Reviewer's report

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

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Reviewer: Frank Besag

Reviewer's report:

The authors have improved this paper significantly but, in the opinion of the reviewer, there are still major reservations. Some of these may be rectifiable.

The abstract remains unclear.
The study was carried out on a selected sample.
There is no control group. The patient group is a selected one. The authors have not taken this adequately into account in their discussion. These factors could affect the results greatly.

If the reviewer has understood the situation correctly, the authors have embarked on carrying out an analysis which could be stated quite simply as follows.

“Health-related quality of life has been assessed in a selected group of adults with epilepsy, examining three age-related factors: age at onset, duration of epilepsy and age of the patient. Because these parameters are inter-related, the statistical analysis has included not only an examination of each of these factors on its own but also a regression analysis examining each of the factors while controlling for the other two.” The authors could then simply state what the results were, according to these types of analyses.

If the authors are of the opinion that details of the statistical analysis should appear then this information could be provided in an appendix, leaving the reader a much simpler task of examining the study outlined in the reviewer’s foregoing comments (in quotation marks above). The body of the paper would then consist of how the patients were recruited, a list of the hypothesis tested, the results obtained and a detailed discussion of the results, including a critical review of how these agree or disagree with previous studies, followed by appropriate conclusions.

Some detailed comments follow.

Comments that would probably not be comprehensible to the non-statistician
reader will be preceded by the words “Statistical comment” in what follows. These should either be rewritten in language that the general scientist could understand or should be moved to an appendix.

Page 1.
The usual word is “multicentre” not “multicentric”.

Statistical comment. “We fitted simple regression models including age-related factor alone. We also fitted multiple regression models including pairs of age-related factors solely, as well as one or two age-related factors together with the same set of confounders.”

Statistical comment. “Multiple regression models including two age-related factors show that duration of epilepsy is still a significant predictor of the overall Epi-QoL score in both pairwise models, whereas age is a significant negative only in the model including age at onset. 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. Adjusted regression models including one or two age-related factors, as well as the selected confounding variables, show that the age-related factors had no significant effect on the overall Epi-QoL score”.

With regard to the last sentence, this appears to contradict the conclusion that age-related factors are important. The authors should explain this apparent contradiction simply and clearly both in the abstract and the body of the paper. The authors need to be more precise in the last line of the abstract. The statement is as follows.

“However, additional information on demographic and clinical factors may provide a better explanation of HRQOL in epilepsy.”

Page 2 (continued).
Replace “each of the previous factors” with “each of these factors”.

The following sentence needs to be rewritten both from the point of view of language and also to enable the reader to understand what the authors intended.

“The simultaneous evaluation of two of these factors allows to take into account existing compounding phenomena.”

The reviewer did not understand the argument that the authors were trying to put forward here. Would it not be more appropriate to suggest that each of the factors was examined with and without controlling for the others?

Page 3.
Statistical comment. “The major implications 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.” Again, the reviewer did not understand this statement. Could the authors not simply state that they avoided analysing any two related factors at the same time, indicating simply how they did this.

The next sentence finishes with the words “compared with other disease-related factors”. The authors have not made clear what they are comparing with what.

Where the authors have written “We identified one study” do they mean “We identified only one study”?

Are the following words necessary or could they be deleted? “Including generic and specific questions about the more relevant determinations of HRQOL measured according to a”?

The sentence could then simply finish “using a variety of validated instruments...” Page 4.

Statistical comment. The section beginning statistical analyses up to and including the heading results should, in the opinion of the reviewer, all be placed in an appendix and should be replaced with a simple explanation of the essentials of the statistical analysis that would be comprehensible to a non-statistician scientist.

Page 5 (continued).

Replace “remission since more than a year” with “remission for more than a year”.

Replace “all showed non-drug-resistance seizures” with “all had non-drug-resistant seizures”.

If the last two sentences on this page are to be included in the body of the paper the authors should explain what the kernel densities are in language that a non-statistician scientist can understand.

Page 6.

In the sentence beginning: “Age was positively correlated with age at onset...”, the authors are referring to relationships between three variables that would be inter-related in any case. It was difficult to see what the point of this was. In the next sentence beginning: “The overall Epi-QoL score was correlated...”, with the potential confounders “psychiatric disturbances, number of drugs and intellectual functions” the authors do not provide details of these very broad variables nor do
they give information on either the degree or the significance of the correlations. Since, two sentences later, they state that in the simple regression models age at onset was not a significant predictor, this issue should be clarified better in the discussion.
Replace “to the one emerged” with “to the one that emerged”.
In the second half of this page the authors use the word “including” or “included” at least five times. Do they mean that the analysis was “controlled for” these factors or what do they mean?
Page 7.
Where the authors have written “to having less than 30 years” do they mean “to being less than 30 years”?
The authors should distinguish more clearly between what a type-1 model and a type-2 model is, for the non-statistician reader.
The second-last sentence before the discussion would be incomprehensible to the non-statistician reader. The authors should explain this in plain English.
Discussion.
Replace “is devoted to elucidate the role” with “is devoted to the elucidation of the role”.
Page 8.
Replace “revealed to” with “were found”.
The authors state: “Ageing is associated with a decline in learning and memory performances”. There is a tremendous spread of variability in older people with some maintaining good function and others not. The authors could overcome this by referring to a “mean” decline. In particular, in the discussion, the authors offer no reason why people with epilepsy should decline more with age than the general population and, it could be argued, that they have no reason for doing so since there is no control group, a fact that greatly weakens the scientific value of the study. The second half of this sentence is a gross over-generalisation: “although this decline was apparently similar for epilepsy patients and healthy subjects, the former group reached poor performance levels much earlier than the latter, as epilepsy patients fail to build up adequate learning and memory performance during childhood and adolescence”. Again, there is an enormous spread of variability; some childhood and adolescent syndromes are associated with gross cognitive deterioration whereas others are apparently not associated with such deterioration at all.
Line 3. Replace “duration” with “found that duration”.
Replace “ot” with “to”.
Replace “on adults operated for” with “adults who had operations for”.
Replace “On the contrary” with “On the contrary, the paper by” and delete the word “paper “after “co-authors”.
Replace “and other to” with “to other”.
Replace “in the long run” with “in the long term”. Again, at this point, the paper lacks any discussion of the deterioration that is associated with some early-onset childhood epilepsy syndromes.
Page 10.
Where the authors have written “resulted to be relevant” do they mean “were found to be relevant”?
Where the authors have stated that early age of onset was associated with a lower quality of life, on this page they quote other work that apparently found “age at onset emerged as negatively associated with HRQOL”, implying that the higher the age of onset, the lower the quality of life. The last half of this sentence, before “Conclusions” might involve some discussion of this matter but this is not clear from what the authors have written.
In the conclusions the authors have stated: “The main conclusions that age, age at onset and duration of epilepsy have only a limited role in determining the overall HRQOL”. With the confusion of different models apparently yielding different results, it would be helpful if the authors could reach some final conclusion that would be meaningful to workers in the field. At present the reader is left wondering what the degree, significance and importance of any correlations might be.

Level of interest: The findings of this article are important to those with closely related research interests
Quality of written English: Needs some language corrections before being published
Statistical review: Yes, but I do not feel adequately qualified to assess the statistics.
Declaration of competing interests:
I declare that I have no competing interests.
**Level of interest:** An article whose findings are important to those with closely related research interests

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**Statistical review:** Yes, but I do not feel adequately qualified to assess the statistics.

**Declaration of competing interests:**

I declare that I have no competing interests