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. We believe that implementing these suggestions has improved our 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,

Jacob J.E. Koopman
Department of Gerontology and Geriatrics, Leiden University Medical Center
RESPONSE TO THE COMMENTS OF THE EDITOR AND REVIEWERS

Editor

1. Individual sections for Methods and Results in the abstract.

Thank you for your suggestion. *In the revised manuscript, we have restructured the abstract as required (lines 42-54).*

2. Please confirm that you have permission to reproduce the data for the USA population. Please cite the sources of data used to generate the portion of the graphs depicting the USA population groups in the figure legends, to distinguish them from data generated in this study.

*Data on the American reference population were derived from three sources:*

1. We have derived data on body mass index (BMI), C-reactive protein (CRP), and hypertension from the NHANES 1999-2000 study. These data are shown in Figure 2. The Centers for Disease Control and Prevention (CDC) have made these data available in the public domain for reproduction without permission, only requesting a reference to this database (see http://www.cdc.gov/nchs/nhanes/nhanes_citation.htm). We refer to this publicly available database by reference 20 (lines 163 and 490).

2. We have derived data on interleukin-6 (IL6) from reference 21. The median levels, as reported in Figure 2 in our manuscript, can be found in Table 1 of this article. We refer to this source in lines 165 and 491.

3. We have derived data on the prevalence of atrial fibrillation from reference 19. The prevalences of atrial fibrillation in the USA, shown in Figure 1 in our manuscript, can be found in the Result’s section on page 2373 and in Figure 2 in this article. This article is freely accessible. We refer to this source in lines 160, 287, and 480.

*All these data concern published factual information. We have not reproduced tables or figures. Reproduction of these data from these sources in this manner is therefore allowed. In the revised manuscript, we have added references to these data sources in the figure legends (lines 480, 490, and 491).*
Reviewer 1

This paper is interesting, well-written and easy to read. It adds to the knowledge on the epidemiology of atrial fibrillation. There are limitations but these are sufficiently addressed. I have a limited number of suggestions.

Thank you for your comments, which have provided the opportunity to improve our manuscript. Below, we answer all questions one by one. In addition we have adapted our manuscript based on these comments in hope that it will meet your expectations.

1. Table 1: please provide the number of participants by age strata (five in 10 years strata).

Thank you for this suggestion. We have included an overview of the age-stratified numbers of participants in the revised manuscript (see Table 1 and the fragment of interest of Table 1 copied below).

Fragment of Table 1 General characteristics of the Ghanaian study population (age ≥ 50 years)

<table>
<thead>
<tr>
<th>Individuals</th>
<th>n</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age median (iqr) years</td>
<td>66 (56–73)</td>
</tr>
<tr>
<td>Age groups n (%)</td>
<td></td>
</tr>
<tr>
<td>50–59 years</td>
<td>307 (33.2)</td>
</tr>
<tr>
<td>60–69 years</td>
<td>291 (31.5)</td>
</tr>
<tr>
<td>70–79 years</td>
<td>242 (26.2)</td>
</tr>
<tr>
<td>80+ years</td>
<td>84 (9.1)</td>
</tr>
</tbody>
</table>

2. Figure 1: Is the method of case finding with respect to the AF cases in the USA the same as in Ghana? Please report.

We agree that it is important to compare the methodologies of our study and the reference study in the USA (reference 19). We discuss this comparison in more detail in the revised manuscript (lines 157-161 and 282-287). In addition, we describe our methodology more clearly (lines 115-119).

The methodologies of our study and the American reference study are similar. Both studies aim to estimate the prevalence of atrial fibrillation in a population-based sample. The results of the American reference study are comparable to those reported by others for the general American population (references 1-3). In both studies, atrial fibrillation is diagnosed by a physician using electrocardiography.
The methodology of the American reference study aids the comparison that we draw between both populations. Because we executed the electrocardiographic measurements once per individual, we may have missed cases with transient atrial fibrillation, but these cases were excluded from the reference study. On the other hand, our single measurements cannot discern between transient and non-transient atrial fibrillation. As a consequence, we cannot exclude transient cases and may underestimate the difference in prevalence of non-transient atrial fibrillation as compared to the USA. An underestimation of this difference reinforces our conclusion that atrial fibrillation is scarce in rural Ghana. We discuss this issue in lines 282-289.

3. Reference 20: not easy to use. I advise a better accessible ref for the prevalence of AF. Several large population-based studies provide these data.

For clarity, we would like to indicate that we have used the following sources to obtain data on the USA as reference population:

1. We have derived data on body mass index (BMI), C-reactive protein (CRP), and hypertension from the NHANES 1999-2000 study, to which is referred in this comment (reference 20).

2. We have derived data on interleukin-6 (IL6) from a population-based study (reference 21). The median levels, as reported in Figure 2 in our manuscript, can be found in Table 1 of this article.

3. We have derived data on the prevalence of atrial fibrillation from a large population-based study, of which the results have been published in reference 19. This article is freely accessible. The prevalences of atrial fibrillation in the USA, given in Figure 1 in our manuscript, can be found in the Result’s section on page 2373 and in Figure 2 of this article. These data are consistent with those from other reports available through references 1 to 3.

In the revised manuscript, we describe the sources of the reference data more clearly (lines 157-165).
Reviewer 2

Thank you for your comments, which have provided the opportunity to improve our manuscript. Below, we answer all questions one by one. In addition we have adapted our manuscript based on these comments in hope that it will meet your expectations.

1. Population-based. It is not clear how the authors are defining the cohort as being population-based. While there may have been some randomness with regard to the selection of participants, the term suggests that this cohort is representative of the population. No data are provided to support the assertion. There may be none, which does not limit the validity of the study but rather its generalizability. Data on AF prevalence in non-Western countries are informative and provide insight into AF epidemiology. However, Africa is an immense continent, there may be profound geographic differences across Africa, and the assertion of this being a population-based study may not be accurate.

Thank you for pointing out that the design of this study can be described more clearly. Our research on the population in the research area does not intend to generalise its findings and conclusions to other African populations. We have changed our wording in the revised manuscript to describe this more clearly (e.g. lines 299-306). For a more detailed response on the generalizability, please see our response to comments 4 and 7 on pages 9 and 10.

To estimate the prevalences of atrial fibrillation and its risk factors in the research area among individuals aged 50 years and older, we set up a mobile field station in different villages during two field visits in 2009 and 2010. From here, all eligible inhabitants were approached. Inclusion was limited by the duration of the field visits. To ensure maximal participation and to avoid selective inclusion of healthy elderly, we brought less mobile participants by car (lines 115-124).

In an additional analysis we compared demographic characteristics, established risk factors of atrial fibrillation, and infectious and inflammatory markers between the entire population living in the research area, the subpopulation that was selected for this study on atrial fibrillation, and the two subpopulations that were previously selected for measurements of infectious and inflammatory parameters in blood and stool samples (see Table R1 on the next page). These characteristics were similar with two exceptions. The median age was slightly higher in the latter two subpopulations, although the interquartile ranges were similar to those of the other populations. Compared to the entire population, the proportion of males was slightly higher in the subpopulation that was selected for this study on atrial fibrillation and slightly lower in the two subpopulations that were selected for measurements of infectious and inflammatory parameters. Stratification by sex did not change these findings. Importantly, the levels and prevalences of the established risk factors of atrial fibrillation, of infections, and of the inflammatory parameters were similar across the subpopulations. In the revised manuscript, we discuss in more detail the relation between the entire registered population and the subpopulation that was selected from it for this study on atrial fibrillation (lines 182-185).
Table R1 General characteristics of the different subpopulations sampled from the Ghanaian study population (age ≥ 50 years)

<table>
<thead>
<tr>
<th></th>
<th>Entire population of the research area</th>
<th>Study on atrial fibrillation</th>
<th>Study on infectious parameters</th>
<th>Study on inflammatory parameters</th>
</tr>
</thead>
<tbody>
<tr>
<td>Individuals n</td>
<td>2,488</td>
<td>924</td>
<td>277</td>
<td>266</td>
</tr>
<tr>
<td>Age median (iqr) years</td>
<td>63 (58–73)</td>
<td>66 (56–73)</td>
<td>70 (59–75)</td>
<td>70 (59–75)</td>
</tr>
<tr>
<td>Male sex n (%)</td>
<td>1,027 (41.3)</td>
<td>480 (51.9)</td>
<td>103 (37.2)</td>
<td>96 (36.1)</td>
</tr>
<tr>
<td>Households n</td>
<td>1,285</td>
<td>636</td>
<td>206</td>
<td>202</td>
</tr>
<tr>
<td>Household property value median (iqr) US$</td>
<td>1,040 (483–1,817)</td>
<td>1,077 (533–1,942)</td>
<td>1,150 (670–2,075)</td>
<td>1,150 (667–2,075)</td>
</tr>
<tr>
<td>Waist circumference median (iqr) cm</td>
<td></td>
<td>76 (72–81)</td>
<td>77 (73–81)</td>
<td>77 (73–81)</td>
</tr>
<tr>
<td>Body mass index median (iqr) kg/m²</td>
<td></td>
<td>18.1 (16.5–19.5)</td>
<td>17.9 (16.5–19.1)</td>
<td>17.9 (16.5–19.1)</td>
</tr>
<tr>
<td>Capillary glucose median (iqr) mmol/l</td>
<td></td>
<td>3.9 (3.4–4.4)</td>
<td>4.1 (3.6–4.8)</td>
<td>4.1 (3.6–4.8)</td>
</tr>
<tr>
<td>Blood pressure median (iqr) mmHg</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>diastolic</td>
<td>70 (65–80)</td>
<td>70 (65–75)</td>
<td>70 (65–75)</td>
<td></td>
</tr>
<tr>
<td>systolic</td>
<td>120 (110–135)</td>
<td>118 (110–130)</td>
<td>120 (110–130)</td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>24.2 %</td>
<td>20.8 %</td>
<td>21.0 %</td>
<td></td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>1.2 %</td>
<td>1.3 %</td>
<td>1.4 %</td>
<td></td>
</tr>
<tr>
<td>Individuals with infectious diseases</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>malaria species</td>
<td>77.7 %</td>
<td>77.2 %</td>
<td>77.1 %</td>
<td></td>
</tr>
<tr>
<td>protozoa</td>
<td>100.0 %</td>
<td>100.0 %</td>
<td>100.0 %</td>
<td></td>
</tr>
<tr>
<td>helminths</td>
<td>21.5 %</td>
<td>21.5 %</td>
<td>22.0 %</td>
<td></td>
</tr>
<tr>
<td>Proinflammatory markers</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>interleukin-6 median (iqr) ng/l</td>
<td>1.9 (1.4–2.7)</td>
<td>1.9 (1.4–2.7)</td>
<td>1.9 (1.4–2.7)</td>
<td></td>
</tr>
<tr>
<td>C-reactive protein median (iqr) mg/l</td>
<td>1.0 (0.4–2.7)</td>
<td>1.0 (0.4–2.7)</td>
<td>1.0 (0.4–2.7)</td>
<td></td>
</tr>
</tbody>
</table>
2. NHANES comparison. To this reviewer the exercise of comparing selected risk factors for AF across two very different studies has and limited informative value. The methods between the two studies are very different. Validity (reliability and quality control) are not reported in the present study. NHANES in its current iteration does not report or adjudicate AF; in NHANES III individuals reporting a history of AF were even excluded from the ECG substudy. The effort to this reviewer only affirms prior research in far larger non-Western cohorts and specifically Africa that selected risk factors for AF have less prevalence than in the NHANES or other US cohorts.

Individuals with a history of atrial fibrillation have been excluded from the electrocardiographic measurements in the NHANES III study. However, we have not used data from the NHANES III study, which has been executed from 1988 until 1994.

For clarity, we would like to indicate that we have used the following sources to obtain data on the USA as reference population:

1. We have derived data on body mass index (BMI), C-reactive protein (CRP), and hypertension from the NHANES 1999-2000 study (reference 20), which has been executed later and following other protocols than the NHANES III study. Both studies have been designed to assess a sample that reflects the American population as a whole. For these three variables, no exclusion criteria have been used in the NHANES 1999-2000 study, except for a lower age limit of 3 years for the measurements of CRP.

2. We have derived data on interleukin-6 (IL6) from a population-based study, in which the subjects have been included by random household selection (reference 21).

3. We have derived data on the prevalence of atrial fibrillation from a large population-based cohort study (reference 19). Cases of transient atrial fibrillation have been excluded, as we discuss in lines 282-287. These data are consistent with those from other reports (references 1-3).

In the revised manuscript, we describe the sources of the reference data more clearly (lines 157-165). For a discussion on the comparison made with the western reference population, please see our reply to comment 7 on page 10.
3. Termination and causality. The terminology of “traditional” risk factors lacks specificity and is ambiguous. The authors intend to describe established risk factors that have also been measured within their cohort. There are many established risk factors that are not measured or identified within this cohort, such as history of cardiovascular disease, valvular heart disease, family history of AF, hyperthyroidism, alcohol use. The selection of a limited number of covariates is problematic, because it ignores other potential risk factors that are not included. Residual confounding is a huge problem; maybe all 3 of the AF cases had hyperthyroidism or suffered from mitral stenosis. There is an implicit assumption in describing risk factors as “traditional” that they inform population-attributable risk for AF. More precise, less general terminology describing risk factors is suggested. One overall recommendation for the authors is to concentrate more on describing the present cohort, acknowledge its limitations, and report the findings without making comparisons across cohorts and hemispheres.

We agree that the terminology of “traditional” risk factors can lead to confusion. We have changed this terminology into “established” risk factors, as suggested (e.g. lines 35, 44, and 57).

We agree that we have not measured all acknowledged risk factors of atrial fibrillation. In the revised manuscript, we discuss this limitation of the study in more depth (lines 289-293). Furthermore, we understand that we may describe more clearly which risk factors are referred to when mentioning the “established” risk factors. Therefore, we describe the risk factors that we have measured by using more specific terminology in the revised manuscript, such as “myocardial infarction” instead of “cardiovascular disease” (e.g. lines 44-53).

It is possible that atrial fibrillation may be caused in the study population by risk factors that we have not measured. We admit that the documentation of risk factors may be limited, especially for prior cardiac disease and family history of cardiac disease. In the revised manuscript, we discuss this limitation in more depth (lines 292-293).

We have documented the most important risk factors of atrial fibrillation, which include hypertension, obesity, diabetes, smoking, and prior cardiac disease. The scarcity of atrial fibrillation is remarkable when comparing it to the high prevalence of atrial fibrillation in western societies. If risk factors other than those documented would be underlying these cases – for instance hyperthyroidism or rheumatic heart disease – our line of thinking is reinforced. We postulate that a sedentary lifestyle leads to the established risk factors mentioned above, and thereby plays an essential role in the pathogenesis of atrial fibrillation. In line with this, atrial fibrillation is scarce if a sedentary lifestyle and the established risk factors are absent. Those cases of atrial fibrillation that are present to a lesser extent may then be caused by other pathogenetic processes.

For a further discussion of possible causal relationships, please see our reply to comment 5 on page 9. For a discussion on the generalisability of our findings and conclusions and on the comparison made with the western reference population, please see our reply to comments 4 and 7 on pages 9 and 10.
4. Generalizability. There are general uses of the term Western or non-Western throughout the description of the cohort and interpretation of the findings. The language and presentation tend to suggest that this cohort is generalizable to anything non-Western, and in turn that AF is defined in Western cohorts by the so-called “traditional” risk factors. The world is very diverse and while Western and non-Western differences exist, the cohort is restricted by number, geography, sampling and inclusion methods, etc. To pretend that 924 people can be compared to a global hemisphere is challenging.

We think it is important that our results are not presented as widely generalisable. Therefore, in the revised manuscript, we have changed the wording and address the study population and the reference population with more specific terminology (e.g. lines 228, 233, 234, and 237).

For a discussion on the terminology of “traditional” risk markers, please see our reply to comment 3 on page 8. For a discussion on the comparison made with the western reference population, please see our reply to comment 7 on page 10.

5. Inflammation. Similar to the comment above, there are comments about the interpretation of the inflammatory biomarkers in the limited segment of this cohort that have CRP and IL6 measured. The investigation at present cannot comment on the “chronic inflammation” of the cohort. First, samples were measured at a single time point, and chronicity reflects longitudinal variability, while this study is cross-sectional. Second, the biomarkers were measured prior to the ECGs and identification of AF. Like any cross-sectional study, causality cannot be inferred. Third, the biomarkers are measured in a limited segment of the cohort. How individuals were selected for biomarker measurement, implicit biases, and how similar these individuals are to the remaining ~700 individuals is not described or discussed.

We understand that the use of the terminology of “chronic” suggests that we have observed follow-up through time. It is right that we have not. Therefore, we have removed those fragments from the manuscript that may imply a longitudinal study design, including the terminology of “chronic” (e.g. lines 38, 47, 57, and 59).

We agree that the cross-sectional nature of this study impairs inferences on causal relationships. In the revised manuscript, we have changed the wording of several fragments to reflect that some of our interpretations are rather postulated than proven (lines 58, 230-231, 240-242, 309-310). Moreover, we have added a discussion of this limitation of the study (lines 295-297).

The infectious and inflammatory parameters were measured in individuals that had been randomly selected within age categories to ensure an even distribution over age. In Table R1 (see page 6) we compare the characteristics of these subpopulations with those of the subpopulation that was selected for this study on atrial fibrillation and with those of the entire population. As discussed in our response to comment 1 on page 5, these characteristics are largely similar across the different populations. In the revised manuscript, we describe these issues in more detail (lines 182-185).
6. AF ascertainment. AF ascertainment is performed by two 10-second electrocardiograms. The authors acknowledge this as a limitation but assert that it is the “best” approach. The authors might qualify very carefully that this is the best approach available to their investigation. Other methods of cardiac rhythm monitoring are conceivable even in isolated, rural, resource-scarce cohorts. 

*We agree that the wording in this context may be improved; we have adjusted this in the revised manuscript (lines 282-285).*

7. Conclusions. The authors assert that the comparison of the epidemiology of AF in this study population with that in a Western population is imperfect but necessary. The validity of cross-cohort and societal comparison is questionable and problematic because it rests on tremendous generalizations that are outside of the scope of the present investigation. In fact, in this reviewer’s estimate, the presentation would be strengthened by simply reporting what was observed, rather than trying to establish differences in very different cohorts with highly contrasting selection and design. 

*We agree that our results should not be presented as widely generalisable. Therefore, in the revised manuscript, we have changed the wording. We present our findings as only applicable to our study population and with the use of reference data only for a careful comparison with known data on the general American population. In addition, we have added a paragraph in the revised manuscript to discuss the limited ability to generalise our findings to other populations as well as the complicated nature of a comparison between different populations (lines 299-306).*

*Although a comparison between our study population and the general population of the USA is complicated and should be assessed with care, we think it may also be valuable. First, to be able to judge whether a prevalence or level of a disease or risk factor is high or low, a comparison with a reference population is needed. Second, as originally posed by Geoffrey Rose, research on the epidemiology and causation of diseases may not only compare the characteristics of different individuals, but also of different populations as a whole, especially with regard to the question why a disease is more common in one population compared to the other (G. Rose, Int. J. Epidemiol. 2001). More recently, it has been acknowledged that these two approaches are fundamentally different, but still needed both (Y.G. Doyle, J. Epidemiol. Commun. Health 2006). Lastly, we have added to the manuscript that further research is needed to confirm our postulates and to extend the scarce knowledge on atrial fibrillation in various non-western societies (lines 297-298, 305-306)*