# PEER REVIEW HISTORY



## ARTICLE DETAILS

### Title (Provisional)

Impact of exercise training in combination with Dapagliflozin on physical function in adults with type 2 diabetes mellitus: Study protocol for the Dapagliflozin, Exercise Training and physicAl function (DETA) randomised controlled trial

### Authors

Sargeant, Jack A; Ahmad, Ehtasham; James, Emily; Baker, Luke; Bilak, Joanna M; Coull, Nicole A; Gulsin, Gaurav Singh; King, James A; Khunti, Kamlesh; Redman, Emma; Rowlands, Alex; Watson, Emma; Wormleighton, Joanne V; McCann, Gerry P; Yates, Thomas; Davies, Melanie J

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## VERSION 1 - REVIEW

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| **Reviewer** | **1** |
| **Name** | **Cersosimo, Eugenio** |
| **Affiliation** | **The University of Texas Health Science Center at San Antonio, Medicine** |
| **Date** | **08-Mar-2024** |
| **COI** | **NONE** |

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There is growing interest in understanding the "functionality outcome" regarding treatment options utilized in individuals with chronic diseases and this project describes an attempt to address this interest with regards to obesity and type 2 diabetes mellitus.

I believe that the methodology and the patient population chosen for this study, as well the application of several sophisticated techniques employed to detect differences between the groups are all within acceptable scientific rigor.

In my view, however, to ascertain that the results will provide some insight into potential mechanisms and be clinically useful, there are some specific issues that need further clarification:

1. AGE - patients between 40-75 will be recruited but there is no mention of stratification by age in the interpretation of the findings. At least, a continuum should be taken into account when analyzing data obtained in younger versus older patients;

2. I am not entirely clear why the diet-induced weight loss group is not subjected to a similar exercise programming as the dapagliflozin-treated group. An explanation by the investigators for the absence of such control may be pertinent;

3. I did not find a clear description of the baseline cardiovascular status required of the patients at entry. Is evidence of heart failure with normal or low ejection fraction an exclusion criteria? Also, although the combination of weight loss and cardiovascular beneficial effects of dapagliflozin are well-known clinically, it is not clear to me how the investigators expect to demonstrate to what extent any improvement in cardiac function contributes to better physical performance.

4. The shift in whole-body substrate oxidation from predominant glucose to fat with weight loss during SGLT-2i-induced glycosuria is well described in the literature. This is unique and very different from those individuals who lose weight simply by adhering to hypocaloric intake [very low sugar diets may be an exception]. The investigators must anticipate this discrepant finding and include it in their discussion, should the hypothesis of superior physical benefits with dapagliflozin therapy be confirmed.

5. In the sub-group of patients who will undergo skeletal muscle biopsy, to uncover differences in metabolic and inflammatory molecular signaling pathways, it might be necessary to utilize some sort of "stimulus", i.e., insulin infusion "in vivo" or high-fat exposure during the tissue analysis.

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| **Reviewer** | **2** |
| **Name** | **Xu, Jun-Wei** |
| **Affiliation** | **Nanjing Medical University Affiliated Brain Hospital, Cardiology** |
| **Date** | **08-Apr-2024** |
| **COI** | **no competing interest** |

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I recommend to accept the paper for publication.

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| **Reviewer** | **3** |
| **Name** | **Quan, Helong** |
| **Affiliation** | **Northeast Normal University, School of Physical Education** |
| **Date** | **10-Apr-2024** |
| **COI** | **Helong Quan declares that there are no conflicts of interest regarding this manuscript.** |

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Thank you for sharing the study protocol for the Dapagliflozin, Exercise Training, and physical function (DETA) trial. Your research aims to address an important gap in understanding the effects of dapagliflozin and exercise training on physical function in adults with type 2 diabetes mellitus (T2DM), which is a valuable contribution to the field.

Overall, the study protocol is well-structured and provides a clear overview of the research design, objectives, and methodology. However, I have a few suggestions for further improvement and clarification:

Clarity on Exercise Training Protocol: It would be beneficial to provide more detailed information about the structured exercise training protocol. Describing the specific exercises, intensity levels, duration, and frequency of training sessions would enhance clarity and reproducibility.

Statistical Analysis Plan: While you've outlined the primary and secondary outcomes, it would be helpful to include details about the planned statistical analyses. Describing the statistical methods, including how you'll handle missing data, adjust for covariates, and address multiple comparisons, would strengthen the methodological rigor of the study.

Consideration of Long-Term Outcomes: Given the chronic nature of T2DM, consider extending the follow-up period beyond 24 weeks to assess long-term outcomes and sustainability of intervention effects. This could provide valuable insights into the durability of improvements in physical function over time.

Generalizability: Discuss the potential limitations in generalizability of the study findings, particularly if the trial is conducted at a single center or with a specific demographic group. Addressing the external validity of the findings would enhance the relevance and applicability of the research.

Conflict of Interest Disclosure: Ensure that all potential conflicts of interest are appropriately disclosed, including financial relationships with pharmaceutical companies or other relevant entities. Transparency in disclosing conflicts of interest is essential for maintaining trust and credibility in the research.

Here's a consideration:

The choice between "physical exercise" and "exercise training" depends on the study's context and objectives. "Exercise training" refers to structured, supervised regimens aimed at improving specific fitness aspects, often prescribed by professionals and used in research for controlled interventions. On the other hand, "physical exercise" encompasses all bodily movements, including daily activities, with varying levels of structure and intensity. Considerations include specificity, flexibility, clarity, and alignment with research objectives. In the DETA trial, if the intervention is structured, "exercise training" is suitable, while "physical exercise" is better if it includes diverse activities. The chosen term should reflect the study's goals, intervention, and clarity of communication.

Overall, your study protocol presents a promising research endeavor with clear objectives and methodology. Addressing these suggestions could further enhance the clarity, rigour, and impact of your research.

Thank you once again for sharing your work, and I look forward to seeing the results of the DETA trial.

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## VERSION 1 - AUTHOR RESPONSE

**Reviewer: 1**

Dr. Eugenio Cersosimo, The University of Texas Health Science Center at San Antonio

Comments to the Author:

There is growing interest in understanding the "functionality outcome" regarding treatment options utilized in individuals with chronic diseases and this project describes an attempt to address this interest with regards to obesity and type 2 diabetes mellitus.

I believe that the methodology and the patient population chosen for this study, as well the application of several sophisticated techniques employed to detect differences between the groups are all within acceptable scientific rigor.

We thank the reviewer for their positive review of our manuscript, and for recognising the importance and rigorous nature of our work.

In my view, however, to ascertain that the results will provide some insight into potential mechanisms and be clinically useful, there are some specific issues that need further clarification:

1. AGE - patients between 40-75 will be recruited but there is no mention of stratification by age in the interpretation of the findings. At least, a continuum should be taken into account when analyzing data obtained in younger versus older patients;

We thank the reviewer for highlighting this omission. We have newly added age to the list of covariates used in the analysis (line 442). We will also stratify our analysis by age and sex, see lines 452-454.

*"...generalised linear modelling adjusted for baseline mPPT score, variables used in stratification of randomisation and age."*

*"The primary outcome results will be stratified by age (threshold at 65 years) and sex. Generalised linear models will include interaction terms for age and sex by group to determine the impact of these variables on the intervention effect."*

2. I am not entirely clear why the diet-induced weight loss group is not subjected to a similar exercise programming as the dapagliflozin-treated group. An explanation by the investigators for the absence of such control may be pertinent;

It is well-established that structured exercise training can preserve lean mass and physical function during weight loss induced by energy restriction (Eglseer et al., 2023; Lopez et al., 2022; Miller et al., 2013; Sardeli et al., 2018; Villareal et al., 2011; Villareal et al., 2017). As the addition of structured exercise training to diet-induced weight loss has been investigated extensively, the study team did not consider this hypothesis required further testing with the inclusion of a fourth 'diet plus exercise' arm. This study aims to further current knowledge by investigating whether exercise-induced preservation of physical function and lean mass (previously seen during weight loss through energy restriction) can be replicated when weight loss occurs as a result of pharmacotherapy.

A summary of this explanation has been added to the manuscript (line 520-523).

*"As it has been well-established that structured exercise training can improve physical function and help preserve lean mass during weight loss induced by energy restriction [10, 28, 60-63], a fourth 'diet plus exercise arm' and supporting hypothesis was not included in this trial."*

3. I did not find a clear description of the baseline cardiovascular status required of the patients at entry. Is evidence of heart failure with normal or low ejection fraction an exclusion criteria? Also, although the combination of weight loss and cardiovascular beneficial effects of dapagliflozin are well-known clinically, it is not clear to me how the investigators expect to demonstrate to what extent any improvement in cardiac function contributes to better physical performance.

An established diagnosis of heart failure, as reported during the study screening process, is an exclusion criterion (listed in Table 1). Participants will not be excluded based on new evidence of heart failure identified from trial data, unless a contraindication to exercise is subsequently established.

Exploratory analyses will be conducted to determine the association between the primary outcome and key secondary outcomes, including changes in reverse cardiac remodelling. A sentence to clarify this has now been added to the statistical analysis section (line 457-458).

*"Exploratory analyses will be conducted to determine the association between the primary outcome and key secondary outcomes."*

4. The shift in whole-body substrate oxidation from predominant glucose to fat with weight loss during SGLT-2i-induced glycosuria is well described in the literature. This is unique and very different from those individuals who lose weight simply by adhering to hypocaloric intake [very low sugar diets may be an exception]. The investigators must anticipate this discrepant finding and include it in their discussion, should the hypothesis of superior physical benefits with dapagliflozin therapy be confirmed.

We thank the reviewer for highlighting this important consideration, and have included it in the discussion as suggested (lines 507-510).

*"However, should changes to body composition and physical function be different in the intervention versus dietary control groups, these findings should be considered within the context of an anticipated shift in substrate utilisation from predominant glucose to lipid in those receiving SGLT2i therapy [59]."*

5. In the sub-group of patients who will undergo skeletal muscle biopsy, to uncover differences in metabolic and inflammatory molecular signaling pathways, it might be necessary to utilize some sort of "stimulus", i.e., insulin infusion "in vivo" or high-fat exposure during the tissue analysis.

Whilst we appreciate that this suggestion would be an interesting addition to the sub-study investigation, it does not align with our intended research objectives. We that appreciate the use of the term 'metabolic signalling pathways' in the table of outcomes (Table 2) might be misleading. We have therefore changed this to ‘anabolic/catabolic signalling pathways’, which more accurately reflects the research questions we look to address.

**Reviewer: 2**

Dr. Jun-Wei Xu, Nanjing Medical University Affiliated Brain Hospital, Nanjing Chest Hospital

Comments to the Author:

I recommend to accept the paper for publication.

We thank the reviewer for their positive evaluation of our manuscript.

**Reviewer: 3**

Dr. Helong Quan, Northeast Normal University

Comments to the Author:

Thank you for sharing the study protocol for the Dapagliflozin, Exercise Training, and physical function (DETA) trial. Your research aims to address an important gap in understanding the effects of dapagliflozin and exercise training on physical function in adults with type 2 diabetes mellitus (T2DM), which is a valuable contribution to the field.

Overall, the study protocol is well-structured and provides a clear overview of the research design, objectives, and methodology. However, I have a few suggestions for further improvement and clarification:

We thank the reviewer for their comments and valuable suggestions.

Clarity on Exercise Training Protocol: It would be beneficial to provide more detailed information about the structured exercise training protocol. Describing the specific exercises, intensity levels, duration, and frequency of training sessions would enhance clarity and reproducibility.

Thank you for this comment. We agree with the reviewer that sufficient detail to replicate the intervention is important. For details of the exercise intervention, please see lines 397 to 412 of the manuscript. Here we have discussed specific exercises (aerobic exercise is performed using a treadmill, cycle ergometer, cross-trainer or static rower; resistance exercise includes gym-based machines, including leg press, leg extension, and chest press; body weight and banded exercises), intensity levels (moderate-intensity [HRmax ~70-80%] aerobic exercise, and resistance exercise at 10-15 repetitions per set to ‘near-failure’ at ~70% of predicted one repetition maximum), duration and frequency (three times per week; ~30 minutes each of aerobic and resistance exercise per session). We have also included details on exercise supervision and location (lines 406 to 412).

*“The DAPA+EX intervention is as described for DAPA, plus progressive, combined exercise (three times per week; ~30 minutes each of aerobic and resistance exercise per session). Moderate-intensity*

*($HR_{max}$ ~70-80%) aerobic exercise is performed using a treadmill, cycle ergometer, cross-trainer or static rower depending on participant preference. Resistance exercises are individualised. One session per week prioritises resistance machines (e.g., leg press, leg extension, chest press) to increase strength and mass of the major muscle groups ("resistance-strength"), for 10-15 repetitions per set to 'near-failure' at ~70% of predicted one repetition maximum. Two sessions per week involve body weight and banded exercises based on functional movements, balance and flexibility ("resistance-function").*

*Initially (Weeks 1 to 12), a minimum of two sessions per week are supervised at the LDC. One session may be unsupervised in a free-living environment; exercise equipment and instructions will be provided. Thereafter (Week 13 onwards), a minimum of one session per week should be supervised, and up to two sessions weekly unsupervised. To monitor adherence when unsupervised, participants will keep an exercise log and wear a heart rate monitor if willing (Polar or equivalent)."*

Statistical Analysis Plan: While you've outlined the primary and secondary outcomes, it would be helpful to include details about the planned statistical analyses. Describing the statistical methods, including how you'll handle missing data, adjust for covariates, and address multiple comparisons, would strengthen the methodological rigor of the study.

We agree with the reviewer that the sufficient description of the statistical analyses is important. For the above requested details, please see the sections detailed below.

Lines 459-465 (handling of missing data, edited to make this clearer):

*"The primary and secondary outcome will be analysed using a complete case approach. Two sensitivity analyses will then be applied for the primary outcome only: 1) full intention-to-treat analysis, with missing data imputed using multiple imputation, and 2) per-protocol analysis, restricting inclusion to those who have adhered to at least 75% of prescribed exercise sessions, where there is no evidence that under 75% of prescribed medication has been taken, and those who achieve at least 3% weight loss at 24 weeks, for exercise, dapagliflozin and dietary interventions, respectively.*

Lines 440-443 (adjustment for covariates):

*"The primary outcome (mPPT at 24 weeks) will be assessed by comparing 1) DAPA+EX and DIET-CON and 2) DAPA and DIET-CON, using generalised linear modelling adjusted for baseline mPPT score, variables used in stratification of randomisation and age."*

Lines 444-445 (methods to account for multiple comparisons):

*"A p-value <0.025 will be considered significant to account for multiple testing."*

We have also covered data distribution and transformation (lines 443-444) and planned statistical models (444-451):

*"Data distribution will be checked for normality and appropriate distributions, and transformed to achieve the best model fit".*

*"The primary outcome (mPPT at 24 weeks) will be assessed by comparing 1) DAPA+EX and DIET-CON and 2) DAPA and DIET-CON, using generalised linear modelling"*

*"To assess the treatment response over time, we will undertake a generalised estimating equation model with an exchangeable correlation matrix to account for repeated measures (12 and 24 weeks)"*

We hope the reviewer agrees that the included details meet the required standard of methodological rigour.

Consideration of Long-Term Outcomes: Given the chronic nature of T2DM, consider extending the follow-up period beyond 24 weeks to assess long-term outcomes and sustainability of intervention effects. This could provide valuable insights into the durability of improvements in physical function over time.

We agree that longer term follow-up would produce interesting and valuable data. However, this was not the focus of our study as an efficacy study. Furthermore, follow-up beyond 24 weeks unfortunately wasn't possible within the funding envelope received for this trial. We are keen to explore opportunities for longer-term follow-up of this cohort, if new funding to facilitate this becomes available.

Generalizability: Discuss the potential limitations in generalizability of the study findings, particularly if the trial is conducted at a single center or with a specific demographic group. Addressing the external validity of the findings would enhance the relevance and applicability of the research.

We thank the reviewer for this valuable suggestion, and have newly added a strengths and limitations section to the manuscript (lines 517-529). Here we cover the potential limited generalisability of our findings, given the inclusion of only high-risk older adults with functional limitations. Whilst we agree that conducting the trial at a single centre is a potential limitation, Leicester, UK is ethnically, culturally and socioeconomical diverse. As such, we are confident that our participant cohort will be representative of the wider population.

*"To our knowledge, this is the first dedicated RCT investigating the impact of dapagliflozin with and without structured exercise training on physical function as a primary outcome. The design of the study is robust and conducted by an expert multi-disciplinary research team. As it has been well-established that structured exercise training can improve physical function and help preserve lean mass during weight loss induced by energy restriction [10, 28, 60-63], a fourth 'diet plus exercise arm' and supporting hypothesis was not included in this trial. The study includes a high-risk cohort of older adults with frailty or functional limitations, which may limit the generalisability of the findings to a wider population of people with T2DM. Finally, participants are recruited from Leicester, Leicestershire and Rutland, UK. Although a single-centre study, Leicester and the surrounding areas are ethnically, culturally and socioeconomically diverse representing a microcosm of modern Britain, increasing the relevance of our findings to the wider population".*

Conflict of Interest Disclosure: Ensure that all potential conflicts of interest are appropriately disclosed, including financial relationships with pharmaceutical companies or other relevant entities. Transparency in disclosing conflicts of interest is essential for maintaining trust and credibility in the research.

All competing interests are stated in full in lines 549-561 of the manuscript, in accordance with BMJ Open publishing requirements.

*"JAS has received funding from Astra Zeneca UK in relation to an investigator-initiated trial. EA has received fellowship funding from Astra Zeneca. KK has acted as a consultant, speaker or received grants for investigator-initiated studies for Astra Zeneca, Bayer, Novartis, Novo Nordisk, Sanofi-Aventis, Lilly and Merck Sharp & Dohme, Boehringer Ingelheim, Oramed Pharmaceuticals, Roche and Applied Therapeutics. GPM has received grant funding from NIHR, BHF and research support from*

*Circle CVi, Resonance Health. TY was a named investigator on the funding application for this trial and has received research funding from Abbott. MJD has acted as consultant, advisory board member and speaker for Boehringer Ingelheim, Eli Lilly, Novo Nordisk and Sanofi, an advisory board member Lexicon, Pfizer, ShouTi Pharma Inc, Astra Zeneca, Zealand Pharma and Medtronic and as a speaker for Astra Zeneca, Napp Pharmaceuticals, Novartis and Amgen. She has received grants from Astra Zeneca, Novo Nordisk, Boehringer Ingelheim, Janssen and Sanofi-Aventis and Eli Lilly. LB, JMB, NAC, GSG, EJ, JK, ER, AVR, EW, and JW have no competing interests to declare."*

Here's a consideration:

The choice between "physical exercise" and "exercise training" depends on the study's context and objectives. "Exercise training" refers to structured, supervised regimens aimed at improving specific fitness aspects, often prescribed by professionals and used in research for controlled interventions. On the other hand, "physical exercise" encompasses all bodily movements, including daily activities, with varying levels of structure and intensity. Considerations include specificity, flexibility, clarity, and alignment with research objectives. In the DETA trial, if the intervention is structured, "exercise training" is suitable, while "physical exercise" is better if it includes diverse activities. The chosen term should reflect the study's goals, intervention, and clarity of communication.

We agree with this important point. The exercise intervention is structured and supervised, as detailed in lines 397-412. Specific fitness goals are referred to in the methods section ("resistance-strength" and "resistance-function"). Accordingly, we have used the phrase "exercise training" throughout the protocol.

Overall, your study protocol presents a promising research endeavor with clear objectives and methodology. Addressing these suggestions could further enhance the clarity, rigour, and impact of your research.

Thank you once again for sharing your work, and I look forward to seeing the results of the DETA trial.

We thank the reviewers for their helpful suggestions, which we agree improve the clarity of our paper.