Author's response to reviews

Title: Genetic analyses of smoking initiation, persistence, quantity, and age-at-onset of cigarette regular use in Brazilian families: the Baependi Heart Study

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São Paulo, December 19th, 2011.

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“Genetic analyses of smoking initiation, persistence, quantity, and age-at-onset of regular cigarette use in Brazilian families: the Baependi Heart Study”

Dear Dr. Tim Sands
In-house Editor, BMC Medical Genetics

Please find attached the revised version of the manuscript MS 1031260017568451. We appreciate the assistance of the reviewer, and we have made all suggested changes. Modifications incorporated in the first revised version of the manuscript were maintained in red text and those made in this second revision are in blue text. We hope this second revised version has reached the high standards of BMC Medical Genetics and that it will be interesting for its readers.

In addition, we have sent our manuscript for English review by a native speaker. We hope the changes made have improved the manuscript and that it will be interesting to BMC Medical genetics readers.
Answers to referee

1) More care needs to be taken with age. Throughout the paper "age" is often used without qualification, and I don't know which is which. For example in table 1 is "age at interview", i.e., what the subject wrote on the form?

   Age in Table 1 refers to age at the time of interview. An observation was provided in the legend of this table to clarify this issue.

In the analysis section it states that smoking initiation compared ever versus never, and persistence as current versus former. In table 3, what does "age" signify: age as in table 1, age at initiation, or something else? Is it the same in all 3 models? Age at initiation would be missing for the never smokers, but an important variable for the others.

   In all analysis, the covariate age refers to age at the time of interview. Two sentences were added to the paragraphs (pages 8 and 9) which describe the models used in the analysis to clarify this issue.

If they are different, should you look at both age variables in the quantity model? For instance, subjects might in general cut down as they get older, so that higher "age at interview" is associated with smaller answers. The age at initiation effect might be the same direction or different.

I expect the authors know the answers to these, please also inform the readers.

   The age-at-onset of regular smoking was only used to define the profile of the smoking behavior of our sample.

2. There is carelessness that makes the paper harder to read. Some examples (but not all):
In defining polygenic heritability the individual level trait is "y" in the text and the Greek letter "gamma" in the formula.

This error was corrected in the text and in the explanation about the covariance between traits. The formula of the variance component model was written with the aid of Equation, and the Greek letter gamma was introduced in the text using option Insert Symbol of the Microsoft Word. So the Greek letter does not appear very similar in the formula and in the text.

The right hand portion of table 5 is cut off.

The Table 5 was remade in the first revision to remove the hazard ratios for age and age x sex, considering that covariate age have been removed of the model. In our revised manuscript (first revision), the Table 5 was complete. Whatever, we checked this table again.

Page 5: "cigarette smoking exposure", not "exposition".

We have sent our manuscript for English revision.

3. Minor: how were the confidence intervals for table 5 created? (An optional addition to the methods.)

A following sentence was provided on first paragraph of page 10 (Statistical analysis section):

"Confidence intervals of the variance components were computed based on a profile-likelihood method [17]. This profile-likelihood method reduces the log-likelihood to a function of a single parameter of interest by treating the others as nuisance parameters and maximizing over them. A code in R [16] was used to obtain such confidence intervals."
Quality of written English: Needs some language corrections before being published.

The English editing was done by Edanz Group Limited. Find attached the invoice of this service.

Thank you very much for your assistance.

Best regards,

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