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

Responses to reviewers’ comments

We are grateful for the reviews we have received for our manuscript.

Editor Comments:
As you would agree the trial is a small study but could be potentially acceptable if the reviewers concerns are addressed.

We are grateful for the reviews we have received and for the opportunity to submit a revised manuscript. Pilot trials can play a crucial role in the design of randomised controlled trials. We hope that our work is considered on its potential to inform future research, rather than the significance of effect sizes.

Please address what are the possible clinical benefits of HIIT or what was the rationale behind this trial (rather than merely stating that such studies have not been done in past)

Thank you for your comment. We have reviewed the introductory text and believe that it adequately captures the rationale for the study. Exercise training may be an important adjunct therapy for people with CD. MICT and HIIT are both common ways of doing aerobic exercise training. Both types of training have not been extensively studied in people with CD. As we state, “A greater understanding of the feasibility, acceptability and effects of different types of exercise training is needed to support the development evidence-based exercise guidelines and promotion strategies that are specific to CD.”

Limitations like non-availability of endoscopic severity stratification, pretrial exercise habits and confounding effect should be emphasised.

We stratified by disease activity based on CDAI scores, which is a common practice in Crohn’s trials. We thought that endoscopic evaluations would add an unnecessary burden for low-severity patients. We do however give due acknowledgement to this potential limitation, and we will consider incorporating capsule endoscopic evaluations in the future trial.

Regarding pre-trial exercise habits, we only recruited people who were not regular exercisers. This prior exercise status was confirmed in the exit interviews. Therefore, we do not consider this a limitation.

We are not sure what you mean by “Confounding effect”. However, the main limitations of this study have been listed in the discussion.

Reviewer reports:

Jessica Elia, DPT (Reviewer 1): General Comments:
1. This study investigates the impact of aerobic exercise in the Crohn's population. Well designed, objective IBD exercise studies including standardized physiologic and inflammatory outcome measures are lacking and needed.

2. This study includes a wide array of objective measures.

3. This study includes supervised exercise and a suitable follow-up period.

Thank you for reviewing our paper, and providing useful comments.

The methodology of this study is unclear. Study subjects were "invited" to participate in supervised exercise sessions. What were the instructions exactly?

Participants were informed that if they were allocated to one of the exercise groups that they would be offered three exercise sessions per week for 12 consecutive weeks. They were also told that the research assistant would work with them to try and identify convenient times for these sessions to be conducted. Participants were encouraged to attend as many sessions as possible. We think that the use of term “invited” is accurate in relation to our protocol.

Was there a mandatory minimum the subjects were expected to complete?

No. We only recruited people who stated that they were able to complete all of the processes of the study, including the thrice-weekly exercise sessions. Following randomisation, there wasn’t a mandatory minimum number of sessions for the participants to complete.

Were the subjects allowed to exercise outside the supervised sessions?

Participants in the exercise groups were instructed to only do the supervised exercise to allow for sufficient recovery time between sessions. Participants in the control group did not receive any specific exercise advice. This approach was taken with the control group because it was deemed unethical to instruct them to not exercise at all during the follow-up period.

What were the instructions after the initial 12 week supervised sessions? Were subjects expected to continue independently or was continued exercise optional?

Please refer to page 6, lines 138-140: “After the initial 12-week supervised training period, all exercise group participants were encouraged to continue a similar exercise regime in their own home or community setting without the support of the trial team.” So in other words, the
participants were encouraged to continue exercising independently. The research assistant discussed options for self-managed exercise with each participant.

Methodology should also include what the HIIT subjects performed between intervals.

Please refer to pages 5-6, lines 130-131: “interspersed with 1-minute bouts at 15% Wpeak”.

HIIT subjects defined RPE as "hard." HIIT is defined as "all out" or "extremely hard." Should this be redefined as "modified HIIT" as heart rate is unreliable in IBD subjects due to dysautonomia?

Thank you for your comment. We think that you may be referring sprint interval training (SIT) as a specific type of interval training. The model of HIIT that we used is intentionally less intense/extreme than that experienced in SIT protocols that use for example repeat Wingates. Gibala has previously described the approach we used as a practical model of HIIT – see for example: https://physoc.onlinelibrary.wiley.com/doi/full/10.1113/jphysiol.2011.224725. The use of “HIIT” in the current study is also consistent with the definitions offered by Talanian (https://openventio.org/Volume1-Issue5/Defining-Different-Types-of-Interval-Training-Do-we-need-to-use-more-specific-terminology-SEMOJ-1-124.pdf) and the terminology used in our previous work:


This study does not provide all objective data collected with analysis. Were the changes seen from baseline, 3, and 6 months statistically significant?

We believe that it is inappropriate to test for statistical significance in small pilot studies. We refer the reviewer to the CONSORT extension to pilot and feasibility studies of Eldridge et al. (2016) which covers this issue: https://www.bmj.com/content/355/bmj.i5239. The recent tutorial of El-Kotob and Giangregorio (2018) on pilot and feasibility studies in exercise research also state that “Outcomes related to the efficacy of the intervention can be measured, but should be treated as exploratory, and not hypothesis-testing.”: https://pilotfeasibilitystudies.biomedcentral.com/articles/10.1186/s40814-018-0326-0

Where is the FS data for pre, post, and 10 minutes post exercise (as stated in previously published pilot)?
Thank you for this question. We presume you mean protocol rather than pilot. Our intention is to present a detailed analysis of the FS data in a separate manuscript. We have clarified this in the revised manuscript.

For example, based on Table 3, fatigue scores for both HIIT and MICT patients increased from baseline to three months. Were these changes statistically significant? Fatigue and over fatigue following exercise is a concern in IBD subject exercise prescription and should be addressed.

Please see previous comment on testing for statistical significance in pilot studies.

Please address all results (including biomarkers, these are important for disease inflammation, especially given adverse events) numerically as well as with interview results.

Thank you. We have added a new table (Table 4), which shows data for the blood markers of inflammation. As mentioned above (and now in the manuscript), we intend to present the FS data elsewhere.

Safety is a concern.

HIIT: Consider that this study population consisted of stable, no or low-inflammation, few co-morbidity, Crohn's patients; a large percentage of whom were in employed. This is a high functioning group.

We think that this depends on how you assess the level of functioning. We objectively assessed functional status using cycle-based cardiopulmonary exercise testing. If you compare the mean peak oxygen uptake value of 28.2 mL/kg/min to the normative data of the Prevention First Registry (https://bmjopen.bmj.com/content/bmjopen/8/3/e018697.full.pdf), the males are below the 10th percentile and the females below the 30th percentile, at 37 years of age (i.e. the group mean age). On this basis, we think that it is reasonable to say that this was not a high functioning group.

This study does not include a threshold for patient safety acceptability.

An independent Trial Steering Committee, comprising clinicians, academics and patients, provided oversight to this study. This committee monitored all aspects of study progress, including the frequency and nature of adverse events. They had the authority to recommend early study closure if they had concerns regarding the safety of the exercise interventions. The TSC
did not express any concerns regarding participant safety. Please see our other responses regarding the adverse events.

3 adverse events occurred during HIIT training with 2 subjects. 2/13 subjects (15%) experienced adverse effects of headache, dizziness, and vomiting. IBD subject safety issues stem from physiologic concerns of dehydration, fatigue/over fatigue and autonomic dysfunction.

We have provided an expanded description of these events, including their likely causes, in the revised manuscript. The two episodes of headache and dizziness after exercise were deemed to be related to dehydration-induced migraine. The participant was re-informed about appropriate dietary and hydration habits around the exercise sessions and these symptoms no longer occurred. The episode of vomiting was likely due to the participant having eaten immediately before the session. This participant was re-informed about appropriate timing of meals in relation to the exercise sessions.

Once a subject had an adverse outcome, was removal from the study considered? Was subject removal from the study considered after the second adverse outcome?

All adverse events were discussed with the local Principal Investigator (a Consultant Gastroenterologist), who confirmed the seriousness and relatedness and decided the appropriate clinical course of action, including whether or not the participant should be withdrawn from the study.

Were steps taken to prevent another episode?

Yes. Please see our previous response.

This should be addressed in the discussion. Add to this number a disease flare in the follow up period, 3/13 (23%). Either way this is not a safe intervention for IBD subjects. It may be cautiously considered for a high-functioning sub-population of IBD subjects under close supervision but re-thinking a pre-training period to establish a baseline of athletic suitability should be considered.

In our opinion, the data do not support that HIIT is an unsafe intervention for CD patients. There were no serious adverse events, very few non-serious adverse events, and the action we took following the NSAEs likely helped these events from reoccurring. Rather, we think that the
results are encouraging in terms of safety, but there is insufficient data to make firm conclusions. As indicated in the discussion, safety will be a key area of focus of a subsequent larger study.

We have looked specifically at the HIIT participant who suffered a disease relapse during the study. This participant was male and aged 29 years. He completed 33 exercise sessions. His CDAI score increased from 62 to 278 and FC increased from 117 to >400. No medications were recorded at baseline or follow-up. In his exit interview, he referred to his stomach “going a bit funny but it not being a complete flare” at approximately one third of the way through the exercise programme. He thought that this mini flare was related to stress and not the exercise, and he was well enough to keep coming. Further review of his results show that a FC result done in the 6 months prior to entry to the trial was also >400. This does predict a risk of flare of disease within the next year. At the time of entry to the trial he was on no medication having previously been on anti-TNF which was stopped due to antibody formation and clinical remission and his faecal calprotectin is now being monitored. It seems likely that the in-trial flare occurred due to the progressive nature of his disease whilst on no treatment. He has since started vedolizumab with a good response. We have added extra details of this case to the results section.

MICT: 1 disease flare in the follow-up period. Moderate aerobic training has been shown to prevent flares in CD. 1/12 should be considered. Is this an anomaly? Was training too regimented/difficult? Would a range of RPE depending upon subject daily sx be a better strategy?

We think that there is currently insufficient published data to conclude that moderate aerobic training prevents flares in CD and that a larger study is needed to clarify this point. It is impossible for us to say if the 1/12 was an anomaly or not. This participant was female and aged 37 years. She was stable on 15 mg/week methotrexate at baseline but and had switched to 50 mg/day azathioprine by week 13 due to troubling hair loss which she perceived as a side effect of methotrexate. Within a few weeks of that switch she was suffering symptoms of a relapse and her FC was raised. She also developed anaemia. Over the course of the trial her CDAI increased from 38 to 181, and FC from 46 to >400. She completed 25 sessions. Of the missed sessions, 6 were missed due to ill health (5 of which due to virus/vomiting). In her exit interview, she referred to feeling tired at the end of the supervised period, and she put this down to anaemia, which she’d only recently become aware of and received treatment for. It seems possible that her Crohn’s relapse was related to her switch in medication. She was eventually started on infliximab with a good response and is currently well. We have added extra details of this case to the results section.
"...groups were offered..." Page 3, Line 35 Were the subjects offered supervised exercise? What were the instructions? Minimum number required? Supposed to attend all three? What were post 12 week instructions? Encouraged to continue? Instructed to continue? Please clarify.

Please see our previous responses.

EXACT follow journal style for abbreviations, write full length meaning first.
Thank you. We have made this change.

Page 4, Line 79 "...cycle ergometer..." Page 6, Line 127 Clarify lower body cycle ergometer
Thank you. We have changed this to “leg cycle ergometer”.

Page 6, Line 127-130 Clarify performance of HIIT participants between intervals
Please see our previous response in relation to this.

"RPE-C, RPE-L" Page 7, Line 133 please define terms
Thank you. These abbreviations are already defined in the text: RPE-C relating to central exertion (cardiopulmonary sensations), RPE-L relating to leg exertion.

Borg Scale Page 7 Initial Pilot stated Borg Scale 6-20, please state clarification
We used the Borg CR-10 scale, which is consistent with what we stated in the published protocol paper.

"encouraged to continue" exact language please. instructed to continue? What was the expectation?
Participants were provided with encouragement, so we are happy with how this is written. The expectation is stated on lines 139-140.
Please include all trial data, biomarker data speaks to disease inflammation. This is an important component of the study.

Thank you. We have reconsidered whether or not to include the blood biomarker data in the current manuscript. We have concluded that this data would be best kept for a separate manuscript in a specialist journal. The current manuscript includes common measures of disease activity, including faecal calprotectin; a marker of intestinal inflammation.

a. Please include statistical analysis of all data results, cannot evaluate results without statistics.

b. It appears the subjects became more fatigued with the exercise program and less fatigued after it was over...is this significant?

c. Were the ventilation or peak oxygen changes statistically significant compared to controls or between groups?

d. Please provide same for body mass, waist circumference, resting heart rate, etc. in addition to interview comments

Thank you. Please see our previous comment about testing for statistical significance in a pilot study.

HITT subjects RPE "hard" is this really "HIIT"? Page 12, Line 269-275

We think so. Please see our response above which justifies our position.

Figure 1 Please clarify 2 subjects with disease flares on follow-up, difficult to discern

This intention of this figure is to show the flow of participants through the study, not the results (including rates of disease flares at follow-up). This is the usual approach when producing a CONSORT flow diagram: http://www.consort-statement.org/consort-statement/flow-diagram.

Micol Artom (Reviewer 2)

Thank you for reviewing our paper, and providing useful comments.

- Please include a summary of how long the exercise sessions were overall
We have added details about session duration to the revised manuscript (HIIT session = 28 min, MICT session = 38 min).

- Please add how the pre-specified progression criteria were selected. Some criteria, i.e. at least 24 patients being recruited within 12 months appear very easily achievable

The criteria were selected following review of other feasibility trials and extensive team discussion. The team has conducted trials of exercise in other patient populations (e.g. PAD, sleep apnoea, prostate cancer, heart failure, aortic aneurysm), and fast recruitment is not easy to achieve.

Whitney Duff (Reviewer 3):

Thank you for reviewing our paper, and providing useful comments.

Exercise trials are desperately needed in individuals with IBD. It is interesting that the authors chose HIIT, considering the general recommendation for those with IBD to avoid high-intensity exercise (due to potential for adverse gastrointestinal effects). However, without trials we have no evidence for or against these potential effects.

We think that it is important to generate trial evidence to establish the effects and safety of different modes of exercise training in people with IBD.

It would be more acceptable to publish blood markers of inflammation in a separate manuscript if there were many significant differences found within that data. However, since no hypothesis testing was completed, and data is only represented as means (SD), this is obviously not the case. This data should be included in the current manuscript.

Thank you. The blood biomarker data, like all the other health and clinical outcome measure data, is exploratory. However, given the sheer volume of blood biomarker data generated in this study, and the fact that this aspect is quite specialist and niche, we think that it would be better to publish this data separately elsewhere. We are clear about this intention in the methods, and believe that the current manuscript works well without this data.

Specific Comments:
Line 62: This reference is about exercise for rheumatoid arthritis. Yes, an inflammatory disease - however, is otherwise not applicable as it is not an inflammatory disease that affects the gastrointestinal system. What are the most current guidelines/recommendations for IBD?

To our knowledge, there aren’t any published evidence-based exercise guidelines/recommendations for IBD, which is one of the motivating factors for doing research on this topic.

Line 78: Why did you choose to exclude individuals with ulcerative colitis?

This decision was taken to make the study population more homogenous. The two diseases have different aetiologies and respond differently to treatments, hence the decision to study one disease first. CD carries a greater overall health burden than UC, so exercise may have a greater relative importance as an adjunct therapy in CD.

Line 91: Please state with certification/designation of the individual's in charge of supervising/training

The research assistants were sport and exercise science graduates with a special interest in clinical populations.

Line 128: I see that RPE and %HRmax are reported and appear to be in line with 'moderate-intensity', but I am having a hard time believing that 35% Wpeak (50-54W) elicited a 'moderate-intensity' effort.

Yes, our RPE and HR data do provide reassurance that the MICT programme was of moderate intensity. The protocol was selected because it had previously been shown to elicit a similar energy expenditure compared with the HIIT programme: http://www.nrcresearchpress.com/doi/10.1139/apnm-2013-0512#.W-Vy0fn7SUl.

In the 2011 Compendium of Physical Activities, stationary cycling at 51-89 W was assigned 4.8 METs and a “light-to-moderate effort”: http://download.lww.com/wolterskluwer_vitalstream_com/permalink/mss/a/mss_43_8_2011_06_13_ainsworth_202093_sdc1.pdf (see code 02017). Given the relatively low in fitness status of the participants (see response to Reviewer 1), we are not surprised that the MICT elicited reports of moderate effort.
Line 157: This seems like a contrived way of defining success. If I'm understanding this correctly, success was 67% of the participants completed 67% of the sessions. What was this decision based on? Wouldn't 80% be typically more acceptable?

This is somewhat arbitrary as there are no clear guidelines in the literature for how best to define success with feasibility criteria. 67% was selected because numerous studies have shown beneficial physiological effects of twice-weekly training over 12 weeks.

Line 170: Although somewhat redundant with questionnaire name, list the outcomes measured via these questionnaires (i.e. QOL, fatigue, depression, anxiety), like how you did for disease status (via CDAI) above in Line 166.

Thank you. We have done this for the EQ-5D because that is the only one which is not immediately apparent from the questionnaire name.

Line 182: Were participants blinded to the hypothesis (i.e. that the HIIT would be superior to MICT exercise on outcomes)? If so, please state here. If not, please consider doing so for future trial.

We didn’t have this hypothesis. The PIS said: “A clearer understanding of the effects of different types of exercise training in adults with Crohn’s is needed so that safe and effective exercise programmes can be designed… The purpose of this study is to explore the feasibility, acceptability and possible benefits of two commonly used exercise programmes in adults with Crohn’s disease.”

Line 224: Was the participant that started aerobic/strength training 3-4d/wk excluded from outcome assessment?

No, as per principles of intention to treat.

Line 234: Why were those with RA excluded, but not this participant with ankylosing spondylitis?

The exclusion criterion relating to this was “coexistent serious autoimmune disease”. In hindsight, this criterion could have been clearer. During the trial, we operationalised it as meaning active autoimmune disease. The participant with ankylosing spondylitis had very mild stable disease, which was deemed not to preclude exercise; hence their inclusion.
Line 259: Please clarify what percentage of the 'illness' category was disease related illness.

The majority of the illness-related missed sessions were due to colds and minor infections. Only two of these sessions were missed due to CD-related reasons. One participant missed a session due to “mild CD symptoms”, and another missed a session due to “not feeling well after an infusion”. We have clarified in the revised manuscript that only two of these missed sessions were CD-related.

Line 332: Valuable feedback! Emphasize this when seeking funding for future studies.

Indeed!

Line 356-363: I am slightly confused by the planned future trial intervention. It appears you wanted to do a combo intervention of HIIT/MCIT for a well-rounded aerobic intervention and then a control exercise group (i.e. flexibility). But then it's mentioned the intervention would include a combination of aerobic, resistance, balance and flexibility exercises in a 2-arm trial (also discussed in Additional File 3). So, what is the other arm in the 2-arm trial if flexibility is included in the intervention? Regardless, I would suggest doing a 3-arm trial: Arm 1 = Aerobic combo of HIIT and MCIT (e.g. 2 days of HIIT and 1 of MCIT); Arm 2 = Strength combo of HIIT and lower intensity circuit (e.g. 2 days of HIIT strength and 1 lower intensity circuit); Arm 3 = Flexibility and balance (e.g. combo of both 3 days per week, as control/sham exercise group).

In an ideal world, we would like to compare aerobic versus resistance versus aerobic + resistance versus neither, but having >2 groups will increase the sample size substantially, reducing the feasibility of such a study. Given this, and the fact that public health guidelines promote a mix of aerobic and muscle-strengthening activities, we think that we should seek to establish the efficacy of a ‘well-rounded’/generic exercise programme in an adequately-powered two-group RCT. The intervention would include aerobic, resistance and flexibility exercises to cover the main aspects of physical fitness and be consistent with most general exercise programmes. The nature of the control group is debatable, but if the focus is on efficacy then we think that the use of flexibility training as an attention control would be a sensible approach (and one that has been used in many previous studies).

Then expand inclusion criteria to include patients with CD and ulcerative colitis to assist with fulfilling the greater recruitment needs.

Line 383: Consider including individuals with UC, which would increase recruitment potential.
Thank you. We agree that this would increase the recruitment potential of a future trial. However, please see our previous response on why we chose to focus on CD only.

Line 381-382: Here is sounds as though the flexibility exercise is placebo, but previous statement it does not. Please clarify.

It is proposed that both groups would do flexibility exercises. The intervention group would be doing these exercise because most general exercise programmes include an element of flexibility training. The comparison group would be doing them to match the intervention group for attention.