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Is a single definition of the metabolic syndrome appropriate?—A comparative study of the USA and Asia

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Abstract

The metabolic syndrome has been identified as an increasingly important precursor to cardiovascular diseases in many Asian populations. Our objective was to compare the contribution of component risk factors to the diagnosis of the metabolic syndrome, as defined by the Third report of the National Cholesterol Education Program Expert Panel Adult Treatment Panel (NCEP-ATPIII), in the US and selected Asian populations. Nationally representative survey data from Hong Kong, Taiwan, Thailand and the US were used. Analyses were restricted to men and women aged ≥35 years. The age-standardized prevalence of the NCEP-ATPIII defined metabolic syndrome was highest in the US (31% in men, 35% in women), and lowest in Taiwan (11% in men, 12% in women). The component risk factors that defined the presence of the metabolic syndrome varied between countries. As expected, abnormal waist circumference was considerably more prevalent among individuals with the metabolic syndrome in the US (72% in men, 94% in women) compared with their Asian counterparts, but substantial variation was also observed between the Asian populations (13–22% in men, 38–63% in women). Furthermore, the relative contribution of other risk factors to the metabolic syndrome was also substantially different between countries. The NCEP-ATPIII definition identifies a heterogeneous group of individuals with the metabolic syndrome in different populations.

Keywords: Asia; Blood pressure; HDL cholesterol; Triglycerides; Central obesity; Metabolic syndrome

The term "metabolic syndrome" describes a clustering of abnormalities in individuals that confers an increased risk of developing cardiovascular disease. Working definitions of this syndrome have recently become available from the World Health Organization (WHO) [1] and the US-based National Cholesterol Education Program Adult Treatment Panel III (NCEP-ATPIII) [2]. Generic components of the syndrome, common to both definitions, include hyperglycaemia or impaired glucose tolerance, dyslipidaemia, obesity or abnormal fat distribution and hypertension; the WHO definition also includes measured insulin resistance and microalbuminuria. While estimates of the prevalence of the metabolic syndrome vary according to the definition used [3,4], studies have confirmed that individuals with a diagnosis of metabolic syndrome on the basis of either definition are at increased risk of diabetes and cardiovascular diseases [5–9].

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Using the NCEP-ATPIII definition, it has been estimated that about one-quarter of US adults aged ≥20 years have the metabolic syndrome [10]. However, the component risk factors chosen as well as the cut-points used to define abnormality for each of these risk factors are somewhat arbitrary, and were selected to be highly sensitive to the presence of insulin resistance, which is known to vary between ethnic groups [11]. Given the continuous nature of the association between each of the component risk factors and the risk of cardiovascular disease, the value of fixed threshold values to define an abnormality can be questioned. However, even if such threshold values are considered necessary for the practice of clinical or public health medicine, differences in the distribution of the component risk factors and their relative contribution to cardiovascular risk between populations may limit the generalisability of the chosen cut-points.

Many countries in Asia are undergoing an epidemiological transition, with chronic non-communicable diseases becoming leading causes of morbidity and mortality. Little is known about the prevalence of the metabolic syndrome in this region, and few studies have investigated the implications of applying metabolic risk factors with cut-points identified in Western countries to Asian populations. In this report, we compare the prevalence of the NCEP-ATPIII defined metabolic syndrome and its components in the US and selected Asian populations.

1. Methods

Data from population-based cross-sectional studies in Hong Kong, Taiwan, Thailand and the US were collected and analyzed. Each study, described in brief below, was designed to obtain nationally representative data; details of each study have been published elsewhere [12–15]. The laboratories for studies conducted in Hong Kong, Thailand and the US were standardized according to the criteria of the Centers for Disease Control—National Heart, Lung and Blood Institute Standardization Program. For the study from Taiwan, the laboratory participates in the College of American Pathologists Accreditation Program.

1.1. Hong Kong

The Hong Kong cardiovascular risk factor prevalence study was conducted in 1995–1996 and included a representative sample of 2900 men and women from Hong Kong Island, Kowloon and the New Territories [14]. Study participants underwent physical assessment, which included measurement of height, weight, waist and hip circumferences and blood pressure using standard methods. After 12 h of fasting, serum samples were collected for lipid analyses and a glucose tolerance test was performed. Biochemical analyses were performed using the Hitachi 747 Autoanalyzer (Hitachi Ltd., Tokyo, Japan). Plasma glucose, total cholesterol and triglycerides were determined using enzymatic methods, and the PEG 6000 precipitation method was used to measure HDL cholesterol.

1.2. Taiwan

Data were collected from four nationwide health screening centres in Taiwan during 1999 [13]. A total of 48,406 subjects with an age and gender distribution similar to the national population [16] were included in the study. For all participants, measurements of height, weight, waist and hip circumferences and blood pressure were obtained using standard techniques. A venous blood sample was taken after 12 h of fasting for measurement of serum glucose and lipids, which were performed using commercially available kits on a Hitachi 7150 Autoanalyzer (Hitachi Ltd., Tokyo, Japan). HDL cholesterol was measured using the dextran sulphate magnesium precipitation method.

1.3. Thailand

Data were collected from a sample of 5305 men and women aged 35 years and over within representative enumerated districts of rural and urban Thailand in 2000 [15]. Physical examination of study participants included standard assessment of blood pressure, height, weight, waist and hip circumference. Biochemical analyses of serum glucose and lipids were performed on venous samples obtained after an 8 h overnight fast, using the Dimension RxLHM clinical chemistry system (Dade Behring Inc., Newark, USA). Serum glucose, total cholesterol and triglycerides were measured using enzymatic methods, with the DADE Accelerator selective detergent method for HDL cholesterol determination.

1.4. United States

The Third National Health and Nutrition Examination Survey (NHANES III) was designed to obtain nationally representative information on the health and nutritional status of the civilian, non-institutionalized US population through interviews and direct physical examinations [12]. The survey was conducted between 1988 and 1994, and included 33,199 men and women aged ≥17 years. After interview, participants were invited to undergo a standard physical assessment, which included measurement of blood pressure, height, weight, and waist circumference. Blood samples were obtained after a period of fasting of at least 8 h, with biochemical analyses performed using a Hitachi 704 Autoanalyzer (Boehringer Mannheim Diagnostics, Indianapolis, IN). Enzymatic methods were used to measure total cholesterol and triglycerides, while a precipitation method (heparin manganese) was used for HDL cholesterol assay. Serum glucose was also analyzed by enzymatic method, using the Cobas Mira Chemistry System (Roche Diagnostics Systems, Inc., Montclair, NJ).

1.5. Definition of metabolic syndrome

As described in the NCEP-ATPIII report [2], individuals within each study were classified as having abnormal levels of risk factors according to the following criteria: (1) blood pressure: abnormal if systolic blood pressure ≥130 mmHg and/or diastolic blood pressure ≥85 mmHg; (2) serum triglycerides: abnormal if ≥150 mg/dl (1.69 mmol/L); (3) serum HDL cholesterol: abnormal if <40 mg/dL (1.04 mmol/L) in men, or <50 mg/dl (1.29 mmol/L) in women; (4) waist circumference: abnormal if >102 cm in men, or >88 cm in women; and (5) fasting blood glucose: abnormal if ≥110 mg/dL (6.1 mmol/L). The metabolic syndrome was defined by the presence of at least three of these five abnormalities.

1.6. Statistical analysis

For each study, analyses were restricted to adults aged 35 years or above (as the study conducted in Thailand was limited to this population) and to those individuals with complete data available for each of the risk factors included in the definition of the metabolic syndrome. Where required to ensure estimates were representative of the populations [14,15], the STATA 8.0 statistical software package (StataCorp., College Station, TX, USA) was used to apply appropriate national census-derived weights to study samples. Estimates (with standard errors) of mean levels of risk factors and proportions with metabolic abnormalities were calculated separately for men and women within each study population. Direct age-standardization [17] of estimates was based on the latest WHO World Standard Population [18], and age-standardized proportions are presented, although the results were similar without adjustment. Comparisons of the proportion of individuals with risk factor abnormalities between populations were performed using χ^2-test, while differences in mean values of continuous variables were examined using *t*-test, with adjustment for multiple comparisons using a Bonferroni correction.

2. Results

The number and characteristics of the participants included in the analysis from each study are shown in Table 1. The mean age of the US population was greater than that of each Asian population. Among the component risk factors of the metabolic syndrome, mean values of blood pressure and waist circumference were similar among the Asian countries, and more favourable than in the US. Lower HDL cholesterol values in Hong Kong and Thailand were observed in the presence of lower mean total cholesterol levels—mean total/HDL cholesterol ratios for each population are also shown in Table 1. Mean triglyceride levels were greatest in Thailand.

In all populations, the majority of men and women aged 35 years or over had abnormal levels of at least one component risk factor of the metabolic syndrome (Fig. 1). The prevalence

Table 1
Characteristics of study populations

Risk Factor	Hong Kong		Taiwan		Thailand		US	
	Male (n = 1155)	Female (n = 1100)	Male (n = 23,380)	Female (n = 25,026)	Male (n = 2453)	Female (n = 2646)	Male (n = 4626)	Female (n = 5092)
Age (years)	49.6 (0.9)	49.6 (0.9)	49.5 (0.1)	49.9 (0.1)	50.3 (1.2)	50.9 (1.2)	58.3 (0.2)	57.5 (0.2)
SBP (mmHg)	122.4 (0.9)	121.2 (1.3)	125.0 (0.1)	122.8 (0.1)	120.3 (1.1)	119.0 (0.9)	134.3 (0.3)	132.0 (0.3)
DBP (mmHg)	77.2 (0.6)	74.0 (0.7)	76.2 (0.1)	72.0 (0.1)	77.0 (0.8)	74.6 (0.4)	79.5 (0.2)	76.0 (0.2)
Triglycerides (mmol/L)	1.50 (0.06)	1.22 (0.03)	1.75 (0.01)	1.34 (0.01)	2.07 (0.06)	1.66 (0.06)	1.86 (0.02)	1.64 (0.02)
Total cholesterol (mmol/L)	5.21 (0.03)	5.19 (0.04)	5.41 (0.01)	5.37 (0.01)	5.03 (0.09)	5.35 (0.07)	5.46 (0.02)	5.65 (0.02)
HDL cholesterol (mmol/L)	1.15 (0.01)	1.32 (0.01)	1.17 (0.001)	1.44 (0.001)	1.10 (0.02)	1.20 (0.02)	1.20 (0.01)	1.42 (0.01)
Total/HDL cholesterol ratio	4.82 (0.06)	4.17 (0.05)	4.84 (0.01)	3.91 (0.01)	4.79 (0.05)	4.68 (0.06)	4.94 (0.03)	4.29 (0.02)
Body mass index (kg/m^2)	24.4 (0.1)	24.3 (0.1)	24.1 (0.01)	23.3 (0.01)	23.1 (0.2)	24.9 (0.2)	27.1 (0.1)	28.1 (0.1)
Waist circumference (cm)	83.7 (0.3)	76.7 (0.5)	83.6 (0.1)	74.5 (0.1)	80.7 (0.9)	80.8 (0.7)	98.4 (0.2)	94.0 (0.2)
Fasting glucose (mmol/L)	5.53 (0.05)	5.52 (0.07)	5.70 (0.01)	5.52 (0.01)	5.60 (0.08)	5.50 (0.07)	5.96 (0.03)	5.89 (0.03)

Mean (S.E.). SBP, systolic blood pressure; DBP, diastolic blood pressure; HDL, high density lipoprotein, $p < 0.05$ for all sex-specific between population comparisons (after correction for multiple comparisons), *except* fasting blood glucose for women in Hong Kong vs. Taiwan.

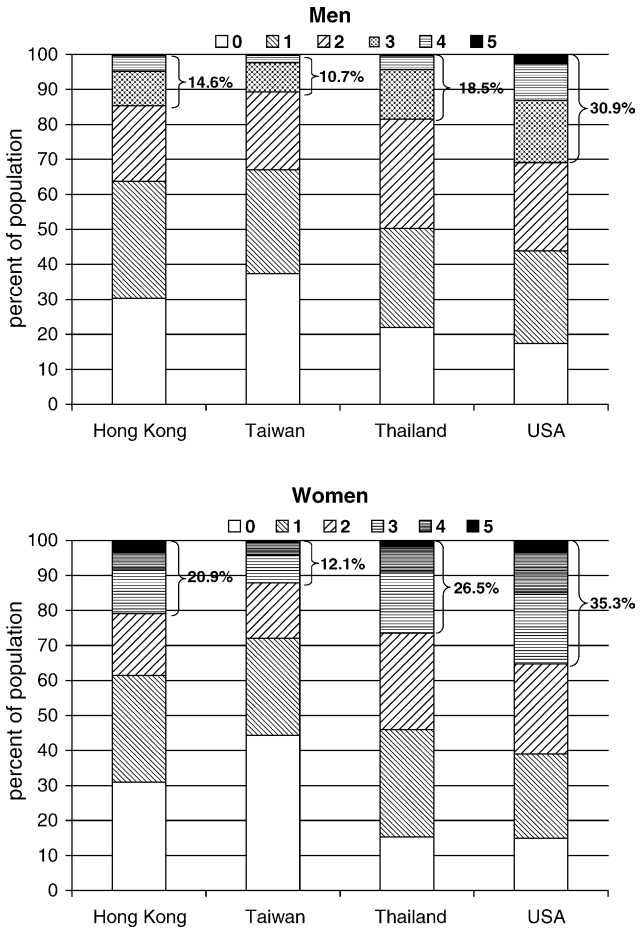

Fig. 1. Age-standardized prevalence of 0, 1, 2, 3, 4 and 5 NCEP-defined metabolic abnormalities among men and women aged ≥35 years in Hong Kong, Taiwan, Thailand and the US. The proportion of individuals with the metabolic syndrome (≥3 NCEP-defined abnormalities) is shown. Estimates have been age-standardised to the World Standard Population 2000 [18].

of the NCEP-ATPIII defined metabolic syndrome (abnormal levels of ≥3 risk factors) was lowest in Taiwan and highest in the US for both men (11% versus 31%, $p < 0.001$) and women (12% versus 35%, $p < 0.001$). Of the Asian populations, the prevalence of the metabolic syndrome was greatest in Thailand (19% in men, 27% in women). In each population, the metabolic syndrome was more prevalent among women than men (all $p < 0.01$).

A comparison of the age-standardized prevalence of abnormal levels of the component risk factors among individuals with the NCEP-ATPIII defined metabolic syndrome between populations is shown in Table 2. The most striking differences observed are in the proportions of individuals with abnormal waist circumference—in the US population with the metabolic syndrome these proportions were 72% for men and 93% for women. The corresponding values for the Asian countries ranged from 14 to 22 and 38 to 64%. Conversely, the Asian populations with the metabolic syndrome were more likely to have abnormal HDL levels than their US counterparts. Individuals with the metabolic syndrome from Taiwan and Thailand had a higher prevalence of abnormal triglyceride levels than in the other countries studied (particularly among men). The proportion of individuals with the metabolic syndrome classified as having an abnormal fasting glucose was lowest in the US, and greatest in Taiwan. There was also considerable variation in the proportion of these individuals with NCEP-ATPIII defined high blood pressure, ranging from about one-half of men and women in Taiwan, to more than 80% of their counterparts in Thailand.

Despite using the same NCEP-ATPIII defined threshold values in each population, there was some variation in the unadjusted mean values for each of the component risk factors among individuals with and without NCEP-defined metabolic syndrome between populations (Table 3). This was particularly true for systolic blood pressure, HDL cholesterol and waist circumference, suggesting differences in the risk profile of individuals both with and without the syndrome,

Table 2
Proportion (S.E.) with each NCEP-defined metabolic abnormality, among adults aged ≥35 years with the metabolic syndrome

Study	Blood pressure[a]	Triglycerides[b]	HDL cholesterol[c]	Waist circumference[d]	Fasting blood glucose[e]
Male					
Hong Kong	85 (3.2)	81 (3.1)	88 (2.7)	22 (3.4)	56 (4.2)
Taiwan	57 (1.1)	94 (0.5)	89 (0.6)	14 (0.8)	67 (1.1)
Thailand	78 (2.0)	92 (1.3)	79 (2.0)	20 (2.0)	58 (2.4)
US	82 (1.1)	84 (1.0)	73 (1.2)	72 (1.2)	39 (1.3)
Female					
Hong Kong	80 (3.9)	65 (4.2)	95 (1.7)	51 (4.4)	51 (4.4)
Taiwan	54 (1.4)	88 (0.8)	91 (0.6)	38 (1.4)	62 (1.4)
Thailand	57 (1.7)	79 (1.5)	93 (0.9)	64 (1.6)	46 (1.8)
US	70 (1.2)	71 (1.2)	78 (1.0)	94 (0.5)	37 (1.2)

Estimates age-standardized to the WHO World Standard Population [18].
[a] Systolic blood pressure ≥130 mmHg and/or diastolic blood pressure ≥85 mmHg.
[b] Serum triglycerides ≥150 mg/dL (1.69 mmol/L).
[c] Serum high density lipoprotein (HDL) cholesterol <40 mg/dL (1.04 mmol/L) in men and <50 mg/dL (1.29 mmol/L) in women.
[d] Waist circumference >102 cm in men and >88 cm in women.
[e] Fasting blood glucose ≥110 mg/dL (6.1 mmol/L).

Table 3
Mean levels (S.E.) of metabolic risk factors among adults aged ≥35 years in each population, according to the presence or absence of NCEP-defined metabolic syndrome (MS)

Study	Systolic blood pressure (mmHg)		Triglycerides (mmol/L)		HDL-cholesterol (mmol/L)		Waist circumference (cm)		Fasting blood glucose (mmol/L)	
	MS	No MS[a]	MS	No MS[a]	MS	No MS[a]	MS	No MS[a]	MS	No MS[a]
Male										
Hong Kong (n = 1155)	139 (1.9)	120 (0.9)	2.6 (0.16)	1.3 (0.03)	0.90 (0.01)	1.18 (0.01)	93 (0.8)	82 (0.3)	6.8 (0.18)	5.3 (0.04)
Taiwan (n = 23,380)	137 (0.4)	124 (0.1)	2.5 (0.02)	1.5 (0.01)	0.91 (0.00)	1.20 (0.00)	91 (0.2)	83 (0.1)	7.1 (0.06)	5.5 (0.01)
Thailand (n = 2453)	134 (1.3)	117 (1.0)	3.4 (0.16)	1.8 (0.07)	0.95 (0.02)	1.13 (0.03)	90 (1.2)	79 (0.8)	7.0 (0.12)	5.3 (0.07)
US (n = 4626)	142 (0.5)	131 (0.3)	2.8 (0.04)	1.4 (0.02)	0.99 (0.01)	1.31 (0.01)	107 (0.3)	94 (0.2)	6.8 (0.08)	5.4 (0.03)
Female										
Hong Kong (n = 1100)	147 (1.7)	116 (1.3)	2.2 (0.11)	1.0 (0.02)	1.02 (0.01)	1.38 (0.01)	88 (0.6)	74 (0.3)	7.4 (0.37)	5.1 (0.02)
Taiwan (n = 25,026)	144 (0.4)	121 (0.1)	2.3 (0.02)	1.2 (0.00)	1.10 (0.00)	1.48 (0.00)	85 (0.2)	73 (0.1)	7.1 (0.06)	5.3 (0.01)
Thailand (n = 2646)	131 (1.0)	115 (0.7)	2.5 (0.08)	1.4 (0.06)	1.04 (0.01)	1.25 (0.03)	90 (0.9)	78 (0.6)	6.5 (0.17)	5.2 (0.05)
US (n = 5092)	142 (0.5)	126 (0.4)	2.4 (0.03)	1.2 (0.01)	1.19 (0.01)	1.56 (0.01)	102 (0.3)	89 (0.2)	6.9 (0.08)	5.1 (0.02)

[a] For individuals without MS—$p < 0.05$ (after correction for multiple comparisons) for all between-population sex-specific comparisons of risk factors, *except* triglycerides—Taiwan vs. US in women; fasting blood glucose—Hong Kong vs. Thailand in men, and Hong Kong vs. US in women.

in different countries. This is exemplified by differences in mean systolic blood pressure between those with and without the metabolic syndrome, ranging from 11 mmHg (US) to 19 mmHg (Hong Kong) among men, and 16 mmHg (US) to 31 mmHg (Hong Kong) among women. Similarly, differences in other risk factor levels between those with and without the metabolic syndrome varied substantially between populations, including for triglycerides (e.g. 1.0 and 1.6 mmol/L for Taiwanese and Thai men, respectively), HDL cholesterol (e.g. 0.18 mmol/L for Thai men versus 0.32 mmol/L among US males), and fasting blood glucose (e.g. 1.3 mmol/L among Thai women versus 2.3 mmol/L for women from Hong Kong).

Across all age and sex strata examined, the prevalence of NCEP-ATPIII defined metabolic syndrome was greater in the US population compared with the Asian populations (Fig. 2). The prevalence of the metabolic syndrome generally increased with age, this observation being least consistent among men in Thailand. With aging, the increasing prevalence of the metabolic syndrome was observed to a greater extent among women than men across all populations studied.

3. Discussion

In these population-based surveys the prevalence of the NCEP-ATPIII defined metabolic syndrome is lower among adults in Hong Kong, Taiwan and Thailand, compared with adults in the United States. However, application of NCEP-ATPIII defined threshold values defined strikingly heterogenous groups of individuals with the metabolic syndrome, not only when comparisons were made between Asian and US populations, but also for comparisons between Asian populations. The use of a single definition identifies individuals with the metabolic syndrome who, in different populations, are likely to have a variable risk of developing cardiovascular disease relative to the remainder of the population. For example, the difference in systolic blood pressure between those with and without the metabolic syndrome among women in the US was 16 mmHg, while the corresponding difference among Thai women was 31 mmHg. Based on blood pressure alone, and using estimates of the association in blood pressure and coronary heart disease from epidemiological studies [19–21] (∼20% higher risk for each 10 mmHg higher level of systolic blood pressure), women with NCEP-ATP III defined "hypertension" in the US would have ∼35% higher risk of coronary heart disease compared with the remainder of the population; the corresponding figure for Thai women would be ∼75%.

The HDL cholesterol cut-point used in the NCEP-ATPIII definition also highlights the difficulty of establishing a single threshold value that is meaningful across populations. In contrast to the general pattern of more unfavourable cardiovascular risk factor levels in the US population compared to the Asian populations, HDL cholesterol levels were higher in the US. However, whether this higher level of HDL in the US population really indicates or confers a lower cardiovascular risk when compared against the Asian populations is uncertain, because total cholesterol levels in the US population are also higher. Likewise, the validity of elevated triglyceride levels as an indicator of increased cardiovascular risk in the Thai population is also uncertain—high mean triglyceride values have been a consistent observation amongst adult Thais, particularly among rural inhabitants who comprise approximately 70% of the adult population [22–25]. The basis for this lipid profile has not been established, but may in part relate to the very high carbohydrate, low fat diets consumed in many regions.

There was marked variation between the populations in the proportion of subjects with waist circumference above the NCEP-ATPIII defined threshold. This reflects the large differences in body mass index and waist circumference between Asian and Western populations. As defined by universal WHO criteria, therefore, the prevalence of abdominal obesity is much lower in Asian countries than in the US. However, there is evidence that the relationship between body fat

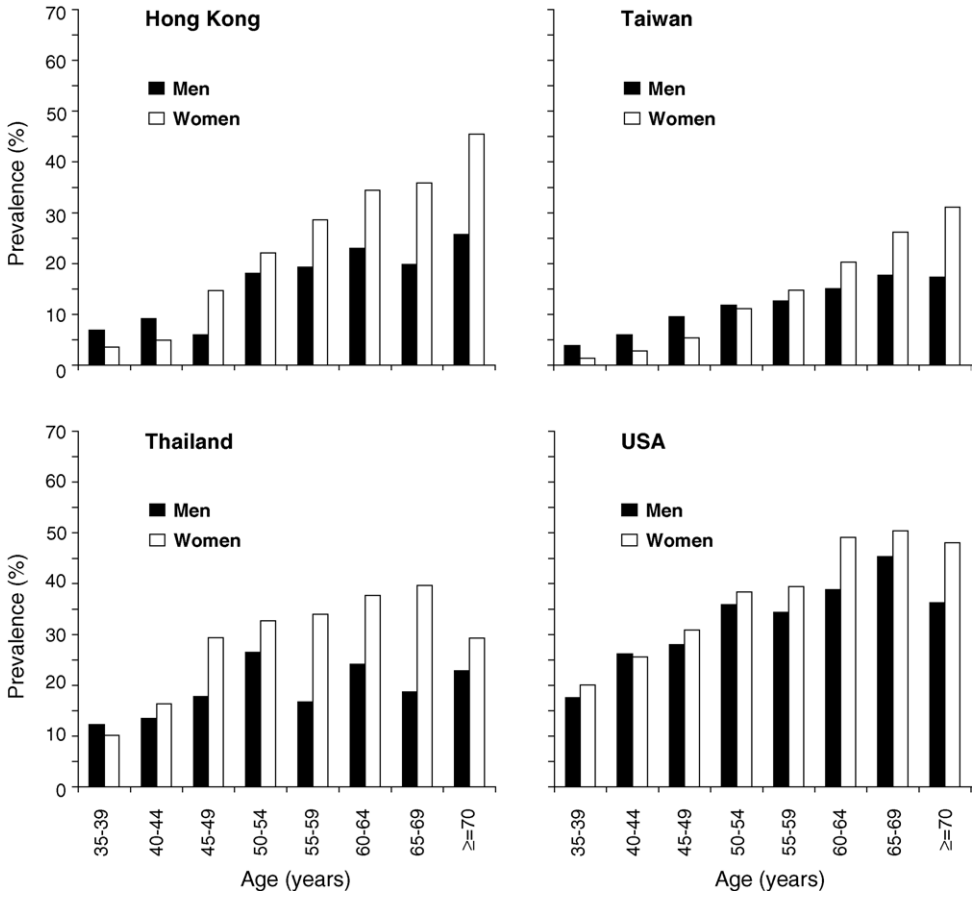

Fig. 2. The prevalence of the metabolic syndrome according to the NCEP criteria, amongst adults aged ≥35 years in Hong Kong, Taiwan, Thailand and the US.

and disease varies between ethnic groups, with some Asian populations experiencing higher levels of disease at lower levels of body mass index than Western populations [26,27]. In one cross-sectional study from Singapore, receiver operator characteristic analysis indicated that waist circumference cut-points that best predicted the clustering of other metabolic abnormalities were substantially lower than those used in the NCEP-ATPIII definition [28]. Thus, it has been suggested that the definition of both overall obesity and abdominal obesity in Asian populations should be based on lower waist circumference cut-points, perhaps 80 and 90 cm for women and men, respectively [28,29]. Indeed, the recent International Atherosclerosis Society recommendations suggest three different waist circumference cut-points for Caucasian populations, Asia-Pacific populations, and the Japanese [30]. Use of different thresholds would significantly affect estimates of the prevalence of the metabolic syndrome, as has been shown in Hong Kong Chinese and in Singaporean populations [28,31]. However, the current analyses indicate substantial variation in the proportion of individuals with the NCEP-defined metabolic syndrome fulfilling the definition of obesity between countries in Asia, thus the appropriateness of a single cut-point within these populations remains questionable.

There are some limitations to these analyses. Data collection was not entirely contemporaneous, and while each laboratory employed rigorous quality control procedures, the exact methods used for lipid and glucose assay differed between studies. Methods for HDL assay, while all based on precipitation, did vary between studies, thus small differences in HDL cholesterol and total/HDL cholesterol ratio between populations should be treated with caution. However, differences in assay are unlikely to account for the large variation in prevalence for most risk factors observed between populations, or alter the conclusions of these analyses.

Another potential limitation is that we did not define those on blood pressure-lowering treatment as having NCEP-defined hypertension regardless of blood pressure levels, and therefore differences in the proportion of individuals treated between populations may confound the results. However, even in the US, where the highest treatment rates are likely to be observed, other data indicate that only ∼7% of the adult population has treated hypertension with blood pressure levels less than 140/90 mmHg [32]. Furthermore, any such "misclassification" is likely to increase the contrast between the US and the Asian populations, in relation to blood pressure differences among those with and without the metabolic syndrome.

The difficulties and uncertainty about the value of establishing a categorical, single, and broadly generalisable clinical definition for the metabolic syndrome does not detract from the importance of identifying patients with clustering of risk factors. These individuals with multiple "metabolic" abnormalities are clearly at increased risk of developing vascular disease. Such recognition is highly consistent with the emerging paradigm in cardiovascular prevention of evaluating and treating the absolute risk of an individual, rather than simply measuring and managing individual risk factors. However, "counting" risk factors (using threshold values to define abnormality) has been abandoned in favour of continuous risk tools (e.g. Framingham risk charts) to estimate an individual's risk of developing cardiovascular disease based on conventional risk factors [33]. Application of such methods to "metabolic" risk factors and further research directed toward the identification of locally relevant indicators of long-term risk may be particularly useful in many low- and middle-income countries of the Asia Pacific region, where efficient targeting of limited health care resources toward those with greatest risk is particularly important.

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