Author's response to reviews

Title: Anxiety and depression lowers blood pressure: 22-year follow-up of the population based HUNT study, Norway

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Author's response to reviews: see over
Authors’ response to reviews

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Authors: Bjørn Hildrum, Ulla Romild, Jostein Holmen

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Dear Editor,

We would like to thank for inviting us to resubmit a revised version of our manuscript.
We also thank the editor and the reviewers for valuable comments and suggestions.

Editor’s comment

Date: 20 April 2011

“The authors should comment on:
i) the differences between the participants and the original 60000 in the HUNT study”

Reply: We have previously (ref 11) reported equal cross-sectional inverse associations between anxiety/depression and blood pressure at HUNT-1 (n= 60,143, age 20-89) and at HUNT-2 (n= 60,799, age 20-89).

Of the 60,143 baseline participants with valid data, 48,907 were 20-67 years old and thus eligible for the present 22-year longitudinal analyses. In a new paragraph in the resubmitted manuscript, we have described the course of these individuals and compared participants with those who did not complete the study.

“ii) the clinical significance of their findings, which could include additional analysis with BP dichotomised into hypertension or not”

Reply: In accordance with the editor’s comment, we have now included analysis with blood pressure dichotomised into hypertension or not, and into hypotension or not. In the “Discussion” we shortly describe the potential clinical significance of our findings.

Please see comment to Referee 1.

“iii) further explanation for their findings? Is it possible cortisol level plays a part?”
Reply: We have included a possible role of cortisol dysregulation in the Discussion.

“iv) reference a recent paper one referee identified published online 21st February in journal Hypertension”
Reply: We have referenced this recent study in the revised manuscript.

Referee 1

Date 17 March 2011, Hermann Nabi

“Minor Essential Revisions

1. Although, the present study could be considered as a large scale study, the sample included represents 1/3 of the initial population of the HUNT study (N >60,000). There is no description of the differences between those included and not included in this study, making it very hard for reader to appreciate any potential bias in the study.”

Reply: Please see our comment to the Editor. We have now included a new paragraph describing our sample.

2. The second major issue is related to the time lag between the three assessments of anxiety, depression and blood pressure. We all know that blood pressure for instance is prone to substantial fluctuations even in relatively short time. Thus, a time lag of 11 years between measurements did not really allow the investigation of the dynamic of the association between depression, anxiety and blood pressure levels.”

Reply: We agree that three assessments during 22 year of follow-up do not fully display the fluctuations in anxiety/depression and blood pressure, and in their association. However, we do not think that this would bias our findings in any particular direction.

In accordance with the reviewer’s comment, we have now included a paragraph discussing this potential limitation.

“Major Compulsory Revisions

3. Thirdly, the authors found that the co-morbid anxiety and depression lowers blood pressure 22 years later. Results may be statistically significant but be clinically unimportant. In fact, I don’t understand the reason why the authors performed the analyses using blood pressure as continuous variables. There are commonly accepted clinical cut-offs for both anxiety/depression and blood pressure and I wondering why the authors did not use them. It will be interesting for readers to know if the associations remained essentially the same when the cut-offs values are considered.”
Reply: We thank the referee for the comment. In the resubmitted manuscript we have included results of additional analyses, using commonly accepted cut-offs for anxiety/depression (HADS-A≥8, HADS-D≥8) and for blood pressure (≥140/90 mm Hg). These analyses confirmed our findings. They also showed that a high level of anxiety/depression reduced the risk of being hypertensive by 20%.

However, there are several reasons to maintain the results of our original analyses:

Regarding anxiety/depression: As the ADI-12 Index has no accepted clinical cut-offs, we defined a high symptom level of anxiety/depression at all three examinations as scores above the 80th percentile of the ADI-12 Index (baseline) and of the HADS (year 11 and 22).

Regarding blood pressure, we have previously (ref 6, 11) argued for the use of other operationalisations than dichotomies like hypertension or not, and hypotension or not. These arguments include that, unlike hypertension, there is no generally accepted definition of hypotension, and that clinically derived categories (for example: ≥140/90) will have very different prevalence rates in younger versus elderly individuals in a general population covering a wide age range.

Therefore, we previously examined the association between anxiety/depression and blood pressure using blood pressure as continuous variables; age- and sex-stratified percentile groups; and change variables (from baseline to 11-year), both continuous and categorical. We used linear, logistic, and generalised additive logistic regression analyses. We repeated analyses after exclusion of hypotensive or hypertensive individuals at baseline, and displayed graphically the dose-response association of change in anxiety/depression with change in blood pressure over time. Across all analyses (cross-sectional and longitudinal) we found an inverse association between mental symptoms and blood pressure.

After considering several approaches to analysing the longitudinal effect of anxiety/depression on blood pressure, for the present study we concluded that the best approach was to use change in mean systolic and diastolic blood pressure as the main outcome measures.

“Discretionary Revisions

4. Fourthly, different methods of measuring blood pressure, anxiety and depression have been used across study phases. This constitutes another major limitation of the present study.”

Reply: We thank the reviewer for the comment and have rewritten the discussion on this potential limitation.

As described in the manuscript, the same methods of measuring blood pressure, anxiety and depression were used at HUNT-2 and HUNT-3, but that different methods were used at HUNT-1.
We agree with the reviewer that this could constitute a limitation of the present study. We have previously discussed this potential limitation (ref 11) and presented data that indicated no major problems applying different instruments at HUNT-1 and HUNT-2. For example: several items of the ADI-12 Index (HUNT-1) and the HADS (HUNT-2) overlapped with high correlations between them. Furthermore, the cross-sectional associations between anxiety/depression and blood pressure were equivalent at HUNT-1 and HUNT-2, despite use of different measures for blood pressure and anxiety/depression (ref 11, Fig 2).

In the present study, using the same methods of measuring blood pressure, anxiety and depression at HUNT-2 and HUNT-3, we found that the effect of anxiety and of depression, respectively, on blood pressure (Table 3) was similar to the effect we previously observed from HUNT-1 to HUNT-2 (ref 11). This underlines that differences in methods did not influence the association we observed.

“Finally, I would like to inform the authors that a large scale study using repeated measures of both depressive symptoms and blood pressure assessed at 5 points in time over 24 years has just been published online first of the HYPERTENSION, 21 February.”

Reply: We are thankful being made aware of the very recently published study and this study is referred to both in the Background and in the Discussion.

Referee 2

Date: 20 March 2011, Jenny van Son

“Minor Essential Revisions

1. Make sure the language you use is U.K. English or U.S. English and not a mixture of both.”

Reply: It has now been done.

“Discretionary Revisions
Remarks concerning the discussion section:

1. Another limitation of the study is the cross-sectional design.”

Reply: This is a 22-year follow-up study in which the same individuals were examined at three waves with 11-year intervals. It differs greatly from the collection of repeated cross-sectional data in which an independent sample is collected at each wave. In other words, we used a longitudinal design.

“2. Another limitation is the fact that the blood pressure was measured at one time point, in stead of (for example) a whole day with an ambulant measurement device.”
Reply: We agree that single measurements give only snap-shots of the participants’ blood pressure. However, in epidemiological studies, screening measurements, and not extensive (clinical) examinations, are the standard.

In the HUNT study, all adult inhabitants in one county of Norway were invited to a general health study. To measure blood pressure over a whole day in the whole population would be logistically and economically an enormous task. And we are not aware of any large epidemiological study on this topic that has monitored blood pressure over a longer period of time. For example, the most recently published study on this topic (Nabi et al, 2011) based their findings on similar blood pressure measurements as in the HUNT study.

We have in the re-submitted manuscript discussed possible limitations on our data.

“3. Another comment is that differences are quickly significant with such a large sample. The differences in blood pressure are very small. Are these differences relevant?”

Reply: In the light of the reviewer’s comment, a new second paragraph in the Discussion has been included.

“4. I would appreciate it when the authors would elaborate more on possible explanations for their findings.”

Reply: We have now extended the discussion on possible mechanisms. Please see our reply to comment 5.

“5. Could there be an association with a lower level of cortisol in people with chronic depressive symptoms?”

Reply: We had no data on the cortisol levels, but discuss a possible role of cortisol dysregulation.

“Other:
1. Background second paragraph: comma after secondly.”

Reply: This has been corrected.