Author's response to reviews

Title: Birth weight and the risk of atrial fibrillation in whites and African Americans: the Atherosclerosis Risk in Communities (ARIC) Study

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Author's response to reviews: see over
Response to Editor’s comments

We appreciate the additional comments provided by the editor. Below we provide a response to these comments and explain the corresponding changes to the manuscript.

“There is still significant concern about how mediating variables were handled in regression analyses. Intermediate variables (on the causal pathway) should NOT be "adjusted for" in regression analyses. There are separate mediation analyses that should be conducted. Moreover, the authors do not clearly articulate the potential relationships between their covariates and their proposed association. If CVD variables are indeed on the causal pathway then this should be explained and warrants more than just a staged regression analysis. When these variables were included in the model, the association became stronger and the authors assumed that this is evidence of no mediation effect. But since they never established that these were truly mediating variables (LBW associated with CVD variables and then CVD variables associated with AF, etc.) this statement is misleading and possibly incorrect. In sum, the mediation analyses should be much more rigorous.”

We agree with the editor that the inclusion of intermediate variables in the models should be done thoughtfully and that the manuscript should make more explicit the relationship between our main independent variable (birth weight), our outcome (atrial fibrillation, AF), and the other covariates in the models. In response to the editor’s comments we have made the following changes. We hope that these changes address the editor’s concerns satisfactorily:

1. The revised manuscript now includes a description of our causal model at the beginning of the statistical analysis section. This description clearly states our assumptions about the relationships between variables and provides references to support these assumptions (mostly from previous publications from the ARIC study). Also, we include a figure that presents those relations visually. In brief, we consider that race and sex can confound the association between birth weight and AF (Model 1): in our data, men and whites had higher birth weight than women and blacks, respectively (table 1), and we and others have shown that male sex and white race are risk factors for AF (see Alonso et al, J Am Heart Assoc 2013, which used ARIC cohort data and is now included in the text). Second, we additionally adjusted for markers of individual SES (education, income, and study center, which may be a proxy for regional SES differences). Though individual SES cannot cause birth weight, it is a marker of maternal SES, a strong determinant of intrauterine growth restriction. Therefore, we consider it a surrogate confounder. Finally, variables included in Model 3 (the major cardiovascular risk factors, which are also risk factors for AF) can be in the causal pathway between intrauterine growth restriction and AF. As our causal model reflects, once we condition (adjust) for all the variables in the figure, the only open path between ‘birth weight’ and atrial fibrillation is through a direct causal effect of intrauterine growth restriction. We agree that a model adjusting for intermediate variables is not useful to identify the total effect of a particular exposure (birth weight in this case), but it can be informative to understand the causal pathways linking the exposure to the outcome.
2. We are aware of the discussion in the epidemiologic literature of the estimation of direct and indirect causal effects, and the assumptions required for a mediation analysis (i.e., no confounding between the main independent variable and the outcome, no confounding between the mediator(s) and the outcome, and no effect modification between the main independent variable and the mediator(s)) (see Kaufman S, et al. Epidemiol Perspect Innov 2004;1:4). As we describe in our previous point, our analysis has tried to address the first two assumptions through multivariable adjustment for the main risk factors for AF. However, we did not formally test the last assumption. To address it, we have conducted an analysis stratifying the sample by presence or absence of CV risk factors:

<table>
<thead>
<tr>
<th></th>
<th>Low</th>
<th>Medium</th>
<th>High</th>
<th>P for trend</th>
</tr>
</thead>
<tbody>
<tr>
<td>No CV risk factors (n=2754), N</td>
<td>91</td>
<td>2365</td>
<td>298</td>
<td></td>
</tr>
<tr>
<td>AF events, N</td>
<td>1</td>
<td>116</td>
<td>16</td>
<td></td>
</tr>
<tr>
<td>HR (95%CI)</td>
<td>0.24 (0.03-1.74)</td>
<td>1 (ref.)</td>
<td>0.91 (0.54 to 1.54)</td>
<td>0.67</td>
</tr>
<tr>
<td>Any CV risk factor present (n=7378), N</td>
<td>358</td>
<td>6232</td>
<td>788</td>
<td></td>
</tr>
<tr>
<td>AF events, N</td>
<td>48</td>
<td>619</td>
<td>82</td>
<td></td>
</tr>
<tr>
<td>HR (95%CI)</td>
<td>1.42 (1.06, 1.91)</td>
<td>1 (ref.)</td>
<td>1.03 (0.82, 1.30)</td>
<td>0.24</td>
</tr>
<tr>
<td>P-value for heterogeneity*</td>
<td>0.09</td>
<td></td>
<td>0.67</td>
<td></td>
</tr>
</tbody>
</table>

Hazard ratios (HR) and 95% confidence intervals (CI) from Cox model adjusted for age, sex, race, study site, education, and income. Any cardiovascular (CV) risk factor present was defined as prevalent hypertension, diabetes, myocardial infarction, heart failure, obesity (BMI ≥30 kg/m²), or current smoking.

* P-value for heterogeneity of HRs in those without CV risk factors compared to those with CV risk factors, calculated with a Cochran’s Q statistic as described in MacLehose R and Kaufman J, Cancer 2013;119:4216-22.

As shown in the table above, the number of events in the low birth weight category without cardiovascular risk factors was quite small, making difficult an assessment of heterogeneity. However, we could not find statistical evidence of heterogeneity and, therefore, we considered that the assumptions for estimation of a direct effect hold. We make explicit our assumptions in the manuscript.

3. We have made a number of text changes to be more precise in our interpretation of the analysis:
   a. In the abstract, we have removed the statement about the associations becoming stronger, and we just say that a model adjusting for mediators did not attenuate the association between birth weight and AF incidence.
   b. As described above, the statistical methods section details our assumptions about the causal relationships between the covariates of interest and includes references supporting them. Also, it makes explicit the assumptions necessary for any mediation analysis.
c. In addition, the description of the models clarifies that Model 1 and 2 are adjusting for potential confounders, while Model 3 is testing for the presence of a direct effect of BW on AF risk independent of potential mediators.

d. In the results, we modified the description of the Model 3 results. Rather than saying that the association became stronger, we just state that the association between BW and AF risk remained, suggesting the presence of other pathways between BW and AF risk. We made a similar change in the discussion.

e. We have added Figure 1 which presents our assumptions about causal relationships between the different covariates.