

# The Prediction of Major Outcomes of Type 1 Diabetes: a 12-Year Prospective Evaluation of Three Separate Definitions of the Metabolic Syndrome and Their Components and Estimated Glucose Disposal Rate

The Pittsburgh Epidemiology of Diabetes Complications Study experience

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variables studied, including HbA<sub>1c</sub>, microalbuminuria appears to be the best single predictor of MOD.

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**OBJECTIVE**— The metabolic syndrome has been shown to confer an increased risk of cardiovascular disease in both the general and type 2 diabetic populations, but few studies have assessed the metabolic syndrome in type 1 diabetic patients. In a type 1 diabetic cohort, we assessed the prevalence and value of the metabolic syndrome in improving the prediction of major complication outcomes compared with its components and a surrogate measure of insulin resistance, estimated glucose disposal rate (eGDR).

**RESEARCH DESIGN AND METHODS**— A total of 514 (78%) subjects participating in the Pittsburgh Epidemiology of Diabetes Complications Study with complete 12-year follow-up clinical data were classified by baseline metabolic syndrome status according to three definitions: those of the National Cholesterol Education Program Adult Treatment Panel III (modified by the American Heart Association), the International Diabetes Federation (IDF), and the World Health Organization (WHO). The complication outcomes included coronary artery disease, renal failure, diabetes-related death, and the aggregate of these three major outcomes of diabetes (MOD).

**RESULTS**— Metabolic syndrome prevalence ranged from 8% (IDF) to 21% (WHO). All definitions showed reasonable specificity ( $\geq 83\%$ ) for each outcome, while the WHO definition had the highest sensitivity for all outcomes except renal failure, for which eGDR was most sensitive. However, the components of each definition predicted better than the overall syndrome. Microalbuminuria was clearly the strongest predictor of all individual measures, yielding hazard ratios of 9 and 6 for mortality and MOD, respectively.

**CONCLUSIONS**— Though the three metabolic syndrome classifications predict major complication outcomes in type 1 diabetes, their individual components predict better. Of the

The metabolic syndrome and its associated insulin resistance have been shown to confer an increased risk of cardiovascular disease both in the general population (1) and in type 2 diabetic patients (2,3). This has led to its use as an overall screening tool for those at cardiovascular risk. The metabolic syndrome has also been shown to have a strong, positive, and significant relationship with kidney disease, irrespective of diabetes (4). The metabolic syndrome is a common condition; for example, in the National Health and Nutrition Examination Survey III conducted from 1988 to 1994, the adjusted prevalence among U.S. adults aged  $\geq 20$  years was 23.7% (5). Two major causal factors for the syndrome have been proposed. Insulin resistance was the original basis for the syndrome as described by Reaven (6) in 1988. An alternative, though related, central feature is abdominal obesity (7–9), which has also been shown to be independently associated with all of the metabolic syndrome criteria (9). However, little is known about the prevalence and predictability of the metabolic syndrome in type 1 diabetes. Insulin resistance has been implicated in the etiology of type 1 diabetes complications like coronary artery disease (CAD) and nephropathy, and the basis of the excessive weight gain in a subgroup of patients receiving intensive insulin therapy is of concern (10). We have also demonstrated in earlier studies that insulin resistance was an underlying risk state for both overt nephropathy (11) and CAD (12).

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**Abbreviations:** AER, albumin excretion rate; AHA, American Heart Association; AIC, Akaike's Information Criterion; ATP III, Adult Treatment Panel III; CAD, coronary artery disease; EDC, Epidemiology of Diabetes Complications; eGDR, estimated glucose disposal rate; IDF, International Diabetes Federation; MOD, major outcomes of diabetes; NCEP, National Cholesterol Education Program; PPV, positive predictive value; ROC, receiver operating characteristic; WHO, World Health Organization; WHR, waist-to-hip ratio.

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

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Given this linkage between CAD and nephropathy, and their joint major influence on mortality, it would seem logical to examine predictors of the combination of major outcomes (CAD, renal failure, and mortality) as well as the individual complications. Therefore, the aim of this study was to determine the prevalence of the metabolic syndrome in type 1 diabetic patients and to assess whether the syndrome improves prediction of these major type 1 diabetes complications compared with its components and to a surrogate measure of insulin resistance, e.g., estimated glucose disposal rate (eGDR). A secondary aim was to compare three different definitions of the metabolic syndrome and determine whether any one has greater applicability to the type 1 diabetic population.

## RESEARCH DESIGN AND METHODS

All participants were identified from the Pittsburgh Epidemiology of Diabetes Complications (EDC) Study, a prospective study of risk factors for complications of childhood-onset (<17 years of age at diagnosis) type 1 diabetes. All participants were diagnosed with type 1 diabetes (or seen within 1 year of diagnosis) at Children's Hospital of Pittsburgh between 1950 and 1980 and were placed on continuous insulin therapy at diagnosis. This population has been shown to be representative of the Allegheny County type 1 diabetic population (13). A total of 658 individuals met the eligibility criteria and participated in the EDC baseline examinations, conducted between 1986 and 1988; participants were assessed biennially thereafter. Five hundred and fourteen participants (78%) provided complete demographic and clinical data for this analysis. Data were censored on 30 November 2000, providing 12 years of follow-up.

### Diagnostic criteria for the metabolic syndrome

The metabolic syndrome was assessed according to each of the following three definitions: the National Cholesterol Education Program (NCEP) Adult Treatment Panel III (ATP III), as modified by the American Heart Association (AHA)/National Heart, Lung, and Blood Institute (14); the International Diabetes Federation (IDF) (15); and the World Health Organization (WHO) (16). eGDR was also examined (17).

### AHA/NCEP

The AHA/NCEP maintains the ATP III criteria, except for minor modifications, and requires that patients have three or more of the following characteristics: 1) waist circumference  $\geq 102$  cm in men and  $\geq 88$  cm in women, 2) triglycerides  $\geq 150$  mg/dl (1.7 mmol/l) or be on drug treatment for elevated triglycerides, 3) HDL  $< 40$  mg/dl (0.9 mmol/l) in men and  $< 50$  mg/dl (1.1 mmol/l) in women or be on drug treatment for reduced HDL cholesterol, 4) systolic blood pressure  $\geq 130$  mmHg or diastolic blood pressure  $\geq 85$  mmHg or be on antihypertensive drug treatment, and 5) fasting glucose  $\geq 100$  mg/dl or be on drug treatment for elevated glucose. As all participants fulfilled the criteria for hyperglycemia, two of the remaining four criteria were required.

### IDF

The IDF considers abdominal obesity a mandatory component of the metabolic syndrome. Patients must, therefore, have a waist circumference  $\geq 94$  cm (men) or  $\geq 80$  cm (women) plus two of the following four factors: 1) triglycerides  $\geq 150$  mg/dl or specific treatment for this lipid abnormality, 2) HDL cholesterol  $< 40$  mg/dl (1.03 mmol/l) in men and  $< 50$  mg/dl (1.29 mmol/l) in women or specific treatment for this abnormality, 3) systolic blood pressure  $\geq 130$  mmHg or diastolic blood pressure  $\geq 85$  mmHg or specific treatment for hypertension, and 4) fasting plasma glucose  $\geq 100$  mg/dl (5.6 mmol/l) or previously diagnosed type 2 diabetes.

### WHO

The WHO definition requires a presence of glucose intolerance, impaired glucose tolerance, diabetes, and/or insulin resistance for the diagnosis of the metabolic syndrome and two of the following factors: 1) systolic blood pressure  $\geq 140$  mmHg or diastolic blood pressure  $\geq 90$  mmHg, 2) triglycerides  $\geq 150$  mg/dl and/or HDL cholesterol  $< 35$  mg/dl (0.9 mmol/l) in men and  $< 39$  mg/dl (1.0 mmol/l) in women, 3) waist-to-hip ratio (WHR)  $> 0.90$  in men and  $> 0.85$  in women, and 4) microalbumuria (albumin excretion rate [AER]  $> 20$   $\mu\text{g}/\text{min}$  determined from timed urine samples).

### eGDR

eGDR (in  $\text{mg} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ ) was calculated using the equation:  $\text{eGDR} = 24.31 - 12.22 (\text{WHR}) - 3.29$  [hypertension status (140/90 mmHg or on medications)]  $- 0.57 (\text{HbA}_{1c})$ . This equation was

derived from a substudy of 24 participants in the EDC Study (12 men and 12 women drawn from low, middle, and high age-specific tertiles of insulin resistance) who underwent euglycemic-hyperinsulinemic clamp studies (17). The eGDR values were examined in sex-specific quintiles and then dichotomized (lowest quintile vs. the upper four quintiles) for analysis of the definition. In subsequent component analysis, two of the components of eGDR were dichotomized as follows: hypertension (systolic blood pressure  $> 140$  mmHg or diastolic blood pressure  $> 90$  mmHg and/or blood pressure medications) and WHR  $> 0.90$  cm for men and  $> 0.85$  cm for women. The WHR cutoff point was based on the WHO criteria (16). The cutoff point for the  $\text{HbA}_{1c}$ ,  $\geq 9.15\%$ , was determined by calculating the area under the receiver operating characteristic (ROC) curve and utilizing the  $\text{HbA}_{1c}$  value corresponding to the optimal discrimination (80% sensitivity) for diabetes-related mortality and the aggregate end point (major outcomes of diabetes [MOD]).

### Outcome variables

**Mortality.** For the death of a participant, the next of kin was contacted, and a copy of the death certificate and, where appropriate, the hospital or autopsy record were requested. Data were reviewed by a physician on the Mortality Classification Committee (MCC chairman T.J.O.), who classified deaths according to standard procedures (18).

**Renal failure and CAD.** Self-reported renal transplantation or renal dialysis defined renal failure. CAD status was defined as death caused by CAD, a history of myocardial infarction confirmed by Q-waves on electrocardiogram (Minnesota codes 1.1 or 1.2) or hospital records, or angiographic stenosis  $\geq 50\%$  confirmed by hospital records, including revascularization.

**MOD.** This variable is defined as the development of CAD, renal failure, or death from any diabetes-related cause. The 38 participants with CAD and/or renal failure (13 with CAD and 25 with renal failure) at baseline were not included in this prospective analysis.

### Risk factors

All participants completed a questionnaire concerning demographic and medical history information before each exam. An ever smoker was a person who smoked  $\geq 100$  cigarettes over their life-

time. Three seated blood pressure readings were taken with a random-zero sphygmomanometer and the mean of the second and third readings used in analyses (19). Hypertension was defined as  $\geq 140/90$  mmHg or use of antihypertensive medication.

Stable HbA<sub>1c</sub> was measured by ion-exchange chromatography (Isolab, Akron, OH) and subsequently by automated high-performance liquid chromatography (Diamat; BioRad, Hercules, CA). Readings with the two methods are almost identical ( $r = 0.95$ ). Our upper limit of normal for HbA<sub>1c</sub> is 7.3%; thus, values are higher than current A1C values. Total, HDL, and LDL cholesterol and triglycerides were determined as previously described (20–24).

**Weekly activity assessment**

The activity questions used to assess current levels of leisure physical activity were originally developed for the Harvard Alumni Study (25). This survey inquires about the number of flights of stairs climbed daily, the number of blocks walked daily, and sports participation during the past week. From the responses to these three questions, a summary estimate of energy expenditure over the past week is derived and expressed as calories (kcal) expended in physical activity per week. In addition, four questions concerning walking, standing, lifting, and the need for breaks “to catch your breath” at work were assessed.

**WHR measurements**

The procedure for measuring waist girth was performed with the participant gowned and standing with their feet together. The waist measurement was determined at the midpoint between the highest point of the iliac crest and the lowest part of the costal margin in the midaxillary line. The mean of two waist measurements was recorded as the waist circumference. If the two measurements differed by  $>0.5$  cm, a third waist measurement was performed and the mean of all three measurements was recorded as the waist circumference. Hip girth measurement was performed at the widest point of the glutei, usually at the level of the greater femoral trochanter.

**Dietary assessment**

Nutrient intake was estimated from a 1-year, 115-item food frequency questionnaire (Harvard-Willet Semi-Quantitative Food Frequency). The

Table 1—Baseline characteristics by metabolic syndrome definition

Variables	AHA/NCEP		IDF		WHO		eGDR	
	Without	With	Without	With	Without	With	Without	With
n (%)	453 (88)	61 (12)	471 (92)	43 (8)	407 (79)	107 (21)	411 (80)	103 (20)
Male (%)	49	53	53	14*	45	67*	50	50
Age (years)	26.8 (7.9)	31.2 (6.4)*	27.1 (7.8)	30.0 (8.0)†	26.3 (7.9)	31.3 (6.6)*	26.7 (7.8)	30.0 (7.7)*
Duration (years)	18.6 (7.5)	22.8 (6.8)*	18.9 (7.5)	21.5 (7.7)†	18.0 (7.4)	23.1 (6.5)*	18.4 (7.3)	21.8 (7.8)*
BMI (kg/m <sup>2</sup> )	23.3 (3.1)	25.3 (3.7)*	23.1 (3.0)	27.8 (3.0)*	23.1 (3.0)	25.0 (3.5)*	23.3 (3.2)	24.5 (3.2)*
WHR	0.81 (0.07)	0.86 (0.08)*	0.82 (0.1)	0.84 (0.1)†	0.80 (0.1)	0.88 (0.7)*	0.81 (0.1)	0.85 (0.1)*
HbA <sub>1c</sub> (%)	10.3 (1.8)	10.2 (2.1)	10.3 (1.8)	10.1 (2.0)	10.3 (1.8)	10.6 (2.0)	10.0 (1.5)	11.5 (2.5)*
eGDR	8.2 (1.6)	6.2 (2.1)*	8.0 (1.7)	7.1 (2.2)*	8.5 (1.4)	6.0 (1.8)*	8.6 (1.2)	5.3 (1.3)*
Cholesterol (mg/dl)								
Total	184.4 (36.0)	220.6 (48.5)*	187.6 (38.6)	201.6 (46.4)†	181.4 (33.0)	216.5 (48.8)*	182.5 (34.9)	213.7 (46.4)*
HDL	56.1 (12.1)	44.7 (9.1)*	55.2 (12.6)	49.1 (6.9)*	56.4 (12.2)	48.3 (10.8)*	55.2 (12.4)	52.7 (11.9)
Triglycerides (mg/dl)†	84.2 (40.2)	175.3 (69.2)*	91.6 (50.3)	132.4 (70.4)*	81.3 (38.1)	147.1 (69.4)*	85.1 (42.9)	134.8 (70.5)*
AER‡	208 (72.4)	1,179 (1,615)*	299 (889)	591 (1,285)*	130 (393)	1,059 (1,705)*	164 (562)	959 (1,605)*
Daily energy intake (kcal)‡	2,092 (728)	2,030 (786)	2,112 (744)	1,783 (543)†	2,082 (754)	2,097 (662)	2,098 (738)	2,033 (725)
Weekly activity (kcal)‡	2,335 (2,301)	1,686 (2,035)†	2,369 (2,334)	1,038 (908)*	2,372 (2,342)	1,823 (1,971)†	2,401 (2,405)	1,687 (1,570)
Insulin (units/kg)‡	0.79 (0.24)	0.80 (0.28)	0.79 (0.24)	0.81 (0.27)	0.79 (0.24)	0.80 (0.26)	0.80 (0.23)	0.76 (0.29)†
Smoking (%)	33	53*	35	35	31	51*	33	44†

Data are n (%) unless otherwise indicated. \*P < 0.01 and †P < 0.05 (within-group differences). ‡Daily energy intake, weekly activity, insulin, AER, and triglycerides were log transformed.

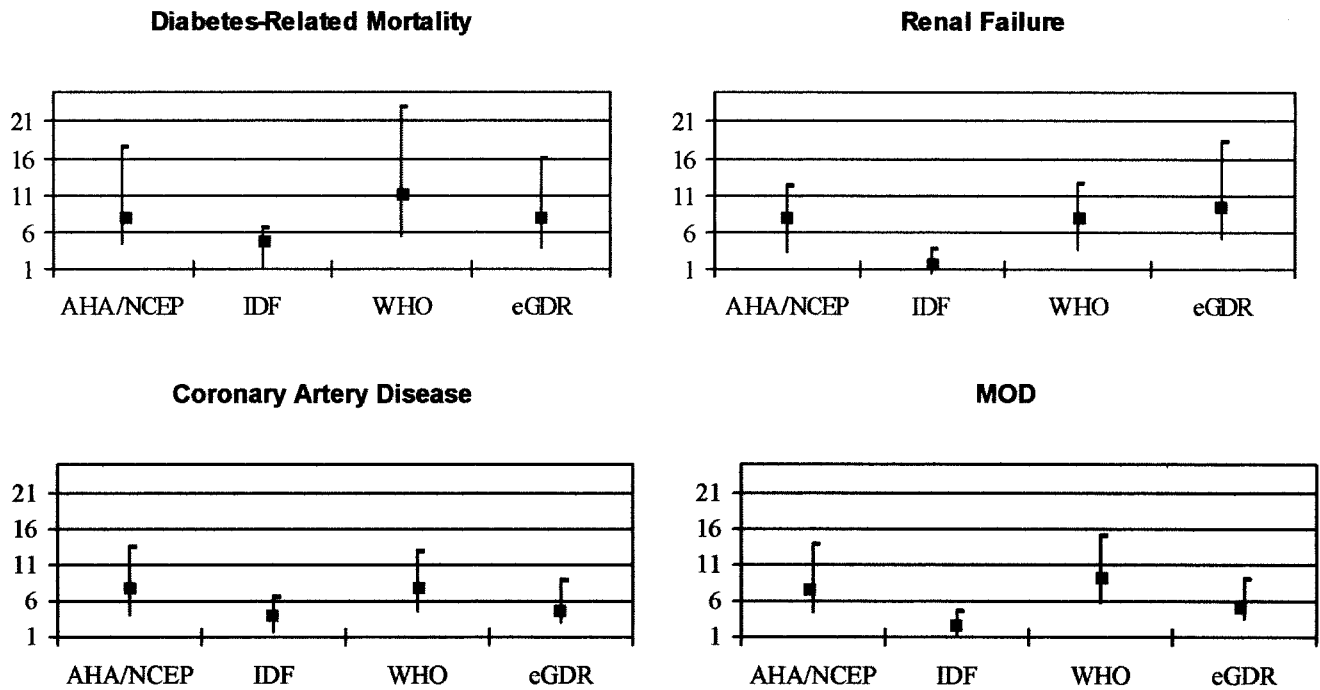


Figure 1—The odds of major outcomes of type 1 diabetes by baseline metabolic syndrome.

questionnaire was administered at the baseline examination (26).

#### Height and weight

Weight was measured by the physician using a balanced-beam scale with clothing during the clinical examination. Height was measured by the physician using the clinic stadiometer, with the Frankfort plane held horizontal.

#### Statistical analysis

SPSS/PC statistical software (SPSS, Chicago, IL) was used for all analyses. Group differences in categorical variables were tested with  $\chi^2$  tests, while Student's *t* test was used for the continuous variables. The Kolmogorov-Smirnov test was used to check for normality. All variables that violated the assumption of normality were log transformed (triglycerides, AER, energy expenditure [weekly activity], and energy intake). The sensitivity, specificity, positive predictive value, and Youden's index were calculated. Separate Cox proportional hazard models were run for each of the metabolic syndrome definitions and eGDR, as well as for each of the components of the three metabolic syndrome definitions and eGDR. Backward stepwise selection was used for all models, and removal testing was based on the probability of the Wald statistic. The Akaike's Information Criterion (AIC) was then calculated to determine the best model.

**RESULTS**— Of the 514 participants with complete clinical data, 7 died from nondiabetes-related causes and were included as a noncase for mortality. The causes of these deaths were as follows: accident/suicide,  $n = 3$ ; other nondiabetes causes,  $n = 3$  (chronic obstructive pulmonary disease, anoxic brain damage after resuscitation, and anoxic necrosis of the brain); and unknown,  $n = 1$ . There were 74 cases of CAD and 52 cases of renal failure, with 26 participants positive for both CAD and renal failure.

The main demographic and clinical characteristics of participants, stratified by the metabolic syndrome definition, are listed in Table 1. The prevalence of the metabolic syndrome was highest according to the WHO definition (21%) and lowest according to the IDF criteria (8%). Participants with the metabolic syndrome were more likely to be men, according to the WHO definition, and more likely to be women according to IDF criteria. Age, duration of diabetes, BMI, WHR, total cholesterol, triglycerides, and AER were significantly higher ( $P < 0.05$ ) in participants with the metabolic syndrome (all definitions). Conversely, eGDR and HDL cholesterol were significantly lower ( $P < 0.01$ ) in participants with the metabolic syndrome. With the exception of HDL cholesterol, similar findings were observed for the eGDR definition.

The smallest difference between the metabolic syndrome groups in triglycer-

ide levels is seen for measurements according to IDF criteria. This finding is likely sex related, as women had significantly lower triglyceride levels when compared with men (data not shown). There were no differences in HbA<sub>1c</sub> for any of the metabolic syndrome definitions, but there was the expected difference with the eGDR group (10.0 vs. 11.5%,  $P < 0.01$ ). Smoking was more prevalent among participants with the metabolic syndrome according to the AHA/NCEP and WHO definitions ( $P < 0.01$ ), but there was no difference according to the IDF classification. In addition, there was a significant difference ( $P < 0.05$ ) in smoking between the two eGDR groups. Weekly leisure time physical activity was lower in those with the metabolic syndrome. However, though occupational activity was not fully assessed, no differences were noted by metabolic syndrome groupings in time spent walking, lifting, or standing at work or the need for breaks to catch one's breath (all  $P$  values  $> 0.40$ ). For eGDR, however, those with low values spent marginally ( $P < 0.07$ ) less time lifting or carrying. There were no differences in daily energy intake (caloric intake) between the groups, except that those positive for the IDF definition consumed significantly less calories ( $P < 0.01$ ). The increased preponderance of women positive by the IDF definition likely accounts for this disparity, as after controlling for sex there was no difference

**Table 2—Cox proportional hazard models for diabetes-related mortality and MOD comparing the metabolic syndrome and eGDR definitions with their components (n = 514)**

	Diabetes-related mortality			MOD		
	HR	CI	AIC	HR	CI	AIC
<b>AHA/NCEP</b>						
Overall syndrome	7.2	3.8–13.7	423.3	5.8	3.9–8.6	1,322.8
Components			414.3			1,273.0
Triglycerides	5.8	3.0–11.3	—	4.4	3.0–6.6	—
Blood pressure	2.9	1.5–5.5	—	4.5	3.1–6.6	—
<b>IDF</b>						
Overall syndrome	2.4	1.1–5.4	450.8	2.0	1.2–3.4	1,376.1
Components			414.3			1,273.0
Triglycerides	5.8	3.0–11.3	—	4.4	3.0–6.6	—
Blood pressure	2.9	1.5–5.5	—	4.5	3.1–6.6	—
<b>WHO</b>						
Overall syndrome	9.1	4.6–18.0	411.4	6.5	4.5–9.4	1,290.3
Components			402.1			1,245.0
Lipids*	3.9	2.1–7.5	—	2.5	1.7–3.7	—
Microalbuminuria	9.2	3.2–26.1	—	6.3	3.8–10.5	—
Blood pressure	—	—	—	2.3	1.5–3.5	—
WHR	—	—	—	1.5	0.97–2.4	—
<b>eGDR</b>						
Overall syndrome	6.6	3.4–12.6	422.5	4.4	3.1–6.4	1,326.2
Components			432.6			1,301.6
Blood pressure	3.9	2.0–7.6	—	5.9	4.0–8.7	—
WHR	2.6	1.3–5.4	—	1.9	1.2–3.0	—
HbA <sub>1c</sub> (%)	—	—	—	1.2	1.1–1.3	—

\*Triglycerides and/or HDL cholesterol.

in the caloric consumption between the two IDF groups.

Figure 1 displays the odds ratios and CIs for mortality, CAD, renal failure, and MOD by the metabolic syndrome and eGDR definitions. Participants with the metabolic syndrome and lower eGDR generally had a much greater risk of each outcome; however, this was notably less marked using the IDF criteria. The sensitivity, specificity, positive predictive value (PPV), and Youden's index of each metabolic syndrome and eGDR definition were calculated for all examined outcomes. All criteria showed a reasonable specificity ( $\geq 83\%$ ) while the WHO definition had the highest sensitivity for all disease outcomes (mortality 69% and CAD 57%) except renal failure, for which eGDR was most sensitive, identifying 63% of incident cases. PPV ranged from 14% (renal failure [IDF]) to 46% (CAD [AHA/NCEP]) for single outcomes. For MOD, however, the PPVs were generally higher (i.e., AHA/NCEP 62%, IDF 39%, WHO 59%, and eGDR 51%).

Table 2 shows the hazard ratios (HRs) and AIC values for mortality and MOD using each metabolic syndrome definitions and their individual components.

The HRs were calculated to compare the three metabolic syndrome definitions and eGDR for prediction of diabetes-related mortality and MOD. The WHO definition was associated with a ninefold increased risk for mortality and over a sixfold increased risk for MOD. However, when the components of the various metabolic syndrome definitions were entered into models as individual dichotomized covariates, dyslipidemia and hypertension were the most frequent independent predictors of each outcome. In addition, the components of the three metabolic syndrome definitions, when considered together in one model, yielded better prediction models of the outcomes than the metabolic syndrome itself. The model containing the components of the WHO definition was the best predictor of both mortality and MOD. The eGDR definition was comparable with AHA/NCEP and IDF as a predictor of mortality and proved to be a better predictor than its components. However, eGDR proved less powerful as a predictor of MOD. Strikingly, microalbuminuria appeared to be the strongest predictor of all the individual measures. Smoking and sex, the two risk factors that varied among metabolic syn-

drome definitions, were added to the unadjusted metabolic syndrome models to account for possible confounding (data not shown). Although the HR and AIC were slightly changed, IDF was still an inferior predictor of mortality and MOD when compared with the AHA/NCEP and WHO definitions.

**CONCLUSIONS**— Our data suggest that, though the metabolic syndrome does generally predict the adverse outcomes, the individual components of the metabolic syndrome, rather than their assemblage, predict better, regardless of the metabolic syndrome definition (AHA/NCEP, IDF, or WHO). For IDF and AHA/NCEP, triglycerides were a better predictor of diabetes-related mortality than blood pressure and are likely related to glycemic control. Strikingly, however, microalbuminuria alone provides the best prediction and appears superior to HbA<sub>1c</sub>.

Unlike the FinnDiane Study (27), which showed the metabolic syndrome to be a frequent finding in type 1 diabetic patients (38% men, 40% women), the prevalence in this study was much lower: 12% by AHA/NCEP criteria, 8% by IDF criteria, and 21% by WHO criteria. Our subjects were younger (mean age for the metabolic syndrome-positive group was 38.7 years in the FinnDiane Study and 30.8 years in the EDC Study) and more insulin sensitive (eGDR was 4.8 in the FinnDiane Study and  $\sim 6.4$   $\text{mg} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$  in the EDC Study), which may explain some of the disparity in the findings.

The metabolic syndrome, however, did convey an increased risk of developing major complications, but the risk was variable across definitions (Fig. 1). Although the metabolic syndrome was developed to focus on decreasing coronary disease rates and diabetes, prior research has also suggested that it is an important factor in the cause of kidney disease (4). Moreover, the metabolic syndrome has been linked to pancreas graft failure in patients with type 1 diabetes at 1 year posttransplantation (28). Since coronary disease in type 1 diabetic patients is often associated with renal disease (29–33), it was hypothesized that the metabolic syndrome would also be helpful for predicting all three major type 1 diabetes complications: mortality, CAD, and renal failure. Current prediction models for CAD, like the Framingham Risk Score and the UK Perspective Diabetes Study (UKPDS) risk engine, do not work well in

type 1 diabetic patients, further underscoring the need for new approaches (34).

The WHO definition was a better predictor of mortality (HR 9.1 [95% CI 4.6–18.0]) and MOD (6.5 [4.5–9.4]) than its counterparts, although the WHO components produced the best model. The inclusion of microalbuminuria as a risk factor in the WHO definition may explain this favorable association, as it alone had a very high HR (6.3 [3.8–10.51]) for MOD and clearly relates to renal disease, which was associated with 39% of the deaths in this study. In addition, 47% of the total EDC Study population was diagnosed with at least microalbuminuria at baseline (1986–1988). The IDF definition was the least useful and, unlike the other two, was largely limited to women. The dominant underlying risk factor for the IDF definition is abdominal obesity, which is determined by a simple waist measurement. The poor performance demonstrated by this definition for the major type 1 diabetes complication outcomes examined in this study is likely attributed to the relatively greater difference between our mean waist circumference in men (82.1 cm) when compared with the IDF cut point (95 cm) than in women (75.2 cm compared with the 80-cm cut point in IDF) at baseline. This led to relatively few diagnoses in men. A recent 4-year study (35), examining the ATP III and IDF definitions and their ability to predict future cardiovascular events in nondiabetic subjects who underwent coronary angiography, concluded that patients with the metabolic syndrome according to the ATP III definition were at a significantly higher risk of future events. The authors suggested that the mandatory IDF waist criteria resulted in a lower prevalence of other metabolic syndrome and CAD risk factors, such as lipids (35). Our data are consistent with this interpretation.

The metabolic syndrome has recently been touted as a method of identifying individuals at increased risk of both type 2 diabetes and cardiovascular disease (36,37). Separately, each component of the definition(s) conveys an increased coronary risk, but as a combination they are believed to become more powerful and were previously known as the “Deadly Quartet” (38). Recently, however, the metabolic syndrome has been shown to be inferior when compared with the established predicting models, such as the Diabetes Predicting Model and the Framingham Risk Score, for either type 2 diabetes or cardiovascular disease (39).

Our data, in a different setting, again strengthens this conclusion. If one is desirous of a single measure to predict these major outcomes in type 1 diabetes, it would seem that microalbuminuria itself is that measure, as it predicts better than the metabolic syndrome and even our surrogate estimate (eGDR) of underlying pathology (insulin resistance). This was surprising to us, as eGDR was a strong independent predictor of both CAD and overt nephropathy in the EDC Study (11,12). However, as microalbuminuria may reflect insulin resistance, which we postulate underlies much of the excess CAD in type 1 diabetic patients, and is an early marker of renal disease, its predictive power may lie in representing not just a risk state but widespread vascular damage, as originally proposed by the Steno Investigators (40). Subsequent analyses (41,42) have reinforced this Steno hypothesis and further stressed the importance of microalbuminuria as a marker of vascular change. Endothelial dysfunction, which has been shown to precede microalbuminuria by 2–3 years (42,43), has been suggested as the possible link to the concomitant development of the renal and cardiovascular complications often seen in type 1 diabetic patients (44,45). In conclusion, microalbuminuria is the best predictor, among those considered here, of cardiovascular risk in type 1 diabetic patients due to its possible role as an early indicator of endothelial dysfunction and renal disease.

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