Author's response to reviews

**Title:** High-normal blood pressure and long-term risk of type 2 diabetes: 35-year prospective population based cohort study of men.

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**Author's response to reviews:** see over
Authors responses to the reviewer’s comments:

Reviewer: Margareta Norberg

This paper evaluates association between blood pressure and the risk of developing diabetes among men during a follow-up period of 35 years. It is a population based prospective study.

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

1. Methods: Throughout the paper the definitions of blood-pressure categories are not clearly defined. Authors use several concepts but it is unclear what they mean by “normal”, “prehypertension”, “mildly raised blood pressure”, “upper normal “, “high normal”. In the Methods section, paragraph Classification of blood pressure, the rationale of the selected definition should be given and authors are strongly recommended to use either the WHO-ISH definition (Journal of Hypertension 1999; 15: 51) or the JNC 7 definition (JAMA; 289: 2560), and to use that definition consistently. For example, according to WHO-ISH “normal “is defined as SBP <130 and DBP < 85 and “high-normal” as 130-139 and 85-89. According to JNC 7 is “normal” SBP <120 and DBP <80 and 120-139 and 80-89 is “prehypertension”. It seems that in this manuscript are SBP<130 and DBP < 80 considered “normal” which seems to be a mixture of WHO-ISH and JNC7 definitions.

Authors reply: Thanks for bringing this to our attention. We have now changed the wording throughout the manuscript. As suggested we have used the WHO-ISH definition and added a new reference. We have also changed the title of the manuscript accordingly.


Added text in Methods, page 8:

Classification of blood pressure levels

The blood pressure categories are based on the WHO-ISH definition [19] where SBP is classified into following four categories: < 130 (normal), 130-139 (high-normal), 140-159 (mild hypertension) and ≥160 (moderate and severe hypertension) mm Hg; and DBP into following three categories: <85 (normal), 85-89 (high-normal), ≥90 (hypertension) mm Hg. We regarded SBP and DBP as independent risk factors and analysed them separately.

2. Discussion: There was a 10% increased risk of diabetes per 10 mmHg increase of SBP and results presented in the figure suggest a graded increase of the risk, which is stated in the first part of the discussion. But there was no difference in the HR for diabetes between the SBP 130-139 and the SBP 140-149 groups. This suggests a more step-wise increase of the risk of diabetes. What could be the reason to this? In the Figure 1 there are three categories, and the 130-139 and the 140-149 categories are collapsed. Why – are the curves for these two groups similar?? Again, the same categories should be used throughout the paper.

Authors reply: Yes, the two middle curves were similar (which is also seen in Table 2). This is most likely a chance finding and we have therefore not commented further in the results or discussion. However, because we changed the grouping according to WHO-ISH and in order to not confuse the reader we now have chosen to show each blood pressure category separately also in the Figure 1.

3. Discussion paragraph first sentence: Here authors present results (64.5% hypertensive) and a definition (systolic hypertension), this should be moved to the results and the methods sections, respectively.

Authors reply: The text has been revised and this text moved from the discussion to the methods as suggested by both reviewers.

4. According to Figure 1 the risk of developing diabetes was practically zero during the first 10 years of observation. This is hardly true for men aged 50+ and should be discussed. A reasonable explanation is that diabetes type 2 is usually taken care of in primary health care and therefore not registered in the registers that were used in this study.

Authors reply: In our study 98/7333 were diagnosed with diabetes during the first 10 years. This is a lower proportion compared to other studies and we agree with the reviewer that this is likely due to the fact that we only have register data from hospitalized patients and not from primary care centers. We have added new text in the discussion to clarify this (see below). We probably have a “delay” in detecting the diabetes cases but since we have a long follow-up, and because most men were hospitalized at some point we believe, as we have mentioned in the discussion that we have detected most of the cases by the end of follow-up.

Added text in Discussion page 11: Compared to other studies [9-13] we have a low proportion of diabetes cases during the first 10 years and this is probably explained by the fact that diabetes is often managed in primary care during the first years after diagnosis. We have a detection delay in the study since we did not have access to
primary care data and were able to identify diabetes only as a hospital discharge diagnosis.

5. Conclusion: This is a population based study according to the methods section. If there is any value of defining 17% of the population as “normal”, and 18% as “pre-hypertensive” and the rest “hypertensive” could be discussed, see for example Epidemiologic reviews 2011; 33: 122. It could be questioned to recommend an individual clinically based approach to reduce the impact of prehypertension and hypertension.

Authors reply: We have read the suggested article with interest and refer to it in our manuscript as a part of our discussion;

Discussion page 12: The benefits of considering high-normal blood pressures as a predisease have been debated [24]. What this and other studies [10-13] show is that the risk of developing diabetes is already increased at blood pressure levels below the limits generally used in considering treatment for hypertension. According to our findings it is important for physicians to be aware when making the individual risk assessment for diabetes and considering what action to take for each patient that there is an increased risk of diabetes even with SBP as low as 130 to 139 mm Hg.

Authors reply: We have also rephrased the conclusion as follows:

Conclusion page 15: In conclusion, the present study has shown that hypertension and high-normal systolic blood pressure at mid life is a significant risk factor for type 2 diabetes in men over a 35-year follow-up period. The association between blood pressure and type 2 diabetes was independent of BMI and other conventional risk factors. This suggests that physicians should also consider high-normal systolic blood pressure when making the risk assessment for diabetes for a patient. Men in the high-normal range of SBP might also benefit from regular glucose measurements in order to detect diabetes earlier.


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

6. Abstract: The metabolic syndrome is questioned during recent years and the rationale of mentioning it in the background is unclear.

Authors reply: We have rephrased the first lines in the abstract as suggested by both reviewers as follows:
The link between type 2 diabetes and hypertension is well established and the conditions often coexist. High normal blood pressure, defined by WHO-ISH as systolic blood pressure (SBP) 130-139 mm Hg or diastolic blood pressure (DBP) 85-89 mm Hg, has been found to be an independent predictor for type 2 diabetes in studies, although with relatively limited follow-up periods of approximately 10 years.

7. Methods: How were the two non-intervention groups defined?

Authors reply: All men in the city born 1915-1923 were randomized into 3 equally large groups. The 2 non-intervention groups each included a random selection of men in the city that was not in the intervention group. This was not very clearly expressed in the text and we have added a clarification.

Text added Methods page 5: Data were derived from the intervention group of the multifactor Primary Prevention Study, which began in 1970. The study population and design have been described in detail elsewhere [16]. In brief, all men (n=approximately 30 000) living in the city of Gothenburg, Sweden and born between 1915 and 1925 (except those born in 1923) were randomised into three equally large groups, where the men in one of the groups (i.e. the intervention group, n=10 004) were offered a medical examination to identify and treat risk factors, with the remaining men randomised into two control groups (i.e. groups without any interventions) [16].

8. Page 8 “100 000 observations years” if that is “100 000 person years” this term should be used.

Authors reply: We have changed the phrasing of observation years into person years throughout the manuscript as suggested.

9. Discussion: First line should be “were followed for 35 years or until death”

Authors reply: We have changed the first sentence as suggested.

Text added Discussion page 11: In this prospective study of middle-aged men who were followed for 35 years or until death, we found that even moderately increased SBP predicted the subsequent development of diabetes.

Level of interest: An article whose findings are important to those with closely related research interests

Quality of written English: Acceptable
Statistical review: No, the manuscript does not need to be seen by a statistician.

Declaration of competing interests:
I declare that I have no competing interests
Authors responses to the reviewers comments:

Reviewer: Konstantinos Tsilidis

Reviewer's report:

This is an interesting study that prospectively evaluates the association between systolic and diastolic blood pressure with type 2 diabetes development. The findings seem to agree with other published work. Please read below for some important comments/suggestions.

Major Compulsory Revisions

1) Please list in the Results what was the median or mean follow-up time in your study (not just the maximum) and compare this number to the length of follow-up in other published studies.

   Authors reply: The median follow up in our study was 28 years and this information including a comparison to other studies is added in the result section and in the discussion as follows:

   Text added in Results page 9: The median follow-up time in our study was 28 years.

   Text added in Discussion page 11: Our median follow-up was 28 years which is considerably longer than in previous studies which were 8.9(9), 7.8(10), 10.2(11), 12.5 (12) or a mean follow-up of 8.3 ±1.0(13) years.

2) You definitively have some residual confounding issues in your study. The limitations section in the Discussion should be expanded, where you should discuss potential residual confounding for specific variables and how this could have affected your results. Specifically, you have a never, former, current variable for smoking. Smoking duration or intensity is missing. Physical activity is crudely measured, no use of times/week of activity or something similar quantitatively. You have measured BMI, but this is an incomplete marker of abdominal obesity, which is important for diabetes development. Diet-related variables are also missing. What have other published studies adjusted for? Any difference in their findings based on which variables they adjusted for? To assure readers that residual confounding does not have a big role on your findings, I would suggest to perform some sensitivity analyses: i) re-run models after excluding all current smokers and ii) re-run models after excluding overweight and obese individuals.

   Authors reply: As suggested, we have performed the proposed sensitivity analysis and it did not alter our results. The figures are attached to this letter in a table. In the interest of space and because we do not feel that this table adds much information we have just commented the findings in the results section of the manuscript, but will obviously add the table if required. Importantly, the relations we found were by and
large true also after excluding all current smokers, and when we only included subjects with BMI <25, with no suggestion of interaction effects.

Text added in Results page 10: We have also calculated the multivariable adjusted HRs for diabetes by SBP categories in different BMI and smoking categories. The effect of increasing blood pressure on risk of diabetes was similar irrespective of BMI category or smoking status, with no suggestion of an interaction effect (data not shown).

Authors reply: We have also expanded the strengths and limitations section in discussion where we discuss residual confounders and we have also added a new reference.

Text added in Strengths and limitations page 14-15: Fifthly, information on important risk factors other than blood pressure may be considered to be somewhat crude; therefore our results might have been affected by residual confounding. For instance, we have only information about BMI and not hip-waist ratio. One study investigating the relationship between blood pressure and diabetes incidence [13] had both BMI and hip-waist measurement and there was a very minor difference in diabetes risk when using BMI instead of hip-waist ratio. For physical activity, no figures for hours per week are available in our study, just classification into 3 groups (sedentary, moderate and active). In their study, Conen et al [11] had information regarding the number of hours per week of physical activity, and even after controlling for this, the relationship between blood pressure and diabetes remained. In our study no information on smoking duration is available, and nor do we have dietary information. Diet pattern has been shown to affect diabetes incidence in a previous study [34] but to our knowledge there are no studies concerning the relationship between blood pressure and diabetes that have adjusted for dietary pattern. Nevertheless, it seems unreasonable that information about smoking duration and dietary pattern would eliminate the significance in our findings. Moreover, the results from our sensitivity analysis showed that the problem of residual confounding is likely to be negligible.

New reference:

3) Another potential explanation for your findings is detection bias, where hypertensive’s have increased medical surveillance and are closely prone for diagnosis of other diseases, like diabetes. For this reason and for reasons of reverse causation as well, I would suggest performing another sensitivity analysis, where diabetes cases that
developed in the first 5-10 years after baseline are excluded. This will most likely not influence your results because of the small number of cases that developed early, but better be safe than sorry.

**Authors reply:** We have performed the analysis adding a sentence concerning this in the strengths and limitations section of our discussion part as follows:

**Text added in strengths and limitations page 13:** We have also performed an analysis in which all the diabetes cases that are identified during the first 7.5 years were excluded which did not alter our results (data not shown).

4) I read with interest the section in the Discussion, where you report the repeated blood pressure measurements in a random subsample. This should be part of the Methods section instead. You should also discuss whether this misclassification of BP is expected for some reason to be differential according to diabetes diagnosis or not?

**Authors reply:** As suggested we have moved the part with the repeated blood pressure measurements to the method part and done some minor rephrasing. We have also added a limitation under the discussion because we are unable to rule out that the participants reacting with high blood pressure at the screening also are more likely to develop diabetes. Unfortunately, we cannot adjust for this in our study, and we consider this as a separate question that we are unable to address.

**Text moved from Discussion to Methods section page 6-7:** A large proportion of the participants were found to have high blood pressure. In a random subsample (n=84/2180) blood pressure was also measured in the morning two weeks later. Mean SBP was then 7.6 mm Hg lower and mean DBP 8.9 mm Hg lower in comparison to the screening blood pressure. Among those with the highest blood pressure levels during the screening, the mean SBP and DBP was even lower two weeks later; 16.1 mm Hg and 18.0 mm Hg respectively. The conclusion made by the original investigators of the Primary Prevention Study was that the circumstances of the blood pressure measurements probably influenced the values and that there was no reason to believe that blood pressure levels were substantially higher in Gothenburg than in other populations at that time [18].

**Text added in Strengths and limitations page 14:** Fourthly, a remaining issue could be whether people reacting with high blood pressure at the screening were more prone to develop diabetes. This is something we are unable to adjust for in the study and, as we see it, a separate issue that must be analysed in another study.

5) The variable for the use of anti-hypertensive medication is not optimal, because it is contaminated by the effect of hypertension. It is better to study and compare the effect between different drug classes among hypertensives. If you do not have such
information, then it is better to develop a hypertension variable using some cut-points for SBP and DBP plus any use of drugs, and test its association with diabetes.

**Authors reply:** Unfortunately, information about different antihypertensive treatments was not available; nor can we adjust for antihypertensive treatment that the participants might have received during follow up which we have mentioned as one of the limitations in the manuscript. However, we have re-run the analyses with the new definition of hypertension as suggested (SBP+DBP+antihypertensive treatment), but the results were similar. In the interest of space and since it did not add anything new, we decided to keep the WHO definition throughout the manuscript instead, which corresponds better to our study aim as well. Use of WHO definition was also suggested by the other referee (see above).

6) In Table 2, please show more than one multivariable models, so that people can judge the amount of confounding present in the study. You could present a model adjusted only for age and/or BMI plus the fully adjusted model next to it, and also discuss which of the adjustment variables influenced more your results, if any.

**Authors reply:** As suggested, we have re-done the analyses and added more models in Table 2. We also comment the findings in the result and discussion section about the findings:

Text added in Results section page 10: *The inclusion of BMI reduced the estimates significantly more than any other variable, taken separately or together.*

Text added in Discussion page 11: *Body weight is a strong determinant for diabetes. The increased risk of diabetes in the higher blood pressure categories was strongly attenuated when adjusting for BMI. This is in coherence with what other studies have found [9, 13] and indicates that BMI is the factor with the greatest influence on diabetes risk.*

Minor Essential Revisions

1) The background section of the Abstract (especially two first sentences) needs some rephrasing because there are several linguistic mistakes.

**Authors reply:** The background section of the Abstract is rephrased as suggested by both reviewers.

Text added in Abstract Background page 2: *The link between type 2 diabetes and hypertension is well established and the conditions often coexist. High normal blood pressure, defined by WHO-ISH as systolic blood pressure (SBP) 130-139 mm Hg or diastolic blood pressure (DBP) 85-89 mm Hg, has been found to be an independent*
predicctor for type 2 diabetes in studies, although with relatively limited follow-up periods of approximately 10 years.

2) How many of the 956 diabetes cases came from the death certificates?

Authors reply: 54 of the diabetes cases were from death certificates. This information is now added under the result section.

Text added in Results page 9: Of the 956 diabetes cases, 54 were from death certificates and thus 902 from hospital discharge registers.

3) It would be interesting if you could offer an explanation for the inverse association seen in Table 1 between smoking and SBP.

Authors reply: We believe that the reverse relationship is caused by the fact that non-smokers often weigh less. This correlation has been described before (see reference below). We have added a new reference and text in the Discussion section:

Text added in Discussion page 11: We found an inverse relation between smoking and blood pressure, probably due to the fact that smokers weigh less, which has also been described elsewhere [21]

New reference:


4) In Table 1, age seems not to be associated with SBP. Is the p-value<0.0001 a typo? Please also add a footnote on how the p-values were evaluated. It would be nice also to see not only the %current smokers, but also the % former and never smokers on the table. The characteristics should be better sorted so that all the blood pressure or obesity variables are near each other.

Authors reply: Yes indeed we have a typo in table 1 and that was the mean age of the population. We thank the reviewer for pointing this out to us. There is a significant increase in age between the SBP groups i.e. SBP is associated with age. Information about how the p-values were evaluated are now also in a footnote to the table. We have also added information about different smoking categories in table 1 and sorted the covariates in a better way.

Level of interest: An article of importance in its field
Quality of written English: Needs some language corrections before being published

Authors reply: The manuscript has once again been reviewed by a professional editing service

Statistical review: Yes, and I have assessed the statistics in my report.

Declaration of competing interests:

I declare that I have no competing interests
**Tabel A**: Hazard ratio for diabetes by SBP category in different BMI categories.

<table>
<thead>
<tr>
<th>Blood pressure categories/treatment</th>
<th>Number at risk</th>
<th>Diabetes cases</th>
<th>Person years</th>
<th>Diabetes cases per 1 00 000 person years</th>
<th>Age adjusted hazard ratios (95% CI)</th>
<th>Age and multivariable adjusted* hazard ratios (95% CI)</th>
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<td></td>
<td></td>
<td>1.12 (1.05-1.18)</td>
<td>1.10 (1.05-1.18)</td>
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<td>1.12 (1.05-1.20)</td>
<td>1.10 (1.03-1.18)</td>
</tr>
</tbody>
</table>

*Mutivariable model was adjusted for age, cholesterol, antihypertensive treatment, smoking, physical activity and social class.
<table>
<thead>
<tr>
<th>Blood pressure categories/treatment</th>
<th>Number at risk</th>
<th>Diabetes cases</th>
<th>Person years</th>
<th>Diabetes cases per 1 00 000 person years</th>
<th>Age adjusted hazard ratios (95% CI)</th>
<th>Age and multivariable adjusted* hazard ratios (95% CI)</th>
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<td>1.17 (1.13-1.22)</td>
<td>1.12 (1.06-1.16)</td>
</tr>
</tbody>
</table>

*Mutivariable model was adjusted for age, BMI, cholesterol, antihypertensive treatment, physical activity and social class.