

Metabolic Syndrome With and Without C-Reactive Protein as a Predictor of Coronary Heart Disease and Diabetes in the West of Scotland Coronary Prevention Study

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Background—The National Cholesterol Education Program (NCEP) recently proposed a simple definition for metabolic syndrome. Information on the prospective association of this definition for coronary heart disease (CHD) and type 2 diabetes is currently limited.

Methods and Results—We used a modified NCEP definition with body mass index in place of waist circumference. Baseline assessments in the West of Scotland Coronary Prevention Study were available for 6447 men to predict CHD risk and for 5974 men to predict incident diabetes over 4.9 years of follow-up. Mean LDL cholesterol was similar but C-reactive protein was higher ($P<0.0001$) in the 26% of men with the syndrome compared with those without. Metabolic syndrome increased the risk for a CHD event [univariate hazard ratio (HR)=1.76 (95% CI, 1.44 to 2.15)] and for diabetes [univariate HR=3.50 (95% CI 2.51 to 4.90)]. Metabolic syndrome continued to predict CHD events (HR=1.30, 95% CI, 1.00 to 1.67, $P=0.045$) in a multivariate model incorporating conventional risk factors. Men with 4 or 5 features of the syndrome had a 3.7-fold increase in risk for CHD and a 24.5-fold increase for diabetes compared with men with none (both $P<0.0001$). C-reactive protein enhanced prognostic information for both outcomes. With pravastatin, men with the syndrome had similar risk reduction for CHD as compared with those without (HR, 0.73 and 0.69; pravastatin versus placebo).

Conclusions—A modified NCEP metabolic syndrome definition predicts CHD events, and, more strikingly, new-onset diabetes, and thus helps identify individuals who may receive particular benefit from lifestyle measures to prevent these diseases. (*Circulation*. 2003;108:414-419.)

Key Words: insulin ■ coronary disease ■ obesity ■ inflammation ■ glucose

The Adult Treatment Panel (ATP) III of the National Cholesterol Education Program (NCEP) recently proposed a definition for metabolic syndrome to aid identification of individuals at risk for both coronary heart disease (CHD) and type 2 diabetes.¹ The definition incorporates thresholds for 5 easily measured variables linked to insulin resistance: waist circumference, triglycerides, HDL cholesterol, fasting plasma glucose concentration, and blood pressure. The earlier World Health Organization (WHO) definition of the metabolic syndrome² is more complex and

prescriptive in that for individuals with normal glucose tolerance there is a requirement to have documented evidence of insulin resistance necessitating at least a fasting insulin measurement. As a result, the focus of the WHO definition tends to fall much more on patients with existing evidence of glucose dysregulation.³ This is a weakness, since by the time impaired glucose tolerance or impaired fasting glucose has developed, the risk of conversion to diabetes is high.

By contrast, the NCEP-defined metabolic syndrome classification is triggered when predefined limits of any 3 of the

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above-mentioned 5 criteria are exceeded. Thus, many such individuals will have normal fasting glucose concentrations. A recent US survey found that the prevalence of metabolic syndrome was $\approx 25\%$ in white Americans but higher in Mexican and black Americans.⁴ From 2000 census data, ≈ 47 million US adults have the metabolic syndrome. However, the extent to which NCEP-defined metabolic syndrome predicts risk for CHD and diabetes is poorly studied.

In the West of Scotland Coronary Prevention Study (WOSCOPS), a primary prevention trial that demonstrated the effectiveness of pravastatin in preventing coronary morbidity and mortality,⁵ 4 of the 5 variables used to determine metabolic syndrome status (triglyceride, HDL cholesterol, blood pressure, fasting glucose) were measured at baseline. We also determined baseline body mass index (BMI), which most observers would accept as a satisfactory substitute for waist circumference in middle-aged men, as it predicts diabetes development and other metabolic disturbances as strongly as waist circumference.^{6–12} Indeed, the use of BMI in place of waist circumference was recently adopted by Ridker et al¹³ in a recent analysis of the metabolic syndrome in the Women's Health Study. We were thus able to define a modified metabolic syndrome status at baseline and link this status to risk for both CHD events and new-onset diabetes. We also investigated whether adding C-reactive protein (CRP)⁶ into the definition strengthened prediction of CHD or diabetes, since CRP appears to be strongly linked to development of both disease states independent of classic risk factors.^{7,14–17} Finally, we examined whether the previously published benefits of pravastatin therapy on the risk of development of CHD were dependent on metabolic syndrome status. A post hoc analysis of the Scandinavian Simvastatin Survival Study indicated a greater risk reduction in subjects with raised triglyceride and low HDL cholesterol levels, both metabolic syndrome characteristics.¹⁸

Methods

The design of the original WOSCOPS study has been described in detail.^{5,6,19} Briefly, 6595 moderately hypercholesterolemic men (LDL cholesterol, 174 to 232 mg/dL; triglycerides, <530 mg/dL) with no history of myocardial infarction were randomly assigned to pravastatin (40 mg daily) or placebo and followed for an average of 4.9 years.

A battery of risk factors and other demographic variables were assessed at baseline.¹⁹ This allowed classification of the men into those with and those without the metabolic syndrome on the basis of the modified NCEP criteria. We excluded men with frank diabetes: 72 subjects with self-reported diabetes and 76 who had a baseline blood glucose ≥ 126 mg/dL (total=148). Thus, 6447 men were considered in the CHD risk analyses. New-onset diabetes was defined by at least 2 postrandomization glucose measurements ≥ 126 mg/dL and at least 1 postrandomization fasting glucose measurement >36 mg/dL above baseline glucose or commencement of hypoglycemic drugs. The inclusion of a requirement of a rise in glucose of 36 mg/dL was introduced because we were primarily interested in examining subjects who had significant deterioration in glucose control.^{7,20} Since only 5974 men had 2 or more postrandomization fasting glucose measurements,^{7,20} the analyses relating to new-onset diabetes used this reduced cohort.

The 5 thresholds used were triglyceride level ≥ 150 mg/dL, HDL cholesterol <40 mg/dL, fasting glucose ≥ 110 mg/dL, systolic blood pressure ≥ 130 mm Hg or diastolic blood pressure ≥ 85 mm Hg or on antihypertensive medication, and BMI >28.8 kg/m². This last cutoff

was equivalent in a regression analysis to a waist circumference of 102 cm in a recent cross-sectional study (Haffner et al, personal communication) and similar to the BMI value (28.2 kg/m²) calculated in a regression of BMI on waist in a large population of local Scottish men.²¹ According to the NCEP, men were classified as having metabolic syndrome if they fulfilled 3 or more of the above criteria.

Risk was assessed for the primary end point of the trial, namely nonfatal myocardial infarction or CHD death,⁵ and for diabetes development as defined previously.^{7,20} Over the course of the study, there were a total of 404 CHD events and 139 new cases of diabetes in the subgroups being investigated.

Variation of the ATP III Definition of Metabolic Syndrome

First, we assessed the influence of reducing the fasting glucose cutoff to 99 mg/dL (5.5 mmol/L), since a cutoff of 110 mg/dL identified only a small number of men in WOSCOPS; we have previously noted that a fasting glucose in the top quintile of the WOSCOPS population (ie, >90 mg/dL) is associated with substantially elevated risk for diabetes.⁷ Second, we examined the effect of adding a CRP cutoff since CRP independently predicts CHD and diabetes.^{7,14–17} We chose a CRP cutoff of 3 mg/L, in agreement with recent American Heart Association/Centers for Disease Control (AHA/CDC) consensus recommendations.²²

Laboratory Analyses

Plasma cholesterol, triglycerides, and cholesterol in LDL and HDL were measured twice before randomization in WOSCOPS, and the baseline level was taken as the average.^{5,19} Lipoprotein profiles were determined according to the Lipid Research Clinics Protocol. Details of the CRP assay are given in Reference 6.⁶ Stored samples for CRP analysis were available for 5657 men.⁶

Statistics

Data are presented as mean (standard deviation) for continuous variables and number of subjects (%) for categorical variables. Plasma triglycerides and CRP were log-transformed. Univariate and multivariate Cox proportional hazards models were fitted to identify predictors of CHD events or new-onset diabetes. Metabolic syndrome status, lifestyle, lipids, and other CHD risk factors at baseline were considered. The multivariate model contained a set of conventional risk factors commonly used to determine individuals' risk for CHD,²³ namely age, smoking status, cholesterol:HDL cholesterol ratio, and systolic blood pressure. The hazard ratios for men fulfilling 1, 2, 3, and 4/5 of the ATP III metabolic syndrome characteristics as against men with none were also calculated. Cumulative time-to-event curves were estimated by use of the Kaplan-Meier method. Interaction between CRP above and below 3 mg/L and the presence of absence of metabolic syndrome was investigated within proportional hazards regression models. Finally, Cox proportional hazards models were used to compare the benefit of pravastatin therapy on risk for CHD and diabetes in the men with and those without the metabolic syndrome at baseline.

Results

As defined by the modified NCEP criteria, 1691 men (26.2%) had the metabolic syndrome at baseline assessment. Table 1 summarizes baseline characteristics of those with and those without the syndrome. Means of age and LDL cholesterol concentration were similar in the two groups, whereas mean CRP was significantly elevated in those with the metabolic syndrome. Interestingly, virtually all men with the metabolic syndrome were hypertensive ($>95\%$), and most ($>85\%$) also had elevated triglyceride and low HDL cholesterol levels (data not shown).

TABLE 1. Baseline Demographic and Biochemical Data for Individuals Fulfilling Metabolic Syndrome Criteria

	Metabolic Syndrome Present n=1691 (26.2%)	Metabolic Syndrome Absent n=4756 (73.8%)	P
Continuous			
Age, y	55.2±5.5	55.1±5.5	0.39
BMI, kg/m ²	28.0±3.5	25.2±2.6	N/A
Cholesterol, mg/dL	276±23.7	271±22.1	<0.0001
Triglycerides, mg/dL*	208.6±118.9	132.2±127.8	N/A
HDL cholesterol, mg/dL	36.8±5.9	46.8±9.1	N/A
LDL cholesterol, mg/dL	192.3±17.6	192.0±17.4	0.51
SBP, mm Hg	141.6±15.6	133.2±17.2	N/A
DBP, mm Hg	87.4±9.8	82.7±10.21	N/A
Fasting glucose, mg/dL	87.8±10.6	84.0±8.29	N/A
CRP, mg/L*	2.36±2.68	1.56±2.97	<0.0001
Categoric, n (%)			
Current smokers	805 (47.6%)	2044 (43.0%)	0.0010
Hypertension	406 (24.0%)	591 (12.4%)	<0.0001
Nitrate use	50 (3.0%)	81 (1.7%)	0.0017

SBP indicates systolic blood pressure, DBP, diastolic blood pressure; N/A, not applicable because criteria for selection of cases is based on these parameters.

*Geometric means.

The risk increased as the number of metabolic abnormalities rose, to 3.7-fold for CHD risk and 24-fold for diabetes in men with 4 or more baseline abnormalities (Table 2, and Figure 1, A and B). Table 3 shows the univariate hazard ratios for CHD events and diabetes in relation to metabolic syndrome status at baseline and other classic and novel risk factors. Men with metabolic syndrome had a 76% greater risk of a CHD event than men without. This level of risk was similar to an increase in age of 10 years, or to the risk in smokers. Interestingly, the metabolic syndrome classification continued to predict outcome (hazard ratio [HR], 1.30; 95% CI, 1.00 to 1.67; $P=0.045$) in multivariate analysis that included conventional risk factors, age, smoking status, cholesterol:HDL cholesterol ratio, and systolic blood pressure (Table 3). Furthermore, its independence was retained with further inclusion of CRP and fasting glucose (data not shown). However, possession of the metabolic syndrome was not a significant predictor in the presence of the effects of its individual components when investigated in a multivariate model (data not shown).

The univariate hazard ratio for new-onset diabetes in men with the syndrome was 3.51 (95% CI, 2.47 to 4.98). On

stepwise multivariate analysis, including the component variables of the syndrome, the risk associated with categorization of metabolic syndrome was no longer evident (data not shown), but BMI, triglycerides, and fasting glucose remained significant ($P<0.01$) independent predictors. Interestingly, CRP remained a significant predictor ($P<0.001$) of both CHD events and diabetes in multivariate analyses, suggesting its measurement may add prognostic value for both end points. To test this suggestion, we adopted the approach of Ridker et al¹³ by dividing the cohort into 4 groups by the presence or absence of metabolic syndrome and by CRP levels less than or greater than or equal to 3.0 mg/L. The Kaplan-Meier curves are presented in Figure 2, A and B. The corresponding hazard ratios for men in the low-CRP/no metabolic syndrome (n=3017), high-CRP/no metabolic syndrome (n=862), low-CRP/yes metabolic syndrome (n=1166), and high-CRP/yes metabolic syndrome (n=612) groups were 1.0 (referent), 1.6 (95% CI, 1.3 to 2.1), 1.6 (95% CI, 1.2 to 2.1), and 2.75 (95% CI, 2.1 to 3.6), respectively, for CHD events, and 1.0 (referent), 1.8 (95% CI, 1.1 to 3.0), 3.6 (95% CI, 2.3 to 5.6), and 5.3 (95% CI, 3.3 to 8.3) for incident

TABLE 2. Hazard Ratios for CHD and Diabetes as Characteristics of the Metabolic Syndrome Accumulate in an Individual With Zero Characteristics as the Referent

No. of Metabolic Characteristics	CHD		Diabetes	
	n (%)	HR (95% CI)	n (%)	HR (95% CI)
0	695 (10.8%)	1	645 (10.8%)	1
1	2077 (32.2%)	1.79 (1.11, 2.89)*	1932 (32.3%)	2.36 (0.71, 7.93)
2	1984 (30.8%)	2.25 (1.40, 3.60)†	1819 (30.5%)	4.50 (1.39, 14.6)*
3	1339 (20.8%)	3.19 (1.98, 5.12)†	1256 (21.0%)	7.26 (2.25, 23.4)†
≥4	352 (5.4%)	3.65 (2.11, 6.33)†	322 (5.4%)	24.4 (7.53, 79.6)†

* $P<0.05$, † $P<0.001$.

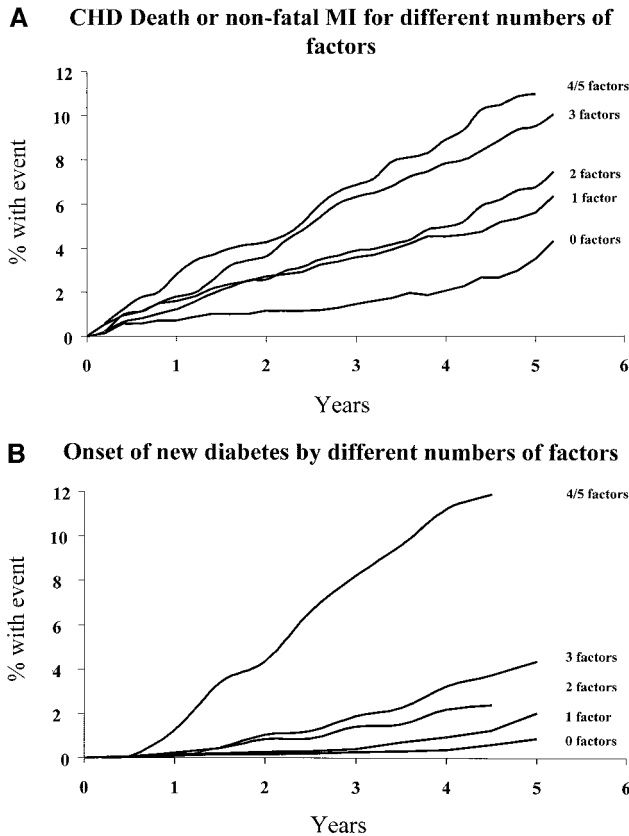


Figure 1. A and B, Kaplan-Meier curves for CHD events and new-onset diabetes in men with zero, 1, 2, 3, or ≥ 4 characteristics of the metabolic syndrome at baseline. Numbers of men in each group are given in Table 2.

diabetes. There was no interaction between the CRP cutoff and possession of the metabolic syndrome in determining risk.

Interestingly, when we reduced the glucose cutoff from 110 mg/dL to 99 mg/dL, 2.1% more men with the syndrome were identified, and their HR for both outcomes was slightly higher, at 1.81 (1.48, 2.20) for CHD events and 4.86 (3.42, 6.89) for incident diabetes.

Finally, the placebo event rate in those with metabolic syndrome was 10.4%, falling to 7.7% in the pravastatin group. The corresponding figures for men without the syndrome were 6.2% and 4.4%. Thus the relative risk reduction in those with and those without the syndrome were very similar, at 0.73 (0.53 to 1.01) and 0.69 (0.54 to 0.89), respectively, although the absolute risk reduction is greatest in those with the metabolic syndrome. For comparison, the CHD event rate in men with diabetes at baseline assigned to placebo was 17.6%.

Discussion

This study helps us understand and evaluate the clinical utility of the NCEP-defined metabolic syndrome. The modified NCEP metabolic syndrome definition identifies men at elevated risk of CHD despite LDL cholesterol concentrations similar to those in men without the syndrome. The risk is

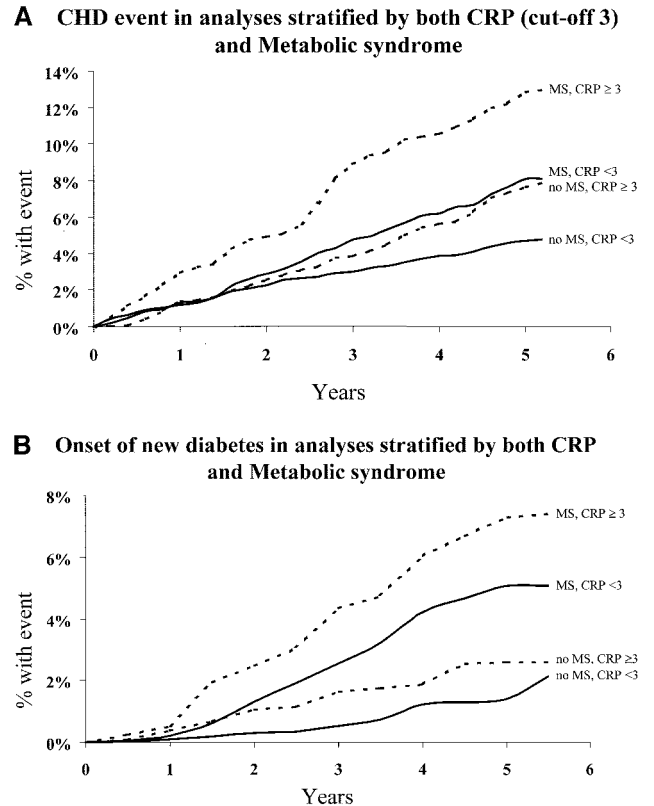


Figure 2. A and B, Kaplan-Meier curves for CHD events and new-onset diabetes stratified by both CRP ($< / \geq 3$ mg/L) and presence of absence of metabolic syndrome (MS). Numbers of men in each group are given in the Results section.

intermediate between those without the syndrome and men with diabetes. It correlates with diabetes risk even more strongly. We demonstrate that risk for each outcome increases with increasing number of metabolic syndrome “disorders,” and again, this is particularly marked for diabetes. Interestingly, the metabolic syndrome confers a risk for CHD (but not diabetes) that appears to be independent of conventional risk factors. However, metabolic syndrome does not improve prediction of CHD events in the presence of its components. We detected substantially higher CRP levels in men with the metabolic syndrome and found that CRP measurement enhances risk prediction in men with the metabolic syndrome. Indeed, CRP continued to predict both CHD and diabetes independent of metabolic syndrome status. Finally, lowering the glucose cutoff to 99 mg/dL appeared to enhance the numbers of men identified without reducing the prediction of CHD and diabetes.

The NCEP version of the metabolic syndrome is more physician-friendly than previous definitions² and supplements CHD risk assessment charts by identifying individuals who may benefit from behavioral therapy targeted toward exercise and weight loss, and, if needed, pharmacological treatment. Such lifestyle measures can reduce diabetes risk by 58%,^{24,25} and metformin²⁴ and acarbose²⁶ are also preventive. It is interesting to note (Table 2) that this NCEP definition is more strikingly correlated to diabetes than to CHD risk, particularly when 4 or 5 features are present, a valuable

TABLE 3. Univariate and Multivariate Analyses of Metabolic Syndrome as a Predictor of CHD Events (Definite CHD Death or Nonfatal Myocardial Infarction) and New-Onset Diabetes

	CHD		New-Onset Diabetes
	Univariate HR (95 % CI)	Multivariate HR (95 % CI)§	Univariate HR (95% CI)
Metabolic syndrome	1.76 (1.44, 2.15)‡	1.30 (1.00, 1.67)*	3.51 (2.47, 4.98)‡
Age, 10 y	1.81 (1.51, 2.18)‡	1.86 (1.54, 2.26)‡	1.09 (0.80, 1.48)
BMI, 5 kg/m ²	1.13 (0.96, 1.31)	...	2.22 (1.78, 2.76)‡
SBP, 20 mm Hg	1.29 (1.17, 1.46)‡	1.17 (1.06, 1.32)†	1.22 (1.02, 1.49)*
DBP, 20 mm Hg	1.40 (1.15, 1.67)‡	...	1.37 (1.00, 1.88)
Triglycerides, log mmol/L	1.49 (1.17, 1.89)†	...	5.04 (3.34, 7.60)‡
LDL cholesterol, 38.7 mg/dL	1.22 (0.99, 1.50)	...	1.24 (0.87, 1.78)
HDL cholesterol, 7.7 mg/dL	0.79 (0.72, 0.87)‡	...	0.69 (0.58, 0.81)‡
Chol:HDL ratio, 1 unit	1.21 (1.13, 1.29)‡	1.13 (1.04, 1.22)†	...
CRP, log mg/L	1.36 (1.24, 1.49)‡	...	1.55 (1.32, 1.82)‡
Fasting glucose, 7.7 mg/dL	1.19 (0.98, 1.43)	...	7.65 (5.99, 9.31)‡
Pravastatin treatment	0.71 (0.58, 0.86)‡	0.70 (0.58, 0.86)‡	0.70 (0.49, 0.98)*
Current smoker	1.73 (1.42, 2.10)‡	1.73 (1.41, 2.11)‡	1.15 (0.82, 1.61)

SBP indicates systolic blood pressure; DBP, diastolic blood pressure.

* $P<0.05$, † $P<0.01$, ‡ $P<0.001$ for 1-SD change or presence/absence of a categorical variable.

§Multivariate analysis considered metabolic syndrome together with classic risk factors (age, lipids, blood pressure, smoking).

benefit since, in contrast to those for CHD, predictive charts for diabetes are lacking. Our data therefore support the view that the NCEP definition strongly predicts future risk for diabetes. This point is particularly important because by the time impaired glucose tolerance has appeared, the conversion rate to diabetes is very high, and opportunities for successful interventions are possibly lessened.

We observed that the “metabolic syndrome” categorization continued to be an independent predictor for CHD in a model containing conventional risk factors. This is probably because this classification incorporates variables such as BMI, triglycerides, glucose, and diastolic blood pressure, which are not included in current risk factor stratification. Of note, our data extend the recent observation that the metabolic syndrome, as defined by NCEP criteria, predicted CHD death after adjustment for conventional cardiovascular risk factors including age, LDL cholesterol, smoking, and family history.²⁷ Our model did not include family history but was perhaps more noteworthy in that we did include a total cholesterol to HDL ratio and systolic blood pressure, factors used in risk factor determination in many countries.

The significantly higher CRP concentration among men with the metabolic syndrome and its independence as a predictor of both CHD and diabetes risk suggests that CRP could be used in future revisions of the syndrome. In line with this, a CRP cutoff of 3 mg/L enhanced prognostic information for CHD and especially diabetes in men with or without the syndrome. It is also of note that lowering the glucose cutoff enhanced prediction of both CHD and diabetes and identified a greater number of men. These data are clearly not comprehensive but demonstrate the potential for refining the NCEP definition to better predict CHD and/or diabetes. It is possible that variant definitions may emerge, depending on the end point of interest.

Ballantyne and colleagues¹⁸ recently reported a greater proportional benefit of simvastatin therapy in subjects with the lipid triad (metabolic syndrome equivalent), that is, elevated triglycerides and LDL cholesterol combined with low HDL cholesterol, as compared with subjects with isolated elevated LDL cholesterol. Our analysis in the primary prevention setting suggests that the CHD benefits of pravastatin is similar in middle-aged men with the syndrome as compared with those without, although the absolute benefit will be greater in the former.

This study has several strengths. Our database is one of the few that has systematically recorded most variables required to define metabolic syndrome at baseline, thereby enabling us to simultaneously associate this “condition” with prospective data on new CHD events and diabetes development. The availability of CRP was also a strength that allowed us to extend recent observations by others.¹³ The results on statin effect in relation to the metabolic syndrome in the primary prevention setting were also noteworthy.

The analyses presented here also have limitations. First, waist circumference measurement was not available. Some data show that waist circumference predicts diabetes marginally better than BMI,^{10,11} whereas other data show the reverse.⁸ In addition, both measures appear to predict CHD to a similar extent.¹² Nevertheless, most physicians routinely assess BMI, whereas the value of waist measurements in clinical practice has not been widely examined and may require modification for different ethnic groups. Moreover, the use of BMI versus waist measurements has been evaluated as a determinant of metabolic syndrome status.¹³ Second, the analyses described in this study represent a post hoc examination and thus should be viewed with caution. Finally, the men examined in WOSCOPS had elevated LDL chole-

terol levels and consequently were at elevated CHD risk at the start.⁵ However, we believe that the application of the metabolic syndrome categorization and its association with outcome was independent of this fact and that our findings can be extrapolated to the general population. In support of this, it should be noted that LDL cholesterol concentrations were near identical in those with or without the metabolic syndrome. Indeed, isolated increase in LDL cholesterol is insufficient in many countries to signal a need for primary preventative strategies. Moreover, our data linking metabolic syndrome to diabetes are widely applicable, since LDL cholesterol has no prediction for diabetes.

In conclusion, we demonstrate that a modified version of the NCEP definition of the metabolic syndrome prospectively identifies risk for CHD and even more strongly predicts new onset diabetes. The risk for each outcome increases as the characteristic components of the syndrome accumulate. Minor modifications of the current definition as achieved by adding CRP or lowering the glucose cutoff may enhance prediction of CHD and diabetes. The data suggest that the NCEP-defined metabolic syndrome will help identify individuals who may receive particular benefit from lifestyle measures to prevent CHD and diabetes.

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