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 REVIEWERS

We appreciate the interest from the Editors and Reviewers in our manuscript on birth weight and incident atrial fibrillation (AF) in the ARIC study. Below, we provide a point-by-point response to the comments. Changes to the manuscript have been marked using the Track Changes tool in Word.

Editor’s comments

1. Requesting Email. Please provide email address of each co-author in the Title page of the manuscript.

As requested, we have added email addresses for all coauthors following their name in the Title page.

2. Requesting ethics statement.

We apologize for the omission of the ethics statement. The ARIC study has been approved by the Institutional Review Boards at all participating institutions and all participants provided written informed consent.

Changes to the manuscript:

The following statement has been added to the methods section:

“The ARIC study is performed in accordance with the Declaration of Helsinki and has been approved by Institutional Review Boards at all participating institutions. Study participants provided written informed consent at all study visits.”

Reviewer 1

1. The authors should consider using the “medium” or average BW category as the reference group in data analysis and presentation of findings rather than the low BW category for at least a couple of reasons. One is that the average BW is the largest group and this alone justifies using it as the norm or reference group. This average BW group is also the usual reference group for most studies of categories of birth weight, making for reasonable comparisons across studies. The upper limit of high BW in this study is not defined and is likely to differ from study to study, making sensible comparisons of findings across studies difficult if not impossible.

As suggested by the reviewer, we have repeated the analysis using the medium BW category as the reference, and presenting the results comparing low and high BW to medium BW. As expected, the overall conclusion of the analysis does not change: low BW is associated with an increased risk of AF independently of other risk factors for AF.

Changes to the manuscript:

Tables 3, 4 and 5 have been redone using medium BW, instead of low BW as the reference category. Throughout the abstract, methods, and results, we have made appropriate edits to reflect the change in the reference category.
2. The low prevalence of low birth weight in this cohort seems odd and may suggest some selection bias but could also reflect in part the exclusions in this study. The authors might comment on the low prevalence of low birth weight or how this prevalence compares with that observed in other cohort studies of chronic diseases and how possible exclusions might have impacted on the results of the study.

The reviewer makes an excellent point. As has been reported previously by Rose and colleagues (ref. 18 in the manuscript), the prevalence of low BW among those who could not recall their actual BW was considerably lower than among those able to recall their BW (2% vs 5%). Concerns about the quality of BW information, therefore, exist. However, the prevalence of low BW among those reporting exact BW was similar to the prevalence in the general US population around the time the ARIC cohort was born. We repeated the analysis including only those who reported exact BW, and the results remained unchanged. Nonetheless, we recognize this is a limitation and highlight it in the revised version.

**Changes to the manuscript:**

In the section on study limitations and strengths in the discussion, we have included the following sentences:

“Second, the overall prevalence of LBW in our sample (4%) is lower than expected, suggesting underreporting of LBW [18]. In an analysis including only those with self-reported exact BW, which possibly provided more valid BW information [18], results remained unchanged.”

**Reviewer 2**

1. It was not possible to examine birth weight (BW) as a continuous variable, because the exposure (BW) was self-reported in approximately 50% of the participants. This may lead to much misclassification of exposure.

We agree with the reviewer and acknowledge the limitation in the discussion. See our response to the second comment from Reviewer 1.

2. BW was categorized into low, medium and high. The number of outcomes in each category was 49, 735 and 98. The low number of outcomes in the low BW category may compromise the robustness of findings.

The reviewer is correct that using the category with the lowest number of events may lead to unstable estimates of association. However, in response to Reviewer 1’s suggestion, we now use the medium BW category as the reference, which has a larger number of events and leads to a more robust analysis. Also, the results were mostly unchanged in the two sensitivity analyses we conducted. We recognize, however, that the relatively low number of events in the low BW is still a limitation and have reviewed the manuscript accordingly.

**Changes to the manuscript:**
We have added the following statement to the discussion:

“Similarly, the relatively low number of AF events in the LBW category may compromise the robustness of our results.”

3. Why is baseline at time of entry to the ARIC cohort? If the exposure is BW, then baseline should be the date of birth.

We agree with the reviewer that ideally we would start our follow up at birth, and identify incident AF cases after that. Unfortunately, we do not have information on the incidence of AF before the study baseline (left censoring). Even if we changed our analysis to include follow-up between birth and baseline, because we do not have any identified events in that period, the Cox models would provide the exact same results since hazard and survival estimates are only calculated at failure times (when an event occurs). Starting the follow-up at the time of BW assessment (in our primary analysis) or the initial recruitment in the ARIC cohort (sensitivity analysis) makes explicit the limitation of not having information on events before information on the exposure was collected. We recognize this limitation already in the manuscript.

4. The authors claim that they adjusted for potential confounders and/or mediators. They do that by putting all information (age, gender, study center, income, education, diabetes, systolic blood pressure, hypertension medication, smoking, height, body mass index, prevalent myocardial infarction and heart failure) in a Cox regression model. There are no clear cut distinctions of confounding and intermediate pathways. This leads to confusion in relation to causality. It could be important to line out models of causation that are easy to understand. For example if higher blood pressure at baseline is associated with lower BW, then blood pressure at baseline should not be adjusted for, because it is in the causal pathway between low BW and AF.

We agree that the distinction between confounders and mediators is important. As the reviewer clearly states, anything in the pathway between low BW and AF incidence, such as hypertension, obesity or diabetes, should be considered a mediator and not a confounder. These considerations led us to run separate models, first adjusting for sociodemographic variables, like race or education, which can be considered confounders (Models 1 and 2), and then additional models adjusting for other risk factors, such as hypertension, diabetes, body mass index, etc, which could be considered mediators (Model 3). We know make this more explicit in the statistical analysis section.

Changes to the manuscript:

In the statistical analysis section we have included the following sentence:

“Variables in models 1 and 2 can be considered confounders since they may be determinants of BW and are also risk factors for AF. Finally, model 3 adjusted additionally for cardiovascular risk factors as potential mediators, i.e. in the causal pathway, of the association between BW and AF risk...”