

ORIGINAL REPORTS: CARDIOVASCULAR DISEASE AND DIABETES

UTILITY OF A SURROGATE MEASURE OF INSULIN RESISTANCE IN AMERICAN INDIANS: THE STRONG HEART STUDY

Objective: 1) Determine in a sample of American Indians (AI) how well insulin sensitivity (S_i) measured by the frequently sampled intravenous glucose test (FSIGT) correlates with a simpler measure of insulin resistance (IR) measured by the homeostasis assessment (HOMA) model; (2) compare insulin sensitivity in a sample of diabetic and non-diabetic AI in the Strong Heart Study (SHS) with that of White, Black, and Hispanic Americans in the Insulin Resistance Atherosclerosis Study (IRAS).

Design: Cross sectional

Setting: Community

Participants: Sixty-one AI participants in SHS

Main Outcome Measures: Mean S_i measured by FSIGT, a complex protocol to evaluate insulin sensitivity, and mean IR measured by the HOMA model, a method based on measures of fasting glucose and fasting insulin.

Results: Although 70% of sample participants were non-diabetic, only 18% were insulin sensitive by S_i . Diabetes status strongly confounded S_i among AI in SHS. At non-diabetic levels of fasting glucose (<126 mg/dL), S_i correlated well with HOMA IR ($\rho = -0.49$, $P = .0009$), but S_i did not reflect HOMA IR at levels of fasting glucose that are diagnostic of diabetes (≥ 126 mg/dL; $\rho = -0.13$, $P = \text{n.s.}$). With the exception of some Hispanic participants in IRAS, mean S_i of non-diabetic AI in SHS was lower than that of their non-diabetic IRAS counterparts. Diabetic AI participants in SHS had markedly lower mean S_i than all diabetic participants in IRAS.

Conclusions: The HOMA model may be a useful tool to identify non-diabetic American Indians who might benefit from early CVD risk factor modification. (*Ethn Dis.* 2002;12:523-529)

Key Words: Insulin Resistance, Diabetes Mellitus, Ethnicity, North American Indians, Insulin, Glucose

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INTRODUCTION

Diabetes mellitus is a heterogeneous group of disorders characterized by a common hyperglycemic phenotype. Factors leading to defects both in the ability of the pancreas to secrete insulin and in tissue sensitivity to the biological effects of insulin are thought to be involved in the development of diabetes, although the relative importance of these defects remains a topic of debate.¹⁻⁴ A reduction in the occurrence, severity, or progression of diabetes may ultimately reduce the risk of diabetic vascular complications, of which cardiovascular disease (CVD) is the most common and costly.⁵

Understanding mechanisms involved in the pathway leading to the development of diabetes, and how these mechanisms may differ across subgroups of the US population, may help in development of tailored interventions aimed at reducing the occurrence of diabetes and diabetes-associated CVD in these subgroups. However, simple indi-

ces of glucose metabolism such as fasting insulin (FI) and fasting glucose (FG), measures commonly collected in epidemiologic studies of diabetes and CVD, do not reflect the complexities of the glucose—insulin feedback loop that exists *in vivo*. The utility of these measures as tools for understanding metabolic defects leading to hyperglycemia is therefore limited.

Methods for studying insulin resistance (IR) *in vivo* have been developed, but they are labor intensive and difficult to perform in the field.⁶ The “Minimal Model” method for evaluating insulin sensitivity (S_i) using data from a frequently sampled intravenous glucose test (FSIGT) is a less demanding protocol that has been used in epidemiologic studies.⁷⁻⁹ Although the Minimal Model provides a good estimate of IR, even this protocol, requiring repeated blood draws over a 3-hour period, has limited application in epidemiologic studies that do not specifically focus on IR.

The homeostasis assessment (HOMA) model is an alternative method for estimating IR (HOMA IR).¹⁰ Using a simple algebraic expression, this method estimates IR using FI and FG data, 2 measures commonly collected in epidemiologic studies and readily available to clinicians. Although appealing because of its potential for widespread clinical application, it is not clear how well HOMA IR model reflects true underlying IR in different populations and across wide ranges of FG.

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Understanding insulin resistance and its correlates is especially important for American Indians (AI) since AI have the highest rate of diabetes in the United States.

Understanding IR and its correlates is especially important for American Indians (AI) since AI have the highest rate of diabetes in the United States.¹¹ Despite the markedly high burden of diabetes among AI, IR and its correlates are not well described in this population, except for studies conducted in Pima Indians.^{4,12} This paper has 4 aims: 1) examine S_1 in a diverse sample of diabetic and non-diabetic AI participants in the Strong Heart Study (SHS); 2) show the degree of correlation between S_1 and HOMA IR with both anthropometric and metabolic characteristics commonly associated with IR; 3) contrast the prevalence of insulin sensitivity in SHS participants with that of other, non-Indian ethnic groups; and 4) examine how well IR calculated from the HOMA model reflects S_1 measured by the Minimal Model.

METHODS

Study Population

Established in 1988, SHS is a population-based longitudinal study of CVD and its risk factors in 13 AI tribes in 3 geographic areas: an area near Phoenix, Arizona, the southwestern area of Oklahoma and the Dakotas. The study design, population, clinical exam, and morbidity and mortality surveillance procedures have been described elsewhere.¹³ Data from the baseline clinical examination (1989–1991) yielded information on the high prevalence of

diabetes in the SHS population.¹¹ From 1994–1997, a sub-study focusing on IR was conducted at the Dakota and Arizona centers with the aim of better quantifying IR across the range of FG in a subset of SHS participants. The 61 participants in the SHS IR sub-study were randomly selected within strata of baseline FG categories. Participants therefore included both diabetic and non-diabetic individuals. According to currently accepted American Diabetes Association (ADA) diagnostic criteria,¹⁴ 18 (30%) of the sample were diabetic ($FG \geq 126$ mg/dL), while the remaining 43 participants were non-diabetic ($FG < 126$ mg/dL).

Measures of Insulin Resistance

The Minimal Model is a computer-based approach (MINMOD) for quantifying IR using data from the FSIGT.^{7,8,15,16} This approach yields models of glucose and insulin kinetics without interrupting the closed-loop between insulin and glucose. MINMOD-based analysis of FSIGT data has been shown to correlate well with the glucose clamp technique,⁶ considered the gold standard of insulin-glucose kinetics.¹⁷ MINMOD yields the insulin sensitivity index (S_1), interpreted as the degree of peripheral tissue sensitivity to insulin. Higher S_1 values indicate greater sensitivity to insulin.

The HOMA model uses a simple algebraic formula to calculate IR: $[FI (uU/mL) \times FG (mmol/L)]/22.5$.^{10,18} Several recent reports have suggested that this estimate of IR correlates well with euglycemic clamp measures in men and women, younger and older adults (up to age 67), in obese and non-obese individuals, and in diabetics and non-diabetics.^{18–21} In contrast to the S_1 metric, *lower* values for HOMA IR indicate greater insulin sensitivity.

Sample Selection

Selection criteria for the SHS IR sub-study and FSIGT protocol were similar, but not identical to those of the

Insulin Resistance and Atherosclerosis Study (IRAS), an epidemiologic study of IR in diabetic and non-diabetic Whites, Blacks, and Hispanics.⁹ IRAS did not include AI. Like IRAS, participants in the SHS IR sub-study included both men and women between the ages of 40 and 69 years, and exclusion criteria included conditions that would interfere with measurement or interpretation of IR data or those that would limit a person's ability to complete the protocol. Additionally, people with unstable angina, those on current cancer treatment, renal dialysis, pregnant women, and those with cognitive dysfunction were excluded.

A key difference between SHS and IRAS is how each defined diabetes: in IRAS, diabetes status was based on World Health Organization (WHO) criteria using data from the OGTT,²² while in SHS diabetes status was based on the newer ADA criteria, which rely on FG values.¹⁴ IR sub-study participants were randomly selected across strata of FG values collected at the second SHS clinical examination. Although the period of data collection for the SHS IR sub-study (1994–1997) overlapped considerably with that of the second SHS examination (1993–1996), in all cases, the second SHS clinical examination preceded the IR sub-study visit. In both IRAS and SHS, participants were advised to eat at least 150g of carbohydrate for each of the 3 days prior to the test. Testing was performed following a 12-hour fast; participants were requested not to smoke on the morning of the test. Testing began before 10 a.m. to avoid the circadian rhythm in insulin sensitivity. Consistent with the IRAS protocol, the dose of glucose was calculated as follows: glucose dose (g) = body weight \times 0.3g.⁹ As in IRAS, 2 modifications of the original FSIGT protocol were made in the SHS IR sub-study: an injection of insulin rather than tolbutamide was used, and the number of samples collected during the test was reduced from 30 to 12. It has been

demonstrated that these changes in protocol do not influence interpretation of the data.^{23,24}

Measurement of Potential Correlates of Insulin Resistance

In the second SHS examination, data on body mass index (BMI), total cholesterol (TC), low density lipoprotein cholesterol (LDL), high density lipoprotein cholesterol (HDL), triglycerides (TG), waist circumference, and blood pressure were collected according to standardized protocols.¹³ These variables are associated with the “insulin resistance” or “metabolic” syndrome, a set of metabolic and anthropometric characteristics associated with increased risk of CVD.^{25,26} An average of 2.16 (range 0.11–4.30) years elapsed between collection of fasting glucose and CVD risk factor data in the second SHS clinical examination and administration of the FSGT in the IR substudy.

Categorization of Insulin Resistance

Using findings from IRAS,²⁷ participants’ IR status was categorized in 2 ways: S_1 values $\geq 1.61 \text{ min}^{-1} \cdot \text{uU}^{-1} \cdot \text{mL}^{-1}$ defined “insulin sensitive” individuals. People with S_1 values $< 1.61 \text{ min}^{-1} \cdot \text{uU}^{-1} \cdot \text{mL}^{-1}$ were categorized as “non-insulin sensitive.” The S_1 cutpoint of $1.61 \text{ min}^{-1} \cdot \text{uU}^{-1} \cdot \text{mL}^{-1}$ was the median value for non-diabetic African-American, Hispanic, and non-Hispanic White participants in IRAS. S_1 values $\geq 2.57 \text{ min}^{-1} \cdot \text{uU}^{-1} \cdot \text{mL}^{-1}$ defined individuals who were “highly insulin sensitive.” People with S_1 values $< 2.57 \text{ min}^{-1} \cdot \text{uU}^{-1} \cdot \text{mL}^{-1}$ were categorized as “not highly insulin sensitive.” S_1 of $\geq 2.57 \text{ min}^{-1} \cdot \text{uU}^{-1} \cdot \text{mL}^{-1}$ was the median value for non-diabetic non-Hispanic Whites in IRAS, the most insulin-sensitive group in that study.

Statistical Methods

Consistent with the small sample size, the non-parametric Wilcoxon rank-sum test was used to test differences in

Table 1. Selected characteristics of participants in the Strong Heart Study Insulin Resistance Substudy, N=61

Characteristic	Mean or (N)	Standard Deviation or (Percentage)
Age	59.3	6.8
Gender		
Women	37	(60)
Center		
Arizona	25	(41)
Dakota	36	(59)
Fasting glucose (mg/dL)	125	51
Fasting insulin ($\mu\text{U}/\text{mL}$)	18.6	11.6
S_1 ($\text{min}^{-1} \cdot \mu\text{U}^{-1} \cdot \text{mL}^{-1}$)†	0.77	1.00
HOMA insulin resistance‡	5.97	4.73
Body mass index (kg/m^2)*	34.4	7.8
Waist circumference (cm)*		
Men	104.6	11.6
Women	118.1	17.0
Total cholesterol (mg/dL)*	193	40
LDL (mg/dL)*	126	33
HDL (mg/dL)*	38	11
Triglycerides (mg/dL)*	171	207
Systolic blood pressure (mm Hg)*	128	17
Diastolic blood pressure (mm Hg)*	76	10

* Measured at the second Strong Heart Study examination.

† Calculated from MINMOD analysis.

‡ Calculated from the equation: [fasting glucose (mmol/L) × fasting insulin ($\mu\text{U}/\text{mL}$)]/22.5.

the distribution of CVD risk factors according to category of insulin sensitivity. Significance tests are presented for the non-parametric test, which is based on ranks, but means are presented for ease of interpretation. Fisher’s Exact test was used for categorical variables. Non-parametric Spearman correlation coefficients were calculated between S_1 and CVD risk factors, adjusted for age. Since a number of participants had $S_1=0$ (highly insulin resistant), values for these individuals were transformed $[\ln(S_1 + 1)]$. S_1 and HOMA IR were plotted against each other according to diabetes status.

RESULTS

Sixty percent of participants in the SHS Insulin Resistance Substudy were women (Table 1). Participants had mean FG of 125 mg/dL; however, by design, there was considerable variability in this measure. Participants were obese, with a mean BMI of 34.4 kg/m^2 , and women tended to have larger waist cir-

cumferences than men. Mean S_1 among the participants was $0.77 \pm 1.00 \text{ min}^{-1} \cdot \text{uU}^{-1} \cdot \text{mL}^{-1}$, and mean HOMA IR values were 5.97 ± 4.73 .

Although 70% of sample participants were non-diabetic by ADA criteria, only 18% were categorized as insulin sensitive according to IRAS cut-points (Table 2). There was no difference in the gender or geographic distribution between insulin sensitive and non-insulin sensitive participants, but a number of metabolic and anthropometric features distinguished the 2 groups. Insulin sensitive participants had significantly lower FG, FI, waist circumferences, and triglycerides level compared to non-insulin sensitive participants. Insulin sensitive participants also had significantly higher levels of HDL cholesterol. By definition, mean S_1 was significantly higher in insulin sensitive, compared to non-insulin sensitive, participants (2.47 vs $0.409 \text{ min}^{-1} \cdot \text{uU}^{-1} \cdot \text{mL}^{-1}$, $P < .0001$). Consistent with findings for S_1 , HOMA IR values were more favorable (lower) among the

Table 2. Selected characteristics of participants in the Strong Heart Study Insulin Resistance Substudy, according to category of insulin sensitivity, N=61

Characteristic	Insulin Sensitive* (N=11)	Non-Insulin Sensitive (N=50)	P†
Age (mean years)	59.8	59.2	n.s.
Gender (N, %)			
Women	6 (16)	31 (84)	
Men	5 (21)	19 (79)	n.s.
Center (N, %)			
Arizona	4 (16)	21 (84)	
Dakota	7 (19)	29 (81)	n.s.
Fasting glucose (mg/dL)	82	117	.005
Fasting insulin (μU/mL)	7.7	21	<.0001
S _i (min ⁻¹ ·μU ⁻¹ ·mL ⁻¹)§	2.47	0.409	N/A
HOMA insulin resistance	1.87	6.87	<.0001
BMI (kg/m ²)‡	32.3	34.9	n.s.
Waist circumference (cm)‡			
Men	91.6	108.1	.0074
Women	116.1	128.5	.0374
Total cholesterol (mg/dL)‡	203	191	n.s.
LDL (mg/dL)‡	134	124	n.s.
HDL (mg/dL)‡	48	36	.0027
Triglycerides (mg/dL)‡	111	185	.027
Systolic blood pressure (mm/Hg)‡	125	128	n.s.
Diastolic blood pressure (mm/Hg)‡	75	76	n.s.

* Insulin sensitive defined as S_i ≥ 1.61 min⁻¹·μU⁻¹·mL⁻¹.

† Significance tests are the Fischer Exact test for categorical variables and the Wilcoxon-rank sum test for continuous variables.

‡ Measured at the second Strong Heart Study examination.

§ Calculated from MINMOD analysis.

|| Calculated from the equation: [fasting glucose (mmol/L) × fasting insulin μU/mL]/22.5.

insulin sensitive, compared to non-insulin sensitive groups (1.87 vs 6.87, *P*<.0001). No differences were observed in BMI, total, or LDL cholesterol, or blood pressure between the groups.

When the highly insulin sensitive cutpoint was applied, only 6.5% of the participants (*N*=4) were in the highly insulin sensitive category. There were significant differences in mean BMI and

systolic blood pressure, as well as marginal differences in HDL and TG, between the highly insulin sensitive and non-highly insulin sensitive individuals, with highly insulin sensitive participants having more favorable profiles (data not shown). Differences in mean HOMA IR values were also more marked between highly insulin sensitive and non-highly insulin sensitive participants (0.77 vs 6.33, *P*<.0012).

Table 3. Age-adjusted correlation between insulin sensitivity measured by the Minimal Model and HOMA Model, and features of the insulin resistance syndrome, Strong Heart Study Insulin Resistance Substudy, N=61

	BMI	HDL	LDL	TC	TG
S _i	-0.14	0.32	-0.04	-0.03	-0.31
<i>P</i>	n.s.	.017	n.s.	n.s.	.022
HOMA IR	0.25	-0.39	-0.03	0.03	0.39
<i>P</i>	n.s.	.003	n.s.	n.s.	.004

BMI=body mass index; HDL=high density lipoprotein cholesterol; LDL=low density lipoprotein cholesterol; TC=total cholesterol; TG=triglycerides.

After adjusting for age, Table 3 shows that both S_i and HOMA IR were significantly correlated with HDL cholesterol and triglycerides, and the magnitude of the correlations was similar for the 2 indices (*ρ*=0.32 and -0.39 for HDL and *ρ*=-0.31 and 0.39 for TG). The age-adjusted correlation between S_i and HOMA IR among all 61 participants was -0.57 (*P*<.0001). The magnitude of this correlation did not change following additional adjustment for BMI.

Figure 1 shows S_i and HOMA IR values for the SHS participants, according to diabetes status. Among non-diabetic individuals, S_i and HOMA IR were strongly correlated (*ρ*=-0.49, *P*=.0009), but the correlation was poor among diabetic individuals (*ρ*=-0.13, *P*=n.s.).

DISCUSSION

This report found that IR measured by FSIGT is common in a sample of SHS participants at levels of FG that do not meet ADA criteria for diabetes mellitus. The finding of IR and associated adverse CVD risk factor profiles at levels of FG that are considered non-diabetic by the ADA suggests that increased CVD risk associated with IR begins at levels of FG that would not typically alert clinicians to evaluate the need for CVD risk factor modification. Data from the Pima Indians⁴ showed that among non-diabetic individuals, IR was a significant predictor of incident diabetes over 5 years of follow-up indicating that identification of insulin resistant individuals may also be useful for interventions designed to prevent the onset of diabetes among high risk AI.

Categories of “insulin sensitive” and “highly insulin sensitive” used in this report were based on median S_i values for non-diabetic White, Black, and Hispanic individuals from IRAS, a large epidemiologic study focused exclusively on IR and CVD.⁹ Ethnic differences in IR among both diabetic and non-diabetic

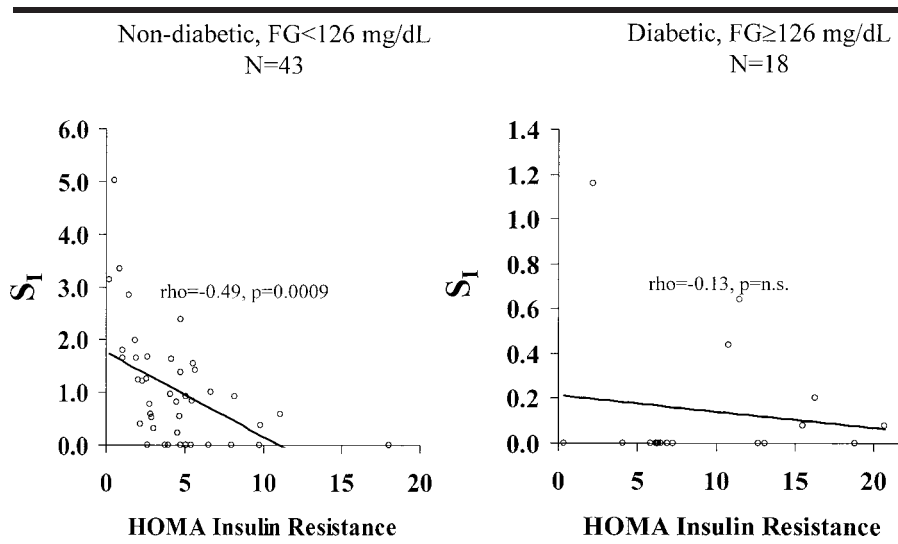


Fig 1. Correlation of HOMA IR with S_1 , by diabetes status, Strong Heart Study

individuals have been reported in IRAS.²⁷ Our S_1 data for diabetic and non-diabetic AI (0.14 and 1.08, respectively) are lower than for their Black, White, and Hispanic counterparts in IRAS, suggesting that AI are more insulin resistant than other ethnic groups. This finding is consistent with those of a study of Pima Indians and Whites in which IR was measured by the steady-state plasma glucose technique.²⁸ The current study, using data from a sample of diverse Indian community members, extends findings of IR in non-diabetic AI to tribes other than the Pima. It is important to note that diabetes-stratified data from the sample of AI in this report are not directly comparable to those from IRAS due to differences in how diabetes was defined in the 2 studies: IRAS defined diabetes based on 1985 WHO criteria²²; this report categorized diabetes on ADA criteria (FG only) in order to maximize clinical application of the results in AI communities.¹⁴ In addition, our sample of AI is relatively small. Despite these limitations, it is clear that few non-diabetic Indians in this study were insulin sensitive according to S_1 criteria defined in IRAS.

The prospective association of IR with CVD morbidity and mortality^{29,30}

suggests that early identification of insulin resistant individuals—especially those in the non-diabetic range of fasting glucose—may be an effective screening tool for initiation of risk factor modification in high risk individuals before the onset of diabetes. Indeed, in the Botnia study, the metabolic syndrome was reported in 10% and 15% of non-diabetic women and men, respectively, and in 42% and 64% of women and men, respectively, with intermediate abnormalities of glucose metabolism (impaired fasting glucose and impaired glucose tolerance).²⁹ This study showed increased risk of CVD morbidity associated with the metabolic syndrome among individuals with normal glucose tolerance, further supporting the idea of early risk factor modification among non-diabetic insulin resistant individuals who exhibit features of the metabolic syndrome.

Since the FSIGT and clamp studies are not standard in clinical practice, detailed evaluation of non-diabetic individuals for IR poses a challenge for clinicians. It is for this reason that alternative indices of IR, such as the HOMA model, are appealing as tools for identification of non-diabetic individuals who may benefit from early risk factor modification. The HOMA model uses

readily available laboratory values (FG and FI) and is easy to calculate. However, there have been persistent concerns about how accurately HOMA IR reflects more physiologic indices of IR, as compared with the FSIGT or clamp. In our sample, there were a few individuals with low levels of FG whose HOMA IR and S_1 values did not appear to reflect each other well. One explanation for this observation is that these non-diabetic individuals might have had post-challenge hyperglycemia had OGTT data been available for analysis. A recent study suggested that HOMA IR poorly reflects IR measured by the hyperinsulinemic-euglycemic clamp among people with IGT compared to those with normal glucose tolerance on an OGTT.³¹

The correlation between HOMA IR and S_1 was strongly confounded by diabetes status. By plotting S_1 and HOMA IR by diabetes status, we demonstrated that HOMA IR reflects S_1 reasonably well at a level of FG at or below that defining diabetes by ADA criteria ($\rho = -0.49$ at glucose < 126 mg/dL), but not well at higher levels ($\rho = -0.13$ at FG ≥ 126 mg/dL). These results show that HOMA is a poor reflection of IR among AI with established diabetes, and that this index may actually provide misleading information on insulin sensitivity among diabetic individuals. The reason for the differential utility of the HOMA model across diabetes strata may lie in the relative decrease in insulin levels that accompanies the onset of diabetes.

As noted by IRAS investigators, a strong correlation between an alternative index of IR and S_1 is a necessary, but not sufficient, assessment of how well the alternative index reflects true underlying IR³²; alternative indices should also correlate well with CVD risk factors. Our findings that HOMA IR and S_1 were correlated at approximately the same magnitude with HDL and TG further supports the utility of HOMA IR as a reflection of underlying

IR in this sample. The absence of a significant correlation with BMI can be explained by the extremely high levels of obesity in the SHS population. Prospective studies of the HOMA model as a predictor of CVD risk in non-diabetic AI are needed to fully establish the utility of this index as a tool for risk factor stratification among non-diabetic AI.

Ethnic differences in IR at relatively low levels of FG, such as those observed in our study in comparison to non-diabetic individuals in IRAS, support a long-standing hypothesis concerning a genetic predisposition to abnormalities of glucose metabolism among certain minority groups.^{33,34} Such a postulated predisposition may be particularly evident in AI, who have the highest rates of diabetes in the United States, and as we demonstrate here, are more insulin resistant than non-diabetic Whites, African Americans, and Hispanics in IRAS. At a time when the potential advances in science and medicine resulting from the sequencing of the human genome are beginning to be understood, it is important not to confuse "race" with "genetics."³⁵ Epidemiological associations apparently attributable to membership in a particular racial or ethnic group may be due to social, behavioral, or environmental factors that: 1) are more common in the group of interest than in other groups; and 2) may increase the risk of a particular health outcome. To fully understand apparent ethnic differences in disease, genetic studies of complex conditions such as IR and diabetes must be designed to investigate not only the "direct" effects of genes on the development of disease, but also the effects of gene-environment interactions on these health outcomes. Until results of these studies are available, however, public health interventions will continue to rely on effective screening and treatment programs for common disorders like diabetes.

In summary, we demonstrated elevated CVD risk factors in a sample of diabetic and non-diabetic AI with high

levels of insulin resistance. The high correlation between HOMA IR and S_1 at non-diabetic levels of FG suggests that HOMA IR may be a useful tool for identification of non-diabetic individuals who are insulin resistant, a group that may benefit from early CVD risk factor modification.

ACKNOWLEDGMENTS

This study was supported by grants U01-HL-41642, U01 HL-41652, and U01 HL-41654.

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