Author’s response to reviews

Title: High-intensity interval training and moderate-intensity continuous training in adults with Crohn’s disease: a pilot randomised controlled trial

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Responses to reviewers’ comments

We are grateful for the latest set of reviews we have received and for the opportunity to submit a revised manuscript.
Reviewer reports:

Jessica Elia, DPT (Reviewer 1):

1. Several of the reviewers as well as the editor asked for an in-depth review of MICT and HIIT in the IBD population. There is sound reasoning for this that must be considered in order for this manuscript to move forward to publication.

Thank you for your comment. We have reviewed the introductory text and believe that it adequately captures the background and rationale for the study. References have been provided for all relevant trials (references 7-11) and for reviews of exercise in the IBD population (references 4-6).

This feasibility study steps into a challenging area. Feasibility studies do not generally address issues of safety. However, HIIT in the IBD population raises concerns, as extreme caution with high intensity cardiovascular training is well documented in the IBD literature. This is compounded by the number of subjects who experienced adverse "symptoms" (we will call them) during the feasibility study. This is why the following are crucial:

a. The introduction, including a through explanation of MICT v. HIIT in the IBD population is so important. (see specific notes below)

Please see our previous comment

b. Describe type of HIIT chosen and why it was chosen

The type of HIIT used is described on lines 124-131. It was chosen because similar HIIT protocols have been shown to be safe and effective for improving cardiorespiratory fitness in a range of clinical and non-clinical populations:


The latter point and references are stated in our published protocol paper, which is cited in the manuscript.

2. The methodology also raised many questions. How was it determined based upon your HITT, MICT, and IBD research and how did you decide to amend it so drastically?

Please see our previous comment regarding the choice of HIIT protocol. We wanted the two exercise protocols to be matched for work. The MICT protocol was therefore chosen because it had been shown to elicit a similar energy expenditure compared with the HIIT protocol (Little et al., 2014). This point is also stated in our published protocol paper.

i. How was everyone who administered the trial across 3 facilities trained?

The exercise sessions were supervised by research assistants, with oversight from the chief investigator (LB), trial manager (GT), and local Principal Investigators. LB is a BASES Accredited Sport and Exercise Scientist and an NSCA Certified Strength and Conditioning Specialist. GT is a BASES Accredited Sport and Exercise Scientist and an ACSM Clinical Exercise Physiologist. The research assistants were sport and exercise science graduates with a special interest in clinical populations. The local Principal Investigators were Consultant Gastroenterologists. LB and GT trained the local study teams in how to deliver the study protocol prior to recruitment.

ii. Did the subjects perform cardiovascular testing prior to the first training session to determine baseline or was that the first session? Is that when anthropomorphic and other data was collected? This is how you figured out your feasibility…so what did you do and what did you decide worked? Write so it could be replicated.

The fitness and health tests were conducted at baseline and 3 months, as stated in lines 165-168. The exercise sessions commenced in the week following the baseline assessments, as stated in lines 125-126.

iii. Perhaps test patients at several points throughout the trial to catch a CDAI moving toward >400?

We agree that it would have been interesting to study the time course of CDAI changes throughout the trial.
iv. Specific instructions regarding eating and hydration behaviors?

Participants were given basic advice which included allowing a couple of hours before exercising after having a main meal and drinking regularly to help stay hydrated.

v. Consider only adult subjects? Over 18?

We had ethics approval to recruit individuals between the ages of 16 and 65 years. However, the youngest participant was 18 years old.

vi. Page 23, Line 386: Is not comparing the MICT and HIIT exercise programmes the goal of this protocol? Essentially you are abandoning your protocol and creating a completely new study with new interventions. How does this make your feasibility study a success? Would this not require a new feasibility study? I would suggest staying with the original protocol as MICT and HIIT studies are needed and you do not yet have any data to compare the two or determine safety, outcomes, etc.

Thank you for your comments. The EXACT study has successfully tested the feasibility of HIIT and MICT in people with CD. We are currently testing the feasibility of resistance exercise training in the ongoing PROTECT trial (https://doi.org/10.1186/ISRCTN11470370). As a next step, we could pursue appropriately-powered trials of these separate interventions; however, we think that it would be better to test a combined intervention for the reasons described in the manuscript. The design features of a subsequent trial are clearly debatable, and we wouldn’t expect everyone to agree.

3. Please name all tables/figures in manuscript as they will appear in the published article ex. (Figure 1) NOT (AdditionalFile2). Please indicate which tables/figures are supplementary ex. (SupplementaryFigure1).

We think that our naming of supplementary files conforms with this journal’s guidelines.

Abstract:

1. Page 10, Line 41: The "overall attendance rate..." The trial looked at two different groups. HIIT and MICT, 62 and 78% participation respectively. Those numbers should be reported separately. Not taken as an average.
Thank you. We have amended the abstract so that it reads, “The exercise session attendance rate was 62% for HIIT (288/465) and 75% for MICT (320/429), with 62% of HIIT participants (8/13) and 67% of MICT participants (8/12) completing at least 24 of 36 sessions.”

Introduction

2. An adequate rationale for this study has not been presented. IBD subjects suffer from a myriad of extra-intestinal symptoms and complications. These disease-specific items must be addressed within the context of cardiovascular training to reassure readers (1) subject safety was well understood, considered, and addressed, (2) methodology was given proper consideration, (3) suitable outcomes and appropriate objective measures were chosen, and (4) [in a feasibility study] is this protocol feasible.

Thank you for your comment. We have reviewed the introductory text and believe that it adequately captures the rationale for the study. The rationale and methods were accepted by both the funder and the ethics committee. Participant safety was a key consideration, and we believe that we had appropriate processes in place to monitor and deal-with this aspect of the study.

3. Page 11, Line 66: The references listed are not from IBD or IBD-similar subjects. Please address:
   a. Why MICT has been the aerobic exercise of choice for IBD subjects both for physiologic and functional outcomes.
   b. Why you believe HIIT is a good cardiovascular exercise choice for IBD subjects and discuss the disease specific physiologic benefits and risks.
   c. What the functional subject outcomes/benefits are for utilizing HIIT in terms of exercise specificity. How will this improve the subject's quality of life?
   d. Physiologic similarities/differences between adult and pediatric IBD

4. Page 11, Line 73: How did you draw the conclusion that HIIT would be safe for adult IBD subjects?
   a. How did you determine the proper HIIT protocol for adult subjects with quiescent or mild-active CD?
   b. Even if you have published this elsewhere, a brief description is warranted.

Thank you. Again, we are satisfied that the introduction provides an adequate background and rationale to the study. Regarding the references on line 66, we are not aware of any previous
studies that have compared cardiometabolic adaptations to HIIT and MICT in people with IBD. On lines 73-75 we state the following: “We hypothesised that supervised endurance exercise training (either as HIIT or MICT) is a safe and effective strategy for improving cardiorespiratory fitness, fatigue, quality of life and mental health in people with CD.” We do not think it will benefit the introduction to describe the physiologic similarities/differences between adult and pediatric IBD. Please see our previous comment about how we chose the HIIT protocol.

Interventions

5. Page 14, Line 136: Feeling Scale Data should be published with exercise data
   a. Given the questions surrounding the best way to measure exertion in IBD subjects due to autonomic dysfunction, HR, Feeling Scale, and Borg CR-10 data should be published together.

As stated in our response to the first round of reviews, our intention is to present a detailed analysis of the Feeling Scale data in a separate manuscript.

6. Page 14, Line 146: Please name the standardized questionnaire used.

   The questionnaire does not have a specific name. We have, however, provided the reference to this questionnaire.

7. Page 15, Line 173: Please change "generic health status" to "quality of life"

   Thank you. We have changed this to “health-related quality of life”.

8. Page 16, Line 193: Please include CONSORT diagram figure number.

   This has now been included.

Results

9. Page 17, Line 212: Please include figure number

   This doesn’t appear to be necessary.
10. Page 19 Line 261-263: Again, report HIIT and MICT figures separately. Two separate groups were studies, two separate groups should be reported.

Thank you. We have decided to simplify the summary of the reasons by combining the exercise groups.

11. Page 19 Line 267: What does the literature say about 2 v. 3x per week aerobic exercise for MICT and HIIT why did you choose 3x per week? This should be addressed in the Introduction

Although we believe that fitness improvements can be observed with two sessions per week (e.g. Currie et al., 2013), we chose three sessions per week because we suspected it would offer superior benefit and because it fitted better with the ACSM recommendations for healthy adults (Garber et al., 2011, Medicine & Science in Sports & Exercise, 45, 1436–1442).

12. Page 19, Line 287: Please give figure number

This doesn’t appear to be necessary.

13. Line 300-308: Please distinguish interviewee groups HIIT v. MICT

Thank you. We have decided to simplify the summary of the perceived benefits by combining the exercise groups.

14. Page 22, Line 359: IBD population & moderate intensity exercise choice is very clear in the literature and should be addressed in the introduction and discussion

a. Again, what are the physiologic & functional goals

b. How does the specificity of MICT and HIIT address each differently?

In lines 73-75 we state the following: “We hypothesised that supervised endurance exercise training (either as HIIT or MICT) is a safe and effective strategy for improving cardiorespiratory fitness, fatigue, quality of life and mental health in people with CD.”
15. Page 22, Line 361: a feasibility trial does not present clinical findings, it cannot say if an intervention works, just if a project can be done. You did no analysis to justify that HIIT concerns are not supported.

Feasibility studies can and do present preliminary data on safety and efficacy/effectiveness. We believe that our statement is appropriate and that it does not over-state the findings.

16. Line 384 I would not remove the HIIT v. MICT component, this has yet to be settled and is worthy of further study

Thank you for this suggestion.

17. For data being published elsewhere, it is appropriate to provide a brief paragraph explaining relevant results and how they informed your conclusions.

The data which we intend to publish elsewhere (blood markers of inflammation and Feeling Scale) does not impact on the conclusions of the current manuscript. We do not want to explain the results of these variables here, because it might jeopardise our ability to publish separate papers.

Recommendations for future trials:

1. Objectively quantify pre-trial exercise habits: average METS, etc.

2. Page 17 Line 231: Consider sex and activity matching groups in future trials


4. Clearly define exercise goal: intervention group to participate x/wk, total x/session/xweeks

5. Basic patient safety exercise instruction:
   a. stop if you develop a headache, feel faint, dizzy, etc.
   b. brief patient interview prior to each exercise session: change in status->back to MD for clearance (stomach feels funny)

Thank you for these suggestions.
Whitney Duff (Reviewer 3): Thank you for the responses to the reviewers comments. I feel the revisions made to the manuscript based on feedback from reviewers is adequate.

Thank you.