Response to Reviewers

We thank the reviewers for their careful reading of the manuscript and especially for their helpful comments. In this revision every attempt has been made to retain these positive features and improve the presentation in terms of both clarity and scientific rigor. We will now address the specific comments of each reviewer. Our responses are following reviewer queries in bold.

Reviewer 1:
 Overall, this manuscript is well-written and provides an informative review of the existing literature on an important topic, and it may be used to inform future research in this area. Despite this, a number of revisions will need to be made before the manuscript is ready for publication. These revisions are detailed below:

ABSTRACT –

1) I recommend removing/changing “mitigation” in the first sentence, since mitigation refers to the action of reducing the severity, seriousness, or painfulness of something, and doesn’t make sense in this case when combined with the terms health and wellbeing. Done

2) Also in the first sentence, “survivors” should be changed to “cancer survivors” since it’s the first time it’s being stated. Done

3) Consider removing “pediatric cancer populations” from the text since the focus throughout is on AYAs. Done

4) A significant portion of the abstract is identical to text presented later in the manuscript. I would suggest paraphrasing or rewording the abstract to avoid exactly duplicating statements made later on in the paper.

SECTION ENTITLED “Physical Mechanisms Underlying Inadequate Physical Activity (PA) and Survivor Health” –

1) Consider deleting the second “often combined” in the first sentence of this section. Done

2) The first paragraph is lacking citations. Please add as appropriate. Citations added.

3) 2nd paragraph: Citation #12 appears to be incorrect, as it does not mention anything about osteopenia/osteoporosis and is focused on adult breast cancer survivors. Please provide correct citation.

4) 3rd paragraph: “one-to-three weeks” does not require the use of hyphens; “muscles function” should instead be “muscle function”; and there should not be a comma after “decreased bone mineralization”. Done

5) 4th paragraph: The first sentence seems to be missing a word after “activated”. This has been amended.

SECTION ENTITLED “What has been done – A Review of the Literature” –

1) 2nd paragraph: “into account for duplicate” should instead be “into account duplicate”. Done
2) 4th paragraph: The citations appear to be incorrect. For example, only four citations are provided in the first sentence, but five of six interventions are discussed. In addition, the citations in the second sentence do not match up with those referenced in the first. Finally, the last sentence includes two citations (in a different format, please be consistent with formatting) that don’t seem to match up with “the one study”. Citations have been corrected. The two papers both reported results in of the ONE study.

3) 4th paragraph: It isn’t clear whether the 5 interventions other than Li et al. measured longer term outcomes or not. Please indicate whether they were measured or not, and if so, what the results were. This has been clarified.

4) 7th paragraph: In the second sentence, I recommend moving up “three times per week” to before “aerobic exercise” to improve the clarity of this statement. Done

SECTION ENTITLED “Exercise Strategies to Promote Health in AYAs” —

1) At the end of this section, it’s stated that the “specific mechanisms of each form of training are presented below”. It appears a section of text is missing from the manuscript since there is a section on mechanisms of strength training but not one for mechanisms of aerobic training. Please add in this section on aerobic training, as it is a crucial aspect of the argument being presented in the remainder of the manuscript.

SECTION ENTITLED “Physiological Mechanisms of Strength Training” —

1) 2nd paragraph: Please provide a citation for the first sentence, or move up citation #18 if appropriate. Done

2) 3rd paragraph: Similarly, I suggest moving up citation #46 to the sentence prior, if appropriate. Citation added

SECTION ENTITLED “Recommendations. Exercise Strategy” —

1) A citation should be provided for the last statement in this paragraph. Citation added

2) An additional supporting point to consider is that resistance training may also be more beneficial than aerobic training for patients who are underweight (due to treatment, loss of muscle mass, etc.). Agree, this sentence has been added to the text.

CONCLUSIONS —

1) In general, I would recommend that no citations be provided in the conclusion section. No new information should be presented in this section, only conclusions based on all the evidence previously discussed in the text. I suggest incorporating all the new information into previous sections of the text, as appropriate. Agree, they have been removed.

Reviewer 2:
This paper reports on a review of the literature about exercise in AYA cancer survivors. The tactic that the authors took is somewhat unique for the general AYA Cancer literature and told me more about muscles and the musculoskeletal system and why I should think about these things when recommending exercise to survivors than I have thought about before. That said, there were a couple of areas that I feel were missing:

In the section "Exercise Strategies to Promote Health..." I was expecting the authors to include a discussion about aerobic exercise as well and spend some time discussing the differences in benefits of the two. As I am sure they are aware, depending on the amount of anthracycline and chest radiation that a patient receives, the guidelines for resistance exercises can vary widely, whereas we generally do not suggest limiting aerobic exercise. **Agree, section has been added.**

In their discussion of the literature review they noted several shortcomings of published studies including specific suggestions and follow-up, I had anticipated some discussion of what might be a good routine and how often and over what period of time, participants should be followed, as well as the best (2-4 at most) parameters to measured serially.

In short, the manuscript seems to be incomplete. **We have added additional information to improve clarity and completeness**

**Reviewer 3:**

This is a most interesting paper that is well researched, well presented and well written. The papers flows well, presents realistic conclusions based on the findings and would make a very important contribution to the literature.

My points of criticism are small, such is this quality of this paper. Firstly, it might be useful if the authors gave mention of the public health aspects of this. What is the population prevalence of this cohort? What might be the impact if exercise was improved e.g. x% of fewer cancers? Reduced pressures on health care services? **We agree this would be an important addition. While we have added some information, these recommendations are a bit beyond the scope of the paper which largely aims to provide a call to action for RT in improving quality of life in AYAs**

Secondly, the authors might want to comment on more general exercise knowledge. For example, is there a case to be made for protein supplementation? Or if energy is a challenge, supplementation with creatine products?

Thirdly, the authors might include or give more prominence to policy aspects. Cost-effectiveness of this? What more research needs to be undertaken? How we can avoid 'reverse causality' & encourage exercise in this cohort.

Finally, the authors might like to put exercise in context. What other interventions might be useful in this population - for example low dose aspirin to reduce risks of cardiovascular disease and perhaps cancer recurrence.

Overall, I would like to congratulate the authors on their excellent submission which I have no hesitation in recommending for publication. It has been a pleasure to review this paper and provide this encouragement. **We thank the reviewer for their positive comments and insightful questions and look forward to conducting RCTs that may be able to more appropriately answer the posed questions.**

**Reviewer 4:**
This paper aims to review physiological mechanisms underlying treatment for cancer in adolescent and young adults and to review empirical evidences on physical therapies aimed to rehabilitate this population.

The topic is not novel but as far as I know, no reviews have been performed yet. Moreover, clinical implications of this topic are clear and of big interest. A lot of research has been carried out regarding physical and psychological consequences after cancer. However, outcomes of physical rehabilitative therapies have been less explored.

The paper is well written and information presented is useful for practitioners and health professionals. Some specific comments to further improve the manuscript are stated below:

TITLE
- I would include “a review of the literature” or “narrative review” or something similar to clarify the type of paper we have and to not mislead the readers. “A Narrative Review” has been added to the title.

ABSTRACT
- I think authors review physical interventions that have been implemented to date to increase AYA survivor exercise but they do not properly “review” physiological mechanisms. That is to say, they present and summarize relevant literature on physiological mechanisms but search strategy does not include text words related to physiological mechanisms. Thus, I would re-write the objectives here in the abstract and in the manuscript.
- The topic presented is very interesting and to date, it was lacking in the scientific literature.
- Perhaps keywords should include “health”, “intervention studies”.
- An abbreviation list could have been provided.

INTRODUCTION
- The introduction is correct and properly addresses main topic of this research.
- I would add some clear definitions of AYAS (e.g. with range of ages). Mainly because in the document there are some inconsistencies in this sense and results are presented depending on the sample ages (adolescents or pediatric or young adults...)
- I consider that some background of previous studies should be mentioned there.

For instance:

Or: http://bjsm.bmj.com/content/43/1/32.full.pdf+html
Or the systematic review Braam et al. performed in 2013:

Thank you for these suggestions we have added as appropriate.

METHODS

- There is no methods section on the article. Information is there, but in my opinion it could have been
  presented in a clearer manner. Perhaps after the title “What has been done – A review of the Literature”
  the METHODS epigraph could be introduced.

- Similarly, headings such as “search strategy” (page 7), “data extraction” (page 8, second paragraph),
  “results”, etc would have made the article more easy to follow. Done

- I believe more than 9 articles can be yielded on this topic. See for instance the study of Braam et al.,
  references are included. I would suggest updating the search and including some more studies since the
  inclusion and exclusion criteria are not that strict to limit the results to only 9 studies.

RESULTS

- In general, results are well presented and tables made this section more comprehensible. I would
  include the heading (lines 11-12 onwards, page 8?) and include references after some statements such
  as: Citation added

  “Of the studies including adolescents, four included survivors only (aged 6-39 years) REF, one included
  on-treatment participants only (age 3-17 years) REF, and one included youth diagnosed with cancer
  regardless of treatment status (aged 14-18 years) REF.” Citation added

- I am not sure if this sentence is correct or has a typo: “Of the studies including adolescents, four
  included survivors only (aged 6-39 years)”. Inclusion criteria indicated (2) … adolescents between the
  ages of 18-29. I understand a 39 survivor is not a young adult survivor anymore and such studies should
  have been excluded. Same problem happens with some studies included in table 1: see the study of
  Rabin et al., 2011; Valle et al., 2015; Jarvela et al., 2012, etc. This has to be checked and corrected. Fixed
  and table added to address below comments

- Line 6, page 9: you mention six interventions but only provided 4 references.

- Format references line 17, page 9 (refs 38, 39). Done

- Format reference page 10, line 10 (ref 41). Done

- Line 18, page 9: age of this “young adult survivors”? (References 43, 44). Added

- Line 9, page 10: range age? Added

o Maybe previous comments could be addressed if a clear definition of AYAs concerning range of ages is
  stated at the beginning of the article.

DISCUSSION
- A subheading could have been included (page 11, line 10?).  
- Discussion is OK but I believe it is not strictly related to the review of results concerning physical interventions (the 9 articles presented in table 1). Moreover, some information might be better presented in the introduction of the article, for instance, information provided in “exercise strategies to promote health in AYAs” or “Physiological mechanisms of strength training”. In the latter case, all references provided has nothing to do with the articles obtained from the search (table 1 articles). It is just an opinion but I believe there is a lot of information from page 11 onwards and I am not sure it is presented in a clear and organized manner. Perhaps a more clear link to articles presented in Table 1 would help. **We thank the reviewer for this important suggestion. We have added the sections**

**RECOMMENDATIONS /CONCLUSIONS**

- I believe recommendations are good, specific and clear. Besides, their clinical relevance is high.  
- References are required after line 20, page 14; and line 21, page 14.  
- A limitations section has to be included.

**FORM, STYLE, SUBSTANCE, REFERENCES Amended/edited as indicated.**

- In general, the readability of this manuscript is very good.  
- The topic is presented in a very clear and rigorous manner.  
- The methods must be improved.  
- More studies have to be included since important references are missing.  
- Overall, references are pertinent and up-to-date but as I have said, some relevant studies are missing (some examples are provided above).

Minor comments

- Some typos:
  - P in table 1 must be p
  - Syntax text in a annex?  
  - Space before “.”, page 3, line 21.  
  - Space before “,”, page 4, line 15.  
  - Space after “.”, page 12, line 5.  
  - Space after “.”, page 13, line 6.  
  - Space after “(18)in” lacking, page 12, line 8.