PEER REVIEW HISTORY

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ARTICLE DETAILS

TITLE (PROVISIONAL)	Protocol for a single-centre, parallel-group, randomised, controlled, superiority trial on the effects of time-restricted eating on body weight, behaviour, and metabolism in individuals at high risk of type 2 diabetes - The Restricted Eating Time (RESET) study
AUTHORS	Quist, Jonas; Christensen, Marie; Clemmensen, Kim; Pedersen, Hanne; Bjerre, Natasja; Størling, Joachim; Blond, Martin; Wewer Albrechtsen, Nicolai; Holst, Jens; Torekov, Signe; Vistisen, Dorte; Jørgensen, Marit; Panda, Satchidananda; Brock, Christina; Finlayson, G; Færch, Kristine

VERSION 1 – REVIEW

REVIEWER	Grant Tinsley Texas Tech University, United States
REVIEW RETURNED	18-Feb-2020

GENERAL COMMENTS	This this study protocol is very clear, detailed, and comprehensive. The proposed study will make a meaningful contribution to the body of knowledge regarding physiological and behavioral effects of time-restricted eating. The authors are commended for their multidisciplinary approach, which will maximize the benefits obtained from this data collection. The lack of detailed comments from this reviewer reflect the very thorough presentation of the study protocol, and the authors are commended for their work. One specific item that was noticed was: Line 353: It may be helpful if a reference to the Danish dietary recommendations could be added so that readers who are unfamiliar with these recommendations can find more information.

REVIEWER	Stefan Kabisch German Institute of Human Nutrition Potsdam-Rehbrücke, Germany
REVIEW RETURNED	19-Mar-2020

GENERAL COMMENTS	The authors present the study protocol of an RCT investigating anthropometric, metabolic and behavioral effects of time-restricted eating in subjects at high risk for imminent type 2 diabetes. Rationale, study design, methods, statistics and work plan are presented transparently and congruently to the clinicaltrials.gov registration. Approval by an ethics commission is present. The overall impression of the study is excellent, covering a broad range of parameters in a reasonable intervention time frame and in a cohort, that actually requires this kind of treatment.

	Some further points need to be addressed in the limitations section and should be evaluated by a statistician reviewer: The inclusion criteria provide a large risk for heterogeneity in (at least) metabolic results. 1) Not all patients have prediabetes. 2) Given the age range of 30-70, elderly subjects above 65 years with a BMI below 30 or 28 kg/m² could be considered normalweight. These persons should not undergo weight-reducing therapies, even though the intended weight loss is rather small. 3) Overt type 2 diabetes is outruled solely on basis of HbA1c levels. However, within the range of prediabetes (5,7-6,4 %), HbA1c is not a very distinctive marker to differentiate prediabetes and overt diabetes. An oGTT is required to precisely define the individual metabolic state, but doesn't seem to have been conducted. 4) Also, within prediabetes, several subtypes are existing. These subtypes differ in their metabolic background and responsiveness to lifestyle treatments. Also, subjects are free to choose their TRE time window, ranging from breakfast skipping to dinner skipping. Given the well-known and clearly cited circadian rhythms in metabolic processes, these differences may vastly influence (possibly blur) the results. It is unclear, why these aspects of heterogeneity in cohort structure and intervention were intended in the first place. This should be clarified. According to clinicaltrials.gov, subject recruitment has almost been finished. It seems impossible to change the main study design right now. A possible way to deal with heterogeneity could be a pre-defined stratified analysis, based on suitable subgroups (early TRE vs. late TRE; obese vs. normalweight-prediabetes, normoglycemic vs. prediabetes). Maybe, preliminary data already allow to decide for a reasonable stratification. This however, would require a larger sample size and prolonged recruitment.

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1
Reviewer Name: Grant Tinsley
Institution and Country: Texas Tech University, United States Please state any competing interests or state ‘None declared’: None declared

Please leave your comments for the authors below This this study protocol is very clear, detailed, and comprehensive. The proposed study will make a meaningful contribution to the body of knowledge regarding physiological and behavioral effects of time-restricted eating. The authors are commended for their multidisciplinary approach, which will maximize the benefits obtained from this data collection. The lack of detailed comments from this reviewer reflect the very thorough presentation of the study protocol, and the authors are commended for their work.

One specific item that was noticed was:
Line 353: It may be helpful if a reference to the Danish dietary recommendations could be added so that readers who are unfamiliar with these recommendations can find more information.

We appreciate the kind feedback - thank you very much. Good point, we have added a reference to the Danish dietary recommendations.

Reviewer: 2
Reviewer Name: Stefan Kabisch
Institution and Country: German Institute of Human Nutrition Potsdam-Rehbrücke, Germany Please state any competing interests or state 'None declared': none declared

Please leave your comments for the authors below The authors present the study protocol of an RCT investigating anthropometric, metabolic and behavioral effects of time-restricted eating in subjects at high risk for imminent type 2 diabetes.

Rationale, study design, methods, statistics and work plan are presented transparently and congruently to the clinicaltrials.gov registration. Approval by an ethics commission is present.

The overall impression of the study is excellent, covering a broad range of parameters in a reasonable intervention time frame and in a cohort, that actually requires this kind of treatment.

We would like to thank the reviewer for the kind words and the relevant comments.

Some further points need to be addressed in the limitations section and should be evaluated by a statistician reviewer:

The inclusion criteria provide a large risk for heterogeneity in (at least) metabolic results.
1) Not all patients have prediabetes.

Our aim is to recruit participants at a high risk of type 2 diabetes. Overweight and glycaemia are two partly independent risk factors for type 2 diabetes. Moderate overweight without any indication of dysglycaemia is only associated with a very modest risk of diabetes (1) *and we therefore included prediabetes as a inclusion criteria for individuals with overweight (BMI 25-30 kg/m^2) in order to ensure that participants are at a risk that is substantial enough to warrant a targeted intervention. Prediabetes is only present in some of the individuals with obesity (BMI ≥30 kg/m^2), but we also include individuals with obesity without concomitant prediabetes since these individuals are considered at high risk of type 2 diabetes, and weight loss is recommended in this population. As you rightly point out, the broad inclusion criteria do increase the risk for heterogeneity in the effects for some of the outcomes evaluated. However, our primary aim is to investigate whether the intervention can reduce bodyweight in individuals at risk for type 2 diabetes and other multifactorial metabolic diseases, and we do not expect the effect on the primary outcome (change in body weight) to be modified by glycaemic status. Other outcomes such as measures of glycaemia, lipidemia and other metabolic outcomes might be affected, but these are only included as descriptive outcomes. We have added this to the limitations of the study (Page 3, L. 77-79)*

2) Given the age range of 30-70, elderly subjects above 65 years with a BMI below 30 or 28 kg/m² could be considered normalweight. These persons should not undergo weight-reducing therapies, even though the intended weight loss is rather small.

We are well aware of the research indicating that a higher BMI limit for overweight might be indicated for people older than 65 years of age, however, our inclusion criteria are compliant with the guidelines issued by the Danish health authorities in which a BMI ≥25 is considered overweight also in elderly people without known disease (2)*.*

3) Overt type 2 diabetes is outruled solely on basis of HbA1c levels. However, within the range of prediabetes (5,7-6,4 %), HbA1c is not a very distinctive marker to differentiate prediabetes and overt diabetes. An OGTT is required to precisely define the individual metabolic state, but doesn't seem to have been conducted.

This is a good point and we somewhat agree with the reviewer. HbA1c has (as it is also the case for other measures of glycaemia) several shortcomings. One important shortcoming of HbA1c is the interindividual variation in glycation which makes HbA1c challenging to use as marker of glycaemia on the individual level. This is, however, what is done daily in healthcare systems around

the world and recommended by the health authorities. As a pragmatic solution, we have chosen to use the HbA1c criterium as this seems to perform as well as the fasting plasma glucose and 2-hour glucose concentrations for predicting diabetes (3) *(though it is to a large degree different individuals that are identified using the different methods). Also, HbA1c is now widely used for the diagnosis of type 1 and type 2 diabetes, whereas OGTTs are unfortunately almost exclusively used to diagnose gestational diabetes, limiting the practical implications of performing an OGTT.*

4) Also, within prediabetes, several subtypes are existing. These subtypes differ in their metabolic background and responsiveness to lifestyle treatments.

Again, we agree with the reviewer, but as stated above the primary aim of the trial is to establish efficacy for the primary outcome (change in body weight), not to study if the effect of the intervention differs between prediabetes subtypes. We believe that prediabetes subtypes will not interact with the effect on this outcome. As the different subtypes of prediabetes/intermediary hyperglycaemia to some degree represent individuals with different physiological defects this could affect certain outcomes, most obliviously the fasting plasma glucose concentration and other measures of glucose concentrations, this is a weakness of our trial in relation to these descriptive outcomes. As mentioned above, we have added this to the limitations of the study (Page 3, L. 77-79)

Also, subjects are free to choose their TRE time window, ranging from breakfast skipping to dinner skipping. Given the well-known and clearly cited circadian rhythms in metabolic processes, these differences may vastly influence (possibly blur) the results.

We agree with the reviewer that, at least theoretically, timing of the window might have an impact on the outcomes of interest and may thus add to variability in response. We have discussed these issues thoroughly during the design phase. However, we think that the evidence from previous studies including head-to-head comparisons between early vs. late TRE is currently limited. We expect the effects of TRE per se to be greater than the potential effect of the specific timing of the time window. Participants in the TRE group seleca 10-hour time window between 6am and 8pm meaning that there is limited room for variability with regards to timing of the window. Furthermore, the present study aims to investigate effects of TRE in the everyday life of the participants and the flexibility may affect feasibility and sustainability of the regimen and thereby the potential to implement the intervention in a clinical setting. Furthermore, interindividual variability in chronotype and habitual eating patterns among participants may also influence effects of the regimen as well as the individual preferences and selection of the timing window. These issues will be discussed when reporting the results of the trial.

It is unclear, why these aspects of heterogeneity in cohort structure and intervention were intended in the first place. This should be clarified.

The intend with the study was to address the effect of TRE in individuals at a high risk for type 2 diabetes, without restricting the inclusion criteria to a degree where the characteristics of the included participants were too far removed from the general population at risk. This was done in order to retain as much generalisability as is possible in a somewhat mechanistic efficacy trial. This, as you rightly point out, increases the risk of heterogeneity and formation of subgroups within the dataset. Our hope and belief are that the randomisation will secure an even distribution of individuals from the potential subgroups in the two groups and that the distribution of relevant metabolic outcomes will be reasonably continuous. Another recruitment strategy could have been to base inclusion on the estimated 10-year risk of diabetes, or the like, which would likely have resulted in a more even distribution of subgroups in the data. These issues are of course something that we expect to discuss in the final paper.

According to clinicaltrials.gov, subject recruitment has almost been finished. It seems impossible to change the main study design right now. A possible way to deal with heterogeneity could be a pre-defined stratified analysis, based on suitable subgroups (early TRE vs. late TRE; obese vs. normalweight-prediabetes, normoglycemic vs. prediabetes). Maybe, preliminary data already allow

to decide for a reasonable stratification. This however, would require a larger sample size and prolonged recruitment.

It is correct that recruitment is well underway and due to a number of practical restraints (funding, staff, lab facilities) we do not have the possibility to increase the size of the trial. As stated above we expect the effect of TRE alone to supersede the impact of whether the TRE is early or late and we would therefore only expect small differences between early and late TRE, meaning that the trial is unfortunately grossly underpowered to perform such an analysis. It is though a very relevant question to investigate in larger scale trials. As also stated above we do not expect the glycaemic status to have a substantial impact on the effects on body weight.

VERSION 2 – REVIEW

REVIEWER	Stefan Kabisch German Institute of Human Nutrition Potsdam-Rehbrücke, Nuthetal, Germany
REVIEW RETURNED	08-May-2020

GENERAL COMMENTS	Thanks a lot for this very detailed, thorough and entirely plausible reply in response to my recent review. I consider all points more than sufficiently addressed and recommend to accept the publication. I'm very much looking forward to the results of your study.