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QUARTERLY FOCUS ISSUE: HEART RHYTHM DISORDERS

Metabolic Syndrome and Risk of Acute Myocardial Infarction

A Case-Control Study of 26,903 Subjects From 52 Countries

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Objectives This study examines the risk of acute myocardial infarction (MI) conferred by the metabolic syndrome (MS) and its individual factors in multiple ethnic populations.

Background The risk of the MS on MI has not been well characterized, especially in multiple ethnic groups.

Methods Participants in the INTERHEART study (n = 26,903) involving 52 countries were classified using the World Health Organization (WHO) and International Diabetes Federation (IDF) criteria for MS, and their odds ratios (ORs) for MI were compared with the individual MS component factors.

Results The MS is associated with an increased risk of MI, both using the WHO (OR: 2.69; 95% confidence interval [CI]: 2.45 to 2.95) and IDF (OR: 2.20; 95% CI: 2.03 to 2.38) definitions, with corresponding population attributable risks of 14.5% (95% CI: 12.7% to 16.3%) and 16.8% (95% CI: 14.8% to 18.8%), respectively. The associations are directionally similar across all regions and ethnic groups. Using the WHO definition, the association with MI by the MS is similar to that of diabetes mellitus (OR: 2.72; 95% CI: 2.53 to 2.92) and hypertension (OR: 2.60; 95% CI: 2.46 to 2.76), and significantly stronger than that of the other component risk factors. The clustering of ≥3 risk factors with subthreshold values is associated with an increased risk of MI (OR: 1.50; 95% CI: 1.24 to 1.81) compared with having component factors with "normal" values. The IDF definition showed similar results.

Conclusions In this large-scale, multi-ethnic, international investigation, the risk of MS on MI is generally comparable to that conferred by some, but not all, of its component risk factors. The characterization of risk factors, especially continuous variables, as dichotomous will underestimate risk and decrease the magnitude of association between MS and MI. (J Am Coll Cardiol 2010;55:2390–8) © 2010 by the American College of Cardiology Foundation

The common clustering of metabolic abnormalities including abdominal obesity, elevated glucose, abnormal lipids, and elevated blood pressure has been extensively referred to in the medical literature as the "metabolic syndrome" (MS) (1,2). The presence of MS is associated with an increased risk of coronary heart disease (3–5), with limited evidence that this risk is greater than that conferred by its constituent components (6). The value of classifying subjects with MS has recently been called into question as the definition of MS is arbitrary (7,8), and the American Diabetes Association and the European Association for the Study of Diabetes have called for an aggressive research agenda to bring clarity to this debate (8). In this large-scale, multi-ethnic, international investigation, the objectives are to: 1) determine the risk of acute myocardial infarction (MI) among patients with MS defined using existing criteria; 2) assess if

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the risk of MS on MI is greater than the risk conferred by the sum of individual component risk factors; 3) examine the impact on MI risk as more component risk factors are present, and the joint effects of these risk factors present in different combinations; 4) evaluate the risk conferred by risk factors with values below the threshold and the aggregation of subthreshold risk factors; and 5) examine whether the association of MS to MI varies across age, sex, and ethnic subgroups.

Methods

Participants. The INTERHEART study is a standardized case-control study of incident acute MI in 52 countries. Study participants consisted of 12,297 cases and 14,606 controls recruited from 262 centers in Asia, Europe, the Middle East, Africa, Australia, North America, and South America. Incident cases of acute MI presenting within 24 h of symptom onset were eligible. At least 1 age-matched (as much as 5 years older or younger) and sex-matched control was recruited per case. Criteria for selection of study subjects have been described in detail previously (Online Appendix 1) (9).

Procedures. Structured questionnaires were administered, and physical examinations and blood samples were undertaken in the same manner in cases and controls. All data were transferred to the Population Health Research Institute, McMaster University and Hamilton Health Sciences, Canada, where quality-control checks and statistical analyses were conducted. Information about risk factors including hypertension and diabetes mellitus, physical measurements including waist and hip circumference, blood pressure, and body weight, and laboratory assessment of apolipoprotein (Apo) B and ApoA1 and hemoglobin (Hb) A1C was obtained using a standardized protocol and laboratory measurement. Waist and hip circumferences were measured with a nonstretchable standard tape measure. Waist measurements were obtained over the unclothed abdomen at the narrowest point between the costal margin and iliac crest, and hip circumferences over light clothing at the level of the widest diameter around the buttocks. Weight, height, and waist and hip measures were missing in 1.28%, 1.35%, and 3.5% of subjects, respectively. Hypertension was assessed using information on self-reported history and/or use of antihypertensive medication (10).

LABORATORY MEASURES. Blood samples were available in 21,508 (79%) of 27,098 cases and controls. Nonfasting blood samples (20 ml) were drawn from every subject and centrifuged within 2 h of admission, separated into 6 equal volumes, and frozen immediately at −20°C or −70°C after processing. Centers were instructed to draw blood from cases within 24 h of symptom onset, although 21% of these samples were obtained after 24 h because of delays in patient presentation. Samples were shipped in nitrogen vapor tanks by courier from every site to a blood storage site, where they were stored at −160°C in liquid nitrogen (Hamilton, Ontario) or at −70°C (India and China). Blood samples from all countries other than China were analyzed in Hamilton for total cholesterol, high-density lipoprotein (HDL) cholesterol, ApoB, ApoA1, and HbA1c. HDL is an established risk factor for coronary artery disease, and recent reports have suggested that ApoB and ApoA1 are superior to traditional lipid measures for coronary heart disease risk prediction (11,12). The HbA1c measures were used to help identify nondiabetic patients with probable hyperglycemia and are a strong indicator of type 2 diabetes (receiver-operating characteristic area under the curve = 0.86) (13). As there is currently no universal demarcation point to define high HbA1c values, we used a cutoff point of ≥6.5% which corresponds to the 90th percentile in nondiabetic subjects and median value among subjects with diabetes.

Abbreviations and Acronyms

Apo = apolipoprotein
CI = confidence interval
Hb = hemoglobin
HDL = high-density lipoprotein
IDF = International Diabetes Federation
MI = myocardial infarction
MS = metabolic syndrome
OR = odds ratio
PAR = population attributable risk
WHO = World Health Organization

The methods for analyses have been reported previously (9) and are summarized in Online Appendix 2. A total of 26,903 subjects, 12,297 cases and 14,606 controls, was available for this analysis, and among these subjects, 6,905 cases and 9,109 controls had both HbA1c and HDL cholesterol measurements. The INTERHEART study was approved by appropriate regulatory and ethics committees in all participating countries and centers (9).

MS DEFINITIONS. The MS was evaluated using 2 definitions, as summarized in Table 1. Both definitions were based on the same component risk factors: 1) self-reported diabetes mellitus or HbA1c ≥6.5%; 2) self-reported hypertension or use of a prescribed antihypertensive medication; 3) abdominal obesity as measured by the ratio of the waist and hip circumference (World Health Organization [WHO]) and waist circumference (International Diabetes Federation [IDF]); and 4) abnormal lipid concentrations determined from serum HDL cholesterol measures. The WHO definition consisted of diabetes/hyperglycemia combined with any 2 other component factors, whereas the IDF definition was composed of abdominal obesity using ethnic-specific cutoffs plus any 2 other factors (Table 1).

Statistical analyses. Simple associations were assessed using frequency tables and Pearson's chi-square tests for 2 independent proportions. Prevalence rates across distinct subgroups (e.g., by region, country, ethnicity) were adjusted for age using the direct standardization approach (14).

The findings presented are for models fit with unconditional logistic regression, adjusted for the matching criteria (age and sex), geographic region, and potential confounders. Unmatched analyses were used because perfect matching was not possible for 14% (1,763 of 12,461) of MI cases and 5% (738 of 14,637) of controls. Performing a strict matched

JACC Vol. 55, No. 21, 2010
May 25, 2010:2390–8

Table 1 2 Definitions of Metabolic Syndrome Used in This Study

Criteria	WHO Definition	IDF Definition
1. Diabetes mellitus	History of diabetes or HbA1c ≥6.5%	History of diabetes or HbA1c ≥6.5%
2. Hypertension	History of treated/untreated hypertension	History of treated/untreated hypertension
3. Abdominal obesity	Males WHR ≥0.90; females WHR ≥0.85	Europeans, sub-Saharan Africans, and Eastern Mediterranean and Arabs: Males WC ≥94 cm; Females WC ≥80 cm South Asians, Chinese, and South and Central Americans: Males WC ≥90 cm; Females WC ≥80 cm Japanese: Males WC ≥90 cm; Females WC ≥80 cm
4. Abnormal lipid profile	Males HDL-C <0.90 mmol/l or taking fibrate/niacin; Females HDL-C <1.03 mmol/l or taking fibrate/niacin	Males HDL-C <1.03 mmol/l or taking fibrate/niacin; Females HDL-C <1.29 mmol/l or taking fibrate/niacin
Total Metabolic syndrome	Diabetes mellitus + 2 or 3 other factors	Abdominal obesity + 2 or 3 other factors

HbA1c = glycated hemoglobin; HDL-C = high-density lipoprotein cholesterol; IDF = International Diabetes Federation; WC = waist circumference; WHO = World Health Organization; WHR = waist to hip ratio.

analysis would lead to a significant loss of information, because missing data on a risk factor in a case or control would result in the exclusion of the case-control pair from all analyses. Therefore, we widened the age-matching criteria, as well as employed frequency matching of cases and controls, utilizing age and sex strata. In addition, the parameter estimates among the many different methods (conditional logistic regression, mixed models, and unconditional logistic regression) were within 5% of each other, with a slight attenuation of effect estimates in the unconditional models compared with the conditional models. Hence, findings presented may be interpreted as providing a slight underestimation of effect sizes for most comparisons.

Statistical analyses and graphics were produced using the SAS system version 9.1 (SAS, Cary, North Carolina). All statistical tests of hypotheses are 2-sided. Population attributable risks (PARs) and 95% confidence intervals (CIs) were calculated for various risk factors in the study, adjusting for confounders in a similar fashion to the corresponding logistic regression models for odds ratio (OR) estimates. All ORs of MS on MI are adjusted for by age, sex, smoking, and region where indicated. The effect on MI by MS was compared with the effect of its component risk factors considered singly and in combination. The effect on MI when 2, 3, and all 4 MS factors occur was assessed to help identify individual factors that strengthened or weakened associations between MS and MI. For these analyses of combined risk factors, the component factors were defined using the previously defined INTERHEART study cutoff points for abdominal obesity (upper tertile of waist-to-hip ratio: ≥0.90 in men and ≥0.83 in women) (15) and elevated ApoB/ApoA1 ratio (1 SD above the sex-specific log-transformed mean value in control subjects: ≥1.054 in men and ≥0.957 in women after retransformation back to the original scale) (11). Lastly, the MI risk conferred by risk factors with values above and slightly below the pre-defined threshold was evaluated, with "normal" values as the reference group. The effect on MI when 3 or more subthreshold risk factors were present was assessed. The range of values used to define subthreshold risk are presented in Online Appendix 3. Likelihood ratio tests were used to compare OR values for component risk factors across study groups (e.g., age, sex, ethnicity, and region) and to test for interactions of these risk factors considered in combination. The adjusted ORs were presented as forest plots, with corresponding PAR values indicated.

Results

MS factors. The proportion of MS component factors varies significantly between MI cases and controls (Table 2). For both definitions of MS, the majority of cases and controls have at least 1 MS-related factor, but cases are more likely to have ≥3 MS-related factors ($p < 0.0001$). Using the WHO definition of MS, the presence of each component factor (diabetes, hypertension, abdominal obesity, and low HDL cholesterol) is more common in cases compared with controls ($p < 0.0001$ for each factor). Similar differences are observed for the IDF-defined risk factors. Subjects who had MS were older (59.5 years vs. 56.9 years, $p < 0.0001$), less likely to be smokers (28.4% vs. 36.0%, $p < 0.0001$), less likely to exercise (11.3% vs. 17.8%, $p < 0.0001$), and proportionately more were women (32.5 vs. 22.7, $p < 0.0001$), compared with subjects who did not have MS.

Using the WHO definition of MS, the age- and obesity-adjusted prevalence of MS among MI cases is 22.1% (95% CI: 21.1% to 23.1%), and among controls it is 10.1% (95% CI: 9.5% to 10.7%; $p < 0.0001$). Using the IDF definition, the age- and obesity-adjusted prevalence of MS among MI cases is 28.1% (95% CI: 27.0% to 29.2%), and among controls it is 17.2% (95% CI: 16.4% to 18.0%; $p < 0.0001$). Using either definition, the unadjusted (and age- and obesity-adjusted) prevalence of MS among MI cases was significantly higher among women (32.1%, 95% CI: 29.9% to 34.4% [29.5%, 95% CI: 27.3% to 31.7%]) compared with men (19.5%, 95% CI: 18.4% to 20.6% [19.6%, 95% CI:

Table 2 Prevalence of Metabolic Syndrome Components in Controls and Cases, Overall and by Sex

Metabolic Syndrome Factors	Overall			Women			Men		
	Controls	Cases	p Value	Controls	Cases	p Value	Controls	Cases	p Value
WHO and IDF definitions									
Diabetes or HbA1c ≥6.5%	1,843 (19.6)	3,045 (39.7)	<0.0001	538 (23.6)	973 (51.1)	<0.0001	1,305 (18.3)	2,072 (36.0)	<0.0001
Hypertension	3,058 (23.4)	5,384 (43.9)	<0.0001	977 (31.1)	1,729 (58.8)	<0.0001	2,081 (20.9)	3,655 (39.2)	<0.0001
WHO definition									
Abdominal obesity	8,318 (63.7)	7,973 (73.0)	<0.0001	1,837 (58.5)	1,825 (70.4)	<0.0001	6,481 (65.3)	6,148 (73.8)	<0.0001
Low HDL-C	4,953 (40.9)	4,470 (46.9)	<0.0001	1,157 (39.4)	1,144 (49.9)	<0.0001	3,796 (41.4)	3,326 (45.9)	<0.0001
Metabolic syndrome	908 (10.0)	1,555 (22.5)	<0.0001	267 (12.1)	533 (32.1)	<0.0001	641 (9.3)	1,022 (19.5)	<0.0001
IDF definition									
Abdominal obesity	6,191 (47.4)	5,744 (52.6)	<0.0001	2,078 (66.2)	1,848 (71.3)	<0.0001	4,113 (41.2)	3,896 (46.8)	<0.0001
Low HDL-C	7,250 (59.9)	6,251 (65.5)	<0.0001	1,889 (64.3)	1,696 (73.9)	<0.0001	5,361 (58.5)	4,555 (62.8)	<0.0001
Metabolic syndrome	1,526 (16.8)	2,008 (29.1)	<0.0001	605 (27.3)	812 (49.0)	<0.0001	921 (13.4)	1,196 (22.8)	<0.0001

Abbreviations as in Table 1.

18.5% to 20.7%]). The age- and obesity-adjusted prevalence of MS in MI cases was significantly higher in South Asians (29.8%, 95% CI: 27.1% to 32.5%), other Asians (28.7%, 95% CI: 24.6% to 32.8%), Arabs (25.4%, 95% CI: 22.7% to 28.1%), Black Africans (33.6%, 95% CI: 24.0% to 47.6%), and Colored Africans (24.6%, 95% CI: 18.9% to 30.3%) compared with Europeans (14.7%, 95% CI: 12.8% to 16.6%), Chinese (20.9%, 95% CI: 19.1% to 22.7%), and Latin Americans (18.9%, 95% CI: 16.0% to 21.8%).

MS and component risk factors. The MS defined by WHO is a risk state for MI (OR: 2.69, 95% CI: 2.45 to 2.95) and the PAR of MS_{WHO} associated with MI is 14.5% (95% CI: 12.7% to 16.3%) (Fig. 1A). Using the IDF definition, MS is also a significant risk state for MI (OR: 2.20, 95% CI: 2.03 to 2.38), and the PAR of MS associated with MI is 16.8% (95% CI: 14.8% to 18.8%) (Fig. 1B).

As shown in Figure 1A, the risk of MI conferred by MS is significantly higher than that of low HDL cholesterol ($p < 0.0001$) or abdominal obesity ($p < 0.0001$) evaluated singly, but virtually the same as the risk conferred by diabetes or hypertension alone. A similar pattern of results is observed when using WHO or IDF criteria to define MS (Fig. 1B).

Figure 2 shows the association of MI with different combinations of risk factors. The presence of additional risk factors is associated with an incremental increase in risk of MI. Diabetes combined with hypertension (OR: 3.59, 95% CI: 3.25 to 3.97) is associated with a risk of MI comparable to having all 4 MS risk factors (OR: 3.76, 95% CI: 3.00 to 4.72). Abdominal obesity and high ApoB/ApoA1 ratio jointly are associated with a significantly lower risk of MI (OR: 2.12, 95% CI: 1.96 to 2.29) compared with having diabetes or hypertension, although considering people in the top and bottom quintiles of ApoB/ApoA1 ratio (men: ≥1.06 and <0.62; women: ≥0.98 and <0.56) plus abdominal obesity confers a higher risk of MI (OR: 2.77, 95% CI: 2.52 to 3.06).

Figure 3A presents the association of MI with risk factor components as defined using cutoff values at or just below the thresholds indicated in Table 1. The clustering of ≥3 subthreshold risk factors is associated with a significantly greater risk of MI (OR: 1.50, 95% CI: 1.24 to 1.81; $p < 0.001$) compared with having component factors with "normal" values, but lower than the risk conferred by an aggregation of risk factors with values above the threshold points (OR: 2.73, 95% CI: 2.49 to 3.00; $p < 0.001$). For diabetes and abdominal obesity, the MI risk increased incrementally with higher values ($p < 0.001$). Similar results are observed when using the WHO and IDF criteria to define MS (Fig. 3B). The PAR of MS associated with MI is <5% for most risk factors just below the threshold cutoff points and for the clustering of these factors (PAR = 1.3, 95% CI: 0.6 to 2.1) (Figs. 3A and B).

Age and sex variation in MS and MI. As shown in Figure 4A, using the WHO definition, the OR of MS is significantly higher in women compared with men (OR: 3.53, 95% CI: 2.97 to 4.18 vs. OR: 2.37, 95% CI: 2.13 to 2.65; $p < 0.05$). By age groups, the association between MS and MI is stronger among younger compared with older subjects (OR: 3.23, 95% CI: 2.80 to 3.72 vs. OR: 2.35, 95% CI: 2.08 to 2.66, $p < 0.05$) (Fig. 4A). Likelihood ratio tests show significant heterogeneity by sex ($p < 0.0001$) and age ($p = 0.002$). The OR is significantly greater in younger women than in younger men (OR: 4.61, 95% CI: 3.61 to 5.90 vs. OR: 2.66, 95% CI: 2.24 to 3.16, $p = 0.001$), but not in older women compared with older men (OR: 2.81, 95% CI: 2.21 to 3.59 vs. OR: 2.19, 95% CI: 1.90 to 2.53) (Fig. 4A). Similar results are observed when using the IDF definition to classify MS (Fig. 4B).

Regional and ethnic variation in MS and MI. The association of MS to MI across geographic regions and ethnic groups is shown in Online Appendixes 4 and 5, respectively. The associations of MS to MI are directionally similar across all groups. Using the WHO definition, a significantly stronger MS-MI association occurs among people living in Southeast Asia, specifically Thailand, Philippines, Singapore, and Japan (OR: 4.51, 95% CI: 3.34 to

JACC Vol. 55, No. 21, 2010
May 25, 2010:2390–8

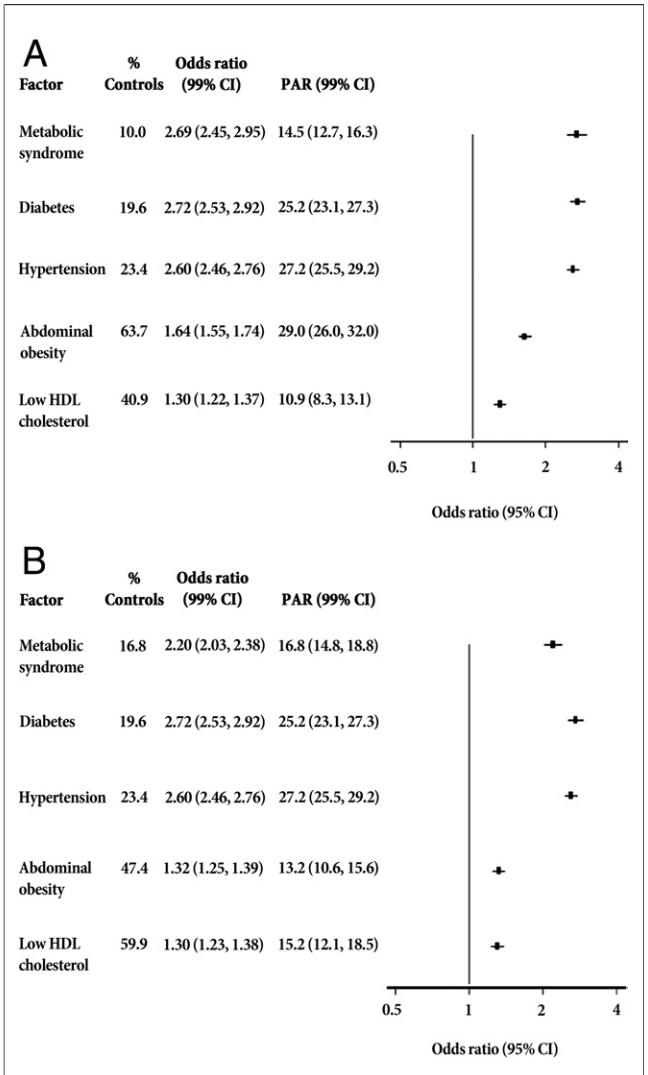

Figure 1 **Odds Ratio and PAR of MI Associated With MS Using WHO and IDF Definitions**

Odds ratio (adjusted for age, sex, region, and smoking status) and population attributable risk (PAR) of myocardial infarction (MI) associated with metabolic syndrome (MS) using the **(A)** World Health Organization (WHO) definitions and the **(B)** International Diabetes Federation (IDF) definitions, by MS component factors. See Table 1 for criterion definitions. CI = confidence interval; HDL = high-density lipoprotein.

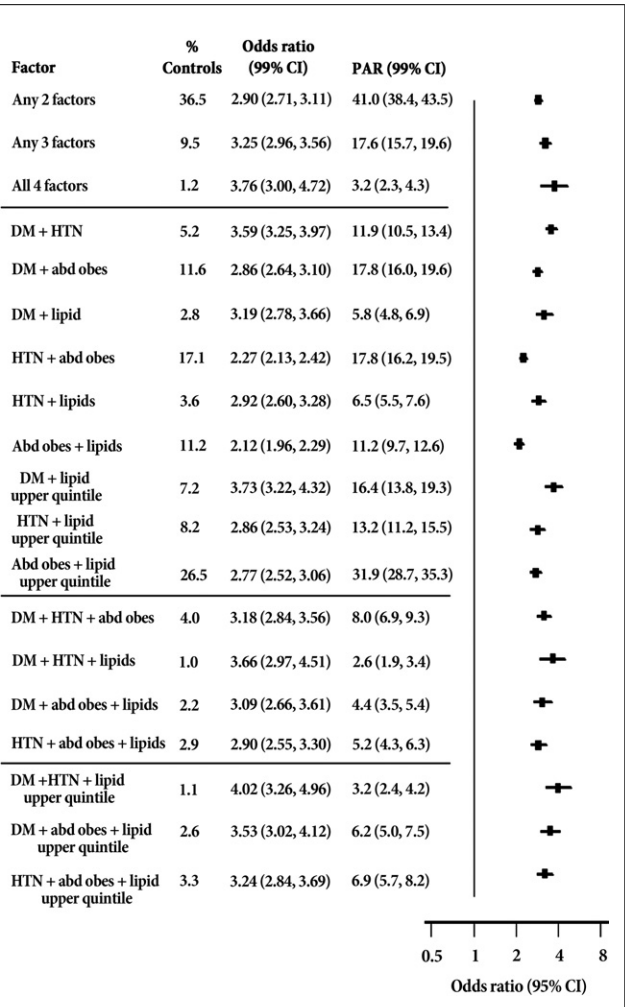

Figure 2 **Odds Ratio and PAR of MI Associated With MS, by INTERHEART Data**

Odds ratio (adjusted for age, sex, region, and smoking status) and PAR of MI associated with MS defined from INTERHEART study data, by MS component factors in combination. The component factors were defined using the previously defined INTERHEART study cutoff points for abdominal obesity (upper tertile of waist-to-hip ratio: ≥0.90 in men and ≥0.83 in women) (15) and elevated apolipoprotein (Apo) B/ApoA1 ratio (1 SD above the sex-specific log-transformed mean value in control subjects: ≥1.054 in men and ≥0.957 in women, after retransformation back to the original scale) (11). Additional analyses assessed the top versus bottom quintiles of ApoB/ApoA1 ratio (men: ≥1.060 and <0.620; women: ≥0.978 and <0.563). Abd Obes = high waist-to-hip ratio; DM = diabetes mellitus; HTN = hypertension; lipids = elevated ApoB/ApoA1 ratio (based on 1 SD above the log-transformed mean value in controls); lipid upper quintile = elevated ApoB/ApoA1 ratio (based on top vs. bottom quintiles of ApoB/ApoA1 ratio); other abbreviations as in Figure 1.

6.08) (Online Appendix 4A), and among subjects classified as "other Asian," comprising people of Thai, Filipino, and Japanese origin (OR: 5.10, 95% CI: 3.61 to 7.19) (Online Appendix 5A), compared with most other regional or ethnic subgroups. The associations for several regions including South Asia, the Middle East, Africa, and China are not significantly different from those of other regions. Overall, similar findings are observed when using the IDF criteria (Online Appendixes 4B and 5B).

Discussion

The INTERHEART study is the first large-scale, multiethnic, international investigation showing that the MS is a significant risk factor for acute MI. The presence of diabetes or HbA1c ≥6.5% combined with 2 or more MS related factors is predictive of MI among men and women, young and old, across all geographic regions and ethnic groups. Additionally, the presence of MS confers a similar risk of MI compared with diabetes or hypertension alone, yet stronger effects than other component factors including abdominal obesity and low HDL cholesterol. Furthermore, the PAR of MS on MI is substantially lower than the PAR

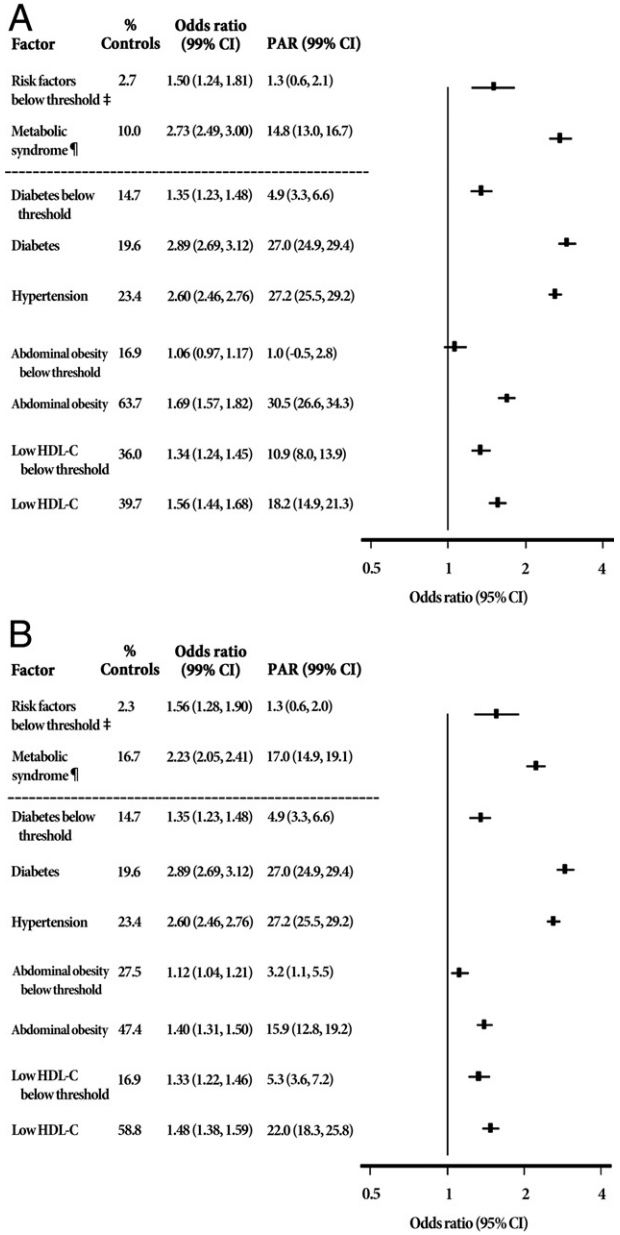

Figure 3 **Odds Ratio and PAR of MI Associated With MS, by MS Component Factors**

Odds ratio (adjusted for age, sex, region, and smoking status) and PAR of MI associated with MS using the **(A)** WHO definitions and the **(B)** IDF definitions, by MS component factors, both at and just below the threshold cutoff values. The range of values used to define subthreshold risk of MI for each MS risk factor is shown in Online Appendix 3. †MI risk conferred by the presence of ≥3 subthreshold risk factors compared with having <3 subthreshold risk factors or "normal" values. ¶MI risk conferred by the presence of ≥3 superthreshold risk factors compared with having <3 superthreshold risk factors or "normal" values. Abbreviations as in Figure 1.

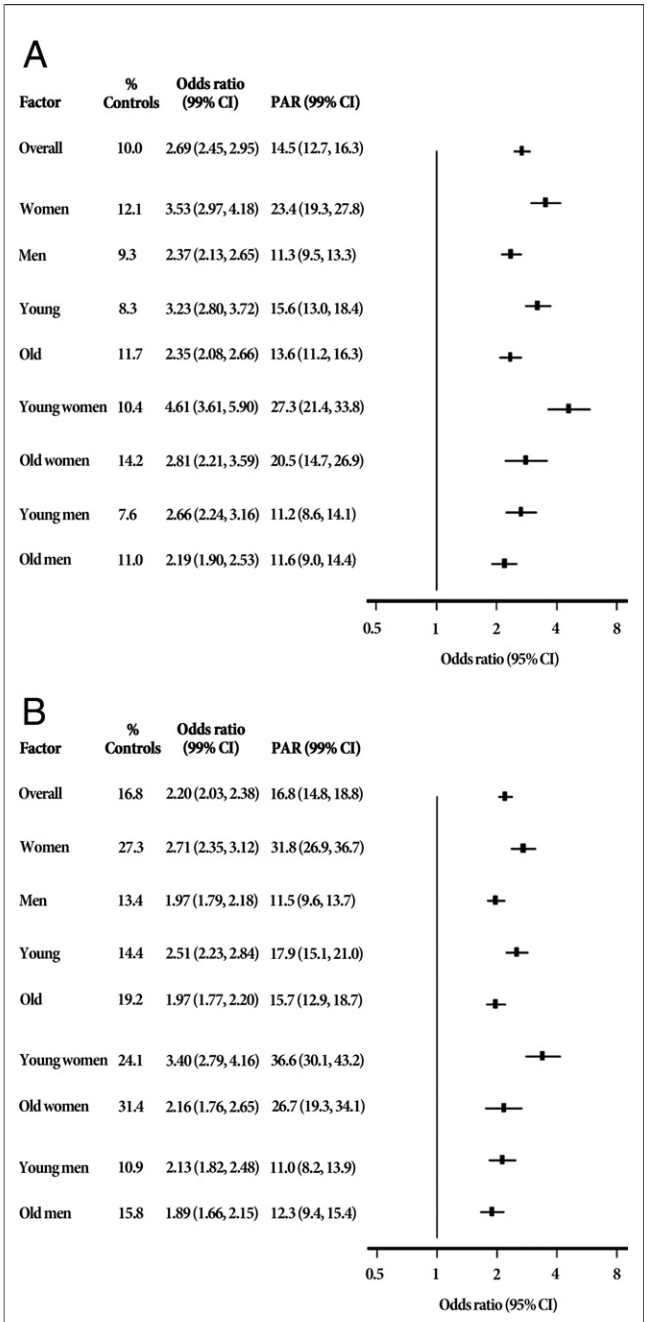

Figure 4 **Odds Ratio and PAR of MI Associated With MS, by Age and Sex**

Odds ratio (adjusted for age, sex, region, and smoking status) and PAR of MI associated with MS using the **(A)** WHO definitions and the **(B)** IDF definitions, by age and sex subgroups. The demarcation point for classifying young subjects was age ≤65 years for women and age ≤55 years for men (9). Abbreviations as in Figure 1.

of several component factors considered separately depending on the definition used, suggesting that MS accounts for a smaller number of MI cases in a population compared with several of its constituent components. Our findings suggest that the risk associated with MS is not greater than the sum of its component factors.

The MS refers to a cluster of risk factors which when present together is believed to confer an increased risk of cardiovascular disease (1,2). Subjects with MS have a higher cardiovascular disease risk than do subjects without the

syndrome (3–5). Using the INTERHEART study data, we have demonstrated that using either the WHO or IDF definition, the presence of MS is associated with >2.5-fold increase in the risk of acute MI. Cabre et al. (16) recently reported similar findings for cardiovascular disease using these definitions. However, the risk of MI when 3 MS factors are present does not appear to be greater than the risk conferred by some of its component parts, namely, diabetes and hypertension. Others have also reported that individual component factors and MS are associated with a similar degree of coronary heart disease risk (17,18). Thus, while it may be clinically feasible to make a diagnosis of "metabolic syndrome," the MS classification appears to serve only as a simple description of multiple risk factors for cardiovascular disease that are commonly identified together, and not a syndrome associated with a cardiovascular risk that is greater than the sum of its parts.

MS has been fraught with definitional problems, including variation in the component factors used and differences in risk factor thresholds (7,8). In our analysis, the use of 2 different syndrome definitions (WHO and IDF) yielded a similar pattern of results relating MI to MS and its component factors, which is consistent with the premise that different definitions of MS have similar predictability in relation to coronary risk (19). There is also considerable evidence of a dose-response relationship between MI and risk factor measures including MS component factors (20). However, to our knowledge, previous studies have yet to report an incremental increase in MI risk as risk factors less than threshold values cluster together (21–23). In our analysis, an aggregation of risk factors with values below their threshold was associated with a significantly greater risk of MI, compared with having component factors with normal values, but lower than the risk conferred by an aggregation of risk factors with values above the threshold points. These findings of a dose-response relationship between risk factor severity and MI risk suggest that a standard definition of MS loses information when continuous variables are converted to categorical variables and provide support for calls to replace the categorical definition of MS with a scoring system (24) that may involve each risk factor being assigned a weight based on its level and a regression formula developed to estimate risk.

The finding that MI risk increases as more component factors are present is consistent with previous observations showing the presence of more risk factors is associated with an incremental increase in subclinical atherosclerosis and (25) incident coronary heart disease (19,26,27). There is substantial evidence showing that diabetes combined with hypertension confers a particularly dangerous MI risk (28), which is in keeping with our observation that the joint effect of diabetes and hypertension on MI is similar to that of having all 4 MS component factors. Both conditions are common and frequently coexist (29), as ~40% to 60% of subjects with type 2 diabetes have hypertension (30). Moreover, a substantial proportion of people with diabetes and hypertension have abdominal obesity (31), which we also observed (77%). In addition, our finding that MI risk increases incrementally as more component factors are present suggests that a dichotomous definition of MS based on ≥3 risk factors is too simplistic and may fail to identify high-risk subjects who have only 1 or 2 risk factors. Moreover, this definition of MS leads to a substantially lower prevalence of MS than its component factors. This partly explains our observation that the PAR of MS is lower than the PAR of several component factors, and indicates that MS accounts for a smaller number of MI cases in a population compared with several of its constituent components. This finding highlights an important limitation associated with MS diagnosis.

Our finding that the syndrome conveys information that is no greater than an assessment of diabetes comprised by self-report and blood HbA1c measures may have important clinical implications. Most subjects with diabetes have MS, as prevalence estimates in the U.S. are in the range of 60% to 70% (32), and HbA1c (33) and blood glucose (34) are independent predictors of intimal-medial thickness. In middle-aged Austrian women, blood glucose was the strongest MS-component related to intimal-medial thickness (34). Biochemical markers of glucose homeostasis are usually routinely available in a clinical setting, and questionnaires to assess cardiovascular risk factors including diabetes may be administered readily. Screening patients for diabetes may provide a more practical and cost efficient approach to assessing MI risk compared with a more involved examination to diagnose MS.

The INTERHEART study is the first large study which clearly shows that the association between the MS and MI is qualitatively similar (although some quantitative differences exist) across sex, region, and ethnic groups. The PAR of MS on MI, which is a function of the OR and the prevalence of the MS in the controls, is higher among women and among Southeast Asians, and is significantly lower among the Chinese compared with most other ethnic subgroups. These findings are concordant with previous observations showing higher prevalence rates of MS component factors in Southeast Asians (9,35). The PAR values for other groups including South Asians, Arabs, and Africans were not significantly different from other groups, despite previous evidence that these groups have higher rates of diabetes or low HDL cholesterol (9,35,36), and more abdominal obesity (9,37). Unlike previous studies, however, the aim of our study was to evaluate the PAR of MS on MI within ethnic subgroups, rather than making between-group comparisons. Lastly, the risk of MI is not significantly associated with MS among North Americans, a finding that has been reported previously (38,39). However, our subanalyses by ethnicity show that MS is consistently associated with MI, which suggests that the null association in North America likely reflects the heterogeneity of the subjects recruited from Canada and the U.S.

We observed that women, particularly young women with MS, have a significantly higher risk of MI and PAR values compared with younger and older men. This finding is consistent with that of previous studies showing that young women with risk factors have an increased relative risk of MI compared with men (albeit a lower absolute risk of having coronary heart disease) (9,40), and supports the premise that risk factors such as diabetes or hypertension should be treated aggressively in younger women when they are detected (41). Whether our finding represents a real difference in the propensity to develop MI when MS is present between women and men or reflects selection differences in cases and controls is unclear.

Study limitations. Some limitations, including selection of and ascertainment of risk factors among cases and controls in the INTERHEART study, have been previously reported in detail (9). In addition, in this analysis we may have underestimated the prevalence of MS, its strength of association with MI, and its PAR, since we relied on self-reported measures of diabetes (without conducting formal oral glucose tolerance tests or fasting glucose assessment) and hypertension (we obtained blood pressure measures in both cases and controls, but the values could be systematically affected by the acute MI and treatment in cases). However, we supplemented the diabetes information with measurements of blood HbA1c to help identify nondiabetic subjects with probable hyperglycemia (13), and data on usage of antihypertensive medication to improve the accuracy of reported risk factors components (10). Moreover, our analysis showed that the prevalence of MS in North American controls (15%) was comparable to the prevalence reported previously in adults residing in the U.S. (~22%) (42). When we repeated the analyses using IDF criteria, the results were similar to those of the WHO definition of MS, which provides further assurance as to the reliability of our findings. The use of frequency matching of cases and controls was not optimal. However, our approach produced virtually the same results or a slight attenuation of the effect estimates compared with conditional logistic regression and mixed models, which suggests that our findings likely provide a slight underestimation of the effect sizes. Because data on blood triglycerides are not available and case subjects and most control subjects were not fasting, triglycerides are not included in the definitions of MS. However, we have incorporated HDL criteria into our definitions of MS. Furthermore, associations between triglycerides and MI are reported to be weaker than the effects of hypertension or diabetes (43), and thus, their absence is unlikely to alter the key findings. Lastly, other definitions of MS exist that also include novel variables, such as prothrombotic or proinflammatory indices, which were not evaluated in this study. The strengths of our analysis included our use of a standardized protocol among large numbers of people including substantial numbers of women and men from multiple ethnic groups sampled across a wide age range.

Conclusions

MS is a risk state for acute MI in women and men, from all regions and ethnic groups worldwide. The risk of MI associated with MS does not appear to be greater than the risk conferred by its component factors. The use of dichotomous risk factors may underestimate risk among persons with subthreshold values and further limit the usefulness of MS classification to predict MI risk.

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Key Words: myocardial infarction ■ metabolic syndrome ■ diabetes mellitus ■ ethnicity ■ epidemiology.

APPENDIX

For an expanded discussion of the INTERHEART study, please see the online version of this article.