Author's response to reviews

Title: A case-control study on the effect of Apolipoprotein E genotype on gastric cancer risk and progression

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Author's response to reviews: see over
Dear Editor,

I am very glad to know that the MS has been considered for publication, thanks a lot for handling it, and I hope the additional revision I implemented in this second revised version are enough for its publication.

In this version all the comments of the 1\textsuperscript{st} reviewer have been addressed, and changes in the text are marked with blue colour.

With many thanks for your assistance.

Best regards,
Stefania Boccia
1st reviewer: A. Bennet

The changes that have been made to the manuscript after the revision have not convinced me that the control group is representative of the general population. I agree with the authors that, since there are only a few cardiovascular patients in the control group there should be less of a selection bias towards ApoE4 carriers, yet the allele frequencies do not correspond to that presented in previous reviews (for example JAMA 298(11):1301-1311, 2007). ApoE4 should be more frequent than e2 but (calculated from the data presented in table 2) in the control group of the present study e2 and e4 appear at almost the same frequency.

The allele frequencies of our control population seem to be in line with those reported by Napolioni v. et al. (Clinica Chimica Acta 412 (2011) 1821–1824) and Panza F. et al. (Neuroscience Letters 292 (2000) 79-82) that reported Apolipoprotein E genotype distribution among individuals from Central and South Italy respectively. Our control population is mostly made of people coming from these Italian regions.

By looking at the allele frequencies reported in the above-referenced papers, the ApoE4 allele does not appear to be not more frequent than the E2 allele. For example as showed by Napolioni et al., the e4 allele frequency was exactly the same of the E2 allele in the same age group of our controls.

In table 1, please include the allele frequencies for e2, e3 and e4 for cases and controls. This is important background information.

As suggested, this information has been added in table 1.

This study has quite low power and the uncertainties concerning the control group makes it difficult to draw conclusions. There are hundreds, if not thousands, of genetic association studies on ApoE that have overestimated the genetic effects of the rare variants due to exactly these problems. Yet, this is the first paper presenting ApoE genotypes in relation to this rather rare disease and that makes the study important. The authors should tone down their conclusions, perhaps by adding something in the line of “but further studies are required to confirm this”. This should be done both in the abstract and the discussion and not just at the “Conclusions” section.

A specific sentence has been added in the last part of the abstract while the consideration about the study’s sample size have been already included in the discussion section where limitations are acknowledged.