Author's response to reviews

Title: Metabolic syndrome is associated with change in subclinical arterial stiffness - A community-based Taichung Community Health Study

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Version: 3  Date: 11 August 2011

Author's response to reviews: see over
Dear Editor:
Thank you for your communication dated July 14, 2011 regarding my manuscript, "Metabolic syndrome is associated with change in subclinical arterial stiffness - A community-based Taichung Community Health Study". Your comments and reviewers’ critique are very helpful. We have responded to reviewers’ comments point by point, and indicated the changes in red color characters. Please feel free to contact me if you have any further question or critique.

With best wishes,

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Reviewer 1

Response to reviewer 1:

1. As you can see their reference 35 and 39, similar findings have been already reported by prospective studies. Therefore, this manuscript has not a sufficient high priority for the publication in BioMed.

Ans:
Thank you for your valuable comments. The reference 35 (Tomiyama et al, 2006) and reference 39 (Safar, 2006) were conducted in persons who were receiving for work-related health check-up and general health check-up, respectively. The study by Tomiyama et al reported a longitudinal relation between PWV and MetS only in men workers. Another 6-year follow-up study performed by Safar et al explored this relationship in subjects selected from receiving general health check-up with prevalence of elevated blood pressure of 50%. Moreover, high prevalence of diabetes and dyslipidemia in the study by Safar et al was found. Thus, it is very likely to have Berkson’s bias. Previous study showed the association may be found significantly in clinical-based studies, but not in community-based studies. Our study is the first community-based study using the probability sampling method to select a random sample from a well-defined population. This is the originality of our study. We have modified our introduction section to point out the importance of our study.

We have modified our introduction section according to your suggestion. The modified second paragraph of introduction section is listed as below and the modified sentences were marked.

The association of MetS with arterial stiffness has been investigated in many studies [28-32]; however, most of these studies were cross-sectional [28-30, 32]. Studies explored the longitudinal effect of MetS on arterial stiffness in specific subjects, such as patients who were systemic lupus erythematosus [33], patients who were newly detected suspected hypothyroidism [34], and persons who received work-related health check-up [35] or general health check-up [36]. None of them was community-based study. One study reported a longitudinal relation between PWV and MetS only in men workers [35]. Another 6-year follow-up study performed by Safar et al explored this relationship in subjects selected from receiving general health check-up population with prevalence of elevated blood pressure of 50% [36]. Moreover, high prevalence of diabetes and dyslipidemia in the study by Safar et al was found. It is very likely to have Berkson’s bias in their study [37]. Previous study
showed the association may be found significantly in clinical-based studies, but not in community-based studies [38]. Our study is the first community-based study using the probability sampling method to select a random sample from a well-defined population. Identifying the effect of MetS on arterial stiffness using a community-based longitudinal study is important. It can provide information for the management of MetS and thereby prevent progression to advanced arterial vascular disease. Therefore, the objective of the current study was to evaluate the effect of MetS on baPWV by considering mean arterial pressure (MAP) and the use of hypertension medicine to reduce the influence of blood pressure on baPWV.
Reviewer 2

Response to Reviewer 2.

1. As mentioned by the authors, the major limitation of this study may be the originality. The study performed by Safar et al have already demonstrated that metabolic syndrome is associated with progression of aortic stiffness (J Am Coll Cardiol 2006;47:72-75). However, since the study by Safar et al was performed on patients with high prevalence of hypertension, diabetes, and dyslipidemia, it would seem that this particular study may be unique in that it was performed in a relatively healthy population cohort. If the study is the first of its kind in a community based cohort, the authors needs to emphasize this finding to increase the originality of this study.

Ans:

(1) Thank you for your valuable comments. The cohort of Safar et al’s study (J Am Coll Cardiol 2006; 47: 72-75) was a clinical-based one. Their study subjects were received from free medical examinations in a French national health system with four subjects being recruited on a daily basis and included as the first 2 normotensive subjects of the day, the first subject with high blood pressure and without any antihypertensive drug treatment, and the first subject with antihypertensive treatment. Thus, high prevalence of hypertension, diabetes, and dyslipidemia was found in the study by Safar et al. It is very likely to have Berkson’s bias in their study. Previous study showed the association may be found significantly in clinical-based studies, but not in community-based studies. Our study is the first community-based study using the probability sampling method to select a random sample from a well-defined population. The originality of this study is to exam the association in a community-based cohort.

(2) We have modified our introduction section according to your suggestion. The modified second paragraph of introduction section is listed as below and the modified sentences were marked.

The association of MetS with arterial stiffness has been investigated in many studies [28-32]; however, most of these studies were cross-sectional [28-30, 32]. Studies explored the longitudinal effect of MetS on arterial stiffness in specific subjects, such as patients who were systemic lupus erythematosus [33], patients who were newly detected suspected hypothyroidism [34], and persons who received work-related health check-up [35] or general health check-up [36]. None of them was community-based study. One study reported a longitudinal relation between PWV and
MetS only in men workers [35]. Another 6-year follow-up study performed by Safar et al explored this relationship in subjects selected from receiving general health check-up population with prevalence of elevated blood pressure of 50% [36]. Moreover, high prevalence of diabetes and dyslipidemia in the study by Safar et al was found. It is very likely to have Berkson’s bias in their study [37]. Previous study showed the association may be found significantly in clinical-based studies, but not in community-based studies [38]. Our study is the first community-based study using the probability sampling method to select a random sample from a well-defined population. Identifying the effect of MetS on arterial stiffness using a community-based longitudinal study is important. It can provide information for the management of MetS and thereby prevent progression to advanced arterial vascular disease. Therefore, the objective of the current study was to evaluate the effect of MetS on baPWV by considering mean arterial pressure (MAP) and the use of hypertension medicine to reduce the influence of blood pressure on baPWV.

2. Descriptions in the statistical analysis is very confusing. Although the authors mention that variables predicting the baPWV change were evaluated with multivariate regression analysis, there are no data in the Results or the Tables section. Please clarify.

Ans:
Each of the predictor variables, such as age, gender, education, marital status, and metabolic syndrome status, et al. in table 2 and table 3, for baPWV change was adjusted for baPWV at baseline due to its strong impact on baPWV change. We consulted a statistician and we were told this method was called analysis of covariance (ANCOVA). The statistical method in figure 1, table 4, and figure 2 were multivariate adjustment. Figure 1 and table 4 used multivariate linear regression with the generalized estimating equations (GEE). Figure 2 used multivariate logistic regression with GEE approach. Therefore, we have modified the statistical method section as below, and the modified sentences were marked.

Statistical analysis
Continuous variables were reported as mean ± standard deviation (SD) and categorical variables were reported as percentage (95% confidence intervals, abbreviated as CI). The variables that predicted the baPWV change were evaluated by analysis of covariate with baPWV at baseline as covariate due to its high impact on the baPWV change. Moreover, to explore the effect of MetS and its components on baPWV, three multivariate models were used. First, the longitudinal effect of MetS and the number of components on the change baPWV at follow-up were examined...
using multivariate linear regression with the generalized estimating equations (GEE) method. Second, we further evaluated how the longitudinal effect of individual MetS components on baPWV was affected by the other components being considered sequentially, using hierarchical linear regression analysis with the GEE approach. The order of entering the variables was elevated blood pressure, fasting glucose, WC, triglyceride, and low HDL cholesterol after adjustment. Last, the top quartile of baseline baPWV was used as the cutoff point to classify the high risk group with arterial stiffness. Multivariate logistic regression with the GEE approach was used to analyze the longitudinal effect of MetS and its components on arterial stiffness. We treated the number of MetS components as continuous variables to examine the linear trend on the risk of arterial stiffness. All reported p values were those of the two-sided tests; statistical significance was set at p < 0.05. All analyses were performed using SAS version 9.1 (SAS Institute Inc, Cary, NC).

3. Figure 1 is very confusing. It seems like the dependent variable is the change in baPWV at followup. However, there is no clear description of this in the Method or the Result. Please clarify.

   Ans:
   Yes, the dependent variable is the change in baPWV at follow up in figure 1. And the independent variables were metabolic syndrome and its number of components. The statistical method in figure 1 was multivariate linear regression with the generalized estimating equations (GEE). It was described as the first of three models which were mentioned in the modified statistical method section. In figure 1, we showed the estimated coefficients and their 95% confidence intervals from multivariate linear regression with GEE.

4. For the multivariate correction, smoking should also be corrected as smoking is associated with increase in baPWV.

   Ans:
   We have followed your suggestion by adding smoking as a confounding factor in multivariate analyses. The modified results in figure 1, table 4, and figure 2 were adjusted for age, gender, smoking, time-dependent hypertension medication, and time-dependent mean arterial pressure.