Author's response to reviews

Title: High pulse pressure and metabolic syndrome are associated with proteinuria in young adult women

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Author's response to reviews: see over
Dear editors and reviewers

We greatly appreciate the opportunity to revise our paper in light of reviewers’ comments and resubmit it for publication on BMC nephrology. Enclosed is a revised version of our manuscript, previously submitted to your attention as MS: 1121456344859867 “High pulse pressure and metabolic syndrome are associated with proteinuria in young adult women”.

We made our best efforts in order to make the requested revisions in light of the editor and reviewer’s comments. Below you can find an itemized, point-by-point detailed response to all the questions and comments of the reviewers.

We hope our paper is now suitable for publication on BMC nephrology in its present form and we are now resubmitting it to your attention.

Reviewer 1:

Comments:
#1. Please make sure the condition of fasting state for blood sampling

Reply:
All blood samples were obtained in the fasting state (added in the “METHOD” section in revised manuscript).

Comments:
#2. I could not find the criteria for metabolic syndrome for Asian in JAMA 2001; 285(19): 2486-97. Waist circumference was shown as more than 88 cm in women in the paper. The authors should show the precise citation.

Reply:
As you pointed, there was an error in reference list. In revised manuscript, we corrected the mistakes. Because of the ethnic differences in abdominal obesity, criteria of abdominal obesity were specified by nationality or ethnicity based on best available population. For Asian population except for Japan, thresholds for waist circumferences were ≥90 cm in men and ≥80 cm in women, as defined by the International Diabetes Foundation (Circulation. 2005;112:2735-2752, Diabet Med. 2006 May;23(5):469-80). (added in the “METHOD” section in revised manuscript).

Comments:
#3. In Table 1, systolic BP in women with proteinuria was significantly higher than those in women without proteinuria. Therefore, systolic BP should be included in univariate and multivariate analysis (Table 2).

Reply:
As you recommended, we reanalyzed the data by adding the variable, systolic BP. With the median value of systolic BP of 110 mmHg, we divided the database into two groups: SBP ≥110 mmHg and SBP <110 mmHg (see new “Table 2” in revised manuscript)

In total patients, systolic BP ≥110 mmHg was a significant factor for predicting proteinuria in univariate analysis, however, it lost its significance in multivariate analysis. In subjects without metabolic syndrome, systolic BP had no significant effect on proteinuria in univariate and multivariate analysis.
In young women, some may have history having painkiller for menstruation. Please confirm the medical history.

In the population, 1515 (14.6%) had been taking medication for dysmenorrhea (added in the “RESULTS” section of revised manuscript).

If pulse pressure affect the prevalence of proteinuria in young women, hormonal background should be discussed.

Generally in postmenopausal women, the loss of estrogenic action on the arterial wall appears to play a specific deleterious role by increasing arterial stiffness and pulse pressure. Therefore, cardiovascular complications are more common in men and postmenopausal women than in premenopausal women. However in this study, we found the harmful effect of increased pulse pressure in young women aged 20 to 39, therefore, our findings could emphasize the importance of pulse pressure on proteinuria independent to other risk factors such as aging process or hormonal changes (FASEB J. 1996 Apr;10(5):615-24, J Am Coll Cardiol 2012;59:1771–7) (add in the “DISCUSSION” section in revised manuscript).

Reviewer 2:

Comments:
1. In this cross-sectional study, less than 1% of the subjects exhibited proteinuria. Analysis. Comparison of categorical variables should be performed by Fischer’s
exact test in this situation.

Reply:
As you pointed, we reanalyzed our data by Fischer’s exact test and corrected “Statistical analysis” section in revised manuscript.

Comments:
2. Authors need to correct some syntactic errors in the text.

Reply:
The English in this revised manuscript has been re-checked by at least two professional editors, both native speakers of English at “textcheck”. For a certificate, please see http://www.textcheck.com/certificate/kDC8Yn

Editorial Comments:

Comments:
1. Abstract: The concluding statement should be modified to state "Specific attention MAY be necessary..."

Reply:
As you recommended, we corrected the concluding statement in abstract and manuscript.

Comments:
2. Methods: Please state the variables included in multivariable models, and the rationale for them. Please add adjustment for age (modeled continuously) and blood pressure to models assessing the ‘independent’ relationship of pulse pressure and proteinuria. Also, please report estimated GFR in Table 1 and consider adjusting for it in the multivariable models.

Reply:
As you recommended, we added age and systolic blood pressure in multivariate analysis in revised manuscript (Table 2). As a result, age had no association with proteinuria. Systolic BP was a significant determinant for persistent proteinuria in univariate analysis, however; it lost its significance in multivariate analysis.

In addition, we added estimated glomerular filtration rate (eGFR) in Table 1 of revised manuscript. GFR was assessed using 2 estimating equations, Modification of Diet in Renal Disease (MDRD) Study equations and CKD Epidemiology Collaboration (CKD-EPI) equations. Subjects with persistent proteinuria had significantly lower eGFR than those without proteinuria.

And then, we re-analyzed the multivariate model using eGFR_{CKD-EPI} instead of serum creatinine, and the results were similar. Only pulse pressure (OR 3.29 95% CI 1.03-11.91) and metabolic syndrome (OR 7.77 95% CI 3.27-18.44) were significant determinants for the presence of proteinuria.

Therefore, in multivariate analysis, included variables were age, smoking, BMI, systolic BP, pulse pressure, cholesterol, metabolic syndrome and eGFR_{CKD-EPI}, which were significantly different between the two groups as shown in Table 1.

Comments:
3. Please avoid the use of "approximately" when referring to the prevalence estimates for
proteinuria, rather please state the exact findings of the study.

Reply:
As you recommended, we changed "the prevalence of persistent proteinuria in young women aged 20-39 years was approximately 1.0%" => “the prevalence of persistent proteinuria in young women aged 20-39 years was 1.0%” in revised manuscript.

Comments:
4. Please carefully review the manuscript for English grammar errors.
   
Reply:
The English in this revised manuscript has been re-checked by at least two professional editors, both native speakers of English at “textcheck”. For a certificate, please see http://www.textcheck.com/certificate/kDC8YN

Thank you for your kind considerations and I am looking forward to hearing a positive reply from you soon.

Yours sincerely