PEER REVIEW HISTORY

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ARTICLE DETAILS

<table>
<thead>
<tr>
<th>TITLE (PROVISIONAL)</th>
<th>Association of early adult modifiable cardiovascular risk factors with left atrial size over a 20-year follow-up period: The CARDIA study</th>
</tr>
</thead>
<tbody>
<tr>
<td>AUTHORS</td>
<td>Armstrong, Anderson; Gidding, Samuel; Colangelo, Laura; Kishi, Satoru; Liu, Kiang; Sidney, Stephen; Konety, Suma; Lewis, Cora; Correia, Luis; Lima, Joao</td>
</tr>
</tbody>
</table>

VERSION 1 - REVIEW

<table>
<thead>
<tr>
<th>REVIEWER</th>
<th>Michael Y.C. Tsang</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mayo Clinic, Rochester, Minnesota, USA</td>
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<tr>
<td>REVIEW RETURNED</td>
<td>15-Oct-2013</td>
</tr>
</tbody>
</table>

GENERAL COMMENTS

In this study, Armstrong et al. examined the association of modifiable cardiovascular risk factors in early adulthood with left atrial size over a 20-year follow-up period using data from the CARDIA study. The authors concluded that higher systolic blood pressure and body mass index were predictors of left atrial dimension. Interesting results were also reported regarding the relationship between baseline BMI or changes in BMI during follow-up and left atrial dimensions or indexed left atrial dimensions. While a positive correlation between BMI and left atrial dimension or left atrial dimension indexed to height was demonstrated, a negative correlation was found between BMI and left atrial dimension indexed to body surface area. My comments are as follows:

1. Data on the linear left atrial dimensions were obtained by M-mode echocardiography. My concern with the use of linear anteroposterior left atrial dimensions measured by M-mode echocardiography is that this method is inaccurate for assessing the size of the left atrium, and that it compares unfavourably to left atrial volume for cardiovascular risk prediction. This was acknowledged by the authors in the manuscript. In the past decade there has been a paradigm shift in left atrial assessment, and the most recent guidelines from the American Society of Echocardiography recommend the use of left atrial volume as the standard method for the assessment of left atrial size. One may wonder if the results of the study would be more robust had the investigators used left atrial volume instead of linear dimension as the surrogate of left atrial size.

2. In both the Abstract and the Results sections, the authors reported a "higher" LAD and LAD/height but "lower" LAD/BSA during follow-up. While these differences may be statistically significant, one caveat is that the magnitude of such differences is small (e.g., a 2 mm increase in LAD, a 0.1 mm/m increase in LAD/height, and a 0.1 mm/2 decrease in LAD/BSA), and their clinical significance is uncertain. The authors may want to add a qualifier statement to wherever these findings are reported.
3. The cohort of the current study consists of 55% white patients and 45% African American patients. It may be interesting to examine the ethnic differences in the correlation between modifiable cardiovascular risk factors and left atrial dimension over a 20-year follow-up.

4. Under the section "Strengths and Limitations", the authors may want to check and modify the last sentence of bullet point #3 since the sentence ("other spatial dimensions in the LA remodelling process left atrial remodelling") does not seem to make sense.

**GENERAL COMMENTS**
- It is not stated in the manuscript that all participants gave written informed consent.
- In Table I variables are not properly presented.
- It is not mentioned that other factors affecting LA size are not addressed.
- Is there any data available on other important cardiac factors that affect LA size (diastolic dysfunction, valvular heart disease, myocardial infarction)? If not, this should be mentioned as a limitation.
- Although statistically significant, the coefficients found in the multivariate regression models (Table III) are fair. It may be valuable to mention this in the discussion.
- Do the authors have an explanation for the fact that a lower resting heart rate is predictive for LA enlargement during follow-up? It is briefly mentioned in the discussion, but it may be interesting for the reader to discuss this more extensively.
- Please check Table I: Probably LAD/BSA should be in cm/m² and LAD/height in cm/m² (or the presented values should be adjusted).

**VERSION 1 – AUTHOR RESPONSE**

Reviewer: 1
Reviewer Name Michael Y.C. Tsang
Institution and Country Mayo Clinic, Rochester, Minnesota, USA
Please state any competing interests or state ‘None declared’: None declared.

In this study, Armstrong et al. examined the association of modifiable cardiovascular risk factors in early adulthood with left atrial size over a 20-year follow-up period using data from the CARDIA study. The authors concluded that higher systolic blood pressure and body mass index were predictors of left atrial dimension. Interesting results were also reported regarding the relationship between baseline BMI or changes in BMI during follow-up and left atrial dimensions or indexed left atrial dimensions. While a positive correlation between BMI and left atrial dimension or left atrial dimension indexed to height was demonstrated, a negative correlation was found between BMI and left atrial dimension indexed to body surface area. My comments are as follows:

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authors in the manuscript. In the past decade there has been a paradigm shift in left atrial assessment, and the most recent guidelines from the American Society of Echocardiography recommend the use of left atrial volume as the standard method for the assessment of left atrial size. One may wonder if the results of the study would be more robust had the investigators used left atrial volume instead of linear dimension as the surrogate of left atrial size.

ANSWER – Thanks for bringing this to discussion; it is indeed a very interesting point. By the time that the CARDIA Year-5 was performed, M-mode technique was the standard assessment of LA size. However, studies have shown that eccentric remodeling is not rare in the left atrium; therefore, anterior-posterior linear dimension would miss some of the left atrial changes. Some other points can be added to this discussion. The CARDIA participants were a healthy cohort in the initial assessment, with low probability for LA enlargement at that point. While M-mode technique has been using the same principles, the 2D echocardiography technique evolved over the 20-year period of follow-up in CARDIA, particularly changing from fundamental imaging to harmonic imaging. Although it is not likely that it affects the linear measurements by M-mode, it is still not totally clear at this point how these technical changes may affect the 2D measurements of LA size. In addition, unpublished data of reproducibility in CARDIA shows higher precision in the M-mode measured compared to the 2D assessment of LA size. Probably, the simplicity of the linear anterior-posterior assessment loses accuracy regarding the total LA size but increases the repeatability of the measurement, therefore representing an adequate method to assess dimension changes over time.

2. In both the Abstract and the Results sections, the authors reported a "higher" LAD and LAD/height but "lower" LAD/BSA during follow-up. While these differences may be statistically significant, one caveat is that the magnitude of such differences is small (e.g., a 2 mm increase in LAD, a 0.1 mm/m increase in LAD/height, and a 0.1 mm/2 decrease in LAD/BSA), and their clinical significance is uncertain. The authors may want to add a qualifier statement to wherever these findings are reported.

ANSWER – Thanks for the comment. We added qualifier statements in the Results sections of both Abstract (page 2) and manuscript (page 7).

3. The cohort of the current study consists of 55% white patients and 45% African American patients. It may be interesting to examine the ethnic differences in the correlation between modifiable cardiovascular risk factors and left atrial dimension over a 20-year follow-up.

ANSWER - We performed ethnic-specific analysis as recommended (pages 7 and 11) and also included the data as supplemental material (Supplement Table S2).

4. Under the section "Strengths and Limitations", the authors may want to check and modify the last sentence of bullet point #3 since the sentence ("other spatial dimensions in the LA remodelling process left atrial remodelling") does not seem to make sense.

ANSWER – Thanks for the comment. We reworded the sentence to clarify it (page 3).

Reviewer: 2
Reviewer Name L. Tops
Institution and Country Leiden University Medical Center
Please state any competing interests or state 'None declared': None declared

- It is not stated in the manuscript that all participants gave written informed consent.

ANSWER – Thanks for the comment. We added the information as recommended (page 5).
- In Table I variables are not properly presented.

ANSWER – we understand that changes in the table presentation may help the reader and would appreciate suggestions on the changes to be addressed.

- It is not mentioned that other factors affecting LA size are not addressed.

ANSWER – Thanks for the comment. As recommended, we stated this limitation when describing the ‘Risk factors assessment’ in Methods (page 6).

- Is there any data available on other important cardiac factors that affect LA size (diastolic dysfunction, valvular heart disease, myocardial infarction)? If not, this should be mentioned as a limitation.

ANSWER – As addressed in the Discussion, LA size has a strong relation to ventricular filling pressures. Thus, enlarged LA may work as an early marker of diastolic dysfunction and cardiac remodeling. The effects of clinical cardiovascular disease on the LA remodeling over the follow-up period were expected in our study, although we do not believe that additional adjustments for CV events would be of high impact on our results. The number of CV events in the CARDIA study is very low (about 30 myocardial infarct cases over the 25-year follow-up period), what can be explained by the fact that CARDIA cohort is a young generally healthy cohort.

- Although statistically significant, the coefficients found in the multivariate regression models (Table III) are fair. It may be valuable to mention this in the discussion.

ANSWER – We expected that the magnitude of the relations would be affected by the fact that we assess a young healthy cohort with mostly subclinical changes. This is now clearer in the discussion (page 13).

- Do the authors have an explanation for the fact that a lower resting heart rate is predictive for LA enlargement during follow-up? It is briefly mentioned in the discussion, but it may be interesting for the reader to discuss this more extensively.

ANSWER – Thanks for the comment. We added a totally restructured paragraph on this point in the Discussion (pages 14 - 15).

- Please check Table I: Probably LAD/BSA should be in cm/m² and LAD/height in cm/m² (or the presented values should be adjusted).

ANSWER – Thanks for bringing this to our attention. The units were corrected accordingly.