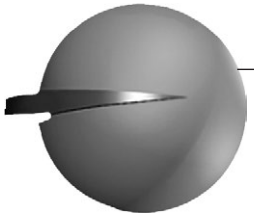

Original Article

Effects of Exercise During or Postchemotherapy in Cancer Patients: A Systematic Review and Meta-Analysis

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Key words

systematic review, meta-analysis, exercise, cancer, chemotherapy

ABSTRACT

Background: Exercise may effectively reduce side effects caused by chemotherapy. However, no meta-analyses of exercise during or postchemotherapy for cancer patients have been definitely performed to guide clinical practice.

Aims: To evaluate and summarize available scientific evidence to provide recommendations of an exercise intervention for cancer patients undergo chemotherapy.

Methods: A systematic review and meta-analysis were performed with databases searching of MEDLINE, Cochrane Library, and Embase from their inception to October 15, 2017. Literature was selected to identify randomized controlled trials of exercise during or postchemotherapy for cancer patients. Risk-of-bias assessment was performed by two reviewers independently. Data were analyzed using the Cochrane Collaboration's RevMan 5.3 (Review Man, Copenhagen, Denmark).

Results: A total of 10 trials with 838 participants were included in our study. Exercise could have a beneficial effect in cancer patients undergo chemotherapy in the outcome of physical fitness (MD: 0.16, 95% CI: 0.08–0.25, $p < .01$ and MD: 2.46, 95% CI: 1.44–3.47, $p < .01$) and depression (MD: −1.36, 95% CI: −2.68 to −0.04, $p = .04$), but not in FACT-G, FACT-B, anxiety, weight, and BMI (all $p > .05$). Exercise sequence (during or postchemotherapy) did not influence the effect of exercise for cancer patients undergo chemotherapy. In total, six studies were assessed as an overall low risk of bias. Subgroup analyses and sensitivity analyses reached results similar to those of the meta-analyses, which reflected our results were reliable and robust.

Linking Evidence to Action: Exercise seems to have a beneficial effect on physical fitness and depression, but not on quality of life, anxiety, weight, and BMI. More specific and detailed description of the implementation of exercise programs should be proposed in the future.

INTRODUCTION

Chemotherapy is helpful for improving survival, while it may also cause adverse consequences in quality of life (QOL; Brahmer et al., 2017; Quinten et al., 2017; Udupa, Rajendranath, & Sagar, 2017; Zietarska, Krawczyk-Lipiec, Kraj, Zaucha, & Malgorzewicz, 2017), fatigue (Levkovich, Cohen, & Karkabi, 2017; Sette et al., 2017; Vardy et al., 2016), depression (Bergerot, Mitchell, Ashing, & Kim, 2017; Bhattacharyya, Bhattacherjee, Mandal, & Das, 2017; Zhang, Zhou, Feng, Xu, & Zeng, 2018), anxiety (Charalambous, Kaite, Charalambous, Tistsi, & Kouta, 2017; Papadopoulou et al., 2017), body composition (Palmela et al., 2017; Rier et al., 2017), and physical functioning (Miaskowski et al., 2017; Timilshina, Breunis, Tomlinson, Brandwein, & Alibhai, 2016). Many non-pharmacological interventions are proposed to prevent or reduce these adverse consequences (Can, Erol, Aydiner, & Topuz, 2011) and accumulating evidence implies that exercise may effectively reduce side effects caused by chemotherapy (Meneses-Echavez, Gonzalez-Jimenez, & Ramirez-Velez, 2015). To date, no meta-analyses of exercise during or postchemotherapy for cancer patients have been definitely performed. However, limited information can be used by medical and nursing staff who want to provide clear exercise recommendations to cancer patients with chemotherapy. Concretely, some clinically relevant questions have not been addressed: Is exercise really helpful in treating side effects related with chemotherapy? Does exercise during or postchemotherapy have the same effect? What are components of a useful exercise for cancer patients?

This systematic review takes into account the evidence from randomized controlled trials on the impact of exercise during or postchemotherapy in cancer patients. The primary aim of our study was to examine the magnitude of the effect of exercise on chemotherapy-related outcomes. The secondary aim was to compare the effect of exercise during and postchemotherapy in cancer patients. The third aim was to combine the evidence available on components of an exercise program to provide recommendations for cancer patients undergo chemotherapy. Therefore, we performed a systemic review and meta-analysis and a summary of all results will help us to choose the best available exercise approach.

METHODS

Eligibility

Types of studies

All randomized trials exploring the effectiveness of exercise during or postchemotherapy in cancer patients were evaluated, regardless of blinding, language, publication status, and length of trial.

Types of participants

Study participants were adults (18 years and older) with a confirmed diagnoses of any type of cancer and undergoing chemotherapy concurrently with or before an exercise intervention in the active group. Gender or ethnicity restrictions were not applied.

Types of interventions

Trials were included that explored the effects of all forms of exercise training or programs (e.g., treadmill exercise, aerobic exercise, trained on cycle ergometers, structured exercise program [SEP], stationary cycling, walking, jogging, running, gymnastics or movement games) in addition to standard care, compared to standard care alone. The exercise in the active group was performed during or postchemotherapy. The standard care was defined as required care without specific exercise training or programs prescribed to increase QOL, body composition or physical functioning, or to decrease depression, anxiety or combination of these. In addition, studies investigating outcomes without any clinical impact were excluded.

Types of outcome measures

Primary outcomes contained QOL (using a validated questionnaire such as Functional Assessment of Cancer Therapy-General [FACT-G] with range of 0–108 and Functional Assessment of Cancer Therapy-Breast [FACT-B] with range of 0–144 [higher score means better]). Secondary outcomes contained physical fitness (objective tests measuring VO2 max or distance walked per time), depression and anxiety (using a validated questionnaire such as Hospital Anxiety and Depression Scale [HADS] with each range of 0–21 [lower score means better]) and weight.

Data Source and Search Strategy

A search of Medline, CENTRAL (Cochrane Library), and Embase databases from their inception until October 2017 was performed to find potentially qualified studies. Medical Subject Heading (MeSH) terms, keywords, or words appearing in the title or abstract were used as the search strategy (details can be found in Table S1). We did not impose language restrictions and examined all relevant studies' reference lists for further studies.

Selection of Reports and Data Extraction

First, one reviewer (LL) identified duplicate literatures using EndNote X6, scanned the titles and abstracts of the literature, and sorted them into different classifications in accordance with the inclusion and exclusion criteria in EndNote X6 (first scanning). Then, two reviewers (LL and JZ) read the full texts of all potentially eligible studies.

A unified structure form in EpiData 3.1 software (The EpiData Association, Odense, Denmark) was used to extract and enter the information from the included trials. Extracted data from each trial included the title, author name; publication year; research site; chemotherapy time; tumor types; exercise types; exercise intensity, frequency, and duration; age; sex; sample size; QOL; physical fitness; depression; anxiety; and funding sources. To clarify the eligibility criteria and to ensure that the criteria could be applied consistently by more than one person, we pilot-tested a draft data abstraction form by randomly including five studies before beginning the formal data abstraction. When there was disagreement (i.e., kappa statistic ≤ .6), two reviewers discussed and reached agreement. After doing this, we modified and supplemented the original eligibility criteria.

Risk-of-Bias Assessment

Risk of bias of each included study was evaluated independently by LL and JZ based on the recommendations in the Cochrane Handbook for Systematic Reviews of interventions (Higgins & Green, 2011). Following this tool, each domain in the assessment was judged as low, unclear, or high risk of bias. Based on these items, studies that contained more than half of high risk or unclear items would be considered as overall high risk, otherwise low risk. Two reviewers discussed with each other to reach agreement if disagreement between them existed.

Data Analysis

For consistency evaluation of risk of data extraction and bias assessment, Kappa coefficient was calculated to assess agreement between two assessors. Agreement was judged as poor if $\kappa \leq .20$; fair if .20 lower than $\kappa \leq .40$; moderate if .40 lower than $\kappa \leq .60$; substantial if .60 lower than $\kappa \leq .80$; good if κ higher than .80; and perfect if $\kappa = 1$. Discrepancies were reviewed in detail and subsequently settled by consensus.

Worldviews on Evidence-Based Nursing, 2019; 1–10.

We performed our meta-analyses based on Cochrane's recommendations (Higgins & Green, 2011). Review Manager 5.3 software for analyses was used (The Nordic Cochrane Centre, The Cochrane Collaboration, 2014). All variables of interest were continuous in our study. We used mean difference (MD) with 95% confidence intervals (CI) to present the combined outcome of continuous variables. We intended to assess statistical heterogeneity using a standard Chi-squared test with a significance level of $\alpha = .1$, as the power of this test is low, and by calculating the I^2 statistic to assess impact on meta-analysis, wherein a value greater than 50% represents at least moderate heterogeneity. If no heterogeneity existed, a fixed-effects model was performed to obtain a pooled estimate of effect; otherwise, a random-effects model was conducted. Statistical heterogeneity was calculated with Cochran's Q ($p < .1$) and I^2 tests. For the primary outcome of FACT-G and FACT-B, we performed the following subgroup analyses: Exercise during or postchemotherapy; trials with overall low risk of bias compared to trials with overall high risk of bias. Robustness of our analysis was assessed by sensitivity analysis, removing studies with high risk of bias in the domain of allocation concealment and blinding of participants and personnel.

RESULTS

Study Characteristics

From the search strategy, we obtained 3,887 potential articles. After screening the articles, 10 reports were included in our study analyses with the sample size of 421 and 417 in the exercise and standard care group, respectively. The article selection process was presented in Figure 1.

Participants' mean age in these studies ranged from 46 to 61 years. The most common exercise intervention in four studies was aerobic exercise program including treadmill, walking, jogging, running, rowing machine, stationary bicycle, or the combination. The other six studies included the intervention of treadmill exercise, trained on cycle ergometers, SEP (face-to-face counseling sessions combined with supervised exercise), multimodal intervention (stationary cycling, dynamic resistance exercises, guided relaxation, and nutrition support), and strength training exercise intervention (supervised strength training and home-based aerobic exercise). The intervention duration ranged from 8 to 96 weeks. The

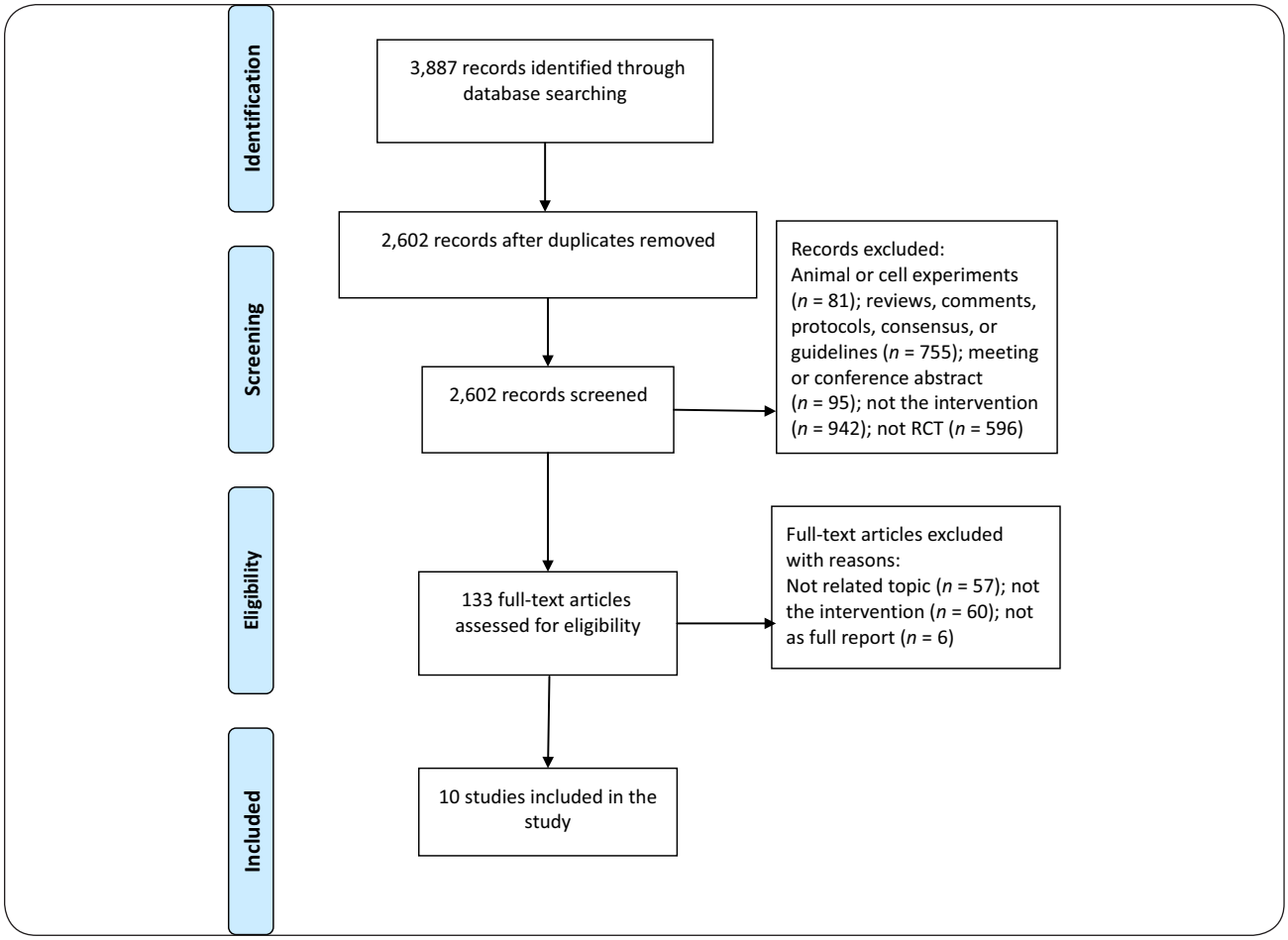


Figure 1. Article selection process.

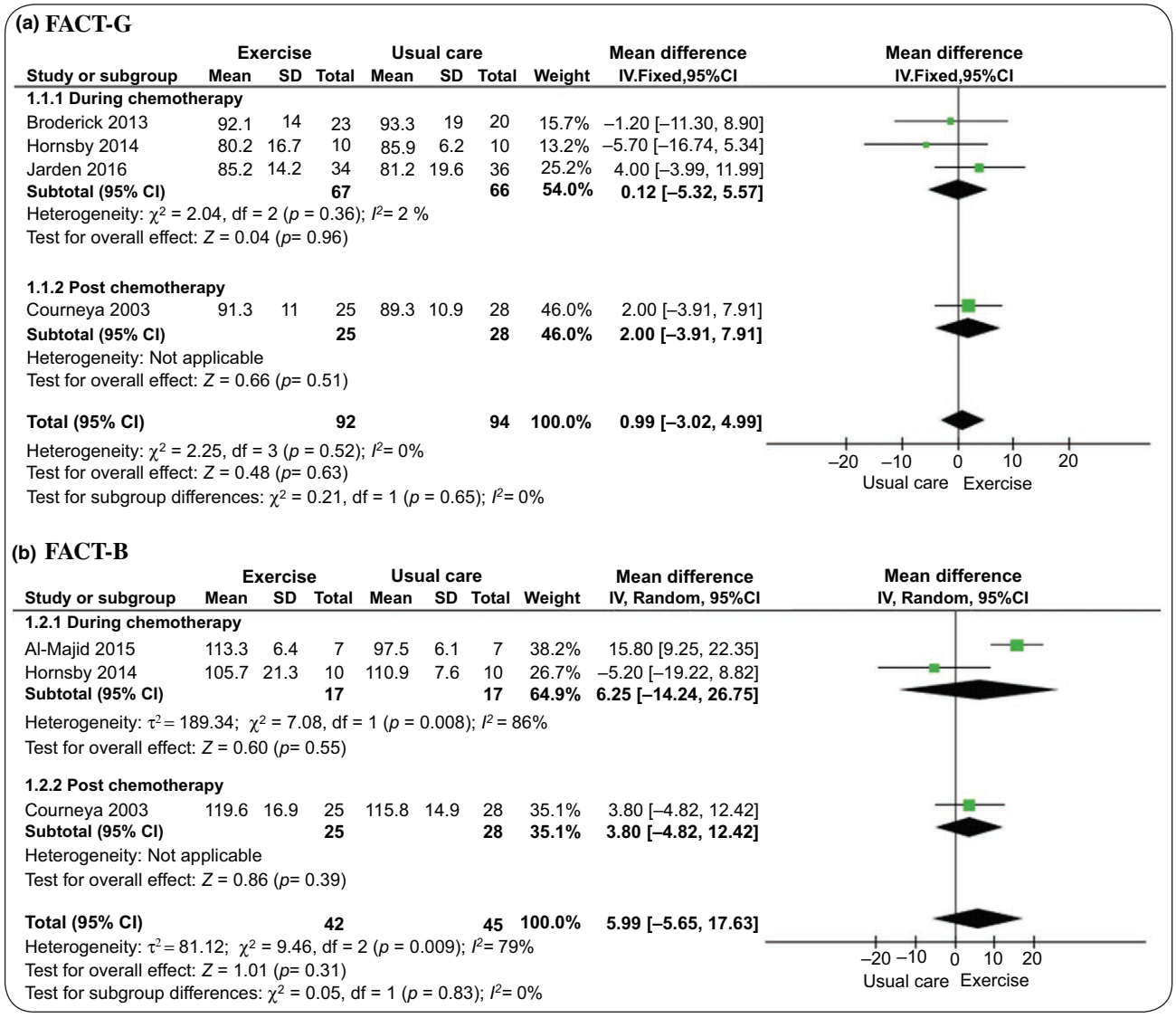


Figure 2. Forest plots of different components of exercise training for fatigue: (a) FACT-G, (b) FACT-B, (c) physical fitness, (d) depression, (e) anxiety, (f) weight, (g) BMI.

studies characteristics and the consistency evaluation of data abstraction are summarized in Tables S2 and S3, respectively.

Quality Assessment

In total, among 10 included studies, 8, 8, 9, and 6 studies were considered as a low risk of bias in the domains of random sequence generation, selective reporting, incomplete outcome data, and other bias, respectively. Only 3, 1, and 3 studies were assessed as a low risk of bias in the domain of allocation concealment, blinding of participants and personnel and blinding of outcome assessment, respectively. In total, six trials were assessed as an overall low risk of bias. A substantial agreement was observed for items 2, 3, 4, and 5; a good agreement was observed for item 7; and perfect for 1 and 6. Risk-of-bias summary and its consistency evaluation are presented in Figure S1 and Table S4.

Effects of Exercise in Cancer Patients

FACT-G

From Figure 2a, four RCTs reporting FACT-G included 92 participants treated with exercise and 94 participants treated with standard care. The overall pooled results did not show a statistically significant improvement in FACT-G (MD: 0.99, 95% CI: −3.02 to 4.99, $p = .63$). No heterogeneity for the trials ($\chi^2 = 2.25$, $p = .52$; $I^2 = 0\%$) existed. Similarly, a nonsignificant difference in FACT-G was observed between the two subgroups of exercise during or postchemotherapy ($\chi^2 = 0.21$, $p = .65$; $I^2 = 0\%$).

FACT-B

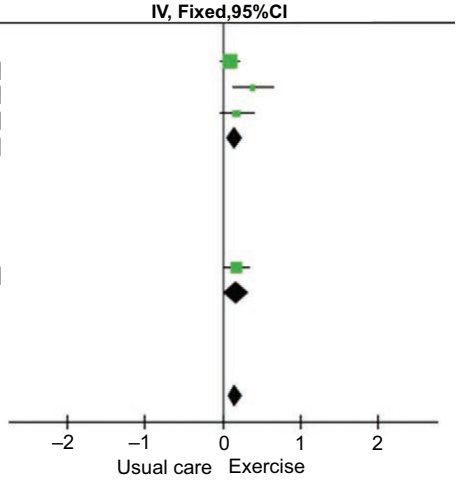
From Figure 2b, three RCTs reporting FACT-B included 42 participants treated with exercise and 45 participants treated with standard care. The overall pooled results did not show a statistically significant improvement in FACT-B

Worldviews on Evidence-Based Nursing, 2019; 1–10.

(c) Physical Fitness

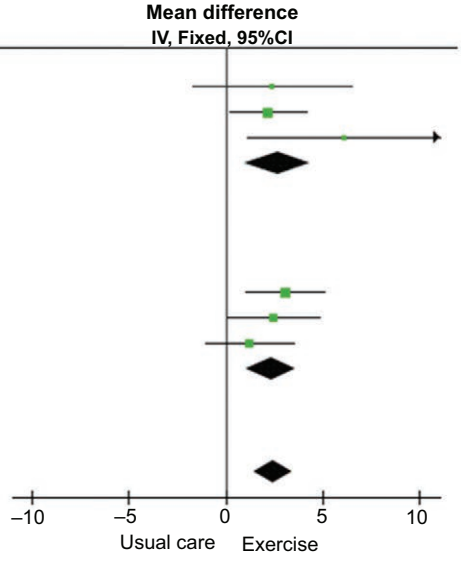
(1) VO_{2peak}, L/min

Study or subgroup	Exercise Mean	SD	Total	Usual care Mean	SD	Total	Weight	Mean difference IV, Fixed,95%CI
1.4.1 During chemotherapy								
Courneya 2007	1.77	0.48	82	1.68	0.36	82	44.6%	0.09 [–0.04, 0.22]
Hornsby 2014	1.59	0.35	10	1.2	0.23	10	11.2%	0.39 [0.13, 0.65]
Kim 2006	1.81	0.37	22	1.63	0.35	19	15.4%	0.18 [–0.04, 0.40]
Subtotal (95% CI)			**114**			**111**	**71.2%**	**0.16 [0.05, 0.26]**
Heterogeneity: χ^2 = 4.16, df = 2 (p = 0.12); I^2 = 52%								
Test for overall effect: Z = 2.99 (p = 0.003)								
1.4.2 Post chemotherapy								
Courneya 2003	1.61	0.29	25	1.43	0.31	28	28.8%	0.18 [0.02, 0.34]
Subtotal (95% CI)			**25**			**28**	**28.8%**	**0.18 [0.02, 0.34]**
Heterogeneity: Not applicable								
Test for overall effect: Z= 2.18 (p= 0.03)								
Total (95% CI)			**139**			**139**	**100.0%**	**0.16 [0.08, 0.25]**
Heterogeneity: χ^2 = 4.22, df = 3 (p = 0.24); I^2= 29%								
Test for overall effect: Z = 3.69 (p = 0.0002)								
Test for subgroup differences: χ^2 = 0.06, df = 1 (p = 0.81); I^2= 0%								



(2) VO_{2peak}, mL/kg/min

Study or subgroup	Exercise Mean	SD	Total	Usual care Mean	SD	Total	Weight	Mean difference IV, Fixed, 95%CI
1.5.1 During chemotherapy								
Broderick 2013	22.8	7.5	23	20.4	6.2	20	6.2%	2.40 [–1.70, 6.50]
Courneya 2007	25.7	7.4	82	23.5	5.4	82	26.3%	2.20 [0.22, 4.18]
Hornsby 2014	22.1	7	10	16	4	10	4.1%	6.10 [1.10, 11.10]
Subtotal (95% CI)			**115**			**112**	**36.6%**	**2.67 [0.99, 4.36]**
Heterogeneity: χ^2 = 2.04, df = 2 (p = 0.36); I^2 = 2%								
Test for overall effect: Z = 3.12 (p = 0.002)								
1.5.2 Post chemotherapy								
Courneya 2003	21.3	3.7	25	18.2	3.9	28	24.7%	3.10 [1.05, 5.15]
Courneya 2016	34.8	10.9	136	32.3	8.9	137	18.6%	2.50 [0.14, 4.86]
Mehnert 2011	26.88	4.38	35	25.65	4.71	28	20.1%	1.23 [–1.04, 3.50]
Subtotal (95% CI)			**196**			**193**	**63.4%**	**2.33 [1.05, 3.61]**
Heterogeneity: χ^2 = 1.47, df = 2 (p = 0.48);I^2 = 0%								
Test for overall effect: Z = 3.57(p = 0.0004)								
Total (95% CI)			**311**			**305**	**100.0%**	**2.46 [1.44, 3.47]**
Heterogeneity:χ^2 = 3.61, df = 5 (p = 0.61); I^2 = 0%								
Test for overall effect:Z= 4.73 (p < 0.00001)								
Test for subgroup differences:χ^2 = 0.10, df = 1 (p = 0.75); I^2 = 0%								



(d) Depression

Study or subgroup	Exercise Mean	SD	Total	Usual care Mean	SD	Total	Weight	Mean difference IV, Fixed, 95%CI
1.6.1 During chemotherapy								
Jarden 2016	3.3	3.2	34	4.1	3.9	36	62.8%	–0.80 [–2.47, 0.87]
Subtotal (95% CI)			**34**			**36**	**62.8%**	**–0.80 [–2.47, 0.87]**
Heterogeneity:Not applicable								
Test for overall effect: Z= 0.94 (p= 0.35)								
1.6.2 Post chemotherapy								
Mehnert 2011	4.83	3.46	35	7.14	4.97	28	37.2%	–2.31 [–4.48, –0.14]
Subtotal (95% CI)			**35**			**28**	**37.2%**	**–2.31 [–4.48, –0.14]**
Heterogeneity:Not applicable								
Test for overall effect: Z= 2.09 (p= 0.04)								
Total (95% CI)			**69**			**64**	**100.0%**	**–1.36 [–2.68, –0.04]**
Heterogeneity: χ^2 = 1.17, df = 1 (p = 0.28); I^2= 15%								
Test for overall effect: Z= 2.02 (p= 0.04)								
Test for subgroup differences: χ^2 = 1.17, df = 1 (p = 0.28); I^2= 14.6%								

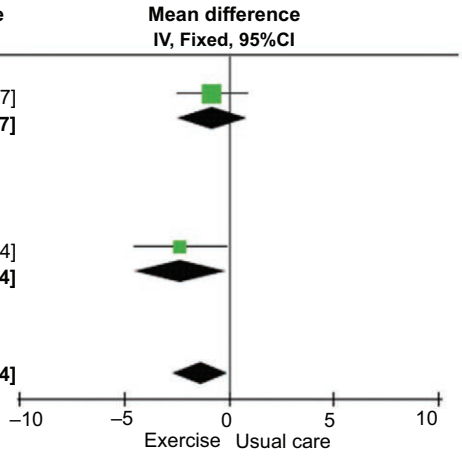


Figure 2. (Continued)

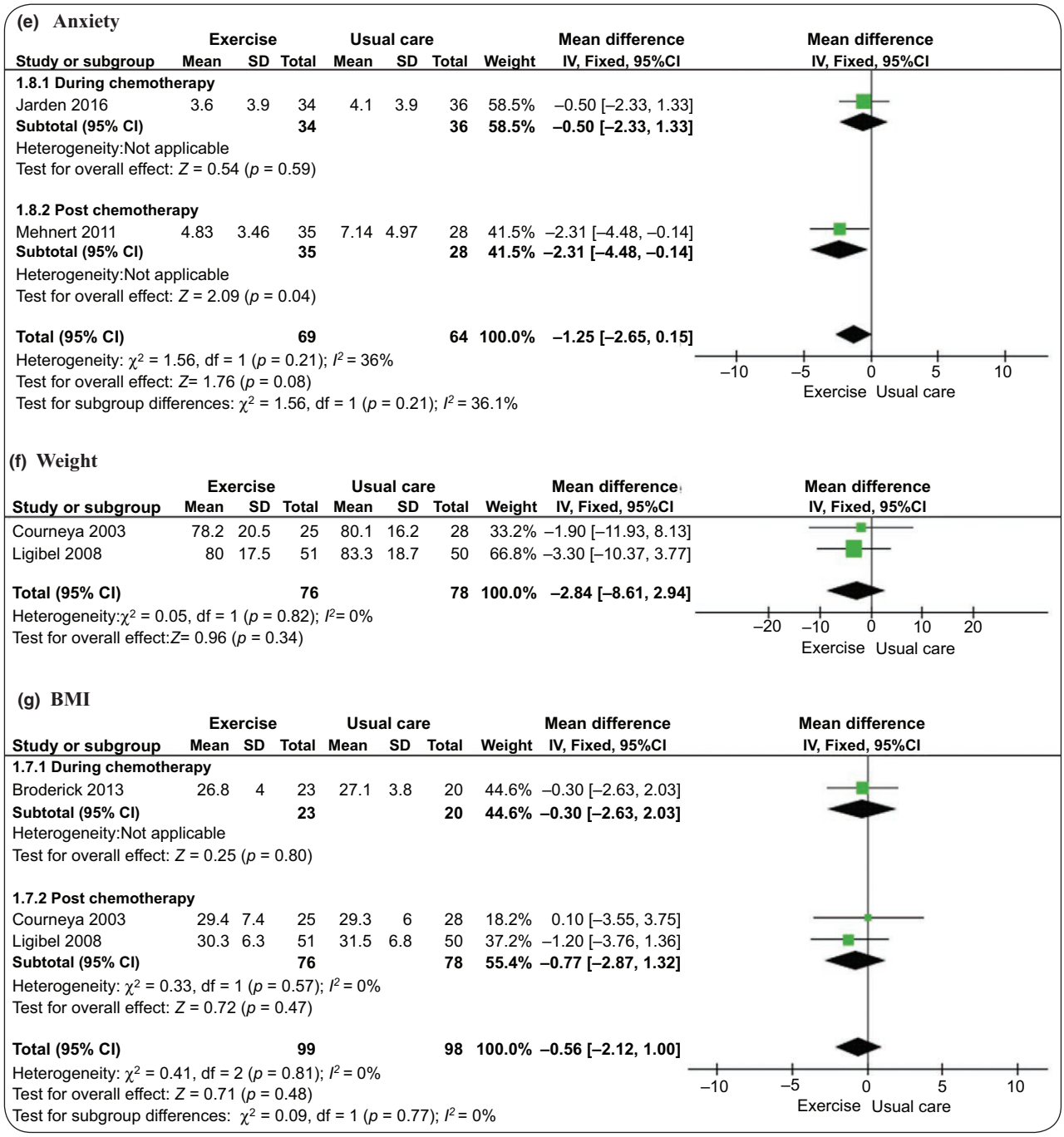


Figure 2. (Continued)

(MD: 5.99, 95% CI: −5.65 to 17.63, $p = .31$). Heterogeneity existed for the trials ($\chi^2 = 9.46$, $p = .009$; $I^2 = 79\%$). Similarly, a nonsignificant difference in FACT-B was observed between the two subgroups of exercise during or postchemotherapy ($\chi^2 = 0.05$, $p = .83$; $I^2 = 0\%$).

Physical fitness

From Figure 2c (1), four RCTs reporting Peak oxygen consumption (VO_{2peak}, L/min) included 139 participants treated with exercise and 139 participants treated with standard care. The overall pooled results showed a statistically significant improvement in this indicator (MD: 0.16, 95% CI: 0.08–0.25, $p < .01$) favoring the exercise group. Heterogeneity did not exist for the trials ($\chi^2 = 4.22$, $p = .24$; $I^2 = 29\%$). Similarly, a nonsignificant difference in this indicator was observed between the two subgroups of exercise during or postchemotherapy ($\chi^2 = .06$, $p = .81$; $I^2 = 0\%$).

From Figure 2c (2), six RCTs reporting peak oxygen consumption (VO_{2peak}, $mL{\cdot}kg^{-1}{\cdot}min^{-1}$) included 311 participants

treated with exercise and 305 participants treated with standard care. The overall pooled results showed a statistically significant improvement in this indicator (MD: 2.46, 95% CI: 1.44–3.47, $p < .01$) favoring the exercise group. Heterogeneity did not exist for the trials ($\chi^2 = 3.61$, $p = .61$; $I^2 = 0\%$). Similarly, a nonsignificant difference in this indicator was observed between the two subgroups of exercise during or postchemotherapy ($\chi^2 = 0.10$, $p = .75$; $I^2 = 0\%$).

Depression

From Figure 2d, two RCTs reporting depression included 69 participants treated with exercise and 64 participants treated with standard care. The overall pooled results showed a statistically significant decrease in depression (MD: −1.36, 95% CI: −2.68 to −0.04, $p = .04$) favoring the exercise group. Heterogeneity did not exist for the trials ($\chi^2 = 1.17$, $p = .28$; $I^2 = 15\%$). Similarly, a nonsignificant difference in depression was observed between the two subgroups of exercise during or postchemotherapy ($\chi^2 = 1.17$, $p = .28$; $I^2 = 14.6\%$).

Anxiety

From Figure 2e, two RCTs reporting anxiety included 69 participants treated with exercise and 64 participants treated with standard care. The overall pooled results did not show a statistically significant decrease in anxiety (MD: −1.25, 95% CI: −2.65 to 0.15, $p = .08$). Heterogeneity did not exist for the trials ($\chi^2 = 1.56$, $p = .21$; $I^2 = 36\%$). Similarly, a nonsignificant difference in anxiety was observed between the two subgroups of exercise during or postchemotherapy ($\chi^2 = 1.56$, $p = .21$; $I^2 = 36.1\%$).

Weight

From Figure 2f, two RCTs reporting weight included 76 participants treated with exercise postchemotherapy and 78 participants treated with standard care. The overall pooled results did not show a statistically significant improvement in weight (MD: −2.84, 95% CI: −8.61 to 2.94, $p = .34$). Heterogeneity did not exist for the trials ($\chi^2 = .05$, $p = .82$; $I^2 = 0\%$).

BMI

From Figure 2g, three RCTs reporting BMI included 99 participants treated with exercise and 98 participants treated with standard care. The overall pooled results did not show a statistically significant improvement in BMI (MD: −0.56, 95% CI: −2.12 to 1, $p = .48$). Heterogeneity did not exist for the trials ($\chi^2 = .41$, $p = .81$; $I^2 = 0\%$). Similarly, a nonsignificant difference in BMI was observed between two the subgroups of exercise during or postchemotherapy ($\chi^2 = .09$, $p = .77$; $I^2 = 0\%$).

Subgroup and Sensitivity Analyses

Subgroup analyses and sensitivity analyses both showed that the pooled effect on primary outcomes remained nonsignificant in statistics, which reached results similar to those of the meta-analysis and reflected our results were reliable and robust. Subgroup and sensitivity analyses were summarized in Figures S2 to S4.

DISCUSSION

This study included 10 RCTs comparing exercise versus standard care for patients with cancer and included a total of 838 participants. Meta-analyses suggest that the exercise group seems to have a beneficial effect on physical fitness and depression, and no effects on FACT-G, FACT-B, anxiety, weight, and BMI, compared with the standard care group. The between-trial heterogeneity did not exist in the meta-analyses of primary outcomes except for the outcome of FACT-B.

Subgroup analyses and sensitivity analyses conducted by removing studies of high risk of bias reached results similar to those of the meta-analyses, which reflected our results were reliable and robust. In addition, we did not observe any significant differences in outcomes between the two subgroups with exercise during or postchemotherapy, which meant the exercise sequence seems to have little impact on the effects of exercise for cancer patients.

All included trials recruited adult patients of 46 to 61 years with the intervention duration in range of 8 to 96 weeks. The most common form of exercise in four trials was aerobic exercise program (multiple components) including treadmill, walking, jogging, running, rowing machine, stationary bicycle, or the combination. Mostly, the exercise duration ranged from 5 to 50 min with the frequency of 2 to 3 times a week. Exercise intensity depended on the exercise component and patients' endurance capacity (e.g., peak oxygen consumption, heart rate).

All included studies were conducted in developed countries, such as Canada, USA, Germany, Ireland, Demark, and Korea. This suggests more attention has been given to cancer patients with chemotherapy in developed countries compared to developing countries. In developed countries, a home-based exercise program (a supervised, moderate-to-high intensity combined resistance and aerobic exercise program) has the advantage of reducing the decline of physical fitness and muscle strength and improving the fatigue and return to work rates, as compared to usual care (van Waart et al., 2017). Although the findings in our review are likely applicable to medical practices in countries with a similar status of cancer patients, the question remains as to how applicable this evidence is to medical practices in developing countries. Due to the data limitations, we could not perform subgroup analysis based on different types of exercise. Thus, we were unable to determine the effect of exercise in relation to different types or different countries.

For the quality of evidence, we assessed 60% of included studies as an overall low risk of bias, which implies that the quality of evidence in our study is moderate. Some bias existed in the domain of allocation concealment, blinding of participants and personnel and blinding of outcome assessment. All biases mentioned above may have affected outcome estimates and confidence (Gao et al., 2015; Lu, Liao, Zeng, & He, 2013). We acknowledge the uncertain aspects

in our results for outcomes mentioned above and look forward to future high-quality studies.

Recommendation for Practice

For clinical implications, our results suggest that exercise seems to have a beneficial effect on physical fitness and depression, but not on QOL, anxiety, weight, and BMI. Based on our findings, the exercise sequence seems to have little impact on the effect of exercise for cancer patients. In a qualitative summary of the included evidence, the range of exercise duration and frequency in aerobic exercise program (multiple components) was 5 to 50 min each time and 2 to 3 times weekly for cancer patients with chemotherapy, respectively. Exercise intensity should be decided by considering the exercise component and patients' endurance capacity (e.g., peak oxygen consumption, heart rate).

Limitations

Study limitations are acknowledged. First, methodological limitations existed as our study included heterogeneousness in some domains with risk of bias in quality assessment. We performed subgroup and sensitivity analyses by removing studies with high risk of bias and reached results similar to those of the meta-analyses, which suggested our results are reliable and robust. Second, the small sample size in the meta-analysis of the primary outcome may lead to false-negative results due to insufficient statistical power. Third, given we found that exercise sequence seems to have little impact on the effect of exercise for cancer patients, more powerful evidence should be included to make a more reliable conclusion.

CONCLUSIONS

In conclusion, our meta-analysis suggests that exercise may play a role in reducing adverse consequences caused by chemotherapy. The evidence confirms that aerobic exercise programs (multiple components) are necessary for cancer patients receiving chemotherapy. More specific and detailed descriptions of the implementation of exercise programs should be proposed in the future.**WVN**

LINKING EVIDENCE TO ACTION

- Exercise seems to have a beneficial effect on physical fitness and depression, but not on QOL, anxiety, weight, and BMI.
- Based on study findings, exercise sequence seems to have little impact on the effect of exercise for cancer patients.
- More specific and detailed descriptions of the implementation of exercise programs should be proposed in the future.

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This research was supported by Guangdong Natural Science Foundation (project no. 2016A030310290), National Natural Science Foundation of China (grant no. 81603494), and The Specific Research Fund for TCM Science and Technology of Guangdong Provincial Hospital of Chinese Medicine (no. YN2015QN20). The funder had no further role in study design, data collection, analysis and interpretation of data, writing of the report, or the decision to submit the paper for publication.

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Accepted 20 May 2018

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SUPPORTING INFORMATION

Additional supporting information may be found in the online version of this article at the publisher's web site:

Figure S1. Risk-of-bias summary.
Figure S2. Forest plots of studies with overall low or high bias risk: (a) FACT-G; (b) FACT-B.
Figure S3. Forest plots of studies with low or high bias risk in allocation concealment: (a) FACT-G; (b) FACT-B.
Figure S4. Forest plots of studies with low or high bias risk in blinding of participants and personnel: (a) FACT-G; (b) FACT-B.
Table S1. Search Strategy
Table S2. Characteristics of the Included Studies
Table S3. Consistency Evaluation of Data Extraction
Table S4. Consistency Evaluation of Risk-of-Bias Assessment

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