

BMJ Open Association of metabolic syndrome with risk of cardiovascular disease mortality and all-cause mortality among Malaysian adults: a retrospective cohort study

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ABSTRACT

Objectives This study is aimed at determining the association between metabolic syndrome and risk of cardiovascular disease (CVD) mortality and all-cause mortality among Malaysian adults.

Design Retrospective cohort study.

Setting The Malaysian Non-Communicable Disease Surveillance (MyNCDS-1) 2005/2006.

Participants A total of 2525 adults (1013 men and 1512 women), aged 24–64 years, who participated in the MyNCDS-1 2005/2006.

Methods Participants' anthropometric indices, blood pressure, fasting lipid profile and fasting blood glucose levels were evaluated to determine the prevalence of metabolic syndrome by the Harmonized criteria. Participants' mortality status were followed up for 13 years from 2006 to 2018. Mortality data were obtained via record linkage with the Malaysian National Registration Department. The Cox proportional hazards regression model was applied to determine association between metabolic syndrome (MetS) and risk of CVD mortality and all-cause mortality with adjustment for selected sociodemographic and lifestyle behavioural factors.

Results The overall point prevalence of MetS was 30.6% (95% CI: 28.0 to 33.3). Total follow-up time was 31 668 person-years with 213 deaths (111 (11.3%) in MetS subjects and 102 (6.1%) in non-MetS subjects) from all-causes, and 50 deaths (33 (2.9%) in MetS group and 17 (1.2%) in non-MetS group) from CVD. Metabolic syndrome was associated with a significantly increased hazard of CVD mortality (adjusted HR: 2.18 (95% CI: 1.03 to 4.61), $p=0.041$) and all-cause mortality (adjusted HR: 1.47 (95% CI: 1.00 to 2.14), $p=0.048$). These associations remained significant after excluding mortalities in the first 2 years.

Conclusions Our study shows that individuals with MetS have a higher hazard of death from all-causes and CVD compared with those without MetS. It is thus imperative to prescribe individuals with MetS, a lifestyle intervention along with pharmacological intervention to improve the individual components of MetS and reduce this risk.

Strengths and limitations of this study

- This study data came from a nationally representative, population-based study with large sample size that makes the findings generalisable to the non-institutionalised population of Malaysia.
- We controlled for potential confounders including age, gender, education level, physical activity, fruit and vegetable intake, smoking and alcohol consumption in the Cox regression models.
- There were deaths that were not medically certified.

INTRODUCTION

Metabolic syndrome (MetS) refers to the clustering of metabolic abnormalities that is linked to higher risk of cardiovascular disease (CVD), type 2 diabetes, cancer mortality,^{1 2} non-alcoholic fatty liver disease³ and all-cause mortality.^{2 4–6} These metabolic abnormalities include generalised obesity/abdominal obesity, glucose intolerance, elevated blood pressure and dyslipidaemia.⁷ Increasing rates of MetS across Asia-Pacific countries are raising concern that it is becoming a public health threat that requires urgent intervention.⁸

Up to around 20 years ago, prevalence of MetS in Asian countries was low compared with Western countries.⁹ Subsequently, changes in lifestyle, namely poor dietary habits, increased refined sugar consumption and inadequate dietary fibre intake coupled with lower physical activity levels, have resulted in an increasing trend of MetS in Asian countries.⁸ Furthermore, Asians tend to have a higher percentage of visceral fat compared with Westerners with the same body mass index (BMI).^{10–12} Since abdominal obesity is a component of MetS, Asians are thus more

likely to have MetS. Given the current trend, MetS will likely become more prevalent in Asian countries than in Western countries.⁸ Previous studies have indicated that MetS is an independent risk factor of all-cause mortality and CVD-related mortality.^{6 13 14} However, prevalence of MetS and its components may have different impacts on CVD mortality risk in different ethnic groups and countries.¹⁵ In Malaysia, the top three causes of death in 2019 were ischaemic heart diseases (15%), pneumonia (12.2%) and CVDs (8%).¹⁶ Data on risk of mortality related to MetS remain unavailable. Most of the studies were confined to estimating MetS prevalence (ranging from 32% to 42%) and its associated factors among Malaysian adults.^{17–21} National data on the risk of CVD and all-cause mortality associated with MetS can provide insight into the burden of this condition that are essential for public health programme managers and clinicians in managing MetS. Therefore, we conducted a retrospective cohort study using data from the first Malaysian Non-Communicable Disease Surveillance (MyNCDS-1) 2005/2006 as baseline data on MetS and lifestyle risk factors.²² Participants of the MyNCDS-1 2005/2006 were followed up prospectively to assess the association between MetS and all-cause and CVD mortality.

METHODS

Study population

We used a retrospective cohort study design using data from the MyNCDS-1 2005/2006. MyNCDS-1 was a nationwide, cross-sectional, population-based baseline survey on non-communicable diseases and its risk factors conducted in 2005–2006.²² A minimum sample size of 2533 was calculated based on prevalence of obesity of 5%, precision of 1.2% and design effect of 2. After adding 20% expected non-response, the final target sample size was 3040. Participants were selected from 13 states and 1 federal territory (Kuala Lumpur) in Malaysia by multi-stage, cluster sampling using the year 2000 National Household Sampling Frame with the assistance of the Malaysian Department of Statistics. Stratifying variables were state and setting (urban/rural), with enumeration blocks, living quarters and households as the primary, secondary and elementary sampling units, respectively. A sample weight variable was created for strata (state and setting) and cluster (enumeration block and living quarters) for use in the analysis to generate population estimates. There was no oversampling of any particular groups in this study. The number of enumeration blocks and living quarters selected per state was based on the desired sample size and proportionate to the size of the 2005 Malaysian adult (age 25–64 years) population of each state. In all, a total of 398 enumeration blocks and 1683 living quarters were selected. All members of households in the selected living quarters who met the eligibility criteria were included in the sample. The inclusion criteria were Malaysian citizens, between 25 and 64 years of age. Excluded from the study were pregnant women,

and mentally ill, very ill, or institutionalised individuals. Participation in the study was voluntary and informed consent was obtained. Eligible individuals who refused to participate and those who could not be reached after three attempts were considered as non-responders. The final sample comprised of 2572 subjects after removing the non-responders yielding a response rate of 84.6%. Data collection was carried out from September 2005 to February 2006, with a total of 2572 adults participating in the survey. The details of the methodology and results of MyNCDS-1 have been described elsewhere.²²

Estimation of minimum sample size required for this study

Sample size for this study was calculated using Power and Sample Size Calculation V.3.1.6.²³ A previous study estimated 2.8% CVD mortality among non-MetS subjects.⁶ If the estimated HR of CVD mortality for individuals with MetS compared with non-MetS was 2.0, we needed to study 805 MetS subjects and 805 non-MetS subjects to be able to reject the null hypothesis that the HR equals 1 with 80% power. The type 1 error probability (α) associated with this hypothesis test was 0.05. We used the uncorrected χ^2 statistic to evaluate this null hypothesis.²³

Baseline data

Baseline data extracted from the MyNCDS-1 2005/2006 survey were participants' sociodemographic characteristics (gender, ethnicity and age), lifestyle factors (physical activity, smoking status and alcohol consumption), anthropomorphic measurements (height, weight and waist circumference (WC)), blood pressure and biochemical measurements (overnight fasting venous blood of lipid profile and glucose).

Assessment of lifestyle risk factors

Current smokers were those who smoked any tobacco product either daily (smokes a tobacco product at least once a day) or occasionally (smokes but not every day).²⁴ Current drinkers were those who consumed alcohol in the past 12 months.²⁵ We dichotomised alcohol consumption as yes/no alcohol consumption in the past 12 months because of poor or incomplete response on the frequency and quantity of alcohol consumption. Intensity and frequency of physical activity were measured using the Global Physical Activity Questionnaire V.2.0.²⁶ Physical activity was quantified in metabolic equivalent (MET) minutes per week (MET min/week). For work and recreation, 1 min of moderate intensity activity merited four METs, while 1 min of vigorous intensity activity merited eight METs. Cycling and walking merited four MET scores each. 'Physically active' was defined by a total score of at least 600 MET min/week. Adequate fruit and vegetable intake was defined as consumption of ≥ 5 servings of fruits and vegetables daily.

Anthropometric and blood pressure measurements

Height was measured without footwear to the nearest 0.1 cm using a stadiometer. Weight was measured to the nearest 0.1 kg using a balance beam scale or Seca

beam scale with minimal clothing and no shoes. WC was measured directly over skin or over light clothing to the nearest 0.1 cm at the smallest circumference below the rib cage and above the umbilicus while standing with abdominal muscles relaxed. Resting blood pressure was measured by the auscultatory method. Blood pressure was measured two times, (three times if the first two readings differed by more than 10 mm Hg) at no less than 30 s between measurements, and averaged.

Biochemical measurements

Overall, 5 mL of venous blood samples after overnight fasting were collected for measurement of total cholesterol, high-density lipoprotein cholesterol (HDL-C), triglycerides and glucose. All blood samples were kept on dry ice prior to laboratory analysis. Concentrations of HDL-C, triglyceride and fasting blood glucose were measured using enzymatic assay kits (Automated HDL Cholesterol Flex, Triglyceride Flex and Glucose Flex). Total cholesterol was determined using an enzymatic colorimetric method.

Definition of metabolic syndrome

There are a number of different definitions of MetS that differ by predetermined criteria and cutoffs. The most commonly used definitions are the National Cholesterol Education Program Expert Panel III (NCEP-ATP III) criteria,²⁷ the revised NCEP-ATP III criteria,²⁸ the International Diabetes Federation criteria (IDF)²⁹ criteria and the 'Harmonized' criteria jointly proposed by the IDF Task Force on Epidemiology and Prevention, National Heart, Lung and Blood Institute, American Heart Association, World Heart Federation and the International Association for the Study of Obesity.³⁰ Previous studies have shown that Asians have increased risk of CVD and mortality at lower levels of adiposity compared with Western populations.^{10 11 31} Therefore, the 'Harmonized' criteria was chosen as it was more appropriate in identifying MetS in the Malaysian population.³² Using the 'Harmonized' criteria, MetS is defined as presence of three or more of the following: central obesity (men: WC \geq 90 cm, women: WC \geq 80 cm), blood pressure \geq 130/85 mm Hg or known hypertension), hyperglycaemic (fasting plasma glucose \geq 5.6 mmol/L or known DM type 2), hypertriglyceridaemia (\geq 1.7 mmol/L), and reduced HDL-C (men: $<$ 1.0 mmol/L, women $<$ 1.3 mmol/L).

Follow-up

Participants of MyNCDS-1 were followed up for approximately 13 years from March 2006 to December 2018. Data on mortality during this period were obtained by matching the survey participants' identification number with records in the death registry administered by the National Registration Department of Malaysia. All deaths from diseases of the circulatory system coded as International Statistical Classification of Diseases and Related Health Problems, 10th revision (ICD-10) I00 to ICD-10 I99 (I00-I099 acute rheumatic fever, I05-I09 chronic

rheumatic heart diseases, I10-I15 hypertensive diseases, I20-I25 ischaemic heart diseases, I26-I28 pulmonary heart disease and diseases of pulmonary circulation, I30-I52 other forms of heart disease, I60-I69 cerebrovascular diseases, I70-I79 diseases of arteries, arterioles and capillaries, I80-I89 diseases of veins, lymphatic vessels and lymph nodes, not elsewhere classified, I95-I99 other and unspecified disorders of the circulatory system) according to the ICD-10 V.2019 were classified as cardiovascular mortalities.³³

Statistical analyses

All statistical analyses were performed using IBM SPSS V.18.0 for Windows (IBM Corp). The analyses took into account the complex survey design and unequal selection probabilities using the sample weight created in the complex sampling design earlier. Poststratification weights were applied in the analysis to account for non-response. Participants without data on identification number were excluded from analysis. The point prevalence of MetS, selected sociodemographic and health risk behaviours are presented in frequencies, percentages and 95% CIs by living status (dead/alive). The Cox proportional hazards regression model was applied to determine the association between MetS and all-cause and CVD mortality adjusting for selected sociodemographic characteristics and health risk behaviours. Sensitivity analysis was performed, whereby Cox regression models were also generated for all-cause mortality and CVD mortality excluding mortalities in the first 2 years of follow-up. Test of proportional hazards assumptions were met ($p>$ 0.05), and there were no significant two-way interactions between all the independent variables (All interactions tested, $p>$ 0.05) in the multiple Cox regression models for both all-cause and CVD deaths.

Patient and public involvement

Patients or the public were not involved in the design, or conduct, or reporting, or dissemination plans of our research.

RESULTS

Of the 2572 participants, a total of 2525 (98.2%) participants were amenable to analysis after excluding participants missing data on identification number. The sample consisted of 1013 (40.1%) men and 1512 (59.9%) women. The sociodemographic characteristics, prevalence of MetS and prevalence of health risk behaviours of the participants at baseline are presented in [table 1](#). There were 845 MetS cases among the 2525 participants at baseline, giving an overall estimated point prevalence of MetS was 30.6%. Univariable analysis showed significant associations between age group, ethnicity and individual MetS components with MetS status, but not for health risk behaviours (smoking, alcohol consumption, fruits and vegetables intake and physical activity), gender and ethnicity. During the 13 years follow-up, a total of 213

Table 1 Baseline characteristics of participants by metabolic syndrome status (n=2525)

Variables	MetS*		Non-MetS	
	n	% (95% CI)	n	% (95% CI)
Overall	845	30.6 (28.0 to 33.3)	1680	69.4 (66.7 to 72.0)
All-cause mortality		*		
No	734	29.4 (26.8 to 32.1)	1578	70.6 (67.8 to 73.2)
Yes	111	44.7 (35.0 to 54.9)	102	55.3 (45.1 to 65.0)
CVD mortality				
No	812	30.2 (27.6 to 32.0)	1663	69.8 (67.1 to 72.4)
Yes	33	50.8 (28.3 to 73.0)	17	49.2 (27.0 to 71.7)
Central obesity		**		
No	127	10.6 (8.2 to 13.4)	1066	89.4 (86.6 to 91.8)
Yes	718	51.9 (48.0 to 55.8)	614	48.1 (44.2 to 52.0)
High blood pressure or known hypertension		**		
No	221	15.3 (12.5 to 18.5)	1257	84.7 (81.5 to 87.5)
Yes	624	59.1 (55.0 to 63.0)	423	40.9 (37.0 to 45.0)
High fasting blood glucose or known DM type 2		**		
No	305	15.4 (13.2 to 17.8)	1402	84.6 (82.2 to 86.8)
Yes	540	61.7 (56.5 to 66.8)	278	38.3 (33.2 to 43.5)
Hypertriglyceridaemia		**		
No	260	12.7 (10.9 to 14.7)	1380	87.3 (85.3 to 89.1)
Yes	585	57.5 (52.2 to 62.7)	300	42.5 (37.3 to 47.8)
Reduced HDL-C		**		
No	378	19.8 (17.4 to 22.6)	1344	80.2 (77.4 to 82.6)
Yes	467	59.1 (54.4 to 63.7)	336	40.9 (36.3 to 45.6)
Gender				
Male	333	28.7 (25.1 to 32.6)	680	71.3 (67.4 to 74.9)
Female	512	32.6 (29.2 to 36.1)	1000	67.4 (63.9 to 70.8)
Ethnicity				
Malays	454	29.6 (26.0 to 33.6)	943	70.4 (66.4 to 74.0)
Chinese	154	30.9 (25.8 to 36.6)	307	69.1 (63.4 to 74.2)
Indians	96	37.7 (28.1 to 48.3)	134	62.3 (51.7 to 71.9)
Others	141	29.3 (24.8 to 34.2)	296	70.7 (65.8 to 75.2)
Age group (year)		**		
55–64	206	45.1 (38.8 to 51.6)	270	54.9 (48.4 to 61.2)
45–54	321	42.0 (36.5 to 47.6)	411	58.0 (52.4 to 63.5)
35–44	205	28.0 (23.8 to 32.5)	516	72.0 (67.5 to 76.2)
25–34	113	20.5 (16.2 to 25.5)	483	79.5 (74.5 to 83.8)
Educational level				
No formal or primary school education	412	39.5 (35.5 to 43.7)	611	60.5 (56.3 to 64.5)
Secondary school	373	26.1 (22.7 to 29.7)	912	73.9 (70.3 to 77.3)
Tertiary (college/ university)	60	25.9 (18.2 to 35.5)	157	74.1 (64.5 to 81.8)
Daily smoker				
No	701	31.8 (28.8 to 34.9)	1376	68.2 (65.1 to 71.2)
Yes	144	26.1 (21.4 to 31.4)	304	73.9 (68.6 to 78.6)
Physical activity				
Active	509	30.7 (27.3 to 34.3)	1047	69.3 (65.7 to 72.7)
Inactive	336	30.3 (27.0 to 33.8)	633	69.7 (66.2 to 73.0)
Alcohol consumption				

Continued

Table 1 Continued

Variables	MetS*		Non-MetS	
	n	% (95% CI)	n	% (95% CI)
No	776	31.1 (28.3 to 34.0)	1497	68.9 (66.0 to 71.7)
Yes	69	27.2 (20.7 to 34.8)	183	72.8 (65.2 to 79.3)
Fruit and vegetable intake				
Inadequate	774	30.5 (27.8 to 33.3)	1528	69.5 (66.7 to 72.2)
Adequate	71	31.5 (23.6 to 40.7)	150	68.5 (59.3 to 76.4)

Pearson's χ^2 test of independence was performed (* $p < 0.01$, ** $p < 0.001$).

*Based on Harmonized criteria: central obesity (men: $WC \geq 90$ cm, women: $WC \geq 80$ cm), blood pressure of $\geq 130/85$ mm Hg or known hypertension, fasting plasma glucose ≥ 5.6 mmol/L or known DM type 2, hypertriglyceridaemia (≥ 1.7 mmol/L), Reduced HDL-C (men: < 1.0 mmol/L, women < 1.3 mmol/L).

CVD, cardiovascular disease; HDL-C, high-density lipoprotein cholesterol.

deaths (111 (11.3%) in MetS group and 102 (6.1% in non-MetS group) from all-causes, and 50 deaths (33 (2.9%) in MetS group and 17 (1.2%) in non-MetS group) from CVD were recorded by the National Registration Department, with total follow-up time of 31 668 person-years (table 1). Baseline characteristics of participants by all-cause mortality and CVD mortality are supplied in online supplemental table 1. We performed univariate analysis to explore associations between the metabolic components and sociodemographic characteristics with all cause and CVD mortality. Central obesity, hypertension, high fasting

blood glucose, hypertriglyceridaemia, reduced HDL-C, male gender, older age group, no formal/primary school education, smoker were significantly associated with all-cause mortality. Whereas hypertriglyceridaemia, male gender and smoker were significantly associated with CVD mortality (online supplemental table 2).

Figure 1A,C shows unadjusted and age and sex-adjusted all-cause mortality curves, whereas figure 1B,D shows unadjusted and age and sex-adjusted CVD mortality curves; for MetS and non-MetS groups. These curves show an increase in mortality over the 13-year follow-up period.

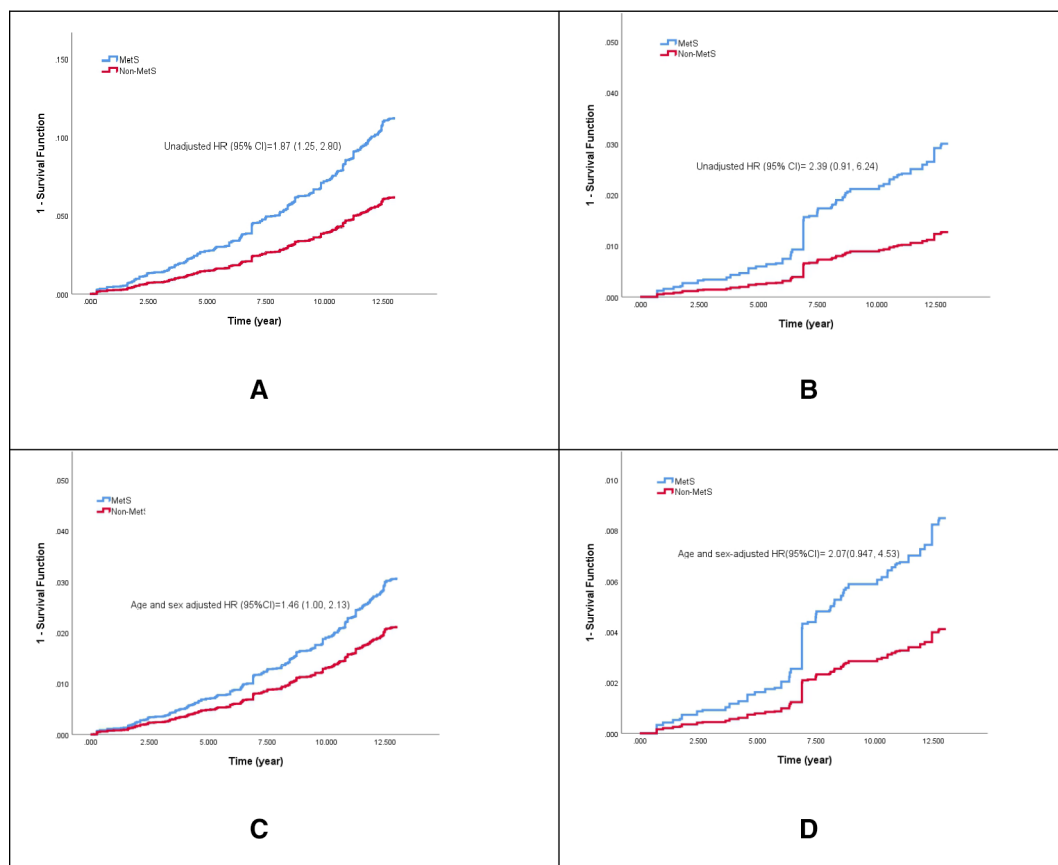


Figure 1 Comparison of mortality curves between MetS and non-MetS groups: (A) Unadjusted all-cause mortality; (B) Unadjusted CVD mortality; (C) Age and sex-adjusted all-cause mortality; and (D) Age and sex-adjusted CVD mortality.

Table 2 The associations between metabolic syndrome and all-cause mortality and cardiovascular disease mortality among Malaysian adults population

Mortality	Unadjusted HR (95% CI)	Age and sex-adjusted HR (95% CI)	Multiple Cox regression, adjusted HR (95% CI)†
Metabolic syndrome‡			
All-cause (n=2525)	1.87 (1.25, 2.80)*	1.46 (1.00, 2.13)	1.47 (1.00, 2.14)*
All-cause (excluding mortalities in the first 2 years) (n=2505)	2.00 (1.31, 3.08)**	1.59 (1.07, 2.37)*	1.60 (1.07, 2.38)*
CVD mortality (n=2525)	2.39 (0.91, 6.24)	2.07 (0.95, 4.53)	2.18 (1.03, 4.61)*
CVD mortality (excluding mortalities in the first 2 years) (n=2505)	2.48 (0.87, 7.08)	2.22 (0.95, 5.21)	2.38 (1.06, 5.34)*

*p value <0.05. **p value <0.01. 95%.

†Complex sample multiple Cox regression analysis was performed, adjusted for gender, age, education (secondary school education and above), physical activity, fruit & vegetable intake, smoking status and alcohol consumption. Test of proportional hazard was performed for all models showed p>0.05. No significant two-way interactions among all the independent variables (p>0.05).

‡Based on Harmonized criteria.

CVD, cardiovascular disease.

Generally, risk of all cause and CVD mortality were higher for the MetS group compared with the non-MetS group.

In the univariable analysis, MetS was significantly associated with all cause mortality (unadjusted HR: 1.87; 95% CI: 1.25 to 2.80). After adjustment for age and sex, association was marginally significant. The unadjusted and age and sex-adjusted hazard of CVD mortality was 2.4 (unadjusted HR: 2.39; 95% CI: 0.91 to 6.24), and 2.1 (age and sex-adjusted HR: 2.07; 95% CI: 0.95 to 4.53) times higher in the MetS compared with the non-MetS group, but no significant association was observed. In the multiple Cox regression models, MetS was significantly associated with increased hazard of CVD mortality (adjusted HR: 2.18, 95% CI: 1.03 to 4.61) and of all-cause mortality (adjusted HR: 1.47, 95% CI: 1.00 to 2.14) after adjusting for gender, age, education level, physical activity, fruit and vegetable intake, smoking status and alcohol consumption. Sensitivity analysis showed these associations remained significant after excluding mortalities in the first 2-year follow-up (table 2). Multiple Cox regression stratified by ethnicity was performed to assess differences in the HR by ethnicity. MetS significantly increased the hazard of all-cause mortality among Malays, but not among the other ethnic groups. No significant increase in hazard of CVD mortality was observed in MetS groups in all ethnic groups. However, these estimates were unstable due to extremely small sample sizes in certain cells and should be interpreted cautiously (online supplemental table 2).

Post hoc power analysis

We calculated post hoc power using PS software, and based on adjusted HR (relative risk) of CVD mortality of MetS subjects relative to non MetS subjects of 2.38, 845 MetS subjects, 1680 non-MetS subjects, we obtained power of 82%. Therefore, the probability of detecting a significant difference between MetS and non-MetS mortality was 82%. The type 1 error probability associated with this test was 0.05.

DISCUSSION

In this study, the overall point prevalence of MetS was 30.6% based on the Harmonized criteria. The reported prevalence is in agreement with a recent review of studies conducted among Malaysian adults who reported prevalences of between 25% and 40%, depending on the criteria used to define MetS.³⁴

Our data show that presence of MetS was associated with approximately 1.5 times the hazard of all-cause mortality and twofold increase in hazard of CVD mortality. Our findings are consistent with numerous past studies. Malik *et al*¹³ followed up participants of the second National Health and Nutrition Examination Survey (NHANES II) 1976–1980 for an average of 13 years. Their analyses reported MetS was associated with 2.02 (95% CI: 1.42 to 2.89) HR with respect to CHD mortality, and 1.82 (1.40–2.37) hour for CVD mortality and 1.40 (1.19–1.66) for all-cause mortality after controlling for age, gender, smoking, physical activity and total cholesterol.¹³ Another study which analysed data from the subsequent survey, the NHANES III, 1988–1994, with a longer follow-up period of 20 years, found MetS was associated with 1.4 times risk of mortality.³⁵ An analysis of the more recent 1999–2010 NHANES cohort suggested that the association of MetS with all-cause mortality could be modified by BMI.² In the study, normal-weight–MetS subjects had an HR for all-cause mortality of 1.70 (1.16–2.51) while obese–MetS had an HR of 1.30 (1.07–1.60), compared with normal-weight–no MetS subjects. However, for CVD mortality, only the normal-weight–MetS group had a higher hazard (HR 2.12 (95% CI: 1.16 to 2.51) of CVD mortality compared with the normal-weight–no MetS group.² A pooled analysis of 87 prospective studies predominantly in western countries, with a total of 951 083 patients, reported that MetS was associated with a 2-fold increase in risk of CVD mortality and a 1.5-fold increase in risk of all-cause mortality.⁶ Another meta-analysis of prospective cohort

studies in the US (six studies), Europe (eight studies) and Asia (seven studies) published from the year 2001 to December 2009 reported similar findings of approximately 1.5-fold risk of all-cause mortality for individuals with MetS.³⁶ However, a large prospective population-based study, which involved Dutch people aged 50 years and above showed a relatively weak association between MetS and risk of all-cause mortality regardless of MetS definition used, whether the NCEP ATP III (HR:1.10, 95% CI: 1.01 to 1.20), or the IDF definition (1.09 (1.01 to 1.19)). For CVD mortality, MetS had a significant association using the IDF definition only (1.29 (1.05 to 1.57)) after adjusting for age and sex.³⁷

Data on MetS-related mortality in Asian countries are still scarce. In an earlier study in Hong Kong, which involved a population-based cohort of 2863 Chinese subjects, those with MetS (revised NCEP-ATP III definition) had increased risk of all-cause (2.02 (1.02 to 4.0)) and CVD mortality (6.39 (1.40 to 29.2)) compared with those without any component of MetS controlling for baseline sociodemographic and lifestyle factors. However, the risk of death due to CVD in the MetS group was lower (3.36 (1.57 to 7.19)) compared with those with ≤ 2 components, and no significant risk of death from all-causes was observed.³⁸ Our findings were also in line with a study conducted in Singapore. Using data from three cross-sectional surveys as baseline, a cohort of 5699 Singaporean adults from different ethnic groups was followed up for an average of 14 years. Those with metabolic syndrome (modified revised NCEP-ATP III) were found to have had an increased risk of death from both all-cause (men:1.4 (1.1–1.8), women: 1.8 (1.3–2.6)) and CVD mortalities (men: 3.0 (1.9–4.8), women: 2.1 (1.1–4.0)) after controlling for age, study, ethnic group, LDL-C, smoking and alcohol intake.³⁹ A prospective study among 96 433 middle aged and elderly Japanese adults who participated in a large community survey also reported an association between MetS and excess CVD deaths regardless of BMI status (overweight or non-overweight), sex and the MetS definition used.⁴⁰ In Taiwan, a cohort which consisted of 10 547 elderly (aged 65 years and older) individuals from nationwide health screenings between 1998 and 1999 were recruited to investigate if there was an association between the presence of MetS and risk cardiovascular mortality.⁴¹ After a follow-up of 8 years, those with MetS (revised NCEP-ATP III criteria) had significantly increased risk of CVD mortality (1.48 (1.16–1.90)). However, the strength of the association was relatively small for all-cause mortality (1.16 (1.03–1.30)) and possibly inconsequential in predicting all-cause mortality in clinical practice. This could be due to the study samples being composed entirely of the elderly, who were equally more prone to other causes of death, which reduces the relative effect of MetS.³⁷ In comparison to our findings, a large retrospective study in Korea showed an insignificant association between MetS and all-cause mortality (1.15 (0.94–1.42)), and a significant but weaker association with CVD mortality (1.60 (1.02–2.20)), after adjusting for age, sex, smoking status, alcohol intake and regular exercise.⁴² But the shorter follow-up period of 3.7 years, compared with the 13 years follow-up in our study,

may have not been sufficient to observe long-term effects of MetS on risk of all-cause mortality.⁴³ In a recent Iranian study involving a sample of 523 healthy and 502 MetS adults from the Zanjan Healthy Heart Study 2013. After a follow-up of approximately 10 years, the study revealed that risk of death from CVD events (3.7 (1.2–11.1)) was significantly higher among the MetS group than the healthy group. However, no significant increase in risk of all-cause mortality (1.75 (0.88–3.47)) was observed.⁴⁴ This is possibly because of their high drop-out rate, resulting in small sample size and insufficient power to detect an association.

Our findings add to the existing evidence on the association of MetS with all-cause and CVD mortality in Asian populations. The HRs found in this study were comparable to studies in Western populations and some Asian countries, bearing in mind possible differences in MetS definition, age and race composition between countries. Our study has several strengths and limitations. A particular strength of this study was the data came from a nationally representative, population-based study and with a large sample size, which makes the findings generalisable to the non-institutionalised population of Malaysia. We also controlled for potential confounders including age, gender, physical activity, fruits and vegetables intake, smoking and alcohol consumption^{45–48} which, in Cox regression models, might undermine the relationship between MetS and risk of death. One of the limitations of this study was we cannot rule out the possibility of patients having undiagnosed cancer or other debilitating illness at baseline. Therefore, a sensitivity analysis was also conducted to assess this association, whereby participants who died in the first 2 years of the study were excluded. An additional limitation is the inability to incorporate time-varying covariates in the Cox model because information on transition from non-MetS to MetS is not available. Finally, there were deaths that were not medically certified. In these cases, CVD deaths may have been misclassified as deaths due to other poorly defined causes such as ‘old age’ or ‘sudden death’, consequently leading to underestimation of CVD mortality.⁴⁹ However, medical certification of deaths in Malaysia has significantly improved over the years. In 1995, the percentage of medically certified deaths was 45% of total deaths, but efforts are constantly being made for improving the death reporting system and by 2010, the rate of medically certified deaths had risen to 57%.⁵⁰

CONCLUSION

Our study showed that metabolic syndrome is associated with increased hazard of all-cause and CVD mortality in the multiethnic Malaysian population, confirming the findings of earlier studies in other populations. Therefore, lifestyle modification and pharmacological treatment approaches might improve the individual components forming the MetS, and thereby reduce mortalities associated with MetS.

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