Author's response to reviews

Title: Health-related Quality of Life in the Cambridge City over-75s Cohort (CC75C). Development of a dementia-specific scale and descriptive analyses.

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Author's response to reviews: see over
Dear Dr. Olino,

**Re: Manuscript ID MS: 1722267795976312** “Health-related Quality of Life in the Cambridge City over-75s Cohort (CC75C). Development of a dementia-specific scale and descriptive analyses”.

Enclosed is a file containing the revised manuscript by Jaime Perales, Theodore D Cosco, Blossom CM Stephan, Jane Fleming, Steven Martin, Josep Maria Haro and Carol Brayne. Thank you for this opportunity to re-submit the present paper.

We also thank the reviewers very much for their suggestions and comments to our manuscript. We have taken all of them into consideration for producing the new version. In the following we have first presented the reviewer’s comments in bold, followed by our responses in regular typeface.

We hope that these responses and the new manuscript prove satisfactory to you and your reviewers.

We are looking forward to hearing from you. Thank you again for your attention to our work.

Sincerely,

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Berlin, September 12th, 2013

**POINT-BY-POINT Responses to Editors**

**E.1. Please update your ethics statement to include the full institutional name of the ethics committee that approved your study.**

Re: suggested change has been made.

**CHANGES IN TEXT: (See methods, page 11):**

Each CC75C study phase was approved by Cambridge Research Ethics Committee and National Research Ethics Service Committee East of England- Cambridge Central (Reference numbers: 05_Q0108_308 and 08_H0308_3).
E.2. Please adhere to PRISMA reporting guidelines in relation to the meta-analysis and include the PRISMA flowchart in the additional file: (PRISMA Systematic Reviews http://www.prisma-statement.org/).

Re: The suggested changes has been made.

E.3. After reading through your manuscript, we feel that the quality of written English needs to be improved before the manuscript can be considered further.

Re: The manuscript has been proofread by native English speakers and a number of changes have been made in the different sections of the text.

POINT-BY-POINT Responses to Reviewer #1

1.1. Page numbers are missing.

RE: The suggested change has been made.

1.2. “Interviews were conducted with both study participants and their caregivers”. Which caregivers, Informal caregivers?

RE: The CC75C study sought interviews with a proxy informant if a participant was unable to complete an interview, ideally person most closely involved. These were usually relatives but sometimes a friend/ neighbour or a housing scheme warden or member of staff in a care home.

CHANGES IN TEXT: (See methods, page 6):

Interviews were conducted with the study participants and a proxy informant if the participant was unable to complete the interview. Proxy informants were usually relatives but could sometimes be a friend/ neighbour or a warden or member of staff in a care home. Observations by the interviewer were also gathered during the course of the interviews.

1.3. Did participants have a formal diagnoses of dementia?

RE: Yes, these are all people with a confirmed diagnosis of dementia. The explanation in the methods section has been improved (page 7) and a subheading saying “dementia diagnosis” has been added. The methods section of the abstract has also been slightly modified for a better understanding.

CHANGES IN TEXT: (Abstract, page 3):

HRQL was estimated in 110 participants aged 80+ years with a confirmed diagnosis of dementia with mild/moderate severity.

CHANGES IN TEXT: (Methods, page 7):

Dementia diagnosis

Dementia was diagnosed using a two-stage approach. At baseline, individuals who scored $\leq 23$ on the MMSE, and one in three individuals with a MMSE score of 24 or
were assessed using the Cambridge Mental Disorders of the Elderly Examination (CAMDEX) [26], a structured schedule specifically designed to detect mild dementia. Between the baseline interview and survey 3, six assessments for dementia were conducted. Based on the CAMDEX results, different dementia types were assessed including: Alzheimer’s disease (AD), vascular dementia (VaD), mixed (AD and VaD), dementia secondary to other causes, clouded/delirious state plus AD and clouded/delirious state plus VaD. Dementia diagnoses were also sought by checking death certificates for any mention of dementia as a cause of death and checking reports from interviews with relatives for the sub-sample of participants who donated their brains to research. No additional people with dementia were identified. For the present study, participants with a last confirmed diagnosis of dementia, from any CAMDEX assessment and MMSE score >10 (n=110, 40 men and 70 women aged 80-99) up until one year after Survey 3 were identified for inclusion in this analysis. Among those without a MMSE score, 2 people were diagnosed with minimal, 2 with mild and 2 with moderate dementia using the CAMDEX. The staging of dementia was calculated using cut-offs on the MMSE as follows: 11–20 = moderate; 21 and above = mild [27].

1.4. Why were participants with an MMSE below 10 excluded?

RE: This has been explained in the methods, page 8. “Due to the high percentage of missing responses to HRQL items in the most cognitively impaired participants, only those with a MMSE score above 10 were included in the study, as has been suggested previously [28–30].”

1.5. What information was retrieved from the caregivers?

RE: When CC75C surveys included proxy informants, the same data (excluding subjective questions such as all HRQL questions and cognitive assessments) were collected from the proxy informant regarding the study participant as would have been collected from the participants themselves.

CHANGES IN TEXT: (Methods, page 6):
Interviews were conducted with the study participants and a proxy informant if the participant was unable to complete the interview. Proxy informants were usually relatives but could sometimes be a friend/neighbour or a warden or member of staff in a care home. Observations by the interviewer were also gathered during the course of the interviews. Core data included information on socio-demographic variables (e.g. place of residence, household structure, marital status and social contact), activities of daily living (ADLs), use of health and social services, cognitive function (e.g., Mini Mental State Examination (MMSE) [25]), health problems and medication. This data except for HRQL and cognitive assessments was retrieved from the caregivers if necessary.

1.6. Add paragraph analysis instead of psychometric evaluation. Be explicit; indicate how the psychometrics are assessed. It is not sufficient to mention standard methods were used.
RE: Following the reviewer’s suggestion, we have replaced the title “psychometric evaluation” with “analysis”. We have also deleted the sentence “Content validity is the extent to which items are representative of the conceptual domain it is intended to cover (operationalisation)” since this was not measured but was implicit in the mapping. The following changes have also been made:

CHANGES IN TEXT: (Methods, page 9):
Criteria for acceptability were: missing data for summary scores <5% and normality of the distribution of the total score (Skewness measured with Shapiro-Francia, Shapiro-Wilk and Skewness test with a p value higher than 0.05 indicating normality). Criteria for internal consistency were Cronbach’s alpha ≥0.7. Convergent and discriminant validity were measured with Spearman correlations (r). Convergent validity is the evidence that the scale is correlated with other measures of the same or similar constructs and was deemed acceptable when r was 0.20 and higher. Discriminant validity is the evidence that the scale is not correlated with measures of different constructs and was deemed acceptable when r was below 0.20. Known group differences refer to the ability of a scale to differentiate groups who are expected to differ on the construct being measured. Differences in HRQOL scores by socio-demographic, functional and measures of disability and cognition were tested using the Wilcoxon Mann-Whitney tests (variables with two groups) and Kruskal-Wallis test (variables with more than two groups). Statistical significance was set at p<0.05.

1.7. On the other hand it is not needed to explain the types of validity. It is more valuable to mention how they were assessed.
RE: As suggested above, we have mentioned how each of the psychometric properties was assessed (point 1.6). We have also kept the explanations of the types of validity since not all the readers have to necessarily be familiar with these terms.

1.8. “Written informed consent was obtained from all participants if possible.” Please explain the if possible?
RE: Perhaps the “if possible” leads to confusion. By saying this we mean that for those deemed to lack capacity to give fully informed consent, and those unable to give consent in writing for reasons of physical disability, we needed a written proxy informed consent from a relative or caregiver well known to the participant. We have therefore deleted the words “if possible”.

1.9. Start with a description of the sample before findings are presented. Please make sure that tables and text are not redundant.
RE: The suggested change has been made.

1.10. Abstract needs revision. Please delete the first two sentences. These are not important in relation to the aim of the manuscript. However the aim remains a little unclear. The method section of the abstract lacks information. What is meant with standard psychometric methods? Results in abstract; values are
missing necessary to interpret the findings. For example high reliability and internal consistency?

RE: Following the reviewer’s suggestion, we have deleted the first 2 sentences of the abstract and made a number of changes. The following changes have also been made:

CHANGES IN TEXT: (Abstract, page 3):
The aim of this study is to explore the distribution of HRQL by functional and socio-demographic variables in a population-based setting.

Acceptability (missing values and normality of the total score), internal consistency (Cronbach’s alpha), convergent, discriminant and known group differences validity (Spearman correlations, Wilcoxon Mann-Whitney and Kruskal-Wallis tests) were assessed.

The HRQL score ranged from 0 to 16 and showed an internal consistency Alpha of 0.74. Validity of the instrument was found to be acceptable. Men had higher HRQL than women. Marital status had a greater effect on HRQL for men than it did for women. The HRQL of those with good self-reported health was higher than those with fair/poor self-reported health. HRQL was not associated with dementia severity.

1.11. “None of them has been validated in population settings.” To my best knowledge the instruments mentioned are validated, so it remains unclear what the authors state here.

RE: With this sentence we mean that even though all the mentioned scales were validated, they haven’t been validated in population-based samples. This is a matter of external validity since it would be more rigorous if the scales had been validated with a sample that is representative of a certain population (for example a representative sample of the UK).

CHANGES IN TEXT: (Background, page 5):
Lastly, a limitation of all scales is that none has been validated in a population-based sample.

1.12. The authors state that the paper has two parts. Preferably the intro would end with two clear research questions.

RE: We have replaced this sentence since we consider that it is more important to state the aim of the paper.

CHANGES IN TEXT: (Background, page 6):
Therefore, the aim of this study was to explore the distribution of HRQL by functional and socio-demographic variables, mapped using items of the DEMQOL scale, using data from the Cambridge City over 75s Cohort (CC75C).

1.13. I would strongly advise the authors to rewrite the method section. The methods start by an extensive explanation of the mapping of the questionnaire. The section is difficult to read. References to for example Survey 3 are unclear.

RE: We think moving the subsection “sample and design” to the beginning of the methods section has helped clarifying this section. The methods section now explains the how the sample and the data were obtained (from survey 3 those who had a
positive diagnosis in their last CAMDEX assessment and MMSE >10). Then it describes the independent variables. Then it explains how the dependent variable was mapped and created (out of items in survey 3 corresponding to subdomains in the DEMQoL conceptual framework). Finally it explains how those psychometric properties were analysed.

This section has been thoroughly modified for a better understanding of the readers.

1.14. The mapping itself or/and the meta analysis may be material for a separate publication.
RE: Whereas it is true that especially the meta-analysis could be material for a separate publication, both the meta-analysis and the mapping are very closely related to our primary objective. We have decided to include the meta analysis as a separate report, deleting information on it from the main text and leaving a reference in the methods-analysis subsection. The psychometric evaluation has been kept in the manuscript.

1.15. It would improve the method section to start with sample and design.
RE: The suggested change has been made.

1.16. There is a lot of emphasis on the psychometrics; however this was not a research question.
RE: It is true that the psychometrics is not the main objective of this paper even though it is important since it determines the validity and reliability of our dependent variable. Therefore we have deleted the “summary of scale development” subsection in the discussion and a sentence on the psychometric properties in the conclusion.

1.17. Presentation of the findings can be improved by using clear subheading that relate to research questions.
RE: since there is now only one research question (the main objective) we have left the original subheadings but we have improved the one that relates to the main objective. This one says now “Distribution of HRQL by socio-demographic and clinical variables” instead of “Distribution of HRQL”

1.18. Tables are too comprehensive and do not provide a clear insight.
RE: Following the reviewer’s suggestion, we have removed the “n” and range off tables 5a and 5b, leaving only the median and interquartile difference.

1.19. The discussion section in general could be more structured with regard to your aim. Please revise this section. It is quite long and on the other hand it does not highlight most important findings.
RE: Following the reviewer’s suggestion, we have re-structured the discussion. For example, given that the main objective of the study was to assess the distribution of HRQL in very old individuals, we have moved the sentence on the acceptable psychometrics of our new instrument to the strengths section. The subsection “summary of scale development” has been deleted leaving only the subsection “summary of distribution of HRQL” (main objective). We have also enriched this subsection strengthening its findings.
2.1. Please provide information as to how many papers were screened and how many selected for the meta analysis. Was any attempt made to source papers that were not published?

RE: We have added three sentences in the results section and a flowchart in the annex in order to provide information on how many papers were screened and selected for meta-analysis. No non-published papers were sourced.

CHANGES IN TEXT: (Annexed report):
Results from our meta-analysis are shown in table 2. The search strategy identified 848 records after duplicates were removed. Title and abstract screening eliminated 772 articles and full-text screening eliminated 47 articles. Twenty-nine studies were finally included in the meta-analysis. From these we predicted that age would not be associated with HRQL in people with dementia and that being a man, having higher cognitive function, more years of education, being married, having less disability and better self reported health would be associated with higher HRQL.

2.2. The authors need to strengthen the discussion comparing the instrument they developed to existing measures, it's strengths and weaknesses.

RE: Following the reviewer’s suggestion, we have added the following sentences to the strengths/weaknesses subsections of the discussion:

CHANGES IN TEXT: (See discussion, pages 15 and 16):
“Strengths”

…
One of the strengths of the DEMQOL conceptual framework is that it was developed using a combination of interviews with people with mild to severe dementia and their non-professional caregivers and a review of the literature and existing instruments. The adapted version of the DEMQOL using the CC75C study questions has been shown to have acceptable psychometric properties suggesting that this scale fulfils standard criteria for acceptability, good internal consistency, and validity, namely content validity, discriminant validity and to some extent, known group differences. These properties have been tested in a population sample, providing therefore evidence of external validity of this instrument. Something no dementia-specific measure has proved yet [18]. Another strength of our instrument is the breadth of dimensions measured compared to dimension-specific instruments such as the Progressive deteriorations Scale (PDS) [33] or a number of other dementia-specific HRQL measures [34–38].

“Weaknesses”

…
There are other limitations, principally arising from the methodology of exploring HRQL, previously un-researched in this sample in which HRQL had not been assessed using existing dementia-specific measures. Firstly, since the instrument has been designed a posteriori, the question stems, response options and time frame of the questions were not identical to those from the DEMQOL framework. A limitation of
our instrument compared to other instruments such as ADRQL [13] or QUALIDEM [20] or DEMQOL proxy [22] is that HRQL in people with severe dementia could not be analysed given the high percentage of missing values and the lack of proxy ratings for HRQL items. Compared to the original DEMQOL [22] and Bath Assessment of Subjective Quality of Life in Dementia (BASQID) [42] our instrument did not include items on worry/satisfaction with cognition and activities of daily living.