Author’s response to reviews

Title: Exercise and Cancer-Related Fatigue in Adults: A Systematic Review of Previous Systematic Reviews with Meta-Analyses

Authors:

George Kelley (gkelley@hsc.wvu.edu)
Kristi Kelley (kskelley@hsc.wvu.edu)

Version: 1 Date: 25 Sep 2017

Author’s response to reviews:

Response to Editor Comment

We have triple-checked the statistics and verify the accuracy and correctness of such.

Responses to Reviewer #1 (Dr. John Saxton)

Thanks so much for taking the time to thoroughly review this manuscript. Based on your great suggestions, I believe the manuscript has now been strengthened considerably. To make it easier for you, we have copied your comments below, designated as “C”, with our responses after each one, designated as “R”. Line numbers refer to those that we have inserted into the manuscript and which correspond exactly with each line.

C1. This is a rigorously conducted and comprehensively reported review of systematic reviews on the important topic of exercise and cancer-related fatigue.

R1. Thank you so much for the positive feedback. It is GREATLY appreciated.

C2. The introduction section states refers to the NCCN reference, recommending that physical activity is a non-pharmacological strategy for the management of CRF and yet it seems that physical activity was not used as a search word for this review. Instead, the term "exercise OR
physical fitness" was used. If this was the case, is it possible that some key references were missed? Although the term "physical activity" includes structured exercise (as rightly pointed out) it is not limited to this.

R2. Excellent observation. While located in a Department of Biostatistics, all of the first author’s degrees are in exercise science. Thus, we are aware of this difference. Now to answer your query – If you look at Additional file 1 and the second line in the Query Translation box of the PubMed Search, you will see that our initial search query “exploded” to include the term “physical” for all fields. As you can surmise, this will include even more citations than including the term “physical activity”. Other databases operate similarly, although you won’t see that with the other databases given what we can copy. Historically, our searches over the past 25 years have been broad. While this creates more work on our part, we’re always concerned about the very issue you raise here, that is, missing studies that meet our eligibility criteria. I’m actually really glad that you asked this.

C3. I think it would help if there was some comment/brief discussion about the two main questionnaires used to assess perceived fatigue in cancer populations. Also, what are the limitations of measuring fatigue by means of a questionnaire?

R3. Good observation. As suggested, we have added additional information about this to the Discussion, including potential limitations. Please see lines 645-668 of revised manuscript.

C4. There is a lot of emphasis on methodological take-home messages, but less emphasis on implications for future original research (i.e., RCTs). In particular, what seems to be missing in the discussion of the limitations of published randomised controlled trials is consideration of the number of trials in the published literature in which fatigue has been measured as a secondary outcome and in which participants have not been recruited on the basis that they are experiencing clinically important levels of CRF at baseline - this may have the effect of diluting the effects of exercise on CRF or may even provide more evidence that exercise can exacerbate fatigue in those experiencing higher levels. This is only one example of a potential limitation of published RCTs that has not been discussed, I'm sure there are others. It would be useful for the research community to understand such limitations and gaps in knowledge so that future RCTs are better informed.
R4. Great. As suggested, we have added additional information about the potential limitation of the randomized controlled trials from which these systematic reviews with meta-analysis were based. See lines 563-578

C5. Some consideration and discussion of the potential mechanisms by which exercise could have a positive impact on fatigue would have been a useful inclusion.

R5. Good suggestion. Based on your observation, we now include information about this. See lines 489-500.

C6. Overall, this is a very useful piece of work, but I would have liked to have seen slightly less emphasis on methodological limitations/directions and more discussion about what can be learned from this to inform future original research (i.e. RCTs).

R6. Thank you for the encouraging feedback. As previously suggested in R4 above, we have added additional information regarding some of the potential limitations of randomized controlled trials. However, we felt it was unethical to delete the already existing information on methodological limitations/directions.

Responses to Reviewer #2 (Dr. Marilynne Kirshbaum)

The authors appreciate you taking time to review this manuscript. We believe that your comments have improved this revised version. To make it easier for you, we have copied your comments below, designated as “C”, with our responses after each one, designated as “R”. Line numbers refer to those that we have inserted into the manuscript and which correspond exactly with each line.

C1. While I appreciate the justification and rigour of this report of a 'systematic review of systematic reviews and meta-analysis', it falls short of providing useful implications to practitioners and the public. Substantially more detail of conclusions are expected. The review is highly critical of well-respected and authoritative authors, yet does not provide much substance
for how the findings can be used. I would suggest that revisions would consist of more detail and depth to the sections on implications for practice and policy.

R1. Thank you for the positive feedback regarding the rigour of our study. As suggested, and while being mindful of the current lack of convincing evidence regarding exercise and CRF as well as an already lengthy manuscript, we have added additional and more specific information to the Implications for Policy (see lines 599-613), Implications for Practice (see lines 586-594), and Conclusions (see lines 670-676). Finally, please understand that we are not being critical of the authors. Rather, we are identifying some of the potential gaps in all prior work. We do understand that every study has flaws, including our own, and hope that these observations would be taken in the spirit of advancing the science base on exercise and CRF in adults.

Responses to Reviewer #3 (Dr. Sungjin Kim)

We want to thank you for taking the time to review this systematic review of previous systematic reviews with meta-analysis. It is our belief that your comments have improved this work. To make it easier for you, we have copied your comments below, designated as “C”, with our responses after each one, designated as “R”. Line numbers refer to those that we have inserted into the manuscript and which correspond exactly with each line.

Overall

C1. The authors well described the results of a systematic review of previous systematic reviews regarding exercise effect on cancer-related fatigue in adults regardless of a type of cancer. However, even though the manuscript is well-written overall, it may be shortened or sub-sectioned as readers may find this manuscript difficult to follow. The authors may leave only essential information in the main body of the manuscript, and move less indispensable descriptions to supplementary documents.

R1. We thank you for the positive feedback. As suggested, we have sub-sectioned 2 parts of the Discussion (see lines 502 and 544). However, given that Reviewers 1 and 2 suggested additional information be added, the revised manuscript is actually longer versus shorter. However, based
on your suggestion, as well as the authors’ inability to agree on what to delete or move, we have asked the editor for guidance on this.

Minor

C1. Have the authors ever conducted a systematic review of exercise on cancer-related fatigue by cancer type? It would be good to know if there are different exercise effects on cancer-related fatigue for different cancer types.

R1. Great question and we agree. In relation to your question – No, we have not conducted a systematic review of our own by cancer types. Based on the available evidence, and as pointed out in the manuscript, the only thing we could conclude was that the meta-analytic results for those with breast cancer were similar to those with all other types of cancer. It may be that an updated and more inclusive meta-analysis that includes all cancer types with comparisons between the different cancer types might be warranted. Based on your observation, we have added information to this effect in the manuscript. Please see lines 540-543.

C2. '̅ ± SD' would better be replaced with 'mean ± SD' throughout the manuscript.

R2. Good. Thank you. As suggested, we have made this change throughout the manuscript. Please see entire manuscript for this change.

C3. Figures 2-5 would look better if they are in the same style.

R3. Thank you. We have removed the y axis line from Figure 5 so that it is similar to figures 2 and 3. However, figure 4 remains the same since 95% confidence intervals based on number-needed-to treat can be misleading. We use a bar graph for figure 4 because we believe that it best represents the data and what we’re trying to illustrate.