

Homeostasis Model Assessment of Insulin Resistance in Relation to the Incidence of Cardiovascular Disease

The San Antonio Heart Study

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OBJECTIVE — The prospective association between insulin levels and risk of cardiovascular disease (CVD) is controversial. The objective of the present study was to investigate the relationship of the homeostasis model assessment of insulin resistance (HOMA-IR), as well as insulin levels, with risk of nonfatal and fatal CVD over the 8-year follow-up of the San Antonio Heart Study.

RESEARCH DESIGN AND METHODS — Between 1984 and 1988, randomly selected Mexican-American and non-Hispanic white residents of San Antonio participated in baseline examinations that included fasting blood samples for glucose, insulin, and lipids, a glucose tolerance test, anthropometric measurements, and a lifestyle questionnaire. Between 1991 and 1996, 2,569 subjects who were free of diabetes at baseline were reexamined using the same protocol.

RESULTS — Over the follow-up period, 187 subjects experienced an incident cardiovascular event (heart attack, stroke, heart surgery, angina, or CVD death). Logistic regression analysis indicated that risk of a CVD event increased across quintiles of HOMA-IR after adjustment for age, sex, and ethnicity (P for trend <0.0001 ; quintile 5 vs. quintile 1, odds ratio [OR] 2.52, 95% CI 1.46–4.36). Additional adjustment for LDL, triglyceride, HDL, systolic blood pressure, smoking, alcohol consumption, exercise, and waist circumference only modestly reduced the magnitude of these associations (P for trend 0.02; quintile 5 vs. quintile 1, OR 1.94, 95% CI 1.05–3.59). Furthermore, there were no significant interactions between HOMA-IR and ethnicity, sex, hypertension, dyslipidemia, glucose tolerance (impaired glucose tolerance versus normal glucose tolerance), or obesity. The magnitude and direction of the relationship between insulin concentration and incident CVD were similar.

CONCLUSIONS — We found a significant association between HOMA-IR and risk of CVD after adjustment for multiple covariates. The topic remains controversial, however, and additional studies are required, particularly among women and minority populations.

Diabetes Care 25:1177–1184, 2002

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Received for publication 6 December 2001 and accepted in revised form 11 April 2002.

Abbreviations: CAD, coronary artery disease; CVD, cardiovascular disease; HOMA-IR, homeostasis model assessment of insulin resistance; IGT, impaired glucose tolerance; MI, myocardial infarction; NGT, normal glucose tolerance; OR, odds ratio; SAHS, San Antonio Heart Study; WHO, World Health Organization.

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

Cardiovascular disease (CVD) accounts for half of the total mortality among individuals with type 2 diabetes (1), and the risk of a first myocardial infarction (MI) among subjects with diabetes approximates that for reinfarction among nondiabetic patients with a previous MI (2). In addition, CVD among nondiabetic individuals is predicted by several risk factors that are also prospectively associated with risk of type 2 diabetes, including total and abdominal obesity, lipid abnormalities, and low levels of physical activity (3–5). Thus, it is clear that risk factors for diabetes and CVD cluster together, and it has been hypothesized that either insulin resistance (IR) or its consequent hyperinsulinemia might provide the unifying pathophysiological mechanism underlying these observations (6–8).

Although cross-sectional and prospective studies have indicated that insulin concentrations are associated with lipid and lipoprotein levels and blood pressure (9,10), the literature is inconsistent regarding the prospective relationship between baseline insulin levels and subsequent risk of CVD (11–15). Studies of elderly subjects in particular have failed to show significant associations, a phenomenon that may be related to survival bias (11). Furthermore, few investigations have included female subjects (14). In a meta-analysis published in 1998, Ruige et al. (15) reported a weak positive association between hyperinsulinemia and CVD, with a summary relative risk of 1.18 (95% CI 1.08–1.29). However, the authors found that this relationship was modified by ethnic background (weaker effect in nonwhites) and type of insulin assay (stronger effect with specific versus nonspecific assays) and that many of the studies took account of only a limited number of potentially confounding variables (15). Studies published subsequent to this data synthesis have also been inconsistent (16–21).

Table 1—Baseline characteristics of participants in the SAHS (Phase II) who were free of diabetes and CVD stratified by sex and ethnicity

Variable*	Mexican-American		Non-Hispanic white		P	
	Men	Women	Men	Women	Ethnicity	Sex
n	668	909	379	457		
Age (years)	40.9 (11.0)	41.8 (10.7)	43.0 (11.0)	42.9 (11.0)	0.0009	0.67
BMI (kg/m ²)	28.1 (4.4)	28.6 (6.3)	26.9 (4.2)	25.2 (5.2)	<0.0001	0.46
Waist circumference (mm)	942.0 (109.5)	864.9 (140.9)	956.8 (109.0)	811.2 (127.5)	0.0003	<0.0001
WHR	0.93 (0.06)	0.83 (0.08)	0.95 (0.07)	0.81 (0.07)	0.61	<0.0001
Fasting glucose (mg/dl)	86.8 (10.3)	84.9 (10.5)	87.0 (10.7)	83.0 (10.3)	0.0359	<0.0001
2-h glucose (mg/dl)	99.2 (32.2)	112.3 (31.0)	94.4 (32.5)	98.2 (28.2)	<0.0001	<0.0001
Fasting insulin (IU/ml)	14.6 (13.5)	14.1 (14.8)	11.6 (11.3)	10.2 (11.6)	<0.0001	0.0052†
HOMA-IR (units)	3.2 (3.3)	3.1 (3.4)	2.6 (2.7)	2.1 (2.7)	<0.0001	0.0009†
HDL cholesterol (mg/dl)	42.7 (11.7)	49.0 (12.9)	42.4 (11.6)	53.6 (15.0)	0.0003	<0.0001
LDL cholesterol (mg/dl)	127.6 (35.7)	119.6 (35.3)	124.9 (34.0)	118.0 (35.3)	0.28	<0.0001
Total cholesterol (mg/dl)	199.6 (38.9)	193.3 (38.9)	195.1 (39.0)	193.0 (40.2)	0.28	0.0019
Triglyceride (mg/dl)	162.5 (113.5)	127.6 (72.4)	149.8 (114.6)	106.7 (71.3)	<0.0001	<0.0001
Systolic BP (mmHg)	122.9 (13.4)	116.0 (15.5)	121.3 (13.0)	113.0 (15.0)	0.0002	<0.0001
Diastolic BP (mmHg)	74.4 (8.9)	70.7 (8.7)	73.9 (8.2)	68.7 (9.1)	0.0013	<0.0001
Alcohol (g/month)	97.9 (141.6)	18.8 (48.8)	84.4 (122.4)	31.5 (56.9)	0.0021	0.0152†
Physical activity (times/week)	1.8 (2.5)	1.6 (2.5)	1.9 (2.6)	2.1 (2.5)	0.51	<0.0001†
Smoking (% current)	33.7	19.1	29.3	22.3	0.78	<0.0001

*Values are means (±SD) or proportions; †test performed on log-transformed variable. BP, blood pressure; WHR, waist-to-hip ratio.

The objective of the present study was to investigate the homeostasis model assessment of IR (HOMA-IR; a widely used surrogate measure), as well as insulin levels, with risk of nonfatal and fatal CVD over the 8-year follow up of the San Antonio Heart Study (SAHS).

RESEARCH DESIGN AND METHODS

The SAHS (Phase II) is a population-based study of diabetes and CVD in Mexican-Americans and non-

Hispanic whites. A detailed description of the study has been published previously (22). In brief, between January 1984 and December 1988, we randomly selected households from low income (barrio), middle income (transitional), and high income (suburban) census tracts in San Antonio, Texas. All men and nonpregnant women aged 25–64 years who resided in the randomly sampled households were eligible to participate. Mexican-Americans were defined as those whose

ancestry derived from a Mexican national origin. All subjects gave informed consent, and the study was approved by the Institutional Review Board of the University of Texas Health Sciences Center at San Antonio.

Between October 1991 and December 1996, we conducted follow-up examinations of the baseline cohort (median follow-up time 7.5 years). The present report includes individuals who were free of documented CVD and diabetes at base-

Table 2—Age-, sex-, and ethnicity-adjusted mean levels of baseline cardiovascular risk factors across quintiles of HOMA-IR among participants in the SAHS (Phase II) who were free of diabetes and CVD

Cardiovascular risk factor	Quintiles of HOMA-IR										P value for trend
	1		2		3		4		5		
	Means	(SE)	Means	(SE)	Means	(SE)	Means	(SE)	Means	(SE)	
BMI (kg/m ²)	23.9	(0.2)	25.0	(0.2)	26.5	(0.2)	28.5	(0.2)	31.6	(0.2)	<0.0001
Waist circumference (mm)	816.4	(5.1)	847.2	(5.1)	881.2	(5.0)	925.1	(5.1)	986.8	(5.1)	<0.0001
Waist-to-hip ratio (×100)	84.7	(0.3)	85.8	(0.3)	87.4	(0.3)	88.8	(0.3)	90.4	(0.3)	<0.0001
Fasting glucose (mg/dl)	81.0	(0.4)	83.1	(0.4)	84.6	(0.4)	87.0	(0.4)	92.8	(0.4)	<0.0001
2-h glucose (mg/dl)	92.4	(1.4)	95.4	(1.3)	101.7	(1.3)	106.6	(1.3)	120.7	(1.4)	<0.0001
Fasting insulin (IU/ml)	3.2	(0.4)	6.3	(0.4)	9.7	(0.4)	14.6	(0.4)	31.9	(0.4)	<0.0001
Total cholesterol (mg/dl)	188.0	(1.7)	191.6	(1.7)	197.9	(1.7)	200.8	(1.7)	199.0	(1.7)	<0.0001
HDL cholesterol (mg/dl)	51.7	(0.6)	49.3	(0.6)	47.8	(0.6)	45.0	(0.6)	41.2	(0.6)	<0.0001
LDL cholesterol (mg/dl)	115.7	(1.6)	119.27	(1.6)	125.0	(1.6)	128.1	(1.6)	124.8	(1.6)	<0.0001
Triglyceride (mg/dl)	105.7	(4.1)	116.6	(4.0)	129.7	(4.0)	145.4	(4.0)	187.2	(4.0)	<0.0001
Systolic BP (mmHg)	114.9	(0.6)	116.5	(0.6)	118.3	(0.6)	119.3	(0.6)	123.0	(0.6)	<0.0001
Diastolic BP (mmHg)	69.0	(0.4)	70.4	(0.4)	71.9	(0.4)	73.1	(0.4)	75.4	(0.4)	<0.0001

All P values for trend <0.0001. BP, blood pressure.

line. Vital status was obtained on 98.1% of the cohort, whereas 92% received a telephone interview, and 65% received a full clinic examination.

Clinical and laboratory measurements

At both baseline and follow-up examinations, blood specimens were obtained after a 12- to 14-h fast for determination of serum lipid and lipoprotein levels and insulin and plasma glucose concentrations. Insulin was measured with a solid-phase radioimmunoassay (Diagnostic Products, Los Angeles) (22), which shows a high degree of cross-reactivity (70–100%) with proinsulin (23). Lipid, lipoprotein, and glucose levels were measured as previously described (24). We estimated IR using the HOMA-IR index (25), which is defined as fasting insulin ($\mu\text{U}/\text{ml}$) times fasting glucose (mmol/l) divided by 22.5. HOMA-IR has been validated in normoglycemic subjects against insulin sensitivity measured directly from the euglycemic-hyperinsulinemic clamp technique ($n = 12$, $r = 0.83$, $P < 0.01$) (25) and has been widely used in epidemiological studies. A 75-g oral glucose tolerance test (Orangedex; Custom Laboratories) was administered, and blood specimens were obtained 30 min, 1 h, and 2 h later for determination of plasma glucose and serum insulin concentrations. Diabetes was diagnosed according to World Health Organization (WHO) criteria (26). Subjects who did not meet WHO plasma glucose criteria but who were undergoing treatment with oral antidiabetic agents or insulin were considered to have diabetes.

Anthropometric measurements (height, weight, and waist circumference) were made after participants had removed their shoes and upper garments and donned an examination gown (23). Systolic (first phase) and diastolic (fifth phase) blood pressure were measured to the nearest even digit by use of a random-zero sphygmomanometer (Hawksley-Gelman). Three readings were made for each individual, and the average of the second and third readings was used in the analysis. Subjects were considered to have hypertension if they were taking antihypertensive medication or if they had a systolic blood pressure ≥ 140 or a diastolic blood pressure ≥ 90 . Lifestyle risk factors, including smoking, alcohol consumption, and participation in planned

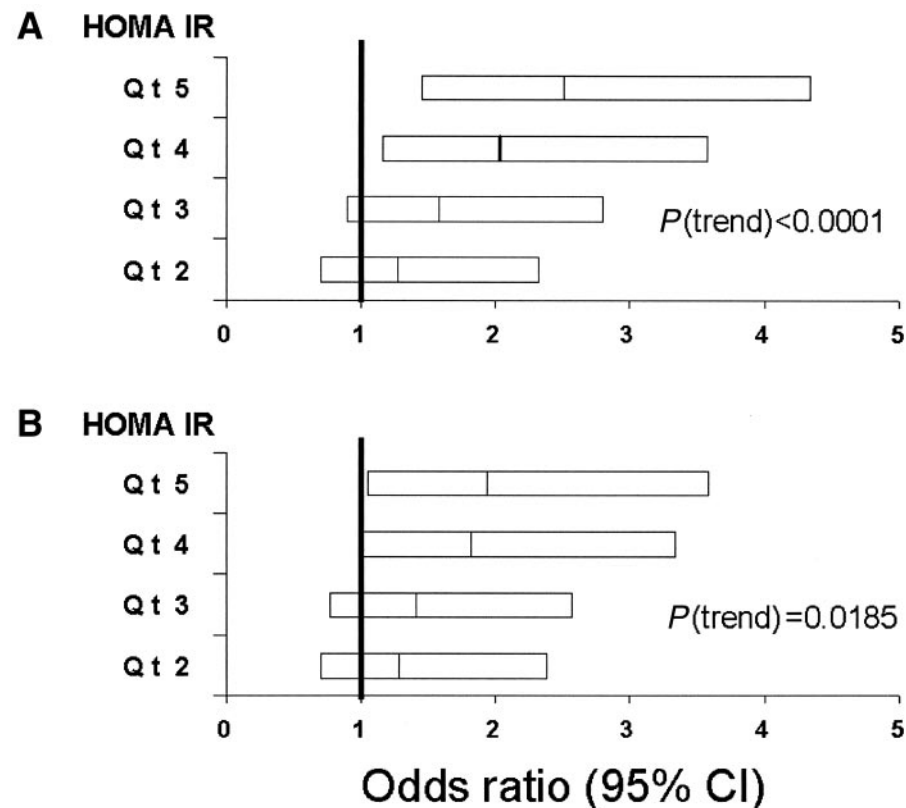


Figure 1—Association between quintiles of HOMA-IR and 8-year risk of cardiovascular outcomes among subjects in the SAHS without diabetes and CVD at baseline. ORs were estimated using logistic regression and refer to risk in the given category relative to quintile 1. A: Quintiles of HOMA-IR (0–1.025, 1.026–1.626, 1.627–2.470, 2.471–4.802, and 4.803–41.700) adjusted for age, sex, and ethnicity. B: Quintiles of HOMA-IR adjusted for age, sex, ethnicity, LDL, triglyceride, HDL, systolic blood pressure, smoking, alcohol consumption, leisure time exercise, and waist circumference (median split). Qt, quintile.

leisure-time exercise, were measured using standardized interviewer-administered questionnaires. Smoking status was categorized for the present analysis as never/former or current smoker. Alcohol consumption was parameterized as grams per month and exercise as number of sessions per week.

Determination of CVD outcomes and vital status

In the present study, we defined incident CVD as death from CVD, incident heart attack, stroke, or heart surgery, or incident angina. Cardiovascular mortality was identified and confirmed by follow-up interviews with next of kin, after which death certificates were obtained (27). Death certificates were coded according to ICD-9 by a certified nosologist; ICD-9 codes for CVD include 390–459. Cause of death was defined as the underlying cause of death. Incident cases of

heart attack, stroke, and heart surgery were determined by self-report during either the telephone interview or the clinic examination. Heart attack and stroke were defined as self-reports of a physician-confirmed event. Heart surgery was defined as coronary revascularization or angioplasty. Incident angina was determined during the clinic examination (65% of the cohort) using the WHO Rose chest pain questionnaire. We confirmed 31 of 32 nonfatal CVD outcomes using chart reviews in local area hospitals. However, this validation was not complete, so our CVD outcomes should be considered as self-reports of physician-diagnosed events.

Statistical analysis

Means and SDs or proportions were presented for subjects stratified by ethnicity and sex. Differences between groups were assessed using t tests or χ^2 tests, with nat-

ural log transformations of skewed variables used as appropriate (Table 1). Associations between baseline metabolic and anthropometric variables were determined using Spearman correlation analysis, adjusted for age, sex, and ethnicity. Mean levels of cardiovascular risk factors, adjusted for age, sex, and ethnicity, were estimated for quintiles of HOMA-IR and fasting insulin using ANCOVA (Table 2).

Eight-year cumulative incidence rates of CVD outcomes were calculated as the proportion of disease-free subjects at baseline who developed the given CVD end point over the follow-up period. These outcomes included CVD death (0.61%), heart attack (2.01%), heart surgery (1.49%), stroke (1.19%), or angina (5.36%). Given the small number of events for individual end points, we considered combined CVD events as the outcome variable of interest. In this combined outcome variable, all subjects known to have experienced any of the CVD incidents listed above were defined as having had an event, whereas those known to have experienced none of these CVD events were defined as disease free. The incidence rate for combined CVD death, heart attack, heart surgery, and stroke was similar to the incidence rate for angina (4.47 vs. 5.36%). The inclusion of angina in the combined outcome was supported by a similar magnitude and direction of association for high versus low HOMA-IR (<2 vs. ≥2; 2 being close to the median value in the population) and risk of both angina (odds ratio [OR] 2.2, 95% CI 1.4–3.5) and nonangina CVD end points (1.6, 1.1–2.4). ORs for associations of HOMA-IR and insulin with the 8-year incidence of combined CVD outcomes were estimated using unconditional logistic regression analysis. In these models, the independent variables (HOMA-IR and fasting insulin) were analyzed as quintiles, with the lowest quintile treated as the reference category. Logistic models were adjusted for 1) age, sex, and ethnicity; and 2) age, sex, ethnicity, LDL, triglyceride, HDL, systolic blood pressure, smoking, alcohol consumption, physical activity, and waist circumference (median split). Trends across quintiles of the independent variables were assessed in separate models using a 5-level categorical variable (Fig. 1A and B; Fig. 2A and B). To examine the association of other variables with risk of CVD, we present models adjusted for 1) age, sex,

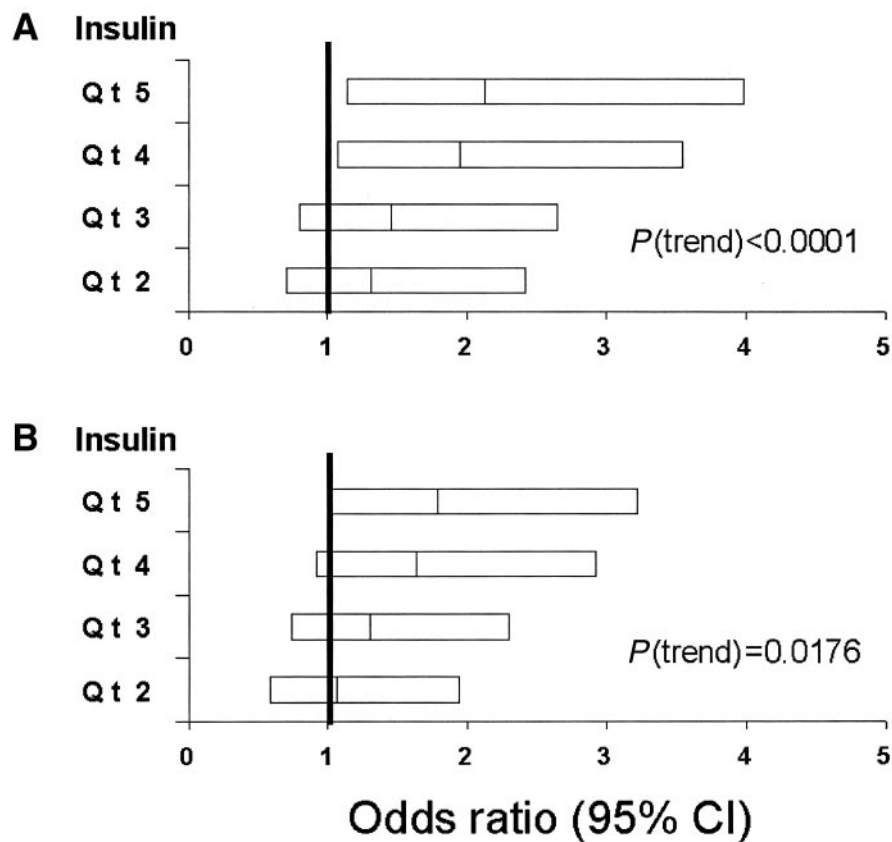


Figure 2—Association between quintiles of fasting insulin and 8-year risk of cardiovascular outcomes among subjects in the SAHS without diabetes and CVD at baseline. ORs were estimated using logistic regression and refer to risk in the given category relative to quintile 1. A: Quintiles of insulin (0.10–5.00, 5.10–7.85, 7.86–11.70, 11.80–18.55, and 18.56–225.00) adjusted for age, sex, and ethnicity. B: Quintiles of insulin, adjusted for age, sex, ethnicity, LDL, triglyceride, HDL, systolic blood pressure, smoking, alcohol consumption, leisure time exercise, and waist circumference (median split). Qt, quintile.

and ethnicity; 2) model 1 plus smoking, alcohol, LDL, and systolic blood pressure; and 3) model 2 plus waist, HDL, triglyceride, and physical activity (Table 3). To determine whether ethnicity (Hispanic versus non-Hispanic white), waist circumference (sex-specific median split), glucose tolerance status (baseline normal glucose tolerance [NGT] versus impaired glucose tolerance [IGT]), dyslipidemia (triglyceride <200 or HDL >35 vs. triglyceride ≥200 or HDL ≤35), hypertension (no versus yes), or sex modified the association between HOMA-IR and risk of CVD, we included interaction terms in separate demographically adjusted models. In addition, we examined this issue by plotting the ORs and 95% CIs for each strata of the interaction variable under consideration (Fig. 3).

RESULTS— Baseline characteristics of nondiabetic participants in the SAHS

(Phase II), stratified by sex and ethnicity, are presented in Table 1. Mexican-Americans were younger but had higher BMI and systolic blood pressure and higher concentrations of 2-h glucose, insulin, HOMA-IR, and triglyceride compared with non-Hispanic whites. Male subjects had higher waist circumference and systolic blood pressure and higher concentrations of fasting glucose and triglyceride but lower concentrations of 2-h glucose and HDL.

Anthropometric variables, fasting and 2-h glucose and fasting insulin, increased in a linear fashion across quintiles of HOMA-IR after adjustment for age, sex, and ethnicity (Table 2). A similar pattern was observed across quintiles of fasting insulin concentration (data not shown). HOMA-IR showed almost perfect correlation with fasting insulin concentration ($r = 0.99$). In addition, HOMA-IR was significantly associated with baseline

Table 3—Multivariate logistic regression analysis of risk factors associated with incident CVD among participants in the San Antonio Heart Study (Phase II) who were free of diabetes and CVD at baseline

Independent variable	Unit*	Model A			Model B			Model C		
		OR	95% CI	P	OR	95% CI	P	OR	95% CI	P
Age	10 years	1.78	1.53–2.07	<0.0001	1.65	1.40–1.95	<0.0001	1.67	1.41–1.98	<0.0001
Ethnicity	NHW = 0, MA = 1	0.89	0.64–1.24	0.47	0.83	0.60–1.16	0.28	0.83	0.58–1.17	0.28
Sex	Female = 0, Male = 1	1.00	0.73–1.38	0.99	0.94	0.66–1.33	0.73	0.88	0.60–1.29	0.51
Smoking	Never/former = 0, current = 1	—	—	—	1.72	1.20–2.48	0.003	1.72	1.19–2.49	0.004
Alcohol	93.7 g/month	—	—	—	0.88	0.73–1.07	0.20	0.90	0.74–1.09	0.30
LDL	35.2 mg/dl	—	—	—	1.13	0.96–1.32	0.14	1.11	0.94–1.30	0.22
Systolic BP	8.2 mmHg	—	—	—	1.09	1.00–1.19	0.06	1.08	0.98–1.18	0.11
Waist	(< vs. ≥ median)	—	—	—	—	—	—	1.15	0.79–1.67	0.47
HDL	13.3 mg/dl	—	—	—	—	—	—	0.93	0.77–1.14	0.49
Triglyceride	97.2 mg/dl	—	—	—	—	—	—	1.10	0.94–1.28	0.24
Physical activity	2.5 times/week	—	—	—	—	—	—	1.10	0.95–1.28	0.23
HOMA-IR	Per quintile	1.26	1.12–1.42	<0.0001	1.24	1.10–1.40	0.0005	1.18	1.03–1.35	0.019

*Units for continuous variables = 1 SD; for waist circumference, < versus ≥ the gender-specific median; †similar conclusions were obtained using the forward elimination procedure. BP, blood pressure; MA, Mexican-American; NHW, non-Hispanic white.

measures of anthropometry (BMI, $r = 0.51$; waist circumference, $r = 0.49$; and waist-to-hip ratio, $r = 0.32$), glucose (fasting, $r = 0.38$ and 2-h, $r = 0.30$; both $P < 0.0001$), and cardiovascular risk factors (HDL, $r = -0.32$; cholesterol, $r = 0.09$; triglyceride, $r = 0.36$; systolic blood pressure, $r = 0.21$; and diastolic blood pressure, $r = 0.24$; all $P < 0.0001$). As would be expected, associations of fasting insulin with anthropometric and metabolic variables were very similar (data not shown), although the magnitude of each of these correlation coefficients was slightly lower compared with those for HOMA-IR.

Figure 1 presents results of multiple logistic regression analyses, with HOMA-IR modeled in quintiles. After adjustment for age, sex, and ethnicity, there was a significant trend in increasing risk for CVD across quintiles of HOMA-IR (P for trend < 0.0001) (Fig. 1A), and this association remained significant with the addition of a sex-specific median split waist circumference variable to the model (data not shown). Subjects in the highest quintile of HOMA-IR experienced a greater than twofold increased cardiovascular risk compared with those in the lowest quintile (OR 2.52, 95% CI 1.46–4.36). Although the magnitude of these associations was reduced slightly after additional adjustment for LDL, triglyceride, HDL, systolic blood pressure, smoking, alcohol consumption, exercise, and waist circumference, the trends and quintile

comparisons remained statistically significant (P for trend 0.02; quintile 5 vs. quintile 1, OR 1.94, 95% CI 1.05–3.59) (Fig. 1B). The magnitude and direction of these associations were similar when stroke and coronary artery disease (CAD) were analyzed separately (HOMA-IR ≥ 2 vs. < 2 ; stroke, OR 2.07, 95% CI 0.89–4.74; CAD, 1.54, 0.91–2.62). In addition, the results were not materially different when Cox regression was used to analyze the association of HOMA-IR with nonfatal CVD events (data not shown). The patterns of association for fasting insulin were similar to those for HOMA-IR (Fig. 2A and B). Although the magnitude of the insulin associations was slightly weaker in each case compared with HOMA-IR, the areas under the receiver-operating characteristic curves for HOMA-IR and fasting insulin were not significantly different ($\chi^2 = 0.20$, $P = 0.65$).

In demographically adjusted analyses, increased risk of CVD was also predicted by 1 SD differences in triglyceride (OR 1.21, 95% CI 1.06–1.37), HDL (0.80, 0.67–0.95), systolic blood pressure (1.18, 1.01–1.38), and smoking (no versus yes: 1.69, 1.20–2.38). In a full multivariate model, HOMA-IR, age, and smoking were significant independent predictors of incident CVD in this population (Table 3). When HOMA-IR was excluded from the model, older age and smoking were significantly associated with risk of CVD (both $P < 0.01$), and elevated triglyceride concentration, ele-

vated systolic blood pressure, and high waist circumference showed associations of borderline significance ($P = 0.12$, 0.07, and 0.12, respectively). A similar analysis using fasting insulin and glucose in place of HOMA-IR yielded very similar results (data not shown).

In Fig. 3, results of demographically adjusted logistic regression analyses are presented after stratification for potential effect-modifying variables. In this figure, HOMA-IR is modeled as a dichotomous variable (< 2 vs. ≥ 2). Tests of heterogeneity were nonsignificant at the 0.05 level between strata of ethnicity, sex, hypertension, dyslipidemia, glucose tolerance (NGT versus IGT), and waist circumference (all $P > 0.10$). However, there were some differences in the point estimates of risk between categories of certain variables. Risk of progression appeared to be lower among non-Hispanic whites (compared with Mexican-Americans) and individuals with NGT, hypertension, dyslipidemia, and low waist circumference.

CONCLUSIONS— In the present study, we have demonstrated significant associations between baseline levels of both HOMA-IR and insulin and subsequent risk of CVD outcomes in a large population-based study. These associations remained significant after adjustment for multiple potential confounding variables, and there was no strong evidence of effect modification by adiposity,

P-values
OR Interaction

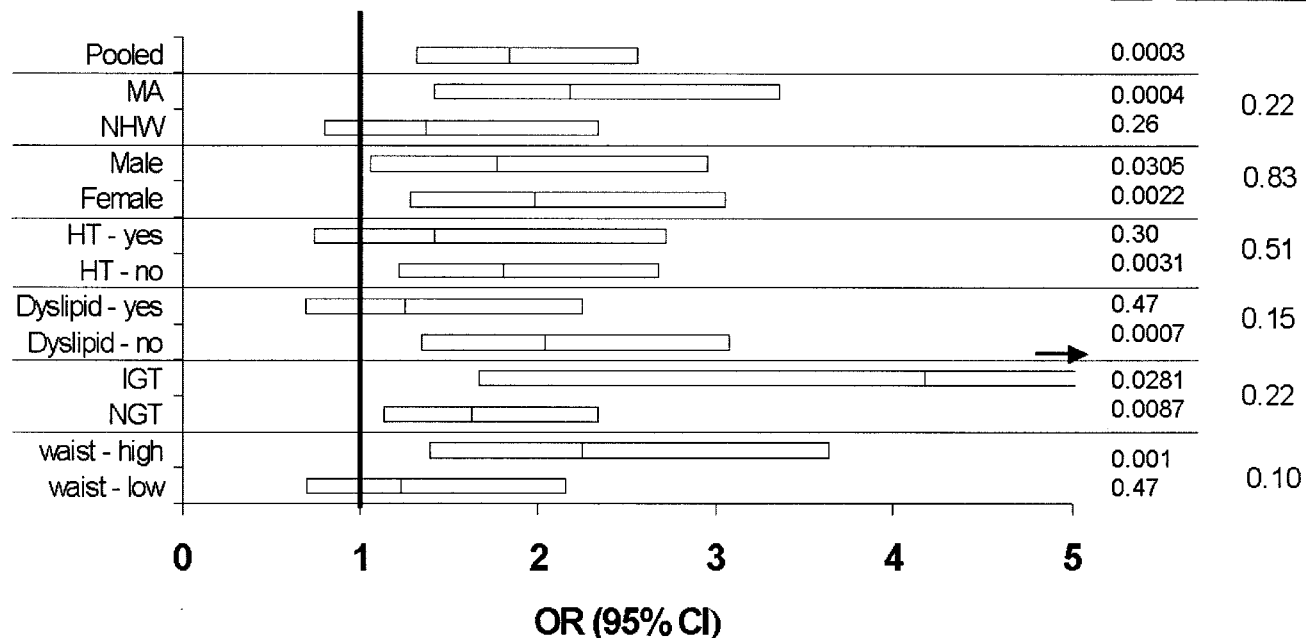


Figure 3—Association between HOMA-IR and 8-year risk of cardiovascular outcomes (adjusted for age, sex, and ethnicity) among subjects in the SAHS without diabetes and CVD at baseline. ORs were estimated using logistic regression and refer to risk associated with HOMA-IR ≥ 2 vs. <2 . Results are presented by strata of ethnicity (Mexican-American [MA] versus non-Hispanic white [NHW]), sex, hypertension (HT; antihypertensive medication or systolic blood pressure ≥ 140 or diastolic blood pressure ≥ 90), dyslipidemia (dyslipid; triglyceride <200 or HDL >35 vs. triglyceride ≥ 200 or HDL ≤ 35), glucose tolerance (IGT versus NGT), and waist circumference (high versus low, defined by the sex-specific median split).

glucose tolerance status, dyslipidemia, hypertension, ethnicity, or sex. In separate analysis of stroke and CAD, the magnitude of association with HOMA-IR was similar. Furthermore, waist circumference was not a significant variable in multivariate analysis, suggesting that IR increases CVD risk independent of central adiposity. Finally, we were able to investigate these associations in both men and women, and this was the first published study to have included Hispanic Americans. In addition to observing significant associations between HOMA-IR and risk of CVD, we also found that fasting insulin demonstrated similar (and only marginally weaker) associations with CVD risk. These results are not surprising given the almost perfect correlation between the two variables (0.99), and they indicate that the HOMA index is probably reflecting hyperinsulinemia in this population. We chose HOMA for this analysis because it is the most widely used surrogate measure of IR. Other surrogate indexes have recently been proposed that show superior correlation with criterion measures in small groups of subjects (28–

30), although HOMA has also recently been shown to perform well in validation studies (31,32).

Previous studies have reported both the presence and the absence of significant associations between insulin levels and risk of CVD (11,13,15–21). A number of review papers have highlighted possible reasons for these inconsistencies in the literature (11,14,15). A recent meta-analysis by Ruige et al. (15) reported that the relationship between insulin and CVD was modified by ethnic background and type of insulin assay, and that there was inconsistency across studies in the adjustment for potentially confounding variables (particularly measures of adiposity). In our analysis (Figs. 1 and 2), we presented both minimally and fully adjusted models, given the present uncertainty regarding confounders in this relationship. It has also been suggested that the association is confined to middle-aged subjects (11).

The present report is one of only a few prospective studies of IR or insulin concentrations and risk of CVD to have included female participants and the

second to demonstrate a significant association in women independent of other cardiovascular risk factors. Folsom et al. (16) reported a significant trend for risk of coronary heart disease across categories of fasting insulin level in women ($P = 0.02$) but not in men. In the four other previous studies that have included women (20,33–35), one did not present analyses separately by sex (20), and the remaining three did not find a significant effect among women (33–35), although these studies may have lacked statistical power to detect associations in stratified analyses. Additional studies of insulin concentrations and IR among women are required.

The biological mechanism to explain the association between HOMA-IR or insulin levels and risk of CVD is not well understood. It is possible that elevated circulating insulin levels have a direct detrimental effect by promoting the proliferation of vascular smooth muscle cells, a suggestion supported by investigations in animal models (36,37). Alternatively, elevated insulin levels may be a marker of the underlying cluster of abnormalities

that characterizes the IR syndrome. In a recent population-based study from Finland, the IR syndrome (parameterized as a score generated by factor analysis of a collection of metabolic variables) was significantly associated with coronary heart disease and stroke (38). In contrast, Yarnell et al. (19) used cluster analysis to identify subjects with metabolic syndrome and found that there was no excess risk associated with this construct beyond that explained by the individual defining variables themselves. The most convincing evidence to date comes from the Insulin Resistance Atherosclerosis Study, in which insulin sensitivity index (S_i) was directly measured using the frequently sampled intravenous glucose tolerance test with minimal model analysis (39). In this study, S_i showed a significant inverse association with ultrasonographically measured carotid artery atherosclerosis that was independent of insulin concentrations and other CVD risk factors. Finally, it is possible that the detrimental effect of IR on CVD might operate through a mechanism of chronic subclinical inflammation (40,41).

The lack of association of male sex, LDL, and blood pressure with CVD was unexpected. This somewhat unique pattern of association may be related to the fact that a large proportion of the SAHS cohort was Mexican-American, an ethnic group that may have a CVD risk profile that differs slightly from that in European Americans. In addition, male sex was not significant because women are at greater risk of angina than men, who in turn are at greater risk of other events included in our outcome variable, and thus they offset each other.

In conclusion, we have demonstrated that HOMA-IR was significantly and independently associated with risk of CVD outcomes in Mexican-American and non-Hispanic white men and women in the SAHS. In addition, we found that there were only minor differences in the prediction of CVD when fasting insulin was used in place of HOMA-IR. The literature remains highly inconsistent on the topic of IR and CVD, however, and additional studies are required, particularly among women and minority populations.

Acknowledgments— This work was supported by grants from the National Heart, Lung and Blood Institute (RO1 HL24799 and

RO1 HL36820). A.J.G.H. was supported by a post-doctoral fellowship from the Canadian Institutes of Health Research.

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