Risks for All-Cause Mortality, Cardiovascular Disease, and Diabetes Associated With the Metabolic Syndrome

A summary of the evidence

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OBJECTIVE — In recent years, several major organizations have endorsed the concept of the metabolic syndrome and developed working definitions for it. How well these definitions predict the risk for adverse events in people with the metabolic syndrome is only now being learned. The purpose of this study was to summarize the estimates of relative risk for all-cause mortality, cardiovascular disease, and diabetes reported from prospective studies in samples from the general population using definitions of the metabolic syndrome developed by the National Cholesterol Education Program (NCEP) and World Health Organization (WHO).

RESEARCH DESIGN AND METHODS — The author reviewed prospective studies from July 1998 through August 2004.

RESULTS — For studies that used the exact NCEP definition of the metabolic syndrome, random-effects estimates of combined relative risk were 1.27 (95% CI 0.90–1.78) for all-cause mortality, 1.65 (1.38–1.99) for cardiovascular disease, and 2.99 (1.96–4.57) for diabetes. For studies that used the most exact WHO definition of the metabolic syndrome, the fixed-effects estimates of relative risk were 1.37 (1.09–1.74) for all-cause mortality and 1.93 (1.39–2.67) for cardiovascular disease; the fixed-effects estimate was 2.60 (1.55–4.38) for coronary heart disease.

CONCLUSIONS — These estimates suggest that the population-attributable fraction for the metabolic syndrome, as it is currently conceived, is ~6–7% for all-cause mortality, 12–17% for cardiovascular disease, and 30–52% for diabetes. Further research is needed to establish the use of the metabolic syndrome in predicting risk for death, cardiovascular disease, and diabetes in various population subgroups.

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Since the World Health Organization (WHO) and National Cholesterol Education Program (NCEP) produced their working definitions of the metabolic syndrome (1,2), a great deal of research has been undertaken to define its epidemiology. However, uncertainty exists about the clinical and public health importance of the metabolic syndrome (3,4). One way to address this uncertainty is to examine the nature of adverse events and the magnitude of the risks associated with the metabolic syndrome. Chief among these risks are all-cause mortality, cardiovascular disease, and diabetes. Although studies using nonstandard definitions of the metabolic syndrome have suggested that the risk of premature death and developing cardiovascular disease or diabetes is higher among people with the metabolic syndrome compared with those who did not have this syndrome, the risks for these outcomes associated with the new definitions of the metabolic syndrome are now emerging. Several studies have produced such risk estimates for all-cause mortality, cardiovascular disease, and diabetes. This report includes a review of these studies and a meta-analysis to determine summary estimates of risk.

RESEARCH DESIGN AND METHODS

— The term "metabolic syndrome" was used to perform a search of PubMed from July 1998, when the WHO definition was first published, through the end of February 2005. All abstracts were reviewed, and articles describing prospective studies were retrieved and evaluated. Only prospective studies that used either the NCEP definition, including those that had substituted BMI for waist circumference, or the WHO definition, including those with limited modifications, were included (Table 1). No attempt was made to locate unpublished studies or contact authors. In the case of duplicate analyses of the same dataset, only the first publication was included.

The following data elements were abstracted: lead author's name, year of publication, study location, sample size, sex composition, age of participants, follow-up time, definition of outcomes, number of events, definition of metabolic syndrome, relative risk estimate and CI, and variables used to adjust estimates of relative risk. For one study, the odds ratio and CI had to be estimated from a figure (5).

SEs for the estimates of relative risk were estimated from the CIs. For each study, a weight was calculated as the inverse of the variance ($1/SE^2$). Fixed-

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Abbreviations: NCEP, National Cholesterol Education Program; WHO, World Health Organization.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

Table 1—*Information about the definition of the metabolic syndrome used in studies of all-cause mortality, cardiovascular disease, and diabetes*

Studies*	NCEP	Modified NCEP	Change made	WHO	Modified WHO	Change made
Studies of all-cause mortality disease						
Lakka 2002	X				X	No impaired glucose tolerance, no microalbuminuria
Katzmarzyk 2004	X					
Hunt 2004	X				X	Used upper quartile of insulin concentration of nondiabetic participants, no microalbuminuria
Ford 2004		X	Men: BMI ≥30; Women: BMI ≥25 kg/m^2			
Studies of cardiovascular disease						
Onat 2002	X					
Lakka 2002	X				X	No impaired glucose tolerance, no microalbuminuria
Resnick 2003	X					
Katzmarzyk 2004	X					
Bonora 2004	X			X		
Rutter 2004	X					
Hunt 2004	X				X	Used upper quartile of insulin concentration of nondiabetic participants, no microalbuminuria
McNeill 2004	X					
Ridker 2003		X	Women: BMI >26.7 kg/m^2			
Sattar 2003		X	Men: BMI >28.8 kg/m^2			
Girman 2004		X	Men: BMI >28.8; Women: BMI >26.2 kg/m^2			
Ford 2004		X	Men: BMI ≥30; Women: BMI ≥25 kg/m^2			
Isomaa 2001				X		
Studies of diabetes						
Laaksonen 2002	X				X	No impaired glucose tolerance, no microalbuminuria
Resnick 2003	X					
Sattar 2003		X	Men: BMI >28.8 kg/m^2			
Lorenzo 2003	X				X	No impaired glucose tolerance, no microalbuminuria
Stern 2004	X			Not stated		

*Studies are identified by author and year of published report.

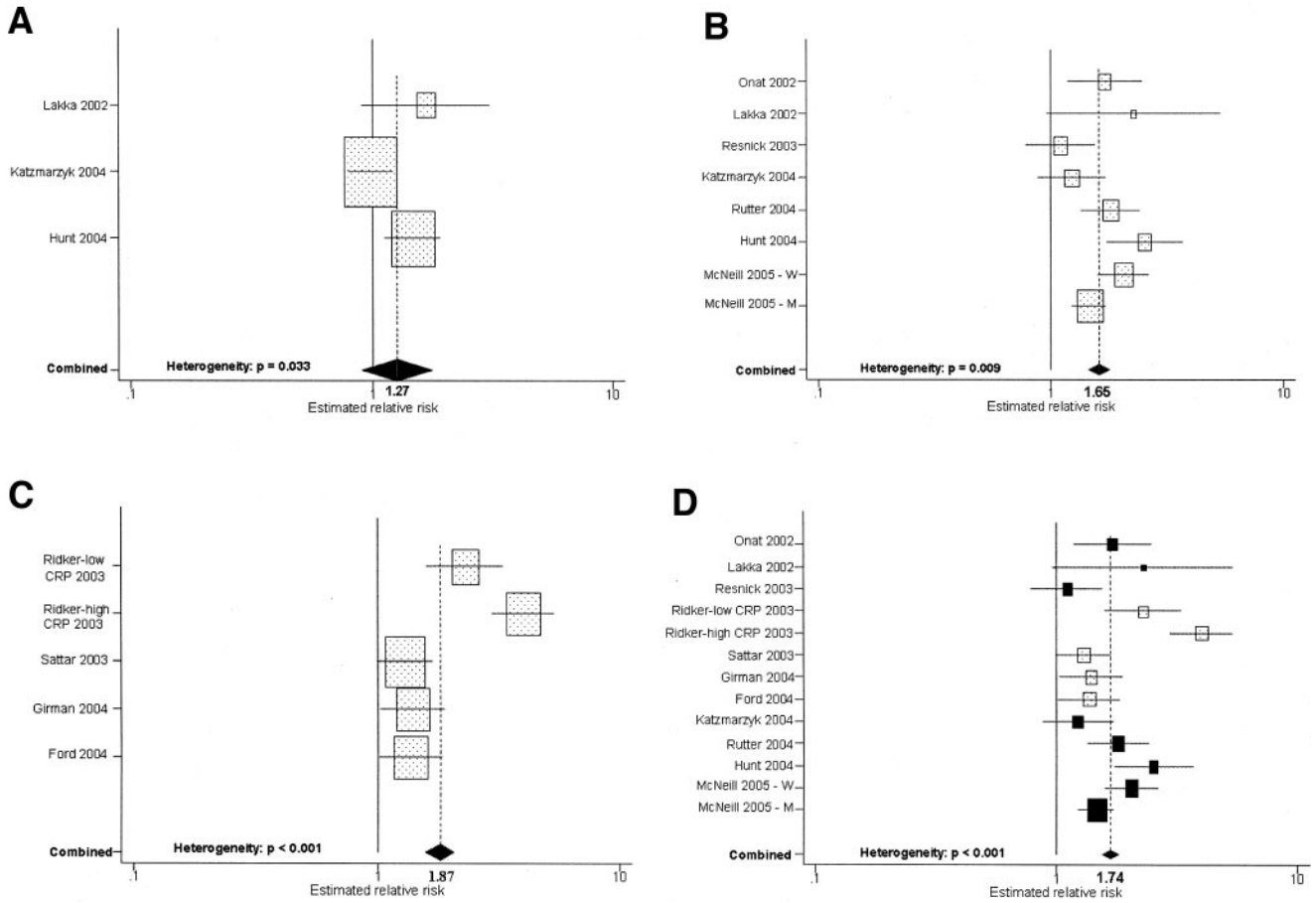

Figure 1—A: *Associations between metabolic syndrome, using the NCEP definition, and all-cause mortality.* B: *Associations between metabolic syndrome, using the NCEP definition, and cardiovascular disease.* C: *Associations between metabolic syndrome, using a modification of the NCEP definition, and cardiovascular disease.* D: *Associations between metabolic syndrome, using the original and modified NCEP definitions, and cardiovascular disease.* ■, *studies used the exact definition.* □, *used a modified definition. CRP, C-reactive protein; M, men; W, women.*

effects estimates of relative risk were calculated according to the Mantel-Haenszel method (6). Random-effects estimates of relative risk were calculated using the approach by DerSimonian and Laird (7). Heterogeneity among studies was assessed using the Q test (7). Forest plots were reviewed. The influence of single studies on the summary estimates was also examined (8). Evidence for bias was assessed by examining funnel plots and assessing funnel plot asymmetry (9,10). Analyses were conducted in Stata 8.2 (11). The population-attributable fraction for adverse events associated with the metabolic syndrome was calculated from the following formula: $[(P_o \times (RR-1)]/\{1 + [P_o \times (RR-1)]\}$, where P_o is the proportion in the population with the metabolic syndrome (21.8%) (12) and RR represents the summary relative risk obtained from the meta-analysis.

RESULTS — Characteristics of the studies included in the analyses are shown in Table 2.

Studies using the NCEP definition of the metabolic syndrome

All-cause mortality. For three studies (13–15), the random-effects estimate of the summary relative estimate was 1.27 (95% CI 0.90–1.78) (Fig. 1*A*). The *P* value for the test of heterogeneity was 0.033. Adding a study (16) that used BMI instead of waist circumference as a criteria yielded a random-effects estimate of relative risk of 1.21 (0.98–1.50) (*P* value for heterogeneity = 0.077).

Cardiovascular disease. For seven studies (eight estimates of relative risk) (13–15,17–19,21) that used the exact NCEP definition of the metabolic syndrome, the random-effects estimate for cardiovascular disease was 1.65 (95% CI 1.38–1.99) (*P* value for heterogeneity = 0.009) (Fig. 1*B*). One other study (20) reported a relative risk of 1.5 for participants with the metabolic syndrome defined according to NCEP criteria but no confidence limits or *P* values.

The authors of four other publications (16,22–24) modified the NCEP definition by using BMI instead of waist circumference to define the metabolic syndrome and produced five estimates of relative risk for cardiovascular disease. The random-effects estimate was 1.87 (95% CI 1.21–2.88) (*P* for heterogeneity <0.001) (Fig. 1*C*). Combining 13 estimates from 11 studies using the original or modified NCEP definition gave a random-effects estimate of 1.74 (1.43–2.12) (*P* for heterogeneity <0.001) (Fig. 1*D*). For seven studies (13,15,18,19,21,23,24) with eight estimates of relative risk that excluded participants with diabetes or

Table 2—*Information about studies that used the original or modified definition by the NCEP of the metabolic syndrome

Reference	Study	Sample size	Sex	Age (years) (range or mean)	Follow-up (years)	Outcomes	No. of events	RR (95% CI)	Adjusted for
Studies of all-cause mortality									
Lakka 2002	Kuopio Ischaemic Heart Disease Risk Factor Study, Finland	1,209	Men	42–60	11.4	All-cause mortality	109	1.67 (0.91–3.08)	Age, examination year, smoking, LDL cholesterol, family history of CHD, fibrinogen, white blood cell count, alcohol, socioeconomic status
Katzmarzyk 2004	Aerobics Center Longitudinal Study	19,223	Men	20–83	10.2	All-cause mortality	480	0.98 (0.79–1.21)	Age, smoking, alcohol, family history of CVD, cardiorespiratory fitness
Hunt 2004	San Antonio Heart Study	2,815	Men, women	25–64	12.7	All-cause mortality	229	1.47 (1.13–1.92)	Age, sex, race
Ford 2004*	National Health and Nutrition Examination Survey II Mortality Study	2,431	Men, women	30–75	13.5	All-cause mortality	500	1.15 (0.92–1.45)	Age, sex, race, education, smoking, non-HDL cholesterol, physical activity, white blood cell count, alcohol use, prevalent heart disease and stroke
Studies of CVD									
Onat 2002	Turkish Adult Risk Factor Study, Turkey	2,398	Men, women	≥28	3.0	Angina pectoris, history of MI, electrocardiography, history of revascularization, fatal CHD	126	1.709 (1.180–2.473)	Age
			Men					1.648 (0.981–2.768)	Age
			Women					1.944 (1.108–3.411)	Age
Lakka 2002	Kuopio Ischemic Heart Disease Risk Factor Study, Finland	1,209	Men	42–60	11.4	CVD deaths (ICD-9 390–459)	46	2.27 (0.96–5.36)	Age, examination year, smoking, LDL cholesterol, family history of CHD, fibrinogen, white blood cell count, alcohol, socioeconomic status
						CHD deaths (ICD-9 410–414)	27	4.26 (1.62–11.2)	Age, examination year, smoking, LDL cholesterol, family history of CHD, fibrinogen, white blood cell count, alcohol, socioeconomic status
Resnick 2003	Strong Heart Study	2,283	Men, women	45–74	7.6	Fatal MI, sudden death due to CHD, definite and possible fatal CHD, definite and possible fatal stroke, definite and possible fatal CHF, other fatal CVD	181	1.11 (0.79–1.56)	Age, center, sex, BMI, fibrinogen, smoking, LDL cholesterol
Katzmarzyk 2004	Aerobics Center Longitudinal Study	19,223	Men	20–83	10.2	CVD mortality (ICD-9 390–449.9)	161	1.23 (0.88–1.73)	Age, smoking, alcohol, family history of CVD, cardiorespiratory fitness
Bonora 2004	Bruneck Study, Italy	888	Men, women	40–79	5	Fatal and nonfatal CHD (medical history, laboratory data, ECG, medical records, death certificates)	46	1.5	RR 1.5 Age, sex, smoking, alcohol, physical activity, social status, LDL cholesterol, baseline carotid atherosclerosis, baseline CHD
Rutter 2004	Framingham Offspring Study	3,037	Men, women	26–82	6.9	New-onset angina, fatal and nonfatal MI or stroke, TIA, heart failure, intermittent claudication	189	1.8 (1.4–2.5)	Age, sex

McNeill 2005	Atherosclerosis Risk in Communities Study	12,089	Men, women	45–64	11	Fatal or nonfatal hospitalized MI, fatal CHD, silent MI from electrocardiography, coronary revascularization	879	—	
		5,208	Men				—	1.46 (1.23–1.74)	Age, race, study center, LDL cholesterol, smoking
		6,881	Women				—	2.05 (1.59–2.64)	Age, race, study center, LDL cholesterol, smoking
						Incident ischemic stroke	216	—	
		5,208	Men				—	1.42 (0.96–2.11)	Age, race, study center, LDL cholesterol, smoking
		6,881	Women				—	1.96 (1.28–3.00)	Age, race, study center, LDL cholesterol, smoking
Hunt 2004	San Antonio Heart Study	2,815	Men, women	25–64	12.7	CVD mortality	117	2.53 (1.74–3.67)	Age, sex, race
		Not stated	Men				Not stated	1.82 (1.14–2.91)	Age, race
		Not stated	Women				Not stated	4.65 (2.35–9.21)	Age, race
Ridker 2003*	Women's Health Study	14,719	Women	≥45	8.0	Nonfatal MI, nonfatal ischemic stroke, coronary revascularization, CV death		—	
		Not stated	Low CRP				Not stated	2.3 (1.6–3.3)	Age
		Not stated	High CRP				Not stated	4.0 (3.0–5.4)	Age
						Coronary events	Not stated	3.1 (2.0–4.9)	Age
		Not stated	High CRP				Not stated	5.5 (3.8–8.0)	Age
Sattar 2003*	West of Scotland Coronary Prevention Study, U.K.	6,447	Men	55.1/55.2	4.9	Nonfatal MI or CHD death	Not stated	1.3 (1.00–1.67)	Age, smoking, total cholesterol/HDLcholesterol, systolic blood pressure Adding CRP and glucose did not change results
Girman 2004*	Air Force/Texas Coronary Atherosclerosis Prevention Study	3,188	Men, women	58	5	Fatal or nonfatal MI, sudden cardiac death, unstable angina	175	1.4 (1.04–1.89)	Age
						Fatal or nonfatal MI or stroke	Not stated	1.46 (1.003–2.1)	Age
						Fatal or nonfatal MI	Not stated	1.49 (0.99–2.25)	Age
Ford 2004*	National Health and Nutrition Examination Survey II Mortality Study	2,431	Men, women	30–75	13.5	Mortality from diseases of the circulatory system (ICD-9 390–459)	317	1.23 (0.95–1.59)	Age, sex, race, education, smoking, non-HDL cholesterol, physical activity, white blood cell count, alcohol use, prevalent heart disease and stroke
						CVD mortality (ICD-9 410–414, 430–438)	200	1.37 (1.02–1.85)	Age, sex, race, education, smoking, non-HDL cholesterol, physical activity, white blood cell count, alcohol use, prevalent heart disease and stroke

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Table 2—*Continued*

Reference	Study	Sample size	Sex	Age (years) (range or mean)	Follow-up (years)	Outcomes	No. of events	RR (95% CI)	Adjusted for
						CHD mortality (ICD-9 410–414)	147	1.29 (0.92–1.82)	Age, sex, race, education, smoking, non-HDL cholesterol, physical activity, white blood cell count, alcohol use, prevalent heart disease
						Stroke mortality (ICD-9 430–438)	67	1.68 (0.86–3.27)	Age, sex, race, education, smoking, non-HDL cholesterol, physical activity, white blood cell count, alcohol use, prevalent heart disease and stroke
Studies of diabetes									
Laaksonen 2002	Kuopio Ischemic Heart Disease Risk Factor Study, Finland	958	Men	42–60	4	FG ≥6.1 mmol/l, clinical diagnosis of diabetes with treatment	51	6 (3.4–11.0)†	Age
Resnick 2003	Strong Heart Study	2,283	Men, women	45–74	7.6	Self-report, use of hypoglycemic agents, FG ≥126 mg/dl	389	1.95 (1.63–2.33)‡	None
Sattar 2003*	West of Scotland Coronary Prevention Study, U.K.	5,947	Men	55.1/55.2	4.9	≥2 FG ≥7.0 mmol/l (one glucose measurement must be ≥2.0 mmol/l above baseline)	Not stated	3.51 (2.47–4.98)	None
Lorenzo 2003	San Antonio Heart Study	1,734	Men, women	25–68	7–8	OGTT, medication use	195	3.3 (2.27–4.80)	Age, sex, ethnicity, family history, impaired glucose tolerance, insulin
Stern 2004	Mexico City Diabetes Study, Mexico	1,353	Men, women	35–64	6.3	OGTT, medication use	125	2.63 (1.80–3.85)	None

*Studies that modified the NCEP definition of the metabolic syndrome by using BMI instead of waist circumference. †Approximated from figure. ‡Calculated from raw data. CHD, coronary heart disease; CHF, congestive heart failure; CRP, C-reactive protein; CVD, cardiovascular disease; FG, fasting glucose; MI, myocardial infarction; OGTT, oral glucose tolerance test; RR, relative risk; TIA, transient ischemic attack.

participants who were using insulin, the random-effects estimate was 1.58 (1.33–1.87) (*P* for heterogeneity = 0.017). For five studies (14–17,22) that included participants with diabetes, the random-effects estimate was 2.02 (1.38–2.95) (*P* for heterogeneity <0.001). For three studies (13,17,21) that used the exact NCEP definition of the metabolic syndrome, the random-effects estimate of relative risk for coronary heart disease was 1.82 (1.38–2.38) (*P* for heterogeneity = 0.038). When three studies (13,16,17,21,23,24) that used the modified NCEP definition were added, the fixed-effects estimate was 1.54 (1.39–1.72) (*P* for heterogeneity = 0.051).

Diabetes. Four studies (5,18,26,27) examined the risk of developing diabetes among people with the metabolic syndrome defined by NCEP criteria. The random-effects estimate of relative risk was 2.99 (95% CI 1.96–4.57) (*P* for heterogeneity = 0.001) (Fig. 2). Adding a study (23) that used a modification of the NCEP definition resulted in a random-effects estimate of 3.08 (2.16–4.40) (*P* for heterogeneity <0.001).

Studies using the WHO definition of the metabolic syndrome

All-cause mortality. Fewer studies have used the WHO definition of the metabolic syndrome to examine the risks for all-cause mortality, cardiovascular disease, and diabetes. No studies of all-cause mortality used the exact WHO definition. For two studies (13,15) that used a modification of the definition, the fixed-effects estimate for all-cause-mortality was 1.37 (95% CI 1.09–1.74) (*P* for heterogeneity = 0.241). Adding the results from a study that made extensive changes to the WHO definition changed the fixed-effects estimate to 1.40 (1.21–1.62) (*P* for heterogeneity = 0.689) (28).

Cardiovascular disease. Among studies of cardiovascular disease, two (20,25) used the most exact WHO definition. For them, the fixed-effects estimate was 1.93 (95% CI 1.39–2.67) (*P* for heterogeneity = 0.527). Adding two other studies (13,15,20,25) that used a modification of the WHO definition gave a fixed-effects estimate of 1.89 (1.50–2.37) (*P* for heterogeneity = 0.497) for the four. Adding the results from a study that made extensive changes to the WHO definition changed the fixed-effects estimate to 2.06 (1.72–2.47) (*P* for heterogeneity =

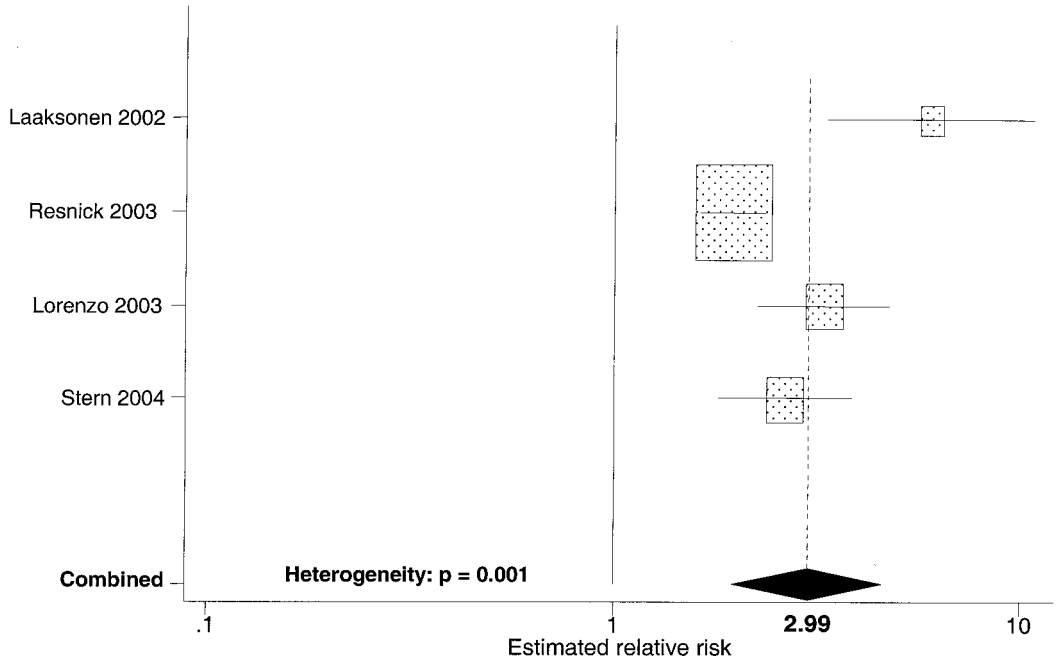

Figure 2—*Associations between metabolic syndrome, using the NCEP definition, and diabetes.*

0.509) (28). For coronary heart disease, the fixed-effects estimate for two studies (13,20) was 2.60 (1.55–4.38) (*P* for heterogeneity = 0.512).

Diabetes. Three studies reported in two publications (5,27) examined the associations between the metabolic syndrome, as defined by modified WHO criteria, and the incidence of diabetes. However, for one (5), it was difficult to obtain risk estimates because the results were presented in a figure. For the other two studies, the unadjusted fixed-effects estimate was 6.08 (95% CI 4.76–7.76) (*P* for heterogeneity = 0.535).

Bias

No evidence of bias was found for studies of all-cause mortality or cardiovascular disease, except for the analysis of the four studies of cardiovascular disease and the metabolic syndrome using the WHO definition (intercept: 2.76, $P = 0.044$; slope: 0.01, $P = 0.952$). For the four studies of diabetes incidence, funnel plot asymmetry was present (intercept: 4.79, $P = 0.035$; slope: 0.22, $P = 0.246$).

CONCLUSIONS — One way to judge the utility of the WHO and NCEP definitions of the metabolic syndrome is to examine what outcomes are linked to it and the strength of these links. The sum of the evidence to date shows that the metabolic syndrome does an unremarkable job of predicting all-cause mortality (estimated summary relative risk of ~1.2–1.4) and only a modest job of predicting cardiovascular disease (estimated summary relative risk of ~1.7–1.9). However, it is more strongly associated with diabetes incidence.

The earliest publications (13,21) reported rather substantial associations between the metabolic syndrome and cardiovascular disease. Consequently, these reports have been cited as proof that the concept of the metabolic syndrome was meaningful and thus deserving diagnosis and treatment. However, in the case of the Finnish study, the estimates of relative risk were based on few events, and the weight of the study was small compared with later studies (13). The low-to-moderate summary estimates of relative risk are perhaps somewhat surprising, given that the metabolic syndrome includes several variables that are strong independent predictors of cardiovascular disease or diabetes.

The definitions of the metabolic syndrome developed by NCEP and WHO include people with diabetes. Diabetes is known to be a strong risk factor for cardiovascular disease. Studies that included participants with diabetes (2.02) produced higher summary risk estimates for cardiovascular disease than studies that excluded participants with diabetes (1.58).

At least three attempts (21,24,27) have been made to compare the predictive ability for cardiovascular disease of the metabolic syndrome with the Framingham Risk Score. In two studies, the metabolic syndrome was not found to improve the risk prediction beyond that achieved by the Framingham Risk Score. In a third study, however, the metabolic syndrome was a significant predictor of cardiovascular disease after adjustment for the Framingham Risk Score (24). In addition, the Diabetes Prediction Model was found to be superior to the metabolic syndrome in predicting risk for diabetes (27).

The majority of prospective studies have presented risks based on the NCEP definition. The estimates of relative risk from studies using the WHO definition are only slightly higher than those from studies using the NCEP definition. However, two studies (13,15) using both the NCEP and modified WHO definitions produced estimates for all-cause mortality and cardiovascular disease associated with the metabolic syndrome. On the basis of the NCEP definition, the fixed-effects estimates were 1.50 (95% CI 1.18–1.91) for all-cause mortality and 2.71 (1.91–3.83) for cardiovascular disease. When the modified WHO definition

was used, the fixed-effects estimates were 1.37 (1.09–1.74) for all-cause mortality and 1.85 (1.34–2.55) for cardiovascular disease.

The mechanisms underlying the metabolic syndrome continue to be debated. Insulin resistance is thought by many to be the most important mechanism, and insulin resistance has been shown to predict cardiovascular disease (29). However, at least four studies (30–33) have shown that ~50–70% of people with the metabolic syndrome have insulin resistance. Chronic activation of the immune system (34), disorders of the hypothalamic-pituitary-adrenal axis (35), altered glucocorticoid hormone action (36), chronic stress (37), and genetic factors may also be involved in the pathogenesis of the metabolic syndrome (38,39). The potential contributions of cytokines, hormones, and other molecules produced by adipocytes in the pathogenesis of the metabolic syndrome are being investigated.

Whether the adverse impact on health by the metabolic syndrome is greater than the sum of its parts remains unclear (40). One possible explanation for the low estimates of relative risk is that people who do not have the metabolic syndrome but who are obese or have hypertension, dyslipidemia, or hyperglycemia are included in the reference group, potentially raising the incidence rate in the reference group and thereby lowering estimates of relative risk. The definitions of the thresholds for defining abnormalities may have also factored in the estimates of relative risk. By using generally "liberal" thresholds, substantial numbers of people who are defined as having abnormalities may have had a relatively low risk of developing various adverse events.

As currently conceptualized, people with the metabolic syndrome experience an increased risk for adverse events that is not affected by the degree of severity of the individual components. However, it is quite likely that a risk gradient for adverse events occurs among people with the metabolic syndrome. Consideration should be given to developing a classification scheme for people with the metabolic syndrome that reflects the degree of abnormalities, analogous to classification schemes for blood pressure and BMI. The risks associated with such classes could then be prospectively evaluated.

Throughout its history, definitions of the metabolic syndrome have changed and are likely to evolve further. Already, a lower glucose threshold to define impaired fasting glucose (100 mg/dl) has been incorporated into the NCEP definition (40,41). How this change will affect risk estimates for adverse events remains to be determined. The WHO definition is difficult to implement in epidemiologic studies, as evidenced by the fact that most studies had to alter it.

Most of the studies that were reviewed adjusted their analyses for various potential confounders, but the degree of adjustment varied. Adjusting for variables such as age, smoking status, lipids, or lipid patterns that are not part of the definition of the metabolic syndrome seems reasonable. An important consideration in choosing potential confounders is deciding whether the factors under consideration are part of the etiologic chain. This can be a challenging decision, however, because the interrelationships among the many anthropometric and physiologic abnormalities are complex. For example, inadequate physical activity and poor dietary habits (especially excess energy intake) lead to excess weight and insulin resistance. In turn, these factors can produce a variety of abnormalities that are collectively termed the metabolic syndrome. Thus, adjusting for physical activity and energy intake could be construed as adjusting for variables that are part of the causal chain and are risk factors for the metabolic syndrome. Adjusting for variables such as inflammatory markers that may be caused by obesity and insulin resistance may be adjusting for variables that lie in the causal chain but are sequellae of obesity/insulin resistance/metabolic syndrome.

The summary of relative risks suggest that the population-attributable fraction due to the metabolic syndrome is limited. Using the NCEP definition of the metabolic syndrome, the population-attributable fraction is ~6% for all-cause mortality, 12% for cardiovascular disease, and 30% for diabetes. Using the WHO definition, the population-attributable fraction is 7% for all-cause mortality, 17% for cardiovascular disease, and 52% for diabetes. Although these population-attributable fractions could be important, they need to be compared with the population-attributable fraction calculated from the sum of the population-attributable fractions of each component or analogous measures. In the case of diabetes, the population-attributable fraction for BMI alone has been estimated to be as high as 70% (42).

The population-attributable fraction may be larger in certain population subgroups. For example, the prevalence of the metabolic syndrome increases with age, reaching a prevalence of ≥40% in people aged ≥60 years (12). If estimates of relative risk in this age-group are similar to those calculated in this report, something that still needs to be established, the population-attributable fraction for cardiovascular disease might be ~17%. Similarly, some evidence suggests that the risk for cardiovascular disease may be higher among women than men (15,21), although in other studies, no such sex-specific difference has been observed (17,24). If women are at higher risk, then the population-attributable fraction among women would exceed that among men, given that the prevalence of the syndrome is similar between the two sexes.

In conclusion, the evidence from published studies suggests that the ability of current definitions of the metabolic syndrome to predict the future risk of all-cause mortality and cardiovascular disease in the general population may be limited. The metabolic syndrome does a better job of predicting the future risk of diabetes. Given the attention that the metabolic syndrome has received in recent years, establishing how well the metabolic syndrome predicts future adverse health outcomes is a matter of some urgency. To improve our current understanding of the prognostic value of the metabolic syndrome, more research is needed that specifically addresses the issue of whether the metabolic syndrome improves risk prediction for adverse events above that of its individual components. In addition, studies in various population subgroups may be helpful in assessing how well the metabolic syndrome predicts risk for future adverse health events.

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