Author’s response to reviews

Title: The Relationship between Vitamin D and Risk of Atrial Fibrillation: A Dose-response Analysis of Observational Studies

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Version: 1 Date: 26 Aug 2019

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Response to the comments of the reviewers and revisions

Introduction: We thank the Expert Reviewers for their constructive comments. In our revised manuscript, we read the reviewers’ comments carefully and responded accordingly. We again thank the reviewers for raising those points that helped us to improve the quality and impact of our study. Point-by-point responses to the editors and reviewers are listed as follows.

Reviewer #1:

Comment 1: The study was well thought out, well designed and well executed and the article clearly written with clear discussion of the findings including propositions of possible explanations/substantiations for the findings.
Response: We appreciate the encouraging comments.
Comment 2: My one observation is that the significant heterogeneity observed in older individuals and not in younger individuals could have contributed to the observed differences in the findings related to effects of vitamin D deficiency in the two groups.

How did the authors deal with or account for heterogeneity?

Response: Thank you for your helpful comments. Actually, there was a great heterogeneity both in the older (I2=95%) and young group (I2=83%) (Tables 3). According to our subgroup analysis, a great heterogeneity between the case-control and cohort studies was observed, which indicated the heterogeneity was derived from the study design (Tables 3). Therefore, we excluded the case-control studies and found both the older (≥ 65 years) (RR: 0.96, 95%CI: 0.93-1.00) and young people (< 65 years) (RR: 0.94, 95%CI: 0.89-1.00) showed a weak inverse association between vitamin D and AF with no evidence of heterogeneity (I2=0%). These results are inconsistent with the recent analysis of ARIC study1, which showed that low vitamin D was a stronger indicator of AF in the youngest group (<54 years) but not in the oldest (>60 years), with an intermediate association in those aged 54–59 years. Therefore, based on current evidence, the age difference in the relationship between vitamin D and risk of AF is still unclear. Further prospective cohort studies are needed to clarify the age difference.

We have added this point in the abstract and updated this part in the discussion section. As follows:

Abstract: Further studies are needed to explore the age difference in the association between serum vitamin D level and the risk of AF and whether vitamin D supplements will prevent AF. (Marked in red, line 31, page 2)

Discussion: When we excluded the case-control studies, both the older (RR: 0.96, 95%CI: 0.93-1.00) and young people (RR:0.94, 95%CI: 0.89-1.00) showed a margined association between vitamin D deficiency and risk of AF. Of note, these results were inconsistent with the recent analysis of ARIC study1, which showed that low vitamin D was a stronger indicator of AF in the youngest group (<54 years) but not in the oldest (>60 years), with an intermediate association in those aged 54–59 years. Therefore, based on current evidence, the age difference in the relationship between vitamin D and risk of AF is still unclear. Further prospective cohort studies are needed to clarify the age difference. (Marked in red, line 201, page 11)

Reviewer #2:

Comment 1: Did the authors follow PRISMA guidelines?
Response: Thank you for comments. Our work has been performed according to PRISMA guidelines (http://www.prisma-statement.org). The PRISMA Checklist was showed in Table S1 Online Data Supplement.

Comment 2: Abstract-Methods: State clearly that this is a meta-analysis.
Response: Thanks for your comments. We have added this point in the Methods section. As follows:
Relative risk (RR) was used to measure the effects in this meta-analysis. (Marked in red, line 18, page 2)

Comment 3: No legend (title) for the figure given on page 26.
Response: The legend was added for the figure on page 26.

Comment 4: No titles given for tables on 27, 27, and 29.
Response: All of the titles were added for tables above mentioned.

Comment 5: Please make all tables and figures stand alone.
Response: We have re-formed the tables and figures as your suggestions.

Comment 6: Move first paragraph of results to the methods section.
Response: Thanks for your comments. Actually, according to the PRISMA Checklist(Table S1, Table S1 Online Data Supplement)[1], study selection should be firstly described in the results section (including numbers of studies screened assessed for eligibility, included in the review,
with reasons for exclusions at each stage and ideally with a flow diagram). Therefore, presenting them in the result section might be more appropriate.