



## Metabolic syndrome vs. its components for prediction of cardiovascular mortality: A cohort study in Chinese elderly adults

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### Abstract

**Objective** The predictive value of the metabolic syndrome (MetS) for mortality from all-cause and cardiovascular disease (CVD) in the Chinese population is unclear. The aim of this present study was to compare MetS with its individual components as predictors of mortality in Chinese elderly adults. **Methods** A cohort of 1,535 subjects (994 men and 541 women) aged 50 years or older was selected from employees of a machinery factory in 1994 and followed until 2009. Cox models were used to estimate the hazard ratios (HRs) predicted by MetS according to the harmonized definition and by its individual components. **Results** The baseline prevalence of MetS was 28.0% in men and 48.4% in women. During a median follow-up of 15 years, 414 deaths occurred, of these, 153 participants died from CVD. Adjusted for age and gender, the HRs of mortality from all-cause and CVD in participants with MetS were 1.47 (95% confidence interval (CI): 1.20–1.80) and 1.96 (95%CI: 1.42–2.72), respectively, compared with those without MetS. Non-significant higher risk of CVD mortality was seen in those with one or two individual components (HR = 1.22, 95%CI: 0.59–2.50; HR = 1.82, 95%CI: 0.91–3.64, respectively), while a substantially higher risk of CVD mortality only appeared in those with 3, 4, or 5 components (HR = 2.81–3.72), compared with those with no components. On evaluating the MetS components individually, we found that, independent of MetS, only hypertension and impaired glucose predicted higher mortality. **Conclusions** The number of positive MetS components seems no more informative than classifying (dichotomous) MetS for CVD risks assessment in this Chinese cohort.

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**Keywords:** Cardiovascular disease; Metabolic syndrome; Cohort study; Chinese adults

## 1 Introduction

The metabolic syndrome (MetS) is characterized by the clustering of cardiovascular risk factors including abdominal obesity, elevated blood pressure, hyperglycemia, and dyslipidemia level. Currently available evidence suggests that MetS is associated with significantly increased risk of incident cardiovascular disease (CVD), all-cause and cardiovascular death.<sup>[1–4]</sup> By comparison, some studies in the elderly show that people with MetS have little, or no increased, CVD risk compared with those without MetS. In Italian individuals,

MetS was not independently associated with all-cause mortality.<sup>[5]</sup> Also, in Finns, MetS predicted CVD mortality, but not all-cause mortality.<sup>[6]</sup> Despite the fact that the determinants of MetS and its contribution to mortality in Europe and North America receive much attention by the research community, it remains one of the least studied factors in China.<sup>[7]</sup>

Despite this progress, the belief that a diagnosis of MetS is useful is not shared by all. The prognostic importance of MetS, compared that of its individual components, has repeatedly been challenged. For example, some studies showed that not all individual components of MetS contributed to the increased risk of all-cause mortality, which was significantly predicted by impaired fasting glucose (IFG) in all subjects, and by IFG and low high density-lipoprotein cholesterol (HDL-C) in women among an Italian population.<sup>[8]</sup> Sattar *et al.*<sup>[9]</sup> also showed that a diagnosis of the MetS had a negligible association with the risk of CVD, and that MetS *per se* was not greater than the sum of its components. In the Cardiovascular

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Health Study, the higher risk of all-cause and CVD mortality due to MetS was confined to subjects having hypertension and/or IFG.<sup>[10]</sup> Thus, another important issue rises as to whether diagnosing MetS improves prediction of mortality risk beyond its individual components, which could not be addressed in the meta-analyses.

Since previous studies investigating the MetS were primarily conducted in western populations, the first objective of the present study was to explore the association of MetS and its individual components with all-cause and CVD mortality in a Chinese cohort. We also tested the hypothesis whether consideration of the counting of MetS components as a risk continuum was a more valuable risk predictor than identifying MetS, *per se*.

## 2 Methods

### 2.1 Study population

We included 1535 persons (994 men and 541 women) who had data on age, gender, marital status (married, or others), education level (received < 9 years of education, or  $\geq 9$  years of education), occupation (workers, or technician), systolic and diastolic blood pressure, serum triglyceride, HDL-C, low density-lipoprotein cholesterol (LDL-C), total cholesterol, glucose, waist circumference, and current smoking (yes or no) and current drinking (yes or no) history at a baseline in 1994.

Each participant was interviewed and completed a standardized questionnaire that included demographic factors, medical history, and lifestyle risk factors (smoking history and alcohol consumption), and so on at baseline in 1994. Physical examinations and face to face interviews were carried out by trained nurses and physicians. All participants gave their written informed consent. The study was approved by the Ethics Committees of Chinese PLA General Hospital in Beijing.

### 2.2 Clinical and laboratory measurements

Waist circumference was measured to the nearest 0.5 cm using a plastic tape measure while the subject was standing. Blood pressure was the mean of three readings while the subject was seated. A venous blood sample was obtained from all participants after fasting for at least 12 hours for biochemical determinations, performed at the central laboratory of the city hospital by standard and quality-controlled procedures. Concentrations of total cholesterol, HDL-C, triglycerides, and glucose were assessed enzymatically with commercially available reagents. LDL-C was calculated by the Friedewald equation, except when triglycerides were > 400 mg/dL.

### 2.3 Definition of metabolic syndrome

MetS at baseline was defined according to the harmonized criteria of 2009,<sup>[11]</sup> which was similar to the International Diabetes Foundation criteria<sup>[12]</sup> without central obesity as an obligatory component. The harmonized definition of MetS included five components: (1) central obesity (waist circumference  $\geq 90$  cm in Chinese men and  $\geq 80$  cm in Chinese women; (2) elevated blood pressure: systolic  $\geq 130$  mmHg, diastolic  $\geq 85$  mmHg, or known treatment for hypertension; (3) elevated triglycerides: fasting plasma triglycerides  $\geq 150$  mg/dL (1.7 mmol/L), drug treatment for elevated triglycerides is an alternate indicator; (4) low HDL-C: fasting HDL-C < 1.0 mmol/L in men and < 1.3 mmol/L in women, drug treatment for reduced HDL-C is an alternate indicator; and (5) hyperglycemia: fasting glucose level of  $\geq 5.6$  mmol/L ( $\geq 100$  mg/dL) or known treatment for diabetes, drug treatment of elevated glucose is an alternate indicator. MetS was positive if an individual had at least three positive of these 5 components.

### 2.4 Outcome ascertainment

Vital status was traced by two senior doctors of the factory hospital until March, 2009. Causes of death were obtained from hospital death certificates or death certificates in the local police departments. Medical information was checked by two senior physicians of the 4<sup>th</sup> Military Medical University teaching hospital, and then coded according to the International Classification of Diseases Ninth Edition (ICD-9). CVD mortality was defined by the ICD-9 (390.0–398.9, 401.0–429.9, and 430.0–438.9). If vital status was unknown, the last date the subjects were known to be alive was recorded.

### 2.5 Statistical analysis

The data were entered (double entry) and analyses were carried out by SPSS for Windows (18.0, No. of Serial: 5076595). The Wald  $\chi^2$  test of proportions or generalized linear models was used to compare the prevalence, or mean levels, of the individual MetS components and other baseline characteristics across clinical conditions. Associations of the MetS with all-cause and CVD mortality were analyzed with forced Cox proportional hazards regression models, with adjustment for age being a continuous variable and gender (Model 1); age, gender, marital status, education, occupation (Model 2); age, gender, marital status, education, occupation, current drinking (yes or no), cigarette smoking (yes or no), and LDL-C, the latter two traditional CVD risk factors being not comprising the definition of the MetS (Model 3). To test the independent association of each individual MetS components with mortality from all-cause and CVD, MetS was introduced simultaneously in model as a proxy for the interactions of other individual components.

We also evaluated risks compared with an optimal risk group (no MetS components) for those with 1 to 2 combined and 3 to 5 combined MetS components, in addition to those groups defined above. Effect modification by specified strata of gender and age (< 65 years and ≥ 65 years) was evaluated using likelihood ratio testing comparing nested models with, and without, a multiplicative interaction term. Because some MetS components could be affected by smoking, or the presence of underlying disease (reverse causation), we performed sensitivity analyses excluding smokers, diabetes, or prevalent CVD at baseline.

### 3 Results

Of the 1535 subjects in the baseline cohort, 540 of them (278 of 994 men and 262 of 541 women) were affected by MetS, with increased waist circumference and IFG being two of the most often positive components (57.0% and 51.9%, respectively). The prevalence of MetS was significantly higher in women than in men (28.0% in men and 48.4% in women, respectively). Compared to subjects without the syndrome, those affected by MetS had increased waist circumference, systolic blood pressure, diastolic blood pressure, triglycerides, total cholesterol, and fasting plasma glucose and lower HDL-C levels (Table 1). Subjects with MetS were

less often current smokers, and more often current drinkers than those without MetS.

During a median of 15.1 years of follow-up, 414 (including 153 CVD) deaths occurred, 164 (including 71 CVD) with MetS and 250 (including 82 CVD) without the syndrome. The mortality incidence for CVD was 5.29 per 1000 person-years among those without MetS and 12.08 per 1000 person-years among those with MetS in the present cohort.

After adjustments for age and gender (Model 1 in Table 2), the risk of all-cause mortality was higher among all subjects with MetS. Confounders associated with increased mortality risk were sequentially included in Model 2 and Model 3 had not changed the strength of the association between MetS and all-cause mortality. MetS was significantly associated with increased all-cause mortality after adjustments for age, gender, marital status, education, occupation, smoking history, alcohol consumption, and LDL cholesterol levels among men (HR = 1.46, 95%CI: 1.15–1.85). In the models considering each of the individual MetS components as covariate and MetS as a proxy for the interactions of individual components, high blood pressure and IFG in men and in women were significant predictors of all-cause mortality. Interestingly, in men, high triglyceride was associated with decreased risk for all-cause mortality (HR = 0.74, 95%CI: 0.54–0.99) (Table 2).

**Table 1. Baseline demographic and clinical characteristics stratified by metabolic syndrome in 1535 Chinese.**

Characteristics	Men		Women		Overall	
	No MetS	MetS	No MetS	MetS	No MetS	MetS
Age (year)	60.8 ± 5.4	61.7 ± 5.9*	59.3 ± 4.6	60.0 ± 4.1*	60.4 ± 5.2	60.9 ± 5.1
WC (cm)	86.0 ± 8.8	95.0 ± 7.3	82.1 ± 9.4	89.3 ± 7.4 <sup>#</sup>	84.9 ± 9.1	92.2 ± 7.8 <sup>#</sup>
Waist to hip ratio	0.86 ± 0.07	0.91 ± 0.05 <sup>#</sup>	0.83 ± 0.05	0.86 ± 0.04 <sup>#</sup>	0.84 ± 0.07	0.89 ± 0.05 <sup>#</sup>
SBP (mmHg)	124.6 ± 15.9	135.2 ± 16.9 <sup>#</sup>	123.3 ± 18.5	132.1 ± 20.4 <sup>#</sup>	124.2 ± 16.7	133.7 ± 18.7 <sup>#</sup>
DBP (mmHg)	82.1 ± 9.7	87.8 ± 9.5 <sup>#</sup>	80.6 ± 9.8	84.7 ± 12.0 <sup>#</sup>	81.6 ± 9.8	86.2 ± 10.8 <sup>#</sup>
TG (mmol/L)	1.14 ± 0.54	2.00 ± 1.27 <sup>#</sup>	1.27 ± 0.68	2.25 ± 1.44 <sup>#</sup>	1.2 ± 0.6	2.1 ± 1.4 <sup>#</sup>
HDL-C (mmol/L)	1.38 ± 0.29	1.19 ± 0.32 <sup>#</sup>	1.54 ± 0.39	1.24 ± 0.23 <sup>#</sup>	1.4 ± 0.3	1.2 ± 0.3 <sup>#</sup>
FPG (mmol/L)	5.82 ± 1.53	6.66 ± 1.85 <sup>#</sup>	5.40 ± 0.96	6.56 ± 2.33 <sup>#</sup>	5.7 ± 1.4	6.6 ± 2.1 <sup>#</sup>
TC (mmol/L)	5.05 ± 0.89	5.10 ± 0.92	5.37 ± 0.92	5.49 ± 1.07	5.1 ± 0.9	5.3 ± 1.0*
LDL-C (mmol/L)	3.24 ± 1.29	3.13 ± 0.75	3.32 ± 0.82	3.37 ± 0.92	3.2 ± 1.2	3.2 ± 0.8
BMI (kg/m <sup>2</sup> )	22.9 ± 2.7	23.4 ± 2.8*	23.1 ± 2.9	23.7 ± 3.1*	23.0 ± 2.8	23.5 ± 2.9 <sup>#</sup>
Married	659 (92.0%)	247 (88.8%)	237 (84.9%)	225 (85.9%)	896 (90.1%)	472 (87.4%)
Education ≥ 9 years	230 (32.1%)	103 (37.1%)	64 (22.9%)	55 (21.0%)	294 (29.5%)	158 (29.3%)*
Workers	346 (48.3%)	146 (52.5%)	216 (77.4%)	188 (71.8%)	562 (56.5%)	334 (61.9%)*
Current smoking	255 (35.6%)	102 (36.7%)	22 (7.9%)	26 (9.9%)	277 (27.8%)	128 (23.7%)*
Current alcohol	173 (24.2%)	59 (21.2%)	6 (2.2%)	2 (0.8%)	179 (18.0%)	61 (11.3%) <sup>#</sup>

Data are means ± SD or n(%); values refer to comparison between those with and without metabolic syndrome; \* $P \leq 0.05$ , <sup>#</sup> $P \leq 0.001$ . BMI: body mass index; DBP: diastolic blood pressure; FPG: fasting plasma glucose; HDL-C: high density-lipoprotein cholesterol; LDL-C: low density-lipoprotein cholesterol; MetS: metabolic syndrome; SBP: systolic blood pressure; TG: triglyceride; WC: waist circumference;

**Table 2.** All-cause and CVD mortality associated with metabolic syndrome and its components in 1535 Chinese.

	Men ( <i>n</i> = 994)		Women ( <i>n</i> = 541)		Overall	
	HR (95%CI)	<i>P</i>	HR (95%CI)	<i>P</i>	HR (95%CI)	<i>P</i>
<b>All-cause death</b>	(all death = 312)		(all death = 102)			
MetS (Model 1)	1.49 (1.18–1.89)	0.001	1.40 (0.95–2.07)	0.092	1.47 (1.20–1.80)	< 0.001
MetS (Model 2)	1.47 (1.16–1.87)	0.001	1.40 (0.95–2.08)	0.092	1.47 (1.20–1.80)	< 0.001
MetS (Model 3)	1.46 (1.15–1.85)	0.002	1.38 (0.93–2.05)	0.108	1.46 (1.19–1.78)	< 0.001
IFG*	1.35 (1.06–1.73)	0.016	1.82 (1.16–2.85)	0.009	1.45 (1.17–1.80)	0.001
HBP*	1.37 (1.07–1.76)	0.012	1.49 (0.99–2.24)	0.054	1.40 (1.13–1.73)	0.002
High TG*	0.74 (0.54–0.99)	0.045	0.73 (0.46–1.16)	0.178	0.73 (0.57–0.94)	0.015
Low HDL-C*	0.93 (0.64–1.35)	0.704	0.72 (0.46–1.12)	0.148	0.84 (0.63–1.12)	0.226
Increased WC*	1.00 (0.77–1.30)	0.977	0.94 (0.55–1.62)	0.824	0.99 (0.79–1.26)	0.952
<b>CVD death</b>	(CVD death = 116)		(CVD death = 37)			
MetS (Model 1)	2.10 (1.45–3.03)	< 0.001	1.56 (0.81–3.01)	0.182	1.96 (1.42–2.72)	< 0.001
MetS (Model 2)	2.13 (1.47–3.08)	< 0.001	1.58 (0.81–3.05)	0.178	1.99 (1.44–2.76)	< 0.001
MetS (Model 3)	2.09 (1.44–3.04)	< 0.001	1.60 (0.82–3.10)	0.168	1.97 (1.42–2.73)	< 0.001
IFG <sup>#</sup>	0.75 (0.49–1.15)	0.191	3.68 (1.63–8.34)	0.002	1.08 (0.75–1.56)	0.674
HBP <sup>#</sup>	3.23 (2.06–5.08)	< 0.001	3.58 (1.68–7.60)	0.001	3.27 (2.22–4.81)	< 0.001
High TG <sup>#</sup>	0.70 (0.43–1.13)	0.143	0.34 (0.15–0.76)	0.009	0.57 (0.38–0.87)	0.009
Low HDL-C <sup>#</sup>	1.35 (0.79–2.32)	0.277	0.48 (0.22–1.03)	0.058	0.91 (0.58–1.45)	0.695
Increased WC <sup>#</sup>	0.69 (0.44–1.07)	0.097	0.71 (0.28–1.78)	0.465	0.71 (0.48–1.06)	0.095

Model 1: adjusting for age, gender (except for gender-specific model); Model 2: adjusting for age, gender, marital status, education, occupation; Model 3: adjusting for age, gender, marital status, education, occupation, current smoking, current drinking, and LDL-C. \*Adjusting for age, gender (except for gender-specific model), and the MetS *per se* remains statistically significant (HR: 1.26–1.69) in the all-cause death models, with *P* values changing from 0.043 to 0.001 in overall; <sup>#</sup>adjusting for age, gender, marital status, education, occupation, current smoking, current drinking, and LDL-C, and HR of MetS were 1.33–2.49 for CVD mortality, with *P* values changing from 0.099 to 0.001 in overall. HBP: high blood pressure; HDL-C: high density-lipoprotein cholesterol; HR: hazard ratios; IFG: impaired fasting glucose; LDL-C: low density-lipoprotein cholesterol; MetS: Metabolic syndrome; TG: triglyceride; WC: waist circumference.

We found an increased risk of CVD mortality among all subjects and in men with MetS after adjustment for age and gender (Model 1). Confounding and cardiovascular risk factors were sequentially included in Model 2 and Model 3, and the strength of the association between MetS and CVD mortality was not attenuated. Models, including individual MetS components, showed a significant association between CVD mortality and high blood pressure in men (HR = 3.23, 95%CI: 2.06–5.08). In women, a significant association of CVD mortality was found with IFG (HR = 3.68, 95%CI: 1.63–8.34), high blood pressure (HR = 3.58, 95%CI: 1.68–7.60), and high triglyceride (HR = 0.34, 95%CI: 0.15–0.76) (Table 2).

Table 3 shows the multivariate-adjusted HRs for the number of positive MetS components in relation to CVD mortality. The HRs seemed to rise regularly as the number of positive components increased, with suggestion of a threshold effect at three positive components. The greatest relative increase in CVD mortality per additional components was for three *versus*. no components (HR = 2.82, 95%CI: 1.42–5.63). The multivariate-adjusted HR was 2.61 (*P* < 0.001) for people with four positive components, 3.72 (*P* < 0.001) for people with five positive components, 2.32 (*P* < 0.01)

for people with ≥ 2 positive components, and 2.81 (*P* < 0.01) for people with ≥ 3 positive components, compared with people with no positive component. However, although the increasing trend in CVD mortality with increasing number of MetS components remained, the HRs for people with only one, or two, or combined risk components did not reach statistical significance, when compared with those with no component.

Table 3 shows the results of sensitivity analyses, excluding smokers or diabetics, at baseline. Trends of the association of CVD mortality with the MetS and its components were also observed for those who were not established diabetics or non-smoking at baseline.

To investigate the relationship between increased waist circumference and CVD mortality, we changed the cut points from 90 cm to 102 cm in men and from 80 cm to 88 cm in women, and the HR for waist circumference decreased to 0.58 (0.33, 1.01; *P* = 0.055) in all subjects in the present study.

We also ascertained these trends of the association between the MetS and its individual components and CVD mortality in the sensitivity analysis, excluding deaths that occurred during the first two years of follow-up (not shown).

**Table 3. Multivariate-adjusted\* hazard ratios (95% confidence interval) for the metabolic syndrome and its components in relation to cardiovascular disease mortality over 15 years in 1,535 Chinese.**

Individual components	n (%)	HR(95%CI)		
		Total, n = 1535	Delete T2DM, n = 1331	Delete current smoking, n = 1130
0 components (ref.)	162 (6.2)	1.00	1.00	1.00
1 component	404 (7.2)	1.22 (0.59–2.50)	1.23 (0.59–2.54)	1.30 (0.52–3.27)
2 components	429 (10.0)	1.82 (0.91–3.64)	1.83 (0.91–3.70)	1.93 (0.78–4.76)
3 components	338 (13.6)	2.82 (1.42–5.63)	2.71 (1.33–5.52)	2.97 (1.22–7.27)
4 components	163 (11.7)	2.61 (1.20–5.71)	2.56 (1.11–5.87)	2.85 (1.05–7.74)
5 components	39 (15.4)	3.72 (1.33–10.4)	4.11 (1.11–15.18)	8.48 (2.59–27.72)
1 or 2 components	833 (8.6)	1.51 (0.78–2.94)	1.52 (0.78–2.96)	1.58 (0.67–3.72)
2, 3, 4, or 5 components	969 (11.8)	2.32 (1.21–4.45)	2.24 (1.16–4.34)	2.53 (1.08–5.90)
3, 4, or 5 components	540 (13.1)	2.81 (1.44–5.50)	2.71 (1.36–5.40)	3.11 (1.30–7.41)

\*Adjusting for age, gender, marital status, education, occupation, smoking history, alcohol consumption, and low density-lipoprotein cholesterol.

## 4 Discussion

In the present study, we studied the MetS and its individual components of all-cause and CVD mortality separately in men and women. This study has provided several novel insights into the relationship between the MetS, defined by the harmonized criteria, and all-cause and CVD mortality among Chinese adults. Firstly, we observed that MetS (as a dichotomous classification) predicted all-cause and CVD mortality in the present Chinese cohort after adjustment for age, gender, marital status, education, occupation, LDL-C, smoking and drinking history. This is consistent with, but somewhat lower than the pooled relative risks of 1.58 (95%CI: 1.39–1.78) and 2.40 (95%CI: 1.87–3.08), respectively, from 87 studies reported earlier.<sup>[4]</sup> However, a previous study found that all-cause mortality was not associated with the MetS (multi-adjusted HR = 1.24, 95%CI: 0.60–2.59), among elderly people in Italy.<sup>[5]</sup> The inconsistency may due to the short follow-up (mean follow-up 3.8 years), and having no statistical power to assess the effect of the study variables on mortality in that study. Another reason was the analysis was conducted in a relatively elderly population (aged 65–97 years) in Italy.<sup>[5]</sup> The MetS predicted CVD and all-cause mortality only in men, not in women, in the present study. Some previous studies showed that the point estimates for CVD mortality associated with MetS were higher in women compared with those in men.<sup>[2–4]</sup> The mechanisms explaining a potentially higher CVD mortality in men with MetS are unclear. However, mortality rates were significantly lower in women than those in men in the present study, suggesting that the lack of statistical power may explain this gender difference.

Secondly, not all of its individual components of MetS significantly contributed to the increased risk of mortality when analyzed individually. The MetS, however, did not predict all-cause mortality above and beyond two of its individual

components, namely hypertension and IFG in women, with no contribution of the low HDL-C and increased waist circumference in both men and women. Insulin resistance could be the reason for the greater predictive value for cardiovascular risk, when MetS is compared to its components.<sup>[11]</sup> Unfortunately, the present study cannot provide any marker of insulin resistance, such as HOMA. Some studies have showed insulin resistance can increase the cardiovascular risk by increasing inflammation<sup>[13]</sup> and impairing endothelial function.<sup>[14]</sup> A previous study had found that only hypertension and IFG predicted higher mortality; persons having both hypertension and IFG had 82% higher mortality (HR = 1.82, 95%CI: 1.58–2.09) compared with individuals having neither hypertension nor IFG.<sup>[10]</sup> For CVD mortality, the components significantly contributing to the increased risk were hypertension in men, hypertension and IFG in women. A study in a Italian elderly population had shown, among MetS components, all-cause mortality is better predicted by IFG in all subjects and in women, and by low HDL-C in women; whereas CVD mortality is better predicted by IFG and low HDL-C in women.<sup>[8]</sup> With respect to CVD mortality among women, our findings confirm the strong impact of IFG, even after adjustment for other cardiovascular risk factors.<sup>[15]</sup>

Interestingly, elevated triglyceride levels did not have any association to high risk for all-cause mortality in men and for CVD mortality in women which is consistent with the previous study.<sup>[10]</sup> We excluded deaths that occurred during the first two years of follow-up in a sensitivity analysis, and the direction of relationship between triglycerides and CVD mortality did not change. A previous study had shown that elevated triglyceride levels did not increase the risk of type 2 diabetes, or increase fasting glucose, or fasting insulin levels in non-diabetic individuals,<sup>[16]</sup> whereas insulin resistance played a major role in the pathogenesis and clinical course of CVD patients.

We noted that an increased waist circumference had no association with risk for both all-cause and CVD mortality in the present study. A possible reason for a larger waist circumference not being a predictor of mortality is its overall high prevalence (46.8% in men and 75.8% in women) in our population. In addition, there might be some confounders, which accounted for the observed effect of large waist circumference on mortality in this analysis. It is a matter of discussion whether overweight and/or modest adiposity is a risk factor in elderly individuals.<sup>[17]</sup>

Third, the hazards ratios for CVD mortality seemed to rise with an increasing number of MetS components, with suggestion of a threshold effect at three positive components. This trend persisted even after deletion of the prevalent diabetics and current smokers at baseline, indicating that the number of MetS components might not be a more informative risk predictor than the dichotomous (< 3 components vs.  $\geq 3$  components) MetS classification in Chinese population. It is not in agreement with previous reports that the incident coronary heart disease<sup>[18]</sup> and incident CVD<sup>[19]</sup> risk shows a progressive increase from one to five MetS components in Scotland and Australia, respectively, with the same follow-up of over 10 years in these two studies.

Compared with previous studies, the present study has several advantages. First, to the best of our knowledge, this is the first prospective study investigating the relationship between all-cause and CVD mortality and MetS, defined by the harmonized criteria, with extended follow-up and strict quality controls in Chinese adults. Second, our study has a large number of deaths (414 deaths) due to a long follow-up, which ensures an adequate power of statistical analyses.

However, limitations of this study should be noted. First, our study included only subjects aged 50 years and more, which would lead to survival bias, and might have caused some reduction of the relative risk in CVD risk prediction models. Second, there were a limited number of CVD deaths which was insufficient for separate analyses by gender in the relationship between the number of individual components and the CVD mortality. Third, the complex interactions between each of the individual MetS components in the pathogenesis of CVD were difficult to disentangle by this analysis. Finally, the present study was conducted in an occupational population sample of convenience rather than in a representative sample of the general population, limiting the generalization to other groups.

In conclusion, this cohort study of Chinese adults has shown that MetS increased all-cause and CVD mortality and this relationship was stronger in men than that in women. Non-significant higher risk of CVD mortality was seen in those with one, or two components, while substantially

higher risk of CVD mortality only appeared in those with 3, 4, or 5 components, compared with those with no component. Identification of people without any MetS component is clinically valuable, as these people seem to have a substantially reduced risk of CVD mortality. More studies are needed to elucidate whether or not the components of metabolic syndrome have partially overlapping mechanisms of pathogenic actions mediated through common metabolic pathways, since their total combined effect is less than the sum of the individual effects.

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