Author's response to reviews

Title: The impact of early life factors on cognitive function in old age: The Hordaland Health Study (HUSK).

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Author's response to reviews: see over
We are most grateful for the positive, constructive review of our manuscript and for the reading of our manuscript from external reviewers.

We have done our best to revise the manuscript informed by the reviewers’ comments. We have included the reviewer’s comments below, 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 the evaluation of the revised manuscript.

Best wishes

Jens Christoffer Skogen
Corresponding author
**Reviewer's report – reviewer #1**

*Manuscript Title: The impact of early life factors on cognitive function in old age. The Hordaland Health Study (HUSK).*

*This is an interesting study on the impact of early life circumstances on late life cognitive function. The Introduction is fluent and the study question is clearly defined and justified.*

**Major Compulsory Revisions**

1. The methods are well described and appropriate; however, my concern is that the results are presented for unadjusted models, and that age and sex adjusted results are only briefly mentioned in the text. As the authors have stated in the Introduction, adjustments may well have effect on the findings (ref 23), thus, I would prefer seeing age and sex adjusted effect estimates in the tables. Other ways it should be well justified why crude models were used (or show results for both analyses).

Response to major comment #1: We agree with the reviewer, and have now included both crude and age/gender-adjusted estimates in the appropriate tables.

2. Also, individuals’ own SES (e.g. measured by education) was not considered in the analyses although it seemed that it was requested from the HUSK participants at some point (under “Additional information – follow-up from HUSK at age 72-74”). Could the authors run sensitivity analyses adjusting for education and self-rated health?

Response to major comment #2: We have carried out additional analyses, taking education and self-reported health into account. However, we feel that the findings should be interpreted with caution because these variables highly likely to be on the causal pathway between the exposures and outcomes of interest. The results of these analyses are presented in table X1 (giving point-estimates only). Based on these results, we conclude that the associations are only slightly affected by the adjustment for self-rated health, while adjusting for educational attainment affects some of the associations more. Specifically, the associations between paternal socioeconomic status and cognitive function in old age are substantially weakened by the adjustment of educational attainment. To reflect this we have incorporated the following in the methods section:

“In sensitivity analyses, we also explored the effect of separate additional adjustment for educational attainment and self-rated general health on those associations found to be significant after age- and gender-adjustment.”

The following in the results section:
"For the significant age- and gender-adjusted associations identified, we carried out additional separate adjustments for educational attainment and self-rated general health. Adjusting for self-rated health only slightly affected the associations, while adjusting for educational attainment affected some of the associations to a larger degree. Specifically, the associations between paternal SES and cognitive function were substantially weakened (60-80% reduction in effect sizes of point-estimates).”

And the following in the discussion section (under interpretation):

“In this respect, it also interesting that adjusting for educational attainment substantially weakened the associations between paternal SES and cognitive function in old age, suggesting that these associations might be substantially mediated through education. On the other hand, self-rated health reported in later life did not appear to influence these associations meaningfully. Further specific causal pathway modeling was felt to be beyond the scope of this study and not warranted by the largely negative associations of interest.”
### Table 1X: Significant associations between risk factors at birth and continuous cognitive outcomes at age 72-74 years (N=346), unadjusted, adjusted for age and gender, age, gender and education, and adjusted for age, gender/self-rated health.

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<th>Composite score</th>
<th>Separate cognitive tests</th>
<th>MMS</th>
<th>Digit Symbol</th>
<th>KOLT</th>
<th>COWAT</th>
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</table>

Significant associations in bold

* $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$

*a* Z-score of the sum of all cognitive tests (mean: 0, standard deviation: 1)

*b* Test-specific raw scores for each cognitive tests (see methods section of the main document for further details)
3. Please provide more information about the statistical analyses performed, e.g. did the authors use logistic regression or what? In the "statistical analyses" paragraph it is only stated that: "Bivariate and age- and gender-adjusted associations were then investigated". (and non-adjusted results were reported in the tables)

Response to major comment #3: We agree that the description of the statistical analyses performed lacked relevant details, and we have now included the following information under “Statistical analyses”, page 10: Bivariate and age- and gender-adjusted associations were then investigated between exposures and outcomes employing linear regression models”.

**Minor Essential Revisions**

1. Has the z-scored composite cognitive scale (described just before “Context for the birth cohort”) been used elsewhere? If so, please provide a reference. If not, please explain why this would be a good outcome measure.

Response to minor comment #1: The employment of composite Z-scores are not unusual in the field of cognitive psychology and other scientific fields investigation cognitive function.\(^1\)\(^2\) This specific z-scored composite cognitive scale has, as far as we know, not been used previously. Our aim was to construct a composite cognitive score which reflected overall cognitive functioning among the participants, as well as investigate specific cognitive tests as outcomes. As the different cognitive tests employed are on different scales (some ranging between 15-154 and others ranging between 2-16), we standardized each of the cognitive tests by setting the mean to “0” and the standard deviation to “1”, which enabled us to sum them up to a composite score for each participant. We believe that this is the most widely used method for constructing a composite measure of cognitive function from individual tests, and has the advantage of being reproducible in other research (compared to for instance a factor analysis output which is sample-specific).

2. Table 2: in the top row authors could join “Mean” and “Standard deviation” as “Mean (SD)” and give explanation for SD in the footnote.

Response to minor comment #2: We agree with the reviewer, and have revised table 2 accordingly.

3. Also in Table 2, the familial characteristics could be presented in the same direction as in the results in Table 4, i.e.: Mother’s condition after birth (% good), Tuberculosis in family (% no), etc.

Response to minor comment #3: We agree with the reviewer, and have revised table 2 accordingly.

4. In Table 3 the title could state: “individual risk factors at birth” and in Table 4:
“familial risk factors at birth”, or such, to make the difference between the exposures.

Response to minor comment #4: We agree with the reviewer, and have revised table 3 and 4 accordingly.

5. If presenting age and sex adjusted results in the tables, please indicate model adjustments in the footnotes.

Response to minor comment #5: Table 3 and 4 now presents both crude and age- and gender-adjusted estimates on separate rows for each investigated association.

6. In the second paragraph of the Results, please discuss the results of Table 3 before the results of Table 4.

Response to minor comment #6: The text has now been changed to:

“Out of the 136 crude associations investigated, only 10 (7.4%) were significant at α=0.05 (Tables 3 and 4), and in general there were few patterns or consistencies observed among these significant associations. Head circumference was positively associated with COWAT and TMA performance but not with the composite score (Table 3). SES was the only exposure that was associated with the composite score, where a higher parental SES was associated with an increased mean score by 0.25 SD (p=0.0146). A higher parental SES was also associated with a better Digit Symbol and TMA performance (Table 4). Adjusting for age and gender rendered the association between head circumference and TMA performance non-significant, but the other significant associations were unaltered (Table 3). None of the other significant associations in our sample were consistent or indicative of any specific pattern.”

7. In paragraph “Additional information – follow-up from HUSK at age 72-74” it was not clear to me where the data for APOE genotype was from. From HUSK records? When was the genotyping done?

Response to minor comment #7: We have tried to clarify this by changing the section to:

“Additional information gathered during follow-up from HUSK at age 72-74

As a crude assessment of potential demographic differences between the participants we were able to trace and the rest of the HUSK participants, gender, self-reported level of educational attainment and general health was obtained from HUSK. Level of educational attainment was divided into “compulsory only” and “post-compulsory”, while general health was divided into “poor” and “good”. As APOE genotype have been associated with cognitive function (34), information about apoE4-status (presence of any E4-allele versus absence of E4-allele) was also included (using nonfasting plasma samples taken during the general physical examination of HUSK).”
8. The authors mention in the paragraph “Context for the birth cohort” that “three social classes began to dominate in Bergen during the same period”, but in the analyses only two social classes were used (lower/higher). So what is the meaning of this information of the context? Why was not three social classes used in these analyses?

Response to minor comment #8: The information given under “context for the birth cohort” was intended to serve as a very general description of the sociodemographic profile of Bergen during the time period when the participants were born. Even though Bergen was dominated by three social classes, most of the participants in our study sample were from the middle and lower socioeconomic strata as judged from paternal occupational status. The occupation of the fathers varied from unskilled manual workers to teachers and general managers. In response to the reviewer, we have no included the following sentence under strengths and limitations:

“Negative findings could have resulted from inaccuracies in the measurement of either exposures or outcomes; for example, information on maternal health and family circumstances was derived from relatively crude measures. However, despite this, the similarly crude measure of parental SES included provided the most consistent significant associations identified with the outcomes. As previously described, three different social classes dominated Bergen during the time when the participants were born. Based on information from paternal occupational status, however, most of the participants in our study sample were from middle to lower socioeconomic strata with the occupation of the fathers varying from unskilled manual workers to teachers and general managers. This should be considered as a characteristic of the analysed sample when interpreting findings.”

9. In paragraph “Additional information – follow-up from HUSK at age 72-74”, the first sentence is a bit vague, perhaps reword it as: “As a crude assessment of potential demographic differences between the participants of this study and the rest of the HUSK participants, we were able to trace gender, self-reported level of educational attainment and general health from the HUSK records.” (Were the data from records? When were these data collected?)

Response to minor comment #9: We have tried to clarify this section by changing the section to:

“As a crude assessment of potential demographic differences between the participants we were able to trace and the rest of the HUSK participants, gender, self-reported level of educational attainment and general health were obtained from HUSK. Level of educational attainment was divided into “compulsory only” and “post-compulsory”, while general health was divided into “poor” and “good”. As APOE genotype has been associated with cognitive function
(34), information about apoE4-status (presence of any E4-allele versus absence of E4-allele) was also included (using nonfasting plasma samples taken during the general physical examination of HUSK).”

10. The Discussion part is also well written and relies on the presented results although in some places the statements are rather strong in regard of the consistency of the results.

For example, the last sentence of the first paragraph of Discussion could be modified as: “This highlights the importance of parental SES in relation to SOME specific domains of cognitive functioning in old age (20, 23), perhaps relatively independent of birth size (23), a notion which was confirmed ALSO in our study SAMPLE.”

Response to minor comment #10a: We have changed the sentence accordingly.

In the last paragraph of Discussion the link between these sentences is vague: “…it is generally accepted that childhood SES is an important predictor for later cognitive function (10, 42), and cognitive reserve (40). Thus, it is possible that, even though anthropometric measures obtained at birth might predict cognitive function later in life…”

The first sentence tells about childhood SES and the second about anthropometric measures. Perhaps delete word “Thus”, or re-word the latter sentence with something like: “Even though anthropometric measures obtained at birth did not predict cognitive function later in life in this study, it is possible that other unmeasured factors mitigated these initial differences, and reduced or eliminated their influence in later adult life.”

Response to minor comment #11a: We have changed the abovementioned sentence to:

“Even though anthropometric measures obtained at birth did not predict cognitive function later in life, it is possible that other unmeasured factors mitigated these initial differences and reduced or eliminated their influence in later adult life.”

11. In all places, please indicate to which direction the association is in statements like:

Abstract “head circumference at birth predicted cognitive function”
page 14 “between higher parental SES (as measured by father’s occupation) and global cognitive function in old age”

page 16 “Both of them seemed to predict cognitive function…”
–better or worse cognitive function?
Response to minor comment #11b: We have now made an effort to make the recommended changes throughout the manuscript.

Discretionary Revisions

1. The reference list seems good, but perhaps some other work not sited here could also be checked:


Response to discretionary revision #1: We have now included some of the suggested references in the introduction and the discussion section.

2. In the Methods section of the abstract I was missing the definitions of the exposures that are now presented in the Background section. Perhaps move the sentence “we investigated the prospective associationS…” to be the second sentence of the next paragraph.

Response to discretionary revision #2: We have now revised the abstract, including this recommendation.

3. Abstract: Authors could also mention that the outcomes were individually analyzed, as results by individual scores are given.

Response to discretionary revision #3: We have now revised the abstract, including this recommendation.

Minor issues not for publication

1. Abstract: The first time “head circumference” is mentioned in the Results, it is not clear that it refers to head circumference at birth.

Response to minor issue #1: We have now added “at birth” to clarify this.

2. In the paragraph “Modified version of the Digit Symbol Test (Digit Symbol)”: the Digit Symbol Test measures perceptual and psychomotor speed, focused ON attention
Response to minor issue #2: The modified version of the Digit Symbol Test measures “focused attention” as opposed to “divided attention”.

3. In the first paragraph of “Statistical analyses” the first sentence is lacking definition “remainder” of what?

Response to minor issue #3: The sentence has now been changed to:

“HUSK participants with traceable birth records were compared to the remainder of the HUSK participants.”

4. In the second paragraph of “Statistical analyses”: “Post-hoc analyses were also performed to investigate WHETHER the effect of SES on cognitive function WAS independent of anthropometric measures, as well as WHETHER the effect of head circumference on cognitive function WAS independent of SES.”

Response to minor issue #4: The sentence has been changed accordingly.

5. In the second paragraph of the Results, please write open what is “SD” (in: by 0.25 SD)

Response to minor issue #5: We have now written “standard deviation” instead of “SD”.

6. The last paragraph of the Discussion: Other studies have ALSO found that social disadvantage and early life stressors are related to cognitive function in later life (10, 41).

Response to minor issue #6: We have now included “also”.
Reviewer's report – reviewer # 2

Comments to the author

This historical cohort study investigates the prospective association between a range of early life factors and cognitive function in community residents aged 72-74 years. The author concluded that although there was no substantial evidence for the association between early life factors and late life cognition, there was some evidence for an association between prenatal SES and some cognitive domains. The paper is generally well-written. Literature on this topic is limited and the topic of the paper is important and this data would certainly be a useful addition to the literature, and of interest to the readership of the journal. However I have some criticisms and concerns (specified below).

Major comments

Abstract
1. Study setting and/a brief description of exposure of interest is worth mentioning.

Response to major comment #1: The abstract has now been revised according to suggestions from reviewer #1 and #2.

Introduction
2. Rationale for the study from public health perspective needs to be mentioned in the introduction

Response to major comment #2: We have now revised the introduction, and it now also includes a paragraph about the public health rationale behind this study.

3. Mention the main objective/hypothesis more clearly with regard to the strength of the available data

Response to major comment #3: We agree, and have changed the last section of the introduction to:

“Employing a unique linkage between a community survey and a historical birth record archive, we were able to investigate a range of early life factors in relation to cognitive function on a battery of assessments in community residents aged 72 to 74 years. Specifically, we investigated the prospective association between anthropometric measures taken at birth, birth complications, parental socioeconomic status, and maternal health status in relation to scores on a cognitive test battery in old age.”

Method
4. The paragraph describing study population is not very clear. I think a proper
sequence is helpful and a flow diagram will enable the reader to understand the details.

Response to major comment #4: The paragraph describing the study population has now been rewritten and figure 1 contains a flowchart of how the final study sample was established:
Figure 1: Flowchart describing the establishing of the final study population.

HUSK 1997-99  
N=3,341

• Did not participate  
  (N=1138)

  Did not participate  
  (N=1138)

Cognitive sub-sample  
N=2,203

• Incomplete cognitive tests  
  (N=47)

  Incomplete cognitive tests  
  (N=47)

Complete cognitive data  
N=2,156

• Not traced  
  (N=1810)

  Not traced  
  (N=1810)

Traced sample  
N=346

• Traceability: 16.0%
• No differences between the traced and untraced identified.
5. Were the participants' term born/ preterm? Was gestational age available?

Response to major comment #5: Gestational age was available for the participants. Most of the participants were born on-term (94.5%), and only 19 participants were born before 37 weeks of gestation. The mean gestational age was 39.6 weeks and the standard deviation was 1.29 weeks.

6. Are the cognitive tests used are validated? Give inter/intra observer variation details of the test administrators.

Response to major comment #6: The cognitive tests used are validated tests, which have been extensively used both in Norway and internationally.³⁻⁸ The specific battery of tests employed in the cognitive testing of the old age cohort of HUSK has also been used in previous international peer-reviewed publications.⁹,¹⁰ For the purposes of the cognitive testing of the old age cohort of HUSK, two, and only two assessors were trained over two days to use the battery of tests. These assessors were trained nurses, and no data on the inter-rater observation was collected, as the two nurses worked closely together with each other on a daily basis during the test period.
In an effort to clarify this, we have added the following to the first paragraph of section on cognitive examination under methods:

“HUSK included a cognitive test battery consisting of six tests. The cognitive tests are in wide use internationally and have been well validated.³⁻⁸ Two assessors were trained over two days to use the test battery (personal communication, Professor Knut Engedal). These assessors were nurses, and the battery was administered on-site by the trained nurses at the end of the study’s examination.”

7. Mention the parameters of pelvic size.

Response to major comment #7: The parameters used for pelvic size is the interspinous distance (between anterior superior iliac spines), the intercristal distance (between furthest lateral points of the iliac crest), the external conjugate (from spinous process of fifth lumbar vertebra to upper edge of symphysis) and the intertrochanteric distance (between femurs). These measurements were combined and the mean was computed. We have now included the following information in the methods section:

“...mother’s pelvic size (the mean of the interspinous distance, the intercristal distance and the external conjugate in centimeters).”

8. Which maternal complications were considered?

Response to major comment #8: The variable “complications during birth” included all of the birth complications noted in the birth journals. As it was part of free text fields in the journal (under the heading “birth process”) it included several different complications and
combinations of these. The most common ones was prolonged labour, abnormal presentation, manual extraction and episiotomy, uterine rupture, discolored amniotic fluid, abnormal fetal souffle, and placenta praevia. We have now included the following information in the methods section to in an effort to clarify this:

“complications during birth (including, but not limited to, prolonged labour, abnormal presentation, manual extraction and episiotomy, uterine rupture, discoloured amniotic fluid, abnormal fetal souffle and placenta praevia; yes/no)”.  

9. Statistical analysis: It is worth mentioning if any variable was transformed. What is the purpose of standardising the cognitive test variable? Mention the statistical method used to compare the groups. What analysis was used to investigate the association between early life factors and cognitive function? No information about looking at interactions are addressed in this section.

Response to major comment #9: No other variable than the composite cognitive variable was transformed in the included statistical analyses. The aim with the z-scored composite cognitive scale was to construct a composite cognitive score which reflected overall cognitive functioning among the participants. As the different cognitive tests employed are on different scales (some ranging between 15-154 and others ranging between 2-16), we standardized each of the cognitive tests by setting the mean to “0” and the standard deviation to “1”, which enabled us to sum them up to a composite score for each participant. The employment of composite Z-scores are not unusual in the field of cognitive psychology and other scientific fields investigation cognitive function.1,2

We have also rephrased parts of the “statistical analyses”-section in order to clarify some of the comments from both reviewers:

“Statistical analyses
HUSK participants with traceable birth records were compared to the remainder of the HUSK participants. Bivariate and age- and gender-adjusted associations were then investigated between exposures and outcomes employing linear regression models. Our approach was to investigate and report all associations between exposures and outcomes, taking into account the number of significant associations that would be expected through chance alone, but also evaluating the output for any consistency in associations for a given exposure or outcome (35). For the main analysis, Stata version 11.0 (36) was employed. Using the software G*Power version 3.1.3 (www.psycho.uni-duesseldorf.de/abteilungen/aap/gpower3/) a post-hoc power analysis indicated that we would be able to detect a small to medium effect size for continuous outcomes (a correlation of 0.13), and mean differences (Cohen’s d of 0.35) at a power of 80% (alpha 0.05) (37). We also investigated the potential two-way interaction between apoE4-status and gender for each of the exposures in relation to the composite score, in a post-hoc analysis. Post-hoc analyses were also performed to investigate whether the effect of SES on cognitive function were independent of anthropometric measures, as well as whether the effect of head circumference on cognitive function was independent of SES.”
Results

10. In Table 1 give the unit for composite score and other cognitive test scores. Mention the method for deriving p or mean difference in the foot note. I did not see any significance difference in bold but the foot note mention significance difference in bold.

Response to major comment #10: We have now reformatted tables 1-4 according to the reviewers’ comments.

11. Table 2 mention the parameter of pelvic size, unit for mother’s age and define parity. For ponderal index what does mass indicates? give the unit for composite score and other cognitive test scores. Reformat the table.

Response to major comment #11: We have now reformatted tables 1-4 according to the reviewers’ comments.

12. Table 3 Reformat the table; mention column headings, units for cognitive test scores, define parity, what does the value indicate and how it is derived and whether crude or adjusted associations. Which parameter of pelvic size used in the analysis? Which maternal complications were considered?

Response to major comment #12: We have now reformatted tables 1-4 according to the reviewers’ comments.

13. Table 4 again reformat the table; mention column headings, units for cognitive test scores, what does the value indicate and how it is derived and whether crude or adjusted associations.

Response to major comment #13: We have now reformatted tables 1-4 according to the reviewers’ comments.

14. In the post-hoc analysis in the results section mention the effect size since the data is not shown

Response to major comment #14: We have now included the age- and gender-adjusted models in tables 3 and 4.

15. The result section needs restructuring with clear interpretation with the data presented in the table.

Response to major comment #15: The results section has now been restructured based on comments from both reviewers.

16. Since maternal age, parity are likely to influence birth size it is worth adjusting
for these variables too.

Response to major comment #16: We agree with the reviewer that maternal age and parity may be associated with factors related to birth and also cognitive function in old age. In our sample maternal age and parity is positively associated with birth weight (both p<0.001), but birth weight, maternal age or parity are not associated with any of the outcomes included in our study. A confounder is usually understood as a being causally associated with the exposure, be a risk factor (or marker of this) for the outcome and be present before both exposure and outcome. In our case, we do not find any direct effects of any of these exposures (birth weight, parity or mother’s age) on any of the outcomes, and any adjustment between these exposures seems unwarranted. Also, it is very unlikely that adjusting for parity or mother’s age would lead to any substantial difference in p-values and effect estimates, as exemplified by table X1 below:
Table X1: Association between birth weight and composite cognitive score in old age, unadjusted, adjusted for parity and adjusted for mother’s age (n=346).

<table>
<thead>
<tr>
<th>Birth weight (kg)</th>
<th>Crude estimate</th>
<th>Adjusted for parity</th>
<th>Adjusted for mother’s age</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.01 (p=0.928)</td>
<td>0.03 (p=0.777)</td>
<td>-0.00 (p=0.990)</td>
<td></td>
</tr>
</tbody>
</table>

Discussion
17. The points made in the discussion are reasonable but limited. Since they have not adjusted to some potential confounders, like gestational age, parity, maternal age which are likely to influence birthweight interpretation of their data needs to be made cautiously.

Response to major comment #17: We agree with the reviewer that cautious interpretation of the results presented is warranted for several reasons. As stated in response to major comment #16 above, we do, however not agree that the issue of potential confounding is among the most pertinent reasons for being cautious. There are several other issues which we deem to be more relevant, such as low traceability and small sample size as mentioned under strengths and limitations. There are no indications in our data that gestational age, parity and maternal age are important confounders in relation to for instance birth weight and cognitive function in old age, and the former factors are not themselves associated with cognitive function.

18. Some of the findings reported in results (dental condition) are not discussed.

Response to major comment #18: Due to the number of associations tested, and consequently the inflation of the likelihood for type I errors, our approach was to mainly evaluate the consistency in associations for a given exposure and outcome. We therefore do not mention all of the significant associations from our analyses, as we chose to rely on the exposures which were associated with our main outcome (composite score) or where multiple associations were present.

19. The authors have not written their conclusions from their study, and implications from this study.

Response to major comment #19: We agree, and have included the following in the last paragraph of discussion:

“In conclusion, we found little evidence to support a substantial association between intrauterine or birth environment and cognitive function in old age in general. There were, however, some findings relating socioeconomic status and head circumference at birth and cognitive functioning in old age that warrants further investigation.”

Minor comments
Check for English language throughout the manuscript.

Response to minor comment #1: The manuscript has now been checked for English language throughout.
References