Author's response to reviews

Title: Screening for type 2 diabetes in a high-risk population: study design and feasibility results of a population-based randomized controlled trial

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Author's response to reviews: see over
Concerning Submission of revised manuscript MS: 6809928116285494

Dear Editor,

We gratefully acknowledge the opportunity given by BMC Public Health for considering a revised manuscript of our article "Screening for type 2 diabetes in a high-risk population: study design and feasibility of a population-based randomized controlled trial".

The comments given by the reviewers were evaluated and the necessary revisions made in the manuscript along these comments. The point-by-point description of the changes made is enclosed; a copy of the revised manuscript is uploaded.

Looking forward to hearing a positive reply from you soon.

Sincerely yours,

on behalf of all authors,

Suzie J. Otto, Ph.D.

Encl.
Point-by-point description of changes made according to the reviewers’ comments

REVIEWER: Sheena McHugh

- Minor Essential Revisions (The author can be trusted to make these. For example, missing labels on figures, the wrong use of a term, spelling mistakes.)

Abstract: How were the original 16,135 respondents reduced to 10,609? Were they eligible based on self-reported waist-circumference? If so then I would suggest outlining the eligibility criteria before the final number randomised.

REPLY: The reduction is due to the number of people consenting to participate. As suggested by the reviewer the eligibility criteria is moved before the final number randomized.

‘Eligible participants had a self-reported waist circumference of ≥80 cm for women and ≥94 cm for men, and no known pre-existing diabetes. Of the respondents (n = 20,578; response rate 26%), 16,135 were abdominally obese. In total, 10,609 individuals gave written informed consent for participation and were randomized into ……………’

Method:
Study Population (p6) - specify at the outset how many people were contacted.

REPLY: This is mentioned on p.10, first sentence of the last paragraph.

P6- Typo- An invitation letter together with the study material, comprising of an information brochure...

REPLY: It has been changed as suggested by the reviewer (‘comprising > comprising of’).

The language has previously been edited by the Edanz Group to improve the quality of written English and they did not make a remark on this. I think it is rather consisting of than comprising of.

P8- typo-1st sentence of outcome measures section.

REPLY: The change has been made as suggested (‘is > was’).

Discussion
P14-Insert (an) - “However an RCT is required…”

P14- Suggest the following change:
“Given the percentage of newly diagnosed diabetes detected by waist circumference, a cut-off value of…”

P14- Missing reference for Korhonen within the text.

REPLY: Changes have been made as suggested by the reviewer and the reference for Korhonen is inserted in the text.

P15- Give % of people screening in the Hoorn study, for consistency with the ADDITION study.

REPLY: The percentage of people screened is now presented for the Hoorn study (‘Of the 7736, 2885 (37.3%) had a high-risk profile and underwent a capillary glucose measurement ….’)

P16- Remove reference to Figure 2 in discussion section.

REPLY: The reference to the Figure is removed.

- Discretionary Revisions

(p4)- Suggest change to the following sentence
“However, the effectiveness of screening as a means of preventing diabetes has not yet been established”.

(p6)- suggest change to the following
“comparing the self-measurements with measurements taken by a trained nurse”
(p7)- suggest change to:
“Participants in the screening arm received an invitation to attend screening...”
REPLY: The sentences were changed as suggested.

Reviewer: Justin Basile Echouffo-Tcheugui

1- Major Compulsory Revisions
b- My main comment is about diabetes-related mortality as an outcome. It is surprising that the authors did not include diabetes-related mortality as an outcome of this study.
Is this a trial of screening for diabetes or of screening for cardiovascular disease? Although cardiovascular events are the main cause of morbidity and mortality as rightly indicated by the authors, there will be diabetes-related deaths not due cardiovascular events (macrovascular complications), and there will be cardiovascular-related deaths not due to diabetes. So, if this study is about screening for diabetes, diabetes-related mortality is more important than cardiovascular-related mortality, thus it should also be part of the outcomes, in addition to all-cause mortality. The target condition is diabetes not cardiovascular conditions. Disease-specific mortality is a commonly accepted and key outcome in trials of screening. The authors might want to consult the literature on planning screening trials, especially that from the field of cancer (from which originated the vast majority of screening trials) to have a better idea on why it is important to assess disease-specific mortality. Here are a few examples of resources:
Screening trials are even more difficult than we thought they were. Juffs HG, Tannock IF. J Natl Cancer Inst. 2002 Feb 6;94(3):156-7.
C- The power of the study to detect a difference in diabetes-related mortality should also be indicated the section on the sample size calculation.
REPLY: The reviewer is correct that in cancer screening the key outcome is disease-specific mortality. We will certainly include diabetes-related mortality other than diabetes-related CVD as outcome. As we mentioned in the introduction (background) section we wanted to ascertain whether early detection and treatment of type 2 diabetes results in a reduction and/or prevention of related morbidity and mortality compared with not offering screening. We have focused on the diabetes-related CVD morbidity and mortality, the macrovascular complications are by far the most important contributor to premature death among patients with diabetes.
The reviewer is correct that also diabetes and its other non-CVD causes of mortality should also be included as key outcome (keeping in mind that diabetes itself is often underreported on death certificates).
We will include these in the secondary analysis, as now mentioned on p8/9. As we primarily focus on the diabetes-related CVD morbidity and mortality, inclusion of the non-CVD events in the secondary analysis will not jeopardize the number needed to show a difference between screening and control arm for the primary outcome.