Author’s response to reviews

Title: The effects of two weeks high-intensity interval training on fasting glucose, glucose tolerance and insulin resistance in adolescent boys; A pilot study

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Re: The effects of two weeks high-intensity interval training on fasting glucose, glucose tolerance and insulin resistance in adolescent boys; A pilot study

Dear Jon Oliver,

We would like to thank you for the opportunity to revise our manuscript.

We are submitting the revised manuscript for reconsideration by the referees. We have changed the manuscript according to the comments of the reviewers. The changes have been highlighted throughout the document using tracked changes. In addition, we have included a detailed response to the reviewers’ comments.

We hope that these revisions are such that you and the reviewers will be satisfied with the changes.

Please do not hesitate to contact me if there is anything further required.
Sincerely,

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The effects of two weeks high-intensity interval training on fasting glucose, glucose tolerance and insulin resistance in adolescent boys; A pilot study

We thank the reviewers for their constructive comments and feedback on this manuscript. We have provided a point by point response to the concerns and queries raised.

Wenzhu Li (Reviewer 1)

General comments:

1.1. This manuscript studied whether HIIT in adolescent boys could improve fasting or postprandial glucose and aerobic fitness etc., which is quite novel. However, currently this paper is not in good quality for publication.

Response: Thank you for your feedback, we hope we have addressed your concerns and made significant improvements to the manuscript such that you now view this paper suitable for publication.

Specific comments:

1.2. Although it is pilot study, the 9 boys may not enough for your conclusion. If it is possible, it could be better to increase participants to have controls.
Response: We appreciate that this is a small sample. However, it is not feasible for us to collect more data for this study as this time. This is intended as a pilot study, which we have acknowledged in the manuscript. We present the data collected and believe the key message has important implications for future research.

1.3. If it is possible, it could be better to include a group of boys with high-risk incidence of diabetes in future, or a group of boys already have impaired glucose tolerance.

Response: We appreciate that this would be interesting, but was not the aim of this study. We focus on the preventative potential of HIIT and not as a treatment option. This is something that we allude to in this paper, that those at high risk / have impaired glucose tolerance may have more scope for improvements to glucose tolerance after a period of high intensity interval exercise. This is one of the implications of this pilot study and will help direct future research (p 13, “the potential for this type on intervention to promote metabolic health in a more clinical population of individuals with elevated baseline IR and is worthy of future investigation”).

1.4. It could be better to think again the statistic method and your study objectives. Example in table 2, you used ANOVA analysis to compare PRE, 20h post and 70h post and then got a neutral conclusion.

Response: Thank you for highlighting this. However, we believe that the statistical analysis approach in this study in the most appropriate for this data set. The approach allows comparison of one group over 3 different time points. It would not be appropriate to adjust the approach to statistical analysis due to the neutral findings, as this would be considered a form of ‘p-hacking’ (Motulsky 2014). However, given the small sample size, we have now included effect size statistics (Partial Eta Squared, and Cohen’s D) in the results, to allow the reader to judge the data from a magnitudes perspective.

1.5. Why the authors use 2 weeks HIIT? The outcomes of physical activity often happen in a longer time.

Response: We appreciate that they are multiple examples of studies over a longer duration. The duration of HIIT varies considerably in the literature (Logan, Harris et al. 2014). The two week duration for this study is based on previous work from our laboratory (Barker, Day et al. 2014) as well as other work in adults (Whyte, Gill et al. 2010) and seems to be a promising approach to improve health outcomes. We have made reference to this short duration HIIT protocol in the discussion. Additionally, it is worth noting that the health outcomes reported in this study are responsive to a single bout of high intensity interval exercise, and may last up to 24 hours after the exercise about (see Cockcroft, Williams et al. (2017))

1.6. Table 1-3, the last row in the table could be better organized as legends below the tables.
Response: Thank you for this feedback, we have removed the bottom line from each of the tables so that this is clearly a table legend and not an extra row.

Dalia El Khoury (Reviewer 2):

General comments:

This manuscript addresses one important aspect to manage glucose homeostasis and insulin sensitivity of adolescent boys. Although this study is described as pilot study, many changes need to be introduced before being reconsidered for publication.

Overall, English editing is needed in different sections, and it is not clear why [glucose] and [insulin] are written in brackets.

Response: Thank you for your constructive feedback. We have made effort to proofread the entire document and ensure appropriate English is used. Additionally, we have removed the square bracket notation. This is frequently used to mean concentration, however we agree this may be confusing for readers and so have changed this.

Specific comments:

Abstract:

2.1. a background explaining the need for this study is missing. Many studies have been done on effects of training in youth on their cardiometabolic health. why this study is needed?

Response: Thank you for this comment. We are limited by the word count of this section of the abstract, but have added to the background as requested: “Current evidence of metabolic health benefits of high-intensity interval training (HIIT) are limited to longer training periods and in overweight youth”.

2.2. In the Methods section, the characteristics of boys should be better highlighted: normal weight? obese? overweight? on line 20 (page 2).

Response: We have now included details of the BMI of participants in this section “Seven healthy boys (age:14.3 ± 0.3 y, BMI: 21.6 ± 2.6, 3 participants classified as overweight)” More descriptive data is not possible due to word count limitations of the abstract.

2.3. Authors mention about V02 max without explaining what it reflects.
Response: Thank you for pointing this out. Due to other requested additions to the abstract we have now removed mention of VO2 max from the abstract to allow expansion of other sections.

2.4. In the Results section, authors need to add info on: any comparison between indices at 20h and 70h POST? for the MMTT, what is the difference between baseline, 20h and 70h at the different time points for the different indices explored?

Response: We have adapted the abstract so that the results are for all indices. The ANOVA p-value was non-significant, therefore post-hoc comparisons of time specific time points were not examined.

2.5. Authors need to add data on fitness; they are only reported glucose/insulin indices-related data.

Response: Please see response above. Word limitations have meant we cannot include all data in the abstract. We have removed reference to fitness in the aims and methods and so have not included fitness data in the results.

2.6. The conclusion is not based on findings from this study; the boys recruited for this study need to be better defined, whether they had normal baseline glucose and insulin levels or not and whether they were insulin resistant or not at baseline - accordingly, authors can then suggest for interventions on a larger sample size and on boys with elevated baseline insulin levels or with baseline insulin resistance. Since this is a pilot study, authors should indicate that future studies should be performed on a larger sample size of adolescents.

Response: We agree with your comment, however in depth discussion of this is beyond the limit of the abstract where we have presented the key findings. The abstract has now been significantly edited to address your concerns.

Background:

2.7. Line 55 (page 3), what does "short duration sprint intervals" mean? Need to be better defined.

Response: This is with reference to a specific study. We have now included the duration of the intervals in the text:

“Consisting of short duration (30 s) sprint intervals, has been shown to improve aerobic fitness [11]”
2.8. On page 4, lines 49 and 50, authors need to explain how 1 day is acute and 3 days is considered chronic. The definition of chronic varies among studies, and needs to be better supported in this study.

Response: Thank you for this comment. This section has been adapted to improve clarity of what we mean by acute and chronic. The research aimed to differentiate between a residual effect of the last training session and the 2 weeks training by measuring glucose and insulin outcomes 24 h and 72 h after the final exercise session. We know that improvements to dynamic glucose and insulin outcomes after a single bout of HIIE can persist for up to 24 h (Cockcroft, Williams et al. 2017) and so changes at this time point may represent an effect of a single bout of exercise and not the 2 weeks of training:

“Therefore, the aim of this paper was to examine changes in glucose and insulin outcomes in adolescents boys after two weeks of HIIT; 1 day after (acute) and 3 days after (chronic) the last training session representing adaptions as a result of the final training session (acute) or longer terms adaptions as a result of the longer training period (chronic)”

2.9. Many more up to date articles are missing, and need to be added - such as Zguira et al, 2019's study on obese young adolescents, as well as Burns et al, 2019's, Marson et al, 2016's and Bea et al, 2017's meta analyses.

Response: Thank you for highlighting this. We have not included all of the references suggested above however we refer specifically to Zguira et al and Marson et al as well as other more recent articles including a systematic review and scoping review of high-intensity interval training interventions in children and adolescents (Bond, Weston et al. 2017, Eddolls, McNarry et al. 2017). We have not referred to Bea et al as this is a review of resistance training and therefore not pertinent for this paper and are unable to find the Burns et al 2019 paper that you refer to.

Methods:

2.10. In Participants, the inclusion and exclusion criteria of participants are missing: normal baseline insulin/glucose levels? normal baseline insulin sensitivity? normal weight or not, etc. Also, the age range for recruited boys needs to be defined.

Response: Thank you for pointing out this omission. We have added exclusion criteria and age range to this section on p 5. There was no exclusion/inclusion criteria for weight status or baseline glucose/insulin:

“Nine boys were recruited from year 10 of a local secondary school. All participants were deemed able to participate in the study by completing an initial health questionnaire to exclude any metabolic or medical conditions that contradict exercise or are known to effect glucose metabolism. Following an explanation of the study procedures and the associated risks and
benefits, parental consent and participant assent were obtained. Ethics approval was granted by the University of Exeter Sport and Health Sciences Ethics Committee. One boy failed to complete the HIIT due to an unrelated illness, and one boy could not complete the training due to an unrelated injury. This left a sample of seven participants (14.3 ± 0.3 y) for analysis.”

2.11. Even if this is a pilot study, authors need to support why a sample size of 9 is good enough - sample size calculation needs to be shown.

Response: Sample size was based on our previous work, this has now been made clear in this section of the manuscript. We have also added effect size statistics to the results section, which can be used to inform the design of subsequent larger studies.

“Nine boys were recruited from year 10 of a local secondary school. “This sample size was based on the ability to detect a moderate to large mean difference for glucose and insulin outcomes based on previous work examining the acute effect of HIIT [20, 29, 30].”

2.12. In Study design, why visits 1 and 2 were separated by 3-5 days?

Response: This time frame was to ensure we allowed at least 3 days between visits so that the fitness assessment conducted in visit 1 did not confound the baseline metabolic assessment in visit 2. The range of up to 5 days was pragmatic and based on the availability of the participants and clearance from their school to miss lesson for a visit to our laboratory.

2.13. Authors need to explain the selection of the numbers 20h and 70h POST.

These time points were selected to allow us to investigate both acute and chronic effects of the training. Our previous work has shown effects of a single bout of exercise to persist for up to 24 h so the first 20 h POST (or 1 day) was to assess acute effects. The 70 h time point allowed us to assess any chronic physiological adaption to exercise training (Way, Hackett et al. 2016). Please also see our response to comment 2.8.

The specific time points or 20 h and 70 h are used as the training sessions took place over lunch. It was felt that due to the request for an overnight fast it was not appropriate to have an afternoon visit for the MMTT. We have added to the text to clarify when the training sessions took place:

“Training took place within a local secondary school and consisted of three supervised HIIT sessions per week. Sessions were carried out during the school lunch break.”

2.14. Page 6 line 32, authors need to cite a supporting article for how to conduct an MMTT; is 80g of glucose typically given in MMTT?
Response: Unlike the oral glucose tolerance test, there is not a standardised test meal composition and this varies across studies.

2.15. Page 7, line 37, were participants asked to keep the same type/amount of physical activity the same before the different visits and exercising sessions?

Response: Participants were asked to avoid structured physical activity outside of the training sessions during the intervention and follow up period. Physical activity data in the 48 h preceding each visit to the laboratory is shown in table 2, which shows no significant different in amount of moderate to vigorous physical activity in the 48 h preceding each experimental visit. We have added to this sentence to improve clarity:

“Participants were asked to avoid any structured physical activity outside of the training intervention and before any laboratory visits”

2.16. on page 8, lines 11-15, authors mention about blood being collected on each training day...this is suddenly mentioned and not previously described. and why authors need to account for changes in plasma volume following training?

Response: This has now been removed for clarity as we do not mention this later.

2.17. In data handling, tAUC and iAUC needs to be further described and discussed.

Response: We have added to this section to further describe tAUC and iAUC and added a reference for its use:

“Changes in plasma glucose and insulin during the postprandial period following the MMTT were quantified using total and incremental area under the curve (tAUC, iAUC) (Matthews, Altman et al. 1990) calculated using the trapezium rule (GraphPad Prism, GraphPad, SanDiego, CA). tAUC is related to basal blood glucose and reflects the amplitude of change. iAUC more accurately describes the glycaemic response to MMTT, and the dynamic change over time, independent of baseline value”

2.18. In statistical analysis, ANOVA exploring effects of time and group for MMTT needs to be added, as previously discussed. Authors need to mention that both tAUC and iAUC will be analyzed.

Response: as requested we have added this to the data analysis section:
“Analysis of the HOMA, QUICKI, FGIR, fasting glucose and insulin, and tAUC and iAUC response to the MMTT across visits was performed using a one-way repeated-measures ANOVA.”

A 2-way (condition\*time) repeated measures analysis was not reported as the data from the MMTT is reported as iAUC and tAUC. These analysis showed no effect of time (from start of MMTT) and condition (PRE, 20h and 70h-POST).

2.19. The sentence "all results are presented as P values, unless stated otherwise" is not clear; please rewrite and clarify. The correlation findings do not add any information. Authors need to clarify what these correlation analyses serve for and what they do inform us about.

Response: We have now removed the sentence (all results are reported as…. ) as we agree this is confusing and is not necessary. We hope that the inclusion of correlation analysis is now clearer given changes to the rest of the paper

“To understand the influence of different parameters on the effectiveness of the HIIT intervention and understand the relationship between pre intervention health outcomes and the effects of HIIT intervention, Pearson’s correlations were performed between HOMA-IR, QUICKI, FGIR, V’O2 max and BMI at baseline (PRE) and change in HOMA-IR after the 2 week training period (20 h-POST)”

Results:

2.20. very concise. Results need to be described in more details.

Response: We have made some adaptions to the text to improve clarity, but have not added more detail, we feel the tables and figures gives the results and do not want to repeat these. We appreciate that these are concise but the non-significant ANOVA means there are few results to expand on in this section.

2.21. It is unclear, page 9 line 7, how the range of BMI is 17.8 to 24.0 and 3 participants were classified as overweight. Why the range does not reflect their BMIs?

Response: The BMI cut points for weight status were calculated used gender and age specific values (Cole, Bellizzi et al. 2000). The classification of overweight in 3 of the participants this is different from the adult value of 25 kg/m2. For example the BMI cut point for overweight in a 14 y old male is 22.6 kg/m2. We have clarified this in the text:
“The BMI of participants ranged from 17.8 to 24.0 kg·m⁻², with 3 participants classified as overweight according to age and gender specific cut points."

2.22. Did authors compare indices at 20h versus 70h? Did authors compare indices between baseline, 20h and 70h at the different time points for the MMTT? This information needs to be added.

Response: We have added to the statistical analysis section to make this clearer. Indices would only be compared if there was a significant main effect in the ANOVA.

“Follow up comparisons between time points were only carried out if there was a significant main effect in the ANOVA”

2.23. Correlation analyses do not in my opinion add any valuable information, unless authors can explain the reason for performing these correlation analyses.

Response: We hope that the inclusion of correlation analyses is now clearer throughout the manuscript and resonates with our second aim to explore “the relationship between pre intervention health outcomes and the effects of the HIIT intervention”. We feel that this is an important and interesting finding of this study as it highlights the need for more targeted approaches to HIIT interventions, which don’t necessarily just include weight status but baseline metabolic health. There is increasing stigma around overweight and obesity and thus finding alternative ways to target interventions is potentially useful.

Discussion:

2.24. Authors need to add more recent studies exploring cardiometabolic parameters in youth in responses to exercise. I have stated some examples in my comments on the Introduction section.

Response: We have now added more recent papers to the discussion. Please also see our response to comments 2.9 and 2.30.

2.25. How did authors reach their conclusion on page 10, lines 4-8 "Short duration...for future intervention work"?; what type of intervention work they are referring to? Authors need to specify whether a study on a larger sample size will be conducted considering the pilot nature of this study.

Response: This sentence has been removed from this first paragraph on the discussion and instead referred to with limitations and future directions:
“Future work should investigate the potential of HIIT interventions targeted at adolescents with impaired insulin resistance (rather than weight status) with a larger sample size”

Conclusion:

2.26. authors are referring to the correlation analyses' findings without explaining what they do mean practically. The conclusion section needs to reflect the practical implications of the findings; not just repeat the findings of the study.

Response: We have now adapted this paragraph. An important practical implication of this work is the baseline insulin resistance is an important predictor of effectiveness of the HIIT intervention, which was not evident for BMI. This is based on the significant correlation between IR indices at baseline and change in IR after HIIT (all P<0.05), whereas there was no correlation between baseline BMI and change in IR after HIIT (P>0.05). This is important for implementing future targeted interventions which focus on metabolic health and could target those at risk of future development of type two diabetes, evidenced with elevated insulin resistance.

“This preliminary study shows that fasting or postprandial measures of insulin and glucose in adolescents were not sensitive to change after two weeks of HIIT. However, a strong negative correlation between baseline IR and change in IR after HIIT, but not for BMI, suggests the potential for this type of intervention to promote metabolic health in individuals with elevated baseline IR, who are at risk of developing type two diabetes”

Tables:

2.27. Table 1: ranges are usually expressed as number-number not as number to number; please adjust.

Response: Thank you. This has now been adjusted.

2.28. In table 2, it is indicated that 20h POST includes the final training session-why so? And why this information was not mentioned in the methods' section?

Response: The measurement period (48 h preceding each experimental visit) of 20 h post intervention visit meant that physical activity was recorded during the time period that also included the final training session of the HIIT intervention. This is stated in the methods section:

“Physical activity was measured during the 48 h period prior to each experimental visit using a wrist worn accelerometer (GENEAActiv, Activinsights, UK). For visit three this 48 h period included the final training session.”
2.29. Please add to the footnote information on how P value was generated. Table 3: please explain in the footnote the stats analysis used to generate P value.

Response: We have added to the table column heading to clarify that these p-values are from the repeated-measures ANOVA.

References:

2.30. Good number; but more up-to-date articles need to be cited.

Response: We have now updated the literature we include in the introduction and discussion to ensure we cite up to date articles. This includes a systematic review of high intensity interval training interventions in children and adolescents. Please also see response to comment 2.9. (Weston, Azevedo et al. 2016, Bond, Weston et al. 2017, Eddolls, McNarry et al. 2017, van Biljon, McKune et al. 2018)

Figures:

2.31. Figure 1: should also show the difference between baseline, 20h and 70h at the different time points.

Response: We are not sure what you mean by this. This figure shows blood glucose and insulin during the mixed meal tolerance at baseline and at 20 and 70 h after HIIT intervention. The difference between baseline, 20h and 70 h is therefore shown in this figure. We feel that including more in this figure would overcomplicate it.

2.32. Figure 2: abbreviations should be defined in the footnote.

Response: thank you for pointing this out. The figure legend has now be adjusted accordingly and reads:

“Figure 2. Correlations between changes in IS indices: Scatter plot showing correlation between change at 20 h POST HIIT and at baseline for Homeostatic Model Assessment of Insulin Resistance (HOMA-IR); Quantitative insulin-sensitivity check index (QUICKI) and Fasting Glucose to Insulin Ratio (FGIR). ** P<0.01 *P<0.05 “

References


