Author's response to reviews

Title: Chewing Areca Nut Increases the Risk of Coronary Artery Disease in Taiwanese Men: A Case-control Study

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Author's response to reviews: see over
RE: MS: 9175486561616983

Research article
Chewing Areca Nut Increases the Risk of Coronary Artery Disease in a Taiwanese Population: A Case-control Study
BMC Public Health

Dear editors of BMC Public Health,

Attached please find our revised research article, entitled “Chewing Areca Nut Increases the Risk of Coronary Artery Disease in a Taiwanese Population: A Case-control Study”. First, thank you very much for the concise comments from you and the reviewers. The reviewers suggested us to focus the analysis on the male subjects, so we followed the suggestions and slightly changed the title to “Chewing Areca Nut Increases the Risk of Coronary Artery Disease in Taiwanese Men: A Case-control Study”. Meanwhile, we have revised the text of this research article and answered the questions based on all of your comments point-by point (see below). The revised parts of main text were underlined. We believe that this research article is greatly improved by your excellent comments. If you have any further questions, please feel free to contact me.

Sincerely,

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Editor’s comments:

Editor:

1. This is a major issue although of local interest.
   The question that should be answered in any case is to clarify the
   contribution of their paper on this issue further than that reported by the 2
   studies below.
   1. Lin WY, Chiu TY, Lee LT, Lin CC, Huang CY, Huang KC. Betel nut
      chewing is associated with increased risk of cardiovascular disease and
   2. Tseng CH. Betel nut chewing and subclinical ischemic heart disease in

Answer 1: Thank you for the comments! We have clarified the differences between
the previous studies and ours in the text (please see the second paragraph of page 5
and the first paragraph of page 14). Meanwhile, compared to the case patients in the
above studies, those in our study were clinical symptomatic, not subclinical. The
symptomatic coronary artery disease has much clinical impact than the subclinical
ischemic heart disease. Our study focused on the specific disease: coronary artery
disease, not on the non-specific diagnosis: cardiovascular disease or ischemic heart
disease.

Reviewers’ comments:

Referee 1:

1. This is a well designed case-control study dealing with a health topic of
   interest to the SE Region. This study is conducted well and concisely reported.
   Statistical tests are appropriate. Data are of interest to public health
   interventions. I would recommend publication.

Answer 1: Thank you for your kindly comments.

Referee 2:

Strengths of the Study.

1. The presence of cardiovascular disease is clinically established through
   coronary angiography to confirm the diagnosis of non-obstructive or obstructive
   coronary artery disease (CAD). Unlike in previous studies in which the diagnosis
   of CAD was not confirmed by cardiologists, and misclassification is less likely in
   this study.

Answer 1: Thanks!
2. The questionnaire to collect the exposure to areca nut chewing in this study is said to be validated [although the reference given is still in press and hence cannot be ascertained].

Answer 2: That in press paper has published in PLoS ONE (please see reference 14). We also added additional information about the verification of areca nut chewing from questionnaire in the text (please see the third paragraph of page 9).

3. The present study strengthens/refines previous research by establishing, for instance, a dose dependence as well as additive interactions with cigarette smoking, hypertension, and dyslipidemia.

Answer 3: Thanks!

Major Compulsory Revisions
The comparisons between the healthy controls and non-obstructive and obstructive CAD patient groups in Results, Paragraph 1 have not been conducted properly. Table 1 is problematic and should be totally revised for the following reasons:

1. "There is an error in the entry: For Age >60 with Obstructive CAD, the percentage should be 61.8 rather than 57.7.

Answer 1: Thanks a lot! We have corrected it.

2. The two columns of ORs with the associated confidence intervals appear to be the odds ratios for the given category (e.g., Age >60) relative to the reference category (e.g., Age <= 40) for the combined Control and CAD groups, with non-obstructive CAD and obstructive CAD as the outcome variables, respectively. These are not appropriate tests for comparing the characteristics of two groups.

Answer 2: Thanks! We have excluded the non-obstructive CAD case patients in this study and used the appropriate statistical analyses to compare obstructive CAD patients and their controls (please see the revised Table 1).

3. Instead of the above odds ratios, the authors should compare the characteristics of the Healthy Control vs. (Non-)obstructive CAD groups using such tests as the Chi-Square for categorical or ordinal variables, or comparable non-parametric tests.

Answer 3: Thanks! Please see the revised Table 1.
4. The inclusion of female subjects in the study is highly problematic as the authors also recognize in Statistical Analysis, Paragraph 2: “Because only one out of 63 women with obstructive CAD and no women in the healthy control group chewed areca nut, we also restricted our analysis to the male subjects.” Why restrict to male subjects only in the data analysis stage? A more logical approach is to redesign the study by restricting the study population to male subject only. I would recommend that the paper be revised and restricted to male subjects only, thus simplifying the presentation, getting rid of non-essentials, and makes the presentation more direct, pertinent, and easier to interpret. If female subjects are to be included in the study, then it is imperative that the control group be expanded to include enough areca nut chewing female subjects.

Answer 4: Thanks! We have revised it and restricted to male subjects only in our study. After restricting to male subjects, the eligible controls were randomly selected and frequency-matched with the case patients based on age category again (please see the section of Methods and revised tables).

5. I would further recommend that this study be further restricted to the cases of obstructive CAD. The focus of this paper really is on the effects of areca nut chewing on obstructive CAD and not at all on non-obstructive CAD – as presented in the key findings in Tables 2 and 3. The inclusion of non-obstructive CAD cases, which has a small sample, is therefore superfluous and does not enhance the study.

Answer 5. Thanks! We have also excluded non-obstructive CAD patients (n = 30) in our study and re-analyzed the data (please see the section of Methods section and revised tables).

6. Results, Paragraph 2, Line 3. It’s not appropriate to state “a significant 3.4-fold increase in risk”, when 3.4 is an odds ratio. Most researchers are comfortable with the terminology of odds ratios, so it’s better to simply present the odds ratio. There are formulas for converting the odds ratio into the relative risk if the authors really want to present the results in terms of the relative risk.

Answer 6. Thanks! We agree with the reviewer’s opinion and rephrase the sentences (please see the second paragraph of page 12).

7. In Questionnaire, Paragraph 3, it is stated that a standard questionnaire regarding the use of the three major substances has been validated. Because the reference quoted is still “in press”, it may be useful to reiterate briefly in this
paper the key findings from that study in order to convince the readers that the questionnaire has been properly validated.

Answer 7. That in press paper has published in PLoS ONE (please see reference 14). We also added additional information about the verification of areca nut chewing from questionnaire in the text (please see the third paragraph of page 9).

8. Results, Paragraph 2. For the dose-response relationship, the variables, Daily Uses and Cumulative Uses have been dichotomized to 1-20 and >20 for both variables. Is the choice of the cut-off at 20 clinically justified? What would the dose-response curve look like empirically?

Answer 8. Thanks! We chose the cut-off value at 20 for the reasons as follows. First, the areca nuts were 10 pieces in one pack in Taiwan; thus, it is convenient to choice 20 as cut-off value for the practical using in public health. Second, the median of the number of areca nuts chewing was 20 pieces per day in our study. Third, according to the previous study [15], the betel quid chewing had clinical effect when the cumulative using >20 pack-years.

9. Results, Paragraph 2. For Table 2 and also Table 3, it is more informative to the readers, and therefore more appropriate, if the full regression models (crude and adjusted ORs), including the covariates and interaction terms, are presented. The descriptive part of the table should then be in Table 1 instead.

Answer 9. Thanks! We have added the full regression models including the covariates and interaction terms in revised Supplementary Table 2 and 3 respectively.

10. Results, Paragraph 4. Should include more information from the findings regarding which additive effects of areca nut chewing on the likelihood of CAD are more or less significant.

Answer 10. Thanks! We have revised it (please see the second paragraph of page 13).

Referee 3:
1. Authors have stated about few epidemiological studies which looked into the association between chewing areca nut and the risk of CAD. More detailed description of findings from those studies and the differences between the study presented in the manuscript and those studies is needed.

Answer 1: We have addressed the differences between our study and the previous ones in the section of Background (please see the second paragraph of page 5). Meanwhile, we have discussed these differences in details in the section of Discussion.
(please see the first paragraph of page 14).

2. Correct the spelling of Table 3. “TaTable 3”.
Answer 2: Thanks! We have corrected it.

3. Supplementary Table 2 does not seem to be appropriate considering this is an original research manuscript. Supplementary Table 2 would be more appropriate for the review article. More discussion regarding the differences between studies by others and the study presented in the manuscript and the shortcomings of the studies by others should be included in the discussion part.
Answer 3: We have deleted the Supplementary Table 2 and moved that information to the section of Discussion (please see page 14-15).

4. Information on the prevalence of areca nut chewing in general population would help to picture whether healthy controls used in this study has some representation of the general population.
Answer 4: Please see the second paragraph of page 15.

Referee 4:
1. Two similar studies have been published in Journal of Clinical Nutrition, Vol. 87, No. 5, 1204-1211, May 2008, "Betel nut chewing is associated with increased risk of cardiovascular disease and all-cause mortality in Taiwanese men" and in Cardiology Research and Practice Volume 2011 doi:10.4061/2011/451489, "Betel Nut Chewing and Subclinical Ischemic Heart Disease in Diabetic Patients". I think it is not so novel and not suitable to be published in BMC public Health.
Answer 1: Thanks! We have answered this question from the comment of Editor early.