PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Can non-responders be 'rescued' by increasing exercise intensity? A quasi-experimental trial of individual responses among humans living with prediabetes or type 2 diabetes mellitus in Canada.
AUTHORS	Hrubeniuk, Travis; Bouchard, Danielle; Gurd, Brendon; Senechal, Martin

VERSION 1 – REVIEW

REVIEWER	Dr Zephanie Tyack The University of Queensland
REVIEW RETURNED	09-Oct-2020

GENERAL COMMENTS	The authors report on a protocol paper for a study examining glycemic responses to exercise intensity using an innovative design. Generally the paper is well written and the methodology appears solid but the paper would benefit from further justification in some parts. I have added comments for various sections of the protocol. Study design: The authors have referred to the study design as a two-phase quasi-experimental design? Is there other terminology and a reference that could be used for the study design which may assist with others wishing to use the same design? Trial registration: Can the authors please confirm that the trial was registered prospectively which is a requirement of the journal if this detail has not already been provided? Inclusion criteria: Was there any assessment of exercise intolerance at the time of potential recruitment following events or illnesses such as COVID-19? Was this considered or accounted for? Would alternate allocation of individuals have been preferable to block assignment of the control group prior to the intervention group? Could there be variables that may influence the control group compared to the intervention group if they are assigned in separate blocks (e.g., seasonal or weather differences that could influence exercise tolerance using a treadmill)? The potential of different influences on the control and intervention groups may be reduced by recruitment within a short time frame, if this is the case. Do participants exercise alongside other participants in the intervention group as social factors could influence motivation to attend sessions and exercise during the trial?

	Can the responder, non-responder and uncertain responder groups be clearly defined earlier in the manuscript possibly in the intervention section as this detail is presented quite late in the manuscript? Will adding an additional week at the end of the trial be sufficient for those who have been ill? It might be good to document the reasons for absence as those absent due to sickness may respond quite differently to those absent for other reasons such as a vacation or family emergency. Adding a justification for the choice of the additional week for these participants would add to the paper. Will the authors request that participants receive doctors' advice to continue in the trial if they are experiencing symptoms that are concerning but they have not yet visited their doctor? Page 13: deviations from protocol Line 13-27: The author state that enrolment will be discontinued if a participant experiences any musculoskeletal injury or other medical event that prevents or limits safe participation in exercise for three consecutive weeks, or if the participant received medical advice to stop participation. Can the authors indicate whether or not data collected up to that point will be included? Using the chosen analysis it seems that all data collected should be able to be included? Outcomes: Additional details could be added as a supplementary file. Could the authors please provide more information regarding the method of measuring HbA1c and the validity of the chosen method of analysis including references? How feasible is it that participants will complete two measurements of HbA1c? What will happen if 2 measurements are not collected? Could the authors also please provide a rationale for measuring the family history of cardiovascular and cardiometabolic disease? Further description is required regarding the Physical Activity and Sedentary behaviour Questionnaire subscales that will be measured and the psychometrics of that measure. Information should also be provided regarding the quality and wearability of the chosen pedometer. What happens if a pedometer is lost or broken? Will it be replaced or is that participants' data for that outcome no longer able to be included? Will this type of data be reported at the end of the study? Are the authors using any incentives to reduce potential imbalance in the number of participants completing the phase 2 trial and will the authors report the number of participants dropping out and reasons for attrition? Blinding Will the participants be masked to the research hypotheses as it appears they could be? Randomisation How will the randomisation be concealed (e.g., sequentially numbered, sealed/opaque envelopes)? This detail seems to be missing. How will the randomisation be communicated to TH as this is not clear? Why will randomisation blocks of 5 be used – could a rationale please be added?

	Statistical analysis Line 17-18: Was the sample size calculation based on the anticipated change in the primary outcome measure HbA1c or on the between group difference in changes in HbA1c? This could be made clearer. At what point is the 20% drop-out rate expected? Please also add detail that clearly indicates the sample size of phase 2. It is not clear which phase the sample size of 42 pertains to. For the chosen study design an intention to treat analysis would seem not appropriate due to the potential re-categorisation of respondents in phase 2. Could the authors please explain why an intention-to-treat analysis may not be appropriate for phase 2 if I have understood the design correctly, as readers will be very familiar with this as part of a randomised trial. Are the authors able to confirm whether the chosen MCID was appropriate for the study by examining this at the end of the study, as study and individual factors may influence the Minimally Clinically Important Difference that was previously established?

REVIEWER	Eric P. Plaisance University of Alabama at Birmingham USA
REVIEW RETURNED	21-Dec-2020

GENERAL COMMENTS	The manuscript is a study protocol for a study that is currently underway. As per the restrictions of the journal, the authors have been compliant with no presenting results. The purpose of this study is to determine whether previously physically inactive individuals with prediabetes or type 2 diabetes (T2DM) whose HbA1c is unresponsive to aerobic exercise performed at 4.5 METs would be rescued at a higher exercise intensity (6 METs). First, I would like to congratulate the authors on a beautifully designed and innovative study that will address an important question for the field. The manuscript is well written and straightforward. Minor comments follow. Abstract: Page 5, line 14: Consider editing the statement to: Participants will be allocated to a control group or assigned to an intervention group…… Article Summary: Add that you are using 150 min/week as the physical activity volume for this study as a strength which is consistent with numerous guiding bodies in the field Methods: 1. Are you using [Hb] to diagnose anemia. If so, please state your criteria for men and women

	2. On page 10, do you have any exclusions for any hypoglycemic agents or all oral/insulin therapies permitted? How are you handling changes in medications 3. Please expand on Page 12 what you mean by an uncertain responder? You cite criteria of HbA1c > 5.7 for inclusion, so it is unclear why this distinction would be made. 4. Page 14 – Please eliminate the reference for the Balke test. The reference included is not for a modified version of the Balke Test. Balke uses 3.3 mph with a 1% increase in grade until volitional fatigue

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1

Dr. Zephanie Tyack, University of Queensland

Comments to the Author:

The authors report on a protocol paper for a study examining glycemic responses to exercise intensity using an innovative design. Generally the paper is well written and the methodology appears solid but the paper would benefit from further justification in some parts. I have added comments for various sections of the protocol.

Comment 1: Study design: The authors have referred to the study design as a two-phase quasi-experimental design? Is there other terminology and a reference that could be used for the study design which may assist with others wishing to use the same design?

Response 1: The unique nature of this design made categorizing it difficult, as phase one could be classified as a single-arm study and phase two as a randomized controlled trial. However, as the control group provides a consistent influence on decision making, and participants were allocated to control or intervention groups, we came to the conclusion that a quasi-experimental design was the best fit for the overall study. We are open to suggestions if the editorial team or reviewers believe alternative terminology would be preferred. Given the individual response research is relatively new, and our attempt to answer a novel research question in Phase Two, we are not aware of any previous work that follows this exact study design to provide an additional reference.

Comment 2: Trial registration: Can the authors please confirm that the trial was registered prospectively which is a requirement of the journal if this detail has not already been provided?

Response 2: The trial was prospectively registered with ClinicalTrials.gov (NCT03787836)

Comment 3: Inclusion criteria: Was there any assessment of exercise intolerance at the time of potential recruitment following events or illnesses such as COVID-19? Was this considered or accounted for?

Response 3: There are no distinct assessments of exercise intolerance at the time of recruitment. However, participants are asked to self-report being able to complete the volume required, and must complete a fitness test to determine the exercising heart rate. In terms of potential side effects of COVID-19, no participants have been diagnosed so far, and the spread of COVID-19 throughout the province is relatively low (only about 1000 cases reported to date, across a population of approximately 800,000).

Comment 4: Would alternate allocation of individuals have been preferable to block assignment of the control group prior to the intervention group? Could there be variables that may influence the control group compared to the intervention group if they are assigned in separate blocks (e.g., seasonal or weather differences that could influence exercise tolerance using a treadmill)? The potential of different influences on the control and intervention groups may be reduced by recruitment within a short time frame, if this is the case.

Response 4: There is s possibility that external variables (e.g., seasonal changes, the unanticipated influence of COVID-19) may influence differences between the control and intervention groups. This is a limitation of the study. This decision was made for several reasons. First, all control participants need to have mid-point assessments completed before the first intervention participant achieved that time point. This is mandatory to allow for response categorizations and subsequent randomization to occur. Second, using an ongoing/continuous recruitment strategy as opposed to a block recruitment approach would introduce significant constraints and feasibility limitations.

Comment 5: Do participants exercise alongside other participants in the intervention group as social factors could influence motivation to attend sessions and exercise during the trial?

Response 5: Participants do exercise alongside other participants, and socialization is permitted. However, given current COVID-19 protocols which require plexiglass to remain between the treadmills, socialization between participants is minimal.

Comment 6: Can the responder, non-responder and uncertain responder groups be clearly defined earlier in the manuscript possibly in the intervention section as this detail is presented quite late in the manuscript?

Response 6: The response categorizations have been clearly defined and moved to the Intervention section, immediately following the explanation of Phase One, see lines 195 - 207.

Comment 7: Will adding an additional week at the end of the trial be sufficient for those who have been ill? It might be good to document the reasons for absence as those absent due to sickness may respond quite differently to those absent for other reasons such as a vacation or family emergency. Adding a justification for the choice of the additional week for these participants would add to the paper.

Response 7: To clarify, for each week missed an additional week will be added to the trial, up to a maximum of three weeks (at which point the participant will be excluded from further participation). Additional clarification was added to the manuscript on lines 226 - 229. As noted in the Deviations from Protocol section, this is to ensure that participants all receive the same dose of exercise over a similar period of time to maximize our confidence in using the SD_{IR}. In addition, the reasons for missing sessions of exercise or a week of exercise will be documented. This information has been added to the manuscript.

Comment 8: Will the authors request that participants receive doctors' advice to continue in the trial if they are experiencing symptoms that are concerning but have not yet visited their doctor?

Response 8: Given the current COVID-19 restrictions, any participant displaying potential symptoms is asked to remain at home. If symptoms persist for two days, they are required to stay home for a week, get tested for COVID-19, and only return to the lab once they receive a negative result. If participants are experiencing symptoms that are concerning, the research staff will encourage that the participant seeks medical advice before continuing.

Comment 9: Line 13-27: The authors state that enrolment will be discontinued if a participant experiences any musculoskeletal injury or other medical event that prevents or limits safe participation in exercise for three consecutive weeks, or if the participant received medical advice to stop participation. Can the authors indicate whether or not data collected up to that point will be included? Using the chosen analysis it seems that all data collected should be able to be included?

Response 9: The nature of individual response research and categorization of individuals as responders, non-responders and uncertain responders requires measurements at two time points and the calculation of a change score. Therefore, participants who drop out or are excluded prior to follow-up assessments cannot be used in the analysis for Objective 1 or Objective 2. However, baseline data will be kept and used to identify potential differences between those participants who were removed from further analysis and those who were not. If a participant was able to reach the end of Phase One, their data will be included in the analysis for Objective 1. This information has been added to lines 232 – 235.

Comment 10: Outcomes: Additional details could be added as a supplementary file. Could the authors please provide more information regarding the method of measuring HbA1c and the validity of the chosen method of analysis including references? How feasible is it that participants will complete two measurements of HbA1c? What will happen if two measurements are not collected?

Response 10: Additional detail was added to the manuscript for the collection of HbA1c, and references were provided to support the validity of the DCA Vantage Analyzer in lines 248 – 255. Given our experience in metabolic testing with this population and the simplicity of these measurements, we have complete confidence that two measurements will be collected at each time point for every participant.

Comment 11: Could the authors also please provide a rationale for measuring the family history of cardiovascular and cardiometabolic disease? Further description is required regarding the Physical Activity and Sedentary behaviour Questionnaire subscales that will be measured and the psychometrics of that measure. Information should also be provided regarding the quality and wearability of the chosen pedometer. What happens if a pedometer is lost or broken? Will it be replaced or is that participants' data for that outcome no longer able to be included? Will this type of data be reported at the end of the study?

Response 11: The use of the Physical Activity and Sedentary Behaviour Questionnaire and the Piezo Rx pedometer is solely to provide two methods of confirming the current activity level of participants at baseline to ensure they are eligible for inclusion. This information has been added to the manuscript (line 261 – 264). If a pedometer is lost or broken, the participant will be asked to wear the pedometer again, and the data collected at that time will be kept (line 269 – 270). The step count results and self-reported physical activity level will be reported in the final manuscript.

Likewise, measuring the family history for cardiovascular and cardiometabolic disease is to allow the research team to provide additional context pertaining to the participant's potential genetic susceptibility to type 2 diabetes and potential Type 2 diabetes complications.

Comment 12: Are the authors using any incentives to reduce the potential imbalance in the number of participants completing the phase 2 trial, and will the authors report the number of participants dropping out and reasons for attrition?

Response 12: There are no incentives put in place to specifically reduce potential imbalances in the number of participants completing Phase Two of the trial. The only incentive would come from participating in a well supervised and controlled exercise program. The number of participants who drop out and the reason for attrition will be reported.

Comment 13: Blinding: Will the participants be masked to the research hypotheses as it appears they could be?

Response 13: No, participants are aware of the research hypothesis. However, as intervention participants are being blocked as responders or non-responders/uncertain responders prior to randomization into the maintained or increased intensity groups, they will not know how they are progressing until study completion.

Comment 14: Randomisation: How will the randomisation be concealed (e.g., sequentially numbered, sealed/opaque envelopes)? This detail seems to be missing. How will the randomisation be communicated to TH as this is not clear? Why will randomisation blocks of 5 be used – could a rationale please be added?

Response 14: More information regarding the randomization procedure was added to lines 324 – 337. Random numbers in blocks of 10 (five per group) were obtained by DRB using an auto-generating software (SPSS version 22.0). A student not related to the trial will collect the HbA1c values at mid-point, calculate the change score, and categorize the participant as a a responder or a non-responder/uncertain responder. The response categorization is relayed to DRB via email to DRB (who has no contact with participants or their data), and based on the automatically generated number, will randomize the participant to the maintained or increased intensity group. The participant's randomization will be relayed to TH via email. The block of 10 (five in each group) was used to ensure a short-term balance between groups as it is possible that only a few participants will be considered as a responder or a non-responder/uncertain responder.

Comment 15: Statistical analysis: Was the sample size calculation based on the anticipated change in the primary outcome measure HbA1c or on the between group difference in changes in HbA1c? This could be made clearer. At what point is the 20% drop-out rate expected? Please also add detail that clearly indicates the sample size of phase 2. It is not clear which phase the sample size of 42 pertains to.

Response 15: As stated on line 339-340, the sample size calculation was based on the anticipated change in the primary outcome measure, HbA1c, following Phase One of the trial. As individual response categorization is based on individual changes, we felt calculating the sample size based on differences between the control and intervention group would not allow us to answer our research question.

The anticipated 20% drop out rate was built into the expectation for Phase One. Given the stated exploratory nature of Phase Two (line 116) and the inability to predetermine the number of responders and non-responders/uncertain responders that would exist following Phase One, we did not conduct a sample size calculation solely for Phase Two. We aim to have all participants continue into Phase Two. This has been clarified on lines 345 - 348.

Comment 16: For the chosen study design an intention to treat analysis would seem not appropriate due to the potential re-categorisation of respondents in phase 2. Could the authors please explain why an intention-to-treat analysis may not be appropriate for phase 2 if I have understood the design correctly, as readers will be very familiar with this as part of a randomised trial.

Response 16: Viewing the entirety of the protocol, a traditional intention to treat analysis would not be appropriate as half of the participants will have their protocols changed at mid-point. It is worth noting that this is by design and will allow us to evaluate if changing the exercise prescription and increasing exercise intensity can “rescue” those who were categorized as non-responders by way of producing beneficial changes in HbA1c. It is important to remember that our design does not involve a group-based analysis comparison. Rather, we are approaching analysis at the individual level, with randomization at the mid-point based on the individual response categorization at that time. As such, statistics such as the relative risk ratio, which are often impacted when transitioning between intention to treat and per protocol analyses, will not be applied or needed to answer our hypotheses.

Comment 17: Are the authors able to confirm whether the chosen MCID was appropriate for the study by examining this at the end of the study, as study and individual factors may influence the Minimally Clinically Important Difference that was previously established?

Response 17: There will undoubtedly always be debate regarding the choice of the threshold used to categorize individuals. Some authors have previously suggested that response thresholds should be lower than the expected change for most; however, previously determined clinically relevant thresholds are often recommended. Following the trial, we will evaluate this decision and speak on its appropriateness as a threshold value given the results.

Reviewer: 2

Dr. Eric Plaisance, The University of Alabama at Birmingham

Comments to the Author:

The manuscript is a study protocol for a study that is currently underway. As per the restrictions of the journal, the authors have been compliant with no presenting results. The purpose of this study is to determine whether previously physically inactive individuals with prediabetes or type 2 diabetes (T2DM) whose HbA1c is unresponsive to aerobic exercise performed at 4.5 METs would be rescued at a higher exercise intensity (6 METs). First, I would like to congratulate the authors on a beautifully designed and innovative study that will address an important question for the field. The manuscript is well written and straightforward. Minor comments follow.

Comment 1: Abstract: Page 5, line 14: Consider editing the statement to: Participants will be allocated to a control group or assigned to an intervention group……

Response 1: This has been changed on line 43.

Comment 2: Article Summary: Add that you are using 150 min/week as the physical activity volume for this study as a strength which is consistent with numerous guiding bodies in the field

Response 2: This has been added on lines 63-65.

Comment 3: Methods: Are you using [Hb] to diagnose anemia. If so, please state your criteria for men and women

Response 3: We are not checking or diagnosing anemia locally. A diagnosis of anemia is self-reported during initial participant screening, with the request of participants to report any diagnoses that occur during the study protocol. This has been specified on line 139-140.

Comment 4: On page 10, do you have any exclusions for any hypoglycemic agents or all oral/insulin therapies permitted? How are you handling changes in medications?

Response 4: All oral/insulin therapies are being permitted. Throughout the trial, participants have been asked to report any changes in medications, which will be reported. Clarification has been added to lines 261 - 264.

Comment 5: Please expand on Page 12 what you mean by an uncertain responder? You cite criteria of HbA1c > 5.7 for inclusion, so it is unclear why this distinction would be made.

Response 5: A clarification of the uncertain responder categorization has been added to lines 201-206.

Comment 6: Page 14 – Please eliminate the reference for the Balke test. The reference included is not for a modified version of the Balke Test. Balke uses 3.3 mph with a 1% increase in grade until volitional fatigue.

Response 6:. To ensure there is no confusion for the reader regarding this reference, we re-phrased this sentence to emphasize that this protocol has been modified. lines 277 - 279.

VERSION 2 – REVIEW

REVIEWER	Eric Plaisance University of Alabama at Birmingham
REVIEW RETURNED	08-Mar-2021

GENERAL COMMENTS	Thank you for addressing the concerns of the reviewers. I have no further concerns