23 May 2017

Dr Tiago Villanueva

Research Editor, The BMJ

Dear Dr Tiago Villanueva,

Manuscript ID BMJ.2016.037184.R1 entitled "Childhood intelligence in relation to major causes of death: 68 years of follow-up of Scotland's whole 1936-born population"

We are delighted to have the opportunity to make a second revision to our manuscript following a provisional offer of acceptance.

Reviewer 2 has continued to provide us with helpful feedback in his reassessment of the paper, and we hope our responses below to his minor comments are satisfactory. We are pleased that our first revision, that included substantial additions, has been received by this reviewer as "comprehensive and well-written", and that Reviewer 1 was also very satisfied with our revisions and suggested no further changes.

We look forward to hearing from you soon.

Yours sincerely,

Catherine Calvin, PhD

pp. co-authors

Please find here our responses to reviewer 2:

1. *I think the following could be written more clearly: "Sensitivity analyses on a representative subsample of the cohort observed only small attenuation effects (by 10 to 26%) on controlling for potential confounders, including three childhood socioeconomic status indicators. In a replication sample from Scotland, of a similar birth-year cohort and follow-up period, smoking and adult socioeconomic status partially attenuated (16 to 58%) the associations."*
   - e.g. change 'small attenuation effects' to 'small attenuation of the estimated effect of intelligence'
   - 'the associations' to 'the association of intelligence with outcome rates'

   Response: Thank you. We have made these two changes.

2. *In the what this study adds: 'The cause-specific mortality risk according to childhood intelligence is consistent in men and women, with the exception of suicide, which is significant in men only' – the latter is irrelevant if there is no evidence of a difference between men and women. Thus, also report whether there is evidence of a difference in the association with suicide for men and women please.*

   Response: On reflection of comment 3 below, and in relation to our written response to that, we have decided to edit this final bullet point of 'what this study adds' as follows:

   > "*Lower childhood intelligence was consistently associated with most leading causes of death in both men and women".*

3. *Indeed, please revisit or extend this point as you say that the mortality risk is CONSISTENT but in the paper and abstract you draw attention to differences between sexes: "In models of the total sample, sex interaction terms were significant for risk of cardiovascular disease, coronary heart disease, smoking-related cancers, respiratory diseases, and dementia"*

   A related point is that the discussion says: "In general, the effect sizes were similar for women and men (albeit marginally greater for women), with the exception of death by suicide that had an inverse association with childhood ability in men but not women"

   - and yet the results say ""In models of the total sample, sex interaction terms were significant for risk of cardiovascular disease, coronary heart disease, smoking-related cancers, respiratory diseases, and dementia"

   Response: Thank you for identifying these inconsistencies in our reporting. In order to stay true to the statements from the Results and Discussion, as quoted above, we have changed the relevant line in the Abstract ("In sex-specific analyses the above inverse associations were observable in both men and women") to the following:

   > "There was a suggestion that *childhood intelligence was somewhat more strongly related to coronary heart disease, smoking-related cancers, respiratory disease, and, dementia in women than men (p-value for interactions: <0.001, 0.02, <0.001, 0.02 respectively)*."

4. *Do not use the FDR abbreviation, as this is not standard. Write in full.*

   Response: We agree. We have provided false discovery rate in full.

5. *I do not understand the methods or interpretation behind this statement: "Sex interaction effects with childhood intelligence were modelled to predict specific-cancer related mortality …" – what exactly is happening here? Could this paragraph simply be removed?*

   Response: We agree and we have edited the sentence in question to help clarify this method: "*An interaction term that included sex and childhood intelligence was introduced in models for IQ and specific-cancer related mortality*". We have also reversed the ordering of the two subsequent sentences, so that the interpretation of 'no clear sex differences' takes prominence, and the potentially chance finding for lung cancer comes second ("*These analyses revealed no clear sex differences in direction or magnitude of the association between childhood intelligence and cancer-specific mortality. A significant sex interaction effect (p=0.013) with mental ability in predicting lung cancer in the total sample may be a chance finding, and the direction of association was the same in men (0.77; 0.74 to 0.81) and women (0.70; 0.66 to 0.75)*").

6. *"0.02 HR points" – what does the word points mean here? Do you mean the HR was reduced by a small absolute value of 0.02?*

   Response: Thank you for clarifying this terminology. We have decided to express the reduction as a percentage rather than an absolute value, which is a standard approach we have used elsewhere in our results. There we have changed the text in the relevant section of the Results section ("*The HRs for cause-specific mortality, and for deaths related to cancer subtype, generally showed small attenuation effects of about 0.02 HR points*") to: "*The HRs for cause-specific mortality, and for deaths related to cancer subtype, mostly showed a reduction by a small amount (attenuation range: 0 to 30%).*"

7. *Re-write the following, as suggested in point 1 above for the abstract: "In confounder-adjusted models that included three childhood socioeconomic status indicators, the effect estimates for these six predictive models attenuated by 7 to 26%. Adding physical status indicators to the list of potential confounders in the model had negligible effect; the attenuation effect from the basic model ranged from 10 to 26%."*

   this is not written in the context of the effect of intelligence. Say explicitly that you are referring (I assume) to attenuation in the effect (HR) of intelligence.

   Response: Thank you. We have changed the text accordingly: "*In confounder-adjusted models that included three childhood socioeconomic status indicators, the relation of intelligence with all-cause mortality or mortality caused by cardiovascular disease, any cancer, smoking-related cancer, respiratory disease, or digestive disease, was attenuated by 7 to 26%. Adding physical status to the model had modest impact (attenuation range: 10 to 26%).*"