PEER REVIEW HISTORY

BMJ Paediatrics Open publishes all reviews undertaken for accepted manuscripts. Reviewers are asked to complete a checklist review form and are provided with free text boxes to elaborate on their assessment. These free text comments are reproduced below.

ARTICLE DETAILS

TITLE (PROVISIONAL)	Health Related Quality of Life (HRQOL) in children and adolescents with congenital heart disease - A cross-sectional survey from South India.
AUTHORS	Raj, Manu; Sudhakar, Abish; Roy, Rinku; Champaneri, Bhavik; Sudevan, Remya; Kabali, Conrad; Kumar, Raman

VERSION 1 – REVIEW

REVIEWER	Reviewer name: Harron, Katie Institution and Country: UCL Great Ormond Street Institute of Child Health Competing interests: None
REVIEW RETURNED	27-Jul-2018

GENERAL COMMENTS	This paper presents results of a cross-sectional survey of Health Related Quality of Life in children and adolescents with CHD in South India. A large amount of results are presented. I understand that the authors are limited by the word count, but there are some important aspects that lack detail (see specific points below). The main issue is the treatment of the likert scale as continuous, and the interpretability of results based on this outcome. 1. A more detailed description of the selection and characteristics of controls should be provided (including in table 1). The basic baseline data of controls should be described alongside that of the subjects in paragraph 1. 2. The definition of adolescents should be provided. 3. The children that were excluded from the study due to acute illness should be described and included in Figure 1 – how many were there are? 4. The transformed likert scale is treated as continuous normal. This should be justified or a non-parametric approach should be used. A mean difference of 19.2 between groups on a transformed likert scale is difficult to interpret, and the authors should consider whether a more interpretable approach could be taken, for example, analysis of the difference in proportion of children with significantly impaired HRQOL in each group / by FCC. 5. In line with the above, more detail of the linear regression models should be provided. Were assumptions met? Which adjustment variables (e.g. gender, socio-economic status and domicile) had an effect on the outcome, and what were the effect sizes? 6. It is difficult to interpret the percentages with significantly impaired HRQOL in children with CHD, as we are not given the numbers with significantly impaired HRQOL in the control group. 7. A large number of comparisons are made. How did the authors deal with multiplicity?

	8. The inclusion of methods within the results section makes the paper difficult to read. For example, details of using Cronbach's alpha for assessing reliability is given in the results – this should be in the methods section. Similarly, how prevalence was estimated, details of the subgroup analysis classification, and use of the ICC to compare parent and child agreement. 9. When comparing proxy and self-reported HRQOL (page 10) it would make sense to compare values for the same age groups. It is not clear whether this was done in the comparison in table 3, nor why some of the lines in Table 3 appear to be repeated. 10. Why were self reports not provided for all children aged over 5? Were those who didn't provide self reports different from those who did? The number and details of those not provided should be included.

VERSION 1 – AUTHOR RESPONSE

Reviewer comments to the Author & Responses from the Author team.

This paper presents results of a cross-sectional survey of Health Related Quality of Life in children and adolescents with CHD in South India. A large amount of results are presented. I understand that the authors are limited by the word count, but there are some important aspects that lack detail (see specific points below). The main issue is the treatment of the Likert scale as continuous, and the interpretability of results based on this outcome.

1. A more detailed description of the selection and characteristics of controls should be provided (including in table 1). The basic baseline data of controls should be described alongside that of the subjects in paragraph 1.

Action: We have included the suggested details of controls in the revised manuscript. Table 1 & Figure 1 are also updated accordingly.

2. The definition of adolescents should be provided.

Action: The PedsQL adolescent module is for ages 13- 18. We are using the same cut-off for adolescents for this study. The definition is also provided in the revised manuscript.

3. The children that were excluded from the study due to acute illness should be described and included in Figure 1 – how many were there are?

Action: There were only 5 children who were excluded from the study due to emergency surgery scheduling. We didn't describe them as the numbers are very small. The excluded number is mentioned in the revised manuscript and also represented in revised Figure 1.

4. The transformed Likert scale is treated as continuous normal. This should be justified or a non-parametric approach should be used. A mean difference of 19.2 between groups on a transformed likert scale is difficult to interpret, and the authors should consider whether a more interpretable approach could be taken, for example, analysis of the difference in proportion of children with significantly impaired HRQOL in each group / by FCC.

Action: We accept the reviewer's observation that the HRQOL data is not normally distributed. We apologize for this error as we were influenced by the multitude of papers published earlier treating HRQOL as a normally distributed variable. We have redone the analysis using quantile regression model and reported the adjusted median difference which is appropriate for this distribution. As we are convinced that the distribution is not normal, a mean – 1SD cut-off is also not appropriate.

So we are removing this categorization as well. We are also avoiding ICC based comparisons of parent child report concurrence due to the same reason.

5. In line with the above, more detail of the linear regression models should be provided. Were assumptions met? Which adjustment variables (e.g. gender, socio-economic status and domicile) had an effect on the outcome, and what were the effect sizes?

Action: We have used a quantile regression instead of the previous linear regression in the revised manuscript. We have adjusted the median difference for probable confounders like age, gender, SES and rural/urban domicile. The effect sized for adjusted variables were minimal (Median Difference of 2 to 4 for those reported significance) and lacked any consistent pattern. Hence, we didn't mention the effect sizes of confounders in the revised manuscript.

6. It is difficult to interpret the percentages with significantly impaired HRQOL in children with CHD, as we are not given the numbers with significantly impaired HRQOL in the control group.

Action: We have removed the percentage wise categorization as mean – 1 SD becomes obsolete in non-normal distributions.

7. A large number of comparisons are made. How did the authors deal with multiplicity?

Action: We have reduced the comparisons and used a reduced alpha error margin (Bonferroni correction) for subgroup comparisons in the revised version. Our initial choice of alpha 0.01 was also in view of multiple comparisons.

8. The inclusion of methods within the results section makes the paper difficult to read. For example, details of using Cronbach's alpha for assessing reliability is given in the results – this should be in the methods section. Similarly, how prevalence was estimated, details of the subgroup analysis classification, and use of the ICC to compare parent and child agreement.

Action: We have moved the corresponding text to the methods section in the revised version.

9. When comparing proxy and self-reported HRQOL (page 10) it would make sense to compare values for the same age groups. It is not clear whether this was done in the comparison in table 3, nor why some of the lines in Table 3 appear to be repeated.

Action: Age stratified comparisons are done in revised Tables 2 & 3 with corresponding CI and p values for median differences specific for each strata in the revised manuscript. Table 3 is revised.

10. Why were self-reports not provided for all children aged over 5? Were those who didn't provide self reports different from those who did? The number and details of those not provided should be included.

Reply: We were unable to collect self-reports from six children. We didn't report the details of the missing population as the same was only 2% of total sample.

VERSION 2 – REVIEW

REVIEWER	Reviewer name: Peter Flom Institution and Country: Peter Flom Consulting, USA Competing interests: None
REVIEW RETURNED	25-Oct-2018

GENERAL COMMENTS	I confine my remarks to statistical aspects of this paper. The general approach is fine; I have some minor suggestions.

	I also reviewed the authors' responses to an earlier stat review, and they seem fine. ABSTRACT The authors need to say what is in the parentheses after the median. I'm guessing it is interquartile range, but I am not sure. More spacing between numbers and words would help readability. What are "summary values"? Page 5 - what does "dual phase" mean? - I think the study by Uzark was used to calculate effect size, then software was used to calculate the required sample Page 7 - Perhaps specify that the transformation was to make interpretability easier. It doesn't change the analysis or the meaning. "Sub group comparisons were interpreted by p values with Bonferroni correction" this can't be good. The comparisons should be based on effect size. The p value is just there to see if the result is statistically sig, but p values should not be used for other purposes. Page 8 - Why were the ratios of CHD to control so different in children and adolescents?

REVIEWER	Reviewer name: Shanti Raman Institution and Country: South Western Sydney Local Health District, Australia Competing interests: None
REVIEW RETURNED	19-Dec-2018

GENERAL COMMENTS	This is a really important topic and the authors are to be congratulated to have got this done in India where there are so many competing priorities. Having said that, there are a number of issues to be addressed to improve the readability and highlight the findings of this study. For example the use of “self-administered” instead of just stating that parents and children filled out this – questionnaire, comprising of components of ---. Also words like “deficiency” perhaps could be replaced by “limitation” or “reduction in HRQOL”. I would like to see more on the context, emphasis and analysis of the complexity receiving appropriate surgical intervention and treatment for CHD in India and LMICs so that the results of this study can be more appropriately appreciated. This paper would benefit from re-writing and judicious editing. Specific edits Abstract Should be re-done for simplicity. Would have been simpler by far, to just have Objectives; Methods (or Design); Results; Conclusions as headings. Text does not fall neatly into the headings. Methods are not explained adequately. For eg: how were patients and controls selected? What language was the HRQOL in, what literacy level expected?

	Objectives: add We sought to compare HRQOL of children and adolescents with uncorrected CHD to (that of) controls using Pediatric Quality of Life Inventory Setting: change to: a) hospital based survey (of) CHD patients and caretakers b) community survey (of) controls This text: “Study questionnaires were self-administered for parents and children (≥8 years) including adolescents. Parents assisted children 5-7 years of age in filling the questionnaires” should not come under Main outcome measures. Instead it describes Methods. Who fills out proxy measures for what age group? Not clear. Would be best to say under Methods, something simple like: Children and parents with CHD enrolled in a previous study (308) and unmatched community controls (719) (children and parents) between ages of 2-18 years were given the ---Pediatric Quality of Life Inventory (PedsQL 4.0 to fill out (self-administered is not necessary). Parents assisted children 5-7 years of age in filling the questionnaires. Say something about proxies. Key words: should include “quality or life”; Introduction I would structure Intro into 2 or 3 paragraphs. Need to make the case for this study: ie that not enough is known about the HRQOL of children with chronic health limitations such as CHD in LMICs. Go from general to the specific. Also what the previous study of HRQOL in this institution already showed. Then what is the reason for doing this study. There is no mention made of the context of this study- ie done in the South Indian State of Kerala, in an institution that draws ? a wide cross section of the society—clarify please. Is reference 1 (superscript) at end of first sentence the same as reference 1 in parenthesis at end of second sentence? Change: These advancements currently reflect in the increased survival of newborns with CHD to adulthood to “These advancements play a significant role in the increased survival of newborns with CHD to adulthood” What does this mean: scholastic as well as professional deficiencies? Educational and employment outcomes? Simplify this statement, too convoluted: Estimation of HRQOL has gained special consideration in childhood due to the effect that its deficiency can cause in long-term, in addition to the benefit that early interventions focusing on its enhancement can deliver The primary objective of the study is stated as: to compare proxy report based generic HRQOL values of children with uncorrected CHD with their control counterparts. Why is this the primary objective- what is special about ‘proxy’ measures of QOL? Are they somehow more accurate than self-reported QOL? Methods Still need more description about recruitment of the sample and controls and also of the setting. What was the cultural, class and linguistic diversity if any? Not enough to say “We recruited 719 controls by means of a community survey, the results of which were published recently”. Were they matched for age/class/gender etc? Just a sentence would do. Although you state that: Children/adolescents with uncorrected CHD were recruited, it is stated elsewhere that a small portion (22%) had previous surgery and many are on cardiac medications. Clarify.

	Also proxies are not clarified? When were proxies filled out? When children were too young or could not understand the language or too sick to fill out? Please re-phrase: Questionnaires were self-administered for parents/caretakers, older children (age > 8 years) and adolescents to: Parents/caretakers, children >8 years and adolescents (13-18 years) filled out the PedsQL 4.0 Generic Core and Cardiac modules for children and adolescents. Ethical approval: one sentence about this should suffice. Results Sub group analysis (LRS, DPB, IPB & SVP) are never spelled out anywhere in the text that I could find, only seem to appear in Tables. Also “and” is just as good if not superior to “&”! Discussion 1st para: Need to have a big opening statement: if this is the first large study of its kind from South Asia or even LMIcs- then state it. Replace: “On the contrary” with “By contrast”. Also “deficiency” can be replaced by limitation. And please don’t use “&” within sentences. P13: The very existence of older children/adolescents with uncorrected CHD in our study points to the late presentation and/or later adoption of corrective treatment in a significant subset of those born with CHD. Can the authors provide more context here? What is known about access to appropriate intervention for CHD in India, LMICs. Strengths and Limitations Do you need to mention the 22% of children in your sample who have had previous surgical correction of CHD? Did they differ in scores? Exclusion of acutely ill CHD patients is not a limitation- it makes perfect sense to do so. The authors mention: “deficiency of geographical and ethnic diversity” but they have not provided any description of the sample or the setting previously. Conclusions I think “reduction in HRQOL” is better than deficiency. Also perhaps ‘deficits’ rather than deficiencies in physical functioning and school functioning is preferable. What is already known (better in point form) Rephrase: HRQOL deficiency during childhood/adolescence in the backdrop of other CHD morbidity including neurodevelopmental issues and treatment related economic impact may have long term consequences to: Reduction in HRQOL during childhood and adolescence for those with CHD and attendant co-morbidities such as neurodevelopmental issues, may have long term negative consequences. What this study adds (better in point form) • Health Related Quality of Life of Indian children and adolescents with uncorrected congenital heart disease (CHD) differ(s) significantly from their control counterparts. • There is an overall ‘reduction’ in total HRQOL as well as…

VERSION 2 – AUTHOR RESPONSE

Reviewer: 1

I confine my remarks to statistical aspects of this paper. The general approach is fine; I have some minor suggestions.

I also reviewed the authors' responses to an earlier stat review, and they seem fine.

1. ABSTRACT

The authors need to say what is in the parentheses after the median. I'm guessing it is interquartile range, but I am not sure.

Response: The values in parentheses are IQR. We have mentioned the same in the revised abstract.

2. More spacing between numbers and words would help readability.

Response: We have complied with this suggestion in the revised version.

3. What are "summary values"?

Response: They were just values. The word summary is removed in the revised version.

4. Page 5 - what does "dual phase" mean?

Response: We actually meant dual setting. The word phase is removed and replaced by setting in the revised version.

5. - I think the study by Uzark was used to calculate effect size, then software was used to calculate the required sample

Response: Yes. The study by Uzark et al was used to calculate effect size and a software was used to calculate the required sample size.

6. Page 7 - Perhaps specify that the transformation was to make interpretability easier. It doesn't change the analysis or the meaning.

Response: We have added the suggested information to the revised version.

7. "Sub group comparisons were interpreted by p values with Bonferroni correction" this can't be good. The comparisons should be based on effect size. The p value is just there to see if the result is statistically sig, but p values should not be used for other purposes.

Response: we apologize for the confusion from the text. What we meant was that the sub group analysis were examined for statistical significance and Bonferroni corrected p values were reported. We agree that clinical interpretation needs to be based on the effect size seen. The text is appropriately modified in the revised version.

Page 8 - Why were the ratios of CHD to control so different in children and adolescents?

Response: The controls were selected from the community and the age distribution represents that seen in the population. The CHD patients have a different age structure. As more and more children are surgically corrected as they age, the age structure will be different from that seen in the population. There will always be more of young children with uncorrected CHD at any given period compared to adolescents with uncorrected CHD.

Reviewer: 2

Comments to the Author

This is a really important topic and the authors are to be congratulated to have got this done in India where there are so many competing priorities. Having said that, there are a number of issues to be addressed to improve the readability and highlight the findings of this study.

1. For example the use of “self-administered” instead of just stating that parents and children filled out this – questionnaire, comprising of components of ---. Also words like “deficiency” perhaps could be replaced by “limitation” or “reduction in HRQOL”.

Response: We agree with the reviewer suggestion. Appropriate corrections are made in the revised version.

2. I would like to see more on the context, emphasis and analysis of the complexity receiving appropriate surgical intervention and treatment for CHD in India and LMICs so that the results of this study can be more appropriately appreciated. This paper would benefit from re-writing and judicious editing.

Response: We agree with the reviewer suggestion. Appropriate corrections are made in the revised version. Additional details are provided in the discussion section to highlight the complexity of receiving appropriate surgical intervention and treatment for CHD in India.

Specific edits

Abstract

3. should be re-done for simplicity. Would have been simpler by far, to just have Objectives; Methods (or Design); Results; Conclusions as headings.

Response: We have restructured the abstract into the four suggested headings.

4. Text does not fall neatly into the headings.

Response: we have redone the sections in the revised abstract.

5. Methods are not explained adequately. For eg: how were patients and controls selected? What language was the HRQOL in, what literacy level expected?

Response: Patients and controls were enrolled sequentially till the required numbers were completed. The tool was available in Malayalam/tamil and the literacy level expected was middle school (grade 7 or above). This detail was not given due to limitation in the abstract word count. The same is stated more clearly in the revised methods section.

6. Objectives: add We sought to compare HRQOL of children and adolescents with uncorrected CHD to (that of) controls using Pediatric Quality of Life Inventory

Response: objectives modified as per reviewer suggestion.

7. Setting: change to: a) hospital based survey (of) CHD patients and caretakers b) community survey (of) controls

Response: setting modified as per reviewer suggestion.

8. This text: “Study questionnaires were self-administered for parents and children (≥8 years) including adolescents. Parents assisted children 5-7 years of age in filling the questionnaires” should not come under Main outcome measures. Instead it describes Methods.

Response: the text moved to the methods section of the abstract as per the suggestion.

9. Who fills out proxy measures for what age group? Not clear.

Response: All enrolled subjects (2-18 years, CHD subjects as well as controls) had a proxy report by the parent/ caretaker. Children 5 years or older (CHD subjects as well as controls) had in addition, a self-report. This detail was not given due to limitation in the abstract word count. The same is stated more clearly in the revised abstract as well as methods section.

10. Would be best to say under Methods, something simple like: Children and parents with CHD enrolled in a previous study (308) and unmatched community controls (719) (children and parents) between ages of 2-18 years were given the ---Pediatric Quality of Life Inventory (PedsQL 4.0 to fill out (self-administered is not necessary). Parents assisted children 5-7 years of age in filling the questionnaires. Say something about proxies.

Response: The methods section of the revised abstract is modified as per the suggestion.

11. Key words: should include “quality or life”;

Response: Keywords can only be picked from a predefined list in the manuscript submission system of the journal. We will notify the editorial section of this suggestion to include quality of life in the keyword list.

Introduction

I would structure Intro into 2 or 3 paragraphs.

12.a Need to make the case for this study: ie that not enough is known about the HRQOL of children with chronic health limitations such as CHD in LMICs. Go from general to the specific.

Response: the suggested change is added to the revised introduction.

12.b Also what the previous study of HRQOL in this institution already showed.

Response: the suggested change is added to the revised introduction.

12.c Then what is the reason for doing this study.

Response: the suggested change is added to the revised introduction.

12.d There is no mention made of the context of this study- ie done in the South Indian State of Kerala, in an institution that draws ? a wide cross section of the society—clarify please.

Response: The introduction is restructured as per the suggestions of the reviewer. The case for the study, reason and context are added to the revised introduction section.

13. Is reference 1 (superscript) at end of first sentence the same as reference 1 in parenthesis at end of second sentence?

Response: Yes. It’s a formatting error.

14. Change: These advancements currently reflect in the increased survival of newborns with CHD to adulthood to “These advancements play a significant role in the increased survival of newborns with CHD to adulthood”

Response: suggested change included in the revised version.

15. What does this mean: scholastic as well as professional deficiencies? Educational and employment outcomes?

Response: Yes. We have modified the text to make it simpler in the revised version of introduction.

16. Simplify this statement, too convoluted: Estimation of HRQOL has gained special consideration in childhood due to the effect that its deficiency can cause in long-term, in addition to the benefit that early interventions focusing on its enhancement can deliver

Response: We have simplified the marked sentence for better readability.

17. The primary objective of the study is stated as: to compare proxy report based generic HRQOL values of children with uncorrected CHD with their control counterparts. Why is this the primary objective- what is special about ‘proxy’ measures of QOL? Are they somehow more accurate than self-reported QOL?

Response: There is no definite opinion on the best available HRQOL report from children/adolescents. Current literature suggests to extract both if possible and look at them collectively (from two different view points). We suggested proxy as primary objective due to the fact that it is the only type that can be extracted from all study subjects (2-18 years) in the current study. Self-reported HRQOL can only be collected from ages 5 years and above (5-18 years of age only) and will be absent in more than half of the study subjects. Hence, we mentioned it as a secondary objective. This discretion was purely on feasibility grounds.

Methods

18. Still need more description about recruitment of the sample and controls and also of the setting.

Response: we have added additional details regarding recruitment and setting.

19. What was the cultural, class and linguistic diversity if any?

Response: There was moderate cultural and wide socio economic class diversity (table 1). Linguistic diversity was restricted to just Malayalam and Tamil speaking (8.8%) subjects. The same is mentioned in the revised version.

20. Not enough to say “We recruited 719 controls by means of a community survey, the results of which were published recently”.

Response: we have added more details about control selection in the revised methods section.

21. Were they matched for age/class/gender etc? Just a sentence would do.

Response: The controls were not matched for age/class/gender. We have added a line to inform the same.

22. Although you state that: Children/adolescents with uncorrected CHD were recruited, it is stated elsewhere that a small portion (22%) had previous surgery and many are on cardiac medications. Clarify.

Response: The uncorrected population of CHD includes a portion of children/adolescents with prior palliative/ stage 1 surgical interventions. Their lesions are not fully corrected and behave more like uncorrected CHD lesions. This detail as well as the proportion taking medications are given as descriptive details to enable future comparisons with other studies. Most studies with CHD patients mention these two proportions for a better understanding of the sample population.

23. Also proxies are not clarified? When were proxies filled out? When children were too young or could not understand the language or too sick to fill out?

Response: All recruited children/adolescents (CHD as well as controls) had a proxy report filled by the parent/caretaker. Children 5 years or older had in addition a self-report filled by themselves. This detail is added to the revised version to avoid the confusion as to who has a proxy and who has a self-report in the study sample.

24. Please re-phrase: Questionnaires were self-administered for parents/caretakers, older children (age > 8 years) and adolescents to: Parents/caretakers, children >8 years and adolescents (13-18 years) filled out the PedsQL 4.0 Generic Core and Cardiac modules for children and adolescents.

Response: The sentence rephrased as per suggestion in the revision.

25. Ethical approval: one sentence about this should suffice.

Response: The section edited to a single sentence in the revised manuscript.

Results

26. Sub group analysis (LRS, DPB, IPB & SVP) are never spelled out anywhere in the text that I could find, only seem to appear in Tables. Also “and” is just as good if not superior to “&”!

Response: The expansions of the abbreviations (LRS, DPB, IPB & SVP) are spelled out in the methods section. In addition, the comparisons are described in the results section.

Discussion

27. 1st para: Need to have a big opening statement: if this is the first large study of its kind from South Asia or even LMIcs- then state it.

Response: The opening paragraph of the revised discussion section states the suggested point.

28. Replace: “On the contrary” with “By contrast”. Also “deficiency” can be replaced by limitation. And please don’t use “&” within sentences.

Response: The suggested changes are included in the revised discussion section.

29. P13: The very existence of older children/adolescents with uncorrected CHD in our study points to the late presentation and/or later adoption of corrective treatment in a significant subset of those born with CHD. Can the authors provide more context here? What is known about access to appropriate intervention for CHD in India, LMICs.

Response: we have provided more context in the revised version of discussion section and the same is supported by appropriate reference.

Strengths and Limitations

30. Do you need to mention the 22% of children in your sample who have had previous surgical correction of CHD? Did they differ in scores?

Response: All studies with uncorrected CHD will likely have a subset of children/adolescents who had palliative/ first stage correction and are waiting for a second surgical intervention. This detail is provided for the sake of future comparisons with similar studies. We didn't look for score differences between previously operated and never operated groups as the sample was not powered to detect such a difference.

31. Exclusion of acutely ill CHD patients is not a limitation- it makes perfect sense to do so.

Response: This detail is removed from the list of limitations.

32. The authors mention: "deficiency of geographical and ethnic diversity" but they have not provided any description of the sample or the setting previously.

Response: The marked portion is removed from the limitations section of the revised manuscript.

Conclusions

33. I think "reduction in HRQOL" is better than deficiency. Also perhaps 'deficits' rather than deficiencies in physical functioning and school functioning is preferable.

Response: The suggested change is included in the conclusions section of the revised manuscript.

What is already known (better in point form)

34. Rephrase: HRQOL deficiency during childhood/adolescence in the backdrop of other CHD morbidity including neurodevelopmental issues and treatment related economic impact may have long term consequences to: Reduction in HRQOL during childhood and adolescence for those with CHD and attendant co-morbidities such as neurodevelopmental issues, may have long term negative consequences.

Response: The suggested change is included in the revised version.

What this study adds (better in point form)

35.

• Health Related Quality of Life of Indian children and adolescents with uncorrected congenital heart disease (CHD) differ(s) significantly from their control counterparts.

• There is an overall 'reduction' in total HRQOL as well as…

Response: The suggested changes are included in the revised version.