Original Article

Insulin Resistance, the Metabolic Syndrome, and Incident Cardiovascular Events in the Framingham Offspring Study

Martin K. Rutter,[1,2] James B. Meigs,[3,4] Lisa M. Sullivan,[5] Ralph B. D'Agostino, Sr.,[5] and Peter W. Wilson[6,7]

The metabolic syndrome and insulin resistance have been related to incident cardiovascular disease (CVD), but it is uncertain if metabolic syndrome predicts CVD independent of insulin resistance. Our study sample included 2,898 people without diabetes or CVD at baseline. Metabolic syndrome was defined by the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) criteria. Insulin resistance was defined by the homeostasis model assessment (HOMA-IR) and by Gutt et al.'s insulin sensitivity index ($ISI_{0,120}$). Age- and sex-adjusted proportional hazards regression models assessed the association of baseline metabolic syndrome and insulin resistance to 7-year CVD risk (186 events). Metabolic syndrome and both measures of insulin resistance were individually related to incident CVD (age- and sex-adjusted hazard ratio [HR] for metabolic syndrome [present versus absent]: 2.0 [95% CI 1.5–2.6], $P = 0.0001$; for HOMA-IR: 1.9 [1.2–2.9], $P = 0.003$; and for $ISI_{0,120}$ [both highest versus lowest quartile]: 0.5 [0.3–0.7], $P = 0.001$). In models adjusted for age, sex, LDL cholesterol, and smoking status and including metabolic syndrome, $ISI_{0,120}$ levels were independently related to incident CVD (0.5 [0.3–0.8], $P = 0.004$), whereas HOMA-IR levels were not (1.3 [0.8–2.1], $P = 0.24$); metabolic syndrome was associated with increased CVD risk in both models (HR 1.6, $P \leq 0.007$ in both). In conclusion, metabolic syndrome and $ISI_{0,120}$ but not HOMA-IR independently predicted incident CVD. Metabolic syndrome may not capture all the CVD risk associated with insulin resistance. *Diabetes* 54:3252–3257, 2005

From the [1]Department of Medicine, Countess of Chester Hospital NHS Trust, Chester, U.K.; the [2]Department of Medicine, University of Manchester, Manchester, U.K.; [3]Harvard Medical School, Boston, Massachusetts; the [4]General Internal Medicine Unit, Department of Medicine, Massachusetts General Hospital, Boston, Massachusetts; the [5]Boston University School of Public Health, Boston, Massachusetts; the [6]Medical University of South Carolina, Charleston, South Carolina; and the [7]National Heart, Lung, and Blood Institute's Framingham Heart Study, Framingham, Massachusetts.

Address correspondence and reprint requests to Martin K. Rutter, MD, Directorate of Medicine, Countess of Chester Hospital NHS Trust, Liverpool Road, Chester, CH2 1UL, U.K. E-mail: martin.rutter@coch.nhs.uk.

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CVD, cardiovascular disease; HOMA-IR, homeostasis model assessment of insulin resistance; ISI, insulin sensitivity index; NCEP, National Cholesterol Education Program.

The National Cholesterol Education Program (NCEP) definition of the metabolic syndrome was proposed as a practical tool for identifying a high-risk cardiovascular disease (CVD) phenotype (1), and several studies have subsequently confirmed that the metabolic syndrome predicts incident CVD (2–5). The metabolic syndrome may also serve as a surrogate measure of the insulin resistance phenotype as it identifies a proportion of subjects with insulin resistance without directly measuring insulin action (6–9).

Insulin resistance may be causally related to increased CVD risk. Direct measurement of insulin resistance using the hyperinsulinemic-euglycemic clamp has practical limitations; consequently, data linking directly measured insulin resistance with CVD is derived mostly from cross-sectional studies (10) and rarely from prospective cohorts (11,12).

Fasting insulin is a simple indirect measure of insulin resistance. Prospective studies using this measure have been equivocal or modest with regard to CVD risk (13–16). Of the remaining indirect measures of insulin resistance, the homeostasis model assessment formula (HOMA-IR), requiring only fasting glucose and insulin measurements, is the most popular. HOMA-IR values correlate reasonably well with "gold standard" clamp-derived values (17–19). Recently, Gutt et al. (20) proposed an index of insulin sensitivity ($ISI_{0,120}$) that uses glucose and insulin levels before and after oral glucose loading. $ISI_{0,120}$ values correlate well with directly measured insulin resistance (20) and have been shown to predict incident diabetes (19). Most (21–23) but not all (24) studies have shown an association of the more sophisticated indirect measures of insulin resistance with CVD.

It is not known if the NCEP Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) definition of the metabolic syndrome identifies all the CVD risk associated with insulin resistance. We therefore studied baseline metabolic syndrome and two surrogate insulin resistance measures, HOMA-IR and $ISI_{0,120}$, and their independent relation to 7-year CVD risk in the Framingham Offspring Study cohort.

RESEARCH DESIGN AND METHODS

Study subjects were participants in the Framingham Offspring Study, a community-based observational study of CVD risk factors. From January 1991 through June 1995 (examination cycle 5), participants, having provided

written informed consent, underwent a standardized clinical examination after an overnight fast. Prevalent diabetes was defined as self-reported use of hypoglycemic drugs at any previous examination or a fasting plasma glucose ≥126 mg/dl (7.0 mmol/l). Participants without diagnosed diabetes underwent a 75-g oral glucose tolerance test; newly diagnosed diabetes was defined in accordance with 1998 World Health Organization guidelines (25). Of the 3,799 participants, we excluded those with prevalent or newly diagnosed diabetes (n = 532), prevalent CVD (n = 270), or missing information on covariates (n = 99), leaving 2,898 subjects (1,596 women) for analysis.

The metabolic syndrome was defined according to 2001 NCEP Adult Treatment Panel III guidelines (1). Plasma glucose was measured in fresh specimens with a hexokinase reagent kit (A-gent glucose test; Abbott, South Pasadena, CA). Glucose assays were run in duplicate; the intra-assay coefficient of variation was <3%. Fasting insulin levels were measured in plasma as total immunoreactive insulin and were standardized to serum levels for reporting purposes. The lower limit of sensitivity was 8.0 pmol/l (1.1 μU/ml) and the intra- and interassay coefficients of variation were 5.0–10.0%. Insulin resistance and sensitivity were defined using validated definitions: *1*) HOMA-IR = [fasting glucose (mmol/l) × fasting insulin (μU/ml)]/22.5 (17,18) and *2*) $ISI_{0,120}$ = (m/MPG)/log MSI, where m is [75,000 mg + (fasting glucose − 2-h glucose) × 0.19 × body wt (kg)]/120 min, MPG is the mean of fasting and 2-h glucose concentrations (mg/dl), and MSI is the mean of fasting and 2-h insulin concentrations (mU/l) (20). Quartiles for the population distribution for the HOMA-IR were Q1, 2.21–5.12; Q2, 5.13–6.23; Q3, 6.24–7.95; and Q4, 7.95–35.53 units; for the $ISI_{0,120}$ they were Q1, 8.09–21.60; Q2, 21.61–25.90; Q3, 25.91–30.33; and Q4, 30.34–58.66 units. Total cholesterol and triglyceride levels were measured enzymatically, and the HDL cholesterol fraction was measured after precipitation of LDL and VLDL particles with dextran sulfate magnesium. The Framingham laboratory participates in the lipoprotein cholesterol laboratory standardization program administered by the Centers for Disease Control and Prevention (Atlanta, GA). Blood pressure was assessed as the average of two measurements taken after subjects had been seated for at least 5 min. Waist circumference was measured at the level of the umbilicus with the subject in the standing position. Subjects who reported smoking at least one cigarette per day during the year before the examination were classified as current smokers.

CVD assessment and follow-up. Incident CVD was assessed using standard Framingham Heart Study criteria and was defined as any of the following: new-onset angina, fatal and nonfatal myocardial infarction or stroke, transient ischemic attack, heart failure, or intermittent claudication. Subjects free from CVD at the fifth (baseline) examination were followed for a median of 6.7 years to the seventh examination cycle (September 1998 to October 2001). Person-years of follow-up were accrued from baseline to the date of first event or censored at the date of the seventh examination if the subject was free of a CVD event.

Statistical analysis. Descriptive statistics included means and medians for continuous variables and frequencies for categorical variables. The distributions of fasting insulin, HOMA-IR, and $ISI_{0,120}$ were log transformed to improve normality before analysis. Tests for differences in age-adjusted mean HOMA-IR and $ISI_{0,120}$ levels across levels of risk factors and individual components of the metabolic syndrome were conducted using multiple linear regression analysis. First-order sex interactions were then assessed between these risk factors and the measures of insulin resistance. Subjects were classified as having zero, one, two, three, four, or five components of the metabolic syndrome, and age-adjusted mean HOMA-IR and $ISI_{0,120}$ levels were estimated for each group. Trends across groups were assessed using the χ^2 test. For the prediction of CVD, men and women were combined and first-order interaction terms for sex-by-insulin resistance measure interactions on the risk of CVD were examined. Because the interactions were not statistically significant, a sex-pooled Cox proportional hazards regression analysis was used to assess the association of risk factors with incident CVD. Similarly, first-order interaction terms for the impaired glucose tolerance × insulin resistance measure were not statistically significant; thus analysis was not stratified by glucose tolerance status. Models were adjusted for age, sex, LDL cholesterol, and smoking status. Risk factors were modeled as indicator variables, and hazard ratios (HRs) (95% CI) are presented. The overall predictive power of the models was assessed with the c-statistic representing the area under the receiver operating characteristic curve. All analyses were performed with SAS Version 8.2; a two-sided $P < 0.05$ was considered statistically significant.

RESULTS

The mean age of the study population was 54 (range 26–82) years. Table 1 shows that the prevalence of the metabolic syndrome was higher in men than in women (P = 0.01) and that a higher proportion of men than women exceeded thresholds defined by the NCEP for blood pressure, HDL cholesterol, and triglycerides (all $P \leq$ 0.03) (1). Although waist circumference and fasting glucose levels were greater in men than in women (both $P <$ 0.0001), a similar proportion of women and men exceeded NCEP thresholds (P = 0.2 and 0.07, respectively). The mean (±SD) BMI and proportion of subjects with BMI >30 kg/m^2 were also higher in men than in women (28 ± 4 vs. 26 ± 5 kg/m^2, $P <$ 0.0001; 26 vs. 19%, P = 0.001, respectively). Insulin resistance, assessed by fasting insulin and HOMA-IR values, was higher in men than in women (both $P <$ 0.0001). The 2-h insulin and 2-h glucose levels were both lower in men than in women (P = 0.002 and 0.0001, respectively). Insulin sensitivity, assessed by the $ISI_{0,120}$, was similar in men and women (P = 0.8).

TABLE 1
Clinical and biochemical characteristics of study subjects

	Women	Men
n	1,596	1,302
Systolic blood pressure (mmHg)	122 ± 19	127 ± 16
Diastolic blood pressure (mmHg)	72 ± 10	77 ± 9
HDL cholesterol (mg/dl)	57 ± 15	44 ± 11
Triglycerides (mg/dl)	109 (78–155)	122 (86–184)
Waist circumference (in)	34 ± 5	39 ± 4
Fasting glucose (mg/dl)	93 ± 9	97 ± 9
Blood pressure ≥130/85 mmHg (%)	38	50
HDL cholesterol <50 (women) or <40 mg/dl (men) (%)	34	39
Triglycerides ≥150 mg/dl (%)	27	36
Waist circumference >35 (women) or >40 in (men) (%)	34	32
Fasting glucose ≥110 mg/dl (%)	6	8
Metabolic syndrome (%)	22	26
BMI (kg/m^2)	26 ± 5	28 ± 4
2-h glucose (mg/dl)	107 ± 28	103 ± 26
2-h insulin (μU/ml)	42 (26–66)	39 (21–68)
Fasting insulin (μU/ml)	6.3 (3.5–9.9)	7.8 (4.5–12.6)
HOMA-IR (units)	5.8 (4.9–7.3)	6.7 (5.5–8.5)
$ISI_{0,120}$ (units)	26 (22–30)	26 (22–31)

Data are means ± SD or median (interquartile range) unless otherwise indicated. Insulin levels were calculated in serum.

$ISI_{0,120}$ levels and HOMA-IR levels were significantly related to age (r = −0.28 and 0.10, respectively; both $P <$ 0.0001). Table 2 shows that age-adjusted HOMA-IR levels were higher and $ISI_{0,120}$ levels were lower when individual components of the metabolic syndrome or the metabolic syndrome itself were present (all $P <$0.0001). Correlation coefficients between the continuously distributed individual components of the metabolic syndrome and HOMA-IR and $ISI_{0,120}$ levels were of a similar magnitude for blood pressure, fasting glucose, and triglycerides. Fasting insulin, waist circumference, and HDL cholesterol were more strongly related to the HOMA-IR than to the $ISI_{0,120}$.

$ISI_{0,120}$ and HOMA-IR levels were inversely related to each other (r = −0.46, $P <$ 0.0001). Mean age-adjusted $ISI_{0,120}$ levels decreased and HOMA-IR levels increased in relation to the increasing number of components of the metabolic syndrome present (Fig. 1).

During the 7 years of follow-up, there were 186 CVD

TABLE 2
Relation of age- and sex-adjusted HOMA-IR and $ISI_{0,120}$ to features of the metabolic syndrome and insulin levels

	HOMA-IR		$ISI_{0,120}$	
	Level	Spearman rank correlation coefficient	Level	Spearman rank correlation coefficient
n	2,898	—	2,898	—
Systolic blood pressure (mmHg)				
<130	6.4 ± 0.06		27.5 ± 0.2	
≥130	7.9 ± 0.09	0.36	24.7 ± 0.2	−0.34
Diastolic blood pressure (mmHg)				
<85	6.7 ± 0.06		26.9 ± 0.1	
≥85	8.2 ± 1.0	0.30	24.1 ± 0.3	−0.21
HDL cholesterol (mg/dl)				
>50	6.0 ± 0.1		28.1 ± 0.2	
40–50	7.2 ± 0.1		25.9 ± 0.2	
<40	8.4 ± 0.1	−0.40	23.8 ± 0.3	0.20
Triglycerides (mg/dl)				
<150	6.3 ± 0.1		27.6 ± 0.1	
≥150	8.2 ± 0.1	0.43	24.0 ± 0.2	−0.36
Waist circumference (in)				
<35	5.6 ± 0.1		28.9 ± 0.2	
35–40	6.9 ± 0.1		26.0 ± 0.2	
>40	9.2 ± 0.1	0.53	23.2 ± 0.2	−0.31
Fasting plasma glucose (mg/dl)				
<110	6.7 ± 0.1		26.9 ± 0.1	
110–126	10.3 ± 0.2	0.56	20.2 ± 0.5	−0.46
Metabolic syndrome				
No	6.2 ± 0.1		27.7 ± 0.1	
Yes	9.3 ± 0.1	—	22.5 ± 0.2	—
Fasting serum insulin (μU/ml)				
<90th percentile	6.2 ± 0.04		27.1 ± 0.1	
≥90th percentile	13.3 ± 0.1	0.95	20.7 ± 0.3	−0.42

Data are means ± SE. Spearman rank correlation coefficients describe the relation between HOMA-IR or $ISI_{0,120}$ and metabolic syndrome risk factor levels. $P < 0.0001$ for all correlation coefficients.

events (new-onset angina, 54; fatal and nonfatal myocardial infarction, 41; fatal and nonfatal stroke, 28; transient ischemic attack, 14; heart failure, 19; intermittent claudication, 17; coronary heart disease death, 6; and coronary insufficiency, 7). In age- and sex-adjusted models, baseline HOMA-IR, $ISI_{0,120}$, and metabolic syndrome were all individually related to incident CVD, and the c-statistic was similar for all univariate models (Table 3). The relation between HOMA-IR and CVD events was similar to that for fasting insulin for the highest versus the lowest quartile (HR 1.8 [95% CI 1.2–2.8], $P = 0.003$). In a model adjusted for age, sex, LDL cholesterol, and smoking status that included the $ISI_{0,120}$ and the metabolic syndrome, both variables were independently related to CVD events (Table 3). The inclusion of both variables produced only a small increase in the c-statistic when compared with that obtained using either variable alone. In a model that included the HOMA-IR and the metabolic syndrome, only the metabolic syndrome was independently related to CVD events. Almost identical results were obtained in a model that included fasting insulin and the metabolic syndrome (upper versus lower quartile insulin levels; 1.5 [0.9–2.2], $P = 0.10$), a model that included the metabolic syndrome (1.7 [1.2–2.3], $P = 0.002$), models adjusted for baseline age and sex only (not shown), and models that included computer-derived HOMA-IR model values (26) rather than values derived from the HOMA-IR formula (not shown).

We also modeled the individual components that com-

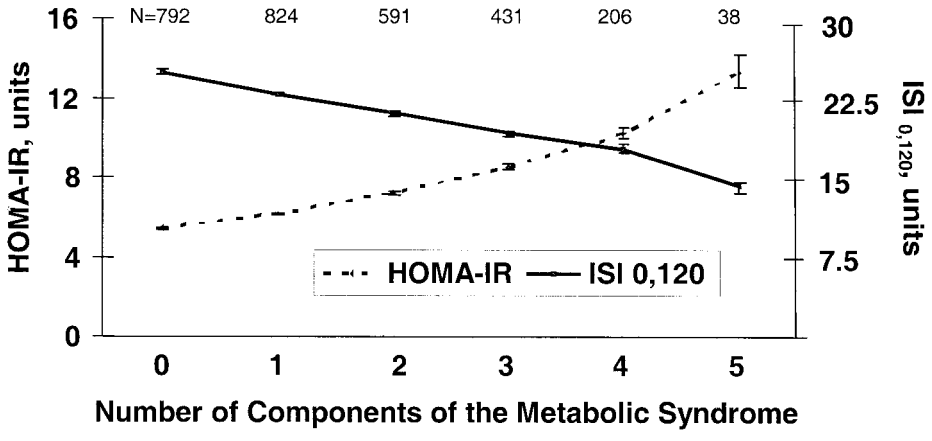

FIG. 1. HOMA-IR and $ISI_{0,120}$ levels according to the number of metabolic syndrome components. Data are means ± SE.

TABLE 3
Multivariable-adjusted for CVD events associated with the HOMA-IR and the $ISI_{0,120}$ in the upper quartile and/or the metabolic syndrome

	Model A			Model B	
	1	2	3	1	2
HOMA-IR (4th quartile)	1.7 (1.1–2.7); 0.01	—	—	1.3 (0.8–2.1); 0.24	—
$ISI_{0,120}$ (4th quartile)	—	0.4 (0.2–0.6); 0.0001	—	—	0.5 (0.3–0.8); 0.004
Metabolic syndrome	—	—	1.9 (1.4–2.5); 0.0001	1.6 (1.1–2.3); 0.007	1.6 (1.2–2.2); 0.003
C-statistic	0.74	0.74	0.75	0.75	0.75

Data are HR (95% CI); *P* value. All data are adjusted for age, sex, LDL cholesterol, and smoking. Model A includes a single measure of insulin resistance. Model B includes two measures of insulin resistance. HR comparisons are with subjects with insulin resistance levels in the lowest quartile and subjects without the metabolic syndrome. All models include all subjects.

prise the $ISI_{0,120}$. In separate models that included 2-h insulin or 2-h glucose individually, only 2-h insulin was related to subsequent CVD events for upper versus lower quartile 2-h insulin (2.0 [1.3–3.1], $P = 0.002$) and 2-h glucose (1.5 [1.0–2.4], $P = 0.054$). However, in a model that included both 2-h insulin and the metabolic syndrome, only the metabolic syndrome was independently related to CVD events (1.5 [0.9–2.2], $P = 0.10$, and 1.7 [1.2–2.3], $P = 0.002$, respectively).

When subjects who developed diabetes during follow-up ($n = 148$) were excluded from the analysis, there was no substantive change in the results.

In age and sex-adjusted models that also adjusted for the components of the metabolic syndrome (systolic and diastolic blood pressure, triglycerides, and HDL cholesterol) treated either as continuous or categorical variables, neither the HOMA-IR nor the $ISI_{0,120}$ was significantly related to CVD events ($P \geq 0.10$ for all models).

DISCUSSION

Cross-sectional study. As shown in previous population-based studies (6,7,24), we found that both surrogate measures of insulin resistance, the HOMA-IR and $ISI_{0,120}$ levels, were related to the number of components of the NCEP-defined metabolic syndrome that were present in individuals. The inverse relation observed with the $ISI_{0,120}$ is explained by this being a measure of insulin sensitivity rather than insulin resistance.

Our data on the prevalence of the metabolic syndrome in men and women and the comparison of insulin and HOMA-IR levels by sex suggest that the men in our sample were more insulin resistant than the women. Because the $ISI_{0,120}$ is a measure of insulin sensitivity, lower levels in men than in women might have been expected. The unexpected finding of similar levels in men and women is probably explained by the calculation mode of the $ISI_{0,120}$, which is directly related to body weight and inversely related to 2-h glucose and 2-h insulin levels. In our sample, the former was higher in men than in women and the latter two factors were lower in men.

Prospective study. Many studies have been equivocal about the CVD risk associated with fasting insulin and glucose levels; nonetheless, we found an association between HOMA-IR and CVD, as have three previous studies (21–23). Here we extended these findings by studying the HOMA-IR and $ISI_{0,120}$ and assessing whether their relation to incident CVD was independent of the metabolic syndrome phenotype. This analysis is of particular importance because the metabolic syndrome phenotype has been proposed as a means of identifying subjects with insulin resistance who are at increased CVD risk (1). We have shown that individually all three indirect measures of insulin resistance predict CVD events. Our main finding was that after adjusting for the presence of the metabolic syndrome, the $ISI_{0,120}$ was an independent CVD risk factor but the HOMA-IR was not. Our analysis demonstrated that the metabolic syndrome is an independent CVD risk factor after adjusting for the $ISI_{0,120}$ or HOMA-IR. We have also shown that at the population level, the HOMA-IR, $ISI_{0,120}$, and metabolic syndrome alone or in combination are equivalent in defining the CVD risk.

HOMA-IR assesses insulin resistance in the fasting state rather than in the postprandial state, and it tends to represent hepatic rather than peripheral insulin resistance. It assesses the β-cell response to energy stress by a process of theoretical modeling rather than by direct measurement of postprandial insulin and glucose levels. On the other hand, $ISI_{0,120}$ is a more complex assessment of insulin resistance that accounts more for peripheral insulin resistance and glucose disposal and uses a direct measurement of the β-cell response to energy stress.

Why is the $ISI_{0,120}$ an independent CVD risk factor after accounting for the metabolic syndrome when the HOMA-IR is not? There are several potential explanations. First, fasting glucose is one of the five components of the NCEP metabolic syndrome and is also one of the two components of the HOMA-IR, but it is a relatively smaller component of the $ISI_{0,120}$. The sharing of a common dominant variable could partly explain why the HOMA-IR does not remain a significant independent CVD risk factor after statistically adjusting for the metabolic syndrome. Second, if the CVD risk associated with the $ISI_{0,120}$ reflects risk "due to" insulin resistance that is not fully captured by the HOMA-IR formula, then our data could be explained as the ability of the $ISI_{0,120}$ to more accurately reflect insulin resistance than the HOMA-IR. Gutt et al. (20) have shown that the $ISI_{0,120}$ is more strongly correlated with directly measured insulin sensitivity than the HOMA-IR formula values; on the other hand, Hanley et al. (19) found that the HOMA-IR and $ISI_{0,120}$ were similarly related to insulin resistance. In a small study of 33 healthy volunteers, Soonthornpun et al. (27) found that the correlation with clamp-derived insulin resistance values was greater for indexes of insulin resistance derived from oral glucose tolerance test data (including the $ISI_{0,120}$) when compared with those derived from fasting measures (including the HOMA-IR). In the present study, we did not directly measure insulin resistance and therefore we are unable to know whether the $ISI_{0,120}$ or the HOMA-IR is superior in this regard. Third, differences in the statistical indepen-

dence of the variables might explain the findings. Our cross-sectional data (Table 2) showed that the HOMA-IR was generally more strongly correlated with the individual components of the metabolic syndrome than the $ISI_{0,120}$. Therefore, in a multivariable model including one of these measures and the metabolic syndrome, the greater statistical independence of the $ISI_{0,120}$ might make it less likely to be displaced by the metabolic syndrome. Fourth, the $ISI_{0,120}$ is a complex function of body weight and fasting and postchallenge glucose and insulin levels. It directly assesses β-cell response to glucose loading and assesses peripheral insulin resistance, hepatic insulin resistance, and glucose disposal. Although the pathological conditions associated with hepatic insulin resistance are often associated with peripheral insulin resistance (18), this is not always the case (28), and it is possible that this distinction is important with regard to CVD risk. If the CVD risk associated with the $ISI_{0,120}$ reflects risk "due to" insulin resistance, then it is possible that the $ISI_{0,120}$ captures some aspects of insulin resistance, perhaps skeletal muscle insulin resistance or postprandial insulin resistance, or some part of β-cell insufficiency that is not captured by the HOMA-IR or the NCEP metabolic syndrome definition. Fifth, the $ISI_{0,120}$ could be linked to CVD events through factors related to insulin resistance that have not been captured by the HOMA-IR or the metabolic syndrome phenotype, such as inflammation, disorders of coagulation and fibrinolysis, postprandial lipemia, small dense LDL, albuminuria, and adiponectin. Previous studies have shown that 2-h insulin and 2-h glucose values are related to insulin resistance (29) and predict CVD (30,31); however, in our analysis, the inclusion of these variables did not appear to explain the link between the $ISI_{0,120}$ and CVD.

The potential mechanisms linking insulin resistance with CVD remain poorly understood but include inflammation (6,32), impaired endothelial function (33), proliferation of vascular smooth muscle cells, increased sympathetic nervous system activity, and increased levels of free fatty acids. An attractive hypothesis is that insulin resistance leads to CVD through the development of diabetes. However, our exploratory analysis excluding subjects who developed diabetes during follow-up suggested that this mechanism explains only a small component of the link between insulin resistance and CVD.

It should be noted that our data are entirely consistent with the hypothesis that all three surrogate markers for insulin resistance studied could reflect aspects of the pathogenesis of CVD that are not related to insulin resistance. In other words, the individual components of the $ISI_{0,120}$ (glucose, insulin, and body weight), HOMA-IR (glucose and insulin), and metabolic syndrome (obesity, hypertension, hyperglycemia, and dyslipidemia) could be acting directly as CVD risk factors, independent of their relation to insulin resistance. Because we did not directly measure insulin resistance, we cannot estimate what proportion of the measured CVD risk was explained by insulin resistance itself independent of these other possible explanations.

Our analysis highlights the loss of potentially valuable CVD risk information through categorizing subjects as having or not having the NCEP-defined metabolic syndrome. In the models that were adjusted for the individual nonglucose components of the metabolic syndrome (blood pressure, waist measurement, and lipids), the $ISI_{0,120}$ was not significantly related to incident CVD, whereas it was significantly related to incident CVD when it was included in a model with the metabolic syndrome (yes/no), as shown in Table 3. The models that adjusted for the individual components of the metabolic syndrome do not clarify the mechanisms leading to CVD because all components of the metabolic syndrome are related to insulin resistance (Table 2). Thus, insulin resistance could cause CVD through increased waist circumference, dyslipidemia, and/or hypertension; however, because of the intercorrelations, the data are also consistent with the hypothesis that the features of metabolic syndrome lead to CVD through insulin resistance.

HRs versus population risk. We have shown that the $ISI_{0,120}$ and metabolic syndrome are independent CVD risk factors but that the inclusion of both variables in the multivariable model produced only a small increase in the c-statistic when compared with that obtained using either variable on its own. The explanation for this apparent paradox was provided in a recent study that showed that for a risk factor to be effective for population risk stratification, the associated HR has to be "of a magnitude rarely seen in epidemiological studies" (34). We have provided evidence of a small but statistically significant HR for the association between insulin resistance and CVD. However, the true strength and nature of the association between insulin resistance and CVD is difficult to determine from this analysis (see STUDY LIMITATIONS below). For example, the true effect of insulin resistance in the pathogenesis of CVD might be best reflected by the results of model A (Table 3) in which the influence of the $ISI_{0,120}$ was unadjusted for the presence of the metabolic syndrome.

Study limitations. We had only fasting and 2-h oral glucose tolerance test information and did not directly measure insulin resistance. We also excluded subjects with CVD and diabetes at baseline to reduce the effect of medical therapies on CVD outcomes; therefore, we have probably provided conservative estimates of the strength of the association among metabolic syndrome, insulin resistance, and CVD events. The size of our male, female, and impaired glucose tolerance subgroups has limited the statistical power to perform stratified survival analysis. Our study sample was largely white, which may limit generalizability to other ethnic groups.

Clinical implications. Recent clamp studies have raised concerns that the current NCEP definition of the metabolic syndrome has low sensitivity for identifying insulin resistance in subjects (8,9); the question that must then be asked is whether this has clinical implications. Our data suggest that the metabolic syndrome, HOMA-IR, and $ISI_{0,120}$ each significantly contribute to CVD risk but that none is superior alone or in combination for population-level prediction of CVD risk.

Conclusion. This study has shown that the $ISI_{0,120}$ and the metabolic syndrome phenotype are independent predictors of CVD events. The NCEP metabolic syndrome phenotype does not appear to fully capture the CVD risk associated with insulin resistance, although this may not be critical for population-level prediction of CVD risk. $ISI_{0,120}$ is a complex insulin resistance phenotype that deserves further analysis as a powerful surrogate predictor of both diabetes (19) and CVD.

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