Author’s response to reviews

Title: Association of kidney function-related dietary pattern, weight status, and cardiovascular risk factors with severity of impaired kidney function in middle-aged and older adults with chronic kidney disease: a cross-sectional population study

Authors:
Adi Lukas Kurniawan (adilukaskurniawan@yahoo.com)
Chien-Yeh Hsu (cyhsu@ntunhs.edu.tw)
Hsiao-Hsien Rau (hh.rau@jct.org.tw)
Li-Yin Lin (jlin11025@gmail.com)
Jane Chao (chenjui@tmu.edu.tw)

Version: 2 Date: 20 Feb 2019

Author’s response to reviews:

Dear Dr. Clare Collins,

Many thanks for the reviewers’ suggestions and comments. We have revised throughout the manuscript (NUTJ-D-18-00363) entitled “Association of kidney function-related dietary pattern, weight status, and cardiovascular risk factors with severity of impaired kidney function in middle-aged and older adults with chronic kidney disease: a cross-sectional population study” according to the reviewers’ comments and suggestions. If you have any questions, please feel free to call me at +886-2-2736-1661 ext. 6548. I am looking forward to your response.

Sincerely,

Jane C.-J. Chao, Ph.D., Professor (corresponding author)
Reviewer #1:

Abstract:
1. Line 28: What is meant by "high"? Can the authors provide specific numbers?

Reply: We have mentioned in the Background section that in Taiwan, the prevalence of CKD stage 1-5 was 9.8%-11.9%, meaning more than 1.5 million individuals suffered from CKD [1] (lines 61-62). Moreover, based on a report by the United States Renal Data System in 2014, Taiwan had the highest prevalence rate and incidence rate of ESRD patients in the world especially in the age groups of 45–65, 65–75, and >75 years [2]. Therefore, we revised the text more precisely and provided the number as follows: “The prevalence of chronic kidney disease (CKD), characterized by impaired kidney function, is nearly two million people in Taiwan.” (lines 27-28).

2. Line 34: Provide age range.

Reply: We used participants who were 40 years old or above. The actual age ranges were 40 to 95 years old (line 34).

3. Line 39: Multivariate implies many outcomes, while multivariable means many predictors. I believe the authors want to use the later here.

Reply: Multivariate analysis refers to the statistical model that have 2 or more dependent or outcome variables, and multivariable analysis refers to the statistical model in which there are multiple independent or response variables [3]. The terms “multivariate” and “multivariable” are often interchangeably used in the literature. Therefore, we have changed the term “multivariate analysis” to “multivariable analysis” accordingly in the entire manuscript.

4. How was moderately/severely impaired kidney function defined?

Reply: According to Kidney Disease Improving Global Outcome (KDIGO) guidelines, CKD can be classified into six stages based on the eGFR levels (Table 1) [4]. We defined participants as mild impaired kidney function if they had eGFR between 60–89 mL/min/1.73 m2. Furthermore moderately/severely impaired kidney function was defined if the participants had eGFR less than 60 mL/min/1.73 m2. We choose the term “moderately/severely” because their eGFR range is combination between moderately decreased and severely decreased. We have added eGFR values for moderately/severely impaired kidney function in the Abstract section (line 41), and mentioned this definition in the Methods section (line151).

Table 1 GFR categories in CKD

<table>
<thead>
<tr>
<th>GRF category</th>
<th>GFR (mL/min/1.73 m2)</th>
<th>Terms</th>
</tr>
</thead>
<tbody>
<tr>
<td>G1</td>
<td>≥ 90</td>
<td>Normal or high</td>
</tr>
<tr>
<td>G2</td>
<td>60–89</td>
<td>Mildly decreased</td>
</tr>
<tr>
<td>G3a</td>
<td>45–59</td>
<td>Mildly to moderately decreased</td>
</tr>
<tr>
<td>Stage</td>
<td>GFR (mL/min/1.73 m²)</td>
<td>Description</td>
</tr>
<tr>
<td>-------</td>
<td>----------------------</td>
<td>---------------------</td>
</tr>
<tr>
<td>G1</td>
<td>&gt; 90</td>
<td>Normal</td>
</tr>
<tr>
<td>G2</td>
<td>60–89</td>
<td>GFR impairment</td>
</tr>
<tr>
<td>G3a</td>
<td>30–59</td>
<td>Moderately decreased</td>
</tr>
<tr>
<td>G3b</td>
<td>30–44</td>
<td>Moderately to severely decreased</td>
</tr>
<tr>
<td>G4</td>
<td>15–29</td>
<td>Severely decreased</td>
</tr>
<tr>
<td>G5</td>
<td>&lt; 15</td>
<td>Kidney failure</td>
</tr>
</tbody>
</table>

Abbreviations: CKD, chronic kidney disease; GFR, glomerular filtration rate.

In the absence of evidence of kidney damage, neither GFR category G1 nor G2 fulfills the criteria for CKD [4].

5. Line 52: The acronym 'RRR' has not been previously defined in the abstract.

Reply: We have added the acronym of RRR in the Methods paragraph of the Abstract section (line 37).

6. Was the main analysis to use the dietary pattern to predict kidney function? Please be more clear about the main model of interest in the method of the abstract.

Reply: The main analysis was to investigate the association of kidney function-related dietary pattern with weight status, cardiovascular risk factors, and severity of impaired kidney function (lines 31-33). The reason we used the term “kidney function-related dietary pattern” because RRR can be designed to retrieve the dietary pattern which is specifically related to kidney function based on the response variables (biomarkers).

Introduction:
1. Line 94-95: Need reference for this sentence.

Reply: We have added the references in the manuscript (line 95 and the references list).

Methods:
1. Line 107/108: What it meant by "periodic health check-up"? Please be more specific. How often did these visits take place?

Reply: MJ Health Institute provided periodic health check-up (mostly one examination per year per person) for its members. We have added this information in the methods section (line 108).

2. Line 155-158: Has the FFQ been previously validated in this population? Please provide a reference.

Reply: The MJ Health Management Services developed, validated, and standardized a self-administered food frequency questionnaire (FFQ) that was used to assess participants’ diet [5-7]. We have added the references in the Methods section (line 157) and the reference list.

3. Line 171: Multivariate implies many outcomes, while multivariable means many predictors-This comments applies throughout manuscript

Reply: We have changed the term “multivariate analysis” to “multivariable analysis” accordingly in the entire manuscript.

Results:
1. Line 238-244: Please indicate what the tertiles represent- more adherent to this dietary pattern or less?

Reply: The dietary score of an individual food group was 1 to 5 from the lowest to the highest consumption frequency, and dietary pattern scores were calculated by multiplying the dietary score of each food group by a factor-loading coefficient associated with the food groups, and then summing up all the food groups. For further analysis, dietary pattern score were divided into tertiles. The higher the tertile, the higher the dietary pattern score (more adherent) (lines 244-245).

Discussion:
1. Line 327: Add reference to this sentence.

Reply: We have added the reference to the sentence (line 332).

Table 1:
1. Include in table or footnote how mildly impaired and moderately/severely impaired kidney function are defined.

Reply: We have added the footnotes about the definitions of mildly and moderately/severely impaired kidney function (page 25).

2. When were these characteristics measured - include in title.

Reply: We have revised the title of Table 1 to make it more clearly as follows: “Characteristics of the participants aged ≥ 40 years old by kidney function status from the database collected between 2008 and 2010” (lines 565-566).

Table 2:
1. Include case numbers for each variable.

Reply: We have added the case number for each variable (page 26).

2. I found the superscripts here confusing. These should be associated with Model 1 and Model 2 at the top of the columns not with variable categories.

Reply: We used the superscripts with independent variable categories previously because we used different adjustment models for each category. For example, category “weight status” in model 1, we adjusted for age and gender, while category “cardiovascular risk factors” in model 1, we adjusted for age, gender, and BMI. We have changed the superscript with the models accordingly and described in the footnotes (page 26).

Figure 2:
1. Would be more interesting to combine A and B to more easily see if there is a dose response relationship with increasing tertiles of the dietary scores.
Reply: We have tried to combine the Figure A and B, but because we made the figure in the Graphpad Prism software. We found that maximum variables in the X-axis should be 15 variables in order to make a good graph. If we combine Figure 2A and B, it would have more than 15 variables (because each variable will have two sub-variables, which are tertile 2 and tertile 3). In our opinion, it would be more easy to combine Figure 2A and B into one table format (as below, page 28-29). We have changed Figure 2 to Table 4 to see more easily if there was a dose response relationship with increasing tertiles of dietary pattern scores, and revised the text accordingly (line 244).

Table 2. The association of dietary pattern score across tertiles with weight status, cardiovascular risk factors, and the severity of impaired kidney function (n = 41,128)

Please see the Table in the manuscript or the supplementary material for the response to the reviewers.

2. In figure 2 caption, please define tertiles 1, 2, 3.

Reply: Tertile 1 was defined as the participants who had dietary pattern scores -1.34 to 1.22 (consumed the dietary pattern less frequently). Tertile 2 was defined as the participants who had dietary pattern scores 1.23-1.89. Tertile 3 was defined as the participants who had dietary pattern scores 1.90-6.55 (consumed the dietary pattern more frequently). We have added the description for the definition of the tertiles 1-3 in the footnotes of Table 4 (pages 28-29).

3. Did the authors consider mediation analyses? Cardiovascular factors are likely a mediator between the dietary pattern the kidney function. Thus, adjusting for cardiovascular risk factors may dilute the effect.

Reply: In our study, cardiovascular status was defined as having a history of CVD and/or the use of cardiovascular medication. However, participants who had been previously diagnosed with CVD might have changed their lifestyle, and thus we decided to adjust for CVD status in the analysis [6] (lines 164-167).

Reviewer #2:
This paper focuses on the association of kidney function-related dietary pattern, weight status, and cardiovascular risk factors with severity of impaired kidney function. The authors report that weight and cardiovascular risk factors were related to increased risk of moderately/severely impaired kidney function. They also mention that kidney function-related dietary pattern was related to bodyweight, increased cardiovascular risk and the risk of impaired kidney function.

The main problem of this analysis is the limitation imposed by the design of the study. This is a cross-sectional study, so any relationship presented by the authors is prone to reverse causation. Even if the authors do not refer to causal relationships, the aforementioned associations are not interesting if there is no evidence whether, eg CVD risk is increased due to a specific dietary pattern.

Reply: The association between dietary patterns and CVD risk has been reported in the previous studies [6, 8, 9]. In our study, we focused on investigating the association between kidney function-related dietary pattern and traditional or non-traditional CVD risk factors such as abnormal weight status, abnormal blood lipids, hypertension, diabetes, and abnormal minerals in the subjects with impaired kidney function. In the results, we found that kidney function-related dietary pattern was positively associated with CVD risk factor components. However, because the cross-sectional study design only
showed a condition of one-point-in-time, we were unable to establish causality between the dietary patterns and CVD risk factor components. We also realized that the possibility of a reverse causation also exists. Therefore, a prospective cohort or randomized trial study design is needed to investigate, explain, and extend the findings of our study. We also have added this limitation in the manuscript as follows: First, the cross-sectional study design cannot identify the causal relationship of the study findings and it only showed a condition of one point-in-time. Hence, the possibility of a reverse causation also exists. Future studies using prospective cohort or randomized trial designs are needed to explain and extend a causal relationship between the dietary patterns and cardiovascular risk factors (lines 362-366).

Another problem of this paper is that they use a method (reduced rank regression, RRR) which is not widely used. They also mention that "RRR-derived dietary pattern is more likely to be associated with health-related outcomes" (lines 94-95), without backing this argument. They could have also used PCA or an a priori score and compare the findings to check if their results remain robust. In any case, they would not overcome the problem of reverse causation I mentioned before.

Reply: RRR was first introduced by Hoffman et al. in 2004 [10]. Since then, more than 60 publications were published for applying the RRR method [11]. The previous study by Nettleton et al. [12] reported that the dietary pattern derived by RRR was associated with coronary artery calcium (CAC) and intima media thickness (IMT), while the dietary pattern derived by PCA was not associated with CAC or IMT. Another study for identifying the association between the dietary pattern and obesity in preschool children found that the dietary pattern extracted from RRR was significantly associated with the prevalence of childhood obesity (OR = 1.11, 95% CI: 1.00-1.28 for each unit increase of dietary pattern) as opposed to the dietary pattern derived from PCA [13]. The previous study comparing both PCA and RRR methods in diabetic Chinese adults also showed that the odd ratio for diabetes from RRR derived dietary pattern had a significant positive association (OR = 2.37, 95% CI: 1.56-3.60), but PCA showed no significant correlation (OR = 0.76, 95% CI: 0.49-1.17) [14]. Moreover, the previous study using PCA and RRR methods to compare disease-related dietary patterns and their association with metabolic syndrome in 905 Northern German adults demonstrated that the increased RRR dietary pattern score was associated with a higher OR (2.18, 95% CI 1.25-3.81) of having metabolic syndrome than the increased PCA dietary pattern score (OR = 1.92, 95% CI: 1.21-3.03) [15].

We have added the reference citations in the text (lines 94-95). Moreover, we did the analysis to compare the association between PCA derived dietary pattern and RRR derived dietary pattern in terms of moderately/severely impaired kidney function (Table 3). Our results showed that RRR was positively associated with moderately/severely impaired kidney function while PCA showed no association (Figure 1) after adjusted for age, gender, BMI, smoking status, drinking status, physical activity, cardiovascular status, hypertension status, diabetes status, albumin, and CRP. The data (Table 3 and Figure 1) were only presented in the response to the reviewer, and not shown in the manuscript because the objective of this present study did not compare the PCA and RRR methods.

Table 3. Comparisons of factor loadings of first dietary pattern derived by PCA and RRR

Figure 1. Multivariable logistic regression for the association between tertile 3 (T3) dietary pattern scores derived by PCA or RRR method and moderately/severely impaired kidney function. Tertile 1 (T1) was used for the reference. Results were adjusted for age, gender, BMI, smoking status, drinking status, physical activity, cardiovascular status, hypertension status, diabetes status, albumin, and CRP. *P < 0.05.
Please see Table 3 and Figure 1 in the supplementary material for the response to the reviewers.

References