Insulin Resistance, the Metabolic Syndrome, and Risk of Incident Cardiovascular Disease in Nondiabetic American Indians

The Strong Heart Study

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OBJECTIVE — Insulin resistance (IR) and the metabolic syndrome (MS) are associated with type 2 diabetes and adverse cardiovascular disease (CVD) risk factor profiles. Whether IR and MS predict CVD independently of diabetes and other CVD risk factors is not known. This study examines whether IR and/or presence of MS are independently associated with CVD in nondiabetic American Indians (AI).

RESEARCH DESIGN AND METHODS — We examined 2,283 nondiabetic AI who were free of CVD at the baseline examination of the Strong Heart Study (SHS). CVD risk factors were measured, IR was quantified using the homeostasis model assessment (HOMA), and MS as defined by the National Cholesterol Education Program Adult Treatment Panel (ATP III) was assessed for each participant. Incident CVD and diabetes were ascertained during follow-up.

RESULTS — MS was present in 798 individuals (35%), and 181 participants (7.9%) developed CVD over 7.6 ± 1.8 years of follow-up. Age, BMI, waist circumference, and triglyceride levels increased and HDL cholesterol decreased across tertiles of HOMA-IR. Risk of diabetes increased as a function of baseline HOMA-IR (6.3, 14.6, and 30.1%; $P < 0.001$) and MS (12.8 vs. 24.5%). In Cox models adjusted for CVD risk factors, risk of CVD did not increase either as a function of baseline HOMA-IR or MS, but individual CVD risk factors predicted subsequent CVD.

CONCLUSIONS — Among nondiabetic AI in the SHS, HOMA-IR and MS both predict diabetes, but neither predicts CVD independently of other established CVD risk factors.

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Abbreviations: AI, American Indians; ATP III, National Cholesterol Education Program Adult Treatment Panel; CVD, cardiovascular disease; FG, fasting glucose; FI, fasting insulin; FSIVGTT, frequently sampled intravenous glucose tolerance test; HOMA, homeostasis model assessment; IR, insulin resistance; MS, metabolic syndrome; SHS, Strong Heart Study.

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

Diabetes increases the risk of both clinical and subclinical cardiovascular disease (CVD) (1–5). American Indians (AI) have the highest prevalence of diabetes in the U.S. (6), and CVD in communities of AI is increasing (4). Insulin resistance (IR) precedes diabetes in AI (7). IR is characterized by a diminished response to the biological effects of insulin and is associated with obesity (8), predominantly abdominal distribution of fat (9), elevated blood pressure and triglyceride levels, low HDL cholesterol (10), small LDL particle size (11), and elevations in inflammatory cytokines (12). The constellation of physical and metabolic features common among insulin-resistant individuals has been called the metabolic syndrome (MS) and has been postulated to increase atherogenesis, thereby leading to increased risk of CVD. In a recent report, the National Cholesterol Education Program Adult Treatment Panel (ATP III) defined MS using cut points for physical and metabolic characteristics long recognized to be associated with IR (13). An advantage of this definition is the potential for structured assessment of those at risk for CVD.

Interrelationships among IR, MS, diabetes, and CVD are of particular interest in AI. Because of the high prevalence of diabetes in this population and the high risk of CVD among those with diabetes, the need for early CVD risk factor modification is greatly increased. This study examines whether a proxy measure of IR and/or presence of MS is associated with risk of CVD in nondiabetic AI independent of established CVD risk factors.

RESEARCH DESIGN AND METHODS

Study population

The Strong Heart Study (SHS) was initiated in 1988 to investigate CVD and its

risk factors in AI (14). The design, methods, and laboratory techniques of the SHS have been reported (14–16).

The SHS cohort consisted of 4,549 participants aged 45–74 years who were seen at the baseline examination, which was conducted between 1989 and 1992. The second and third examinations were conducted in 1993–1995 and 1997–1999. Nonparticipants were similar to participants in age, BMI, and self-reported frequency of diabetes and hypertension (16).

Measurement of baseline CVD risk factors

Methods for measurement of CVD risk factors, including BMI, waist circumference, blood pressure, and renal function, have been described, and laboratory methods have been published (14,15). Cholesterol, triglyceride, and fasting glucose (FG) levels were determined by enzymatic methods using a Hitachi chemistry analyzer and consistent, standardized reagents (Boehringer Mannheim, Indianapolis, IN). Fasting insulin (FI) and fibrinogen levels were measured by established methods (17,18). Participants were considered hypertensive if they were taking antihypertension medication or if systolic blood pressure was ≥130 mmHg or diastolic blood pressure was ≥85 mmHg. Smoking status was determined by questionnaire. Urinary albumin excretion was estimated by the ratio of albumin (mg) to creatinine (g) in a morning urine sample. Microalbuminuria was defined as a ratio of urinary albumin (mg/ml) to creatinine (g/ml) of 30–299 mg/g and macroalbuminuria was defined as a ratio ≥300 mg/g.

Measurement of baseline IR

The homeostasis model assessment (HOMA) estimates IR with the expression [FI (μU/ml) · FG (mmol/l)]/22.5 (19). HOMA-IR correlates with euglycemic clamp measures in men and women, younger and older adults, and obese and nonobese individuals (20–22). Data from the SHS (23) show that at FG <126 mg/dl (the FG cut point used to select this analysis sample), HOMA-IR correlates well with insulin sensitivity measured by the Minimal Model (24).

Definition of MS

Participants were considered as having MS if three or more of the following characteristics were present at baseline: waist circumference >102 cm in men and >88 cm in women, triglycerides ≥150 mg/dl, HDL cholesterol <40 mg/dl in men and <50 mg/dl in women, blood pressure ≥130/85 mmHg, and FG ≥110 mg/dl (13).

Ascertainment of incident CVD and diabetes

Methods for ascertaining incident CVD in the SHS have been described (4,14,16). Incident diabetes was identified by self-report, use of hypoglycemic agents, or FG ≥126 mg/dl. No distinction was made between incident diabetes cases identified at the second examination and those identified at the third examination.

Sample selection

Diabetic participants were excluded based on self-report of diabetes or documented use of oral hypoglycemic agents or insulin. We excluded diabetic individuals for several reasons. First, the SHS data have demonstrated that the HOMA model, a key predictor in this report, is not an accurate reflection of IR measured by the Minimal Model at FG >126 mg/dl. Second, because the objective of this study is to examine the effect of IR on subsequent CVD risk, we chose to exclude individuals with known diabetes because longstanding diabetes is a potent risk factor for CVD in this population. However, we examine the role of incident diabetes in our analyses. Among those not reporting diabetes or using oral agents or insulin, undiagnosed diabetes was identified using American Diabetes Association criteria (25) (FG ≥126 mg/dl), and these individuals were excluded (n = 2,126 participants with diagnosed and undiagnosed diabetes). The definition of undiagnosed diabetes in this study is consistent with Indian Health Service screening practices for diabetes in the communities in which the SHS data were collected. Participants with prevalent CVD (16) were also excluded. Methods for ascertainment of prevalent coronary heart disease at the SHS baseline examination have been published and include abnormal electrocardiography data and/or history of myocardial infarction or coronary heart disease verified by chart review and confirmed by a panel of SHS physicians (14,16). Participants were excluded if FG or FI data were missing (n = 86) or if diabetes status could not be determined at baseline (n = 2).

Statistical methodology

HOMA-IR and MS were considered the primary independent variables of interest, and incident CVD was the dependent variable of interest. Using the t test, mean levels of continuously distributed variables were examined according to category of incident CVD. The χ^2 test was used to examine incident CVD in relation to categorical variables. Tertiles of HOMA-IR were examined in relation to continuous variables using generalized linear models. In these analyses, total, LDL, and non–HDL cholesterol values were adjusted for study center due to known differences in lipid levels across the three SHS field centers (16). The χ^2 test for trend was used to examine tertiles of HOMA-IR in relation to the distribution of categorical CVD risk factors. Tertiles of HOMA-IR were cross-tabulated with the binary MS variable.

Cox proportional hazards models were used to examine tertiles of baseline HOMA-IR as a predictor of time to incident CVD as well as presence of MS as a predictor of CVD. We examined a series of models in which variable covariates were selected based on findings from the generalized linear models. We focused on how age-adjusted β-coefficients for HOMA tertiles and the age-adjusted coefficient for MS changed with adjustment for other risk factors. This strategy allowed direct examination of the degree to which the relationship between HOMA tertiles and MS and incident CVD were confounded by other risk factors. Importantly, when modeling MS as a predictor of CVD, individual components of MS (e.g., waist circumference, HDL cholesterol, and hypertension) were replaced with the binary MS variable. We tested the proportional hazards assumption for both the HOMA and MS models by plotting these variables against the log of time, and this assumption was not violated. We also tested for a nonlinear relationship between HOMA-IR and CVD by using the continuous HOMA variable and a quadratic term. No evidence of nonlinearity was observed. We report findings for HOMA tertile data only.

RESULTS

— The selection criteria yielded an analysis sample of 2,283 nondiabetic participants without CVD

Table 1—*Comparison of selected baseline CVD risk factors in nondiabetic individuals according to CVD status at follow-up, the SHS* (N = 2,283)

Known or potential CVD risk factor	Incident CVD (n = 181)	No incident CVD (n = 2,102)	P*
Age (years; mean ± SD)	60.0 ± 8.3	55.1 ± 8.0	<0.001
Sex (% women)	33.1	59.1	<0.001
BMI (kg/m^2; mean ± SD)	29.0 ± 4.6	29.8 ± 6.1	0.027
Waist circumference			
Men	100.3 ± 10.9	100.6 ± 12.5	0.787
Women	102.2 ± 12.4	102.8 ± 15.5	0.706
Systolic blood pressure (mmHg)	133 ± 21	124 ± 18	<0.001
Total cholesterol (mg/dl; mean ± SE)†	192 ± 2.7	190 ± 0.82	0.493
LDL cholesterol (mg/dl; mean ± SE)†	113 ± 2.3	108 ± 0.71	0.026
HDL cholesterol (mg/dl; mean ± SD)	46 ± 13	48 ± 15	0.001
Triglycerides (mg/dl; mean ± SD)	127 ± 81	127 ± 92	0.959
Current smoking (%)	44.8	40.2	0.231
FG (mg/dl; mean ± SD)	102 ± 12.0	102 ± 11.0	0.955
FI (μU/ml; mean ± SD)	14.2 ± 10.0	15.6 ± 13.4	0.087
Log (fibrinogen) (mg/dl; mean ± SD)	5.7 ± 0.2	5.6 ± 0.3	0.024
Albumin:creatinine ratio (% >30 mg/g)	17.7	10.7	0.005
HOMA-IR‡	3.6 ± 2.7	4.0 ± 3.6	0.084
ATP-III MS (%)§	35.9	34.9	0.778
Incident diabetes (%)‖	13.8	17.3	0.229

*P values are for the t test of differences in means or the χ^2 test of differences in proportions for continuous and categorical variables, respectively, in comparisons between participants with and without incident CVD; †means are adjusted for study center; ‡(FI [μU/ml] · FG [mmol/l])/22.5; §three or more of the following characteristics at baseline: waist circumference >102 cm in men and >88 cm in women; triglycerides ≥150 mg/dl; HDL cholesterol <40 mg/dl in men and <50 mg/dl in women; blood pressure ≥130/85 mmHg; or FG ≥110 mg/dl; ‖any of the following: FG ≥126 mg/dl; self-reported physician-diagnosed diabetes during standardized interview; medication inventory data indicating current use of oral hypoglycemic medications or insulin.

(50.2% of the original cohort). Table 1 shows baseline CVD risk factors and measures of glucose metabolism according to CVD status at follow-up. Of the 2,283 participants in the analysis sample, 181 developed a CVD event during a mean follow-up of 7.6 ± 1.8 years (4.6 ± 2.6 and 7.8 ± 1.5 years in participants with and without incident CVD, respectively). Participants with CVD were significantly older (60.0 vs. 55.1 years, $P < 0.0001$), were less likely to be female (33 vs. 59%, $P < 0.0001$), and had higher systolic blood pressure (133 vs. 124 mmHg, $P < 0.0001$) than individuals without CVD. In addition, participants with incident CVD had higher LDL cholesterol (113 vs. 108, $P = 0.0262$), lower HDL cholesterol (46 vs. 48, $P = 0.001$), and higher prevalence of albuminuria (17.7 vs. 10.7%, $P = 0.0045$) than individuals without CVD. No differences were observed between participants with and without CVD in mean baseline triglyceride, FG, or FI levels. Diabetes developed in individuals with and without incident CVD at similar rates after baseline (13.8 vs. 17.3%, $P = 0.2288$). Participants with and without CVD were similar in both mean baseline HOMA-IR (3.6 and 4.0) and baseline prevalence of MS (35.9 and 34.9%).

As the tertile of HOMA-IR increased, percentage of women, BMI, waist circumference, and triglyceride, FG, and FI levels increased, whereas HDL cholesterol and smoking decreased (tests for trend, all $P < 0.0001$). Details are shown in Table 2. Small but significant increases in systolic blood pressure were also observed across the tertiles.

MS was present in 35% (n = 798) of the analysis sample and represented 13.4, 32.6 and 58.9% of people in the first, second, and third HOMA-IR tertiles, respectively ($P < 0.0001$; Fig. 1). Diabetes developed in 389 (17.0%) of the analysis sample, and risk of diabetes increased as a function of both baseline HOMA-IR and MS. In contrast, risk of CVD did not increase with tertile of baseline HOMA-IR or in those with baseline MS (Fig. 2).

Table 3 shows modeling of HOMA tertiles in prediction of CVD. These data indicate little difference in magnitude of the risk ratios between the age-adjusted and age- and center-adjusted models. However, the risk ratios did increase slightly after adjustment for waist circumference and BMI but remained essentially unchanged after additional adjustment. The final model showed no significant increase in risk of CVD in participants in the second and third HOMA tertiles compared with the first. We observed similar results in analyses of MS as a predictor of CVD (Table 4). The initial, modest, age-adjusted association (relative risk 1.35, CI 1.13–1.62) between MS and CVD risk was attenuated below significance by adjustment for study center. Although the magnitude of the association increased slightly upon further adjustment for sex and BMI, this relationship was not statistically significant and remained essentially unchanged after adjustment for additional risk factors. It is important to note, however, that key CVD risk factors, especially LDL cholesterol, were significant predictors of CVD in all multivariable analyses.

CONCLUSIONS — In nondiabetic AI, IR estimated by HOMA is associated with established CVD risk factors, including BMI, waist circumference, blood pressure, incident diabetes, and lipids levels, but it does not predict incident CVD alone after adjustment for these risk factors. Consistent with findings for HOMA-IR, we also show that ATP III–defined MS predicts diabetes but not CVD in nondiabetic AI in the SHS.

Previous reports from cohorts containing both diabetic and nondiabetic adults have shown cross-sectional relationships between IR and both subclinical CVD and history of CVD (26,27), suggesting that IR is a clinically meaningful state with respect to existing disease. These studies, which quantified IR by frequently sampled intravenous glucose tolerance test (FSIVGTT) or HOMA, are limited by their cross-sectional design, which does not allow determination of whether the state of IR, rather than its component risk factors, is predictive of future events. In most cases, the strength of IR as a predictor of CVD (in studies that do show such a relationship) is substantially attenuated after adjustment for risk factors. A review of studies examining both fasting and stimulated insulin concentrations concluded that there is little association between IR and CVD when

Table 2—*Baseline CVD risk factors according to tertile of baseline HOMA-IR among nondiabetic participants, the SHS* (N = 2,283)

CVD risk factor	HOMA-IR*			*P*†
	First tertile	Second tertile	Third tertile	
Age (years; mean ± SD)	55.4 ± 8.1	55.6 ± 8.2	55.5 ± 8.0	0.853
Sex (% women)	49.9	60.1	61.1	<0.001
BMI (kg/m^2; mean ± SD)	25.6 ± 4.1	29.9 ± 4.9	33.8 ± 5.7	<0.001
Waist circumference				
Men	92.4 ± 9.1	102.2 ± 9.38	109.5 ± 11.7	<0.001
Women	91.6 ± 12.7	102.6 ± 13.1	112.0 ± 13.2	<0.001
Systolic blood pressure (mmHg)	121 ± 19	124 ± 17	128 ± 18	<0.001
Total cholesterol (mg/dl; mean ± SE)‡	190 ± 1.37	193 ± 1.34	187 ± 1.30	0.003
Non-HDL cholesterol (mg/dl; mean ± SE)‡	136 ± 1.94	142 ± 1.90	144 ± 1.85	0.015
LDL cholesterol (mg/dl; mean ± SE)‡	112 ± 1.19	111 ± 1.16	106 ± 1.32	0.013
HDL cholesterol (mg/dl; mean ± SD)	54 ± 17	48 ± 14	43 ± 11	<0.001
Log (fibrinogen) (mg/dl; mean ± SD)	5.59 ± 0.24	5.61 ± 0.25	5.64 ± 0.25	0.069
Triglycerides (mg/dl; mean ± SD)	101 ± 58	130 ± 73	150 ± 124	<0.001
Current smoking (%)	55%	38%	28%	<0.001
FG (mg/dl; mean ± SD)	96 ± 10	102 ± 10	108 ± 9	<0.001
FI (μU/ml; mean ± SD)	5.9 ± 2.1	12.5 ± 2.4	28.0 ± 15.8	<0.001
Albumin:creatinine ratio (% >30 mg/g)	11.7	6.5	15.6	<0.001

*(FI [μU/ml] • FG [mmol/l])/22.5; †*P* values are tests for trend from generalized linear models or χ^2 tests for trend for continuous and categorical variables, respectively; ‡means adjusted for study center.

risk factors are considered (28). However, a recent study (29) showed the opposite result in persons with type 2 diabetes. In that study, HOMA-IR was an independent predictor of both prevalent and incident CVD among diabetic individuals, even after adjustment for sex, age, smoking status, lipid levels, and hypertension. A study published simultaneously (30) showed that among nondiabetic individuals in the San Antonio Heart Study, the fourth and fifth quintiles of HOMA-IR were significant predictors of incident CVD over 8 years of follow-up, adjusted for a series of risk factors. The inconsistency in these findings may be due to differences in the distribution of key risk factors between the cohorts, notably obesity, or to differences in the distribution of currently unknown genetic factors that may modify the effects of IR on heart disease in different ethnic groups.

Before publication of the ATP III guidelines, other reports used various definitions of MS (e.g., a count of abnormalities) and related this count of abnormalities to risk of events. These studies showed significant relationships between MS and risk of subsequent events (31,32). The SHS dataset allows assessment of both the "physiologic" (i.e., HOMA) and "count" (i.e., MS) approaches relating metabolic abnormalities to risk of CVD. We show that the HOMA index of IR, although strongly associated cross-sectionally with metabolic abnormalities that are common in the IR syndrome, is not associated with CVD events, either alone or independently of these features. The risk factors, however, do predict future events. Our results are consistent with earlier studies showing relationships between IR and CVD risk factors and also with those showing the importance of multiple components of MS in prediction of future CVD.

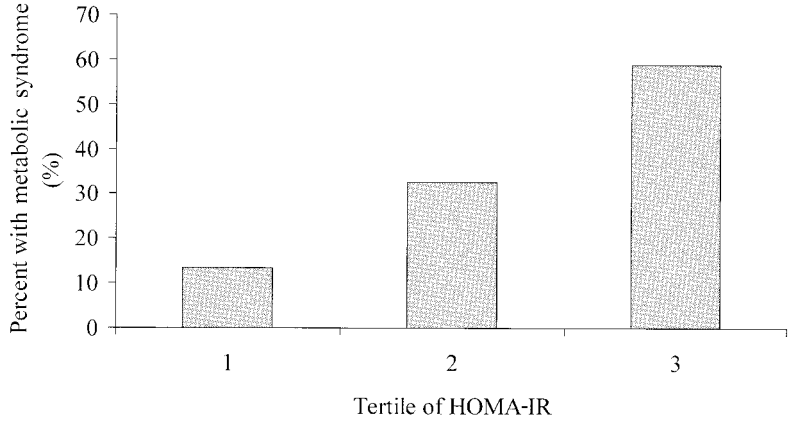

Figure 1—*Prevalence of ATP III–defined MS, according to tertile of HOMA: the SHS.*

Tertile of baseline HOMA-IR was strongly associated with subsequent risk of diabetes: 6.3, 14.6, and 30.1% of participants developed diabetes in the first, second, and third HOMA tertiles, respectively. This finding is consistent with results of another study in which HOMA-IR was shown to be a strong predictor of diabetes over 3.5 years of follow-up in 1,449 nondiabetic Mexicans (20). It bears emphasis that in AI in this study, the risk of diabetes in the third tertile of baseline HOMA-IR was 4.8 times that in the first tertile. The risk of diabetes in those with MS at baseline was 1.9 times higher than those without baseline MS (24.9 vs. 12.8%). Therefore, both HOMA-IR and ATP III–defined MS are potentially useful tools for evaluation of diabetes risk in this population.

ATP III guidelines defining MS (13) yielded an overall age-adjusted preva-

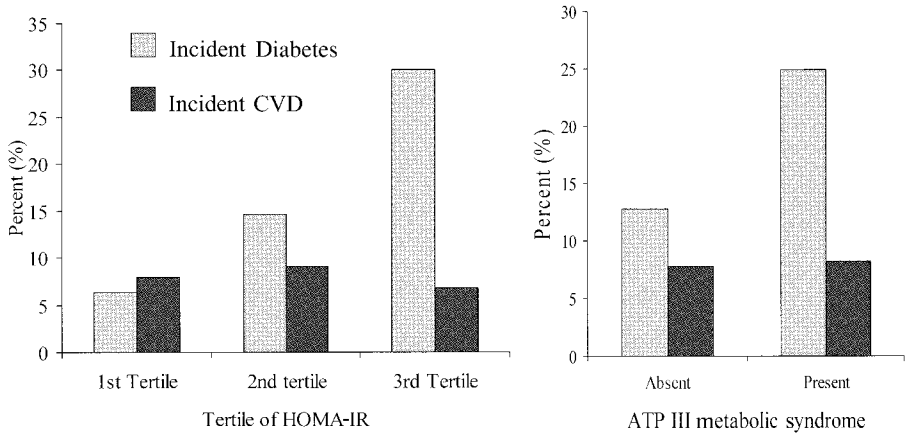

Figure 2—*Incident CVD and diabetes according to baseline tertile of HOMA-IR and ATP III–defined MS: the SHS.*

lence of 23.7% among Americans aged ≥20 years, a percentage corresponding to 47 million residents of the U.S. (33). Although this report showed that MS is present in a considerable proportion of American adults, it did not include data for AI and could not, therefore, highlight the dramatic ethnic differences in prevalence of MS. AI men in the SHS aged 45–49 years had 118% higher prevalence of MS than American men (whites, blacks, and Mexican Americans), and the prevalence in AI women in the SHS in the same age group was 145% higher than American women. The overall prevalence of MS at the baseline examination of SHS was 55.2% in individuals aged 45–74 years and 35% in the nondiabetic individuals examined (34). It should be stressed that the 23.7% estimated prevalence of MS in American adults included both diabetic and nondiabetic individuals; the 35% prevalence of MS in nondiabetic AI in this study exceeds that of diabetic and nondiabetic American adults as a whole.

An obvious question raised in this report is why IR and MS were weak predictors of CVD in nondiabetic AI. One explanation is that there was not adequate power to detect a relationship because our results were based on a total of 181 cases of incident CVD. Although this is possible, it was observed some time ago that despite their IR and obesity, few AI experience CVD (35). Research from the SHS has shown that CVD rates did not increase among AI until diabetes had been present for a substantial period of time, and then most events occurred in AI with diabetes (4). Another explanation for the relatively weak relationship is that the effect of IR on CVD risk factors (with the exception of HDL cholesterol) is relatively small. For example, across HOMA tertiles, systolic blood pressure increased only 7 mmHg and triglyceride levels increased by only 49 mg/dl. Therefore, IR may exert most of its effect on CVD through its association with development of diabetes. A third explanation is that indexes such as ATP III–defined MS do not adequately capture the health risks associated the physical and metabolic abnormalities present in IR. Finally, the high prevalence of smoking, although adjusted for in our models, may have overwhelmed the effects of IR/MS on CVD risk in this population.

One of the key assumptions underlying some findings in this report is that the HOMA model is an accurate reflection of more physiologic measures of IR. In epidemiologic studies such as the SHS, it is not feasible to conduct physiologic tests of insulin-glucose kinetics, such as the FSIVGTT or glucose clamp. Indexes such as HOMA-IR are proxies for these complex measures, but they do not provide the depth of physiologic information. Despite this limitation, the SHS data in a subset of participants show that HOMA-IR correlates well with the FSIVGTT at FG levels <126 mg/dl, the cut point used to select the analysis sample for this report (23). Therefore, we believe that HOMA-IR is a reasonably accurate reflection of IR among the nondiabetic AI examined here. Importantly, the HOMA index can be calculated from FG and FI values, two measures that are available to Indian Health Service physicians. The HOMA index, therefore, is a more clinically relevant measure than the FSIVGTT. Supplemental analyses of these data using tertiles of FI instead of tertiles

Table 3—*Cox proportional hazards regression analysis of the relationship of baseline tertile of HOMA-IR and MS and risk of CVD in nondiabetic participants in the SHS*

Model	Risk ratio	95% CI
Model 1*		
HOMA tertile 2 versus tertile 1	1.14	0.80–1.61
HOMA tertile 3 versus tertile 1	0.85	0.58–1.23
Model 2†		
HOMA tertile 2 versus tertile 1	1.19	0.84–1.69
HOMA tertile 3 versus tertile 1	0.95	0.65–1.39
Model 3‡		
HOMA tertile 2 versus tertile 1	1.41	0.97–2.05
HOMA tertile 3 versus tertile 1	1.09	0.69–1.71
Model 4§		
HOMA tertile 2 versus tertile 1	1.45	1.01–2.17
HOMA tertile 3 versus tertile 1	1.16	0.73–1.83
Model 5‖		
HOMA tertile 2 versus tertile 1	1.41	0.96–2.08
HOMA tertile 3 versus tertile 1	1.09	0.68–1.75
Model 6¶		
HOMA tertile 2 versus tertile 1	1.44	0.98–2.13
HOMA tertile 3 versus tertile 1	1.09	0.68–1.74

*Adjusted for age; †adjusted for age and center; ‡adjusted for age, center, sex, BMI, and waist circumference; §adjusted for age, center, sex, BMI, waist circumference, hypertension, fibrinogen, and smoking; ‖adjusted for age, center, sex, BMI, waist circumference, hypertension, fibrinogen, smoking, LDL cholesterol, and HDL cholesterol; ¶adjusted for age, center, sex, BMI, waist circumference, hypertension, fibrinogen, smoking, LDL cholesterol, HDL cholesterol, and albuminuria.

Table 4—*Cox proportional hazards regression analysis of the relationship of baseline ATP III–defined metabolic syndrome* and risk of CVD in nondiabetic participants in the SHS*

Model	Risk ratio	95% CI
Model 1*	1.35	1.13–1.62
Model 2†	0.94	0.69–1.29
Model 3‡	1.13	0.81–1.58
Model 4§	1.18	0.85–1.65
Model 5‖	1.17	0.84–1.64
Model 6¶	1.11	0.79–1.56

*Present versus absent; †adjusted for age; ‡adjusted for age and center; §adjusted for age, center, sex, and BMI; ‖adjusted for age, center, sex, BMI, fibrinogen, and smoking; ¶adjusted for age, center, sex, BMI, fibrinogen, smoking, and LDL cholesterol.

of HOMA-IR yielded results similar to those reported here (data not shown).

In summary, we show that among nondiabetic AI in the SHS, HOMA-IR and ATP III–defined MS both predict future risk of diabetes, but neither predicts CVD independently of other established CVD risk factors. The relevance of IR for CVD in American Indians is its ability to predict diabetes, which is potent risk factor for CVD in this population.

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