Author's response to reviews

Title: Health-related quality of life in epilepsy adults: the effect of age-related factors in a multicentric Italian study

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Author's response to reviews: see over
Melissa Norton,
Editor-in-Chief
BMC Neurology

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Dear Dr. Norton,

following the letter written on June, 23rd, 2010, thank you for considering our manuscript, “Health-related quality of life in epilepsy adults: the effect of age-related factors in a multicentric Italian study”.

We are enclosing the revised manuscript after the suggested modifications. The comments from the reviewers were quite helpful, and we believe the revisions have made this a clearer and stronger manuscript. Please find our point-by-point responses to the reviewer’s comments below (Q for question and A for answer).

According to the author’s instructions, tables 1 and 2 were originally uploaded as additional files, as table 1 was in landscape format, and table 2 was more than 2 pages long. However, both tables are quite important for us and we want every reader to see them. For this reason, we put table 1 in a portrait format using acronyms to define the relevant variables, and we divided the original table 2 into two new tables (tables 2 and 3) of about 2 pages each. We did not make any modification to the text within the tables. We would be more happy if you can consider to insert the old table 1 (landscape format) into the main document, but we are still ok with the new table 1 (portrait format) in the text.

I would be happy to assist your editorial staff in the event that further questions arise, and I look forward to receiving your final decision.

Thank you for your attention.

Yours Sincerely,

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Reviewer: Mike Kerr

All the following are minor comment:

This is an interesting secondary analysis of a large data set exploring QOL in people with epilepsy. The authors make a good case for their project in the introduction, rightly identifying the need to explore age related impacts on QOL. I feel further clarification of the points below may improve this already good paper.

Q1. I think the title could reflect better the paper and could say age, age of onset and duration of epilepsy.

A1. We modified the title as: “Health-related quality of life in adults with epilepsy: the effect of age, age at onset and duration of epilepsy in a multicentric Italian study”.

Q2. The introduction: firstly I believe the nature of the sample should be recognised.

1. The reader should be aware this is a non epidemiological convenience sample of refractory? Or at least certainly not new onset epilepsy.

2. Secondly, the results are a little hard to understand-it would be help for the paper to say exactly what it found.

A2.1. Our sample is basically a convenience sample, but we tried to make it more representative and to avoid potential selection bias through the enrollment of consecutive patients. Moreover, a small portion of the sample was represented by new onset epilepsy patients (3.9%), but more than 50% of the sample included subjects being in remission for more than a year. We specified this point in the Results subsection (see A3.).

A2.2. We modified the abstract in the following way (see also Q6): “Although age at onset is a positive predictor of the overall HRQOL of borderline significance, age and duration of epilepsy can be expected to have a significant negative association with HRQOL in epilepsy - if no other known correlates of the overall Epi-QoL score are considered - with the effect of duration being stronger and more consistent across models than the one of age.”

We also modified the conclusions in the following way: “The main conclusion is that age, age at onset, and duration of epilepsy have only a limited role in determining the overall HRQOL: although age and duration of epilepsy show a generally significant negative effect (with the effect of duration being stronger and more consistent across models than the one of age), and age at onset a positive effect of borderline significance, when other correlates of the overall Epi-QoL score are considered in the regression models, any significant effect of the age-related factors disappears.”

Q3. In the methods-Whilst I acknowledge the sample is described elsewhere –it is essentially impossible to judge the paper without more information. In particular number of drugs taken current seizure frequency etc that may help the reader visualise the sample and thus understand better the QOL information.

A3. We added the following sentence in the Results section: “Briefly, patients had a median age of 36 years, a median epilepsy duration of 16 years, and a median age at onset of seizures of 16 years (see also Table 2 (Additional file 2)). Almost 40% of patients had no seizures in preceding 12 months, 25.5% had from 1 to 5 seizures, 13% from 6 to 20, and 21.7% had more than 20 seizures. Most of the
patients had focal (74.3%) or generalized (22.2%) epilepsy, were in remission since more than a year (53.4%) or showed non-drug-resistant seizures (20.3%), and were in monotherapy (54.1%) or polytherapy (44.3%).”

Q4. I am not a statistician so could only review this aspect from a point of view of its clarity and understandability-I felt this was good.

Q5. The results section is interesting though I was a little confused about when age was a positive factor-I wonder if there is any diagrammatic way of representing these results to add to clarity?

A5. The age parameters showed some positive signs across the fitted models, but in all these cases they were not significant. For this reason, we did not comment on a potential positive effect of age on quality of life in the discussion. Unfortunately, there is no way to represent graphically results from multiple regression models.

Q6. The discussion: this is clear and excellent-in fact it is a more clear description of the very small effect of age on QOL then the abstract-again the abstract should state more clearly that ageing has a small impact with a greater influence of other age related factors.

A6. We modified the abstract and the conclusion accordingly (see also A2.2.). The new sentences are the following ones: “Although age at onset is a positive predictor of the overall HRQOL of borderline significance, age and duration of epilepsy can be expected to have a significant negative association with HRQOL in epilepsy - if no other known correlates of the overall Epi-QoL score are considered - with the effect of duration being stronger and more consistent across models than the one of age.”
Reviewer: Frank Besag

The authors have reported on statistical analyses of results from 815 adults recruited from a multi-centre study and have concluded that the age of the patient and the duration of the epilepsy are significantly associated with a poorer quality of life whereas age of onset of the epilepsy is associated with a better quality of life, although the last association was of only borderline significance.

The reviewer is not a statistician. Some of the issues that follow might not be relevant to readers of the paper that are statisticians but would be relevant to a general readership.

There appear to be major problems with this study. These include the following.

Q1.1. There was no control group.
Q1.2. It is hardly surprising that age should be associated with decreased quality of life, because comorbidity is likely to increase as age increases, regardless of whether the person has epilepsy or not.
A.1.1. We agree with the reviewer that this may be a limitation of the study; however, a comparison between epilepsy and the general population was not a major issue here as our aim was to correlate the score of the inventory to selected demographic and clinical features of the sample.
A.1.2. We definitely agree with this explanation. The question arises as to whether this is also true for adults with epilepsy. Anyway, most subjects in our study were young adults and relevant comorbidities were reported only in the 18.2% of the sample.

Q2. The authors have not discussed the issue of possible selection bias (see below).
A2. See reply A6.

Q3. The finding that early age of epilepsy onset was, if anything, associated with a higher quality of life rather than a lower quality of life, is counterintuitive and requires explanation. There are many reasons why exactly the opposite would be expected; these reasons include the fact that some of the severe, difficult-to-control epilepsies begin early in life and a lifetime of seizures is likely to represent a lifetime of decreased opportunities for the individual.
A3. According to our results, an older age at onset had a positive effect on HRQOL: HRQOL increased for categories of age at onset >10 years, compared to the reference one (0-10 years). So, an early age of epilepsy onset was associated with a lower quality of life, and it is exactly what you expected to see.
To further clarify the point: we added the following sentences in the Results section in the abstract:
“Simple regression models show that age and duration of epilepsy are significant negative predictors of the overall Epi-QoL score: the higher is each age-related factor, the lower is the overall Epi-QoL score.”
“Age at onset emerges as a significant positive predictor of the overall Epi-QoL score only in the model including age: the higher is age at onset, the higher is the overall Epi-QoL score.”

There are several specific issues that also need to be addressed.
Q4. The paper is rather repetitious.
A4. We tried to make it better.
For instance, in the Regression Models section-first sentence we deleted the parenthesis: (patient's age, age at seizure onset, and duration of epilepsy) and simplified this sentence and the next one.

Q5. The title needs to be corrected from: “Health-related quality of life in epilepsy adults...” to “Health-related quality of life in adults with epilepsy...”.
A5. We modified the title as: “Health-related quality of life in adults with epilepsy: the effect of age, age at onset and duration of epilepsy in a multicentric Italian study”.

Abstract and methods.

Q6. The patients were “recruited” but no indication is given of how they were “recruited”. This implies that the group might have been a highly-selected, biased population, with little or no relevance to the general population of the people with epilepsy.
A6. The paper already specified that patients were recruited consecutively from secondary and tertiary Italian centers for the care of epilepsy. However, it referred to a previous publication (reference 34) for details on the clinical characteristics of the sample.
In order to clarify that the sample was representative of the population of adults with epilepsy followed in those centers (and to reply to a point by Reviewer 1), we added the following sentence in the Results section: “Briefly, patients had a median age of 36 years, a median epilepsy duration of 16 years, and a median age at onset of seizures of 16 years (see also Table 2 (Additional file 2)). Almost 40% of patients had no seizures in preceding 12 months, 25.5% had from 1 to 5 seizures, 13% from 6 to 20, and 21.7% had more than 20 seizures. Most of the patients had focal (74.3%) or generalized (22.2%) epilepsy, were in remission since more than a year (53.4%) or showed non-drug-resistant seizures (20.3%), and were in monotherapy (54.1%) or polytherapy (44.3%).”
Except for the low proportion of cases with newly diagnosed epilepsy and the high proportion of patients receiving polytherapy, the main clinical characteristics of the sample do not differ significantly from those seen in population-based samples. We also managed to enroll consecutive cases among those seen in the centers’ outpatient services.
Moreover, in the discussion section, we also reported how our analysis would have changed if a subsample of adult patients with medication-resistant epilepsy were considered.

Q7. Epilepsy is not a disease, it is a disorder which may result from a number of different identifiable diseases or from no identifiable disease.
A7. We changed the term “disease” with “disorder” throughout the text.

Page 2. Background.

Q8. The second part (“given the impact…position in life”) of the first sentence is vague and probably should be deleted.
A8. We agree with you but this the way the World Health Organization introduced
epilepsy and its implications.

Page 3.

Q9. It is anticipated that most readers would find the first two sentences on this page obscure and difficult to understand.
A9. We tried to explain this point in a clearer way. We modified the text in the following way: “However, the linear relationship that links the three age-related factors (say, epilepsy duration = age - age at onset) prevents the inclusion in the same model of all the factors as continuous variables. The major implication of this issue is that the overall picture on age-related morbidity and HRQOL is only provided by the joint evaluation of the three models including single pairs of age-related factors.”

Q10. In the next sentence, correct: “has been rarely analysed” to “has rarely been analysed”.
A10. We changed it three times in the text.

Methods.

Q11. In the first sentence of this section what does “elaborated” mean?
A11. We changed the term “elaborated” with “developed”.

Q12. In the last sentence on this page what does “during ambulatory time” mean?
We changed the sentence as: “A semistructured questionnaire including information on socio-demographic characteristics and clinical variables was administered to outpatients by trained interviewers.”

Page 4.

Q13. The translation of the categories on the scale does not seem to make sense. What is the difference between “very frequently” and “very much”. The category “quite enough” in particular, does not appear to make sense.
A13. We checked the text and the categories were consistent with the ones presented in a previous publication assessing the psychometric properties of the questionnaire (reference 34). For this reason, we initially thought to keep these categories, although they do not appear to make sense. Then we looked at the questionnaire in Italian (the language we used for administering it) and we changed the categories in the text in the following way: “quite enough”=“sometimes”, “very frequently”= “almost always” and “very much”=“very frequently”.

Statistical analysis.

Q14. Much of this section would be incomprehensible to the general reader. The authors should give consideration to putting the statistical analysis into an extended appendix, leaving the body of the paper to the presentation of the results and the discussion of the clinical relevance of these results.
A14. We deleted most of this section. In detail, we deleted the following sentences: “The potential confounders were the same in all the fitted models.”
“Corresponding raw frequency and percentage distributions were calculated.”

“The skewed distribution of the residuals suggested to adopt a transformation of the dependent variable. As the dependent variable was strictly positive, we adopted the one-parameter Box-Cox method. We determined a suitable transformation of the form ….. The value corresponding to the maximum of the profile likelihood was between 2.3 and 2.4 in each of the fitted models. To improve comparisons across transformed models, we refitted all the models assuming the same transformation of the dependent variable …., and using the ordinary least-squares method.”

and modified the text of the next sentence as:

“However, as the p-values obtained from the corresponding models with a Box-Cox transformation of the response variable (y: $y^{\lambda=2.3}$) [39, 40] were similar to those obtained from the original models, we decided to present the results obtained with the original models with no transformation of the dependent variable.”

We also modified results and title of Figure 1 to make it easier.

Q15. The first sentence in this section needs to be rewritten, perhaps along the following lines.
“In accordance with the defined aim of the analysis, we carried out a preliminary identification of a set of variables of interest.”
A15. We changed the sentence as indicated.

Q16. In the third line of this section, where the authors have written “as the effects of interest” do they mean “as the parameters of interest”?
A16. We changed the term “effects of interest” with “main variables of interest”.

Q17. The sentence referring to the “reversal of those scales” needs to be rewritten in such a way as to make the meaning clear.
A17. We changed the sentence in the following way: “after reverse coding was applied to those scores corresponding to questions that were positively formulated”.

Descriptive analyses.

Q18. Where the authors have written “the elevated number” do they mean “the large number”.
A18. Yes, and we changed the text accordingly.

Regression models.

Q19. Second sentence. Where the authors have written “score was assumed as the dependent variable, whereas the age related factors…”, do they mean “score was chosen as the dependent variable, with the age related factors…”.
A19. We modified the sentence in the following way: “Ordinary least-squares regression models were used to assess the relationships between age-related factors, potential confounders, and overall Epi-QoL score, with overall Epi-QoL
score being the dependent variable, and age-related factors and potential confounders the independent ones.”

Q20. The following sentence is an example of the type of expression that would probably be meaningless to the non-statistician reader, as is the case for many of the sentences in this section.
“Checks of regression diagnostics were carried out for all the fitted models and revealed only limited adherence to the model assumption on normality of the error.”
A20. We tried to simplify the paper for non-statistician readers. For instance, we deleted the following sentences with some statistical details from the abstract: “We considered the age-related factors as continuous and categorical variables. Checks of regression diagnostics were carried out for all the fitted models.”
We also deleted most of the sentences in the statistical analysis section (see A14.).

Q21. What are “MASS” and “faraway”?
A21. We added the double quotes to the names, to give the general reader the idea that these are the names of specific packages provided with the R software.

Page 9.

Q22. Where the authors have written “copying mechanisms” do they mean “coping mechanisms”?
A22. Yes we did. We modified the text accordingly.