Author's response to reviews

Title: An investigation of factors identified at birth in relation to anxiety and depression in old age. The Hordaland Health Study (HUSK).

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Version: 3 Date: 23 March 2013

Author's response to reviews: see over
Dear Editor,

We are most grateful for the positive, constructive review of our manuscript, and are grateful for the reading of our manuscript from external reviewers. We have done our best to revise the manuscript informed by the constructive and important comments from the reviewers. In this letter, we have included the original comments, and present our replies as well as a description of the changes made to the manuscript and the analyses. We think the revision process have made our manuscript more clear and informative.

We look forward to your evaluation of the revised manuscript.

Best regards on behalf of the author group,

Jens Christoffer Skogen
PhD, Corresponding author
Reviewer's report #1

Title: An investigation of factors identified at birth in relation to anxiety and depression in old age. The Hordaland Health Study

Version: 2 Date: 12 January 2013

Reviewer: Johannes Wancata

Reviewer's report:
This is an excellent paper reporting a study of very high quality and high scientific interest. I suggest to publish this paper.

Level of interest: An exceptional article
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.

Response: We thank the reviewer for his positive remarks. Based on the comments from the other reviewers we have however made some changes to improve the manuscript further.
Reviewer's report #2
Title: An investigation of factors identified at birth in relation to anxiety and depression in old age. The Hordaland Health Study
Version: 2 Date: 4 March 2013
Reviewer: Ian Colman
Reviewer's report:
This study examined the association between early-life factors and symptoms of depression and anxiety in late adult life. The authors used data from a Norwegian population-based cross-sectional survey (the HUSK study) and linked 406 respondents aged 72-74 years to birth records at a local birth clinic. The authors found no associations between anthropometric measures at birth and depression or anxiety in late adult life. Depression and anxiety were associated with younger maternal age; anxiety was associated with small maternal pelvic size and poor maternal health; depression was associated with low paternal occupation.

Major compulsory revisions:
1. This is a well-written paper on an interesting topic. It is unfortunate that the authors were only able to link 406 of 3,341 elderly members of the HUSK study; however they show that those whose records were linkable did not differ dramatically from those who could not be traced back to birth. The small sample size (relative to other studies in this area) is a concern due to statistical power. The authors do a fine job of highlighting mechanisms that may explain why early-life factors may not be associated with late life mental health, such as changing social environments or stressors across the life course, however they neglect to mention the likely limited statistical power they had to detect small but meaningful effects. For example, the meta-analysis on low birth weight and depression that they cite found only a small magnitude of effect; such an effect may not be detectable with this sample. This must be addressed in the discussion.

Response: With regards to traceability, there are several reasons as to why some HUSK-participants could not be traced to the birth records. The maternity ward/hospital in question was the main hospital for the Bergen area during the time period in question. In the second decade of the 20th century, about one quarter of all births in the Bergen area took place in the public maternity ward (called “Fødestiftelsen”). The proportion of deliveries taking place there increased when the new Women’s Clinic (“Kvinneklinikken”) was inaugurated in 1926, so that in the 1930s, as much eight or nine out of ten births in Bergen took place at the clinic (information from personal communication with the State archivist). The relevant birth records for the present study were those detailing births between 1st of January 1925 and 31st of December 1927. The project group also considered including information from other hospitals/field hospital in Bergen during the same period. This was abandoned after careful consideration. Birth records from other sites would be less reliable, with less information and generally of poorer quality. They would also be very difficult to retrieve as only a proportion of them would be stored in the regional state archive.
People who immigrated to Bergen (after birth), those born at other hospitals and people born in private homes, could all be included in the HUSK-survey (outcome data) but with no birth record available (exposure). During the period between 1920s (time of exposure) and 1990s (time of HUSK study) there has been a considerable immigration to (as well as emigration from) Bergen. Immigration and emigration has not been confined to a certain socioeconomic strata. Although there were other hospitals in the Bergen area – the clinic employed in this study was the largest and the catchment area included people of both lower and middle socioeconomic status (and to a smaller degree higher social strata). Being born at home would for the most part be the case for rich families that could afford home-visits from doctors and midwives. This became less common after the inauguration of new Women’s Clinic, and we find it unlikely that this could substantially bias our results. Some less affluent people would also have given birth at home (or not at hospital), but these would be even smaller numbers, and prone to early morbidity and mortality.

Regarding the second question on statistical power: We agree with the reviewer that insufficient power to detect associations of interest is a relevant objection. Even small shifts of continuous distributions in the adverse direction could have a sizeable impact on the population level. Our study is rather small, and lack of precision in effect estimates is a valid concern.

Based on this comment we have provided more detail regarding the hospital and the maternity ward in the methods section:

Page 6: “This information was used to trace the participants born in Bergen to the public maternity ward (“Fødestiftelsen i Bergen”) birth records located at the Regional State Archives of Bergen. In the second decade of the 20th century, about one quarter of all births in the Bergen area took place in the official maternity ward (personal communication, State archivist). The portion of deliveries taking place at hospitals increased steeply when the new Women’s Clinic (“Kvinneklinikken”) was inaugurated in 1926, replacing the old maternity ward. The relevant birth records for the present study were those detailing births between 1st of January 1925 and 31st of December 1927. These records contain detailed information about the pregnancy, the birth and the mother’s health recorded by midwives and obstetricians during the hospital stay. The Women’s Clinic in question was the main teaching facility for midwives at the time, and the records were integral to the training, and are therefore considered to be of high quality (Rosenberg 1987).”

And included the following in the discussion section:

Page 9: “The small sample size reduces our ability to detect potential small but meaningful effects. A recent meta-analysis investigating the association between low birth weight and depression later on found only small effects (Wojcik, Lee et al.) – and given the lack of precision in our estimates such small effects may not be detectable in our study.”
Minor essential revisions:
1. Given the authors have access to gestational age, a more appropriate measure of fetal adversity is low birth weight corrected for gestational age. This adjusts the focus from pre-term birth to adverse conditions in the womb.

**Response:** We agree with the reviewer, and we do have information regarding the gestational age in whole weeks as presented in the original manuscript. The variance in gestational age was however rather small, and most individuals included have a registered gestational age of 40 weeks (91.1%; see table X1 for more details). Also, there is reason to believe that the variable on gestational age is less accurate than birth weight. The birth weight was measured using the same technology as today (a simple weight), while estimated gestational age is today aided by use of ultrasound (Geirsson 1991), which was developed much later than the exposure data in our study. Ideally, the birth weight adjusted for gestational age should be informed by reference data on expected weight in relation to gestational age (such as Kramer and colleagues (2001)), but reliable reference data was not available for the time-period of interest. Despite these limitations regarding our information on gestational age, we have tried two different approaches in order to correct for gestational age in relation to birth weight. The first approach was to adjust for gestational age in the multivariate regression in addition to age and gender. In the second approach we made two Z-scored birth weight variables based on whether or not they were pre-term (>37 weeks), these two Z-scores were then collapsed and employed in the regression model (Skjærven, Gjessing et al. 2000; Basso, Frydenberg et al. 2005). Both of these approaches only marginally changed the estimates (Table X2).

Table X1: Range of gestational age in our sample (N=406).

<table>
<thead>
<tr>
<th>Gestational age (weeks)</th>
<th>N</th>
<th>Percent</th>
</tr>
</thead>
<tbody>
<tr>
<td>30</td>
<td>1</td>
<td>0.25</td>
</tr>
<tr>
<td>32</td>
<td>1</td>
<td>0.25</td>
</tr>
<tr>
<td>34</td>
<td>1</td>
<td>0.25</td>
</tr>
<tr>
<td>35</td>
<td>4</td>
<td>0.99</td>
</tr>
<tr>
<td>35.5</td>
<td>1</td>
<td>0.25</td>
</tr>
<tr>
<td>36</td>
<td>5</td>
<td>1.23</td>
</tr>
<tr>
<td>36.5</td>
<td>9</td>
<td>2.22</td>
</tr>
<tr>
<td>37</td>
<td>6</td>
<td>1.48</td>
</tr>
<tr>
<td>37.5</td>
<td>5</td>
<td>1.23</td>
</tr>
<tr>
<td>38</td>
<td>2</td>
<td>0.49</td>
</tr>
<tr>
<td>39</td>
<td>1</td>
<td>0.25</td>
</tr>
<tr>
<td>40</td>
<td>370</td>
<td>91.13</td>
</tr>
</tbody>
</table>

Table X2: Associations between late life anxiety and depression case status and birth weight.

<table>
<thead>
<tr>
<th></th>
<th>Adjusted for age and gender (95% CI)</th>
<th>Adjusted for age, gender and gestational age (95% CI)</th>
<th>Z-scored gestational-adjusted weight, adjusted for age and gender</th>
</tr>
</thead>
</table>

5
<table>
<thead>
<tr>
<th>Birth weight and case-level anxiety</th>
<th>-0.06 (-0.20, 0.08)</th>
<th>-0.06 (-0.18, 0.06)</th>
<th>-0.09 (-0.37, 0.19)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Birth weight and case-level depression</td>
<td>-0.07 (-0.24, 0.10)</td>
<td>-0.05 (-0.20, 0.09)</td>
<td>-0.05 (-0.39, 0.28)</td>
</tr>
</tbody>
</table>

We chose to include the first approach in the revised manuscript. To reflect this change, we have included the following under section “Statistical analyses”:

Page 7: “In order to assess adverse conditions in the womb, the association between birth weight and case-level anxiety and depression was adjusted for gestational age in addition to age and gender.”

2. Some studies of birth weight and depression have reported a J-shaped relationship, whereby increased birth weight reduces the risk of depression up to a certain point, beyond which the risk increases. While there may be limited power to examine this, choosing a reference group that is of appropriate weight, instead of appropriate and very large combined, may change the results for LBW. Papers that discuss this include:


Response: We agree with the reviewer that there seems to be a J-shaped association between birth weight and some outcomes in adulthood. In our study, we used birth weight as a continuous exposure for case-level anxiety and depression. Further investigations of the “shape” of the association between birth weight and case-level anxiety and depression indicated a potential curvilinear relationship in our sample. However, including a quadratic term did not add explained variance in the model and the coefficients for the quadratic term were not significant. In line with the reviewer’s previous comment, this may be due to limited statistical power. Also, due to insufficient statistical power, we are not able to investigate the association between low (<2.5 kg) or high (>4.5 kg) birth weight as compared to normal birth weight in relation to case-level anxiety and depression. Based on the reviewer’s comment we have included the following in the discussion section:

Page 11: “For birthweight in particular, the small sample size precluded any investigation of low birth weight (<2.5 kg) or high birthweight (>4.5 kg) per se, which is associated with later...
psychopathology in some studies (Colman, Ploubidis et al. 2007; Vasiliadis, Buka et al. 2010)."

3. I found it odd that after the focus on birth weight in the introduction that there was no specific mention of birth weight or gestational age in the Results section.

Response: We agree, and have now included the following in the results section:

Page 9: “In the main analyses, none of the anthropometric measures at birth, such as weight and length, differed significantly between cases and controls in either comparison…”

4. The authors mention in the Conclusions that "there was no clear evidence of mediation". The authors have not specifically tested for mediation effects, only confounding effects.

Response: We agree - we have merely adjusted for education in a multivariate regression model. Consequently, the previous text:

“Although there was no clear evidence of mediation by educational attainment and physical health measured in later life, a better perspective might be to adopt a life-course perspective or developmental origins of health and disease perspective, where foetal and early life-factors are considered in conjunction with physical and social exposures across the whole life-span.”

Is in the revised manuscript changed to:

“Although there was no clear evidence of any impact from educational attainment and physical health later in life for the investigated associations, a better perspective might be to adopt a life-course perspective or developmental origins of health and disease perspective, where foetal and early life-factors are considered in conjunction with physical and social exposures across the whole life-span.”

5. The authors use the acronym FOAD for the foetal origins of adult disease hypothesis. The more widely term found in the field is the DOHAD hypothesis, which refers to the developmental origins of health and disease.

Response: We agree that DOHAD is preferable (Davey Smith 2012). Based on the reviewer’s comment, we have changed the denotation and acronym from FOAD/foetal origins of adult disease to DOHAD/developmental origins of health and disease where applicable.

6. This may be splitting hairs, but this study doesn't appear to be a case-control study. It is a retrospective cohort study where all cohort members with available data are included.

Response: We agree, and have changed the description of the design from «case-control study» to «retrospective cohort study» where applicable in the manuscript.
Reviewer's report #2
Title: An investigation of factors identified at birth in relation to anxiety and depression in old age. The Hordaland Health Study
Version: 2 Date: 28 February 2013
Reviewer: Daniela Goncalves
Reviewer's report:
This is an interesting study that might provide further information about a topic that has been seldom considered. I have some concerns, however, regarding its methodology, which I would like the authors to address. It is my understanding that by replying to these comments the authors will be able to clarify some questions that are not so straightforward in the current version of the manuscript, overall improving its readability and conclusions.

Major concerns
• Overall, it is not clear to me how this study was conducted. The authors mention in the methods that the HUSK is a cohort study, but in the abstract it is referred to as a cross-sectional survey sample of community residents. These studies would include different designs. It would also be helpful to be explicit about the original study sample here, including non-participation rates and to what extent the original sample was representative of Bergen’s inhabitants (considering this has been ascertained already).

Response: Based on this comment and also comments from reviewer #2 we realized that our description of our study needed to be improved. We have therefore changed the description of the sample in both the abstract and in the main text under “Study population” (page 6). The old age part of the HUSK is a cross-sectional community-based study of all residents in Bergen born between 1925 and 1927 at the time of invitation (end of 1990s). Based on this we constructed a retrospective cohort study by linking HUSK with the participant’s birth records where available. We have also included information about the participation rate (77%) on page six of the manuscript. Information about the representativeness of the entire sample is not available, but the aim was to establish a population-based sample of people born between 1925 and 1927.

• The authors use 2 outcome variables and 36 potential explanatory variables; thus, 72 possible associations are being considered, which means that if adopting a conservative position, only one of all the considered results would be considered significant (case-level anxiety associated with mother’s condition after birth, with p=0.001). Could the authors please comment on why they decided not to apply any type of correction to their analysis, thanking into account the considerably high amount of variables analysed?

Response: We chose not to adjust for multiple comparisons based on the consideration that this study is primarily explorative. Based on advice from in-house statisticians and leading epidemiologists such as Rothman (Rothman 1990), we have maintained our original approach of not adjusting for multiple comparisons. Although not entirely uncontroversial, we found it too restrictive to use Bonferroni adjustments in our study, especially due to the limited statistical power as noted by the reviewer in a previous comment. Also, given our results,
adjusting for multiple comparisons would not drastically change our conclusions. Based on the reviewer’s concerns, we have included the following text in the manuscript under “Statistical analysis” and “Strengths and limitations”:

Statistical analysis, page 8: “Although not entirely uncontroversial, considering the explorative nature of the study and the limited sample size, we chose not to adjust for multiple comparisons.”

Strengths and limitations, page 12: “In relation to the number of associations investigated (72 in total), we decided not to adjust for multiple comparison, which is in line with some recommendations (Rothman 1990). Applying Bonferroni adjustments would reduce the number of significant associations to one (case-level anxiety associated with mother’s condition after birth) but not change our conclusions dramatically.”

• Conclusions (p.12): the authors mention that “although there was no clear evidence of mediation by educational attainment (…)”; how was this ascertained by their analysis?

Response: The statement in the submitted manuscript was not entirely correct, as we merely adjusted for education in a multivariate regression model. As such, it was treated as a confounding factor with no specific test of mediation. Consequently, we have changed the following text from:

“Although there was no clear evidence of mediation by educational attainment and physical health measured in later life, a better perspective might be to adopt a life-course perspective or developmental origins of health and disease perspective, where foetal and early life-factors are considered in conjunction with physical and social exposures across the whole life-span.”

To:

“Although there was no clear evidence of any impact from educational attainment and physical health later in life for the investigated associations, a better perspective might be to adopt a life-course perspective or developmental origins of health and disease perspective, where foetal and early life-factors are considered in conjunction with physical and social exposures across the whole life-span.”

• For this study, the authors had access to birth records data for 14% of the original sample (which, as previously stated, is not even described, e.g., how high was the initial non-response, amongst other relevant aspects); of these, they lost further 15% of the potential sample due to missing data (which, as below stated, it would be relevant to comment). This is a remarkably small sample, which the authors acknowledge but justify by saying that previous studies retrieved data for proportions as low as 2-5%; whereas that is true, the reference they have provided also presents plenty of studies where the authors were able to trace down as much as 60% of the original sample, often averaging 40%. These are substantially different numbers, which will have an impact upon the generalisability of results, and I believe further
thought should be put into it. Does this study really shed further light upon the relationship between early factors and later mental health problems, or was it just considerably underpowered, thus the lack of significant results where other studies have found so?

Response: With regards to the traceability, there are several different potential reasons as to why HUSK-participants were not traced to the birth records, including immigration to Bergen after birth, being born at another maternity ward/hospital and being born at home. During the period between 1920s (time of exposure) and 1990s (time of HUSK study) there has been a considerable immigration to (as well as emigration from) Bergen within most socioeconomic strata. Although there were other hospitals in the Bergen area – the clinic employed in this study was the largest and the catchment area included people of both lower and middle socioeconomic status (and to a smaller degree higher social strata). Being born at home would for the most part be the case for rich families which could afford home-visits from doctors and mid-wives. Some less affluent people would also have given birth at home (or not at hospital), but these would be even smaller numbers, and prone to early morbidity and mortality. This became less common after the inauguration of the new Women’s Clinic, and we find it unlikely that this could substantially bias our results.

We agree with the reviewer that insufficient power to detect associations of interest is a relevant objection. Even small shift of continuous distributions in the adverse direction could have a sizeable impact on the population level. Our study is rather small, and lack of precision in effect estimates is a valid concern.

Based on this and other comments we have rewritten the first part of the limitations section (page 11):

“Limitations include the relatively small sample size and proportion of the HUSK-participants that could be traced back to their birth records. There are several reasons for this: the birth records were only available for a subgroup as not everyone who participated in HUSK was born in the Bergen area, and some born at home or at other hospitals. Based on a conservative estimate, at least one-third of the HUSK sample would not be within the catchment area of the regional hospital at the time of birth. The small sample size reduces our ability to detect potential small but meaningful effects. A recent meta-analysis investigating the association between low birth weight and depression later on found only small effects (Wojcik, Lee et al.) – and given the lack of precision in our estimates such small effects may not be detectable in our study. In previous DOHAD-studies which have used birth cohorts to trace individuals in their adulthood (i.e. forward tracing), the identified proportions of the original sample are sometimes as low as 2-5% (Joseph and Kramer 1996). The low traceability and small sample size constitute central limitations to our study, and warrants caution with regards to the interpretation and generalisability of the present study. For birthweight in particular, the small sample size precluded any investigation of low birth weight (<2.5 kg) or high birthweight (>4.5 kg) per se, which is associated with later psychopathology in some studies (Colman, Ploubidis et al. 2007; Vasiliadis, Buka et al. 2010).”
Also related with my previous point, the authors state that “in these studies it has been argued that as long as comparisons are made within the identified subgroups, it is unlikely for substantial bias to be introduced in the tested associations”. This has been advocated not by further studies but by a particular study, by Martyn and colleagues, where the authors were able to retrieve data for 66-77% of their original sample, totalling 13,000+ participants. Again, the comparisons between both studies are limited by the sample size, which obviously also constrains assertions about the results and subsequent implications.

Response: We agree that the representativeness of our sample is of concern due to the low traceability. The long time gap between the exposures and outcomes when studying the FOAD-hypothesis has posed a considerable challenge with regards to how representative the studied sample is compared to the target population. Many FOAD-studies have had a substantially less complete study sample than conventional epidemiological studies, some as low as <5% making these studies particularly vulnerable to selection bias and selective survival bias.

We were able to trace 480 of the 3341 participants. There are several reasons for the low traceability, the most important being that many of the HUSK-participants were not born in or around Bergen city, and would therefore never be eligible for registration in the birth records in the first place. Other HUSK-participants, albeit born in the Bergen area, would have been born at other hospitals or at home and again ineligible as study participants. Unfortunately, it is impossible to quantify how many that would be ineligible, but based on the HUSK-participants birthplace recorded in the National Population Register, there is reason to believe that not being born at the regional hospital is a considerable contributor with respect to the traceability: At least one-third of the HUSK-participants were not born within the catchment area of the regional hospital. This, in turn, leads to at least 33% augmented traceability, yielding a catchment area-based traceability of at least 20 percent for this study. It is also important to remember, that the reported traceability does not reflect loss to follow-up or attrition, as the tracing were done backwards in time – and is not a tracing of a birth cohort forwards in time. Considering the reasons for the reported traceability and the temporal direction of the tracing, the estimated traceability figures are very conservative compared to true number of HUSK-participants that actually were born at the regional hospital.

Based on this comment and comments from reviewer #2, we have removed the sentence regarding comparisons of subgroups (page 11) and added the following sentence:

“The low traceability and small sample size, is constitute central limitations to our study, and warrants caution with regards to the interpretation and generalisability of the present study.”

Minor concerns
- For the study population (p.5): could the authors please explain what “all residents...of a previously established cohort” means?
Response: The old age part of the HUSK-study is based on a previous population-based study of 18,044 subjects living in Hordaland County in Western Norway. The first investigation was carried out in 1992-1993 and those still alive were re-invited to a more extensive population-based study (including questionnaires related to anxiety and depression) known as HUSK. More detailed information about the sampling procedure and design is available from several publication, but most notably in publication by Refsum and colleagues (Refsum, Nurk et al. 2006). We agree that the phrasing is unclear, and have changed the text on page six to:

“In summary, all residents of Bergen city or neighbouring areas born between 1925 and 1927 of previously established study population were invited to participate in a general physical examination and to complete questionnaires on socio-demographic status, general health and health-related behaviour.”

- Still related with study description, authors mention that the records from one hospital were retrieved/consulted; is it possible to describe how many hospitals existed in Bergen at the time, and whether any attempts were made to consult records from those?

Response: The hospital in question was the main hospital for deliveries in the Bergen area during the time period in question. In the second decade of the 20th century, about one quarter of all births in the Bergen area took place in the public maternity ward (“Fødestiftelsen”). The portion of deliveries taking place there increased steeply when the new Women’s Clinic (“Kvinneklinikken”) was inaugurated in 1926, so that in the 1930s, as much eight or nine out of ten births in Bergen took place at the clinic. The relevant birth records for the present study were those detailing births between 1st of January 1925 and 31st of December 1927. The project group also considered including information from other hospitals/field hospital in Bergen during the same period. This was abandoned after careful deliberation, mainly due to a significantly poorer quality of and limited information available from the birth records, and difficulties in retrieving birth records since only a proportion of these records are stored in the regional state archive. We acknowledge that our approach probably limited the traceability to certain degree, but it also ensured a higher quality regarding of the information extracted from the birth records.

- Regarding the values chosen for establishing caseness: it is not clear to what extent self-reports developed for other groups swiftly apply to older populations (e.g., http://www.ncbi.nlm.nih.gov/pubmed/18074254), and I would recommend the authors to, at least, acknowledge it. Furthermore, the same paper they cite (Flint & Rifat) seems to suggest a cut-off point of 11 (p.122), which should also be addressed.

Response: We agree that self-report questionnaire developed for other groups do not necessarily apply to older populations, and acknowledge that the chosen cut-off does not reflect anxiety/depression in clinical range. We chose the cutoff $\geq 8$ since this has been shown to provide the optimal balance between sensitivity and specificity in many studies (Bjelland, Dahl et al. 2002), and since we due to a small sample size would even further limit the precision of our estimates if we employed a cut-off of $\geq 11$. Also, using the HADS as
continuous measures yields similar results as those presented in the manuscript. Based on the reviewer’s comments, we have included the following in the discussion part of the paper:

Page 11: “Furthermore, the cutoff ≥8 have been shown to provide the optimal balance between sensitivity and specificity in previous studies, but it is not clear whether this cutoff is optimal in older age groups. Some studies have suggested a cutoff ≥11 in older populations (Flint and Rifat 2002), but we chose to use ≥8 due to limitations in sample size.”

• **Cohort context (p.7): interesting information, but probably better placed in the introduction?**

**Response:** Based on this suggestion, we have moved the contextual information and placed it at the end of the introduction, and agree it was better placed there.

• **Related with cohort context, is it possible for the authors, using the information available regarding parental characteristics, to place this “traced” cohort within 1925/1927 Bergen’s society?**

**Response:** Based on information from father’s occupational status, it seems that most of the participants in our study sample are from the middle and lower socioeconomic strata. The occupation of the fathers varied from unskilled manual workers to teachers and general managers.

• **Statistical analyses (p.7): 15% of the “traced” participants did not have a valid HADS; this seems to be a considerably high number, would the authors be able to explain a bit more?**

**Response:** We agree that this is a high proportion of non-response but it is comparable to the complete old age part of HUSK, which had 14.7% non-response on the HADS-questionnaire. The reason why the proportion of participants with insufficient answers on HADS may is so high, may be related to many aspects, including unwillingness to disclose information about mental health or inadvertently skipping some of the questions. We have no reason to believe that this substantially biases our sample.
References


