Author's response to reviews

Title: The correlates of urinary albumin to creatinine ratio (ACR) in a high risk Australian Aboriginal community

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Author's response to reviews: see over
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Dear Editor,

Thanks for your email of 13 March 2013 indicating a major compulsory revision on our manuscript (MS: 1822249488926016). We have completed the revision according to your and two reviewers’ comments. Below please find our point to point answers to the comments. The copy of revised manuscript and two figures were submitted separately. Thank you.

Yours Sincerely,

Zaimin Wang, Wendy Hoy, Zhiqiang Wang
Responses to editorial and reviewers’ comments

Editorial Comments:
Thank you for the interesting manuscript. We have had 2 reviewers evaluate the manuscript, and unfortunately both reviewers have suggested they are unable to decide on acceptance or rejection until response to the major compulsory revisions are complete. Please see the individual reviews for complete details, and respond to those in your revision.

In particular, please also comment on the following:
1) Since this is a cross-sectional analysis, identifying the research question and hypothesis early in the manuscript is a key issue identified by Reviewer 2.

Responses

The background in Abstract and full text have been rewritten to clearly identify the research questions and objectives. See background in page 2 and page 3.

2) Both reviewers ask for more discussion about causality as it relates to both risk prediction and population attributable fraction.

Responses

Population attributable fraction has been removed and discussion has been rewritten in the revised manuscript. See statistical analysis in page 4, and discussion between page 5 and page 8.

3) As mentioned by reviewer 1, the authors should reexamine and expand on the utility of factor analysis. What is meant by ?BP factor? and ?body mass factor?? Why is PFA more advantageous than continuous levels?

Responses

Factor analysis has been removed and sex-specific ACR cut-off points have been applied in the revised manuscript. See methods in page 4.

4) In addition, the authors should examine associations using continuous variables rather than at or above the median versus. This would include linear terms, splines, quadratic terms, or whatever modelling and clinical criteria suggest are appropriate.
Responses

Continuous variables rather than categorical variables as potential predictors have been added in the regression modelling in the revised manuscript. See methods in page 4 and logistic regression in page 5.

Editorial Request:
1. Please state in Methods section that you obtained informed patient consent for the original patient screening program.

Responses

The statement has been added in methods. See the last paragraph in methods in page 4 in the revised manuscript.

2. Copyediting - We recommend that you copyedit the paper to improve the style of written English. If this is not possible, you may need to use a professional language editing service. For authors who wish to have the language in their manuscript edited by a native-English speaker with scientific expertise, BioMed Central recommends Edanz (www.edanzediting.com/bmc1). BioMed Central has negotiated a 10% discount to the fee charged to BioMed Central authors by Edanz. Use of an editing service is neither a requirement nor a guarantee of acceptance for publication. For more information, see our FAQ on language editing services at http://www.biomedcentral.com/info/authors/authorfaqs#12.

Responses

The revised manuscript has been copyedited to improve its style of written English.

Reviewer 1 report

Reviewer: Alex Chang

Reviewer's report:
In this manuscript, the authors examine correlates of albuminuria as measured by ACR in an interesting high-risk Australian Aboriginal population.
Major Compulsory Revisions
In the introduction, the authors state the innovations of their study including measurement of novel risk factors and modelling outcomes around their median values as well as the use of factor analysis. While using some interesting analytical strategies, I am not clear the added value of using factor analysis to represent blood pressure and body mass instead of simply choosing systolic blood pressure or body mass index or waist circumference. This may just make it more challenging to understand for the reader.

Responses
Factor analysis has been removed and introduction has been rewritten in the revised manuscript. See background in page 3 and methods in page 4.

An important point to consider is the use of sex-specific ACR cutpoints. Warram et al (JASN 1996) suggest using a cutpoint of 25-355ug/mg for men and 17-250 ug/mg for women since women have lower muscle mass and urinary creatinine excretion than men. Certainly others have used the cutpoints used the authors have and this likely is not too be too important since most of the analyses are sex and age-adjusted. However, they should make some mention of this rather than imply that female gender is associated with micro/macroalbuminuria. It would be interesting to know if this still holds true using sex-specific cutpoints of ACR.

Responses
The sex-specific ACR cutpoints (25-355ug/mg for men and 17-250 ug/mg for women) have been used in the revised manuscript. See methods in page 4, Table 2 and Table 3 in page 18 and 19 and reference 13.

Use of population attributable fraction is an interesting concept especially in this high-risk Aboriginal population. However, I do wonder about the validity of this analysis that the authors have conducted. They state that the "simultaneous presence of all the factors with significant independent associations predicted probabilities of ACR>=30 of about 90% and of ACR>=300mg/g of about 80%, in people by 45 years of age."
However, each of these factors could be closely associated with each other. For example, a PAF of 20% for obesity would imply that if this risk factor were eliminated from the population, 25% of cases would be eliminated after elimination of this risk factor. This would hold true if these factors were not associated with each other. However, it is likely that GGT, body mass factor, diabetes, and CRP are all correlated (probably mostly due to the body mass). Thus, summing these factors together for a combined population attributable fraction may overrepresent the true estimate. Moreover, there should be causal relationships between purported risk factors and the disease in order to estimate population attributable fraction. Certainly, arguments could be made for the role of some of these factors. However, as the authors note, there is no proof of a causal relationship between serum albumin and albuminuria, and it may be the albuminuria that results in the lower serum albumin levels. The authors acknowledge the limitations of the cross-sectional study, but should also mention the limitations of their analysis using population attributable fraction and possible misinterpretations.

Responses

We agree with above comments. Population attributable fraction has been removed from the revised manuscript. The discussion has been also modified accordingly. See methods in page 5 and discussion between page 5 and page 8.

The authors mention urine albumin being measured by immoassay or HPLC in the introduction but do not make mention of this in the methods, so this makes this statement confusing.

Responses

The measuring method of urine albumin by immoassay or HPLC has been added in methods. See last paragraph in page 3 and the first paragraph in page 4 in the revised manuscript.
I believe study and understanding of the risk factors of albuminuria in such a high-risk population are very interesting, but question if the methods used are appropriate in summing up population attributable fractions.

Responses
As mentioned in previous responses, only logistic regression modelling was applied in the revised manuscript. Factor analysis and use of population attributable fractions have been removed.

Level of interest: An article whose findings are important to those with closely related research interests
Quality of written English: Acceptable
Statistical review: No, the manuscript does not need to be seen by a statistician.

Reviewer 2 report

Reviewer: Paul Komenda
Reviewer's report:
Wang et al. provide here a study correlating demographic and clinical parameters with urinary ACR in a high risk aboriginal community from Australia. Urinary ACR is a well-accepted risk factors for mortality and morbidity such as kidney failure. It is a modifiable risk factor for targeted intervention such as blood pressure control and RAAS inhibition.
This study is part of a larger screening study performed in the mid 90’s by the co-authors. I believe the statistical methods to be used of reasonable quality and I have no issue with the methodology.
I have some concerns with this paper as written:
1) (MAJOR) There does not appear to be a well-articulated research question or hypothesis in the introduction. It reads somewhat like a "fishing expedition" for parameters that correlate with Urine ACR. Please provide a concise research question and hypothesis in the introduction.
Responses
As the responses to reviewer 1, the background in Abstract and in full text have been rewritten to clearly identify the research questions and objectives. See background in page 2 and page 3.

2) (MINOR) The introduction reads more like a discussion in parts. The paper could be strengthened by moving other studies that have correlated Urine ACR with some parameters (paragraph2). Focus on the introduction instead, on building the case why this is important, and stating a testable hypothesis.

Responses
We agree with this point. Introduction has been rewritten to be more concise and clear. See page 3 in the revised manuscript.

3) (MAJOR) These data were collected 10-15 years ago. Why is it being published only now? The discussion states that studies are now ongoing to link findings of the screening study with outcomes - this should be tied into the premise of the paper somehow. Why not have this paper connect to the outcomes paper in a more formal way?

Responses
There were no reports on this topic although the data were collected 10-15 years ago, and this study is important as it is related to an interesting high-risk Australian Aboriginal population. One of recent longitudinal studies revealed that albuminuria was still a significant predictor of all-cause natural death after a 14-year interval in this Aboriginal community. However more longitudinal outcomes related to this topic are not available. See discussion in page 8 in the revised manuscript.

4) A significant number of risk prediction equations now exist for kidney failure incorporating GFR, Urine ACR, etc....Tying some of these in to the discussion may help frame this paper better (Tangri et al, JAMA 2012).
I would be happy to review a revision of this paper with a more focused question as to why all of these correlations are important?

**Responses**

More discussions have been added in the revised manuscript to emphasize the importance of the correlates of ACR. Tangril’s study was also cited. See discussion in page 7 and reference 48 in the revised manuscript.

**Level of interest:** An article whose findings are important to those with closely related research interests

**Quality of written English:** Acceptable

**Statistical review:** Yes, but I do not feel adequately qualified to assess the statistics.