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
To Dr. Leila Azadbakht  
Associate Editor  
c/o Mr. Victorino Silvestre  
BMC Public Health

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. Each comment has been answered in detail and necessary revisions were made in the manuscript along these comments. The point-by-point response to each reviewer is enclosed and a copy of the revised manuscript is uploaded.

The language has been edited by the Edanz Group to improve the quality of written English, as recommended by the Editor.

We feel that with the revisions our manuscript has now become acceptable for publication in BMC Public Health.

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 response and changes made according to the editor’s and reviewers’ comments

EDITORIAL REQUIREMENT

- The English language in the manuscript has been edited by the Edanz Group as recommended by the Editor.
- Merged cells were deleted from the tables.
- The figure number in the figure files were also deleted.

REVIEWER: Sheena McHugh

Major Compulsory Revisions (which the author must respond to before a decision on publication can be reached)

- Abstract: I don’t think it is clear from the abstract that this is targeted screening based on ‘at risk’ individuals, at risk being defined in terms of waist circumference. Screening in certain circumstances (e.g. presence of risk factors) is advocated however the opening sentence of the abstract gives the impression that this is screening of the general population.
  
  **REPLY:** To avoid the impression that this RCT is of screening of the general population, the opening sentence of the abstract has been deleted and this paragraph re-written.

- Background: suggest rearranging the flow of the argument. 2nd paragraph should deal with screening for diabetes (Wilson & Jungner, effectiveness hasn’t been proven etc), then go on to discuss waist circumference as a screening tool and how it has not been evaluated. This will lead on directly to the aim of your study.
  
  **REPLY:** The paragraph is rearranged as suggested.

- Final paragraph- 1st sentence is not clear. Suggest change: ‘The current RCT was set up to assess the performance of waist circumference measurement as a first step screening tool to identify individuals at high-risk of developing diabetes, to examine the effectiveness of screening for diabetes and to ascertain whether early detection and treatment of type 2 diabetes results in a reduction and/or prevention of the related morbidity and mortality compared to not offering screening’.
  
  **REPLY:** The final paragraph is changed as suggested and edited by the Language editor.

- Method: Are the intermediate endpoints the focus of this paper? If so make that explicit and perhaps state that future publications will deal with the primary end points.
  
  **REPLY:** In the paragraph describing the feasibility phase, it is now made clear that this paper focuses on the intermediate endpoints (the performance of waist circumference measurement as a first-step screening tool to identify individuals at high risk of developing diabetes and the yield of this screening).

- Results: (p11-12) specify the % and p values for the differences between attendees and non-attendees.
  
  **REPLY:** As the other reviewer suggested to analyze the determinants of screening attendance with regression analysis, the percentages and p-values are not specified for the two group, but the odds ratios and respective 95% confidence intervals in stead.
  See bottom page 12/top page 13: Screening attendance was significantly related to age at randomization (OR=1.03, 95% CI 1.02-1.04, p<0.001), being married (OR=1.69, 95%CI 1.44-1.97, p<0.001), not-smoking currently (OR=0.47, 95%CI 0.40-0.56, p<0.001) and born in the
Netherlands (OR=1.34, 95% CI 1.05-1.70, p=0.017). In the multivariate analysis, only country of birth was no longer statistically significant.

O Implications: (p12): The aim of the pilot should refer explicitly to examining the feasibility of using the waist circumference measurement as a first-line screening tool.

REPLY: The aim has been changed and now reads (page 14):

The aim of our extensive feasibility assessment was to examine the performance of home-assessed and self-reported waist circumference measurements as first-step screening tools for recruiting high-risk individuals.

O Conclusion: I think it is necessary to state that while self-reported waist circumference was feasible to detect people at risk further work is necessary to increase the use/uptake of this first-line screening tool (low initial response rate). Also the last sentence should be more specific about how the results will inform the screening strategy.

REPLY: The conclusion paragraph has been rewritten to include the suggestions of the reviewer (see page 17):

Conclusions

Self-reported home-assessed waist circumference proved to be a feasible method for detecting persons at high risk of hyperglycemia, but further work is necessary to increase the uptake of this anthropometric measure as a first-step screening tool. Continuation of this large-scale RCT is warranted to establish whether diabetes screening leads to a significant reduction in cardiovascular morbidity and mortality. The results will contribute to the evidence for or against the provision of screening for type 2 diabetes, and to the development of a strategy for the identification and selection of the population at risk.

Minor Essential Revisions (such as missing labels on figures, or the wrong use of a term, which the author can be trusted to correct)

REPLY: The term ‘subjects’ has been changed into individuals or participants throughout manuscript as suggested.

Abstract

• In method section, suggest change to “were approached to participate in screening”. And: ‘obesity is often associated with cardiovascular risk factors’.
• Opening sentence of results section would be better placed in the method section to explain how the final number of 10,609 people took part in randomization.
• Include % in results section of abstract to show extent of differences between attendees and non-attendees.

REPLY: Changes have been made in the Abstract as suggested (see page 2).

Method

• Change to past tense in study population section, intervention
• P9: b) the proportion of high-risk individuals among the respondents and the proportion that consented (past tense) to randomisation.
• Move the explanation of one and two-step approach to section outlining recruitment. After 1st sentence (In 2006 and 2007, 79,142 inhabitants...), state that 2 approaches to consenting participants were piloted and include explanation followed by ‘All potential participants received an invitation letter etc...’

REPLY: Changes have been made in the Methods section as suggested (see page 10).
Results
• Separate section from discussion

REPLY: Results and discussion section are separated. The paragraphs Implication, Limitations and Conclusion make up the Discussion section.

• P11- typo ‘prevalence’;
• P11- In total, 10609 subjects were eligible and randomized as part of the RCT
• P12-The distribution of the detection rates of IFG and diabetes across males and females according to their waist circumference are presented in Figure 3.

REPLY: Changes have been made in the Results section as suggested (see pages 12 and 13).

Implications
• P12
  o 2 full-stops at the end of sentence ‘However an RCT is required to confirm this hypothesis and to assess whether screening is cost effective’.
  o Use of ‘large-scale’ to describe pilot and RCT.
  o Insert word: The feasibility of using abdominal obesity to detect.

REPLY: Changes have been made as suggested (see page 14).

• P13
  o When describing the Dutch Hoorn study, it is advisable not to start sentences with numbers.
  o Was the 26% response rate to the initial invitation to provide waist circumference measurements rather than the response rate to participate in the screening RCT?
  o Clarify that the delayed linguistic development RCT was also a screening study.

REPLY: Changes have been made as suggested and the 26% is indeed the response rate following the initial invitation to provide waist circumference measurements (see page 15).

• P14
  o Sentence starting with 49%, start with ‘only 49%...’ to avoid starting sentence with number.
  o Suggested edit: ‘For this pilot study, the study materials were written in easy-to-understand Dutch () and advertisements were placed...'’
  o Suggested edit: ‘This approach was undertaken to ensure the study information was accessible to people with a low level of educational attainment and also to reach the immigrant population.’ Remove the word ‘also’ from the last sentence in this paragraph.

REPLY: The sentences have been edited as suggested (see page 15).

Discretionary Revisions (which are recommendations for improvement but which the author can choose to ignore)

Method section: Change ‘First Year’ sub-heading to Pilot Phase:

REPLY: The subheading has been change into Feasibility phase

Implications (p13)- ’In the Netherlands, diabetes screening has previously been examined in at least two studies.’

REPLY: The sentence is changed as suggested (see page 15).
Reviewer: Justin Basile Echouffo-Tcheugui

- Major Compulsory Revisions

1- General comments
a. The authors might want to consider writing two different small but clear papers, as the current presentation is very confusing. One on the trial methods, and another on the uptake and yield of screening. Otherwise, if they choose to stick to one paper, they should then make sure that the presentation is done in a manner that allows understanding.
REPLY: We have kept it to one paper and have enhanced the understanding by re-arranging the paragraphs (see Methods section).

2- Methods
a. How were the participants contacted? How were the eligible individual identified? This should be stated early enough in this section to allow the reader to clearly follow.
REPLY: The paragraph ‘Study population’ in the Method section has been rewritten to include the required information on strategy for approaching participants and ascertainment of eligibility (see page 6).

b. No detail is given by the authors on randomization. How was this done? Was it a simple or a stratified randomization, individual or group randomization, one to one or a different type of randomization? Was there any blinding? What steps were taken by the authors to prevent or minimize contamination?
REPLY: The paragraph ‘Randomization’ in the Method section has been rewritten to include the information on the randomization method (see page 7).

Randomization
Eligible consenting respondents were stratified by gender and individually randomized at a 1:1 ratio to the intervention (screening) arm or the control arm using a random number generator.
Participants in the intervention arm received an invitation for screening, which consisted of fasting plasma glucose (FPG) measurement and information about the importance of a healthy lifestyle (Netherlands Nutrition Centre). Those in the control arm only received the healthy lifestyle information.

REPLY: In contrast to clinical trials, blinding to whom receive or do not receive screening is not possible.
REPLY: As we mentioned in the manuscript (page 8), all participants in received the same information, in order to give informed consent before randomization. Therefore, we cannot prevent or minimize that those assigned to the control arm might take opportunistic testing after learning about the simplicity of the screening test.

c. Which biological method was used to measure fasting plasma glucose?
REPLY: FPG concentrations were determined using the hexokinase method. Fasting serum total cholesterol, HDL cholesterol and triglycerides were quantified using an enzymatic colorimetric method. All analyses were performed on the Beckman AU2700 chemical analyzer (Beckman Coulter Nederland BV, Woerden, Netherlands), using kits supplied by Beckman. This is now mentioned on page 7.

d. Regarding the intervention, how were the screen-detected people group treated or managed? Are they being managed according to the national guidelines in the Netherlands? This should be clearly stated.
REPLY: The treatment or management of the screen-detected individuals is not part of the RCT; they are referred to their own GP. Whether the GP follows the guidelines is part of the evaluation process of the RCT.
e. The sample size calculation is unclear. Is the expected rate of cardiovascular derived from the hospital registry for non-fatal events, fatal events or both? The authors talk about a 20% reduction. This is a reduction in what? Non-fatal events? Cardiovascular mortality? A composite outcome? This should be clarified. What is the basis of the estimate of the contamination rate?

REPLY: This paragraph is rewritten to increase the comprehensibility and include the information asked by the reviewer.

Sample size
In the sample size calculations we estimated the minimum number of participants required to identify a statistically significant 20% reduction in non-fatal and fatal cardiovascular events in the screening compared with the control arm. The expected rate of the composite outcome of cardiovascular events in an aging cohort of 40–74 years at entry was estimated at 2% per year, based on 2003 age and gender specific data obtained from the Hospital Admission Registry for non-fatal events and Statistics Netherlands for fatal events.

REPLY: The estimate of the contamination rate is based on the rate of effective PSA testing in the ERSPC Rotterdam section as described in the paper ‘Otto e.a. Int J Cancer 2003, 105(3):394-9’ (reference 25).

f. The presentation about the first year is very confusing; this can be done in a much better way. The source of participants to this study should have been mentioned at the beginning of this methods section, not after having presented everything else. This section should be re-written.

REPLY: As also suggested by the other reviewer, this paragraph has been rewritten (see page 10).

g. Please clearly state what the questionnaire was all about. What information were the authors trying to obtain with the questionnaire?

h. The authors should make it crystal clear to the reader that participants were either directly invited or invited only after having given their consent. This is far from being clear in the current presentation.

REPLY: The information lacking has been added to the ‘Study population’ paragraph.

Study population
Participants were recruited among the inhabitants (males and females aged 40–74 years) of the working area of two Municipal Health Services in the Southwest Region of the Netherlands. Their name and address information was obtained from municipal authority records. An invitation letter together with the study material, comprising an information brochure, a consent form, a tape measure and a questionnaire were sent by mail to the target population. The questionnaire contained questions on demographic features such as marital status and education, self-perceived health, weight and height, lifestyle, symptoms and diabetes related risk factors, family history of diabetes and personal history of selected diseases, including cardiovascular diseases, stroke, and diabetes.

3- Results
a. The authors mention the costs of various screening strategies in the results, but nowhere in the methods section did they talk about costs as an outcome of this study.

REPLY: The reason why the costs are mentioned in the Results section is now clearly stated in the methods section on bottom of page 10:

We aimed to find out which method produced the greatest response from people at high risk, and what the costs of each strategy were. In either approach strategy, those eligible for participation were randomized only if they gave their informed consent.

b. As this seems to be a paper on the uptake and yield of screening, can the authors investigate the determinant of attendance more analytically, using regression analysis for example?
The data is now analyzed with the logistic regression analysis as shown in Table 2 and bottom page 12/top page 13:

Screening attendance was significantly related to age at randomization (OR=1.03, 95% CI 1.02-1.04, p<0.001), being married (OR=1.69, 95% CI 1.44-1.97, p<0.001), not-smoking currently (OR=0.47, 95% CI 0.40-0.56, p<0.001) and born in the Netherlands (OR=1.34, 95% CI 1.05-1.70, p=0.017). In the multivariate analysis, only country of birth was no longer statistically significant.

c. Why merging the results and the discussion sections? These should be separate.

REPLY: As also suggested by the other reviewer, the two sections are separated.

4- Discussion

a. Can the authors clearly justify their approach to screening? There several risk scores developed and validated on the Dutch population that could have achieved better results. Why not using them, especially as these are questionnaire based?

REPLY: The issue raised by the reviewer is now discussed as a limitation in the Discussion section (bottom page 16, top page 17):

In our study, we chose to use waist circumference as the first-step screening tool rather than a questionnaire. We did collect information using the nine questions of the Dutch-validated SRQ, which was used as first screening step in the Hoorn Study [31] and the ADDITION Netherlands study [30], but we did not use this information. Several other risk questionnaires have been developed to identify individuals with increased risk of developing type 2 diabetes, of which the FINDRISC tool was found to be the best available for use in clinical practice [38]. However, this tool has not yet been validated in a Dutch population. Chamnan and colleagues recently calculated that using anthropometric measures (BMI \( \geq 25 \) kg/m2 or waist circumference >94 cm in men and >80 cm in women) showed slightly higher sensitivity and discriminatory ability compared with inviting individuals based on the FINDRISC cut off or the Cambridge risk score [39].

b. The power calculation was adjusted based on the results of the feasibility phase, but the authors do not tell us how?

REPLY: These lines have been deleted from the Discussion section.

- Minor Essential Revisions

1- Abstract

a. In the results section of the abstract, first sentence: which respondents are the authors talking about? Respondents to what?

REPLY: These were respondents to the initial invitation to provide waist circumference measurements. This sentence has been moved to the methods (of the abstract) as suggested by the other reviewer.

b. The authors state that “6% of people had hyperglycemia”. Is this just diabetes or is it any form of hyperglycemia (impaired fasting glycemia included)? This figure does not square with figures included in Table 2

REPLY: This is the total for people with either IFG or diabetes. The figures in Table 2 were shifted (one cell up). They’re now corrected.

c. In the conclusion section, the authors talk about “systematic screening for type 2 diabetes”. What does systematic screening mean? Does is mean universal or targeted or population-based?

REPLY: This means targeted screening; to avoid confusion the sentence now reads:
Continuation of the large-scale RCT is warranted to test the hypothesis that targeted population-based screening for type 2 diabetes leads to a significant reduction in cardiovascular morbidity and mortality.

2- Introduction
a. The authors should not say “Screening for diabetes fulfills many of the Wilson & Junger criteria”. It is diabetes that fulfills the criteria. Furthermore, the authors should clarify what these criteria are used for; many readers will not be familiar with these.

REPLY: The sentence is changed according to the suggestion of the reviewer:

Type 2 diabetes meets many of the criteria for screening which were formulated by Wilson & Jungner [11] to aid the decision regarding whether or not to introduce a population-based screening program.

b. There are much better references for substantiating the fact that the effectiveness of screening has not been established than the ones used by the authors (references 5 to 8). Please see an example of a reference below: Norris SL, Kansagara D, Bougatsos C, Fu R; U.S. Preventive Services Task Force. Screening adults for type 2 diabetes: a review of the evidence for the U.S. Preventive Services Task Force. Ann Intern Med. 2008 Jun 3;148(11):855-68.

REPLY: The following references are added:


3- Methods
a. Is this screening program about diabetes only or also about cardiovascular disease? Is there evidence on the effectiveness of screening for cardiovascular disease using the SCORE risk tools? Can the authors make it clear for the readers what the components of the SCORE model are (i.e. the various risk factors use for calculating the disease probability)?

REPLY: This study is on screening for type 2 diabetes. As dyslipidemia are often present in overweight and obese subjects, and it is clinical practice to measure blood lipids in patients with diabetes, we opted to additionally measure serum lipids (total cholesterol, HDL-cholesterol and triglycerides). As far as we know there are the effectiveness of screening for CVD using the SCORE risk tools has not been established yet.

The components of the SCORE model are now mentioned (see page 8):
The SCORE risk estimates are calculated based on age, blood pressure level, current smoking status and the ratio of total cholesterol to HDL cholesterol.

4- Results
a. Table 2: what was the proportion of people in the screening group with a SCORE score greater or equal to 5%?

REPLY: It is 11.6%; the figures were shifted in previous manuscript.