

PEER REVIEW HISTORY

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ARTICLE DETAILS

TITLE (PROVISIONAL)	Personalising activity to target peak hyperglycaemia and improve cardiometabolic health in people with type 2 diabetes: protocol for a randomised controlled trial
AUTHORS	Chang, Courtney R.; Astell-Burt, Thomas; Russell, Brooke M.; Francois, Monique E

VERSION 1 – REVIEW

REVIEWER	Whipple, Mary University of Minnesota Twin Cities, School of Nursing
REVIEW RETURNED	19-Dec-2021

GENERAL COMMENTS	<p>This is a protocol for an interesting and timely study of the effects of exercising at the time of peak glycemia on glycemic control and cardiovascular risk among adults with type 2 diabetes. The protocol is well written, and the study is poised to fill a meaningful gap in the literature. Below are my specific comments/suggestions for the authors' consideration.</p> <ol style="list-style-type: none">1. I appreciate the authors' careful consideration of methods to continue the study in the context of the pandemic and potentially limited ability for in-person visits.2. Line 158 – Would suggest including a reference for the REDCap software.3. Line 177 – This could be written as simply >150 minutes of exercise per week (since I am assuming a participant who obtains 301 minutes would also be excluded).4. Line 223 – Although the timing will not be prescribed, I am curious if the timing of exercise for participants in the wait list control group will be monitored (since they will be encouraged to exercise), so that if a participant tends to exercise post-lunch (potentially coinciding with peak glycemia), for example, that these data could be captured.5. Line 297 – Given the effects of menstrual cycle on macrovascular outcomes, will the authors assess the timing of menstrual cycle/perform the study testing in the early follicular phase of the menstrual cycle (days 1–7 of the menstrual cycle) for premenopausal participants, as is typically recommended? Would suggest addressing this in the methods for the FMD testing.6. Lines 438-442 – appears to be a part of the paragraph missing, please review.
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REVIEWER	Rein, Michal Weizmann Institute of Science, Computer Science and Applied Mathematics
REVIEW RETURNED	01-Jan-2022

GENERAL COMMENTS	<p>This study, led by Courtney R. Chang et al, "Personalising Activity to Target Peak Hyperglycaemia and Prevent Cardiovascular Disease 2 in People with Type 2 Diabetes: A Protocol for A Randomised Controlled Trial" raise an important and relevant question regarding the potential effect of the timing of the exercise on diabetes control. In general the study protocol well written and designed and I only have several comments / questions that should be addressed within the protocol.</p> <p>Note: I could not find the protocol registration</p> <p>Time of peak determination: How the author is dealing with several peaks during the day? will the highest peak be chosen? will participants be instructed to eat in specific times? Can the author please clarify?</p> <p>Main outcome : HbA1c levels represent the mean blood glucose in the last 3 months. Why the author chose it as the main objective? Could the author explain or re-consider to evaluate the glycated hemoglobin after 3 months? Currently it is evaluated after 2 months only although A1c levels represent the last 3 months.</p> <p>Covid-19: The authors well addressed the unique situation of Covid-19 pandemic and allowed a follow up and blood tests at home. Can the author explain how the results will be treated and analyzed and what are the differences between the tests at the clinic and at home?</p>
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VERSION 1 – AUTHOR RESPONSE

Reviewer: 1

Dr. Mary Whipple, University of Colorado - Anschutz Medical Campus

Comments to the Author:

This is a protocol for an interesting and timely study of the effects of exercising at the time of peak glycemia on glycemic control and cardiovascular risk among adults with type 2 diabetes. The protocol is well written, and the study is poised to fill a meaningful gap in the literature. Below are my specific comments/suggestions for the authors' consideration.

1. I appreciate the authors' careful consideration of methods to continue the study in the context of the pandemic and potentially limited ability for in-person visits.

Reply: Thank you, we have also updated the strengths and limitations to reflect this.

2. Line 158 – Would suggest including a reference for the REDCap software.

Reply: Thank you, we have added this to line 163.

3. Line 177 – This could be written as simply >150 minutes of exercise per week (since I am assuming a participant who obtains 301 minutes would also be excluded).

Reply: Thank you, we have amended Line 188.

Line 188 now reads: ">150 min of moderate to vigorous intensity exercise/week..."

4. Line 223 – Although the timing will not be prescribed, I am curious if the timing of exercise for participants in the wait list control group will be monitored (since they will be encouraged to exercise), so that if a participant tends to exercise post-lunch (potentially coinciding with peak glycemia), for example, that these data could be captured.

Reply: This is a great point. We will be able to obtain information on this from the paired accelerometer and CGM and from the questionnaire which asks “on how many days they exercised, how many min/wk and their preferred time of day to exercise”.

5. Line 297 – Given the effects of menstrual cycle on macrovascular outcomes, will the authors assess the timing of menstrual cycle/perform the study testing in the early follicular phase of the menstrual cycle (days 1–7 of the menstrual cycle) for premenopausal participants, as is typically recommended? Would suggest addressing this in the methods for the FMD testing.

Reply: We are not controlling for the timing of menstrual cycle, given that cycle length can range from 21-35 days (PMID: 31482137) and the vascular assessments for this trial occur immediately before and after the 8-week exercise intervention.

- There is an interesting view point which is inline with our real-work translation approach PubMed[32702274](#) Contrary to this common approach, we propose that limiting testing of women to this single phase 1) decreases external validity of the findings, 2) obfuscates potential physiological differences contributable to differences in sex hormone concentrations between men and women, and 3) is, in many instances, contradicted by literature that demonstrates limited or no variability in vascular measurements across the menstrual cycle.

We anticipate most will be postmenopausal, however we will importantly report this in characteristics and can run statistical analyses with and without these subjects if appropriate.

6. Lines 438-442 – appears to be a part of the paragraph missing, please review.

Reply: Appologies, we have removed this as it was repetition left from the edition of the discussion.

Reviewer: 2

Mrs. Michal Rein, Weizmann Institute of Science

Comments to the Author:

This study, led by Courtney R. Chang et al, "Personalising Activity to Target Peak Hyperglycaemia and Prevent Cardiovascular Disease 2 in People with Type 2 Diabetes: A Protocol for A Randomised Controlled Trial" raise an important and relevant question regarding the potential effect of the timing of the exercise on diabetes control. In general the study protocol well written and designed and I only have several comments / questions that should be addressed within the protocol.

Note: I could not find the protocol registration

Reply: Appologies, we have corrected the trial registration number in Line 59. We have also made revisiosns as above to the outcomes (removed those taken out because of COVID-19 and had missed CGM secondary outcomes). Trial amendments currently under review.

Time of peak determination: How the author is dealing with several peaks during the day? will the highest peak be chosen? will participants be instructed to eat in specific times? Can the author please clarify?

Reply: Yes good point, correct, when there is more than one peak the highest will be chosen for interventions. However, when it is no clear difference for someone with multiple peaks (often two) we give participants the choice of exercising at one of the two times (this has happened on three occurrences so far). They choose the one time point (cannot switch between) for the rest of the intervention.

Diet will not be controlled for this trial. However, participants will be asked to maintain regular dietary habits for the duration of the study period. Diet records will also be collected and used to confirm that no change in dietary habits occurred across the trial.

Main outcome: HbA1c levels represent the mean blood glucose in the last 3 months. Why the author chose it as the main objective? Could the author explain or re-consider to evaluate the glycated hemoglobin after 3 months? Currently it is evaluated after 2 months only although A1c levels represent the last 3 months.

Reply: HbA1c is commonly measured every 3 months, however, reflects mean plasma glucose levels from the past 8-12 weeks (PMID: 26158184) with 50% of glycosylation occurring over the last 30 days and 10% of change occurring over 90-120 days (PMID: 27422013; PMID: 32913038). Further to this, the trial has measures pre-post 8-weeks and then 3 month follow-up.

Covid-19: The authors well addressed the unique situation of Covid-19 pandemic and allowed a follow up and blood tests at home. Can the author explain how the results will be treated and analyzed and what are the differences between the tests at the clinic and at home?

Reply: Results will be analysed with remote and local participants together and separately, that way we can see any differences in the measures for cobas vs blood spot. We are hoping any differences are systematic as participants performed the same measure for all timepoints. Another trial (xxxx) has measured HbA1c from blood spot and pathology and we are currently analysing those results.

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COI statements:

Reviewer: 1

Competing interests of Reviewer: None.

Reviewer: 2

Competing interests of Reviewer: I have no relevant competing interests to report.

VERSION 2 – REVIEW

REVIEWER	Whipple, Mary University of Minnesota Twin Cities, School of Nursing
REVIEW RETURNED	09-Feb-2022

GENERAL COMMENTS	I appreciate the authors' thoughtful responses to my questions/comments. The authors have adequately addressed my original concerns and I do not have any additional questions or recommendations.
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REVIEWER	Rein, Michal
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	Weizmann Institute of Science, Computer Science and Applied Mathematics
REVIEW RETURNED	01-Feb-2022

GENERAL COMMENTS	<p>Thank you for the answers. The Authors addressed my comments. Only minor suggestion: For better understanding I would suggests to add the method on how the researchers choose the glycemc peak into the study methods (the author answer to my second point on the previous revision).</p> <p>2. Line 159 - 'electronic data capture' appears twice.</p>
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VERSION 2 – AUTHOR RESPONSE

Reviewer: 2

Mrs. Michal Rein, Weizmann Institute of Science

Comments to the Author:

Thank you for the answers. The Authors addressed my comments.

Reply: Thank you for your feedback!

Only minor suggestions:

*For better understanding I would suggests to add the method on how the researchers choose the glycemc peak into the study methods (the author answer to my second point on the previous revision).

Reply: Thank you, we have amended line 271-274 of the manuscript to reflect this information.

Line 271-274 now reads: "Exercise for the ExPeak group will be prescribed in relation to the highest peak (i.e., greatest glucose excursion); if there are multiple glucose excursions throughout the day with the same peak level, participants will be given an option of the times to exercise, but must stick with one time for the duration of the intervention."

*Line 159 - 'electronic data capture' appears twice.

Reply: Thank you, we have removed the second appearance of 'electronic data capture' in line 171 of the manuscript.

Reviewer: 1

Dr. Mary Whipple, University of Minnesota Twin Cities

Comments to the Author:

I appreciate the authors' thoughtful responses to my questions/comments. The authors have adequately addressed my original concerns and I do not have any additional questions or recommendations.

Reply: Thank you for your feedback!