Author’s response to reviews

Title: Modeling delay to diagnosis for Amiotrophic lateral sclerosis: under reporting and incidence estimates

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Author’s response to reviews: see over
Modeling delay to diagnosis for Amiotrophic lateral sclerosis: under reporting and incidence estimates

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First of all, we would like to thank the Referees for their careful reading of the paper and for giving suggestions which helped us improve (we hope) the quality of the paper. Below are the changes we have introduced in the paper following these suggestions.

Referee 1 comments

We have modified the paper according to Referee’s suggestions.

Q1 Most of Section 2 (Methods) is a copy of Section 3.1 in Rocchetti et al 2012. It can be considerably shortened, adding appropriate references. Essential formulas can be moved in the Appendix, along with the computation of standard errors.

A1 We have shortened the section appropriately and moved essential formulas to the Appendix.

Q2 Appendix, last two formulas: terms with a bar must be defined explicitly

A2 The terms have now been explicitly defined.

Q3 References: I think that Rocchetti et al 2012 should be included in the bibliography

A3 It has now been added to the References.

Q4 Editing: There are several typos in the body text: please check.

A4 Typos have now been corrected.

Referee 2 comments

Specifics

Q1 Throughout the text: Amyotrophic is a preferred spelling vs. Amiotrophic

A1 We changed the text accordingly.

Q2 Title page, author affiliations should be in English
A2 We would prefer, if possible, maintain the original affiliations.

Q3 Background. Paragraph 2: the onset time is ascertained of the time of diagnosis is awkward, perhaps the onset time is ascertained at the time of diagnosis or as the time of diagnosis?

A3 We changed the sentence accordingly.

Q4 Page 4, Assumption 1 and other places in text, experimenting should probably be experiencing

A4 We changed the word accordingly.

Other issues

Q5 Background, Page 2, article 3, D.M. 279/2001 Please provide reference

A5 We added the appropriate reference.

Q6 Methods, Page 3, for this reason it could be biased the bias increasing with delay to diagnosis. This text is awkward and the meaning is unclear.

A6 We changed the text to make it clearer.

Q7 Methods, Page 5, assumption 3: This hypothesis holds obviously only in case the considered time period is not too long. Does time period refer to delay in diagnosis? If so, since ALS has a comparably long average delay in diagnosis (458 day mean; given on page 12), how long would be too long?

A7 Time period refers to the observational window. We changed the text accordingly.

Q8 Methods, middle of Page 6: is concerned years are concerned Text is unclear.

A8 We corrected the text accordingly.

Q9 Methods, top of Page 9: However, in this case, the male and female samples are substantially homogeneous both in size and characteristics, thus gender does not seem to play a significant role. There is a known gender bias in incidence of ALS. Males are more likely to suffer the disease. Therefore, the author’s homogenous samples may indicate some bias in acquiring samples.

A9 The available data do not support significant differences between genders in the distribution of the delay to diagnosis. Some forms of selection may effectively have been influencing the data collection; however, we do not have any possibility to ascertain this point at least at the moment.
Some mention would be appropriate of known reasons for delayed diagnosis for ALS: 1) the lack of any one definitive test for ALS; 2) ALS symptoms tend to mimic more common neurodegenerative diseases which must be excluded prior to ALS diagnosis.

We have mentioned possible reasons for delayed diagnosis and added some appropriate references.

Page 11, Exploratory Data Analysis: Due to register vs registry quality. What is the difference between register and registry?

We have changed the text and used only registry.

Does the estimation include possibilities of ALS misdiagnosis?

If You mean false positives, the standard procedure for diagnosis should lead to a low observed proportion. If You mean false negatives, the misdiagnosis would imply a delay in diagnosing the disease and, therefore, the estimation procedure we suggest would handle it.

Figures: x axis should be clearly labeled with units (days, weeks, years?)

We changed the figures’ captions accordingly.

Referee 3 comments

(...) I suggest to better explain the advantages of such a method compared with a national register for ALS, aimed at the epidemiological findings that the NRRD can only roughly estimate.

The NRRD is the national registry for rare disease (ALS included) even if it is not explicitly designed for epidemiological findings. However, even a national registry with a complete geographical coverage would probably suffer from underreporting due to the nature (in this case the complex nature) of the disease, and the empirical evidence that diagnosis needs an a priori unknown period to be done, due to differential access to health services, to the procedure that must be followed to excluding more common neurodegenerative diseases, and to other causes which can be environment as well as individual-specific. Therefore, the proposed approach could be used as well with an epidemiologic registry.

Also, the assumption that delay to diagnosis is related to underreporting should be better explained and demonstrated (it is possible that cases underreported are cases with very fast disease course, early death, and conversely short diagnostic delay).

The delay to diagnosis may be influenced by several causes, including underreporting, and/or anomalous individual patterns of diagnosis due to fast disease courses, etc. At the present time, the available data do not allow us to deepen this point; should an individual record linkage...
with death certificates database be possible, we could, at least understand how early deaths influence non registration, but due to privacy laws, this can not be done at the moment.