]. Risk of bias due to attrition bias was high in 9 trials (31%)[34,39,46,47,50,51,54,57,64] for the following reasons: (1) the number of dropouts (n = 5, 17%),[39,46,47,50,54] (2) patient mortality (n = 3, 10%),[51,54,57] (3) cancer progression or side effects (n = 3, 10%),[34,51,54] or (4) reasons not reported (n = 2, 7%).[47,64] Risk of bias due to reporting bias was high in 4 trials (14%) due to incomplete reporting of outcome measures (n = 2, 7%)[43,56] or using a cognitive function outcome measure not specified in the trial registration for secondary data analyses (n = 2, 7%).[44,64] Nine trials (31%) had a high risk of bias due to other sources of bias because of adherence rates <75% (n = 8, 28%)[33,34,39,45,46,48,51,60] and baseline between-group differences in physical fitness that could plausibly affect cognitive outcomes (n = 1, 3%).[47]

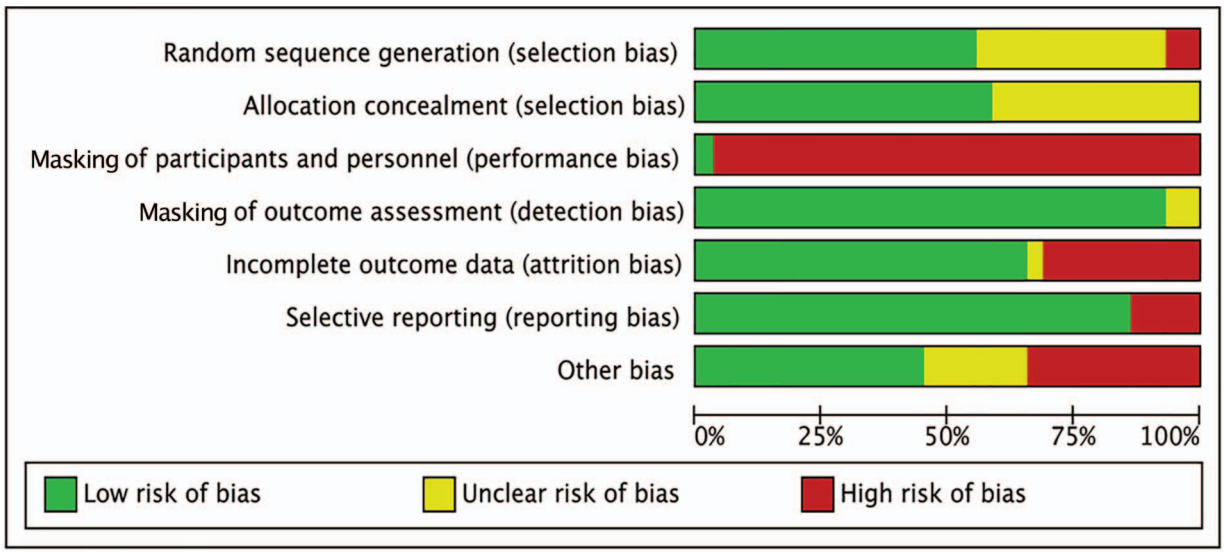

Figure 2.
Authors' risk of bias assessment using the Cochrane Risk of Bias tool.

Intervention Effects on Cognitive Function

Cohen *d* effect sizes for all trials are shown for the EORTC QLQ-C30 cognitive function subscale, other self-reported outcome measures, and objective neuropsychological test outcomes in Figures 3, 4, and 5, respectively.

Self-Reported Cognitive Function. Overall, 12 of the 28 trials that evaluated self-reported cognitive function reported a statistically significant improvement in the exercise group compared with a control or comparison group, including 2 aerobic exercise,[35,48] 6 combined aerobic and resistance exercise,[33,38,42,54,56,59] and 4 mind-body interventions.[40,46,50,64] Six of these trials prescribed exercise during cancer treatment,[33,36,50,54,56,59] 5 took place posttreatment,[38,42,46,48,64] and 1 included participants both during and posttreatment.[40]

Of the 17 trials[33,34,38,40,47–51,53,55–61] that used the self-reported EORTC QLQ-C30 cognitive function subscale, a statisically significant benefit of exercise was reported in 6 trials[33,38,40,48,50,59] and 7 different interventions, with Mijwel et al.[33] reporting a significant effect in both intervention arms tested (ie, aerobic high-intensity interval training and resistance high-intensity interval training) (Cohen *d* range: 0.27–1.1) (Fig. 3). One trial used aerobic exercise during treatment,[48] 2 prescribed a combination of aerobic and resistance training either during[59] or after[38] treatment, and 1 included both an aerobic and resistance training intervention arm.[33] All 4 trials had a relatively low risk of overall bias. The remaining 2 trials used mind-body exercise and took place during treatment[50] or in a mixture of participants during and posttreatment.[40] However, both of these trials had a moderate to high risk of overall bias.

Two trials, both using mind-body exercise, reported statistically significant improvements in self-reported cognitive function as assessed by the FACT-Cog.[40,46] Five trials reported statistically significant improvements in other measures of self-reported cognitive function using the Cognitive Failures Questionnaire,[35] Stem Cell Transplantation Symptom–Cognitive Cluster,[54] Piper Fatigue Scale–Cognitive/Mood Fatigue subscale,[42] MD Anderson Symptom Inventory–Memory Difficulty item,[64] or Modified Fatigue Impact Scale–Cognition subscale[56] (Cohen *d* range: 0.24–0.92) (Fig. 4). Effect size could not be calculated for Oechsle et al (2014) as no means or standard deviations were reported.

Objectively Measured Cognitive Function. Two of the 9 trials that used objective neuropsychological testing reported statistically significant improvements in cognitive function with exercise using the Digit Span Forwards test[35] and Auditory Consonant Trigram.[37] Cohen *d* effect sizes for these outcome measures were 0.89 and 0.41, respectively (Fig. 5). Campbell et al.[41] also reported an improvement in time to complete TMT A. However, this test is associated with improved motor and visuospatial abilities rather than cognitive function, which is more accurately captured by TMT B or the difference between TMT A and TMT B.[51] All 3 trials were conducted in women with breast cancer. Two delivered aerobic exercise, 1 during treatment[35] and the other following treatment,[41] while the third delivered aerobic and resistance exercise in women posttreatment but undergoing hormonal therapy.[37]

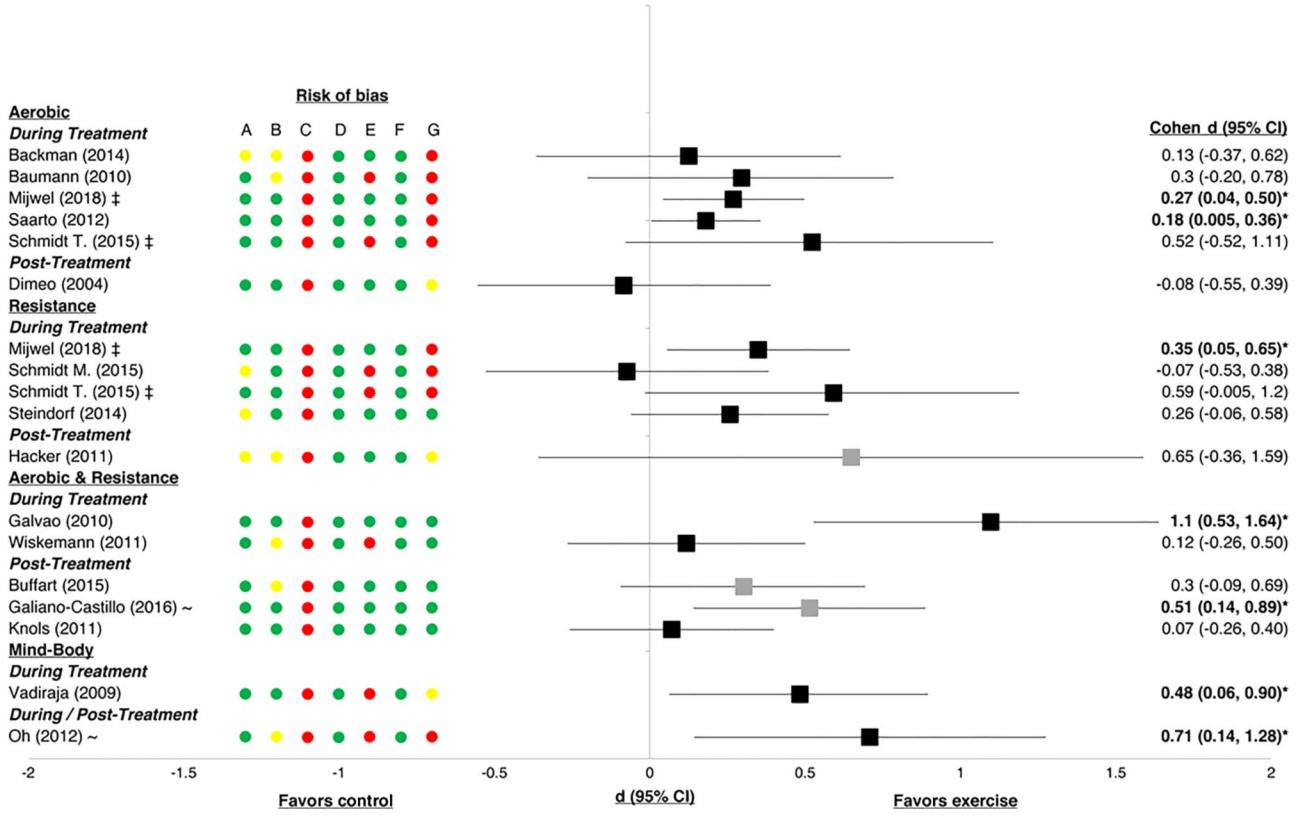

Figure 3.
Effect sizes for interventions using the cognitive function subscale of the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire–Core 30 (EORTC QLQ-C30) as a self-reported outcome measure of cognitive function. Oechsle et al (2014) also used the EORTC QLQ-C30 but did not report means or SDs. As such, effect size could not be calculated. Risk of bias: A = random sequence generation; B = allocation concealment; C = masking of participants/personnel; D = masking of outcome assessors; E = incomplete outcome data; F = selective reporting; G = other bias. Red = high risk of bias; yellow = unclear risk of bias; green = low risk of bias. *Statistically significant effect at $P < .05$ as reported in original data. ‡Different exercise intervention arm of the same trial. ~, data from different publication of the same trial. Black markers = group effect. Gray markers = group x time effect.

Discussion

To our knowledge, this is the first published systematic review of randomized controlled trials in humans that assessed the impact of physical and mind-body exercise on CRCI. Of the trials identified in this review, 13 (45%)[33,35,38,40–42,46,48,50,54,56,59,64] identified a benefit of exercise compared with a control or a comparison group, where exercise resulted in improved cognitive function. In particular, a statistically significant benefit on self-reported cognitive function was observed in 12 of these trials,[33,35,38,40,42,46,48,50,54,56,59,64] most frequently using the EORTC QLQ-C30 cognitive function subscale.[33,38,40,48,50,59] Two trials reported statistically significant effects of aerobic exercise or combined aerobic and resistance exercise on objective neuropsychological tests of cognitive function, namely the Digit Span Forwards[35] and Auditory Consonant Trigram.[37] Thus, although limited, emerging evidence points towards a possible impact of exercise on measures of CRCI.

A key consideration is that despite the number of trials identified in our database search, only 3 trials included cognitive function, either self-reported or objectively tested, as a primary outcome.[36,41,62] As such, most trials were likely not appropriately powered for their analyses of CRCI, potentially leading to an overall bias toward a null effect. The 3 trials where cognitive function was the primary outcome were published in either 2017 or 2018, suggesting that more trials are now being initiated with a specific focus on the impact of exercise on CRCI. This trend may allow for an improved understanding of the potential role of exercise in managing CRCI in the future.

Findings from the current review suggest that benefits of exercise on indices of cognitive function are equally likely among interventions undertaken during and following cancer treatment. For the interventions during treatment, the type of treatment varied, including chemotherapy, radiation, androgen deprivation therapy, and stem cell

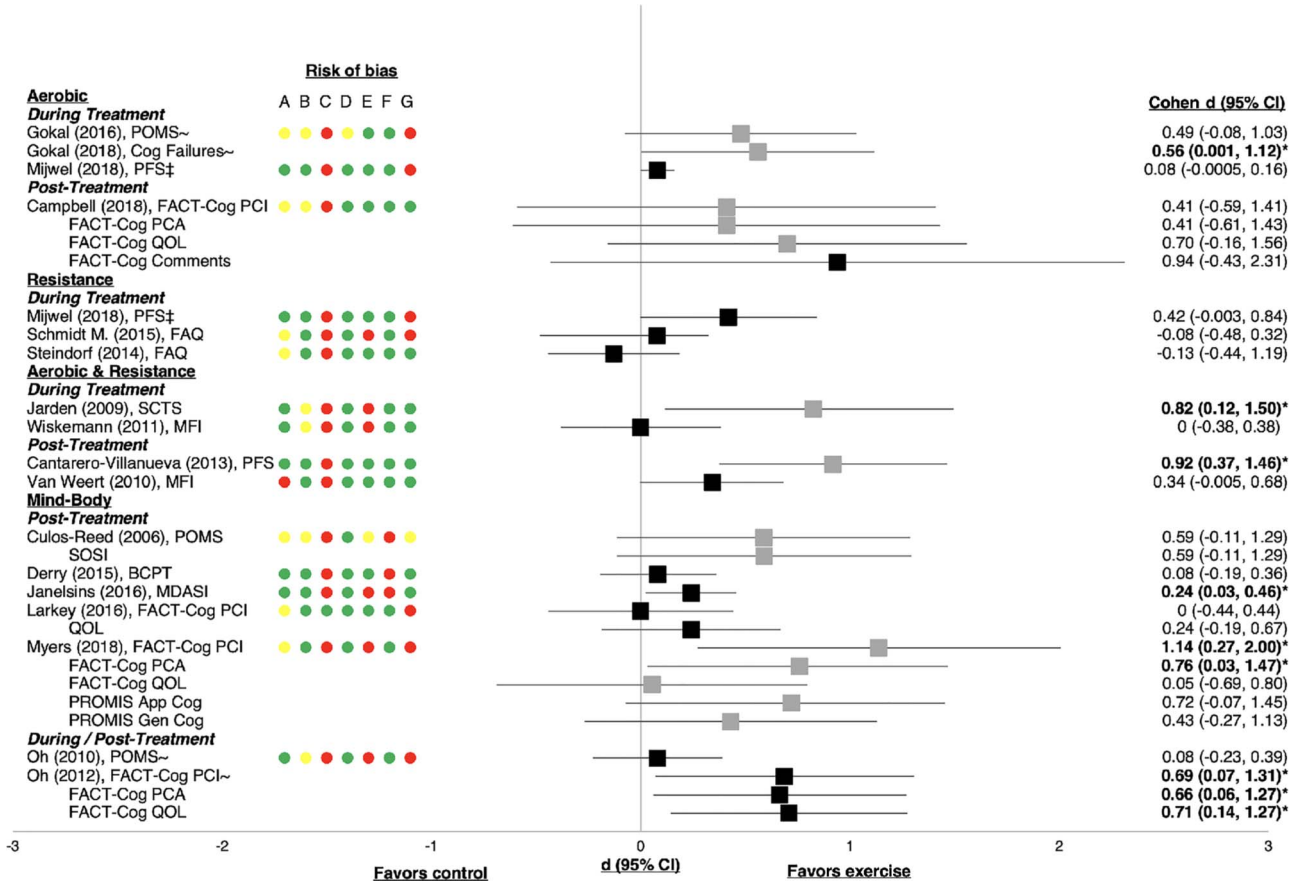

Figure 4.
Effect sizes for interventions using other self-reported outcome measures of cognitive function. Oechsle et al (2014) noted a significant benefit of exercise for self-reported cognitive function as measured by the Modified Fatigue Impact Scale (MFIS)–Cognition subscale. Bryant et al (2018) used the Patient-Reported Outcomes Measurement Information System (PROMIS)–Applied Cognition and General Cognitive Concerns as a self-reported outcome measure of cognitive function but did not observe a significant effect. Neither trial reported means or SDs, so effect sizes could not be calculated. App Cog = Applied Cognition; BCPT = Breast Cancer Prevention Trial–Cognitive Problems; Cog Failures = Cognitive Failures Questionnaire; Comments = Comments of others; FACT-Cog = Functional Assessment of Cancer Therapy–Cognitive Function; FAQ = Fatigue Assessment Questionnaire–Cognitive Fatigue; Gen Cog = General Cognition Concerns; MDASI = MD Anderson Symptom Inventory–Memory Difficulty; MFI = Multidimensional Fatigue Index–Mental Fatigue; PCA = Perceived Cognitive Abilities; PCI = Perceived Cognitive Impairments; PFS = Piper Fatigue Scale–Cognitive/Mood Fatigue; POMS = Profile of Mood States–Confusion; QOL = Quality of Life; SCTS = Stem Cell Transplantation Symptoms–Cognitive Cluster; SOSI = Symptoms of Stress Inventory–Cognitive Disorganization. Risk of bias: A = random sequence generation; B = allocation concealment; C = masking of participants/personnel; D = masking of outcome assessors; E = incomplete outcome data; F = selective reporting; G = other bias. Red = high risk of bias; yellow = unclear risk of bias; green = low risk of bias. *Statistically significant effect at $P < .05$ as reported in original data. ‡Different exercise intervention arm of the same trial. ~, data from different publication of the same trial. Black markers = group effect. Gray markers = group x time effect.

transplantation. The benefits observed were also not restricted to any specific intervention, because these trials included interventions that were aerobic exercise only, a combination of aerobic and resistance exercise, or mind-body interventions. Intervention duration also ranged from 4 to 52 weeks and from 2 sessions per week to daily. Aerobic exercise interventions that showed a beneficial effect on both self-reported and objectively measured cognitive function ranged from 10 to 60 minutes, and 20 minutes of aerobic exercise combined with a standard whole-body resistance training program also showed a benefit. The prescribed exercise intensity for both aerobic and resistance training was moderate to vigorous, suggesting this level of intensity may be required to elicit a benefit. However, given the select number of trials to report significant effects of exercise to date, as outlined above, these parameters of exercise prescription should be judged with caution. At this point, given the heterogeneity among trials identified in this review, it is unknown which cancer population with CRCI

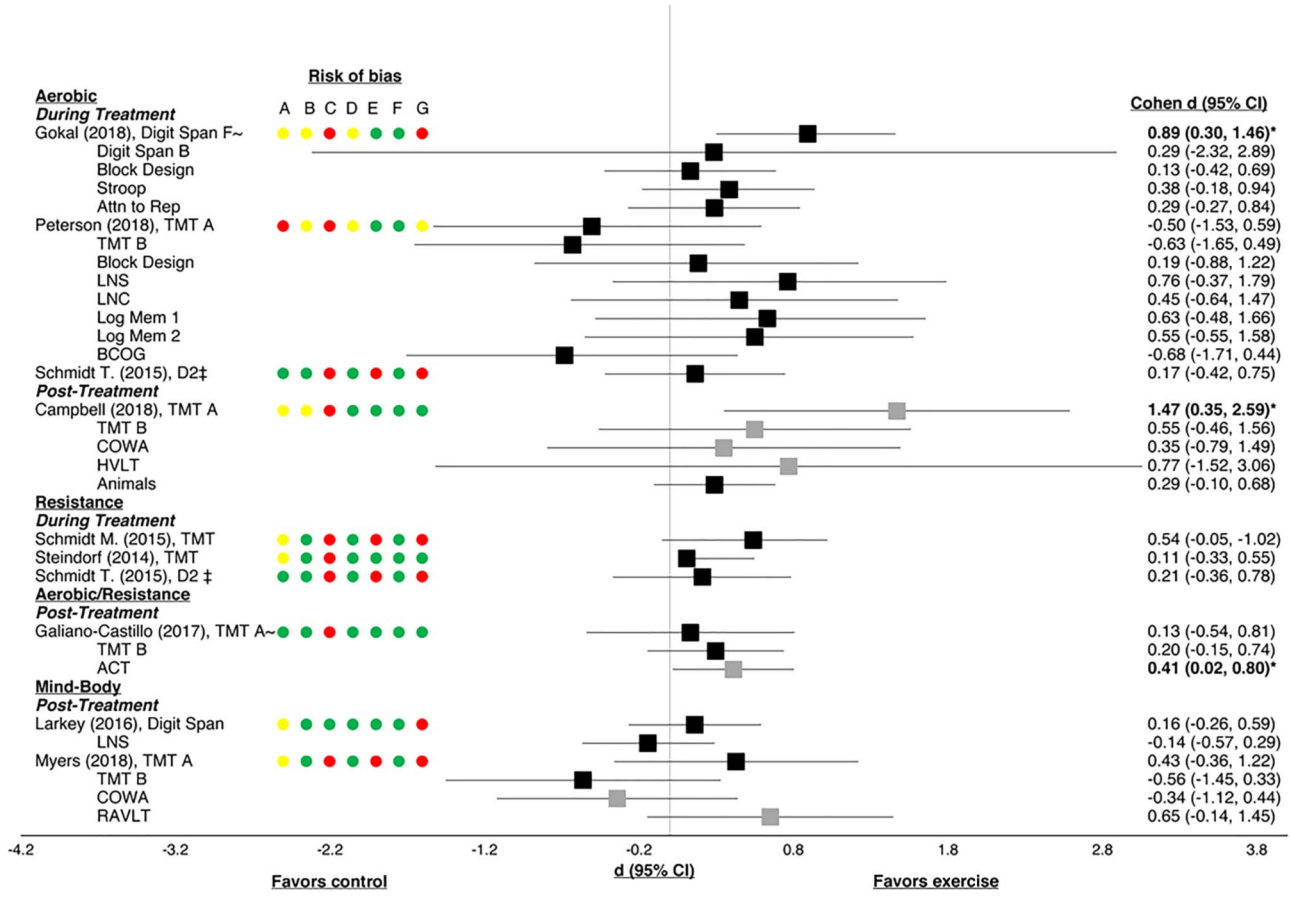

Figure 5.
Effect sizes for interventions using objective outcome measures of cognitive function. Campbell et al (2018) used the Stroop test and Peterson et al (2018) used the Controlled Oral Word Association Test (COWA) as objective measures of cognitive function. Neither study noted a significant effect. Neither study reported means or SDs, so effect sizes could not be calculated. ACT = Auditory Consonant Trigram; Animals = animal naming; Attn to Rep = Attention to Response Task; BCOG = Brief Cognitive Status; D2 = D2 Test of Attention; Digit Span B = Digit Span Backwards; Digit Span F = Digit Span Forwards; HVLT = Hopkins Verbal Learning Test; LNC = Letter/Number Coding; LNS = Letter/Number Sequencing; Log Mem 1/2 = Logical Memory 1/2; RAVLT = Rey Auditory Verbal Learning Test; TMT A/B = Trail Making Test A/B. Risk of bias: A = random sequence generation; B = allocation concealment; C = masking of participants/personnel; D = masking of outcome assessors; E = incomplete outcome data; F = selective reporting; G = other bias. Red = high risk of bias; yellow = unclear risk of bias; green = low risk of bias. *Statistically significant effect at $P < .05$ as reported in original data. ‡Different exercise intervention arm of the same trial. ~Data from different publication of the same trial. Black markers = group effect. Gray markers = group x time effect.

may benefit the most from a physical rehabilitation intervention. Further, identifying the optimal exercise intervention type and timing to prevent or ameliorate CRCI is a topic for future investigations.

A key consideration remains regarding how to measure CRCI. The majority of RCTs in the present review used the EORTC QLQ-C30 questionnaire,[66] a well-regarded cancer-specific quality-of-life questionnaire that includes only 2 items on cognitive function: (1) "Have you had difficulty in concentrating on things, like reading a newspaper, or watching television?" and (2) "Have you had difficulty remembering things?" Reporting cognition as an outcome in a RCT using a small number of items from a more comprehensive symptom inventory was common across the majority of included trials, as cognition was often reported as an exploratory or secondary aim. The FACT-Cog,[67] which was used in 4 RCTs, is a standard cancer-specific questionnaire that was developed specifically for cognition and how it impacts quality of life. Such a self-report tool designed specifically to examine CRCI may serve to better capture CRCI than tools that include only 1 or 2 items on cognition. Objective testing is the standard approach to capture cognitive function in other clinical populations, such as dementia. The International Cancer Cognition Task Force published guidelines for an objective neuropsychological test battery for CRCI based on the best available evidence

and called for investigators to use this battery in an effort to harmonize outcome measures across trials.[68] Although self-reported cognitive function has been reported to correlate with objective testing and relate to abnormalities on neuroimaging even in the absence of objective deficits in some studies of breast cancer survivors,[70–72] there more broadly remains a lack of reported association between self-reported cognitive impairment and objectively tested performance in the field.[9] There was limited demonstrated change in the included trials that reported using objective tests, and more robust findings from objective tests could strengthen the rationale for an observed benefit in the future. Furthermore, future trials assessing CRCI must determine whether exercise interventions are directly influencing both objectively measured and self-reported cognitive function versus other related impairments, such as psychological distress, disrupted sleep, and cancer-related fatigue. These factors need to be considered and potentially controlled for in future analyses. Investigators need to build on this literature to develop and test more innovative approaches to capture what can be subtle, but clinically meaningful, cognitive impairments. Ultimately, a combination of self-reported and objective testing is likely ideal to encompass the influence of exercise on CRCI and the individual's experience.

Presently, empirical evidence supporting exercise as a therapy for CRCI in humans is preliminary. However, results from preclinical trials, combined with the potential biological plausibility that exercise may improve CRCI, suggest future research on this topic is an important endeavor. Fardell et al.[71] reported that rodents treated with chemotherapy randomized to voluntary exercise displayed preserved cognitive function, particularly novel object recognition and spatial reference memory, compared with reduced cognitive function in rodents that did not exercise. These findings are consistent with those of Winocur et al.[72] who tested the effect of exercise using voluntary wheel running following administration of chemotherapy in rodents. Exercise prevented the significant decrease in performance on cognitive tasks and the reduction in hippocampal neurogenesis seen in rodents treated with chemotherapy in the non-exercise group. The findings are potentially explained by the possible impact of aerobic exercise on brain structure and function.[73] Biological mechanisms relating exercise to improved cognitive function that have been proposed from animal and human research include decreased systemic inflammation and oxidative stress, enhanced plasticity of the brain, increased levels of brain derived neurotropic factor, and improved cerebral blood flow and hemoglobin levels.[74–79] However, it is unclear whether the potential benefits of exercise for CRCI are directly from an influence on cognitive function relative to other physiological and psychological systems. To better understand how exercise acts on CRCI, RCTs focused specifically on identifying mechanistic pathways relating to exercise and cognitive function are needed.

Physical therapists should be aware that CRCI is a common side effect experienced by individuals following a cancer diagnosis and treatment. As a result, physical therapist treatment plans may need to account for CRCI and incorporate possible strategies to improve the delivery of physical therapy care in an oncology setting. For example, therapy can try to ensure information and instructions are delivered clearly and provide reminders or written information for the client to refer back to as needed. If future evidence for the benefits of exercise to prevent or mitigate CRCI emerges, physical therapists are ideally suited for the delivery of this therapeutic intervention. Physical therapists possess the ability to assess and prescribe an appropriate exercise program in the context of potential mobility or physical limitations that result from cancer treatment and that may fluctuate during active cancer treatment. We therefore recommend that physical therapists who work with oncology patients review the current physical activity guidelines for cancer survivors.[20]

There are several limitations of this review. This review comprehensively summarizes all the available evidence of *any* exercise intervention on CRCI to date and includes heterogeneous patient populations (eg, cancer type, stage, and time point along cancer treatment trajectory), intervention types and length, and outcome measures. As a result, it was not possible to perform a meta-analysis of the current literature. In addition, we did not include any RCTs of physical activity behavior change interventions, including a trial by Hartman et al.[80] that showed a distance-based intervention using an activity monitor to encourage women to increase aerobic activity, such as walking, showed improved processing speed in participants who had received surgery for breast cancer within the past 2 years. Further, a high risk of attrition bias (ie, due to missing >20% outcome data) and other sources of bias, including low intervention adherence, was detected in more than 25% of studies. This finding further limits the ability to fully interpret the reported findings. Frequently, trials identified in this review did not enroll individuals complaining of cognitive problems at baseline with the exception of Campbell et al.[41] This a common issue in the cancer survivorship literature. Namely, examining the effect of exercise on common symptoms known to result from cancer treatment in individuals who are going to receive treatment or have received treatment, rather than enrolling those with a high level of symptomology for a given outcome, limits the ability to develop a targeted exercise prescription for specific side effects of cancer treatment. Finally, effect size was often not reported and had to be calculated, which was not possible for some RCTs based on the reported

data, limiting the ability to compare findings from the included trials.

Conclusion

Although there is the potential for exercise to address CRCI based on evidence from animal models and observational studies, this systematic review found limited evidence from clinical randomized controlled trials supporting the effect of exercise on cognitive function in individuals with cancer. More high-quality and appropriately powered randomized controlled trials designed to specifically evaluate the effect of exercise on cognitive function as the primary outcome, especially using objective outcome measures, are needed. Furthermore, future research should explore the role of exercise as a preventative strategy for CRCI in patients scheduled to undergo or actively receiving treatment as well as an approach to remediate CRCI in cancer populations experiencing persistent cognitive symptoms posttreatment.

Author Contributions

Concept/idea/research design: K.L. Campbell, M.C. Janelsins
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Data analysis: K.L. Campbell, K. Zadravec, K.A. Bland, E. Chesley
Project management: K.L. Campbell, K. Zadravec
Providing facilities/equipment: K. Campbell
Consultation (including review of manuscript before submitting): K.L Campbell, K. Zadravec, F. Wolf

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Appendix 1.

MEDLINE Search Strategy

1.	Neoplasms/OR exp neoplasms by site/
2.	(neoplasm* OR cancer* OR tumo?r* OR malignan).mp
3.	Cancer survivors/
4.	(cancer adj3 (survivor* OR patient*)).mp
5.	exp Antineoplastic agents/ OR exp antineoplastic protocols/ OR exp chemoradiotherapy/OR chemotherapy, adjuvant/
6.	(chemotherap* OR hormone therap* OR induction therap*).mp
7.	exp Radiotherapy/
8.	(radiotherap* OR radiation therap*).mp
9.	OR/1-8
10.	Exercise/ OR circuit-based exercise/ OR high-intensity interval training/ OR resistance training/ OR exp running/ OR swimming/OR walking/
11.	((resistance OR strength* OR weight* OR aerobic OR endurance OR cardiovasc*) adj3 (exercis* OR train*)).mp
12.	(physical adj3 (activit* OR fitness)).mp
13.	Sports/ OR bicycling/OR weight lifting/
14.	(running OR jogging OR walk* OR swim* OR cycling OR biking OR bicycling).mp
15.	Exercise movement techniques/ OR exp breathing exercises/ OR tai ji/OR yoga/
16.	(Tai Chi OR yoga OR pilates OR Qigong OR Tai Ji).mp
17.	OR/10-16
18.	Cognition/ OR executive function/ OR learning/ OR memory/ OR problem solving/ OR thinking/OR attention/
19.	(cognition OR cognitive function* OR executive function* OR learn* OR memory OR problem solv* OR thinking OR attention).mp
20.	exp Neuropsychological tests/
21.	((neuropsychological OR cognitive) adj3 (assess* OR test*)).mp
22.	Cognitive dysfunction/
23.	(chemobrain OR chemo-brain OR brain fog OR chemo fog OR cancer-related cognitive* OR chemotherapy-related cognitive*).mp
24.	(cognitive adj3 (disorder OR impairment OR dysfunction* OR defect).mp
25.	OR/18-24
26.	9 AND 17 AND 25

Appendix 2.
EMBASE Search Strategy

1.	Malignant neoplasm/OR exp malignant neoplasms subdivided by anatomical site/
2.	(neoplasm* OR cancer* OR tumo?r* OR malignan*).mp
3.	Cancer survivor/OR cancer patient/
4.	(cancer adj3 (survivor* OR patient*)).mp
5.	exp Antineoplastic agent/ OR exp cancer chemotherapy/OR cancer hormone therapy/
6.	(chemotherap* OR hormone therap* OR induction therap*).mp
7.	exp Cancer radiotherapy/
8.	(radiotherap* OR radiation therap*).mp
9.	OR/1-8
10.	Exercise/ OR aerobic exercise/ OR circuit training/ OR high intensity interval training/ OR pilates/OR resistance training/
11.	((resistance OR strength* OR weight* OR aerobic OR endurance OR cardiovasc*) adj3 (exercis* OR train*)).mp
12.	(physical adj3 (activit* OR fitness)).mp
13.	Sport/ OR qigong/ OR Tai Chi/ OR cycling/ OR jogging/ OR running/ OR swimming/OR yoga/
14.	(running OR jogging OR walk* OR swim* OR cycling OR biking OR bicycling).mp
15.	Kinesiotherapy/
16.	(Tai Chi OR yoga OR pilates OR Qigong).mp
17.	OR/10-16
18.	Cognition/ OR attention/ OR executive function/ OR learning/ OR memory/ OR thinking/ OR problem solving/OR brain function/
19.	(cognition OR cognitive function* OR executive function* OR learn* OR memory OR problem solv* OR thinking OR attention).mp
20.	exp Neuropsychological test/
21.	((neuropsychological OR cognitive) adj3 (assess* OR test*)).mp
22.	Cognitive defect/
23.	(chemobrain OR chemo-brain OR brain fog OR chemo fog OR cancer-related cognitive* OR chemotherapy-related cognitive*).mp
24.	(cognitive adj3 (disorder OR impairment OR dysfunction* OR defect).mp
25.	OR/18-24
26.	9 AND 17 AND 25

Appendix 3.
CINAHL Search Strategy

1.	(MH "Neoplasms" OR (MH "Neoplasms by Site+")
2.	neoplasm* OR cancer* OR tumo#r* OR malignan*
3.	(MH "Cancer Survivors") OR (MH "Cancer Patients")
4.	cancer n3 (survivor* OR patient*)
5.	(MH "Antineoplastic Agents+") OR (MH "Chemotherapy, Cancer+") OR (MH "Hormone Therapy+")
6.	chemotherap* OR hormone therap* OR induction therap*
7.	(MH "Radiotherapy+")
8.	radiotherap* OR radiation therap*
9.	OR/1-8
10.	(MH "Exercise") OR (MH "Aerobic Exercises+") OR MH "Resistance Training")
11.	(resistance OR strength* OR aerobic OR endurance OR cardiovasc* OR weight*) n3 (exercis* OR train*)
12.	physical n3 (activit* OR fitness)
13.	(MH "Sports") OR (MH "Swimming") OR (MH "Cycling") OR (MH "Weight Lifting")
14.	running OR walk* OR swim* OR cycling OR biking OR bicycling
15.	(MH "Yoga+") OR (MH "Tai Chi") OR (MH "Qigong") OR (MH "Pilates")
16.	Tai Chi OR yoga OR pilates OR Qigong
17.	OR/S10-S16
18.	(MH "Cognition") OR (MH "Executive Function") OR MH "Learning") OR (MH "Thinking") OR (MH "Memory") OR (MH "Attention") (
19.	cognition OR cognitive function* OR brain function* OR executive function* OR learn* OR memory OR problem solv* OR thinking OR attention
20.	(MH "Neuropsychological Tests")
21.	(neuropsychological OR cognitive) n3 (assess* OR test*)
22.	(MH "Cognition Disorders")
23.	chemobrain OR chemo-brain OR brain fog OR chemo fog OR cancer-related cognitive* OR chemotherapy-related cognitive*
24.	cognitive n3 (disorder OR impairment OR dysfunction* OR defect)
25.	OR/S18-S24
26.	S9 AND S17 AND S25