Author's response to reviews

Title: Fast food increases postprandial cardiac workload in T2D, which pre-exercise cannot modify: A pilot study.

Authors:

Siri Marte Hollekim-Strand (siri.m.hollekim@ntnu.no)
Vegard Malmo (Vegard.malmo@ntnu.no)
Turid Follestad (turid.follestad@ntnu.no)
Ulrik Wisløff (ulrik.wisloff@ntnu.no)
Charlotte Bjork Ingul (charlotte.b.ingul@ntnu.no)

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Author's response to reviews: see over
Dear Editor,

Thank you for giving us the opportunity to correct our work for further consideration to publish in the Nutrition Journal. We hereby re-submit the manuscript. We have addressed the comments and concerns from the reviewers and hope our response is satisfactory. Our changes in the manuscript have been written in red text. However the grammatical changes done through a professional editing service is not marked. We can provide all the grammatical changes upon request.

Response to the reviewer’s 1-3 comments.

Reviewer 1, Louise Purtell:

“While it would have been interesting to see a control meal included to further test the putative fast-food effects, this study is well-designed and generally well written.”

Reply: Thank you very much. We completely agree that it would have strengthened the study to investigate a control meal. However, the study was extremely time consuming and resource demanding and as we finished the fast food trial we had no possibility to follow up with a control meal which we wished to do. Nevertheless, this is certainly something we would like to investigate further.

1. Major compulsory revisions:

“There are two separate comparisons in this study: between T2D subjects and controls postprandially and between exercise and non-exercise. While equally as interesting as the first, the second comparison is not given as much weight, possibly due to a lack of significant results. While exercise conditions are already included in the mixed model, and exercise didn’t have an effect on results, it would be illuminating to show at least one figure with the three exercise conditions presented separately for each group.”

Reply: We understand why this is considered interesting and do have the figures for exercise (HIIE and MIE combined) versus no exercise. We have attached the figures that combine postprandial effect of fast food (left panel) as well as effect of pre-exercise (mid panel for T2D and right panel for controls) at the end of this document. Would you like these to be added to the manuscript?
“Some parameters mentioned in the methods section are not referred to in the results section, figures or discussion (i.e. late diastolic tissue velocity, deceleration time, cholesterol, hs-CRP etc). All parameters assessed should be presented and discussed.”

Reply: We have added the results of a’, DT, E/A, cholesterol and hs-CRP to the result and discussion section.

2. Minor essential revisions:

Abstract

“Prior to-‘ does not need a hyphen.”

Reply: This has been deleted.

Results

“There is a missing end-bracket in the first sentence. I assume it should go after (E). Also, global strain rate should be given its abbreviation here.”

Reply: Thank you, we have corrected the missing end-bracket. In regard to global strain rate, we do not have an abbreviation for this variable throughout the article. Of course we will change this if this is required.

“BMI should be defined here”

Reply: This is now corrected.

Background

“Page 3, paragraph 3 – ‘increase in’ should be ‘increased’ or ‘increases in’; Page 3, paragraph 5 (last two lines) – should be ‘improvements in endothelial function’”

Reply: These points are corrected

Methods

“Page 4, paragraph 5 – no hyphen is necessary after cardiovascular.”

Reply: This is corrected

“Page 5, paragraph 1 – please define ‘resting (>48 h); presumably they refrained from exercise rather than rested the whole time?’”

Reply: Hereby changed to: “(sedate behavior/ refrained from exercise >48 h)”

“Page 5, paragraph 2/page 6, paragraph 1 – Global strain and strain rate should be given their abbreviations.”

Reply: As replied earlier, we could do this, however most commonly these do not have any abbreviations. We would of course change this if this is required.
“Page 7, paragraph 3 – please describe the methods used for assessing blood glucose, insulin, C-peptide, plasma triglycerides, cholesterols and hs-CRP. There should be a comma after insulin.* HbA1C should be followed by ‘was’.”

Reply: Insulin has been removed as this was not measured, and is an error that has sunk into the manuscript. The biochemical measurements were analyzed at St.Olavs Hospital according to standard procedures. The blood tests were sent to the biochemical laboratory at the St.Olavs Hospital straight after the blood samples were collected. The verb after HbA1c is corrected.

“Page 8 – power calculations for determining group size should be described.”

Reply: As we consider the study to be a pilot study, formal power calculations are not described. We aimed at including at least the number of participants as in ref. 8 (finding a significant change in endothelial function due to pre-exercise in 8 individuals). As it was a time-consuming and demanding study to participate in, it was a challenge to get a hold of the twenty individuals that were eventually included in the study. In particular it was a challenge to recruit the healthy participants.

Results

“Page 9-11 – as previously stated, all parameters measured should be presented here.”

Reply: We have now corrected this.

3. Discretionary revisions:

Abstract

“Methods – Consider deleting ‘randomized’ here; it gives the impression that subjects were randomly assigned to groups or to exercise condition, rather than receiving all 3 exercise conditions in random order.”

Reply: We have removed randomized in the method section of the abstract and added “in a random order” after presenting the intervention trials.

Discussion

“Page 15, paragraph 2 – in my opinion, the similarity in BMI and WC between groups is a strength of the study rather than a limitation, as it excludes potentially confounding effects of adiposity; consider leaving this out of the discussion of limitations. * minor issue not for publication.”

Reply: This has been corrected and we thank you for pointing it out.

“Quality of written English: Needs some language corrections before being published.”

Reply: The manuscript has now been edited through professional journal editing and we hope the language is more suitable for publishing compared to manuscript 1.
Reviewer 2, Hidetaka Hamasaki:

1. Major Compulsory Revisions:

“1) The authors put the title as if exercise has some effects on postprandial cardiac function in type 2 diabetes. However, as the authors mentioned, pre-exercise did not influence postprandial cardiac function, heart rate, blood pressure, RPP, and biochemical markers. Therefore, the authors should change the title to avoid a misleading and to focus on the effect of fast-food.”

Reply: We have changed the heading to: “Fast food increase postprandial cardiac workload in T2D, which pre-exercise cannot modify: A pilot study.”

“2) According to ref [8] which the authors repeatedly cited in the text, endothelial function in high intensity interval exercise trial and continuous moderate-intensity exercise trial were investigated each other. The present study has also 3 randomised trails (HIIE, MIE and NE). Please describe the study results in each trials and investigate the differences among 3 groups.”

Reply: It is correct that each participant was subjected to each of the three trials. And the effect of trial was indeed investigated by including trial as well as group (T2D or control) and time after the meal, as factors in the linear mixed models for each variable. However, it turned out that the effect of trial was not found to be statistically significant for any of the variables. Thus, the results shown in the Figures are based on models for which the trial factor has been left out, focusing on the remaining factors group and time. This has now been added to results.

“3) The study participants have good glycemic control (HbA1c 6.4%). I think that the participants were diagnosed as having early type 2 diabetes, however, the authors should show medication including oral hypoglycemic agents (e.g metformin), antihypertensive agents (e.g. angiotensin receptor antagonists) and lipid-lowering agents (e.g statins and fibrates) because these drugs may affect cardiac function. “

Reply: See list of medical agents used in the respective groups below the reply to all referees.

“Additionally, the authors should show how they diagnosed type 2 diabetes.“

The participants had all been diagnosed by their respective medical doctors and the T2D duration was set according to the time they were diagnosed. Norwegian medical doctors diagnose T2D according to the standards of the World Health Organization/International Diabetes Association/ American Diabetes Association [1, 2].
“4) The author stated "The diverse findings may be due to different times of measurement..." in the part of Discussion with respect to the increased LV systolic workload after fast-food ingestion in this study. Exercise was performed 16-18 hours before the meal and biochemical measurements were performed 30 minutes, 2 hours and 4 hours after the meal in this study as well as ref [8], but I cannot figure out why the authors make such study protocol. Please tell me the reason, if possible.”

Reply: We decided to repeat the study protocol of ref. 8 as this had been performed previously at our department, where they found a protective effect of acute exercise (16-18 h pre) on the vasculature that was exercise intensity dependent on post-prandial lipemia. In the present study, we wanted to investigate whether we could find modifying effects to cardiac function (especially endocardial function) similar to effects on endothelial function. Timing of exercise is essential and another study on obese women with pre-diabetes and exercise 15 minutes before a meal had no protective effect postprandial TAS and oxidative stress [3]. Future studies should concentrate on the timing, duration and intensity of exercise in relation to the meal.

“5) Why did the authors exclude obese class # and # from study participants?”

Reply: We are sorry to not entirely understand this question, please elaborate so that we in the best way can reply your question. We chose not to include participants which had BMI > 35 to make the matching with non-diabetes controls easier.

“6) The authors measured serum levels of insulin, LDL-cholesterol, HDL-cholesterol and high sensitive c-reactive protein, however, they did not refer to them in the section of Results. The authors should show the results and discuss.”

Reply: This has been added these to the results and discussion.

2. Minor Essential Revisions:

“1) I would suggest that "c-peptide" should be changed to "C-peptide" in page 6, line 2 and 16.”

Reply: This is corrected.

“2) I would suggest to insert comma between "insulin" and "C-peptide" in page 7.”

Reply: This was also addressed by referee 1 and is corrected.

“3) I would suggest that HDL and LDL should not be abbreviated in page 7. “

Reply: This has been corrected

“4) In the section of "Abstract", abbreviations such as e’, E, S7 and RPP are not needed.”

Reply: This has been corrected.

“5) References should be changed to suitable form (Nutrition Journal reference style).”


Reply: We have corrected this by downloading and changing to nutrition journal reference style from:

“Quality of written English: Needs some language corrections before being published”

Reply: The manuscript has been edited and we hope the language is more suitable for publishing now, compared to manuscript 1.

Reviewer 3, Bryan H Hackfort:

1. Major Compulsory Revisions:

“*It would be interesting to see the cardiac response to a normal Norwegian meal. It was stressed that a fast food meal induces greater cardiac workload in Type II diabetics but does the response to a normal meal differ in type II diabetics and normal volunteers.*”

Reply: We hereby refer to our reply to referee 1 in regard to this topic.

“The discussion states: “The lack of exercise-induced improvements in postprandial TAS in the present study may be explained by the lack of postprandial changes in circulating glucose- and triglyceride levels.” P14. However, figures 3A (Glucose) and 3C (Triglycerides) show significant increases in postprandial glucose and triglyceride levels for both T2D and controls. Please elaborate.”

We apologize for not being clear in this point. We mean that the lack of exercise induced change in glucose- and triglyceride levels may be the reason why we did not see any exercise induced change in TAS as was observed in ref. 8. We have tried to correct this point in the manuscript: “The lack of exercise-induced improvements in postprandial TAS in the present study may be explained by the lack of *exercise induced* postprandial changes in circulating glucose- and triglyceride levels.”

“Are there differences in response to gender? You have n = 10, but in the abstract and table 1 you specify only 7 males. The way it is written in the abstract it looks like the age and weight is only for males. It may be interesting to increase the number of females or remove them completely to measure gender difference or remove confounding results based on gender, respectively.”

Reply: We agree with the referee in regard to the limitation of including both genders. We have however not analyzed differences between genders as we only had three women in each group. We apologize for not being clear on this point and have specified also the number of women in the study.
1. **Minor Essential Revisions:**

“The significance labeling on the figures needs to be more evident as to which point it is denoting as significant (on all figures). Text says significance at one time point but often times it looks like it is denoting significance on the wrong time point. “

**Reply:** We have chosen to place the significance labels on the path between two time points for which a significant difference has been found, and use different symbols to indicate what is the earliest of these two time point. We have chosen to keep the labels on the path, although this might not be optimal, but have aligned the symbols for the two groups vertically, hoping that this will increase the readability of the figures.

1. **Discretionary revisions:**

“Do you have any data on drug use that may confound your results such as NSAID use? A heavy exercise session after abstaining from exercise for a couple of days may elicit sore muscles.”

**Reply:** See list below this section. The participants did not report DOMS after the exercise sessions. I personally talked with them after exercising. The participants were instructed not to change or administer new medication than what they used regularly during the intervention period and no one reported to have done otherwise.
Figure 1. Effects of fast-food and exercise on left ventricular diastolic and systolic function
Abbreviations: C, control group; e', peak early diastolic tissue Doppler velocity; E/e', filling pressure; E, peak early filling velocity; HIIE, high intensity interval exercise; IVRT, isovolumic relaxation time; MIE, moderate intensity exercise; NE, no exercise; S', peak systolic tissue Doppler velocity; T2D, type 2 diabetes group. Left panel: Effects of fast food (trials combined). Estimated means and 95% CIs for each group and time for LMMs with time and group interactions. Significant (p<0.01) time differences are indicated by *(from BL1), † (from BL2), ‡ (from food+30min) and § (from food +2h). For E, Global strain rate and S' there is no significant time and group interaction, and the indicated significant time differences refer to the main effect of time for both groups. Mid and right panel: Effects of exercise. Similar estimates from a full model (HIIE and MIE combined).

Figure 2. Effects of fast-food and exercise on resting heart rate and blood pressure.

Abbreviations: BP, blood pressure; C, control group; FMD, flow mediated dilatation; HIIE, high intensity interval exercise; HR, resting heart rate; MIE, moderate intensity exercise; NE, no exercise; RPP, rate pressure product; T2D, type 2 diabetes group. Left panel: Effects of fast food (trials combined). Estimated means and 95% CIs for each group and time point for LMMs with time and group as factors. Significant (p<0.01) time differences are indicated by *(from BL1), † (from BL2), ‡ (from food+30min) and § (from food +2h). For diastolic BP there is no significant time and group interaction, and the indicated significant time differences refer to the main effect of time for both groups. Mid and right panel: Effects of exercise. Similar estimates from a full model (HIIE and MIE combined). For
the rate pressure product, the means and CIs are shown as back-transformed values, computed by direct exponentiation of the means and CIs from the LMM based on log-transformed data.

Figure 3. Effects of fast-food and exercise on blood glucose, C-peptide, triglycerides and total antioxidant status. Abbreviations: C, control group; HIIE, high intensity interval exercise; MIE, moderate intensity exercise; NE, no exercise; TAS, total antioxidant status; T2D, type 2 diabetes group. Left panel: Effects of fast food (trials combined) Estimated means and 95% CIs for each group and time point for LMMs with time and group as factors. Significant (p<0.01) time differences are indicated by *(from BL1), † (from BL2), ‡ (from food+30min) and § (from food +2h). For triglycerides there is no significant time and group interaction, and the indicated significant time differences refer to the main effect of time for both groups. Mid and right panel: Effects of exercise. Similar estimates from a full model (HIIE and MIE combined). Except for TAS, the means and CIs are shown as back-transformed values, computed by direct exponentiation of the means and CIs from the LMMs based on log-transformed data.
List of medical use, participants:

T2D participants using:

*Oral hypoglycemic agents (n=6, n=2 using concomitant oral hypoglycemic agents):*
- Metformin: n=4
- Eucras: n=2
- Glucophag: n=1
- Januvia (Sitagliptin): n=1

*Antihypertensive agents:*
- Angiotensin II receptor-antagonist (n=6, n=1 using concomitant antihypertensive medication sub-class):
  - Aprovel: n=4
  - Atacand plus: n=1
- Angiotensin-converting enzyme inhibitor:
  - Zestoretic: n=1
- Calcium antagonist:
  - Cardizem: n=1

*Lipid lowering agents:*
- Statins:
  - Simvastatin: n=1

*Acetylsalicylic acid:*
- Albyl-E: n=2

Non-diabetic participants using:

*Oral hypoglycemic agents: none*

*Antihypertensive agents (n=1):*
- Diuretica:
  - Centyl: n=1

*Lipid lowering agents (n=1):*
- Statins:
  - Simvastatin: n=1

*Acetylsalicylic acid:*
- Albyl-E: n=1

Reported concomitant antihypertensive medication sub-class:

**T2D- group :**
n=1: Calcium antagonist + angiotensin II-receptor antagonist

**Non-diabetes group:**
n=0
References