Reviewer’s report

Title: Metabolic characteristics of individuals at a high risk of type 2 diabetes - a comparative cross-sectional study

Version: 0 Date: 16 Feb 2017

Reviewer: Katia Bloch

Reviewer’s report:

Manuscript Number: BEND-D-16-00219

Full Title: Metabolic characteristics of individuals at a high risk of type 2 diabetes - a comparative cross-sectional study

This is a relevant study for the evaluation of subjects at high risk for diabetes, however, some epidemiological concepts need to be corrected as I point out in the following comments.

In the abstract there are too many abbreviations.

Page 3, L46: insulin sensitivity (MI) is not in the list on page 2, neither does M.

Page 4, L44: ...to today include well documented perturbations is (in?) adipose tissue metabolism

Page 5, L18-19: between a cohort of healthy FDR and a cohort of healthy controls, recruited from the background population.

The participants were being followed in a cohort study?

Methods

What is the study design? A cross-sectional study? A case control study or a cohort study?

If it is a cross-sectional study you don’t have "controls" and you don’t analyse (and have not to describe) measurements done in different moments, as cross-sectional studies estimates prevalences and means in exposed and not exposed individuals measuring exposition and outcomes of interest at the same time.

Page 5

L44-45 and L50-51: Body weight and height, and waist and hip circumferences were measured manually. Blood pressure was measured in a sitting position after a five minutes rest with a mercury sphygmomanometer.
Describe methods used and training strategies of examiners. There were quality control monitoring during the study?

Page 6

L30-31: A total of 273 subjects were recruited, starting in 2003. 200 subjects were FDRs and 73 were control persons with no known family history of T2D.

How long did the recruitment period last?

L35-36: were recruited, through advertisements in local newspapers and public areas throughout the Gothenburg urban area.

Volunteers may be a problem. Did the authors asked the motivation to participate in the study?

Page 8

L15: continuous variables are given as means ± SD, it should be means AND SD. Don´t use ± as it is not a confidence interval, whose limits are computed by adding and subtracting 1.96 standard deviations to/from the mean.

L25-28: We used linear regression to compare IGI, HOMA-β, DI, M, MI and plasma insulin and glucose, as well as insulin and glucose AUC, between controls and FDRs. Adjustment was made for age, sex, BMI, physical exercise and smoking.

The linear relationship of the variables were explored? The exposure were being or not a FDR?

L37-38: I am not sure if you need to use a "1-to-1 matching, using a propensity score" in a cross-sectional study. The authors some times seems to confuse the study design with a case-control study. If there are confunding (there well established criterias) you can adjust for the confounding variables using multivariate models.

Results

It would be interesting to have information on the frequency different kinds of FDRs (mothers, fathers, sons, brothers)

Page 11

L19-22: if these characteristics (sex, age, BMI) were used to match, their distribution don´t need to be compared.

Page 13

L16: The quality of figure 6 is not good.
L15-16: Also, the recruited study groups were taken from the background population, to further make results applicable to the general population.

It is a group of volunteers, not a probabilistic sample, so it can not be said that it is a representative sample. Volunteers can be very different from the general population and this is a limitation of the study that must be pointed out.

L32-33: wee established = well

Page 17

L37-39: As this study has included the recruited groups in their totality, taken from the background population and using minimal exclusion criteria, avoiding bias and confounders would be very difficult.

I don’t agree, as it was said before, and also stated by the authors, volunteers can be different from the general population, being healthier or having reasons (relatives or themselves with health issues) to worry about health, leading to selection bias. Confounding effects can be reduced only with random allocation, in clinical trials, or by controlling in the analysis. The fact of having a not probabilistic sample affects the representativity and generalizability of the study.

L40-44: We consider it important to include broadly ...? from a background population to explore correlations and tendencies of ...?, as an important complement ? to more narrow study designs ? (smaller study populations?), from which causative factors can be determined.

This sentence is confusing. A large general population group does not a guarantee lack of bias, and confounding, representativness and generalizability. Causality can only be inferred from longitudinal studies.

L50: In this cross-sectional study of 200 FDRs of T2D patients and 73 healthy controls, we found that the FDRs display glucose tolerance disturbances when compared to healthy controls,

As this is a cross-sectional study the authors should not call the non-FDRs of controls. Controls is the denomination of non-cases in case-control studies. In cross-sectional studies you can study prevalences or means in exposed (FDRs) and non-exposed (non-FDRs) individuals. Also when it is said that the "controls" are healthy it gives the impression that the FDRs are not

**Are the methods appropriate and well described?**
If not, please specify what is required in your comments to the authors.

No

**Does the work include the necessary controls?**
If not, please specify which controls are required in your comments to the authors.
Unable to assess

**Are the conclusions drawn adequately supported by the data shown?**
If not, please explain in your comments to the authors.

Yes

**Are you able to assess any statistics in the manuscript or would you recommend an additional statistical review?**
If an additional statistical review is recommended, please specify what aspects require further assessment in your comments to the editors.

I recommend additional statistical review

**Quality of written English**
Please indicate the quality of language in the manuscript:

Needs some language corrections before being published

**Declaration of competing interests**
Please complete a declaration of competing interests, considering the following questions:

1. Have you in the past five years received reimbursements, fees, funding, or salary from an organisation that may in any way gain or lose financially from the publication of this manuscript, either now or in the future?

2. Do you hold any stocks or shares in an organisation that may in any way gain or lose financially from the publication of this manuscript, either now or in the future?

3. Do you hold or are you currently applying for any patents relating to the content of the manuscript?

4. Have you received reimbursements, fees, funding, or salary from an organization that holds or has applied for patents relating to the content of the manuscript?

5. Do you have any other financial competing interests?

6. Do you have any non-financial competing interests in relation to this paper?

If you can answer no to all of the above, write 'I declare that I have no competing interests' below. If your reply is yes to any, please give details below.

I declare that I have no competing interests

I agree to the open peer review policy of the journal. I understand that my name will be included on my report to the authors and, if the manuscript is accepted for publication, my named report
including any attachments I upload will be posted on the website along with the authors' responses. I agree for my report to be made available under an Open Access Creative Commons CC-BY license (http://creativecommons.org/licenses/by/4.0/). I understand that any comments which I do not wish to be included in my named report can be included as confidential comments to the editors, which will not be published.

I agree to the open peer review policy of the journal