

Author's response to reviews

Title: Association between lowered endothelial function measured by peripheral arterial tonometry and cardio-metabolic risk factors - a cross-sectional study of Finnish municipal workers at risk of diabetes and cardiovascular disease

Authors:

Jussi Konttinen (jussi.konttinen@ttl.fi)

Harri Lindholm (harri.lindholm@ttl.fi)

Juha Sinisalo (juha.sinisalo@hus.fi)

Eeva Kuosma (eeva.kuosma@ttl.fi)

Janne Halonen (janne.halonen@ttl.fi)

Leila Hopsu (leila.hopsu@ttl.fi)

Jukka Uitti (jukka.uitti@ttl.fi)

Version: 2 Date: 23 August 2013

Author's response to reviews: see over

Point-by-point responses to Reviewer 1

Thank you for the comments and constructive criticism, which have improved the manuscript. Please find our point-by-point responses below. The corrections in the manuscript are highlighted using red font.

Major Revisions:

1. *The modeling that was used for the step-wise models is not clear. Were all the variables entered at once? Many of the variables may be co-linear (for example weight circumference and BMI) and may be more informative to select in advance which to enter as potential covariate. Similarly diabetes, glucose, and hgaic may be colinear and thus falling out of the model.*

Our response: Earlier all the variables were entered at once in the stepwise procedure. We agree with you that it could be better to use selected variables.

We rebuilt the model selecting the variables for the step-wise model in advance. Concerning potentially co-linear variables we selected the best candidate based on our knowledge on the importance the variable as a risk factor. We also considered the reliability of the method used especially for different measurements of overweight. Most of the variables that are now allowed to enter the model were associated with F-RHI in separate models. In addition, we wanted to include age, LDL, blood pressure and family history in the model because they are strong risk factors for CVD or diabetes. Changes in the results were modest: the order in which the variables entered the model was changed and the partial correlations of the variables changed a little, while the variables entered and the model R^2 stayed the same. We corrected the results in Table 4 and the text in Results and the order of variables in the model in Conclusions and the Abstract.

Description of the statistical methods has also been modified in order to make it more detailed than previously.

Minor Revisions:

1. *Would include description that this is a selected population at risk for diabetes in the title and abstract*

Response: Description that this is a population at risk for diabetes and cardiovascular disease is added in the title and abstract, and also in discussion.

3. *Would label table 2 as gender-adjusted association risk factors and PAT response.*

Response: Table 2 presents the dichotomous risk factors and medication among the subjects as percentages. We assume you might have meant table 3, which shows the gender-adjusted models. Table 3 is labeled as suggested.

4. *the figure could be separately labeled for men and women*

Response: Figure 1 is now labeled separately for men and women.

Discretionary Revisions:

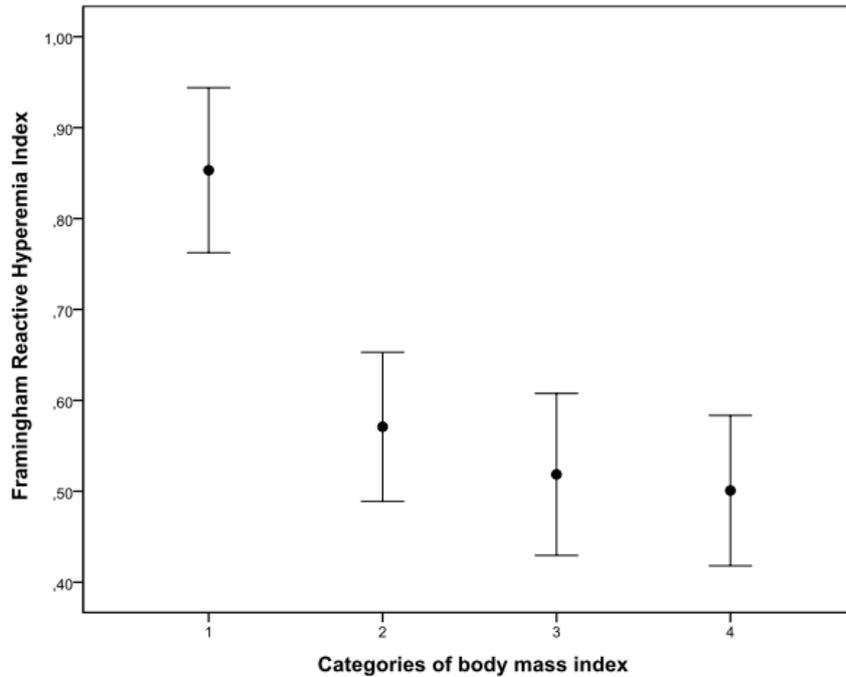
1. *It would be interesting to include baseline PAT amplitude associations*

Response: We are also interested in the associations and meaning of baseline amplitude, but in this manuscript we would like to focus on adding to the knowledge on this index and its associations with risk factors to keep it compact. We are planning a separate paper to present and discuss these associations together with some other more methodological questions and technical aspects.

2. I would like to see PAT response by obesity categories.

Response: Since we felt that it would be logical to publish the figures presenting FRHI in also categories of other crucial variables along with some statistical results about the differences between means we decided to leave this outside this manuscript to keep it compact, even though it would be interesting.

For your interest we include here a picture with mean FRHI in quartiles of BMI.



Picture 1. Mean FRHI in quartiles of Body mass index. Bars showing the 95% confidence interval for the mean.

Point-by-point responses to Reviewer 2

Thank you for the comments and constructive criticism, which have improved the manuscript. Please find our responses below. The corrections in the manuscript are highlighted using red font.

Major Compulsory Revisions:

1. The reproducibility of a method in adolescents does not necessarily translate to better reproducibility in adults. Why not utilize both the RHI and F-RHI in this study as you would have both measurements at baseling and after the intervention and could make a statement about reproducibility in your population. Please publish both RHI and F-RHI values.

Our response: The sentence about reproducibility has been defined and the text about methods has been corrected so that both measurements are utilized. (Methods/ Measurements of endothelial function).

Both F-RHI and RHI values are now published in Table 1.

2. Since sex is a strong variable, why did you not analyze the F-RHI dicotomously by sex and the other variables as continuous variables in the models? The various risk factors may play differently in women compared to men.

Response: One challenge in our study is that the number of male subjects is rather low compared with women. The main reason for this is that the proportion of female workers among Finnish municipal workers is significantly higher.

Mainly because of this we originally chose not to build models separately for sexes: instead we built those separate sex-adjusted linear regression models for every variable, both continuous and dichotomous, and built the multivariable model using sex as one of the variables.

To estimate if the risk factors play differently in men and women we now made separate multivariable models for women and men as additional analyses. The model for women is quite similar to the model in whole population. In men's model, probably because the low number of men, only BMI entered the model. In our opinion this adds more to the knowledge about the associations of risk factors with F-RHI in women.

These new models are described and discussed in the paper: Statistical methods, Results/Additional analysis, Discussion, Tables 5 and 6.

We understand the importance of this, but we also assume that a more equally divided population may be required to give detailed information about the sex differences. This limitation is also now discussed in the Discussion. We will also take this in to account in planning of future studies.

3. The range of women were peri- to post-menopausal but hormonal status was not taken in to account and sleep disturbances could be related to menopausal symptoms.

Response: We agree with this. Unfortunately the data about hormonal status or use of menopausal hormones was not collected. This has now been addressed in the limitations of the study in Discussion and will be taken in to account in planning of future studies.

4. Please provide criteria for coding presence or absence of risk factor (range of values or cut off limits).

Response: Criteria for coding is now added in the Methods.

Discretionary Revisions:

Figure 1. Use a different symbol to differentiate men and women.

Response: Figure 1 is now labeled separately for men and women.