Insulin Response in a Triethnic Population: Effects of Sex, Ethnic Origin, and Body Fat

The Miami Community Health Study

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OBJECTIVE — To assess sex and ethnic differences in hyperinsulinemia/insulin resistance and to examine the impact of percent body fat on such differences.

RESEARCH DESIGN AND METHODS — A cross-sectional epidemiological study was performed in a normoglycemic population of African-Americans (n = 159), Cuban Americans (n =128), and non-Hispanic whites (n = 207) who resided in Dade County, Florida, from 1990 to 1995. The insulin area under the curve (AUC) in response to a standard 75-g oral glucose tolerance test (OGTT) was used as an indicator of hyperinsulinemia/insulin resistance. Analysis of covariance was performed to compare sex and ethnic differences in the insulin AUC. Multiple linear regression was used to evaluate the independent correlates of the insulin AUC.

RESULTS — After covariate adjustment for percent body fat, men displayed a significantly higher insulin AUC than did women ($P < 0.001$). African-Americans and Cuban-Americans each had a significantly higher insulin AUC than did non-Hispanic white participants (P = 0.01). Alcohol consumption was inversely related to AUC (P = 0.04).

CONCLUSIONS — Despite the greater percentage of body fat in women, the insulin AUC was similar in women and men. After adjustment for the sex difference in percent body fat, women displayed a lower insulin AUC than did men, indicating enhanced insulin sensitivity. These differences by sex and ethnicity in insulin resistance are consistent with established differences in heart-disease risk (i.e., higher in men and African-Americans) and suggest that hyperinsulinemia/insulin resistance may partly underlie such differences.

The male excess in mortality from coronary heart disease is well known, but the reasons for it are only partially understood. Consideration of standard coronary heart disease (CHD) risk factors such as age, blood pressure, lipoprotein levels, cigarette smoking, and psychological variables does not fully account for the greater risk observed among men (1–3). NIDDM, however, diminishes or eliminates this sex difference, though again apparently not due entirely to the more adverse risk factor profile experienced by people with diabetes (4–7).

Hyperinsulinemia/insulin resistance is thought to precede both CHD and NIDDM in several populations (8–12). Concentrations of fasting and postchallenge insulin are elevated among people who later develop CHD or NIDDM. We and others (13,14) have hypothesized that young men are more insulin resistant than women, and hyperinsulinemia (or a resistance to its actions) could explain some of the sex difference in CHD risk-factor distribution and mortality. Using the hyperinsulinemic clamp technique, we have previously shown that healthy premenopausal women are more insulin sensitive than are their male counterparts (13). Loss of this "female insulin advantage" may underlie some of the increase in CHD risk observed in diabetic women.

Of the extant studies in the literature, few have included Hispanic subjects other than Mexican-Americans. Data from the Hispanic Health and Nutrition Examination Survey suggest that the prevalence of NIDDM is lower among Cuban-Americans than among either Mexican-Americans or Puerto Ricans (15). Although the risk of NIDDM is greater among Mexican-Americans than among non-Hispanic whites, relevant information among Cuban-Americans is lacking. Measurements of insulin levels among Cuban-Americans are virtually nonexistent.

Recently, it has been demonstrated that the area under the insulin curve (AUC) in response to a standard 75-g oral glucose tolerance test (OGTT) is a reasonably good correlate of the degree of insulin resistance among normoglycemic people (Pearson r = 0.65) (16). In this report, we tested the hypothesis that after adjustment for the percent body fat and other covariates, normoglycemic women would have a lower insulin response (i.e., enhanced insulin sensitivity) than would their male counterparts. If supported, this hypothesis would provide additional insight into the protective effect against CHD risk provided by female sex. We also hypothesized that non-Hispanic whites would have a lower insulin AUC than either African-Americans or Cuban-Americans after consideration of body fat and other covariates.

RESEARCH DESIGN AND METHODS

— The methodology of the Miami Community Health Study has been described elsewhere (R.P.D., R.J.P., J.A.B., R.A.D.D., R.B.G., unpublished observations). Briefly, eligibility was limited to 25- to 44-year-old men and women who self-

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Received for publication 5 November 1996 and accepted in revised form 17 June 1997.

Abbreviations: AUC, area under the curve; CHD, coronary heart disease; CVD, cardiovascular disease; OGTT, oral glucose tolerance test; WHR, waist-to-hip ratio.

Table 1—*Levels of selected variables according to sex and ethnicity*

	Non-Hispanic white		Cuban-American		African-American	
	Women	Men	Women	Men	Women	Men
n	17	97	53	58	75	56
Age (years)	36.3 ± 5.1	36.0 ± 5.6	34.6 ± 5.5*	32.3 ± 4.7	35.9 ± 5.8	34.9 ± 5.9
BMI (kg/m^2)	25.5 ± 6.7	26.0 ± 3.7	25.3 ± 5.4	28.9 ± 5.9†	28.0 ± 6.6	27.2 ± 4.2
Body fat (%)	34.7 ± 6.3†	27.8 ± 5.8	36.6 ± 6.1†	28.0 ± 5.2	39.3 ± 6.0†	30.3 ± 5.2
Insulin AUC (pmol · l^{-1} · 120 min^{-1})	532 ± 300	540 ± 375	654 ± 420	762 ± 582	708 ± 450	778 ± 540
Glucose AUC (mmol · l^{-1} · 120 min^{-1})	12.2 ± 1.9	12.7 ± 2.0	12.1 ± 2.2	12.4 ± 4.4	11.8 ± 1.6	11.6 ± 2.1
Number of cigarettes/day	3.0 ± 6.4	3.2 ± 8.6	2.6 ± 5.8	5.2 ± 10.1	3.0 ± 7.5	2.8 ± 5.5
Number of alcoholic drinks/week	2.5 ± 4.3	6.3 ± 8.5†	2.8 ± 4.0	5.1 ± 7.4*	3.4 ± 7.2	6.5 ± 8.7
Natural log of physical activity score (kcal/week)	5.7 ± 2.5	7.1 ± 1.8†	5.6 ± 2.8	6.2 ± 2.4	5.6 ± 2.5	7.0 ± 1.9†
Parental history of CVD (%)	2.6	4.1	5.7	5.2	6.7	5.4

Data are means ± SD. *$P < 0.05$; †$P < 0.001$, men vs. women of the same ethnicity.

reported their ethnic background as either African-American, Cuban-American, or non-Hispanic white. People with past or present diagnoses of hypertension, CHD, stroke, diabetes (type 1 or type 2), psychiatric disorders, or lipid abnormalities, or who reported medication use for any of these conditions were considered ineligible. Letters of invitation were sent to all known addresses within defined census tracts in Dade County, FL (1990 U.S. Census). These letters were followed up by phone calls, and if necessary, additional letters were mailed. Only one eligible person per household was selected. Of the 958 known eligible people contacted, 514 (53%) participated in this study. Compared to nonparticipants, participants were significantly more likely to be men (53% vs. 47%) and were slightly more educated (14.0 vs. 13.7 years; $P = 0.03$). There was no difference in overall participation rate according to ethnicity, although Cuban-Americans had the lowest rate (26%) of the three groups.

The components of the clinical examination included measurements of several cardiovascular risk factors, including a 12-lead resting electrocardiogram to identify prevalent CHD, resting blood pressure, anthropometric measurements, and several standardized questionnaires to assess lifestyle and health habits such as cigarette smoking (recorded as number of cigarettes smoked per day), alcohol use (recorded as number of alcoholic beverages consumed per week), and physical activity (recorded as kilocalories expended per week) (18). A parental history of premature cardiovascular disease (CVD) was considered positive if a participant reported a maternal death from heart attack, stroke, or diabetes before age 60 or a paternal death before age 55 (natural parents only). Deaths among siblings from these causes were virtually absent and were not considered.

Anthropometric measurements

Several estimates of body composition were assessed. All anthropometric measurements were made with the participant wearing light clothes without shoes. Weight was recorded on a balance-beam scale and recorded to the nearest quarter pound. Height was measured to the nearest one-half centimeter. BMI was calculated as weight in kilograms divided by height in meters, squared. The waist girth was measured in the standing position by applying a linen tape measure horizontally midway between the iliac crest and the lowest lateral portion of the rib cage, and anteriorly midway between the umbilicus and the xiphoid process. This measure is the smallest circumference at waist level. The mean of two measurements (recorded to the nearest 0.5 cm) was used. To estimate percent body fat, body density was calculated from subcutaneous skinfold thickness measurements using age- and sex-specific prediction equations published by Durnin and Womersley (19). For example, the equation for men aged 30–39 years is: body density = 1.1165 − 0.0484 log (triceps skinfold + subscapular skinfold). For white non-Hispanic and Cuban-American participants, percent body fat was calculated from body density using the Siri equation (20): percent body fat = (4.95/density − 4.50) × 100. For African-Americans (who have a greater density of lean body mass than do whites), percent body fat was calculated using the equation published by Schutte et al (21): percent body fat = (4.374/density − 3.928) × 100. Direct measures of lean body mass such as hydrostatic weighing were not performed due to the unfavorable cost, feasibility, and acceptance in this free-living population. The study was approved by the University of Miami School of Medicine Internal Review Board, and all participants gave written informed consent.

OGTT

All participants were required to fast (except water) for 12 h and to refrain from smoking or vigorous physical activity before coming into the clinic. A standard 75-g OGTT was administered with determinations of glucose and insulin at −15, 0, 60, and 120 min. The first two sample results were averaged to provide a fasting value. Diabetes (fasting glucose >140 mg/dl or a 2-h glucose >200 mg/dl) and impaired glucose tolerance (fasting glucose < 140 mg/dl and 2-h glucose between 140 mg/dl and 199 mg/dl) were defined according to World Health Organization criteria (22). People testing positive for either condition ($n = 97$) were not included in this report. Glucose was assayed by the glucose-oxidase method (Yellow Springs Instrument, Yellow Springs, OH). Insulin was assayed with a double antibody immunoassay (Diagnostic Products, Los Angeles, CA). The lower limit of detection was 3.0 μU/ml. All those with fasting levels below the minimum were assigned a value of 3.0 μU/ml. The interassay coefficient of variation was 2.7% for fasting glucose and 15% for fasting insulin. Intra-assay coefficients were less than 2% and 11%, respectively. The glucose and insulin AUCs were calculated with the trapezoidal rule.

Statistical analysis

Differences between mean values of continuous variables were assessed with Student's

t test, and χ^2 or Fisher's exact test was used for categorical variables. Analysis of covariance was used to evaluate the effects of sex and ethnicity on the dependent variable after controlling for selected covariates. Forward stepwise multiple linear regression models were fitted using insulin AUC as the dependent variable. Preliminary analyses indicated that distributions of insulin AUC, number of cigarettes smoked per day, and number of alcoholic drinks consumed per week were skewed toward the right. Log transformation (natural log) was used, which yielded data that were more normally distributed. Because the latter two variables included zero (for nonsmokers and nondrinkers), one was added to each data point before transformation. Interaction terms among independent variables were evaluated by including the appropriate cross-product terms. All analyses were performed using the Statistical Analysis System (23). All statistical tests were two-sided.

RESULTS — Table 1 presents selected descriptive information according to sex and ethnicity. Study participants averaged about 35 years of age. Men had a greater mean BMI than did women except among the African-Americans, whereas women had a greater percent body fat than did men across all ethnic groups. The mean insulin AUC in response to a standard 75-g OGTT did not differ significantly by sex and was lowest among non-Hispanic whites (Fig. 1). The lack of a sex difference was not due to different levels of glycemia (Fig. 2) because they were identical between the sexes. The mean number of cigarettes smoked per day in the entire cohort (i.e., smokers plus nonsmokers) was low. The reported weekly consumption of alcoholic beverages ranged from approximately two to seven drinks. Physical activity was generally higher among men. The reported frequency of a parental history of premature death from CVD varied from 2.6 to 6.7%.

Table 2 presents covariate-adjusted mean levels of the insulin AUC and indicates whether sex or ethnic differences remained after each adjustment. Adjustment solely for age revealed that men had a somewhat higher insulin AUC than did women, though not significantly so ($P = 0.35$). Non-Hispanic whites had the lowest insulin AUC of the three ethnic groups ($P < 0.001$). There was no difference between Cuban-Americans and African-Americans in subsequent pairwise comparisons (data not shown). Of importance is the observation

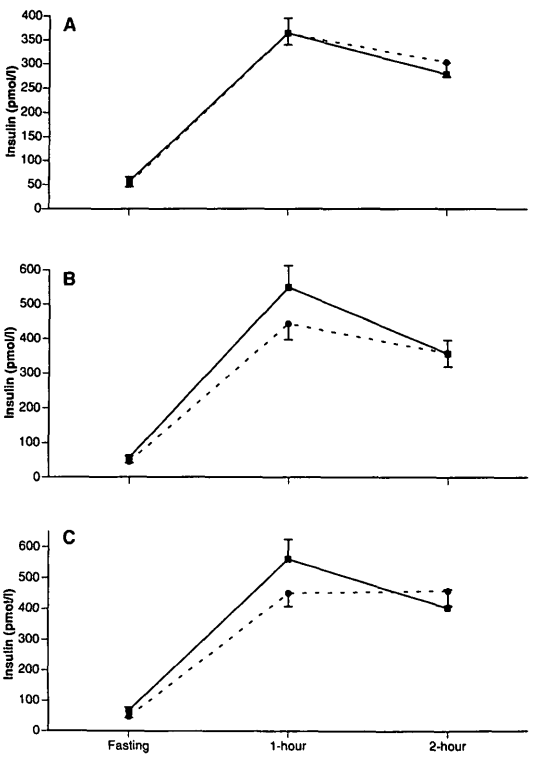

Figure 1—*Mean (± SE) of serum insulin during a 75-g OGTT among non-Hispanic whites (A), Cuban-Americans (B), and African-Americans (C) according to sex (—, men; ----, women).*

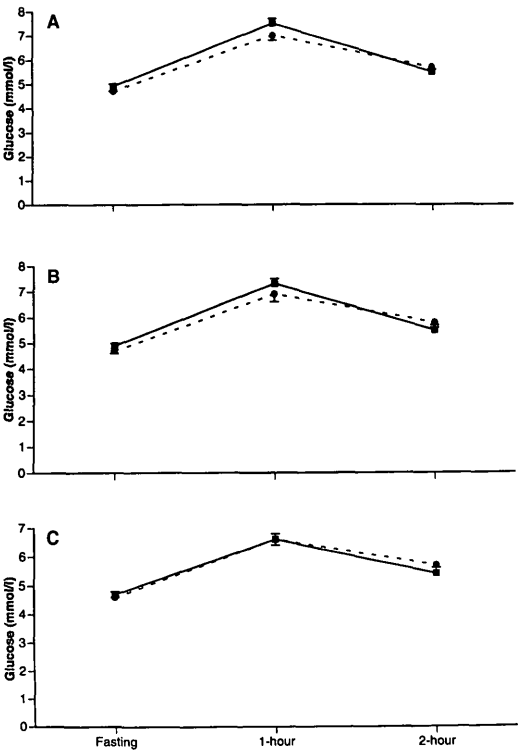

Figure 2—*Mean (± SE) of serum glucose during a 75-g OGTT among non-Hispanic whites (A), Cuban-Americans (B), and African-Americans (C) according to sex (—, men; ----, women).*

Table 2—*Covariate-adjusted mean levels of insulin AUC according to sex and ethnicity*

Adjusted for:	Non-Hispanic white		Cuban-American		African-American		ANCOVA *P* value	
	Women	Men	Women	Men	Women	Men	Sex	Ethnicity
Age (years)	75.1	71.4	88.0	99.2	108.4	94.4	0.35	<0.001
BMI (kg/m²)	80.1	73.9	90.0	87.1	91.3	106.0	0.89	0.01
Body fat (%)	69.1	85.8	93.6	115.7	73.2	118.2	<0.001	0.03
Natural log of the number of cigarettes smoked per day + 1	75.9	71.7	88.0	97.3	95.4	107.9	0.44	<0.001
Natural log of the number of alcoholic drinks per week + 1	74.7	72.9	86.5	99.0	93.8	111.7	0.20	<0.001
Natural log of the physical activity score + 1	74.7	73.4	86.7	96.5	94.7	109.4	0.29	<0.001
Parental history of CVD (%)	75.8	72.0	87.9	96.8	95.2	108.1	0.41	<0.001

that men had a significantly higher insulin response than did women after adjustment for percent body fat ($P < 0.001$), which was not evident after adjustment for BMI ($P = 0.62$). With regard to anatomic location and fat distribution, it was not possible to adjust the sex differences for the waist girth or waist-to-hip ratio (WHR) due to the small degree of overlap between the sexes, i.e., adjustment for WHR was equivalent to adjustment for sex. For example, the 90th percentile of WHR in non-Hispanic white women was similar to the 10th percentile in men (0.82 and 0.83, respectively). Among Cuban-Americans, the 90th percentile of WHR in women (0.83) was comparable to the 10th percentile in men (0.82). The data among African-Americans was similar. Covariate adjustment for the number of cigarettes smoked per day, number of alcoholic drinks per week, or frequency of parental history of premature CVD in turn revealed no significant effects of sex or ethnicity on the insulin AUC.

Multiple stepwise linear regression was used to determine the significant correlates of the insulin AUC in each ethnic group separately (Table 3). Among non-Hispanic whites, percent body fat was independently related to insulin AUC. Sex was also related to insulin AUC (indicating a higher insulin response among women), although at a borderline level of statistical significance. A total of 9.5% of the variance in the insulin AUC was explained by these two variables. Among Cuban-Americans, these same variables along with alcohol intake (inversely) explained 16.7% of the variance in insulin AUC. A similar finding was noted among African-Americans. After adjustment for percent body fat, men had a significantly higher insulin AUC than did women ($P < 0.01$). These two factors explained 5.9% of the variance in insulin AUC among African-Americans.

To examine the effect of ethnicity per se on insulin AUC, a stepwise regression model was performed that included two indicator variables for ethnicity (Table 4). Compared with non-Hispanic whites, African-Americans and Cuban-Americans had a significantly greater insulin response, suggesting a significantly higher degree of insulin resistance. In this regression model, alcohol intake was significantly and inversely related to insulin AUC ($P = 0.04$). Although all subjects were normoglycemic according to World Health Organization criteria, some residual confounding due to level of glycemia may remain. We therefore reanalyzed this model including a term for the glucose AUC. The glucose AUC was independently and positively correlated with the insulin AUC, as expected. The coefficients for the main effects were essentially unchanged, however.

To investigate the effect of fat distribution on the insulin AUC, regression analyses were performed substituting WHR for sex (Table 5). The results indicated that WHR was positively associated with the insulin AUC ($P < 0.001$), while alcohol use was no longer statistically significant. The model explained 16.4% of the variance in the insulin AUC.

CONCLUSIONS — The results of this study confirm and extend our previous findings (13) that these premenopausal, normoglycemic women were less insulin resistant (or more insulin sensitive) than were their male counterparts. Despite their greater percentage of body fat, women had an unadjusted insulin AUC similar to that of men (Fig. 1). After adjustment for per-

Table 3—*Multiple linear stepwise regression of selected variables on ln insulin AUC according to ethnicity*

Independent variable	β ± SE	*P* value
Non-Hispanic whites		
Body fat (%)	0.03 ± 0.01	0.0001
Sex	0.20 ± 0.11	0.08
Multiple R^2 = 9.5%		
Cuban-American		
Body fat (%)	0.01 ± 0.01	<0.001
Sex	0.61 ± 0.17	<0.001
Natural log of the number of alcoholic drinks per week + 1	−0.17 ± 0.06	0.01
Multiple R^2 = 16.7%		
African-American		
Sex	0.49 ± 0.18	<0.01
Body fat (%)	0.03 ± 0.01	0.01
Multiple R^2 = 5.9%		

Sex is coded as 0 for women, 1 for men.

Table 4—*Multiple linear stepwise regression of selected variables on insulin AUC: total cohort*

Independent variable	β ± SE	*P* value
Body fat (%)	0.03 ± 0.006	0.0001
Sex	0.38 ± 0.08	0.0001
African-American vs. non-Hispanic whites	0.20 ± 0.08	0.01
Cuban-American vs. non-Hispanic whites	0.19 ± 0.08	0.01
Natural log of the number of alcoholic drinks per week + 1	−0.06 ± 0.03	0.04

Multiple R^2 = 13.7%. Sex is coded as 0 for women, 1 for men.

cent body fat, however, women had a significantly lower insulin response than men—a finding we interpret as showing a higher degree of insulin sensitivity in these women. Other potentially confounding factors could not explain this result, nor did glucose level, which was similar between the sexes (Table 1 and Fig. 2).

Although the association between obesity and insulin has long been known, there have been few population-based studies of insulin levels in multi-ethnic populations of men and women. The level of obesity and its anatomic distribution have previously been shown to correlate with insulin levels in both non-Hispanic white (24) and Hispanic men and women (25). As previously noted, adjustment for fat distribution was uninformative due to the limited overlap in the distribution of WHR (or waist girth). Nevertheless, current evidence (26–28) suggests that waist girth or, perhaps more importantly, the amount of intra-abdominal fat greatly influences circulating insulin levels. In the current study, both percent body fat and WHR were related to insulin AUC (Table 5), suggesting that the sex differences are due in large part to differences in fat distribution as indexed by the WHR.

Several lifestyle variables related to obesity and fat distribution were examined in this report, including cigarette and alcohol use and physical activity. Of these, alcohol intake was inversely related to the insulin AUC. Although heavy consumption has been related to impaired glucose tolerance (29), light or moderate consumption may be beneficial in terms of increased insulin sensitivity (30). Whether enhanced insulin sensitivity may mediate the inverse relation between moderate alcohol use and risk of CHD in the general population is not known, but the link with insulin does suggest an epidemiological avenue worth further exploration.

Contrary to reports from other studies (31,32), we did not find cigarette smoking or a positive family history to be independently related to insulin AUC. This could well be due to the low prevalence of cigarette smoking in this cohort (25%) and to the modest number of reported cigarettes smoked per day among smokers (mean of 15 to 20 per day). Likewise, due to the youthful age of the study cohort, the frequency of parental death was very low and thus not a statistically powerful predictor.

Certain limitations of this study should be noted. Because our eligibility criteria excluded the most insulin-resistant people, these results are even more striking given that the distribution of insulin resistance was truncated. These participants may represent a select group of volunteers, but differences between participants and nonparticipants were minor (R.P.D., R.J.P., J.A.B., R.A.D.D., R.B.G., unpublished observations). Nevertheless, caution should be exercised when extrapolating these results to larger groups. The potential role of sex steroid hormone levels in these results is not known. Less than 7% (14/205) of the women in the current study reported current oral contraceptive use, and those data were included here. The effects of endogenous estrogen concentrations on insulin resistance have not been systematically investigated. The women in this study were examined without reference to their menstrual cycle. However, previous studies have noted only a slight increase in insulin binding in the second half of the cycle, suggesting increased insulin resistance. This would serve to make women more comparable to men in terms of insulin resistance. Thus, our results may underestimate the true sex difference (33).

The use of equations to estimate percent body fat rather than direct methods is another limitation of this study. Validation studies among nonwhite populations are uncommon. Epidemiological studies of multicultural populations often use BMI as the measure of obesity, yet its validity has been examined almost exclusively in non-Hispanic white men and women. BMI has been demonstrated to correlate well with percent body fat (r = 0.89) (34). This correlation may not be as strong in African-Americans, however, among whom women have greater bone mass and skeletal muscle compared with non-Hispanic white women (35). Without a correction for this (as we used in the estimating equations) adiposity would be overestimated in African-Americans compared with non-Hispanic whites at a given level of BMI. Nevertheless, some bias in our findings may remain, though they would be insufficient to account for the sex differences. Direct measures, such as computed tomography scan or dual energy X-ray absorptiometry, involve exposure to ionizing radiation, which could adversely affect participation. Other methods, including underwater weighing, are not feasible in a large epidemiological investigation. Our results may be population-specific and applicable to these healthy, young to middle-aged people. We also did not directly measure the amount of intra-abdominal fat, which is the most metabolically active fat depot and is probably imprecisely estimated by anthropometric measurements (36). These are clearly important avenues for future epidemiological research. Such studies may aid a better understanding of the nature of the sex and ethnic differences in macrovascular disease risk.

In summary, the enhanced insulin sensitivity among women compared with men

Table 5—*Multiple linear stepwise regression of selected variables on insulin AUC substituting WHR for sex: total cohort*

Independent variable	β ± SE	*P* value
Body fat (%)	2.97 ± 0.65	0.0001
WHR	296.0 ± 48.8	0.0001
African-American	24.7 ± 11.2	0.02
Cuban-American	32.2 ± 10.7	0.02

Multiple R^2 = 16.4%.

confirms and extends our previous results from using the euglycemic/hyperinsulinemic clamp (13) and indicates that the measurement of insulin AUC may serve as a reasonable proxy for insulin resistance among these normoglycemic people. The current study adds further support to the hypothesis that sex differences in insulin resistance may, in part, underlie differences in the relative contributions of risk factors (37) for cardiovascular disease. The findings also highlight the importance of studies of multi-ethnic populations, which provide insight into ethnic differences in risk-factor distributions and their correlates and may help us to better design more targeted and effective intervention strategies.

Acknowledgments — This work was supported by National Institutes of Health Grant HL-44600.

The authors wish to acknowledge the contributions of Killiam Lopez, Delia A. Stephens, MS, and Linda Jones, BS, in the preparation of this article.

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