Metabolic syndrome increases all-cause and vascular mortality: the Hong Kong Cardiovascular Risk Factor Study

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Abstract

Objective: The metabolic syndrome has been associated with increased mortality in some Caucasian populations, but data in Asian populations are not available. We present data describing the association of the metabolic syndrome with mortality, and potential differences by smoking and drinking status.

Methods: The impact of the US National Cholesterol Education Programme Adult Treatment Panel-III (NCEP ATP-III) metabolic syndrome guidelines definition (using Asian central obesity criteria) on mortality was examined using Cox regression analyses in a population-based cohort (n=2863) of Chinese subjects.

Results: The cohort was followed up for a mean duration of 8.45 years, a total of 24,101 person-years, with 89 deaths (33.7% of vascular origin). Compared to those without any component of the metabolic syndrome, following adjustment for age, socio-economic status and a range of lifestyle habits those with the metabolic syndrome had increased risk of both all-cause (hazard ratio 2.02 (95%CI 1.02-4.00), p for trend=0.037) and vascular disease ((hazard ratio 6.39 (95%CI 1.40-29.2), p<0.05, p for trend=0.002) mortality. When those with 0-2 components were compared to those with the metabolic syndrome, the hazard ratios were 1.49 (95%CI 0.95-2.33), p=0.084, and 3.36 (95%CI 1.57-7.19), p=0.002, respectively.

Conclusion: This study shows that the metabolic syndrome was associated with increased mortality risk in an Asian population. The high prevalence of the metabolic syndrome, particularly in the elderly, forewarns a rapidly increasing problem in Mainland China, and other Asian populations, which could have overwhelming public health ramifications.

Keywords: cardiovascular disease, hypertension, metabolic syndrome, mortality, obesity.

Introduction

In Caucasian populations, individuals with the metabolic syndrome have increased morbidity and mortality,[1-10] but data are absent in Asian populations. Although the prevalence of the metabolic syndrome in some westernised Asian populations, such as Hong Kong, China is similar to that in Caucasian populations,[1-11] the prevalence of vascular disease mortality is one third to one fifth,[12] thus potentially negating the significance of the metabolic syndrome as a public health concern in Chinese populations. Understanding the risks associated with the metabolic syndrome is key to developing appropriate and effective preventative strategies in a population, such as China, where prevalence rates of the metabolic syndrome have risen to 9.8% in males and 17.8% in females,[13], and 30.5% (17.6% in males and 39.2% in females) in older (60-95 years) Chinese from Beijing,[14] and are likely to continue to increase with economic growth and modernisation. Furthermore, the clear age related increases in the prevalence of the metabolic syndrome observed in all populations would further impact on the Chinese population as the proportion of older individuals continues to increase.[13,14,11] In Asian populations, although several studies refer to metabolic syndrome and mortality and some describe cross-sectional relationships,[14] we do not know of any prospective studies that report the effect of metabolic syndrome on survival. We therefore investigated the effect of the metabolic syndrome and its components on all-cause and vascular disease mortality in a population-based cohort study of Chinese adults.

Methods

Cohort study

In a cardiovascular risk factors prevalence study, 7730 Chinese, aged 25 to 74 years were randomly selected for telephone interviews using random dialling in Hong Kong from 1994 to 1996, with a response rate of 78%. One household member, who was a Chinese Hong Kong resident was randomly selected for an interview. Pregnant women and those with serious diseases such as cancer or who were hospitalised were excluded. A standardised questionnaire modified from the questionnaire used in the 1992 Singapore National Health Survey was used. Information collected included demographic

characteristics, lifestyle factors and various aspects of health status. The method of telephone interview was validated in a morbidity survey in Hong Kong.[15] At the end of the interview, the respondent was invited to come to the Clinical Biochemistry Unit of Queen Mary Hospital, a teaching hospital of the Faculty of Medicine, the University of Hong Kong, for physical examination and blood-testing. One to two days before the appointment to the hospital, the subjects were reminded to fast for 12 hours before their visit. On arrival, the subjects' identity was checked, an information sheet provided and a consent form signed. The study complied with the Declaration of Helsinki and was approved by the University of Hong Kong Faculty of Medicine Ethics Committee.

Study parameters and mortality data

From the overall sample, a subset of 2900 subjects (1488 women and 1412 men) responded to our invitation to attend the hospital clinic, where they underwent physical examination, including anthropometry and fasting blood tests. The detailed methods of measurement have been reported elsewhere.[16,17] The attendees and non-attendees were shown to match the general population and non-attendance bias should be small,[16] for example for place of birth, exercise, smoking status, self-reported diabetes, hypertension and general health, the Cohen effect sizes were negligible (<0.1), though they were slightly larger but acceptable for job type (0.16) and education (0.23). This study is the only representative population-based study performed to date in Hong Kong investigating vascular disease risk factors.

The NCEP ATP III guidelines classify individuals as having the metabolic syndrome if they possess three or more of the components,: hyperglycaemia: fasting plasma glucose was $\geq$6.1 mmol/L (110 mg/dL) or were receiving glucose lowering drugs; hypertension: systolic and/or diastolic blood pressures were $\geq$130/85 mm Hg or were receiving blood pressure lowering drugs; hypertriglyceridaemia: fasting plasma triglycerides $\geq$1.69 mmol/L (150 mg/dL); hypoHDL-cholesterolaemia: fasting HDL-cholesterol <1.04 or 1.29 mmol (40 or 50 mg/dL) in males and females, respectively, and central obesity: waist circumference >88 or 102 cm in females and males, respectively.[18] However, the World Health

Organisation and other organisations such as the American Heart Association/National Heart, Lung, and Blood Institute have recognised the disproportionate contribution of obesity to the development of cardiovascular risk factors in Asians and has provisionally lowered the classification of central obesity to ≥80 or ≥90 cm in females and males, respectively,[19,20] which we therefore used in the present analyses.

All deaths in Hong Kong are recorded in the Hong Kong Death Registry, which is checked by the Department of Health, Government of Hong Kong SAR, who linked the mortality data to the subject's unique Hong Kong identity number recorded during initial recruitment. As most deaths were certified in hospitals and the remainder by coroners, the validity of the information should be high. Deaths were coded using the International Classification of Disease, Ninth revision (ICD-9) until the end of 2000, followed by the Tenth revision coding. The censor date for all subjects in the study was 31st December 2003 or the date of death for the deceased.

Statistical analyses

Data from normally distributed parameters are presented as mean±SD, whereas skewed data were logarithmically transformed and expressed as geometric mean with 95% confidence intervals. Multivariable Cox regression was used to assess the effect of the metabolic syndrome and its components on survival for all-cause and cause-specific survival.[21] Potential confounders included were age (in 5 year age-bands), sex (where appropriate), education (primary or less, secondary, matriculation or above), job activity level (no job, sedentary, light, moderate, heavy) and frequency of leisure-time activity of at least 30 minutes (none in last month, less than 3 times a week, 3 or more times a week), smoking (ever, never) and use of alcohol (ever, never) Effect modification was assessed from the significance of interaction terms and the heterogeneity of effect across strata. The validity of the proportional hazards assumption for variables included in the model was checked from the significance of scaled Schoenfeld residuals and by visual inspection of the log (-log (survival)) versus log of survival time. Intercooled Stata (version 8.2 for windows, TX, USA) was used in the analyses.

Results

The baseline demographic characteristics of the 2863 subjects, with complete biochemical, anthropometric, socio-economic and lifestyle data and excluding 5 currently pregnant females, with and without the metabolic syndrome are described in Table 1. As expected those subjects with the metabolic syndrome had an adverse biochemical and anthropometric vascular risk factor profile. They were older, but their gender distribution was similar, as was the prevalence of smoking and alcohol consumption (Table 1). The overall proportion of subjects with the metabolic syndrome was 17.6% with 17.2% and 17.7% in the males and females, respectively, and the prevalence increased significantly with age ranging from 8.0% for those 25-34 years, and reaching 39.8% in those aged 65-74 years. The prevalence of current smokers in the males and females were 47.8% and 4.5%, respectively, and 55.4% and 19.4% for current alcohol consumption. The subjects were followed-up for 24,101 person-years, with a mean duration of 8.45 years. A total of 89 deaths (62.9% male) were identified, of which 30 (33.7%) were related to vascular disease (36.7% stroke). We classified vascular deaths as ischaemic heart disease (IHD) (ICD9 410-414 or ICD10 I200-I259), stroke (ICD9 430-438, ICD10 I600-I699), other heart disease (ICD9 390-405, 415-417, 420-429, 440-448, 451-459 and ICD10 I100-I159, I260-I289, I300-I529, I700-I999) and diabetes (ICD9 250 and ICD10 E100-149). Of the 30 vascular deaths (20 in men and 10 in women), 12 were from IHD (10 in men and 2 in women), 11 were from stroke (6 in men and 5 in women), 6 were from other heart disease (3 in men and 3 in women) and 1 in a man from diabetes. There were 40 malignancies (ICD9/10 140-239/C00-D48), and 19 deaths due to a variety of other causes. The all-cause mortality incidence rate was 3,069 per 100,000 person-years, and 1,244 and 1,379 per 100,000 person-years for vascular disease and cancer, respectively. Following adjustment for age, socio-economic status and a range of lifestyle habits, an increasing number of components of the metabolic syndrome was associated with an increased risk of all-cause (hazard ratio 2.02 (95%CI 1.02-4.00), $p < 0.05$) and vascular disease mortality (hazard ratio 6.39 (95%CI 1.40-29.2), $p < 0.05$, Table 2). Further adjustment for LDL-cholesterol levels did not significantly influence any of the observations (data not shown). The effect of the metabolic syndrome on all-cause mortality varied with sex ($p = 0.006$). When we compared those with

0-2 components to those with 3 or more, ie the metabolic syndrome (Table 3), the metabolic syndrome tended to increase all-cause mortality by 49% (p=0.084), which reached statistical significance in the male subjects, increasing the risk by 129%, p=0.003. The metabolic syndrome increased the risk of vascular disease mortality in the males and in the combined group (p≤0.002, Table 3). When we examined the individual components of the metabolic syndrome (Table 4), hypertension tended to increase all-cause mortality by 53% (p=0.081) and significantly increased the risk of all-cause mortality in the males, and vascular disease mortality in the males and the combined group. High fasting glucose levels were associated with increased risk of vascular disease mortality, and tended to increase the risk in the females by over 200% (p=0.056). High triglyceride levels significantly increased the risk of vascular disease in the males and tended to raise the risk by 105% in the combined group (p=0.064). The observations with the increased risk for central obesity were similar to those for hypertension, with central obesity tending to increase the risk of all-cause and vascular disease mortality by 50% (p=0.074) and 112% (p=0.053), respectively, reaching significance for all-cause and vascular disease mortality in the male subjects.

Discussion

In this longitudinal Chinese population-based study the metabolic syndrome was associated with all-cause and vascular disease mortality. These relationships existed even after adjustment for a range of socioeconomic and lifestyle factors, including job-related physical activity. This study confirms the observations in Caucasians of the increased risk of mortality from the metabolic syndrome and its components and extends them to Asian populations. Each of the individual components of the metabolic syndrome, except low HDL-cholesterol significantly increased the risk of vascular disease mortality in either the male or combined gender analyses, supporting the cumulative effect observed with the metabolic syndrome analyses. To date, in Asians such observations have only been made in cross-sectional analyses between the metabolic syndrome and prevalent vascular disease.[14]

There appeared to be a different effect of the metabolic syndrome on mortality between males and females, with males at greatest risk of all-cause and vascular mortality. Different effects of the metabolic syndrome on mortality in men and women have been reported in western populations, but in those populations the metabolic syndrome was often a better predictor in females,[1,22] but not in all studies,[23] which suggests that gender per se may not fully explain the observation. A number of lifestyle factors have been shown to differ between the genders, including alcohol consumption and smoking, both of which are predominantly found in the males, which has been observed in most Asian populations. It is possible that lifestyle factors, such as smoking, differentially exacerbate the effects of the metabolic syndrome. However, adjustment for potential confounding from a range of lifestyle factors was made, yet the association between the metabolic syndrome and all-cause and vascular disease mortality remained significant, although the association with all-cause mortality was marginally not significant when those with 0-2 components were compared to those with the metabolic syndrome (p=0.084).

A small proportion of the subjects in the study may have died following emigration or had accidental deaths overseas and thus may not have been recorded in the death registry. However, such deaths would only bias the findings towards no association. There were only a limited number of vascular deaths after 8.45 years of follow-up, due to the low incidence of vascular disease mortality in this population, although the proportionate vascular mortality in our cohort resembles that for the Hong Kong population as a whole. There were particularly few deaths in those without components of the metabolic syndrome, and the low number of deaths in this reference group was partly the reason behind the wide confidence intervals in the analysis of the association with increasing components of the metabolic syndrome. Despite the relatively small number of deaths, our observation of increased risk of mortality associated with the metabolic syndrome is unlikely to be due to chance, and these biologically plausible findings are consistent with other evidence from Caucasian populations.[1-8]

Our findings forewarn the potentially disastrous consequences at a population level as modernisation rapidly proceeds in China with the associated increases in the prevalence of the metabolic syndrome. If levels of the metabolic syndrome observed in Hong Kong, particularly in the older age

groups, for instance 65-74 years where almost 40% have this condition, are reached in China, a large proportion of its 1.2 billion population will be at risk of dying as a result of this condition.[13] Intensive treatment of blood pressure, glucose, and lipids in patients with the metabolic syndrome may prevent between 50 to 80% of coronary heart disease events.[24] However, effective delivery of these treatments requires commitment, expenditure and comprehensive health infrastructure. Therefore, in developing populations with a relatively young population and limited health care resources, prevention now before the metabolic syndrome is widespread, during the opportunity provided by the demographic dividend, i.e. a relatively high worker to dependency ratio[25] is a key public health strategy.[26] Clearly, without public health programs to prevent the development of the metabolic syndrome and to curb adverse lifestyle factors such as smoking, the potential medical and societal ramifications may be overwhelming. Urgent public health actions are needed to control the potentially worsening situation in China and in the Asia-Pacific Region, before the narrow window of opportunity provided by the current demographic dividend is closed.

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Table 1 Baseline anthropometric, blood pressure and plasma biochemical characteristics in the male and female subjects.

	Metabolic syndrome		p value
	Without	With	
Number (n=2863)	2361	502	-
Age (years)	43.9±12.2	54.7±12.2	<0.001
Gender (% female)	51.0	51.9	NS
Systolic blood pressure (mm Hg)	115±17	139±20	<0.001
Diastolic blood pressure (mm Hg)	73±10	84±10	<0.001
Total cholesterol (mmol/L)	5.0±0.9	5.5±1.0	<0.001
HDL-cholesterol (mmol/L)	1.31±0.32	0.99±0.21	<0.001
LDL-cholesterol (mmol/L)	3.2±0.9	3.6±0.9	<0.001
Triglyceride (mmol/L)	0.97 (0.94-1.00)	1.86 (1.73-2.00)	<0.001
Fasting glucose (FPG, mmol/L)	5.16 (5.12-5.20)	5.47 (5.39-5.56)	<0.001
Fasting insulin (FPI, pmol/L)	4.9 (4.7-5.1)	8.5 (7.8-9.3)	<0.001
OGTT 2 hour glucose (mmol/L)	6.5 (6.3-6.6)	7.9 (7.6-8.2)	<0.001
OGTT 2 hour insulin (pmol/L)	48.5 (45.9-51.3)	81.1 (73.6-90.4)	<0.001
Body mass index (kg/m^2)	23.4±3.2	27.7±3.2	<0.001
Waist circumference (cm)	76.7±9.0	90.2±8.3	<0.001
Alcohol consumption (ever, %)	37.6	33.8	NS
Tobacco consumption (ever, %)	25.3	27.8	NS

Normal data, Mean±SD; Skewed data, Geometric mean (geometric 95 % confidence intervals of the mean); NS=non-significant.

Table 2: Adjusted hazard ratios for all-cause and vascular disease mortality associated with the metabolic syndrome

	All-cause mortality			Vascular disease mortality		
	All	**Male**	**Female**	**All**	**Male**	**Female**
Number of total deaths/ subjects, and for each group	89/2863	56/1400	33/1463	30/2863	20	10
	0: 13/1014	8/483	5/536	2/1014	1/483	1/536
	1-2: 41/1334	22/667	19/667	11/1334	7/667	4/667
	3+: 35/502	26/242	9/260	17/502	12/242	5/260
Metabolic syndrome						
No components	1	1	1	1	1	1
1-2 components	1.49 (0.78-2.83)	1.20 (0.52-2.77)	1.81 (0.65-5.03)	2.23 (0.48-10.36)	3.28 (0.39-27.94)	1.03 (0.10-10.11)
≥3 components	2.02* (1.02-4.00)	2.62* (1.13-6.06)	1.19 (0.36-3.94)	6.39* (1.40-29.20)	13.51* (1.68-109)	1.13 (0.11-11.87)
p for trend	0.037	0.007	NS	0.002	0.001	NS

p value *<0.05. Adjusted for age, gender (where appropriate), education, job activity, leisure-time activity frequency, smoking, use of alcohol.

Table 3: Adjusted hazard ratios for all-cause and vascular disease mortality associated with the components of the metabolic syndrome

	All-cause mortality			Vascular disease mortality		
	All	**Male**	**Female**	**All**	**Male**	**Female**
Number of deaths	89	56	33	30	20	10
Metabolic syndrome						
0-2 components	1	1	1	1	1	1
≥3 components	1.49 (0.95, 2.33)	2.29* (1.32, 3.98)	0.73 (0.32, 1.67)	3.36* (1.57, 7.19)	5.26* (2.06, 13.43)	1.10 (0.29, 4.17)

p value *<0.05. Adjusted for age, gender (where appropriate), education, job activity, leisure-time activity frequency, smoking, use of alcohol.

Table 4: Adjusted hazard ratios for all-cause and vascular disease mortality associated with the components of the metabolic syndrome

Metabolic syndrome components	All-cause mortality			Vascular disease mortality		
	All	Male	Female	All	Male	Female
Hypertension	1.53 (0.95, 2.48)	2.12* (1.12, 4.01)	0.90 (0.41, 1.99)	3.70* (1.40, 9.80)	4.36* (1.30, 14.63)	2.48 (0.45, 13.61)
High fasting glucose	1.21 (0.72, 2.03)	1.17 (0.60, 2.26)	1.33 (0.57, 3.13)	2.96* (1.38, 6.36)	2.12 (0.78, 5.76)	3.81 (0.97, 15.1)
High triglycerides	1.03 (0.63, 1.68)	1.42 (0.79, 2.55)	0.59 (0.22, 1.56)	2.05 (0.96, 4.39)	3.41* (1.35, 8.59)	0.63 (0.13, 3.05)
Low HDL-cholesterol	0.96 (0.63, 1.48)	1.18 (0.69, 2.01)	0.77 (0.38, 1.56)	1.24 (0.60, 2.61)	1.46 (0.60, 3.57)	0.82 (0.22, 3.10)
Central obesity	1.50 (0.96, 2.32)	1.75* (1.01, 3.02)	1.25 (0.59, 2.63)	2.12 (0.99, 4.52)	3.09* (1.25, 7.59)	0.77 (0.21, 2.89)

p value *<0.05. Adjusted for age, gender (where appropriate), education, job activity, leisure-time activity frequency, smoking, use of alcohol.