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The Metabolic Syndrome and Cardiovascular Risk

A Systematic Review and Meta-Analysis

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Objectives We sought to conduct a systematic review and meta-analysis of the cardiovascular risk associated with the metabolic syndrome as defined by the 2001 National Cholesterol Education Program (NCEP) and 2004 revised National Cholesterol Education Program (rNCEP) definitions.

Background Numerous studies have investigated the cardiovascular risk associated with the NCEP and rNCEP definitions of the metabolic syndrome. There is debate regarding the prognostic significance of the metabolic syndrome for cardiovascular outcomes.

Methods We searched the Cochrane Library, EMBASE, and Medline databases through June 2009 for prospective observational studies investigating the cardiovascular effects of the metabolic syndrome. Two reviewers extracted data, which were aggregated using random-effects models.

Results We identified 87 studies, which included 951,083 patients (NCEP: 63 studies, 497,651 patients; rNCEP: 33 studies, 453,432 patients). There was little variation between the cardiovascular risk associated with NCEP and rNCEP definitions. When both definitions were pooled, the metabolic syndrome was associated with an increased risk of cardiovascular disease (CVD) (relative risk [RR]: 2.35; 95% confidence interval [CI]: 2.02 to 2.73), CVD mortality (RR: 2.40; 95% CI: 1.87 to 3.08), all-cause mortality (RR: 1.58; 95% CI: 1.39 to 1.78), myocardial infarction (RR: 1.99; 95% CI: 1.61 to 2.46), and stroke (RR: 2.27; 95% CI: 1.80 to 2.85). Patients with the metabolic syndrome, but without diabetes, maintained a high cardiovascular risk.

Conclusions The metabolic syndrome is associated with a 2-fold increase in cardiovascular outcomes and a 1.5-fold increase in all-cause mortality. Studies are needed to investigate whether or not the prognostic significance of the metabolic syndrome exceeds the risk associated with the sum of its individual components. Furthermore, studies are needed to elucidate the mechanisms by which the metabolic syndrome increases cardiovascular risk. (J Am Coll Cardiol 2010;56:1113–32) © 2010 by the American College of Cardiology Foundation

The metabolic syndrome affects approximately one-quarter of North Americans and has become a leading health concern due to its link to cardiovascular disease (1). Ever since the metabolic syndrome was described by Reaven in 1988 (2), a number of definitions have been published by organizations including the National Cholesterol Education Program (NCEP) (3), the International Diabetes Federation (4), and the World Health Organization (5), among others. Of these, the 2001 Third Report of the NCEP's Adult Treatment Panel has emerged as the most widely used definition, primarily because it provides a relatively simple approach for diagnosing the metabolic syndrome by

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Abbreviations and Acronyms

BMI = body mass index
CI = confidence interval
CVD = cardiovascular disease
HDL = high-density lipoprotein
HR = hazard ratio
LDL = low-density lipoprotein
MI = myocardial infarction
NCEP = National Cholesterol Education Program
rNCEP = revised National Cholesterol Education Program
RR = relative risk

employing easily measurable risk factors (3,6). Specifically, the NCEP defines the metabolic syndrome as having 3 or more of the following 5 cardiovascular risk factors: 1) central obesity (waist circumference: men >102 cm; women >88 cm); 2) elevated triglycerides (≥150 mg/dl); 3) diminished high-density lipoprotein (HDL) cholesterol (men <40 mg/dl; women <50 mg/dl); 4) systemic hypertension (≥130/≥85 mm Hg); and 5) elevated fasting glucose (≥110 mg/dl). In 2004, this NCEP definition was revised (rNCEP) by lowering the threshold for fasting glucose to ≥100 mg/dl in concordance with American Diabetes Association criteria for impaired fasting glucose (7). Also, thresholds for central obesity were lowered from strictly >102 cm in men and 88 cm in women to greater than or equal to these values. Finally, the rNCEP definition includes patients being treated for dyslipidemia, hyperglycemia, or systemic hypertension.

The value of the metabolic syndrome as a predictor of cardiovascular risk has been met with much debate. In 2005, the American Diabetes Association and the European Association for the Study of Diabetes issued a joint statement summarizing the issues surrounding the metabolic syndrome (8). In this statement, they underscore the need to identify the cardiovascular risk associated with the metabolic syndrome. A large number of observational studies have been carried out to investigate this risk, and there is a need to synthesize the results of these studies. Two previous meta-analyses investigating the metabolic syndrome only included studies published prior to 2005 and did not investigate the rNCEP definition (9,10). Since then, 71 studies have been published that used the NCEP and rNCEP definitions to investigate the cardiovascular effects of the metabolic syndrome. Thus, our objective was to carry out a systematic review and meta-analysis to estimate the cardiovascular risk associated with the metabolic syndrome according to the NCEP and rNCEP definitions in the general population and the subpopulations of men, women, and patients without type 2 diabetes mellitus.

Methods

Data sources and searches. We systematically searched the Cochrane Library, EMBASE, and Medline databases through June 2009 using the following key words: all-cause mortality, cardiovascular risk, cardiovascular disease, cardiovascular mortality, fatal myocardial infarction (MI), metabolic syndrome, National Cholesterol Education Program Adult Treatment Panel III, nonfatal MI, revised National Cholesterol Education Program Adult Treatment Panel III, stroke, and syndrome X. References from published prospective studies, relevant reviews, and previous meta-analyses were hand searched for additional studies not identified in the database search.

Study selection. Eligible studies: 1) were prospective, observational studies; 2) stratified patients based on the presence or absence of the metabolic syndrome using the NCEP or rNCEP definitions; 3) reported cardiovascular outcomes and/or all-cause mortality; 4) reported outcomes as count data, or as relative risk (RR) or hazard ratio (HR) with a corresponding measure of variance; and 5) were published in the English language. Studies investigating more than 1 cardiovascular outcome or more than 1 definition of the metabolic syndrome were also eligible for inclusion. Studies not meeting these criteria were excluded.

Data extraction. Two reviewers independently extracted data using standardized data extraction forms. Disagreements were resolved by consensus or, when necessary, by a third reviewer. Reviewers extracted information on study design, including the duration of follow-up, the setting, and the number of participants with and without the metabolic syndrome according to each definition. Extracted baseline participant characteristics included age, sex, mean blood pressure, body mass index (BMI), cholesterol, triglycerides, waist circumference, and the prevalence of cardiovascular disease (CVD), type 2 diabetes mellitus, systemic hypertension, obesity, and smoking. Reviewers extracted the following outcomes: all-cause mortality, CVD, CVD mortality, MI, and stroke. Outcomes data presented as count data, nonadjusted risk estimates (RR or HR) with corresponding measures of variance, or multivariable adjusted risk estimates were extracted for participants with and without the metabolic syndrome. The variables included in the multivariable models were also extracted. In addition, when available, outcomes were extracted for different subpopulations, which included men, women, and patients without type 2 diabetes mellitus.

Data synthesis and analysis. We synthesized the results of included studies using random-effects meta-analyses, and synthesized results are presented as RRs with corresponding 95% confidence intervals (CIs). Heterogeneity was assessed using I^2 statistics. We only conducted these meta-analyses for studies that reported outcomes as count data; studies that reported outcomes as risk estimates only (HR and RR) were excluded from these analyses. In the general population, we estimated the cardiovascular risk associated with the NCEP, modified NCEP, the rNCEP, and modified rNCEP definitions of the metabolic syndrome separately. The modified NCEP and modified rNCEP definitions typically used measurements of BMI (typically, BMI >30 kg/m^2 or BMI ranging from >25 to 27 kg/m^2 for Asian populations) instead of waist circumference to define central obesity.

We also assessed the cardiovascular risk when all definitions were pooled. With the pooled definitions, we determined the

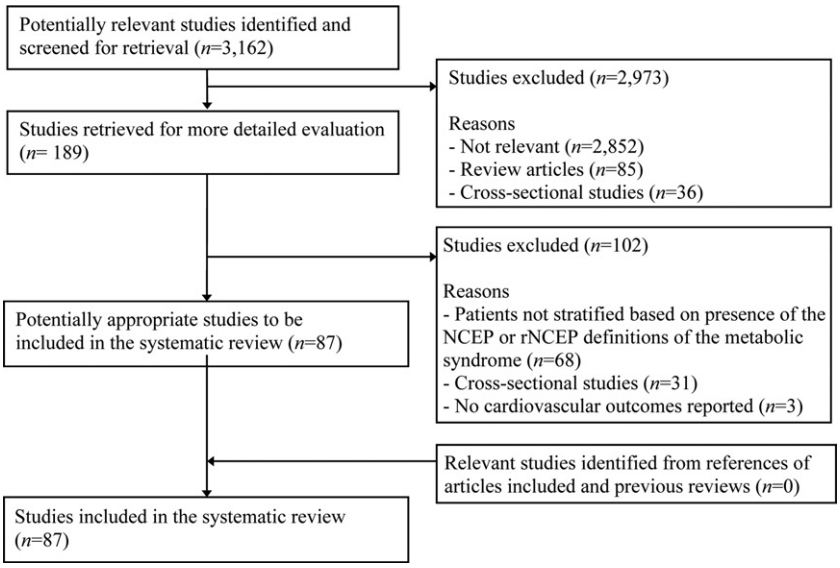

Figure 1 **Flow Diagram of Studies Included in the Systematic Review**

NCEP = National Cholesterol Education Program; rNCEP = revised National Cholesterol Education Program.

risk in the general population, in men, in women, and in patients without type 2 diabetes mellitus. Pooled analyses were conducted for the following 5 outcomes: 1) all-cause mortality; 2) CVD; 3) CVD mortality; 4) MI; and 5) stroke. For each outcome, a meta-analysis was performed to summarize the overall effects across all relevant studies.

We reported risk estimates (HR and RR) in tables as part of our systematic review. We classified nonadjusted risk estimates and risk estimates adjusting exclusively for age and/or sex as "least adjusted." In contrast, risk estimates adjusting for any cardiovascular risk factor (i.e., smoking status, low-density lipoprotein [LDL] cholesterol, and physical activity) were classified as "most adjusted." The length of follow-up varied considerably between studies. Therefore, we conducted a sensitivity analysis in which we stratified studies using the median length of follow-up. In addition, funnel plots were constructed and visually assessed for the possible presence of publication bias. All analyses were conducted using MIX software version 1.7 (11,12).

Results

Search results and study inclusion. A total of 3,162 potentially relevant studies were identified in our initial literature search (Fig. 1). After screening the abstracts of these studies, the full-length papers of 189 studies were retrieved and assessed for eligibility. Of the retrieved studies, a total of 87 met our inclusion criteria and were included in our systematic review (Tables 1 to 5). The remaining 102 studies were excluded either because they did not use the NCEP or rNCEP definitions of the metabolic syndrome to stratify patients (n = 68), they used a cross-sectional study design (n = 31), or they did not report any cardiovascular outcomes (n = 3). No additional studies were identified through our hand search of references from published studies, relevant reviews, and previous meta-analyses.

All included studies were published since 2002, had sample sizes ranging from 76 to 124,513 patients, and had follow-up durations ranging from 1.0 to 32.7 years (Online Tables 1 to 4). The prevalence of the metabolic syndrome in these studies ranged from 1% in a study of women without type 2 diabetes mellitus (13) and 78% in a study of patients with type 2 diabetes mellitus (14). There were also variations in the mean values for each of the 5 components of the metabolic syndrome: 1) BMI ranged from 22 to 33 kg/m^2; 2) fasting glucose ranged from 82 to 196 mg/dl; 3) HDL cholesterol ranged from 37 to 64 mg/dl; 4) triglycerides ranged from 88 to 199 mg/dl; and 5) systolic blood pressure ranged from 117 to 174 mm Hg. Many studies followed specific subpopulations, accounting for much of the variability. In particular, several studies reported outcomes for men (28 studies; n = 172,548), women (24 studies; n = 164,768), and participants without diabetes (17 studies; n = 172,367).

Of the 87 studies (n = 951,083) included in our systematic review, 43 reported all-cause mortality data (n = 536,864) (Table 1), 19 reported CVD (n = 116,202) (Table 2), 38 reported CVD mortality (n = 407,350) (Table 3), 12 reported MI (n = 29,470) (Table 4), and 26 reported stroke (n = 126,633) (Table 5). A total of 38 studies investigated the NCEP definition (n = 345,560) (Online Table 1), and 26 studies investigated the rNCEP definition (n = 433,808) (Online Table 2). In addition, 25 studies investigated the modified NCEP definition (n = 152,091) (Online Table 3), and 7 studies investigated the modified rNCEP definition (n = 19,624) (Online Table 4).

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Table 1 MetS Studies Reporting the Incidence of All-Cause Mortality

First Author, Year (Ref. #)*	Population	n	MetS (%)	Follow-Up (yrs)	Effect Measure	Risk of All-Cause Mortality† (95% CI)		All-Cause Mortality (%)	
						Least Adjusted	Most Adjusted	MetS Group	Non-MetS Group
NCEP definition‡									
Benetos et al., 2008 (33)	Pts without CVD	84,730	9.6	4.7§	HR	—	1.63 (1.38–1.93)	—	—
Butler et al., 2006 (14)	General population	3,035	38.5	6.0‖	RR	1.02 (0.85–1.22)	—	14.5	14.2
	Men	1,473	—	6.0‖	RR	—	—	15.9	19.0
	Women	1,562	—	6.0‖	RR	—	—	13.4	9.0
	Pts with T2DM	461	77.9	6.0‖	RR	0.71 (0.48–1.06)	—	18.1	25.5
	Pts without T2DM	2,562	31.6	6.0‖	RR	0.95 (0.76–1.17)	—	12.9	13.6
Dekker et al., 2005 (34)	Men	615	19.0	11.0‖	HR	1.98 (1.28–3.05)	—	—	—
	Women	749	25.8	11.0‖	HR	1.18 (0.72–1.94)	—	—	—
Guize et al., 2007 (35)	General population	60,754	10.3	3.6§	HR	—	1.79 (1.35–2.38)	—	—
Hillier et al., 2005 (36)	Elderly women with no T2DM	921	27.1	12.2§	HR	—	1.30 (1.00–1.70)	—	—
Hong et al., 2007 (37)	Pts with atherosclerosis	14,699	—	9.0§	RR	—	1.39 (1.22–1.58)	9.6	5.9
	Men with atherosclerosis	6,389	32.4	9.0§	RR	—	1.57 (1.31–1.89)	10.2	8.0
	Women with atherosclerosis	8,310	29.1	9.0§	RR	—	1.22 (1.02–1.47)	9.2	4.3
Hunt et al., 2004 (28)	General population	2,107	9.4	12.7§	HR	1.47 (1.13–1.92)	—	—	—
	Subjects with CVD	1,947	—	12.7§	HR	1.06 (0.71–1.58)	—	—	—
Katzmarzyk et al., 2005 (38)	Nonobese men	7,505	4.7	10.0§	RR	—	0.92 (0.53–1.60)	3.98	2.24
	Overweight men	9,048	19.8	10.2§	RR	—	—	3.52	2.21
	Obese men	2,620	61.1	10.2§	RR	—	—	3.44	2.45
Katzmarzyk et al., 2006 (39)	Men	20,789	19.7	11.0§	RR	1.46 (1.23–1.74)	1.36 (1.14–1.62)	4.5	2.7
Lakka et al., 2002 (40)	Middle-aged men	707	15.0	12.0¶	RR	1.67 (0.95–2.92)	1.67 (0.91–3.08)	—	—
Langenberg et al., 2006 (41)	General population	2,118	—	20.0‖	HR	—	1.43 (1.24–1.65)	71.5	58.8
	Men	977	16.9	20.0‖	HR	—	1.44 (1.18–1.76)	74.5	65.8
	Women	1,141	15.1	20.0‖	HR	—	1.46 (1.19–1.80)	68.6	53.0
Mancia et al., 2007 (42)	General population	2,013	16.2	12.3‖	HR	2.39 (1.79–3.18)	1.37 (1.02–1.84)	20.2	9.2
Marroquin et al., 2004 (43)	Women with CAD	147	42.2	3.5¶	HR	—	4.93 (1.02–23.76)	14.5	2.11
	Women without CAD	362	34.5	3.5¶	HR	—	1.41 (0.32–6.32)	3.2	3.5
	Women with T2DM without CAD	340	30.3	3.5¶	RR	2.20 (0.60–8.04)	—	7.8	3.5
Monami et al., 2008 (44)	Pts with T2DM	1,716	67.1	4.7§	HR	1.36 (1.10–1.69)	—	—	—
Pannier et al., 2008 (45)	Normotensive pts	34,577	4.5	4.7§	HR	—	1.09 (0.68–1.75)	—	—
	Hypertensive pts	26,447	17.7	4.7§	HR	—	1.40 (1.13–1.74)	—	—
Ramkumar et al., 2007 (46)	Pts with moderate CKD	710	48.9	9.0‖	HR	—	1.40 (1.01–1.94)	—	—
Sundstrom et al., 2006 (47)	70-year-old men	1,221	24.1	32.7‖	HR	1.58 (1.24–2.01)	1.26 (0.95–1.66)	—	—
Takeno et al., 2008 (48)	Pts with AMI	461	37.3	1.5¶	HR	—	1.27 (0.54–3.04)	—	—
Wang et al., 2007 (49)	Elderly without T2DM	1,025	42.7	13.5¶	HR	1.13 (0.93–1.37)	1.08 (0.89–1.31)	—	—
	Elderly men without T2DM	—	—	13.5¶	HR	—	1.08 (0.82–1.42)	—	—
	Elderly women without T2DM	—	—	13.5¶	HR	—	1.08 (0.83–1.40)	—	—
Wassink et al., 2008 (50)	Pts with CV risk factor	3,196	42.6	3.2¶	HR	1.45 (1.17–1.80)	1.43 (1.14–1.78)	—	—
Zambon et al., 2009 (51)	Elderly	2,910	39.0	4.4§	HR	1.30 (1.11–1.54)	—	—	—
	Elderly men	1,174	25.6	4.4§	HR	1.26 (0.99–1.60)	—	—	—
	Elderly women	1,736	48.1	4.4§	HR	1.33 (1.06–1.68)	—	—	—
Modified NCEP definition#									
Chen et al., 2006 (52)	Pts with renal disease and ACS	76	76.3	18.1§	RR	2.82 (0.72–11.09)	—	31.4	11.1
Feinberg et al., 2007 (53)	Pts with ACS, without T2DM	1,060	33.9	1.0‖	HR	—	1.96 (1.18–3.24)	8.9	4.6
Kasai et al., 2006 (54)	Pts who underwent PCI	748	42.5	12.0§	HR	—	1.34 (0.88–2.05)	13.5	10.5
Levantesi et al., 2005 (55)	Pts post-MI	8,245	37.0	3.5‖	RR	1.15 (0.99–1.33)	1.29 (1.10–1.51)	8.5	7.4
Malik et al., 2004 (56)	General population	4,576	37.1	13.3§	HR	—	1.40 (1.19–1.66)	—	—
	Subjects with T2DM	4,056	29.0	13.3§	HR	—	1.17 (0.96–1.42)	—	—
Nigam et al., 2006 (57)	General population	24,358	13.5	12.6§	HR	1.23 (1.16–1.29)	1.21 (1.14–1.29)	—	—
Sundstrom et al., 2006 (47)	50-year-old-men	2,322	17.4	32.7‖	HR	1.67 (1.45–1.93)	1.36 (1.17–1.58)	—	—
	70-year-old-men	1,221	23.1	32.7‖	HR	1.52 (1.19–1.94)	1.20 (0.90–1.59)	—	—
Thomas et al., 2007 (58)	General population	2,863	17.5	8.5§	RR	3.03 (2.00–4.59)	—	7.0	2.3
Revised NCEP definition**									
Benetos et al., 2008 (33)	Pts without CVD	84,730	16.5	4.7§	HR	—	1.32 (1.13–1.53)	—	—
Davis et al., 2007 (59)	Subjects with type 1 diabetes	127	41.7	11.0§	HR	—	0.74 (0.32–1.74)	—	—
Guize et al., 2007 (35)	General population	60,754	17.7	3.6§	HR	—	1.46 (1.14–1.88)	—	—
Hildrum et al., 2009 (60)	Age 40–59 yrs	3,789	28.0	7.9§	HR	2.06 (1.35–3.13)	2.14 (1.40–3.29)	—	—
	Age 60–74 yrs	1,973	47.0	7.9§	HR	1.10 (0.90–1.36)	1.14 (0.92–1.41)	—	—
	Age 75–89 yrs	986	57.0	7.9§	HR	1.05 (0.88–1.25)	1.05 (0.87–1.26)	—	—
Huang et al., 2008 (61)	Men	58,771	—	8.0‖	RR	2.09 (1.90–2.30)	1.21 (1.09–1.34)	4.7	2.3
	Women	65,742	—	8.0‖	RR	4.33 (3.85–4.88)	1.30 (1.12–1.49)	4.4	4.1
	Pts without T2DM without CVD	117,045	—	8.0‖	RR	—	1.04 (0.94–1.15)	3.1	1.4
Kajimoto et al., 2008 (62)	Pts with T2DM who underwent CABG	274	65.3	10.5§	HR	0.84 (0.56–1.27)	—	—	—
	Pts without T2DM who underwent CABG	909	40.9	10.5§	HR	1.34 (1.03–1.74)	—	—	—
Katzmarzyk et al., 2006 (39)	Men	20,789	26.9	11.0§	RR	1.41 (1.21–1.67)	1.31 (1.11–1.54)	4.2	2.6
Lee et al., 2008 (63)	Men	2,787	24.3	14.1§	HR	3.20 (2.50–4.10)	1.40 (1.10–1.80)	16.8	6.3
	Women	2,912	21.4	14.1§	HR	5.00 (3.50–6.90)	1.80 (1.30–2.60)	11.7	2.7

(continued on next page)

Table 1 Continued

First Author, Year (Ref. #)*	Population	n	MetS (%)	Follow-Up (yrs)	Effect Measure	Risk of All-Cause Mortality† (95% CI) Least Adjusted	Risk of All-Cause Mortality† (95% CI) Most Adjusted	All-Cause Mortality (%) MetS Group	All-Cause Mortality (%) Non-MetS Group
Lopes et al., 2008 (64)	Pts with CAD	589	52.3	2.0‖	HR	—	2.50 (1.15–5.47)	—	—
	Pts with CAD with T2DM	—	—	2.0‖	HR	—	1.06 (0.38–2.91)	—	—
	Pts with CAD without T2DM	—	—	2.0‖	HR	—	3.57 (1.38–9.19)	—	—
Mozaffarian et al., 2008 (65)	Elderly	4,258	35.0	15.0‖	HR	1.31 (1.19–1.43)	1.22 (1.11–1.34)	53.1	47.9
Noto et al., 2008 (66)	General population	685	22.9	15.0‖	HR	—	1.00 (0.81–1.24)	25.6	23.7
	Men	—	12.4	15.0‖	HR	—	0.95 (0.61–1.47)	18.8	19.6
	Women	—	31.5	15.0‖	HR	—	1.04 (0.82–1.32)	28.0	28.2
Saito et al., 2009 (67)	Men	12,412	—	12.3‖	HR	1.07 (0.94–1.23)	1.06 (0.92–1.23)	—	—
	Women	21,639	—	12.3‖	HR	1.23 (1.05–1.44)	1.22 (1.03–1.43)	—	—
Simons et al., 2007 (68)	Elderly men	1,233	31.1	16.0‖	HR	1.60 (1.37–1.86)	1.53 (1.30–1.79)	66.7	52.8
	Elderly women	1,572	34.1	16.0‖	HR	1.43 (1.23–1.67)	1.35 (1.15–1.59)	51.3	39.4
Wassink et al., 2008 (50)	Pts with CV risk factor	3,196	50.1	3.2¶	HR	1.43 (1.15–1.78)	1.40 (1.12–1.75)	—	—
	Pts with CV risk factor without T2DM	2,472	—	3.2¶	HR	1.36 (1.05–1.76)	1.34 (1.03–1.74)	—	—
Wen et al., 2008 (69)	Elderly men	5,761	45.6	8.0‖	RR	1.24 (1.08–1.42)	1.18 (1.02–1.36)	—	—
	Elderly women	4,786	54.4	8.0‖	RR	1.27 (1.05–1.54)	1.15 (0.94–1.40)	—	—
Modified revised NCEP definition#									
Hsu et al., 2008 (70)	Men	4,888	22.0	4.7§	HR	1.05 (0.87–1.28)	—	—	—
	Women	6,170	28.0	4.7§	HR	1.46 (1.19–1.80)	—	—	—
Kasai et al., 2008 (71)	Pts without T2DM who underwent PCI	450	28.7	12§	HR	0.90 (0.45–1.79)	0.88 (0.42–1.85)	—	—
Niwa et al., 2007 (72)	Men	914	9.0	12.5§	HR	1.05 (0.60–1.82)	1.13 (0.64–1.98)	17.1	15.3
	Women	1,262	1.7	12.5§	HR	1.24 (0.39–3.95)	1.31 (0.41–4.18)	13.6	6.2
Tanomsup et al., 2007 (73)	Men	2,545	19.3	17.0‖	HR	—	1.60 (1.23–2.09)	—	—
Wang et al., 2007 (49)	Elderly without T2DM	1,025	51.3	13.5¶	HR	1.10 (0.91–1.33)	1.08 (0.88–1.28)	—	—
	Elderly men without T2DM	648	—	13.5¶	HR	—	1.05 (0.80–1.37)	—	—
	Elderly women without T2DM	377	—	13.5¶	HR	—	1.09 (0.83–1.43)	—	—

*Studies are listed by category and then alphabetically by author. †Nonadjusted risk estimates and risk estimates adjusting exclusively for age and/or sex were classified as "least adjusted." Risk estimates adjusting for any cardiovascular risk factor or component of the metabolic syndrome (i.e., smoking, cholesterol, obesity) were classified as "most adjusted." ‡The NCEP defines the metabolic syndrome as having 3 or more of the following 5 cardiovascular risk factors: 1) central obesity (waist circumference: men >102 cm; women >88 cm); 2) elevated triglycerides (≥150 mg/dl); 3) diminished high-density lipoprotein (HDL) cholesterol (men <40 mg/dl; women <50 mg/dl); and 4) hypertension (≥130/≥85 mm Hg); and 5) elevated fasting glucose (≥110 mg/dl). §Mean follow-up. ‖Maximum follow-up. ¶Median follow-up. #The modified NCEP and modified revised NCEP definitions use measurements of BMI (typically BMI ≥30 kg/m^2 or BMI ≥27 kg/m^2 in Asian populations) to define central obesity. **The revised NCEP definition uses a lower cutoff for elevated fasting glucose of ≥100 mg/dl.

ACS = acute coronary syndrome; AMI = acute myocardial infarction; BMI = body mass index; CABG = coronary artery bypass graft; CAD = coronary artery disease; CI = confidence interval; CV = cardiovascular; CVD = cardiovascular disease; HR = hazard ratio; MetS = metabolic syndrome; MI = myocardial infarction; NCEP = National Cholesterol Education Program; PCI = percutaneous coronary intervention; Pts = patients; RR = relative risk; T2DM = type 2 diabetes mellitus.

Some studies investigated more than 1 cardiovascular outcome or more than 1 definition of the metabolic syndrome.

The metabolic syndrome and cardiovascular risk. The association between the metabolic syndrome and cardiovascular risk was similar for the NCEP and rNCEP definitions (Table 6). Specifically, the metabolic syndrome as defined by the NCEP definition was associated with an increase in risk for all-cause mortality (RR: 1.54; 95% CI: 1.29 to 1.84; I^2 = 84%; 95% CI: 73% to 91%) similar to that of the metabolic syndrome as defined by the rNCEP definition (RR: 1.63; 95% CI: 1.30 to 2.04; I^2 = 95%; 95% CI: 92% to 97%). There was also little variation in cardiovascular risk between the modified NCEP and modified rNCEP definitions compared with the original NCEP definition. Overall, when studies investigating all definitions were pooled, the metabolic syndrome was associated with an increase in the risk for CVD (RR: 2.35; 95% CI: 2.02 to 2.73; I^2 = 64%; 95% CI: 39% to 79%), CVD mortality (RR: 2.40; 95% CI: 1.87 to 3.08; I^2 = 81%; 95% CI: 72% to 88%), all-cause mortality (RR: 1.58; 95% CI: 1.39 to 1.78; I^2 = 89%; 95% CI: 85% to 92%), MI (RR: 1.99; 95% CI: 1.61 to 2.46; I^2 = 40%; 95% CI: 0% to 73%), and stroke (RR: 2.27; 95% CI: 1.80 to 2.85; I^2 = 88%; 95% CI: 82% to 91%) (Table 6, Figs. 2 to 6). The point estimates for cardiovascular risk were consistently higher in women compared with men, especially for all-cause mortality (RR: 1.86; 95% CI: 1.37 to 2.52; I^2 = 91%; 95% CI: 85% to 94% for women vs. RR: 1.42; 95% CI: 1.16 to 1.74; I^2 = 90%; 95% CI: 81% to 94% for men).

A small number of studies reported outcomes for patients without type 2 diabetes mellitus. However, even in the absence of type 2 diabetes mellitus, the metabolic syndrome was still associated with an increased risk of CVD mortality (RR: 1.75; 95% CI: 1.19 to 2.58; I^2 = 68%; 95% CI: 8% to 89%), MI (RR: 1.62; 95% CI: 1.31 to 2.01; I^2 = 0%; 95% CI: 0% to 90%), and stroke (RR: 1.86; 95% CI: 1.10 to 3.17; I^2 = 89%; 95% CI: 56% to 97%). The confidence interval for our assessment of the effect of the metabolic syndrome on all-cause mortality in this subpopulation was inconclusive (RR: 1.32; 95% CI: 0.65 to 2.67; I^2 = 87%; 95% CI: 47% to 97%). Finally, there were an insufficient number of studies investigating patients with type 2 diabetes available to pool these data.

Sensitivity analyses. In sensitivity analyses, we assessed the potential impact of follow-up duration on our results. These sensitivity analyses showed that studies with longer follow-up times had risk estimates that were similar to those with shorter follow-up times. Specifically, in studies with a follow-up time that was longer than the median duration (12.3 years), the risk for CVD mortality associated with the

Table 2 MetS Studies Reporting the Incidence of CVD

First Author, Year (Ref. #)*	Population	n	MetS (%)	Follow-Up (yrs)	Effect Measure	Risk of CVD† (95% CI)		CVD (%)	
						Least Adjusted	Most Adjusted	MetS Group	Non-MetS Group
NCEP definition‡									
Andreadis et al., 2007 (74)	Pts with hypertension	1,007	42.1	2.1§	HR	1.75 (1.15–2.66)	—	11.8	8.1
Dekker et al., 2005 (34)	Men	615	19.0	11.0‖	HR	1.91 (1.31–2.79)	1.64 (1.11–2.44)	—	—
	Women	749	25.8	11.0‖	HR	1.68 (1.11–2.55)	1.17 (0.73–1.87)	—	—
Jeppesen et al., 2007 (75)	General population	2,135	19.2	9.4§	HR	—	1.86 (1.39–2.45)	—	—
Resnick et al., 2003 (76)	American Indians without T2DM	2,283	35.0	7.8¶	HR	1.35 (1.13–1.62)	1.11 (0.79–1.56)	—	—
Sattar et al., 2008 (77)	Elderly (age 70–82 yrs) without T2DM	4,812	27.7	3.2¶	HR	1.07 (0.86–1.32)	—	—	—
	Elderly (age 60–79 yrs) men without T2DM	2,737	27.2	7.0¶	HR	1.27 (1.04–1.56)	—	—	—
Wilson et al., 2005 (78)	Men	1,549	22.5	8.0‖	RR	2.88 (1.99–4.16)	—	17.9	4.9
	Women	1,774	14.9	8.0‖	RR	2.25 (1.31–3.88)	—	7.7	2.6
Modified NCEP definition#									
Guzder et al., 2006 (79)	Pts with T2DM	428	82.5	4.2¶	HR	1.27 (0.72–2.23)	2.05 (1.13–3.74)	—	—
Hwang et al., 2009 (80)	Men	1,761	21.7	8.7¶	RR	2.02 (1.38–2.95)	—	10.0	4.9
	Women	674	11.4	8.7¶	RR	5.17 (2.59–10.31)	—	15.6	3.0
Kokubo et al., 2008 (81)	Men	2,492	18.0	—	HR	1.70 (1.23–2.34)	1.75 (1.27–2.41)	12.3	6.5
	Elderly men	—	—	—	HR	1.67 (1.16–2.40)	1.73 (1.20–2.48)	—	—
	Women	2,840	20.7	—	HR	1.93 (1.35–2.77)	1.90 (1.31–2.77)	9.5	3.2
	Elderly women	—	—	—	HR	1.78 (1.19–2.66)	1.70 (1.12–2.59)	—	—
Ninomiya et al., 2007 (82)	Men	1,050	20.6	14.0‖	HR	1.93 (1.38–2.70)	1.86 (1.32–2.62)	23.2	13.0
	Women	1,402	29.9	14.0‖	HR	1.68 (1.22–2.33)	1.70 (1.22–2.36)	17.0	7.9
Schillaci et al., 2004 (83)	Hypertensive pts	1,742	34.0	4.1¶	HR	—	1.73 (1.25–2.38)	—	—
Song et al. 2007 (84)	Women with BMI <25 kg/m^2	13,526	4.3	10.0§	RR	2.58 (1.88–3.53)	2.40 (1.71–3.37)	7.9	2.2
	Women with BMI 25–29.9 kg/m^2	7,834	14.1	10.0§	RR	2.92 (2.24–3.79)	—	7.1	2.4
	Women with BMI ≥30 kg/m^2	4,266	31.4	10.0§	RR	2.32 (1.71–3.15)	—	6.1	2.6
Takeuchi et al., 2005 (85)	Men	780	25.3	6.0‖	HR	—	2.23 (1.14–4.34)	11.7	6.7
Worm et al., 2009 (86)	HIV-infected pts	23,202	4.4	5.1§	RR	2.89 (2.34–3.59)	0.94 (0.69–1.27)	—	—
Revised NCEP definition**									
Ingelsson et al., 2007 (87)	Pts without T2DM	1,830	31.8	7.2¶	RR	2.08 (1.47–2.93)	—	10.2	4.9
Liu et al., 2007 (88)	General population	30,378	18.2	10.0‖	HR	—	2.01 (1.73–2.33)	—	—
Meigs et al., 2007 (89)	Pts without insulin resistance	2,104	16.2	12.0¶	RR	1.40 (1.00–2.10)	1.30 (0.90–1.90)	10.6	6.1
	Pts with insulin resistance	699	63.0	12.0¶	RR	2.01 (1.28–3.15)	—	17.1	8.5
Vaccarino et al., 2008 (90)	Women received CA angiography	652	60.0	5.9§	RR	2.44 (1.51–3.92)	1.81 (1.10–2.99)	—	—
Wand et al., 2007 (91)	HIV-infected pts	881	8.5	3.0‖	HR	—	2.56 (0.86–7.60)	—	—

*Studies are listed by category and then alphabetically by author. †Nonadjusted risk estimates and risk estimates adjusting exclusively for age and/or sex were classified as "least adjusted." Risk estimates adjusting for any cardiovascular risk factor or component of the metabolic syndrome (i.e., smoking, cholesterol, obesity) were classified as "most adjusted." ‡The NCEP defines the metabolic syndrome as having 3 or more of the following 5 cardiovascular risk factors: 1) central obesity (waist circumference: men >102 cm; women >88 cm); 2) elevated triglycerides (≥150 mg/dl); 3) diminished high-density lipoprotein (HDL) cholesterol (men <40 mg/dl; women <50 mg/dl); 4) hypertension (≥130/≥85 mm Hg); and 5) elevated fasting glucose (≥110 mg/dl). §Median follow-up. ‖Maximum follow-up. ¶Mean follow-up. #The modified NCEP and modified revised NCEP definitions use measurements of BMI (typically, BMI ≥30 kg/m^2 or BMI ≥27 kg/m^2 in Asian populations) to define central obesity. **The revised NCEP definition uses a lower cutoff for elevated fasting glucose of ≥100 mg/dl.

CA = coronary artery; HIV = human immunodeficiency virus; other abbreviations as in Table 1.

metabolic syndrome (RR: 2.62; 95% CI: 1.56 to 4.38; I^2 = 88%; 95% CI: 80% to 93%) was similar to the risk in studies with a follow-up time shorter than the median duration (RR: 2.23; 95% CI: 1.74 to 2.86; I^2 = 65%; 95% CI: 30% to 82%).

Some studies also reported outcomes for patient populations with cardiovascular risk factors (systemic hypertension, atherosclerosis, or a history of CVD). Our sensitivity analysis showed that studies of subjects without these risk factors had risk estimates for CVD mortality (RR: 2.36; 95% CI: 1.79 to 3.1; I^2 = 84%; 95% CI: 75% to 89%) consistent with those obtained in our primary analysis (RR: 2.40; 95% CI: 1.87 to 3.08; I^2 = 81%; 95% CI: 72% to 88%).

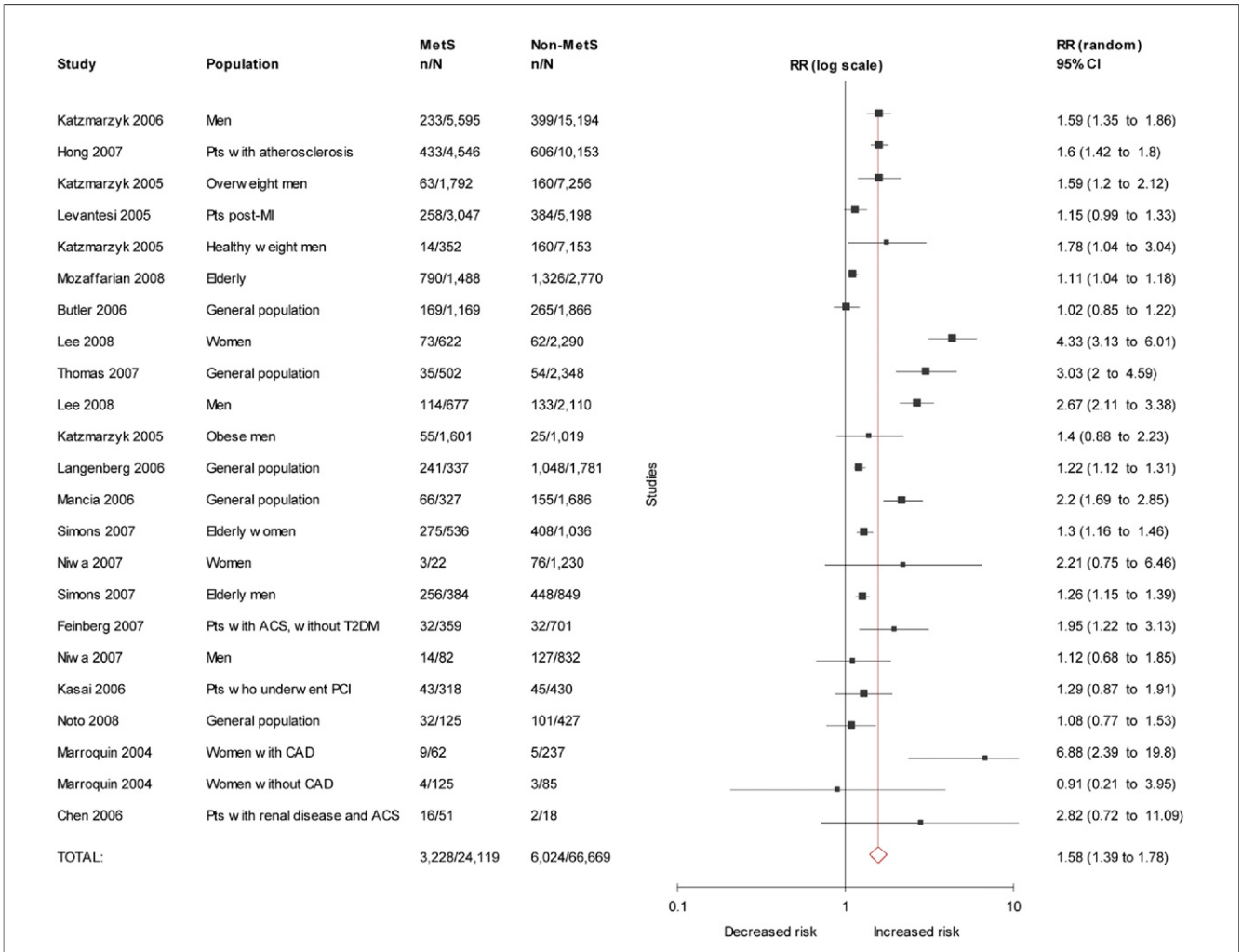

Figure 2 The Metabolic Syndrome and the Relative Risk for All-Cause Mortality

I^2 = 89%; 95% confidence interval (CI): 85% to 92%. ACS = acute coronary syndrome; CAD = coronary artery disease; MetS = metabolic syndrome; MI = myocardial infarction; PCI = percutaneous coronary intervention; Pts = patients; RR = relative risk; T2DM = type 2 diabetes mellitus.

Funnel plots suggest that mild publication bias may be present (data not shown).

Discussion

Our systematic review and meta-analysis was designed to estimate the cardiovascular risk associated with the metabolic syndrome as defined by the NCEP and rNCEP definitions. Our literature search was designed to include all prospective studies investigating the NCEP and rNCEP definitions, thereby allowing us to include a large number of studies (87 studies; n = 951,083).

Overall, the metabolic syndrome was associated with a 2-fold increase in risk of CVD, CVD mortality, and stroke, and a 1.5-fold increase in risk of all-cause mortality. Thus, patients with the metabolic syndrome were at higher risk for cardiovascular outcomes than for all-cause mortality, although these patients were at elevated risk for either outcome compared with those without this syndrome. The metabolic syndrome was also associated with an approximate 2-fold increase in risk for MI. There was little variation in cardiovascular risk between the NCEP and rNCEP definitions, which principally differ in their threshold for impaired fasting glucose (≥110 mg/dl vs. ≥100 mg/dl, respectively). The modified NCEP and modified rNCEP definitions also showed little variation compared with the original NCEP definition; these definitions only differ in their measurement of central obesity (use of BMI versus waist circumference, respectively).

The pathophysiological mechanism by which the metabolic syndrome increases cardiovascular risk remains under debate (15). Earlier definitions by the World Health Organization (5) and the European Group for the Study of Insulin Resistance (16) emphasize the independent role of insulin resistance as the underlying component of the metabolic syndrome. Insulin resistance progresses toward hyperinsulinemia and hyperglycemia, thus triggering pe-

Table 3 MetS Studies Reporting the Incidence of CVD Mortality

First Author, Year (Ref. #)*	Population	n	MetS (%)	Follow-Up (yrs)	Effect Measure	Risk of CVD Mortality† (95% CI)		CVD Mortality (%)	
						Least Adjusted	Most Adjusted	MetS Group	Non-MetS Group
NCEP definition‡									
Benetos et al., 2008 (33)	Pts without CVD	84,730	9.6	4.7§	HR	—	2.05 (1.28–3.28)	—	—
Butler et al., 2006 (14)	General population	3,035	38.5	6.0‖	RR	1.37 (0.98–1.92)	—	5.13	3.75
	Men	1,473	—	6.0‖	—	—	—	6.2	5.5
	Women	1,562	—	6.0‖	—	—	—	4.4	1.9
	Pts with T2DM	461	77.9	6.0‖	RR	0.77 (0.38–1.53)	—	7.5	9.8
	Pts without T2DM	2,562	31.6	6.0‖	RR	1.19 (0.79–1.81)	—	4.1	3.4
DECODE study, 2007 (92)	Men without T2DM age 50–69 yrs	2,790	26.5	10.0‖	RR	1.48 (1.02–2.14)	—	5.55	3.75
Dekker et al., 2005 (34)	Men	615	19.0	11.0‖	HR	2.25 (1.16–4.34)	—	—	—
	Women	749	25.8	11.0‖	HR	0.76 (0.32–1.83)	—	—	—
Hillier et al., 2005 (36)	Elderly women with no T2DM	921	27.1	12.2§	HR	—	1.60 (1.10–2.30)	—	—
Hunt et al., 2004 (28)	General population	2,107	9.4	12.7§	HR	2.53 (1.74–3.67)	—	—	—
	Subjects with CVD	1,947	—	12.7§	HR	2.01 (1.13–3.57)	—	—	—
Katzmarzyk et al., 2005 (38)	Nonobese men	7,505	4.7	10.2§	RR	3.74 (1.68–8.32)	1.60 (0.71–3.61)	1.99	0.53
	Overweight men	9,048	19.8	10.2§	RR	2.14 (1.35–3.41)	—	1.51	0.7
	Obese men	2,620	61.1	10.2§	RR	1.33 (0.67–2.63)	—	1.56	1.18
Katzmarzyk et al., 2006 (39)	Men	20,789	19.7	11.4§	RR	2.03 (1.54–2.69)	1.79 (1.35–2.37)	1.93	0.8
Lakka et al., 2002 (40)	Men	707	15.0	11.6§	RR	2.08 (0.93–4.65)	2.27 (0.96–5.36)	—	—
Langenberg et al., 2006 (41)	General population	2,118	—	20.0‖	HR	—	1.50 (1.23–1.83)	38.0	29.1
	Men	977	16.9	20.0‖	HR	—	1.28 (0.95–1.71)	32.7	33.7
	Women	1,141	15.1	20.0‖	HR	—	1.18 (1.38–2.39)	43.0	25.3
Maggi et al., 2006 (93)	Men	1,359	31.4	4.0‖	HR	3.35 (1.35–8.30)	1.12 (1.09–1.16)	—	—
	Women	1,724	59.5	4.0‖	HR	1.06 (0.63–1.39)	0.82 (0.56–1.19)	—	—
Mancia et al., 2007 (42)	General population	2,013	16.2	12.3‖	HR	3.27 (1.97–5.41)	1.71 (1.02–2.85)	7.3	2.4
Monami et al., 2008 (44)	Pts with T2DM	1,716	67.1	4.7§	HR	1.82 (1.24–2.68)	—	—	—
Solymoss et al., 2009 (94)	Pts with >50% stenosis of CA	876	53.0	12.6§	HR	1.43 (0.97–2.11)	1.42 (0.96–2.10)	—	—
Sundstrom et al., 2006 (47)	70-year-old men	1,221	24.1	32.7‖	HR	2.01 (1.41–2.85)	1.43 (0.95–2.17)	—	—
Wang et al., 2007 (49)	Elderly without T2DM	1,025	42.7	13.5¶	HR	1.43 (1.12–1.84)	1.35 (1.05–1.74)	—	—
	Elderly men without T2DM	—	—	13.5¶	HR	—	1.43 (1.00–2.03)	—	—
	Elderly women without T2DM	—	—	13.5¶	HR	—	1.27 (0.89–1.82)	—	—
Wassink et al., 2008 (50)	Pts with CV risk factor	3,196	42.6	3.2¶	HR	1.71 (1.31–2.24)	1.65 (1.25–2.17)	—	—
Zambon et al., 2009 (51)	Elderly	2,910	39.0	4.4§	HR	1.36 (1.03–1.78)	—	—	—
	Elderly men	1,174	25.6	4.4§	HR	1.51 (0.98–2.33)	—	—	—
	Elderly women	1,736	48.1	4.4§	HR	1.27 (0.90–1.79)	—	—	—

(continued on next page)

Table 3 Continued

First Author, Year (Ref. #)*	Population	n	MetS (%)	Follow-Up (yrs)	Effect Measure	Risk of CVD Mortality† (95% CI)		CVD Mortality (%)	
						Least Adjusted	Most Adjusted	MetS Group	Non-MetS Group
Modified NCEP definition#									
Chen et al., 2006 (52)	Pts with renal disease and ACS	76	73.7	18.2§	—	—	—	24.0	0.0
de Simone et al., 2007 (95)	Hypertensive subjects	8,243	19.3	10.0‖	HR	—	1.73 (1.38–2.17)	—	—
Kasai et al., 2006 (54)	Pts who underwent PCI	748	28.7	12§	RR	2.70 (1.28–5.70)	—	6.3	2.3
Malik et al., 2004 (56)	General population	4,576	37.1	13.3§	HR	—	1.82 (1.40–2.37)	—	—
	Subjects with T2DM	4,056	29.0	13.3§	HR	—	1.65 (1.10–2.47)	—	—
Nigam et al., 2006 (57)	General population	24,358	13.5	12.6§	HR	1.26 (1.19–1.35)	1.22 (1.14–1.31)	—	—
Nakatani et al., 2007 (96)	Japanese pts with AMI	3,858	42.7	2.0¶	HR	—	1.08 (0.62–1.90)	—	—
Sundstrom et al., 2006 (47)	50-year-old men	2,322	17.4	32.7‖	HR	2.21 (1.82–2.68)	1.59 (1.29–1.95)	—	—
	70-year-old men	1,221	23.1	32.7‖	HR	2.11 (1.49–3.00)	1.55 (1.02–2.35)	—	—
Thomas et al., 2007 (58)	General population	2,863	17.5	8.5§	RR	6.12 (2.99–12.51)	—	3.4	0.6
Revised NCEP definition**									
Benetos et al., 2008 (33)	Pts without CVD	84,730	16.5	4.7§	HR	—	1.64 (1.08–2.50)	—	—
Davis et al., 2007 (59)	Subjects with type 1 diabetes	127	41.7	11.0§	HR	1.37 (0.40–4.74)	—	—	—
Hildrum et al., 2009 (60)	Age 40–59 yrs	3,789	28.0	7.9§	HR	3.97 (2.00–7.88)	3.95 (1.96–7.97)	—	—
	Age 60–74 yrs	1,973	47.0	7.9§	HR	1.07 (0.82–1.39)	1.09 (0.83–1.43)	—	—
	Age 75–89 yrs	986	57.0	7.9§	HR	1.12 (0.90–1.40)	1.11 (0.89–1.39)	—	—
Huang et al., 2008 (61)	Men	58,771	—	8.0‖	RR	3.17 (2.56–3.93)	1.77 (1.40–2.24)	1.2	0.4
	Women	65,742	—	8.0‖	RR	7.46 (5.55–10.02)	1.69 (1.19–2.42)	1.0	0.1
	Pts without T2DM and CVD	117,045	—	8.0‖	RR	—	1.68 (1.32–2.16)	0.7	0.2
Hunt et al., 2007 (97)	Men without T2DM	1,940	15.6	15.5§	RR	3.38 (1.95–5.85)	—	5.1	1.5
	Women without T2DM	2,532	19.4	15.5§	RR	1.81 (1.17–2.81)	—	7.2	4.0
Kajimoto et al., 2008 (62)	Nondiabetic pts who had CABG	909	40.9	10.5§	HR	2.31 (1.36–3.92)	—	—	—
	Diabetic pts who had CABG	274	65.3	10.5§	HR	0.75 (0.41–1.36)	—	—	—
Katzmarzyk et al., 2006 (39)	Men	20,789	26.9	11.4§	RR	1.89 (1.44–2.47)	1.67 (1.27–2.19)	1.7	0.8
Lee et al., 2008 (63)	Men	2,787	24.3	14.1§	HR	6.70 (4.30–10.40)	3.00 (1.90–4.80)	8.1	1.4
	Women	2,912	21.4	14.1§	HR	7.40 (4.00–13.80)	2.10 (1.10–4.00)	4.3	0.7
Mozaffarian et al., 2008 (65)	Elderly	4,258	35.0	15.0‖	RR	1.51 (1.29–1.76)	—	—	—
Noto et al., 2008 (66)	General population	685	22.9	15.0‖	HR	1.33 (0.96–1.83)	—	10.6	7.8
	Men	—	12.4	15.0‖	HR	1.45 (0.83–2.52)	—	11.8	7.6
	Women	—	31.5	15.0‖	HR	1.31 (0.88–1.93)	—	10.2	7.9
Saito et al., 2009 (67)	Men	12,412	—	12.3¶	HR	1.61 (1.16–2.23)	1.41 (0.99–2.02)	—	—
	Women	21,639	—	12.3¶	HR	1.46 (1.00–2.13)	1.44 (0.98–2.11)	—	—
Wassink et al., 2008 (50)	Pts with CV risk factor	3,196	50.1	3.2¶	HR	1.69 (1.28–2.22)	1.61 (1.22–2.14)	—	—
	Pts with CV factor without T2DM	2,472	—	3.2¶	HR	1.55 (1.12–2.14)	1.49 (1.07–2.08)	—	—
Wen et al., 2008 (69)	Elderly men	5,761	45.6	8.0‖	RR	1.70 (1.28–2.23)	1.45 (1.07–1.96)	—	—
	Elderly women	4,786	54.4	8.0‖	RR	1.86 (1.21–2.84)	1.66 (1.05–2.60)	—	—
Modified revised NCEP definition#									
Espinola-Klein et al., 2007 (98)	Pts with CAD	811	43.0	6.7¶	HR	—	2.50 (1.60–3.80)	18.4	7.4
Hsu et al., 2008 (70)	Men	4,888	22.0	4.7§	HR	—	1.40 (0.96–2.04)	—	—
	Women	6,170	28.0	4.7§	HR	—	1.85 (1.25–2.73)	—	—
Niwa et al., 2007 (72)	Men	914	9.0	12.5§	HR	1.67 (0.65–4.34)	1.84 (0.68–4.96)	6.1	3.7
	Women	1,262	1.7	12.5§	HR	1.12 (0.15–8.39)	1.31 (0.17–9.96)	4.5	2.03
Wang et al., 2007 (49)	Elderly without T2DM	1,025	51.3	13.5¶	HR	1.37 (1.07–1.77)	1.31 (1.02–1.69)	—	—
	Elderly men without T2DM	648	—	13.5¶	HR	—	1.32 (0.93–1.87)	—	—
	Elderly women without T2DM	377	—	13.5¶	HR	—	1.29 (0.89–1.87)	—	—

*Studies are listed by category and then alphabetically by author. †Nonadjusted risk estimates and risk estimates adjusting exclusively for age and/or sex were classified as "least adjusted." Risk estimates adjusting for any cardiovascular risk factor or component of the metabolic syndrome (i.e., smoking, cholesterol, obesity) were classified as "most adjusted." ‡The NCEP defines the metabolic syndrome as having 3 or more of the following 5 cardiovascular risk factors: 1) central obesity (waist circumference: men >102 cm; women >88 cm); 2) elevated triglycerides (≥150 mg/dl); 3) diminished high-density lipoprotein (HDL) cholesterol (men <40 mg/dl; women <50 mg/dl); 4) hypertension (≥130/≥85 mm Hg); and 5) elevated fasting glucose (≥110 mg/dl). §Mean follow-up. ‖Maximum follow-up. ¶Median follow-up. #The modified NCEP and modified revised NCEP definitions use measurements of BMI (typically BMI ≥30 kg/m^2 or BMI ≥27 kg/m^2 in Asian populations) to define central obesity. **The revised NCEP definition uses a lower cutoff for elevated fasting glucose of ≥ 100 mg/dl.

Abbreviations as in Tables 1 and 2.

Table 4 MetS Studies Reporting the Incidence of MI

First Author, Year (Ref. #)*	Population	n	MetS (%)	Follow-Up (yrs)	Effect Measure	Risk of MI† (95% CI)		MI (%)	
						Least Adjusted	Most Adjusted	MetS Group	Non-MetS Group
NCEP definition‡									
Butler et al., 2006 (14)	General population	3,035	38.5	6.0§	HR	—	1.51 (1.12–2.05)	9.1	5.7
	Men	1,473	—	6.0§	HR	—	—	12.1	8.1
	Women	1,562	—	6.0§	HR	—	—	6.8	3.1
	Pts with T2DM	461	77.9	6.0§	RR	0.95 (0.52–1.74)	—	11.1	11.8
	Pts without T2DM	2,562	31.6	6.0§	RR	1.51 (1.11–2.04)	—	8.2	5.4
Girman et al., 2004 (99)	Pts without T2DM	1,991	20.6	5.4¶‖	HR	1.49 (1.21–1.83)	—	—	—
	Pts without T2DM	3,188	46.0	5.0§	HR	1.49 (0.99–2.25)	—	—	—
Holvoet et al., 2004 (100)	Elderly	3,033	37.8	5.0§	RR	1.91 (1.35–2.72)	1.97 (1.35–2.86)	5.6	2.9
Solymoss et al., 2009 (94)	Pts with <50% stenosis of CA	204	53.0	12.6¶	HR	2.36 (1.00–5.57)	2.25 (0.93–5.43)	—	—
Takeno et al., 2008 (48)	Pts with AMI	461	37.3	1.5‖	HR	—	0.84 (0.23–2.70)	—	—
Thorn et al., 2009 (101)	Pts with type 1 diabetes	2,474	—	5.7‖	HR	2.61 (1.90–3.59)	1.85 (1.32–2.59)	—	—
Wassink et al., 2008 (50)	Pts with CV risk factor	3,196	42.6	3.2‖	HR	1.54 (1.16–2.04)	1.61 (1.21–2.15)	—	—
Modified NCEP definition#									
Chen et al., 2006 (52)	Pts with renal disease and ACS	76	76.3	18.1¶	HR	—	—	16.0	0.0
Kasai et al., 2006 (54)	Pts who underwent PCI	748	28.7	12¶	RR	1.35 (0.70–2.61)	—	5.4	4.0
Kokubo et al., 2008 (81)	Men	2,492	18.0	—	HR	2.09 (1.30–3.37)	2.12 (1.31–3.43)	5.8	2.6
	Women	2,840	20.7	—	HR	2.68 (1.41–5.10)	2.77 (1.44–5.32)	3.6	0.8
Revised NCEP definition**									
Nilsson et al., 2007 (102)	Pts without T2DM	5,047	20.7	10.7¶	RR	1.99 (1.47–2.69)	—	5.8	2.9
	Men without T2DM	3,008	26.0	10.7¶	RR	1.87 (1.30–2.67)	—	8.7	4.6
	Women without T2DM	2,039	17.0	10.7¶	RR	1.48 (0.82–2.68)	—	2.7	1.8
Noto et al., 2008 (66)	General population	685	22.9	15.0§	HR	—	1.91 (1.28–2.83)	7.5	3.9
Wassink et al., 2008 (50)	Pts with CV risk factor	3,196	50.1	3.2‖	HR	1.60 (1.20–2.14)	1.68 (1.25–2.26)	—	—
	Pts with CV factor without T2DM	2,472	—	3.2‖	HR	1.57 (1.12–2.20)	1.65 (1.16–2.34)	—	—

*Studies are listed by category and then alphabetically by author. †Nonadjusted risk estimates and risk estimates adjusting exclusively for age and/or sex were classified as "least adjusted." Risk estimates adjusting for any cardiovascular risk factor or component of the metabolic syndrome (i.e., smoking, cholesterol, obesity) were classified as "most adjusted." ‡The NCEP defines the metabolic syndrome as having 3 or more of the following 5 cardiovascular risk factors: 1) central obesity (waist circumference: men >102 cm; women >88 cm); 2) elevated triglycerides (≥150 mg/dl); 3) diminished high-density lipoprotein (HDL) cholesterol (men <40 mg/dl; women <50 mg/dl); 4) hypertension (≥130/≥85 mm Hg); and 5) elevated fasting glucose (≥110 mg/dl). §Maximum follow-up. ‖Median follow-up. ¶Mean follow-up. #The modified NCEP and modified revised NCEP definitions use measurements of BMI (typically BMI ≥30 kg/m^2 or BMI ≥27 kg/m^2 in Asian populations) to define central obesity. **The revised NCEP definition uses a lower cutoff for elevated fasting glucose of ≥100 mg/dl.

Abbreviations as in Tables 1 and 2.

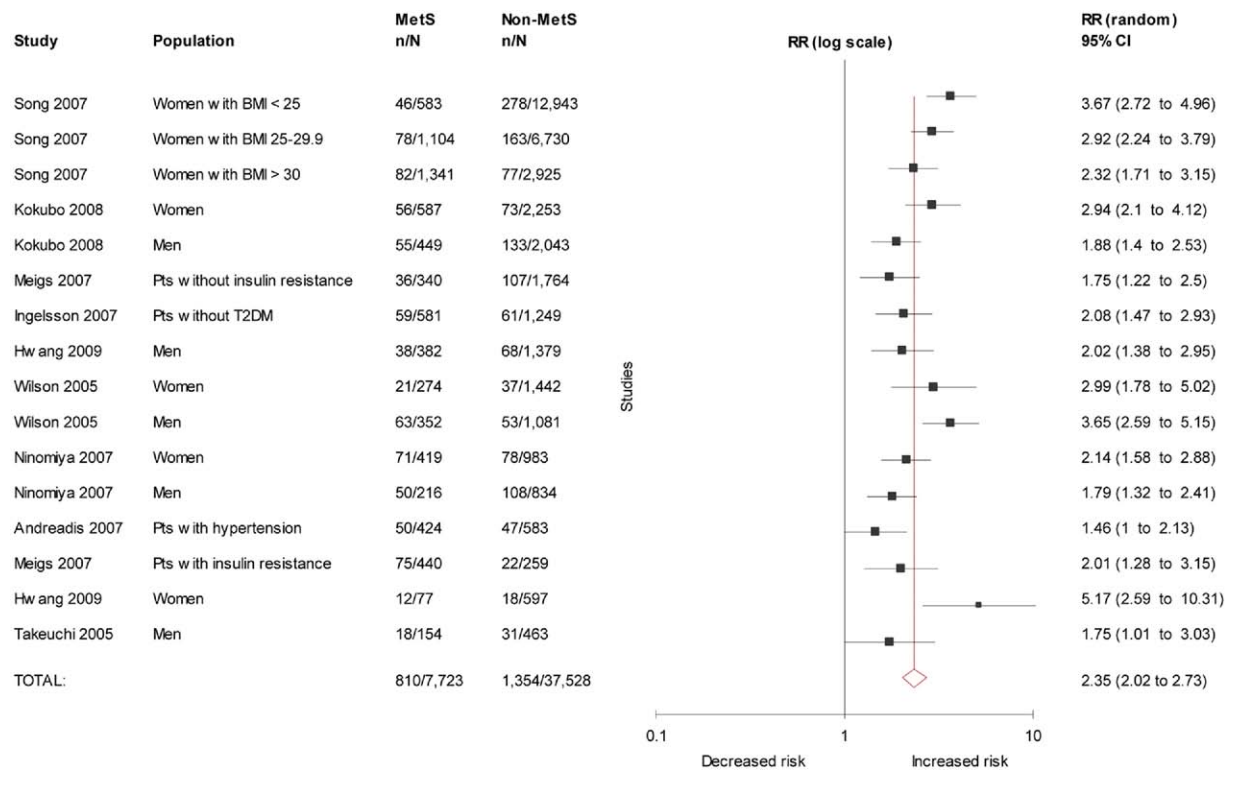

Figure 3 **The Metabolic Syndrome and the Relative Risk for CVD**

I^2 = 64%; 95% CI: 39% to 79%. BMI = body mass index; CVD = cardiovascular disease; other abbreviations as in Figure 2.

ripheral vasoconstriction and sodium retention. Hepatic production of very low-density lipoprotein also increases, leading to hypertriglyceridemia, low HDL cholesterol, elevated apolipoprotein B, elevated small LDL cholesterol, and consequently, atherosclerosis. As a result of these lipid imbalances, individuals with the metabolic syndrome typically exhibit a prothrombotic and proinflammatory state (15,17). More recent definitions by the NCEP (3), rNCEP (7), and the International Diabetes Federation (4) emphasize central obesity as the underlying component. Adipocytes secrete mediators including TNF-α, leptin, adiponectin, and resistin, which lead to insulin resistance. In these definitions, it is postulated that central obesity causes systemic hypertension and dyslipidemia independently and through the induction of insulin resistance.

Regardless of which definition is used, insulin resistance and central obesity are postulated to be the key components of the metabolic syndrome, and both lead to glucose intolerance and dysglycemia. Consequently, even a small change in the fasting glucose threshold may have an important impact on the associated cardiovascular risk. For this reason, there has been considerable debate over the impact of lowering the fasting glucose threshold from ≥110 to ≥100 mg/dl. We therefore carried out a meta-analysis of the cardiovascular risk associated with the rNCEP definition in addition to the original NCEP definition.

Previous meta-analyses showed that the metabolic syndrome was associated with higher cardiovascular risk in women relative to men (9,10). In our meta-analysis, the point estimates for cardiovascular risk were consistently higher in women compared with men. However, patient-level data are needed to confirm this finding. The mechanisms explaining a potentially higher cardiovascular risk in women with the metabolic syndrome are unclear; however, several theories have been postulated (18–20). First, central adiposity tends to be more pronounced in women post-menopause than in men, and thus may be linked to a higher risk of cardiovascular disease (18). Second, the cholesterol profile is different in women compared with men. HDL cholesterol decreases post-menopause and LDL cholesterol increases post-menopause, with LDL particles becoming denser, and therefore, more atherogenic (19). Third, there is evidence that elevated triglycerides are more highly associated with coronary artery disease in women than in men. In a meta-analysis, it was shown that an increase in triglycerides of 18 mg/dl was associated with a 76% increased cardiovascular risk in women compared with a 32% increased risk in men (20). Finally, several studies have suggested a number of other unique risk factors that may be responsible for a stronger association between the metabolic syndrome and cardiovascular risk in women. These risk

Table 5 MetS Studies Reporting the Incidence of Stroke

First Author, Year (Ref. #)*	Population	n	MetS (%)	Follow-Up (yrs)	Effect Measure	Risk of Stroke† (95% CI)		Stroke (%)	
						Least Adjusted	Most Adjusted	MetS Group	Non-MetS Group
NCEP definition‡									
Boden-Albala et al., 2007 (103)	General population	3,297	44.0	6.4§	HR	—	1.50 (1.10–2.20)	—	—
	Men	1,220	38.0	6.4§	HR	—	1.10 (0.60–1.90)	—	—
	Women	2,077	48.0	6.4§	HR	—	2.00 (1.30–3.10)	—	—
Hsia et al., 2003 (104)	Women with angiographic disease	397	61.2	2.8§	RR	1.90 (0.52–6.91)	—	3.7	1.9
McNeill et al., 2005 (105)	Men	6,881	23.7	11.0§	RR	1.28 (0.87–1.89)	—	2.2	1.7
	Women	5,208	22.7	11.0§	RR	5.45 (3.92–7.59)	—	7.4	1.4
Qiao et al., 2009 (106)	Men without CAD and T2DM	4,041	—	21.0‖	HR	1.30 (0.92–1.83)	—	—	—
	Women without CAD and T2DM	3,812	—	21.0‖	HR	2.30 (1.36–1.90)	—	—	—
Solymoss et al., 2009 (94)	Pts with >50% stenosis of CA	876	53.0	12.6§	HR	1.67 (1.18–2.37)	1.68 (1.18–2.39)	—	—
Thorn et al., 2009 (101)	Pts with type 1 diabetes	2,474	—	5.7¶	HR	1.94 (1.25–3.02)	1.51 (0.94–2.44)	—	—
Vlek et al., 2008 (107)	Hypertensive pts without T2DM	1,815	42.7	3.9§	HR	1.36 (0.85–2.16)	—	—	—
Wang et al., 2008 (108)	Elderly without T2DM	991	42.1	13.8¶	HR	1.62 (1.17–2.24)	—	—	—
Wassink et al.,2008 (50)	Pts with CV risk factor	3,196	42.6	3.2¶	HR	1.66 (1.10–2.49)	1.73 (1.13–2.65)	—	—
Modified NCEP definition#									
Chen et al. 2006 (109)	Men	725	45.5	10.4§	HR	5.80 (2.00–16.50)	—	9.1	1.0
	Women	831	58.7	10.4§	HR	2.50 (0.70–8.40)	—	7.7	0.7
Chien et al., 2007 (110)	General population	3,507	24.2	9.0¶	HR	—	2.05 (1.45–2.91)	—	—
Hwang et al., 2009 (80)	Men	1,761	21.7	8.7§	RR	1.35 (0.80–2.25)	—	5.0	3.7
	Women	674	11.4	8.7§	RR	4.98 (2.23–11.13)	—	11.7	2.4
Iso et al., 2007 (111)	Men	3,813	—	18.3¶	HR	1.90 (1.30–2.80)	2.00 (1.30–3.10)	—	—
	Women	5,646	—	18.3¶	HR	1.40 (1.00–2.10)	1.50 (1.00–2.30)	—	—
Kokubo et al., 2008 (81)	Men	2,492	18.0	—	HR	1.52 (0.99–2.34)	1.58 (1.02–2.43)	6.5	4.0
	Women	2,840	20.7	—	HR	1.70 (1.09–2.64)	1.62 (1.02–2.58)	6.0	2.5
Koren-Morag et al., 2005 (112)	Pts with CAD without T2DM	10,784	34.3	8.1‖	RR	1.44 (1.18–1.76)	—	4.3	3.0
	Men with CAD without T2DM	8,844	—	8.1‖	RR	1.31 (1.05–1.64)	—	4.2	3.2
	Women with CAD without T2DM	1,903	—	8.1‖	RR	2.09 (1.28–3.42)	—	4.8	2.3
Kurl et al., 2006 (113)	Men without T2DM	1,264	9.0	14.3§	RR	2.00 (1.01–3.95)	2.39 (1.17–4.89)	—	—
Ninomiya et al., 2007 (82)	Men	1,050	20.6	14.0‖	HR	2.04 (1.33–3.14)	1.92 (1.23–2.98)	14.4	7.6
	Women	1,402	29.9	14.0‖	HR	1.43 (0.99–2.08)	1.50 (1.03–2.19)	11.9	6.6
Song et al., 2007 (84)	Women with BMI <25 kg/m^2	13,256	4.3	10.0¶	RR	1.35 (0.74–2.45)	1.24 (0.64–2.39)	2.1	1.0
	Women with BMI 25–29.9 kg/m^2	7,834	4.3	10.0¶	RR	2.07 (1.23–3.47)	—	1.7	0.8
	Women with BMI ≥30 kg/m^2	4,266	4.3	10.0¶	RR	1.79 (0.96–3.32)	—	1.3	0.8
Takahashi et al., 2007 (13)	Women without T2DM	726	1.1	6.4§	RR	—	23.1 (2.7–19.6)	—	—
Takeuchi et al., 2005 (85)	Men	780	25.3	6.0‖	RR	—	1.61 (1.26–2.06)	—	—
Wannamethee et al., 2005 (114)	Men	5,228	25.5	20.0‖	RR	1.51 (1.20–1.91)	—	7.6	5.0

(continued on next page)

Table 5 Continued

First Author, Year (Ref. #)*	Population	n	MetS (%)	Follow-Up (yrs)	Effect Measure	Risk of Stroke† (95% CI)		Stroke (%)	
						Least Adjusted	Most Adjusted	MetS Group	Non-MetS Group
Revised NCEP definition**									
Nilsson et al., 2008 (102)	Pts without T2DM	5,047	20.7	10.7§	RR	2.47 (1.83–3.34)	—	6.4	2.6
	Men without T2DM	3,008	26.0	10.7§	RR	2.10 (1.39–3.18)	—	7.0	3.3
	Women without T2DM	2,039	17.0	10.7§	RR	2.71 (1.75–4.19)	—	5.9	2.2
Noto et al., 2008 (66)	General population	685	22.9	15.0‖	HR	1.44 (0.94–2.19)	—	6.8	3.5
Qiao et al., 2009 (106)	Men without CAD and T2DM	4,041	—	21.0‖	HR	1.13 (0.81–1.58)	—	—	—
	Women without CAD and T2DM	3,812	—	21.0‖	HR	2.08 (1.24–3.51)	—	—	—
Rodriguez-Colon et al., 2009 (115)	General population	14,993	39.0	9.0‖	RR	2.45 (1.96–3.08)	2.24 (1.78–2.82)	3.2	1.3
	Men	6,732	39.0	9.0‖	RR	1.98 (1.47–2.67)	2.11 (1.56–2.85)	3.7	1.9
	Women	8,261	39.0	9.0‖	RR	3.27 (2.29–4.67)	2.41 (1.69–3.49)	2.9	1.1
Simons et al., 2007 (68)	Elderly men	1,233	31.1	16.0‖	HR	1.43 (1.07–1.92)	1.31 (0.96–1.77)	70.1	15.8
	Elderly women	1,572	34.1	16.0‖	HR	1.53 (1.17–2.01)	1.37 (1.04–1.82)	17.0	12.2
Wang et al., 2008 (108)	Elderly without T2DM	991	50.8	13.8¶	HR	1.52 (1.10–2.11)	—	—	—
Wassink et al., 2008 (50)	Pts with CV risk factor	3,196	50.1	3.2¶	HR	1.75 (1.15–2.66)	1.77 (1.14–2.75)	—	—
	Pts with CV factor without T2DM	2,472	—	3.2¶	HR	1.88 (1.18–2.99)	1.96 (1.21–3.18)	—	—
Wild et al., 2009 (116)	General population	762	34.7	15.0‖	RR	2.61 (1.52–4.48)	—	4.2	11.0
Modified revised NCEP definition#									
Chen et al., 2006 (109)	Men	709	48.6	10.4§	HR	8.20 (2.00–34.30)	—	8.9	0.7
	Women	850	57.3	10.4§	HR	2.60 (0.60–11.30)	—	6.8	0.6

*Studies are listed by category and then alphabetically by author. †Nonadjusted risk estimates and risk estimates adjusting exclusively for age and/or sex were classified as "least adjusted." Risk estimates adjusting for any cardiovascular risk factor or component of the metabolic syndrome (i.e., smoking, cholesterol, obesity) were classified as "most adjusted." ‡The NCEP defines the metabolic syndrome as having 3 or more of the following 5 cardiovascular risk factors: 1) central obesity (waist circumference: men >102 cm; women >88 cm); 2) elevated triglycerides (≥150 mg/dl); 3) diminished high-density lipoprotein (HDL) cholesterol (men <40 mg/dl; women <50 mg/dl); 4) hypertension (≥130/≥85 mm Hg); and 5) elevated fasting glucose (≥110 mg/dl). §Mean follow-up. ‖Maximum follow-up. ¶Median follow-up. #The modified NCEP and modified revised NCEP definitions use measurements of BMI (typically BMI ≥30 kg/m^2 or BMI ≥27 kg/m^2 in Asian populations) to define central obesity. **The revised NCEP definition uses a lower cutoff for elevated fasting glucose of ≥100 mg/dl.

Abbreviations as in Tables 1 and 2.

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Table 6 Summary of the Cardiovascular Risk Associated With the MetS*

Population	CVD			CVD Mortality			All-Cause Mortality			MI			Stroke		
	No. of Pop Arms†	No. of Pts	RR (95% CI)	No. of Pop Arms†	No. of Pts	RR (95% CI)	No. of Pop Arms†	No. of Pts	RR (95% CI)	No. of Pop Arms†	No. of Pts	RR (95% CI)	No. of Pop Arms†	No. of Pts	RR (95% CI)
All MetS definitions	16	45,251	2.35 (2.02–2.73)	19	67,365	2.40 (1.87–3.08)	23	90,788	1.58 (1.39–1.78)	8	17,918	1.99 (1.61–2.46)	22	90,166	2.27 (1.80–2.85)
NCEP definition‡	3	4,156	2.51 (1.38–4.55)	8	49,918	1.85 (1.42–2.41)	10	62,336	1.54 (1.29–1.84)	2	6,068	1.69 (1.37–2.08)	3	12,486	2.43 (0.77–7.68)
Modified NCEP definition§	10	36,462	2.44 (2.03–2.92)	3	3,667	4.28 (2.25–8.14)	5	12,972	1.74 (1.13–2.68)	4	6,149	2.49 (1.41–4.42)	13	53,413	2.03 (1.64–2.50)
rNCEP definition‖	3	4,633	1.93 (1.56–2.40)	6	31,592	2.91 (1.85–4.58)	7	34,103	1.63 (1.30–2.04)	2	5,701	1.97 (1.49–2.61)	8	25,823	2.92 (1.94–4.39)
Modified rNCEP definition§	0	0	—	3	2,977	2.37 (1.66–3.38)	2	2,166	1.32 (0.74–2.35)	0	0	—	0	0	—
Men¶	5	7,353	2.14 (1.62–2.83)	7	30,481	1.94 (1.20–3.14)	7	33,346	1.42 (1.16–1.74)	2	4,531	2.01 (1.52–2.67)	10	36,985	2.00 (1.38–2.88)
Women¶	7	32,258	2.87 (2.40–3.43)	5	8,185	2.55 (1.41–4.60)	9	16,179	1.86 (1.37–2.52)	2	5,848	2.57 (0.87–7.57)	13	51,722	2.59 (1.94–3.46)
Pts without T2DM¶	1	1,830	—	4	9,824	1.75 (1.19–2.58)	2	3,622	1.32 (0.65–2.67)	3	7,609	1.62 (1.31–2.01)	2	15,831	1.86 (1.10–3.17)

*The RRs provided are pooled estimates using random-effects modeling. †The number of population arms (Pop Arms) refers to all the different population subgroups for which studies reported risk estimates. ‡The NCEP defines the metabolic syndrome as having 3 or more of the following 5 cardiovascular risk factors: 1) central obesity (waist circumference: men >102 cm; women >88 cm); 2) elevated triglycerides (≥150 mg/dl); 3) diminished high-density lipoprotein (HDL) cholesterol (men <40 mg/dl; women <50 mg/dl); 4) hypertension (≥130/≥85 mm Hg); and 5) elevated fasting glucose (≥110 mg/dl). §The modified NCEP and modified revised NCEP definitions use measurements of BMI (typically BMI ≥30 kg/m^2 or BMI ≥27 kg/m^2 in Asian populations) to define central obesity. ‖The revised NCEP definition uses a lower cutoff for elevated fasting glucose of ≥100 mg/dl. ¶We evaluated the relative risk of CVD, CVD mortality, all-cause mortality, MI, and stroke in men with the metabolic syndrome, women with the metabolic syndrome, and patients without type 2 diabetes mellitus, but with the metabolic syndrome.

CI = confidence interval; rNCEP = revised National Cholesterol Education Program; Pop = population; other abbreviations as in Table 1.

factors include polycystic ovary syndrome (21), hormonal contraceptive use (22–24), and gestational diabetes (25).

Our results also suggest that the metabolic syndrome maintains its prognostic value for cardiovascular outcomes in the absence of type 2 diabetes mellitus. Some experts have suggested that the reason the metabolic syndrome is associated with an increase in cardiovascular risk is because most patients with the metabolic syndrome also have type 2 diabetes mellitus (8). However, after synthesizing the results of studies conducted in patients without type 2 diabetes mellitus, the metabolic syndrome remained associated with a high cardiovascular risk, ranging from RR: 1.62 (95% CI: 1.31 to 2.01; I^2 = 0%; 95% CI: 0% to 90%) for MI, to RR: 1.86 (95% CI: 1.10 to 3.17; I^2 = 89; 95% CI: 56% to 97%) for stroke. The risk for all-cause mortality in patients without type 2 diabetes mellitus (RR: 1.32; 95% CI: 0.65 to 2.67; I^2 = 87; 95% CI: 47% to 97%) was accompanied by a wide and therefore inconclusive confidence interval because this analysis involved only 2 studies (n = 3,622 patients). More studies are needed to confirm whether or not the metabolic syndrome is prognostic in this population.

Our systematic review allowed us to identify an important gap in the literature. The prognostic importance of the metabolic syndrome, compared with that of the sum of its individual components (obesity, systemic hypertension, elevated fasting glucose, elevated triglycerides, and low HDL cholesterol), has repeatedly been challenged (8,26,27). In a cohort study of 2,815 patients, the risk of CVD mortality associated with the metabolic syndrome as defined by the NCEP definition (HR: 2.53; 95% CI: 1.74 to 3.67) was similar to the risk associated with impaired fasting glucose (HR: 2.87; 95% CI: 1.96 to 4.20) and systemic hypertension (HR: 1.71; 95% CI: 1.15 to 2.54) (28). Furthermore, in a systematic review of 7 clinical trials (n = 3,459), the metabolic syndrome as defined by the NCEP definition was no longer an independent predictor of atherosclerotic plaque progression after adjustment for its individual components (29). Despite these studies, there remains debate as to whether or not the metabolic syndrome provides a synergistic effect that increases its association with cardiovascular risk. Of the 87 studies included in our systematic review, only 5 reported risk estimates that were adjusted for at least 1 component of the metabolic syndrome (Online Table 5). Of these 5 studies, 3 adjusted for obesity, 3 adjusted for systemic hypertension, and 1 adjusted for fasting glucose. There is a need for prospective studies that investigate the risk associated with the metabolic syndrome independent of the risk of its individual components in order to establish whether or not the metabolic syndrome adds any prognostic significance.

Our results allow us to confirm the strong association of the 2001 NCEP definition of the metabolic syndrome with cardiovascular risk. Furthermore, to our knowledge, no previous meta-analyses have been conducted to establish the cardiovascular risk associated with the 2004 rNCEP definition. We recommend that health care workers use the

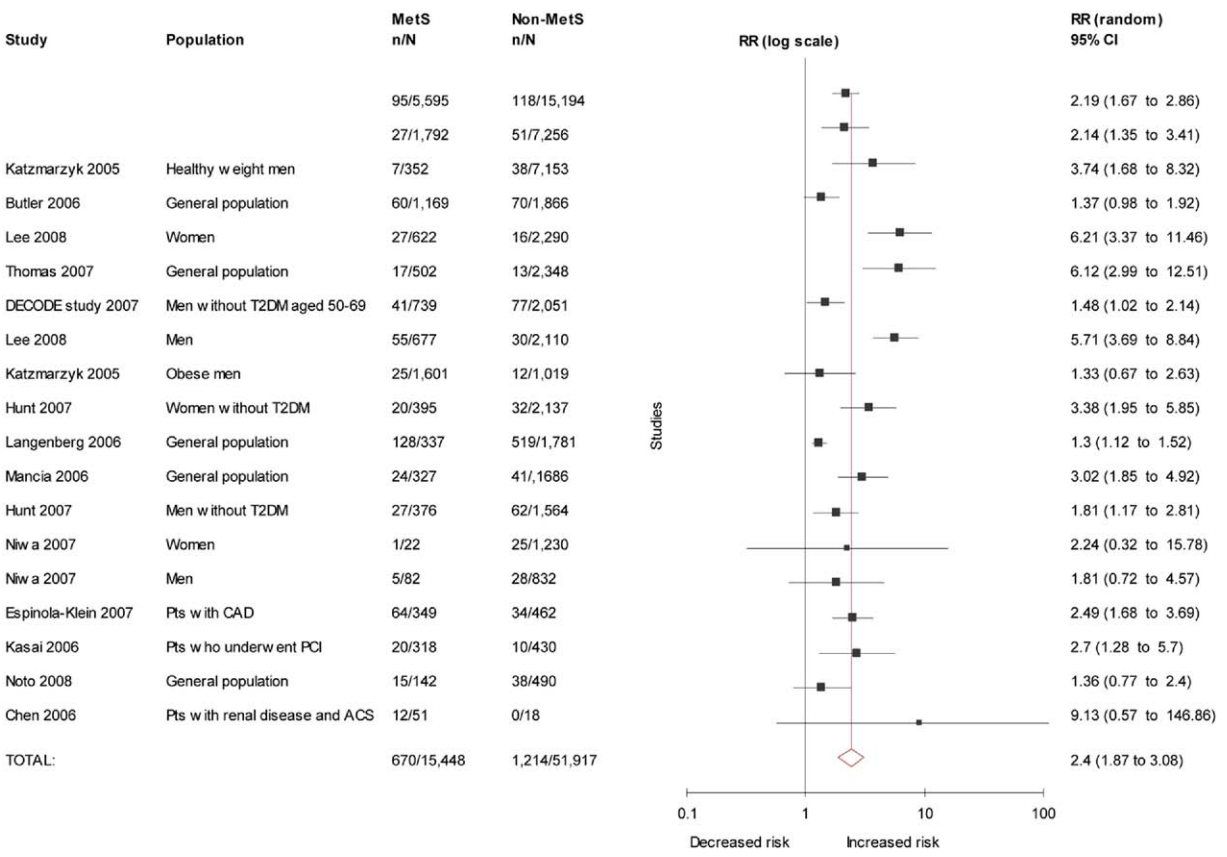

Figure 4 **The Metabolic Syndrome and the Relative Risk for CVD Mortality**

I^2 = 81%; 95% CI: 72% to 88%. Abbreviations as in Figure 2.

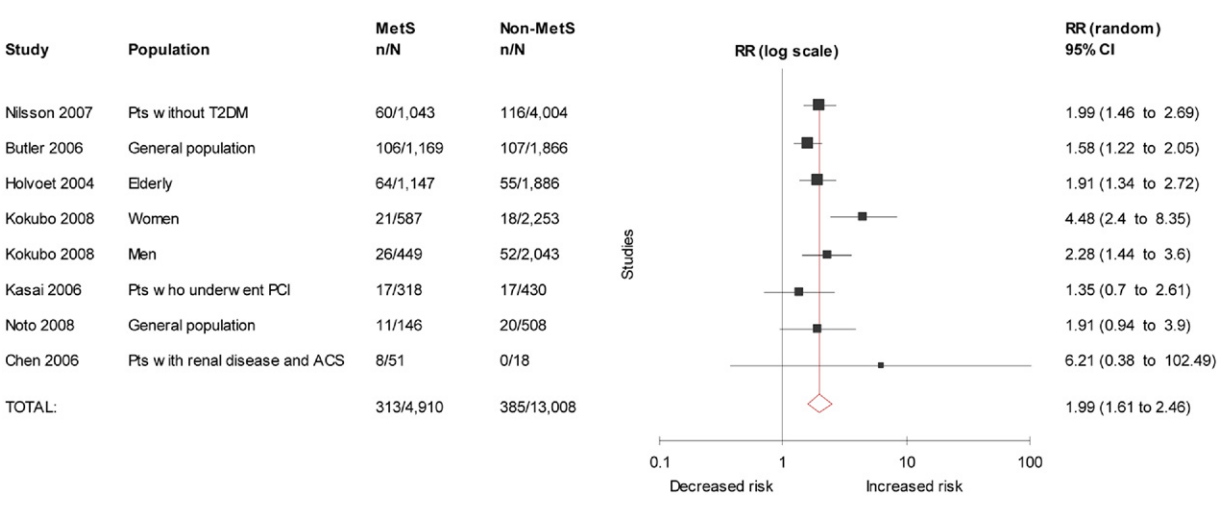

Figure 5 **The Metabolic Syndrome and the Relative Risk for MI**

I^2 = 40%; 95% CI: 0% to 73%. Abbreviations as in Figure 2.

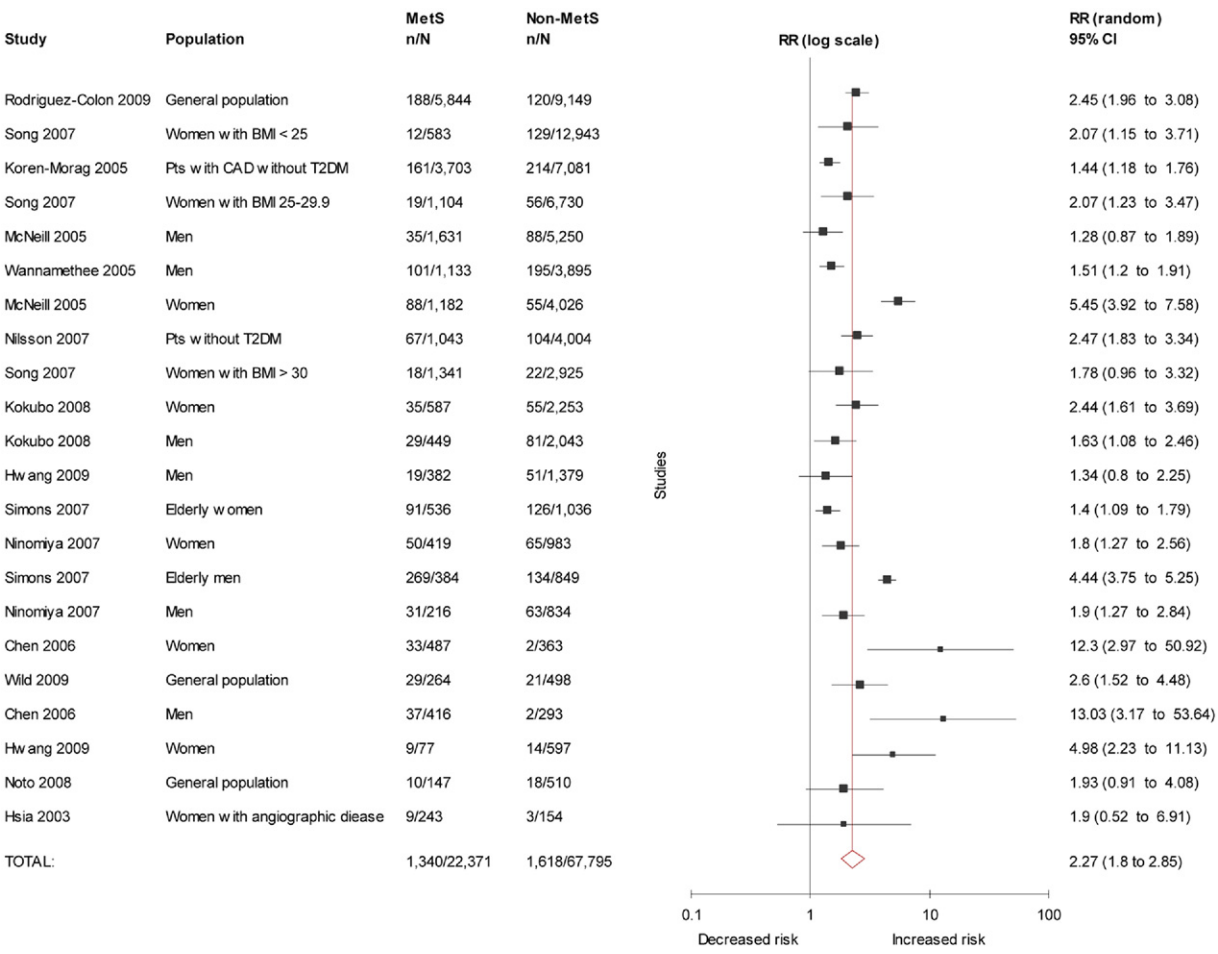

Figure 6 **The Metabolic Syndrome and the Relative Risk for Stroke**

I^2 = 88%; 95% CI: 82% to 91%. Abbreviations as in Figures 2 and 3.

metabolic syndrome as a diagnostic tool for identifying patients who are at risk for cardiovascular events. There is an urgent need to develop and implement prevention and treatment strategies, such as lifestyle programs, diets, and pharmacotherapies to reduce the prevalence of the metabolic syndrome and its associated cardiovascular risk (30,31).

Previous studies. Two previous meta-analyses, which included studies published prior to 2005, investigated the cardiovascular risk associated with the metabolic syndrome (9,10). An additional 71 studies investigating the NCEP and rNCEP definitions have been published since the conduct of these meta-analyses, and these studies were included in our meta-analysis (32). We also established the cardiovascular risk associated with the rNCEP definition of the metabolic syndrome, which was only released in 2004 (7). Finally, we confirmed that there was little variation in cardiovascular risk between the modified NCEP and rNCEP definitions compared with the original NCEP definition.

The 2 previous meta-analyses concluded that the metabolic syndrome nearly doubled the risk of cardiovascular events. We obtained consistently higher point estimates for cardiovascular outcomes (RR >2) and showed that the risk for CVD, CVD mortality, and stroke exceeds that of all-cause mortality. However, there remains a need for future studies to investigate the cardiovascular risk associated with the metabolic syndrome after its individual components have been adjusted for.

Study limitations. Our meta-analysis has a number of potential limitations. The inclusion of observational cohort studies in our meta-analysis presented challenges beyond those typically encountered in meta-analyses of randomized controlled trials. First, of the 87 studies included in our paper, only 34 studies reported count data that we pooled. The remaining 53 studies only reported risk estimates (RR or HR), which were not included in our pooled analyses. However, we included these 53 studies in tables as part of our systematic review. Second, the length of follow-up varied considerably between studies. However, in a sensi-

tivity analysis, we stratified studies by the length of follow-up and found that studies with longer follow-up times had risk estimates that were similar to those in studies with shorter follow-up times. There was also some heterogeneity in baseline patient characteristics, such as the inclusion of patients with atherosclerosis, systemic hypertension, or a history of CVD. Due to the presence of potential heterogeneity between studies, data were analyzed using random-effects models, which incorporate both within- and between-study variability. In addition, we conducted a sensitivity analysis in which we restricted our analyses to studies of subjects without systemic hypertension, atherosclerosis, or cardiovascular disease. The results of these analyses are consistent with those of our primary analysis. A third potential limitation was the limited number of studies available to estimate the cardiovascular risk associated with the metabolic syndrome in our subgroup analyses of men, women, and patients without type 2 diabetes mellitus. We could not conduct meta-regression analyses to estimate the effect of these covariates on the metabolic syndrome–cardiovascular risk association since the number of studies investigating these subgroups was small. A fourth limitation includes the inherent assumptions of meta-analysis. We were limited to data reported in published articles and did not have access to individual patient-level data. Access to patient-level data would have been particularly helpful for our subgroup analyses. Fifth, visual assessment of funnel plots suggests that mild publication bias may be present. Publication bias is an inherent limitation to virtually all meta-analyses. Finally, our meta-analysis was limited to studies published in English. However, <5% of studies identified in our literature search were published in a language other than English, and their exclusion is unlikely to substantially affect the conclusions of our meta-analysis.

Conclusions

The metabolic syndrome is associated with a 2-fold increase in risk for CVD, CVD mortality, MI, and stroke, and a 1.5-fold increase in risk for all-cause mortality. There is little variation in risk between the NCEP and rNCEP definitions of the metabolic syndrome. There is also little variation in risk for the modified NCEP and rNCEP definitions compared with the original NCEP definition. In addition, our results indicate that patients with the metabolic syndrome, but without type 2 diabetes mellitus, are still at high risk for CVD mortality, MI, and stroke. We therefore suggest that the metabolic syndrome does not require type 2 diabetes mellitus in its definition in order to be closely associated with cardiovascular risk. Our systematic review identified an important gap in the literature; studies are needed to investigate whether or not the prognostic significance of the metabolic syndrome exceeds the risk associated with the sum of its individual components. We recommend that health care workers use the metabolic syndrome to identify patients who are at particularly high risk for cardiovascular complications. The prevention and reduction of the metabolic syndrome is essential to reduce cardiovascular disease and to extend life in the adult population.

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REFERENCES

1. Ford ES, Giles WH, Dietz WH. Prevalence of the metabolic syndrome among US adults: findings from the third National Health and Nutrition Examination Survey. JAMA 2002;287:356–9.
2. Reaven GM. Banting lecture 1988. Role of insulin resistance in human disease. Diabetes 1988;37:1595–607.
3. Executive Summary of The Third Report of The National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). JAMA 2001;285:2486–97.
4. International Diabetes Federation. The IDF Consensus Worldwide Definition of the Metabolic Syndrome. Brussels, Belgium: International Diabetes Federation; 2006.
5. WHO Consultation. Definition, diagnosis and classification of diabetes mellitus and its complications. Geneva, Switzerland: World Health Organization; 1999:31–3.
6. Moebus S, Hanisch J, Neuhäuser M, Aidelsburger P, Wasem J, Jöckel K. Assessing the prevalence of the Metabolic Syndrome according to NCEP ATP III in Germany: feasibility and quality aspects of a two step approach in 1550 randomly selected primary health care practices. Ger Med Sci 2006;4:Doc07.
7. Grundy SM, Brewer HB Jr., Cleeman JI, Smith SC Jr., Lenfant C. Definition of metabolic syndrome: report of the National Heart, Lung, and Blood Institute/American Heart Association conference on scientific issues related to definition. Circulation 2004;109:433–8.
8. Kahn R, Buse J, Ferrannini E, Stern M. The metabolic syndrome: time for a critical appraisal: joint statement from the American Diabetes Association and the European Association for the Study of Diabetes. Diabetes Care 2005;28:2289–304.
9. Gami AS, Witt BJ, Howard DE, et al. Metabolic syndrome and risk of incident cardiovascular events and death: a systematic review and meta-analysis of longitudinal studies. J Am Coll Cardiol 2007;49:403–14.
10. Galassi A, Reynolds K, He J. Metabolic syndrome and risk of cardiovascular disease: a meta-analysis. Am J Med 2006;119:812–9.
11. Bax L, Yu LM, Ikeda N, Tsuruta H, Moons KG. Development and validation of MIX: comprehensive free software for meta-analysis of causal research data. BMC Med Res Methodol 2006;6:50.
12. Bax L, Yu LM, Ikeda N, Tsuruta H, Moons KG. MIX: comprehensive free software for meta-analysis of causal research data [computer program]. Version 1.7. 2008.
13. Takahashi K, Bokura H, Kobayashi S, Iijima K, Nagai A, Yamaguchi S. Metabolic syndrome increases the risk of ischemic stroke in women. Intern Med 2007;46:643–8.
14. Butler J, Rodondi N, Zhu Y, et al. Metabolic syndrome and the risk of cardiovascular disease in older adults. J Am Coll Cardiol 2006;47:1595–602.
15. Alberti KG, Eckel RH, Grundy SM, et al. Harmonizing the metabolic syndrome: a joint interim statement of the International Diabetes Federation Task Force on Epidemiology and Prevention; National Heart, Lung, and Blood Institute; American Heart Association; World Heart Federation; International Atherosclerosis Society; and International Association for the Study of Obesity. Circulation 2009;120:1640–5.

16. Ferrannini E, Natali A, Bell P, Cavallo-Perin P, Lalic N, Mingrone G, European Group for the Study of Insulin Resistance (EGIR). Insulin resistance and hypersecretion in obesity. J Clin Invest 1997; 100:1166–73.
17. Onat A, Can G, Hergenc G, Yazici M, Karabulut A, Albayrak S. Serum apolipoprotein B predicts dyslipidemia, metabolic syndrome and, in women, hypertension and diabetes, independent of markers of central obesity and inflammation. Int J Obes (Lond) 2007;31: 1119–25.
18. Donato GB, Fuchs SC, Oppermann K, Bastos C, Spritzer PM. Association between menopause status and central adiposity measured at different cutoffs of waist circumference and waist-to-hip ratio. Menopause 2006;13:280–5.
19. Blake GJ, Otvos JD, Rifai N, Ridker PM. Low-density lipoprotein particle concentration and size as determined by nuclear magnetic resonance spectroscopy as predictors of cardiovascular disease in women. Circulation 2002;106:1930–7.
20. Hokanson JE, Austin MA. Plasma triglyceride level is a risk factor for cardiovascular disease independent of high-density lipoprotein cholesterol level: a meta-analysis of population-based prospective studies. J Cardiovasc Risk 1996;3:213–9.
21. Legro RS. Polycystic ovary syndrome and cardiovascular disease: a premature association? Endocr Rev 2003;24:302–12.
22. Anderson GL, Limacher M, Assaf AR, et al. Effects of conjugated equine estrogen in postmenopausal women with hysterectomy: the Women's Health Initiative randomized controlled trial. JAMA 2004; 291:1701–12.
23. Hsia J, Langer RD, Manson JE, et al. Conjugated equine estrogens and coronary heart disease: the Women's Health Initiative. Arch Intern Med 2006;166:357–65.
24. Manson JE, Hsia J, Johnson KC, et al. Estrogen plus progestin and the risk of coronary heart disease. N Engl J Med 2003;349:523–34.
25. Carr DB, Utzschneider KM, Hull RL, et al. Gestational diabetes mellitus increases the risk of cardiovascular disease in women with a family history of type 2 diabetes. Diabetes Care 2006;29:2078–83.
26. Grundy SM. Metabolic syndrome: a multiplex cardiovascular risk factor. J Clin Endocrinol Metab 2007;92:399–404.
27. Johnson LW, Weinstock RS. The metabolic syndrome: concepts and controversy. Mayo Clin Proc 2006;81:1615–20.
28. Hunt KJ, Resendez RG, Williams K, Haffner SM, Stern MP. National Cholesterol Education Program versus World Health Organization metabolic syndrome in relation to all-cause and cardiovascular mortality in the San Antonio Heart Study. Circulation 2004;110:1251–7.
29. Bayturan O, Tuzcu EM, Lavoie A, et al. The metabolic syndrome, its component risk factors, and progression of coronary atherosclerosis. Arch Intern Med 2010;170:478–84.
30. Poirier P, Despres JP. Waist circumference, visceral obesity, and cardiovascular risk. J Cardiopulm Rehabil 2003;23:161–9.
31. Drolet B, Simard C, Poirier P. Impact of weight-loss medications on the cardiovascular system: focus on current and future anti-obesity drugs. Am J Cardiovasc Drugs 2007;7:273–88.
32. Shojania KG, Sampson M, Ansari MT, Ji J, Doucette S, Moher D. How quickly do systematic reviews go out of date? A survival analysis. Ann Intern Med 2007;147:224–33.
33. Benetos A, Thomas F, Pannier B, Bean K, Jego B, Guize L. All-cause and cardiovascular mortality using the different definitions of metabolic syndrome. Am J Cardiol 2008;102:188–91.
34. Dekker JM, Girman C, Rhodes T, et al. Metabolic syndrome and 10-year cardiovascular disease risk in the Hoorn Study. Circulation 2005;112:666–73.
35. Guize L, Thomas F, Pannier B, Bean K, Jego B, Benetos A. All-cause mortality associated with specific combinations of the metabolic syndrome according to recent definitions. Diabetes Care 2007;30:2381–7.
36. Hillier TA, Rizzo JH, Pedula KL, et al. Increased mortality associated with the metabolic syndrome in older women with diabetes. Diabetes Care 2005;28:2258–60.
37. Hong Y, Jin X, Mo J, et al. Metabolic syndrome, its preeminent clusters, incident coronary heart disease and all-cause mortality—results of prospective analysis for the Atherosclerosis Risk in Communities study. J Intern Med 2007;262:113–22.
38. Katzmarzyk PT, Church TS, Janssen I, Ross R, Blair SN. Metabolic syndrome, obesity, and mortality: impact of cardiorespiratory fitness. Diabetes Care 2005;28:391–7.
39. Katzmarzyk PT, Janssen I, Ross R, Church TS, Blair SN. The importance of waist circumference in the definition of metabolic syndrome: prospective analyses of mortality in men. Diabetes Care 2006;29:404–9.
40. Lakka HM, Laaksonen DE, Lakka TA, et al. The metabolic syndrome and total and cardiovascular disease mortality in middle-aged men. JAMA 2002;288:2709–16.
41. Langenberg C, Bergstrom J, Scheidt-Nave C, Pfeilschifter J, Barrett-Connor E. Cardiovascular death and the metabolic syndrome: role of adiposity-signaling hormones and inflammatory markers. Diabetes Care 2006;29:1363–9.
42. Mancia G, Bombelli M, Corrao G, et al. Metabolic syndrome in the Pressioni Arteriose Monitorate E Loro Associazioni (PAMELA) study: daily life blood pressure, cardiac damage, and prognosis. Hypertension 2007;49:40–7.
43. Marroquin OC, Kip KE, Kelley DE, et al. Metabolic syndrome modifies the cardiovascular risk associated with angiographic coronary artery disease in women: a report from the Women's Ischemia Syndrome Evaluation. Circulation 2004;109:714–21.
44. Monami M, Lamanna C, Balzi D, et al. Metabolic syndrome and cardiovascular mortality in older type 2 diabetic patients: a longitudinal study. J Gerontol A Biol Sci Med Sci 2008;63:646–9.
45. Pannier B, Thomas F, Bean K, Jego B, Benetos A, Guize L. The metabolic syndrome: similar deleterious impact on all-cause mortality in hypertensive and normotensive subjects. J Hypertens 2008;26: 1223–8.
46. Ramkumar N, Murtaugh MA, Cheung AK, Beddhu S. Lack of synergistic effects of metabolic syndrome and plasma fibrinogen on coronary events and mortality in moderate CKD. Am J Kidney Dis 2007;49:356–64.
47. Sundstrom J, Riserus U, Byberg L, Zethelius B, Lithell H, Lind L. Clinical value of the metabolic syndrome for long term prediction of total and cardiovascular mortality: prospective, population based cohort study. BMJ 2006;332:878–82.
48. Takeno M, Yasuda S, Otsuka Y, et al. Impact of metabolic syndrome on the long-term survival of patients with acute myocardial infarction: potential association with C-reactive protein. Circ J 2008;72: 415–9.
49. Wang J, Ruotsalainen S, Moilanen L, Lepisto P, Laakso M, Kuusisto J. The metabolic syndrome predicts cardiovascular mortality: a 13-year follow-up study in elderly non-diabetic Finns. Eur Heart J 2007;28:857–64.
50. Wassink AM, van der Graaf Y, Olijhoek JK, Visseren FL. Metabolic syndrome and the risk of new vascular events and all-cause mortality in patients with coronary artery disease, cerebrovascular disease, peripheral arterial disease or abdominal aortic aneurysm. Eur Heart J 2008;29:213–23.
51. Zambon S, Zanoni S, Romanato G, et al. Metabolic syndrome and all-cause and cardiovascular mortality in an Italian elderly population: the Progetto Veneto Anziani Pro.V.A. Study. Diabetes Care 2009; 32:153–9.
52. Chen HH, Wu CJ, Chen YC, Tsai CS, Lin FJ, Yeh HI. Metabolic syndrome is associated with severe coronary artery disease and poor cardiac outcome in end-stage renal disease patients with acute coronary syndrome. Coron Artery Dis 2006;17:593–6.
53. Feinberg MS, Schwartz R, Tanne D, et al. Impact of the metabolic syndrome on the clinical outcomes of non-clinically diagnosed diabetic patients with acute coronary syndrome. Am J Cardiol 2007;99:667–72.
54. Kasai T, Miyauchi K, Kurata T, et al. Prognostic value of the metabolic syndrome for long-term outcomes in patients undergoing percutaneous coronary intervention. Circ J 2006;70:1531–7.
55. Levantesi G, Macchia A, Marfisi R, et al. Metabolic syndrome and risk of cardiovascular events after myocardial infarction. J Am Coll Cardiol 2005;46:277–83.
56. Malik S, Wong ND, Franklin SS, et al. Impact of the metabolic syndrome on mortality from coronary heart disease, cardiovascular disease, and all causes in United States adults. Circulation 2004;110: 1245–50.
57. Nigam A, Bourassa MG, Fortier A, Guertin MC, Tardif JC. The metabolic syndrome and its components and the long-term risk of

death in patients with coronary heart disease. Am Heart J 2006;151:514–21.
58. Thomas GN, Schooling CM, McGhee SM, et al. Metabolic syndrome increases all-cause and vascular mortality: the Hong Kong Cardiovascular Risk Factor Study. Clin Endocrinol (Oxf) 2007;66:666–71.
59. Davis TM, Bruce DG, Davis WA. Prevalence and prognostic implications of the metabolic syndrome in community-based patients with type 1 diabetes: the Fremantle Diabetes Study. Diabetes Res Clin Pract 2007;78:412–7.
60. Hildrum B, Mykletun A, Dahl AA, Midthjell K. Metabolic syndrome and risk of mortality in middle-aged versus elderly individuals: the Nord-Trondelag Health Study (HUNT). Diabetologia 2009;52:583–90.
61. Huang KC, Lee LT, Chen CY, Sung PK. All-cause and cardiovascular disease mortality increased with metabolic syndrome in Taiwanese. Obesity (Silver Spring) 2008;16:684–9.
62. Kajimoto K, Kasai T, Miyauchi K, et al. Metabolic syndrome predicts 10-year mortality in non-diabetic patients following coronary artery bypass surgery. Circ J 2008;72:1481–6.
63. Lee J, Heng D, Ma S, Chew SK, Hughes K, Tai ES. The metabolic syndrome and mortality: the Singapore Cardiovascular Cohort Study. Clin Endocrinol (Oxf) 2008;69:225–30.
64. Lopes NH, Paulitsch FS, Pereira AC, et al. Impact of metabolic syndrome on the outcome of patients with stable coronary artery disease: 2-year follow-up of the MASS II study. Coron Artery Dis 2008;19:383–8.
65. Mozaffarian D, Kamineni A, Prineas RJ, Siscovick DS. Metabolic syndrome and mortality in older adults: the Cardiovascular Health Study. Arch Intern Med 2008;168:969–78.
66. Noto D, Barbagallo CM, Cefalu AB, et al. The metabolic syndrome predicts cardiovascular events in subjects with normal fasting glucose: results of a 15 years follow-up in a Mediterranean population. Atherosclerosis 2008;197:147–53.
67. Saito I, Iso H, Kokubo Y, Inoue M, Tsugane S. Metabolic syndrome and all-cause and cardiovascular disease mortality: Japan Public Health Center-based Prospective JPHC Study. Circ J 2009;73:878–84.
68. Simons LA, Simons J, Friedlander Y, McCallum J. Does a diagnosis of the metabolic syndrome provide additional prediction of cardiovascular disease and total mortality in the elderly? The Dubbo Study. Med J Aust 2007;186:400–3.
69. Wen CJ, Lee YS, Lin WY, et al. The metabolic syndrome increases cardiovascular mortality in Taiwanese elderly. Eur J Clin Invest 2008;38:469–75.
70. Hsu PF, Chuang SY, Cheng HM, Tsai ST, Chou P, Chen CH. Clinical significance of the metabolic syndrome in the absence of established hypertension and diabetes: a community-based study. Diabetes Res Clin Pract 2008;79:461–7.
71. Kasai T, Miyauchi K, Kurata T, et al. Impact of metabolic syndrome among patients with and without diabetes mellitus on long-term outcomes after percutaneous coronary intervention. Hypertens Res 2008;31:235–41.
72. Niwa Y, Ishikawa S, Gotoh T, Kayaba K, Nakamura Y, Kajii E. Metabolic syndrome mortality in a population-based cohort study: Jichi Medical School (JMS) Cohort Study. J Epidemiol 2007;17:203–9.
73. Tanomsup S, Aekplakorn W, Sritara P, et al. A comparison of components of two definitions of the metabolic syndrome related to cardiovascular disease and all-cause mortality in a cohort study in Thailand. Diabetes Care 2007;30:2138–40.
74. Andreadis EA, Tsourous GI, Tzavara CK, et al. Metabolic syndrome and incident cardiovascular morbidity and mortality in a Mediterranean hypertensive population. Am J Hypertens 2007;20:558–64.
75. Jeppesen J, Hansen TW, Rasmussen S, Ibsen H, Torp-Pedersen C, Madsbad S. Insulin resistance, the metabolic syndrome, and risk of incident cardiovascular disease: a population-based study. J Am Coll Cardiol 2007;49:2112–9.
76. Resnick HE, Jones K, Ruotolo G, et al. Insulin resistance, the metabolic syndrome, and risk of incident cardiovascular disease in nondiabetic american indians: the Strong Heart Study. Diabetes Care 2003;26:861–7.
77. Sattar N, McConnachie A, Shaper AG, et al. Can metabolic syndrome usefully predict cardiovascular disease and diabetes? Outcome data from two prospective studies. Lancet 2008;371:1927–35.
78. Wilson PW, D'Agostino RB, Parise H, Sullivan L, Meigs JB. Metabolic syndrome as a precursor of cardiovascular disease and type 2 diabetes mellitus. Circulation 2005;112:3066–72.
79. Guzder RN, Gatling W, Mullee MA, Byrne CD. Impact of metabolic syndrome criteria on cardiovascular disease risk in people with newly diagnosed type 2 diabetes. Diabetologia 2006;49:49–55.
80. Hwang YC, Jee JH, Oh EY, et al. Metabolic syndrome as a predictor of cardiovascular diseases and type 2 diabetes in Koreans. Int J Cardiol 2009;134:313–21.
81. Kokubo Y, Okamura T, Yoshimasa Y, et al. Impact of metabolic syndrome components on the incidence of cardiovascular disease in a general urban Japanese population: the Suita study. Hypertens Res 2008;31:2027–35.
82. Ninomiya T, Kubo M, Doi Y, et al. Impact of metabolic syndrome on the development of cardiovascular disease in a general Japanese population: the Hisayama study. Stroke 2007;38:2063–9.
83. Schillaci G, Pirro M, Vaudo G, et al. Prognostic value of the metabolic syndrome in essential hypertension. J Am Coll Cardiol 2004;43:1817–22.
84. Song Y, Manson JE, Meigs JB, Ridker PM, Buring JE, Liu S. Comparison of usefulness of body mass index versus metabolic risk factors in predicting 10-year risk of cardiovascular events in women. Am J Cardiol 2007;100:1654–8.
85. Takeuchi H, Saitoh S, Takagi S, et al. Metabolic syndrome and cardiac disease in Japanese men: applicability of the concept of metabolic syndrome defined by the National Cholesterol Education Program-Adult Treatment Panel III to Japanese men—the Tanno and Sobetsu Study. Hypertens Res 2005;28:203–8.
86. Worm SW, De Wit S, Weber R, et al. Diabetes mellitus, preexisting coronary heart disease, and the risk of subsequent coronary heart disease events in patients infected with human immunodeficiency virus: the Data Collection on Adverse Events of Anti-HIV Drugs (D:A:D Study). Circulation 2009;119:805–11.
87. Ingelsson E, Sullivan LM, Murabito JM, et al. Prevalence and prognostic impact of subclinical cardiovascular disease in individuals with the metabolic syndrome and diabetes. Diabetes 2007;56:1718–26.
88. Liu J, Grundy SM, Wang W, et al. Ten-year risk of cardiovascular incidence related to diabetes, prediabetes, and the metabolic syndrome. Am Heart J 2007;153:552–8.
89. Meigs JB, Rutter MK, Sullivan LM, Fox CS, D'Agostino RB Sr., Wilson PW. Impact of insulin resistance on risk of type 2 diabetes and cardiovascular disease in people with metabolic syndrome. Diabetes Care 2007;30:1219–25.
90. Vaccarino V, McClure C, Johnson BD, et al. Depression, the metabolic syndrome and cardiovascular risk. Psychosom Med 2008;70:40–8.
91. Wand H, Calmy A, Carey DL, et al. Metabolic syndrome, cardiovascular disease and type 2 diabetes mellitus after initiation of antiretroviral therapy in HIV infection. AIDS 2007;21:2445–53.
92. Does diagnosis of the metabolic syndrome detect further men at high risk of cardiovascular death beyond those identified by a conventional cardiovascular risk score? The DECODE study. Eur J Cardiovasc Prev Rehabil 2007;14:192–9.
93. Maggi S, Noale M, Gallina P, et al. Metabolic syndrome, diabetes, and cardiovascular disease in an elderly Caucasian cohort: the Italian Longitudinal Study on Aging. J Gerontol A Biol Sci Med Sci 2006;61:505–10.
94. Solymoss BC, Bourassa MG, Marcil M, Levesque S, Varga S, Campeau L. Long-term rates of cardiovascular events in patients with the metabolic syndrome according to severity of coronary-angiographic alterations. Coron Artery Dis 2009;20:1–8.
95. de Simone G, Olsen MH, Wachtell K, et al. Clusters of metabolic risk factors predict cardiovascular events in hypertension with target-organ damage: the LIFE study. J Hum Hypertens 2007;21:625–32.
96. Nakatani D, Sakata Y, Sato H, et al. Clinical impact of metabolic syndrome and its additive effect with smoking on subsequent cardiac events after acute myocardial infarction. Am J Cardiol 2007;99:885–9.
97. Hunt KJ, Williams K, Hazuda HP, Stern MP, Haffner SM. The metabolic syndrome and the impact of diabetes on coronary heart

disease mortality in women and men: the San Antonio Heart Study. Ann Epidemiol 2007;17:870–7.
98. Espinola-Klein C, Rupprecht HJ, Bickel C, et al. Impact of metabolic syndrome on atherosclerotic burden and cardiovascular prognosis. Am J Cardiol 2007;99:1623–8.
99. Girman CJ, Rhodes T, Mercuri M, et al. The metabolic syndrome and risk of major coronary events in the Scandinavian Simvastatin Survival Study (4S) and the Air Force/Texas Coronary Atherosclerosis Prevention Study (AFCAPS/TexCAPS). Am J Cardiol 2004; 93:136–41.
100. Holvoet P, Kritchevsky SB, Tracy RP, et al. The metabolic syndrome, circulating oxidized LDL, and risk of myocardial infarction in well-functioning elderly people in the health, aging, and body composition cohort. Diabetes 2004;53:1068–73.
101. Thorn LM, Forsblom C, Waden J, et al. Metabolic syndrome as a risk factor for cardiovascular disease, mortality, and progression of diabetic nephropathy in type 1 diabetes. Diabetes Care 2009;32: 950–2.
102. Nilsson PM, Engstrom G, Hedblad B. The metabolic syndrome and incidence of cardiovascular disease in non-diabetic subjects—a population-based study comparing three different definitions. Diabet Med 2007;24:464–72.
103. Boden-Albala B, Sacco RL, Lee HS, et al. Metabolic syndrome and ischemic stroke risk: Northern Manhattan Study. Stroke 2008;39: 30–5.
104. Hsia J, Bittner V, Tripputi M, Howard BV. Metabolic syndrome and coronary angiographic disease progression: the Women's Angiographic Vitamin & Estrogen trial. Am Heart J 2003;146:439–45.
105. McNeill AM, Rosamond WD, Girman CJ, et al. The metabolic syndrome and 11-year risk of incident cardiovascular disease in the atherosclerosis risk in communities study. Diabetes Care 2005;28: 385–90.
106. Qiao Q, Laatikainen T, Zethelius B, et al. Comparison of definitions of metabolic syndrome in relation to the risk of developing stroke and coronary heart disease in Finnish and Swedish cohorts. Stroke 2009;40:337–43.
107. Vlek AL, van der Graaf Y, Spiering W, Visseren FL. Effect of metabolic syndrome or type II diabetes mellitus on the occurrence of recurrent vascular events in hypertensive patients. J Hum Hypertens 2008;22:358–65.
108. Wang J, Ruotsalainen S, Moilanen L, Lepisto P, Laakso M, Kuusisto J. The metabolic syndrome predicts incident stroke: a 14-year follow-up study in elderly people in Finland. Stroke 2008;39: 1078–83.
109. Chen HJ, Bai CH, Yeh WT, Chiu HC, Pan WH. Influence of metabolic syndrome and general obesity on the risk of ischemic stroke. Stroke 2006;37:1060–4.
110. Chien KL, Hsu HC, Sung FC, Su TC, Chen MF, Lee YT. Metabolic syndrome as a risk factor for coronary heart disease and stroke: an 11-year prospective cohort in Taiwan community. Atherosclerosis 2007;194:214–21.
111. Iso H, Sato S, Kitamura A, et al. Metabolic syndrome and the risk of ischemic heart disease and stroke among Japanese men and women. Stroke 2007;38:1744–51.
112. Koren-Morag N, Goldbourt U, Tanne D. Relation between the metabolic syndrome and ischemic stroke or transient ischemic attack: a prospective cohort study in patients with atherosclerotic cardiovascular disease. Stroke 2005;36:1366–71.
113. Kurl S, Laukkanen JA, Niskanen L, et al. Metabolic syndrome and the risk of stroke in middle-aged men. Stroke 2006;37:806–11.
114. Wannamethee SG, Shaper AG, Lennon L, Morris RW. Metabolic syndrome vs Framingham Risk Score for prediction of coronary heart disease, stroke, and type 2 diabetes mellitus. Arch Intern Med 2005;165:2644–50.
115. Rodriguez-Colon SM, Mo J, Duan Y, et al. Metabolic syndrome clusters and the risk of incident stroke: the atherosclerosis risk in communities (ARIC) study. Stroke 2009;40:200–5.
116. Wild SH, Byrne CD, Tzoulaki I, et al. Metabolic syndrome, haemostatic and inflammatory markers, cerebrovascular and peripheral arterial disease: the Edinburgh Artery Study. Atherosclerosis 2009;203:604–9.

Key Words: cardiovascular disease ■ cardiovascular risk ■ meta-analysis ■ metabolic syndrome ■ mortality ■ National Cholesterol Education Program.

APPENDIX

For supplementary tables, please see the online version of this article.