Author's response to reviews

Title: Scarcity of atrial fibrillation in a traditional African population: a population-based study

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

We thank you and the reviewers for the constructive comments on the abovementioned manuscript. Hereby we submit a revised version of the manuscript, in which the changes have been underlined.

Our responses to the remarks of the editor and the reviewers are given below in italics. Changes in the manuscript are referred to by line numbers and by reference numbers corresponding with the revised version of the manuscript.

We hope to have answered the comments and questions satisfactorily. If necessary, we are glad to respond to further inquiries.

We look forward to your response. Thank you in advance.

On behalf of the coauthors,

Yours sincerely,

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RESPONSE TO THE COMMENTS OF THE REVIEWERS

Reviewer 1

1. My previous remark (nr 2) is not satisfactorily addressed to in this rebuttal. The case finding in the study under consideration is definitely not comparable to the case ascertainment in the ATRIA study. The case finding is based on EKG measurement only. In the ATRIA study the diagnosis is based on searches in clinical databases from ambulatory visits, in an electrocardiographic database and on searches in a hospital discharges diagnosis databases. Both approaches have their own limitations, but it must be clear that the results of the ATRIA study will give a better approximation of the real prevalence of atrial fibrillation in the general population than the study of Koopman ea. The remarks with respect to transient atrial fibrillation (lines 282-290) do not solve this problem. Transient atrial fibrillation is a disturbing conception. It is quite well defined in the ATRIA paper but explains only partially the missing cases due to EKG measurements only. The case ascertainment in the study of Koopmans is a real limitation and has to be qualified as such. But it does not affect the interesting conclusions of the paper.

We understand that the methodological differences between the ATRIA Study and our study can be explained better. In the revised manuscript, we have included an explicit description of the methodology of the ATRIA Study (lines 157-162). In addition, we now discuss that our methods for case ascertainment may be insufficient to detect all cases of atrial fibrillation and that our methods differ from those applied in western populations as limitations of our study (lines 292-297).
Reviewer 2

The authors have made significant revisions to the manuscript. Thank you for incorporating a range of suggestions. In my perception, this presentation is stronger than the prior version. The manuscript is well written and informative. Further considerations for the authors are:

1. Please change the wording in the abstract conclusion by removing the word "essential." As you point out in your responses, causes for AF are diverse. It is hard to argue in the epidemiology of AF (or any disease, for that matter) that an exposure is essential. There is a lot of residual confounding in the cohort being studied; we don't know if there is a protective effect from lifestyle, environment, or perhaps genetics that informs the low prevalence of AF that was observed.

We agree that our conclusions should not imply that a single risk factor is fully responsible for the causation of atrial fibrillation. Grossly, we envision that three groups of risk factors can differ between the traditional African study population and western societies, are involved in its causation and can therefore explain why atrial fibrillation is scarce in the Ghanaian study population. These groups include: firstly, the established risk factors of atrial fibrillation that are closely related to lifestyle, such as obesity, diabetes, hypertension, and cardiovascular disease; secondly, other risk factors that were not measured in our study, such as thyroid disease and alcohol use; and thirdly, genetic factors.

In the revised manuscript, we have rewritten the abstract’s conclusion and have removed the word “essential” from it (lines 55-58). We now describe more clearly that our measurements concern the first group of risk factors only and that the second and third groups were not measured (lines 55-58, 264-280, 297-299, and 312-317).
2. In Western AF literature (meaning essentially the U.S.), there has been a growing recognition that AF has been less commonly identified in individuals of African ancestry. It is particularly interesting because African-Americans have a higher prevalence of diabetes, hypertension and obesity (in general) than whites. These racial differences have been studied in the REGARDS Study, for example. However, AF has been shown to be less prevalent in American blacks. Some have called this dissonance between risk factor burden and AF prevalence a "racial paradox." (For further discussion, please see Soliman EZ, Alonso A, Goff DC Jr. Future Cardiol. 2009 Nov;5(6):547-56. PMID: 19886781 doi: 10.2217/fca.09.49). The authors may consider integrating what is known about racial differences in other populations into their introduction and discussion. Including this material may contribute to the manuscript.

Thank you for this suggestion. The phenomenon of the "racial paradox" underscores the importance of studying the epidemiology of atrial fibrillation in populations other than western society, as explained by Soliman and colleagues in the article mentioned above. In the revised manuscript, we have included a discussion of this phenomenon (lines 77-84 and 256-263) and references to the publications mentioned above (references 16, 45, and 46).

3. The last sentence of the introduction is again troubling. As an epidemiologist, I am always aware of the unknown, the burden of residual confounding. In my view it is a hollow argument to say that taking away the western lifestyle takes away the disease. These measured, defined exposures (obesity, hypertension, etc.) are surely not the only differences between this cohort and those who have a "western lifestyle."

We have removed the last sentence of the introduction (line 90). Please, also see our reply to comment 1.

4. Further, in keeping with my prior concerns about generalizability, I find it difficult to refer to a "western lifestyle." The world is far too complex and while differences do exist, and are profound, between nations and cultures and hemispheres, it seems like a vast over-simplification to compare a limited-sized cohort to the West.

In the revised manuscript, we have removed the term "western lifestyle" (e.g. lines 86 and 210). Please, also see our replies to comments 1 and 7.
5. On the contrary, the authors may use the introduction to establish a hypothesis or objective for performing the assessment. Identifying risk factors and cardiovascular disease prevalence in an African cohort is informative.

*We have clarified the objective of the study in the introduction (lines 72-84). Please, also see our reply to comment 2.*

6. The statistical analysis section can be enhanced.

*We have enhanced the statistical analysis section (lines 173-175).*

7. The comparison with the U.S. cohort regarding AF prevalence is problematic. In the ATRIA study, individuals may have had more than one electrocardiogram and had opportunities for serial monitoring. ATRIA is data from a health maintenance organization, so is also difficult to compare to this cohort. In that study also, sicker individuals, those with a greater number of AF risk factors, would likely selection for more likely detection of AF. My stance is that the comparison with ATRIA is very limited and – in my point of view – without meaning. Instead, I think these data are informative on their own. My opinion is that comparing to ATRIA, because of the markedly different methods and design, has limited validity and is a distraction.

*Compared with the prevalences reported by the ATRIA Study, similar or even higher prevalences have been reported in other population-based studies in the USA and in the Netherlands and Sweden (lines 161-162, references 2, 3, 4, and 5).*

*Please note that we have not performed statistical testing to formally compare the Ghanaian study population with the general population of the USA. Still, we believe that, for a proper appreciation and interpretation of the epidemiology of atrial fibrillation in the Ghanaian study population, a comparison with reference data from the well-studied western society is of importance. This thinking is in line with the conclusion by Soliman and colleagues that knowledge on the epidemiology of atrial fibrillation in the context of different environmental and genetic influences should be integrated, as discussed in their article mentioned in comment 2.*

*We understand that the methodological differences between the ATRIA Study and our study can be explained better. In the revised manuscript, we have included an explicit description of the methodology of the ATRIA Study (lines 157-161). In addition, we now discuss that our methods for case ascertainment differ from those applied in western populations as a limitation of the comparison (lines 292-297).*
8. The concluding paragraph again backs into implicit causality that this western lifestyle is causative for AF. The findings here do not explain the high prevalence of AF in Asian countries. These findings do not control for many factors that contribute to AF risk.

*We have rewritten the concluding paragraph (lines 312-317). Please, also see our reply to comment 1.*