Reviewer’s report

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

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Reviewer: Christina N. Lessov-Schlaggar

Reviewer’s report:

It is truly a missed opportunity that a heart study started in 2005-06 has such poor assessment of smoking behavior. I am willing to overlook that considering that many other studies also do not adequately assess smoking behavior, however it is up to the authors to exercise vigilance in what kind of smokers the smoking variables actually capture and how these smoking variables map onto the definitions of seemingly similar smoking variables in other studies. I detail some of my concerns below:

Major compulsory revisions:

1. It is difficult to believe that such a large proportion of the sample is non-smokers, especially in the 18-24 year-old group. Are these numbers consistent with the smoking prevalence in Brazil? Could there be some selection bias in this study? It is likely that individuals who self-identify as non-smokers do have some smoking experience, but likely never smoked on some sort of a regular basis to think of themselves as smokers. Therefore, the measure of “smoking initiation” likely does not reflect initiating smoking per se, but initiating some kind of regular smoking, perhaps daily smoking. There is substantial evidence that heritability is more pronounced at heavier levels of smoking, and considering the high heritability estimates for “smoking initiation” in this study, I would guess that this phenotype reflects a transition to regular or daily smoking, not initiation of smoking per se.

2. Age of onset of cigarette use is actually age of onset of regular use. Again, these two definitions are very different and have different meanings. Please provide the means and range of the age of onset variable.

3. Please, remove all conclusions about lack of evidence of household effects. Age is the only household effect variable that was controlled for. Relatedly, please remove mention of the influence of additive genetic factors on the smoking phenotypes. Additive genetic effects cannot be estimated in family data. The authors need to make sure that it is clear that the heritability that is estimated in this study refers to broad sense heritability.

4. Getting back to the point of non-specific smoking phenotypes, the results of this study need to be placed in the context of the specific smoking definitions of prior studies, not just based on how prior studies called their variables.

5. It sounds like the cigarettes per day variable was collected as an open-ended question where no specific response categories were provided. In Table 1, this
variable is shown in categories – were these categories generated by the authors and if so, what was the rationale for them? Please, provide the skew and kurtosis statistics for the cigarettes per day variable before and after normalization.

Minor essential revisions:
1. Discussion of measured genetics is not relevant for this paper.

**Level of interest:** An article of limited interest

**Quality of written English:** Acceptable

**Statistical review:** No, the manuscript does not need to be seen by a statistician.

**Declaration of competing interests:**

I declare that I have no competing interests