PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Comparison of coronary heart disease risk assessments among individuals with metabolic syndrome using three diagnostic definitions: A cross-sectional study from China
AUTHORS	Zhou, Juan; Gao, Qin; Wang, Jun; Zhang, Ming; Ma, Jianping; Wang, Changyi; Chen, Hongen; Peng, Xiaolin; Hao, Liping

VERSION 1 – REVIEW

REVIEWER	Angelo Scuteri University of Sassari Italy
REVIEW RETURNED	09-Apr-2018

GENERAL COMMENTS	Auhtors investigated three definitions of MetS in a large Chinese population. This is a cross-sectional study. Therefore any wording or inference about "predictive" power is inaccurate and inappropriate. For example, different MetS definitions are ACCOMPANIED by different CV risk according to Framingham risk score, but they do not predict Greater number of CV events (also because it should be demonstrated the reliability of Framingham risk score in Chinese population). Additionally, if not validated in longitudinal outcome study, it may be also likely that CDS definition of MetS just overestimates CV risk (as illustrated in Table 4). If so, this may be unethical for subjects and may result in an inappropriate allocation /use of healthcare resources. Concerning the conceptual framework and the literature quoted in its support, Authors should acknowledge that previous works compared predictive power of different MetS definition (for instance Diabetes Care. 2005; 28: 882-7). When reporting MetS prevalence, it should be compared with that reported in other population studies conducted (Nutr Metab Cardiovasc Dis. 2009; 19: 532-41 -- Eur J Prev Cardiol. 2015; 22: 486-91). Last, but not least, when proposing the superiority of a MetS definition adopting BMI rather than waist circumference as an index of adiposity, it should be discussed that studies reported the predictive role of waist circumference for new onset MetS (J Gerontol A Biol Sci Med Sci. 2009; 64: 590-8), that it has stronger association with arterial aging (Atherosclerosis. 2012; 221: 189-97), and that cluster of MetS including abdominal adiposity have been consistenly associated with arterial damage (Atherosclerosis 2014; 233:654-660 --- Eur Heart J. 2010;31:602-13).

	The meaning of the values for Framingham score reported in Table 2 is not clear, based upon the definition given in Methods.

REVIEWER	Carl J Lavie MD Ochsner, USA
REVIEW RETURNED	29-May-2018

GENERAL COMMENTS	This is a nice study and well-written manuscript that should be publishable in a solid Journal. Since these data are more applicable to China than worldwide and it assessed risk as opposed to specifically CHD/CVD events, I suspect it is more suitable for a Journal in the IF 1.5-2.5 (or 3) range as opposed to higher.Also, the authors use FRS which is not used currently in the US , which uses the Pooled Cohort equation to assess not only risk of CHD but ASCVD.Also, for a non-Asian population, using a BMI cut-point of 25 would not be very useful , as almost the whole US adult population has a BMI above this.Third, both the FRS and Pooled Cohort equation over-estimate risk in the Hispanic and Asian populations and underestimate risk in the Indian population.Obviously, if they actually had CHD /CVD event data instead of just risk the results would be considerably stronger.Finally, I have recently published papers on fitness being extremely important for assessing risk of cardiometabolic diseases, which could be mentioned (Kennedy AB et al. JAMA 2018; 319: 231-232; Deedwania P , Lavie CJ . JACC 2018;71:1866-1868; and Lavie CJ et al Lancet Diabetes& Endocrinology 2018; being released today May 29/30, 2018.)

VERSION 1 – AUTHOR RESPONSE

Responses to the reviewer's comments:

Reviewer: 1

Comments 1: This is a cross-sectional study. Therefore, any wording or inference about "predictive" power is inaccurate and inappropriate. For example, different MetS definitions are accompanied by different CV risk according to Framingham risk score, but they do not predict greater number of CV events (also because it should be demonstrated the reliability of Framingham risk score in Chinese population). Additionally, if not validated in longitudinal outcome study, it may be also likely that CDS definition of MetS just overestimates CV risk (as illustrated in Table 4). If so, this may be unethical for subjects and may result in an inappropriate allocation /use of healthcare resources.

Response: We would like to thank you very much for your very reasonable and good suggestions, which are quite beneficial to our further studies.

First, we agree with your views that any wording or inference about "predictive" power is inaccurate and inappropriate since the study is an observational cross-sectional study. We are very sorry for our inaccuracy in the original manuscript, and we corrected these sentences in the revised manuscript and hope that the revisions meet your requirements.

Second, we need to acknowledge that we do not have the CHD event data. Therefore, we cannot determine which diagnostic criteria are more advantageous in predicting the CHD risk. However, we are particularly interested in the discrepancy among the three different MetS definitions not only in prevalence but also in the ability to reflect the risk of developing CHD. Additionally, the Framingham risk score (FRS) is a standard tool used to predict the incidence of coronary heart disease (CHD). However, there have been concerns regarding its generalizability to other population [1] since 99% of the Framingham cohort participants were Caucasian [2]. Honestly, there is a limitation in predicting the CHD risk in some other populations. For example, the FRS resulted in an overestimation of the

CHD risk in Asians [3 4]. However, the FRS may be an effective method for predicting the risk of CHD before there are better predictors.
Third, as you note, the CDS definition might overestimate the CV risk (as illustrated in Table 4). Thus, this may result in the inappropriate allocation/use of healthcare resources. Based on your guidance, we added the statement “the results should be interpreted with caution” to the limitation of the manuscript since we use the Framingham risk algorithm to estimate the risk instead of actual CHD events. Undoubtedly, we agree with your highly perspicacious viewpoint, and we aim to perform longitudinal studies in the future to not only demonstrate the reliability of the Framingham risk score in the Chinese population but also determine which MetS definition is best suited for predicting CHD.
We greatly appreciate your careful review of our manuscript, especially your constructive comments and valuable advice regarding our follow-up research designs.

Comments 2: Concerning the conceptual framework and the literature quoted in its support, Authors should acknowledge that previous works compared predictive power of different MetS definition (for instance Diabetes Care. 2005; 28: 882-7). When reporting MetS prevalence, it should be compared with that reported in other population studies conducted (Nutr Metab Cardiovasc Dis. 2009; 19: 532-41 -- Eur J Prev Cardiol. 2015; 22: 486-91). Last, but not least, when proposing the superiority of a MetS definition adopting BMI rather than waist circumference as an index of adiposity, it should be discussed that studies reported the predictive role of waist circumference for new onset MetS (J Gerontol A Biol Sci Med Sci. 2009; 64: 590-8), that it has stronger association with arterial aging (Atherosclerosis. 2012; 221: 189-97), and that cluster of MetS including abdominal adiposity have been consistenly associated with arterial damage (Atherosclerosis 2014; 233:654-660 --- Eur Heart J. 2010;31:602-13).
Response: We sincerely thank you for the constructive suggestions, which greatly improved our work. According to your advice, we added these studies to the discussion; the revisions are marked in red in the resubmitted manuscript.
First, as you mentioned, the previous study have compared the applicability of different MetS definitions in predicting cardiovascular diseases. [5-9] However, to the best of our knowledge, the results remain inconsistent. We assume that the racially and regionally diverse population may have partially led to the difference. In addition, another explanation is the multiple diagnoses of MetS. For example, Hosseinpanah et al. [5] assessed the predictability of the development of CVD by the definitions by the National Cholesterol Education Program Adult Treatment Panel III (NCEP-ATP III), the International Diabetes Federation (IDF), the American Heart Association/National Heart, Lung, and Blood Institute (AHA/NHLBI), and the joint interim statement (JIS). Furthermore, Scuteri et al. [9] compared the difference between the WHO criteria and ATP III criteria. Undoubtedly, these studies greatly helped me in the conceptual framework and played an essential role in this article.
Compared with the results of studies conducted on other populations [10 11], the difference in the prevalence of MetS between males and females is consistent to a certain degree. For instance, a greater number of females met the diagnostic criteria of MetS using the IDF criteria, while this phenomenon was not observed using the ATP III criteria. As revealed in the paper, the prevalence of abdominal obesity was higher in women than in men. Therefore, the IDF criteria led to a greater number of women having MetS since it require abdominal obesity as the obligatory for the diagnosis of MetS. In addition, if the threshold value of abdominal obesity differs among different MetS definitions, the discrepancy in prevalence might be reversed. For instance, Scuteri et al. [11] reported that the prevalence of MetS using the IDF criteria was higher than that using the ATP criteria, which may result from the lower waist circumstance threshold values applied to the European population by the IDF.
Compared with the other criteria, the CDS criteria led to the lowest prevalence of MetS. As we described in the paper, subjects diagnosed with obesity (BMI ≥25 kg/m2) were more common than those diagnosed with central obesity (32.31% vs 24.17%). Therefore, the lowest prevalence and the highest risk for CHD are mainly caused by the thresholds of high blood pressure and elevated blood glucose of the CDS criteria, which are higher than those of the other criteria. However, discussing the

superiority of the MetS definition adopting BMI or waist circumference as an index of adiposity is necessary. Some studies posit that waist circumference is a more advantageous index of adiposity. According to Scuteri et al. [12], waist circumference is a significant predictor of new onset metabolic syndrome. In addition, Scuteri et al. [13] indicated that waist circumference correlated with arterial properties better than BMI, and as the waist circumference increases, the arterial structure and function significantly change within each BMI quartile, even though the cluster of MetS including abdominal adiposity has been consistently associated with arterial damage [14 15].
Comments 3: The meaning of the values for Framingham score reported in Table 2 is not clear, based upon the definition given in Methods.
Response: Thank you for your valuable comments! We appreciate your efforts and noting your concern. We apologize for our carelessness. After careful examination and verification, there is indeed an error in the expression of the Framingham risk score (%) in Table 2. We earnestly apologize for our error, and to clarify the meaning of the value, we use the "10-year probability of developing CHD (%)" rather than "Framingham risk score (%)" as the indicator in Table 2. In addition, following your suggestion, we enriched the content as follows: "The Framingham risk score was calculated using the NCEP-ATP III algorithm, which uses the following variables: sex, age, TC, smoking status, HDL-C, and SBP (treatment for hypertension and SBP value). The 10-year probability of developing CHD was calculated based on the risk score by gender." The revisions are marked in red in the Methods section in the resubmitted manuscript
We appreciate your kind-hearted help.

References:
1. D'Agostino RB, Sr., Grundy S, Sullivan LM, et al. Validation of the Framingham coronary heart disease prediction scores: results of a multiple ethnic groups investigation. Jama 2001;286(2):180-7
2. National Cholesterol Education Program Expert Panel on Detection E, Treatment of High Blood Cholesterol in A. Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) final report. Circulation 2002;106(25):3143-421
3. Nishimura K, Okamura T, Watanabe M, et al. Predicting coronary heart disease using risk factor categories for a Japanese urban population, and comparison with the framingham risk score: the suita study. Journal of atherosclerosis and thrombosis 2014;21(8):784-98
4. Liu J, Hong Y, D'Agostino RB, Sr., et al. Predictive value for the Chinese population of the Framingham CHD risk assessment tool compared with the Chinese Multi-Provincial Cohort Study. Jama 2004;291(21):2591-9 doi: 10.1001/jama.291.21.2591[published Online First: Epub Date]|.
5. Hosseinpanah F, Asghari G, Barzin M, et al. Prognostic impact of different definitions of metabolic syndrome in predicting cardiovascular events in a cohort of non-diabetic Tehranian adults. International journal of cardiology 2013;168(1):369-74 doi: 10.1016/j.ijcard.2012.09.037[published Online First: Epub Date]|.
6. Kastorini CM, Panagiotakos DB, Georgousopoulou EN, et al. Metabolic syndrome and 10-year cardiovascular disease incidence: The ATTICA study. Nutrition, metabolism, and cardiovascular diseases : NMCD 2016;26(3):223-31 doi: 10.1016/j.numecd.2015.12.010[published Online First: Epub Date]|.
7. Qiao Q, Group DS. Comparison of different definitions of the metabolic syndrome in relation to cardiovascular mortality in European men and women. Diabetologia 2006;49(12):2837-46 doi: 10.1007/s00125-006-0438-6[published Online First: Epub Date]|.
8. Zhou H, Guo ZR, Yu LG, et al. Evidence on the applicability of the ATPIII, IDF and CDS metabolic syndrome diagnostic criteria to identify CVD and T2DM in the Chinese population from a 6.3-year cohort study in mid-eastern China. Diabetes research and clinical practice 2010;90(3):319-25 doi: 10.1016/j.diabres.2010.09.001[published Online First: Epub Date]|.
9. Scuteri A, Najjar SS, Morrell CH, et al. The metabolic syndrome in older individuals: prevalence and prediction of cardiovascular events: the Cardiovascular Health Study. Diabetes care 2005;28(4):882-7

10. Scuteri A, Laurent S, Cucca F, et al. Metabolic syndrome across Europe: different clusters of risk factors. European journal of preventive cardiology 2015;22(4):486-91 doi: 10.1177/2047487314525529[published Online First: Epub Date]|.
11. Scuteri A, Najjar SS, Orru M, et al. Age- and gender-specific awareness, treatment, and control of cardiovascular risk factors and subclinical vascular lesions in a founder population: the SardiNIA Study. Nutrition, metabolism, and cardiovascular diseases : NMCD 2009;19(8):532-41 doi: 10.1016/j.numecd.2008.11.004[published Online First: Epub Date]|.
12. Scuteri A, Morrell CH, Najjar SS, et al. Longitudinal paths to the metabolic syndrome: can the incidence of the metabolic syndrome be predicted? The Baltimore Longitudinal Study of Aging. The journals of gerontology Series A, Biological sciences and medical sciences 2009;64(5):590-8 doi: 10.1093/gerona/glp004[published Online First: Epub Date]|.
13. Scuteri A, Orru M, Morrell CH, et al. Associations of large artery structure and function with adiposity: effects of age, gender, and hypertension. The SardiNIA Study. Atherosclerosis 2012;221(1):189-97 doi: 10.1016/j.atherosclerosis.2011.11.045[published Online First: Epub Date]|.
14. Scuteri A, Cunha PG, Rosei EA, et al. Arterial stiffness and influences of the metabolic syndrome: a cross-countries study. Atherosclerosis 2014;233(2):654-60 doi: 10.1016/j.atherosclerosis.2014.01.041[published Online First: Epub Date]|.
15. Scuteri A, Najjar SS, Orru M, et al. The central arterial burden of the metabolic syndrome is similar in men and women: the SardiNIA Study. European heart journal 2010;31(5):602-13 doi: 10.1093/eurheartj/ehp491[published Online First: Epub Date]|.

Reviewer: 2
Comments 1: This is a nice study and well-written manuscript that should be publishable in a solid Journal. Since these data are more applicable to China than worldwide and it assessed risk as opposed to specifically CHD/CVD events, I suspect it is more suitable for a Journal in the IF 1.5-2.5 (or 3) range as opposed to higher. Also, the authors use FRS which is not used currently in the US, which uses the Pooled Cohort equation to assess not only risk of CHD but ASCVD. Also, for a non-Asian population, using a BMI cut-point of 25 would not be very useful, as almost the whole US adult population has a BMI above this. Third, both the FRS and Pooled Cohort equation over-estimate risk in the Hispanic and Asian populations and underestimate risk in the Indian population. Obviously, if they actually had CHD /CVD event data instead of just risk the results would be considerably stronger.
Response: We thank you for commenting that "This is a nice study and well-written manuscript that should be publishable in a solid Journal". We thank you for your kind comments regarding our paper and deeply admire your scientific ability and profound knowledge. Thank you for the in-depth question, which has inspired us to enhance our learning! It is our great honour to have thought about the question before performing the work you mentioned.
The Framingham risk score (FRS) is a standard tool used to predict the incidence of coronary heart disease (CHD). However, there have been concerns regarding its generalizability in other populations [1] since 99% of the Framingham cohort participants were Caucasian [2]. The Pooled Cohort equation (PCE) was developed using pooled community-based population cohorts, which provide sex- and race-specific estimates of the 10-year risk for ASCVD for African-American or White men and women 40 to 79 years of age [3]. In addition, the FRS score was calculated using the following variables: age (continuous, in years), sex (male and female), history of smoking (yes vs no), total cholesterol (continuous in mg/dL), HDL-C (continuous, in mg/dL), SBP (continuous, in mmHg) and treatment for hypertension (yes vs no). The PCE was calculated using each of the variables used for the FRS score with the addition of race (white vs black vs other) and history of diabetes (yes vs no). It seems that PCE tended to the more advantageous than FRS due to its race-specific estimates of the 10-year risk for ASCVD. However, to the best of our knowledge, the use of PCE does not show more advantages than FRS in this paper. First, both the FRS and Pooled Cohort equation (PCE) lack data from Asian and over-estimate the risk in Asian [4 5] and European [6] populations. As the assessment guide

points out, estimated 10-year risk for ASCVD is generally lower in Hispanic- American and Asian-American population and higher in American-Indian population [3]. Furthermore, both the FRS and PCE does not include obesity or cardiorespiratory fitness, which could potentially influence the risk estimation. Last but most important, the age of the participants is between 20 to 80 years, while the PCE estimate the 10-year risk for ASCVD for people aged 40 to 79 years. However, there is a parts of people were identified as MetS(+) in people aged 20 to 39 years (as illustrated in Table 2). After deliberation, we finally decided to use the FRS as an indicator reflecting the risk of CHD. In addition, as we mentioned in the Methods, we classified individuals with pre-existing diabetes into the high-risk group since diabetes is a risk factor for CHD/CVD.

As you noted, the BMI cut-point (25 kg/m2) would not be very useful in a non-Asian population as almost the entire US adult population has a BMI above this value. Undoubtedly, we agree with your highly perspicuous viewpoint that these results are more applicable to China than elsewhere worldwide. As described in the paper, the subjects were more commonly diagnosed with obesity (BMI ≥25 kg/m2) than with central obesity (32.31% vs 24.17%). Therefore, the lowest prevalence and highest risk of developing CHD are mainly caused by the thresholds of high blood pressure and elevated blood glucose of the CDS criteria, which are higher than those of the other criteria. However, discussing the superiority of the MetS definition that adopts BMI or waist circumference as an index of adiposity is necessary. Some studies posit that waist circumference is a more advantageous index of adiposity. According to Scuteri et al. [7], waist circumference is a significant predictor of new onset metabolic syndrome. In addition, Scuteri et al. [8] indicated that waist circumference correlated with arterial properties better than BMI, and as the waist circumference increased, the arterial structure and function significantly change within each BMI quartile, even though the cluster of MetS including abdominal adiposity has been consistently associated with arterial damage [9 10]. If BMI is found to be more advantageous in subsequent longitudinal studies, we recommend using BMI rather than WC as a component of MetS. Considering the different characteristics of obesity in different regions, we are inclined to adapt different thresholds of BMI in the definition of Mets similar to the current diagnostic criteria for central obesity.

Finally, we acknowledge that we do not have CHD event data. We cannot determine which diagnostic criteria are more advantageous in predicting the risk of CHD. As previously stated, the FRS resulted in an overestimation of the CHD risk in Asian populations [4 5]; however, the FRS may be an effective method for predicting the risk of CHD before there are better predictors. However, we thoroughly agree with your views and aim to perform longitudinal studies in the future to not only demonstrate the reliability of FRS and PCE in the Chinese population but also to determine which MetS definition is best suited for predicting CHD.

Comments 2: Finally, I have recently published papers on fitness being extremely important for assessing risk of cardiometabolic diseases, which could be mentioned (Kennedy AB et al. JAMA 2018; 319: 231-232; Deedwania P, Lavie CJ. JACC 2018;71:1866-1868; and Lavie CJ et al Lancet Diabetes& Endocrinology 2018; being released today May 29/30, 2018.)

Response: Thank for your comments, according to your advice, we added these studies to the discussion; the revisions are marked in red in the resubmitted manuscript.

First, to be honest, we learned much from these papers, especially regarding metabolically healthy obesity (MHO) and cardiorespiratory fitness (CRF). It is well established that obesity has many adverse effects on CVD [11]. However, several studies have indicated that MHO might not be an increased risk of CVD, especially CHD [12]. However, Bell et al. [13] and Mongraw-Chaffin et al. [14] successively suggested that a higher number of those with MHO eventually develop “metabolic un-healthiness” over time. Therefore, obesity may still be associated with an elevated risk of developing CVD and is rarely healthy [15 16]. In addition, as you stated, most studies suggesting that there is an association between MHO and increased mortality risk did not include assessments of CRF or physical exercise. When CRF is rigorously measured and other important confounders are considered, relatively fit individuals with MHO are not significantly higher risk of CVD morbidity or mortality than metabolically healthy normal-weight individuals. These results indicated that CRF is extremely important in assessing the risk of cardiometabolic diseases, which greatly influences the "obesity paradox". Therefore, improving fitness may be relatively more important, or at least as important, as preventing obesity [17]. However, the FRS and PCE does not include the obesity and cardiorespiratory fitness, which could potentially influence the risk estimation.