Author's response to reviews

Title: Risk Factors and Their Interaction on Chronic Kidney Disease: A Multi-Center Case-Control Study in Taiwan

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Version: 6 Date: 6 January 2015

Author's response to reviews: see over
Response to reviewer comments

Revised Title: Risk factors and their interaction on chronic kidney disease: A multi-centre case control study in Taiwan.


Manuscript ID: 1010521391144534

Dear Sir,

Thank you for giving us an opportunity to respond to the reviewers’ comments. The responses to the points raised by reviewers are indicated below. We have made appropriate changes to the manuscript as indicated.
Editorial Comments:

Comments to the Author
1. As identified by Reviewer 1, please have the manuscript reviewed and edited by a professional English-speaking medical writer.

Response
We used the BioMed Central-recommended language editing company, Edanz, to review and edit our manuscript.

2. The title needs refinement. In particular, a "survey" typically refers to administration of a questionnaire to participants asking their opinion. A better title might be "Risk Factors and Their Interaction on Chronic Kidney Disease: A Multi-Center Case-Control Study in Taiwan".

Response
Thank you for your valuable comment. We changed the title as you have suggested.

3. The abstract has some area that need refinement: (1) Methodology and Results should be separated, (2) Some elements in Results read as conclusions. In particular, this statement "We determined that hepatitis B, smoking, alcohol intake and groundwater use might not be important risk factors in CKD. However, the associations between hepatitis C/betelnut chewing and CKD requires further research" should be changed to "hepatitis B, hepatitis C, betelnut chewing, smoking, alcohol intake and groundwater use were not associated with CKD in multivariate analysis."

Response
We re-organised the abstract and added some descriptions. The sentence in the Results section that read as a conclusion has been changed (Page 3 Line 58–63; Page 3 Line 72–74).

4. The Introduction should be clarified as identified by Reviewer 1. We already understand many risk factors for CKD, so some clarity what this study is trying to achieve would be helpful. In particular, are we looking at the traditional definition of interaction: to see if the risk of CKD in those with HTN and DM is modified if there is concomitant anemia/hyperlipidemia/etc? How would
**Response**

We have reduced the description of the current situation, and added more to the research motive (Page 5 Line 2–12). In addition, we rewrote a part of the introduction to focus on the potential impact of this study (Page 6 Line 12–15).

5. **The methodology should be revised as outlined by both reviewers.**

**Response**

We have followed the recommendations of the two reviewers and revised the methodology section.

6. **The discussion should also be edited for clarity. Since other studies have identified risk factors for CKD, the authors should focus on what this study adds, and how it impacts clinical management. While the authors do summarize on page 21, this still is not entirely clear from the discussion and should be refined.**

**Response**

We re-organised our conclusion and described the clinical impact of this study. The Discussion has been appropriately edited for clarity (Page 22 Line 7–Page 23 Line 5).
Reviewer 1:

Comments to the Author

1. **English editing by relevant service or English-speaking colleagues might be needed in order to improve the manuscript flow and wordings.** Also, too many abbreviations were used in the abstract, and some were not spelled fully during their first mention.

Response

We used the BioMed Central-recommended language editing company, Edanz, to review and edit our manuscript.

2. **The authors should state their study objective more clearly. The first paragraph could be shortened and re-organized, that is, to focus more on their study intent instead of making general assumptions.**

Response

As suggested, the opening paragraph has been appropriately edited and has focused more on our research motive (Page 5 Line 84–94).

3. **The authors might have to provide explanation for excluding patients with cancer and those from smaller institutes.**

Response

The number of patients with cancer in Kaohsiung Municipal Hsiao-Kang Hospital, E-DA Hospital, Show Chwan Memorial Hospital, and Taipei Veterans General Hospital in this study were 1, 0, 7, and 16, respectively. However, this information is not needed in the manuscript because the patients with cancer were excluded at the initial recruitment step. Therefore, they would be excluded in analyses.

4. **The definitions of several variables need more clarification.** For example, smokers with less than 100 cigarettes consumed previously were classified as never-smokers? So did alcohol consumption history. Could the authors use the same definitions like the ones in betel nuts/exercise variable? The ascertainment of different comorbidities based upon questionnaires could suffer from recall bias. Some aid from the patients’ concurrent medications could be utilized as a hint.
Response

We have added a reference used for conventional epidemiological classification for smokers that we used in our study (Page 11 Line 16–18). We also added further descriptions of our classification methods (Page 12 Line 1–2; Page 12 Line 12-13). It is worth noting that habits of betel nut chewing do not have a clear definition. However, a regular betel nut chewer has many obvious features, including stained teeth. Therefore, we think that misclassification bias, particularly with betel nut chewing, might not happen in our study.

5. The rationale described in statistical analyses about not focusing on hypertension and diabetes mellitus as CKD-associated factors needed more elaboration and clarification.

Response

Further elaboration and clarification of hypertension and diabetes mellitus has been added to the statistical analysis section (Page 10 Line 232–Page 11 Line 239). As an example to explain our reasoning, if the true proportion of hypertension in CKD patients and healthy controls is 0.5 and 0.2, respectively, and assuming the ratio of case/control is 1 and the true CKD prevalence is 0.1, the proportion of patients from the hypertension outpatients is $0.1 \times 0.5 / (0.1 \times 0.5 + 0.9 \times 0.2) = 0.217$. Therefore, the odds ratio of hypertension to CKD would be 4.00, 1.28, and 1.02 when the proportion of people from the hypertension outpatients is 0.0, 0.2, and 0.4, respectively.

Using a mixture of factors may cause bias when the exposure is associated with one of the sources. This study only focuses on the effect of other factors and we used the stratified analysis to investigate their associations, and therefore, we believe this method is robust and unbiased.

6. The link to website “OpenEpi” in Method section did not work. The authors might have to provide other resources.

Response

Thank you for pointing this out. We have changed the website URL and checked that it now works (Page 6 Line 127–128).
Reviewer 2:

Comments to the Author

1. The study parameters (anemia, kidney disease, hypertension) are not clearly defined.

   (1) ANEMIA: values are not defined anemia. The relationship: Anemia and Hypertension is clearly documented (Biju P. Clinical and Experimental Pharmacology and physiology 2008)

   (2) HYPERTENSION. Diagnostic methodology is defined. It is this clinical HTA with ABPM? What is the range? 130/80 mmHg? Etc.

   It is well known that:

   Nocturnal hypertension or not clinical hypertension and daytime is the greatest risk factor for progression of Chronic Kidney Disease (Minutolo, Arch Inter Med 2011 Agrawall R; Kidney Int 2006, Davidson RA, ARCV Inter Med 2006)

   (3) CHRONIC KIDNEY DISEASE: I think it is not enough to define it by the MDRD formula. It is necessary to stratify progression by association with the Alb/creatinine (The HUNT II Study, JAMA 2007)

Response

Thank you for your valuable comments.

(1) Anaemia

We agree with the relationship between anaemia and hypertension documented in the reference article that you mentioned (Biju P. Clinical and Experimental Pharmacology and physiology 2008). However, the aim of our study was to survey risk factors and to identify their effects on CKD. The definition of anaemia used in this study is defined by the WHO as haemoglobin <12 g/dL in women and <13 g/dL in men [1]. We have added it in the revised manuscript (Page 9 Line 192–193).

(2) Hypertension

We agree with the prognostic role of ambulatory blood pressure measurement in CKD patients without dialysis as demonstrated by Dr. Minutolo. In CKD, ambulatory BP measurement provides a more accurate prediction of renal and cardiovascular risk than office measurement of BP. In addition, nocturnal hypertension is the greatest risk factor for CKD progression. The main goal of our study was to survey common risk factors of CKD in general and especially in a specific high risk population. It remains for future studies to analyse the impact
of individual risks on CKD progression.

Hypertension was diagnosed in our study by a systolic BP >130 mmHg and/or diastolic BP >80 mm Hg or patients receiving antihypertensive treatment. Owing to the limitation of study design and facilities available, we used office BP. The office BP was measured according to the recommendations of the European Society of Hypertension. BP was measured with the patient seated and taken three times at 5-minute intervals. The definition of hypertension used in the study has been added to the Methods section (Page 8 Lines 160–162).

(3) CKD
Our definition of CKD was based on that of the National Kidney Foundation’s Kidney Disease Outcomes Quality Initiative (K/DOQI) in 2002. The CKD is defined as either kidney damage for >3 months, as defined by structural or functional abnormalities of the kidney with or without decreased glomerular filtration rate (GFR) or GFR <60 mL/min/1.73 m$^2$ for >3 months with or without kidney damage. The CKD is further classified into Stages I–V according to the calculated eGFR using the MDRD formula. Albuminuria has been found to be an independent risk factor for cardiovascular death and CKD progression. Recently, 2012 KDIGO (Kidney Disease: Improving Global Outcomes) published an updated guideline to clarify the definition and classification of CKD to include the cause of kidney disease and the level of albuminuria, as well as the level of GFR. Our multi-centre project was started in January 2008 and ended in July 2010. Hence, we used the original KDOQI definition. The definition of CKD is stated in our revised manuscript (Page 7 Line 149–Page 8 Line 158).

2. **The relation to age, is a "confounding" relationship from the Baltimore study (J Am Geriatr Lindeman RD Soc 1985) is already known that Chronic Kidney Disease is not parallel to the old. The relationship between aging and GFR is possibly due to a podocyte disease (JE Wiggins J Am Soc Nephrol 2005) and Age is the 7th cause of entry into renal replacement therapy (Chi-yuan Hsu, A. Arch Inter Med Go 2010).**

Response
The kidneys are affected by the aging process. There are morphological and functional changes of the aging kidney. The Baltimore study has been widely cited to challenge the concept that the decline in renal function with age is inexorable [2]. However, the elderly population is heterogeneous; some have a
decline in GFR explained by diseases that complicate aging such as arteriosclerosis with hypertension. But in most healthy adults, the decline in GFR is more modest and not inevitable [3,4]. Recent studies have also highlighted that a reduction in podocyte number directly causes proteinuria and glomerulosclerosis. Furthermore, podocyte hypertrophy, "adaptation," and "decompensation" associated with glomerular enlargement and glomerulosclerosis were found in the aging rat kidney. The relationship between aging and GFR is possibly due to a podocyte disease [5]. Age is a major cause of entry into renal replacement therapy. It is also still unknown whether and how age influences the predictive role of other risk factors for ESRD and death. Hence, we analysed its impact. In order to avoid the confounding bias, we adjusted all factors in multivariate analysis. The odds ratio of age on CKD was 1.44 (95% CI 1.13 to 1.83) [Table 2 in our study]. Therefore, we believe this result is robust and age is an independent risk factor.