Author's response to reviews

Title: Ocular fundus pathology and chronic kidney disease in a Chinese population

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Author's response to reviews: see over
Re:  Ocular fundus pathology and chronic kidney disease in a Chinese population

July 22, 2011

Dear Editor:

Thank you for your potential interest in our manuscript. We greatly appreciate the thoughtful and helpful comments from the reviewer.

In our response, we have responded to each comment from the reviewer and have revised the manuscript accordingly. Each comment is listed verbatim, followed directly by our response. When the manuscript was altered according to a comment, we have included both the location of the change and a quotation of the change. We believe that the reviewer’s suggestions have substantially enhanced our manuscript.

Sincerely,

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Response to Reviewer 1 (Line Kessel)

**Major Compulsory Revisions:**

**Methods:**

∂ *Recruitment:* The authors should be more precise on how where the subjects recruited – where they invited from the local area using door-to-door screening or were they recruited among patients attending the hospital for other reasons or? In other words – is this study based on the background population or on a specific (perhaps sick) population?

- The study population comes consisted of participants enrolled in a medical program run by the Health Examination Center of Beijing Hospital. The Health Examination Center attracted paying participants from all over Beijing because of its known quality service, and about 70% of them receive annually health examination at the Center. Although the Center affiliated to the Beijing Hospital, participants are more like general population instead of a hospital-based population. We have made corresponding statement at Page 2, last paragraph, which reads: “Those participants come from all over Beijing to receive a regular paid health examination.”

∂ *Why did 7% not have fundus examination?*

- The major reason why 6.7% of participants did not receive fundus examination is that they did not agree to receive the examination. We have added the statement in Page 3, first paragraph: “The following participants did not agree to receive the examination and were therefore excluded from the present analysis.”

∂ *Fundus examination: an undilated fundus examination is not as precise as the standard dilated, photographic fundus examination that has been used in most epidemiologic studies for the last couple of decades. Did the authors check the validity of their examination procedure by dilating and photographing a subset of the population and grading fundus abnormalities to check how many were missed using the undilated procedure? It does not appear that the authors used standardized grading systems – so how did the authors ensure that what one ophthalmologist said was normal or abnormal would not by another ophthalmologist be graded as the reverse? Eg. how many microaneurisms or drusen was need to grade the fundus abnormal? Why was the funduscopic examination not compared to standardized systems.***

- We do not have data of the validation and between-observer variation. However, as we have pointed out in the Discussion, this type of between-observer misclassification would tend to bias our study towards not finding an association. Therefore, it is possible that we underestimated the
true association between proteinuria and eye pathology. The presence of microanurisms, or $\geq 3$ drusens, or drusens with other abnormalities suggestive of retinopathy were defined as having retinopathy.

Definition of chronic kidney disease: the authors used eGFR and proteinuria (measured by dipstick). The prevalence of $\text{eGFR}<60\text{ml/min}$ was 3.8% but CKD was found in 13.9% meaning that the majority of patients were diagnosed with CKD because of the urine dipstick. A urine dipstick is not very accurate and there may be many false positives (infection, menstruation, poor hygiene etc). Did you check the urine dipstick on a separate day? The authors should justify that their method is accurate and that the subjects were not incorrectly classified as having chronic kidney disease due to false positives on the dipstick. Did you measure the urinary albumin excretion ratio in a subset of the population to validate your diagnosis?

- In our study, we excluded participants with pyuria due to concern of urinary tract infection. Women during menstruation were asked to receive urine routine test 3 days after menstruation. We have made those clear in Page 3, last paragraph, which now reads:

  “Participants with pyuria were excluded from the analysis of proteinuria due to concern of urinary tract infection; women during menstruation were asked to receive urine routine test 3 days after menstruation.”

  We admit that urine routine test is not as sensitive as urinary albumin/creatinine ratio (ACR). However, a recent meta-analysis indicates that urine protein on dipstick is associated with adverse patient’s outcome, and could be used for screening of CKD (Chronic Kidney Disease Prognosis Consortium. Lancet, 2010, 375: 2073-2081). Since the urine protein on dipstick includes both albumin and other small molecular weight protein, we do not think that it is justifiable to validate our results using urinary ACR. Actually, the single test of urine sample was adopted by most epidemiological studies of CKD (Coresh J et al. JAMA 2007; 298:2038-2047).

Other conditions: did you use a specific questionnaire or did you simply ask if the participants were healthy?

- We use a questionnaire to ask about the medical history of the participants, including history of hypertension, diabetes, cardiovascular disease and so on.
Diabetes definition: how many hours of fasting were required? Surely, the authors have not examined nearly 10,000 subjects in the morning.

- Ten hours of fasting was required, as we have pointed out in the last paragraph of Page 3. The study was performed from 2007-2010, as we have pointed out in the last paragraph of Page 2.

Cardiovascular disease: which disease entities were included?

- All participants were asked, “Have you ever been told by a doctor that you had a heart attack?” and, “Have you ever been told by a doctor that you had a stroke?”

Why did the authors analyse for the risk of retinopathy and not for whether retinopathy was a risk factor for CKD? Do the authors think that CKD can cause retinopathy? I would expect that retinopathy was a risk indicator for common etiologies leading to CKD and turn the analysis around.

- We could not make any causal inference due to the cross-sectional design of the study. We could only conclude that we observe an association between proteinuria and ocular fundus pathology. And we agree that it is highly possible that retinopathy and CKD shared many common risk factors.

Results:

Prevalence of retinopathy in subjects with or without CKD. Using the more reliable method of eGFR, I do not find an overrepresentation of subjects with glaucoma (Chi-Sq 0.15) or AMD (Chi-Sq 0.25).

- Yes, there is no significant association between eGFR, glaucoma suspect and age-related macular degeneration. The possible reasons include: 1) relatively small percentage of participants with those abnormalities; 2) relatively well-preserved renal function in our study population; 3) misclassification.

Table 1: What is retinopathy compared to?

- As we have pointed out in the legend of Table 1, they were compared with participants without any ocular fundus pathology.

Why did the authors not show the no-retinopaty column?

- The participants without retinopathy might also have other fundus abnormalities, therefore we compared them with participants without any ocular fundus pathology.

If I read the table correctly nearly 80% of those with retinopathy did not have diabetes – so why did they have retinopathy? According to the table 967 of the total study population had diabetes
but only 359 had diabetes and retinopathy. Thus, 62% of those with diabetes did not have retinopathy. Is this what you would expect or was your method of estimating retinopathy not accurate?

- The major cause for the rest of participants was hypertension. We could not exclude the possibility of misclassification, as we have already pointed out in the discussion of limitation.

Why did you not include the number of subject with chronic kidney disease in the Table?

- We have added the corresponding contents in Table1.

Secondary analysis: why do you not show these results in detail? And why did you not perform a subset analysis only including those with diabetes?

- We have provided the detailed methods, point estimates with 95% confidence intervals in the manuscript. If the reviewer needs other information, we would be happy to provide. Since the association among diabetes-proteinuria-retinopathy has been well-established, we did not perform the analysis, while we would be happy to do so at the discretion of the editor.

Discussion:
There is a well-established association between diabetes, diabetic kidney disease and diabetic retinopathy. I do not understand why the authors did not use their data to stratify for diabetes and perform the analyses for subjects with or without diabetes. How many of the subjects with diabetes had CKD (see my comments previously for definition of CKD) and were they more likely to have retinopathy and was retinopathy a risk factor for having kidney disease as a diabetic? Those are the interesting questions. Secondly, you can look for other reasons for CKD and then look at whether retinopathy or other types of retinal abnormalities are risk factors for CKD in non-diabetics.

- We have tested for the interaction between diabetes status and proteinuria in our data and got insignificant P value (0.57), therefore we did not perform the stratified analysis. Among diabetic patients, 21.8% of them had CKD. Among diabetic participants, the prevalence of CKD was higher among with retinopathy compared with those without (25.3% vs. 19.0%). We would be happy to include the results in the manuscript at the discretion of the editor. As for the risk factors of CKD, we did not explore that due to the cross-sectional design of the study and limited information of potential candidates.
The authors conclude that the prevalence of retinopathy was increased in subjects with CKD and that may be what the authors found when proteinuria was used to diagnose CKD. When the analyses were restricted to eGFR in the multivariate analysis the authors did not find an effect of retinopathy or ocular pathology and this is quite an important remark that should at least be included in the conclusion.

- We have revised the conclusion as “Regular eye exam among persons with proteinuria is warranted”.

Minor Essential Revisions:

Table 1: Plasma UA should most likely be Plasma UA
- We have corrected that typo.

“Diabetic nephropathy, age-related macular degeneration and glaucoma are important cause of blindness in United States” – do you really mean that diabetic nephropathy is a cause of blindness?
- It should be “diabetic retinopathy”. We have made the correction.
Response to Reviewer 2 (Charumathi Sabanayagam)

Major compulsory revisions:

1. The authors defined CKD as a composite measure of eGFR<60 and/or proteinuria. However, analysis related to this composite measure is not presented anywhere in the manuscript. I suggest the authors present the results of this measure separately in addition to stratification by the 2 indicators.

   - We used the definition of CKD in order to address the prevalence of fundus pathology among participants with CKD, which is also the widely acknowledged definition. As for the association analysis, we do present the results separately. We have revised Table 2 according to the suggestion of the reviewer.

2. Methods, Evaluation of ocular fundus pathology: Retinopathy assessment could be explained further. How retinopathy was defined and was severity of retinopathy assessed? What was the intra or inter-rater reliability of retinopathy assessment?

   - We have added corresponding contents in Page 2, the second paragraph, which now reads: “The presence of retinal microaneurysms only, blot and/or flame hemorrhages only, hemorrhages and/or microaneurysms, cotton-wool spots, hard exudates, intraretinal microvascular abnormalities, venous beading, arteriovenous nicking, new vessels on the disc and elsewhere, and preretinal and vitreous hemorrhages was defined as retinopathy. Arteriolar narrowing and arteriovenous nicking were also defined as retinopathy.”

   We do not have data of intra or inter-rater reliability of retinopathy assessment. However, all of 3 ophthalmologists performing tests have clinical experience of more than 20 years. And as we have pointed out in the manuscript, this type of between-observer misclassification would tend to bias our study towards not finding an association; therefore, it is possible that we underestimated the true association between proteinuria and eye pathology.

3. Results: Is there any association between AMD or glaucoma suspect and CKD?

   - The prevalence of AMD and glaucoma suspect was higher among participants with CKD compared with those without CKD (1.7% vs. 0.9%, P=0.01; 3.1% vs. 1.8%, P=0.004). However, after we adjusted for age and gender, the association between AMD or glaucoma suspect and CKD (both indicators) became non-significant.
4. A separate Table showing analysis of eGFR, proteinuria and the combined CKD would be helpful. This can include additional columns showing number of persons and cases under each exposure category, and a simple model unadjusted or adjusted for basic confounders including age, sex before the multivariable model.
- We have revised Table 2 according to suggestions from the reviewer, which is in Page 16.

5. In Table 1, those with retinopathy have been compared to those without any ocular fundus pathology. Ideally, they should be compared to those without retinopathy.
- Since participants without retinopathy and without any ocular fundus pathology were largely overlapped (95%), we did not add extra column. However, we would be happy to do depending on the reviewer’s request.

Minor essential revisions:
6. Introduction: “A recent study indicated ---- among those patients”. Please mention the population in which this study was conducted.
- We have added the corresponding contents in Page 1, the first paragraph, which now reads:
“A recent study among 1 904 CKD patients in the United States indicated the overall prevalence of ocular fundus pathology among CKD patients was as high as 45%…”

7. Discussion, paragraph 2: “In our analysis …… consistent with previous reports”. Please provide references supporting this statement.
- We have added the reference.

8. Table 1 and 2: Please provide the full forms of abbreviations in the footnotes.
- We have added the corresponding contents.

Discretionary revisions:
9. Discussion: “the prevalence of blindness and low vision in the united states is projected to increase,…”. How is it relevant in the context of the present study?
- We have deleted the sentence.

10. Methods, Statistical analysis: Since duration of diabetes is an established risk factor for retinopathy, this could be included in the multivariable model if this information is available.
- We do not have such kind of information.