Author's response to reviews

Title: Discontinuation of anti-hypertensive drugs increases 11-year cardiovascular mortality risk in community-dwelling elderly (the Bambui Cohort Study of Ageing)

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

we would like to resubmit our revised manuscript for publication in the *BMC Public Health* journal.

We agree that the interpretation of our results regarding non-cardiovascular mortality presents some drawbacks. Although the results of previous detailed qualitative studies about beliefs and behaviours of the hypertensive subjects of our cohort provide a meaningful contribution to the interpretation of our findings, unfortunately, we don’t know the specific reasons for the discontinuation of AHDs. Then, we decided to focus our study on the effects of AHD discontinuation on cardiovascular mortality. Consequently to this choice and to the suggestions given by the Reviewers, we made a major revision of the manuscript, including the results of analyses made after classifying events by duration of drug discontinuation.

The subjects who never received AHD treatment are presumably those for whom the clinicians did not find it necessary to prescribe any medication. Since this is a well-monitored cohort, it is also possible that the physicians recommended lifestyle modifications instead of prescribing drug treatment in absence of another cardiovascular risk factors or target organ damage, according to guidelines in effect at the time of the survey. Furthermore, it is important to highlight that the principal aim of considering this “exposure group” was to ensure that the comparison of most interest (stoppers vs. current users) was made including subjects for whom drug treatment had been prescribed.

Please, find enclosed our responses to the comments of the Reviewers and a description of the changes made in the manuscript.

Thank you for your consideration.

Sincerely,

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Responses to Reviewer 1:
- The term “2-fold” (or 200%) refers to the change between initial and final value, and indicates a ratio of about 3.0. This approach can lead to confusion, then we replaced it with the term “three times higher”. It refers to the overall rate ratio (3.12) of cardiovascular mortality estimated for the AHD stoppers.
- We included a new paragraph into the Methods section (Study design and population) to specify that Bambui is a former endemic area for Chagas disease and that the examination of the consequences of the double burden of non-communicable diseases and this parasitic chronic infection in old age was the main objective of the Bambui Cohort Study of Ageing.
- All of the interviewers and health technicians were certified after training at a specialized center at the School of Medicine of the Minas Gerais Federal University.
- “Next of kin” is the closest relative.
- We replaced “schooling” with “educational level”.

Thank you.
Response to Reviewer 2

The interpretation of our results regarding non-CV mortality presents some limitations difficult to overcome since that, although results of previous studies about the behaviours of our hypertensive elderly provide useful interpretative elements, we don’t know the specific reasons of the AHD discontinuation. Then, we decided to focus our study on the association between AHD discontinuation and CV mortality.

We believe that our results should be interpreted at the light of the fact that the exposure groups are not randomized, but they reflect real clinical dynamics. Thus, a clinical judgement behind the decision to pharmacologically treat (or not treat) our subjects was implicit in the characterization of the AHD exposure groups. Equally important is to note that the main objective of to consider the group “non-AHD users” was to ensure that the comparison of interest (stoppers vs. current users) was made including subjects for whom drug treatment had been prescribed. However, it should not be surprising if the CV mortality rates in the non-AHD users were comparable to those of the current users. We interpreted this finding by considering that the non-users were not just “non-treated”, but they were patients for whom AHDs were clinically judged unnecessary and, presumably, for these subjects CV mortality rates were kept low by only lifestyle modifications. Up the levels of 160 mmHg, lifestyle modifications instead of prescribing drug therapy in absence of another risk factors or target organ damage were the guidelines’ recommendations for the olders in effect at the time of the survey. Moreover, mechanism have been proposed to explain the protective effect of lifestyle interventions against CV diseases in the elderly (Abete, 2006). These results, rather than lead to conclude that there is no significant effect of AHDs on CV mortality, suggest that pharmacological treatment could be not always necessary to reduce risk. On the other hand, those regarding the “drug stoppers” suggest that once AHDs were prescribed, they should not be discontinued.

We repeated the analyses including two new variables into the model: conjugal status and monthly family income. We included a new paragraph into the Background section containing some details about the Brazilian governmental pharmaceutical policies, as strategies to promote access to essential medicines.

Thank you.
Description of the changes in the revised manuscript:

We made a number of changes in our manuscript as a consequence of our decision to focus on cardiovascular mortality and according to the suggestions of Reviewers:

- We reanalysed our data including into the model two new control variables: conjugal status and monthly family income. Results were only slightly changed; Abstract, Results section Tables and Figure were corrected.
- The new variables were included in table 1.
- Old tables 2 and 3 were collapsed into the new table 2 showing the CV mortality risk results.
- We repeated the analyses with events classified into those <1 year of AHD discontinuation, 1-2 years, >= 2 years and the results are shown in the new table 3.
- We removed figure 2.
- We added 10 new references and removed 3 of them.
- We added the Acknowledgements section containing the funding sources.

- New title contains the word “cardiovascular”
- We included a new paragraph into the Background section containing some details about the Brazilian governmental pharmaceutical policies.
- A sentence was inserted into the first paragraph of the Methods section.
- A new paragraph was inserted into the Methods section.
- A new paragraph was included at the end of the Results section.
- The whole Discussion section was reorganized:
  - The 3° paragraph was rewritten.
  - New sentences were added at the end of the 4° and 5° paragraphs.
  - The 6° and 7° paragraphs were rewritten.