Ethnic Differences in Insulin Sensitivity and β-Cell Function in Premenopausal or Early Perimenopausal Women Without Diabetes

The Study of Women's Health Across the Nation (SWAN)

JAVIER I. TORRÉNS, MD[1]
JOAN SKURNICK, PHD[2]
AMY L. DAVIDOW, PHD[2]
STANLEY G. KORENMAN, MD[3]
NANETTE SANTORO, MD[4]
MARIA SOTO-GREENE, MD[5]
NORMAN LASSER, MD, PHD[6]
GERSON WEISS, MD[1]

OBJECTIVE — To assess differences in insulin sensitivity and β-cell function between nondiabetic premenopausal or early perimenopausal non-Hispanic white women and African American, Chinese American, Japanese American, and non–Mexican-American Latino women.

RESEARCH DESIGN AND METHODS — Homeostasis model assessments (HOMAs) of insulin sensitivity (HOMA%S) and β-cell function (HOMA%β) were used. Stepwise multivariable ethnic-specific ANCOVA models were used to compare HOMA%S and HOMA%β between non-Hispanic whites and each of the four ethnic groups.

RESULTS — HOMA%S was lower in African Americans, Chinese Americans, and Japanese Americans when compared with non-Hispanic white women after correcting for waist circumference, presence of impaired fasting glucose, and site. Significant differences persisted only between African Americans and non-Hispanic whites after inclusion of triglycerides in the model. Triglycerides indirectly corrected for the differences in HOMA%S in the other two groups. There were no differences in HOMA%S between the non–Mexican-American Latinos and the non-Hispanic whites. Japanese Americans and Chinese Americans had lower HOMA%β than non-Hispanic whites, whereas African Americans had higher HOMA%β than non-Hispanic whites after correcting for confounders. HOMA%β was similar between non–Mexican-American Latinos and non-Hispanic whites.

CONCLUSIONS — These data suggest that type 2 diabetes prevention strategies for African-American women should initially target decreased insulin sensitivity, whereas strategies for Japanese-American and Chinese-American women may initially need to target both decreased insulin sensitivity and β-cell function. Previous studies of Mexican-American populations may not apply to non–Mexican-American Latino women.

Diabetes Care 27:354–361, 2004

From the [1]Department of Obstetrics Gynecology and Women's Health, New Jersey Medical School, University of Medicine and Dentistry of New Jersey, Newark, New Jersey; the [2]Department of Preventive Medicine, New Jersey Medical School, University of Medicine and Dentistry of New Jersey, Newark, New Jersey; [3]David Geffen School of Medicine, University of California, Los Angeles, Los Angeles, California; the [4]Division of Reproductive Medicine, Albert Einstein School of Medicine, New York, New York; the [5]Hispanic Center of Excellence, New Jersey Medical School, University of Medicine and Dentistry of New Jersey, Newark, New Jersey; and the [6]Department of Medicine, New Jersey Medical School, University of Medicine and Dentistry of New Jersey, Newark, New Jersey.

Address correspondence and reprint requests to Javier I. Torréns, MD, New Jersey Medical School, UMDNJ Department of Obstetrics, Gynecology and Women's Health MSB-E-506, 185 South Orange Ave., Newark, NJ 07103. E-mail: torrenji@umdnj. edu.

Received for publication 2 May 2003 and accepted in revised form 15 October 2003.

Abbreviations: GENNID, Genetics of Non-Insulin Dependent Diabetes Mellitus; HOMA, homeostasis model assessment; HOMA%β, HOMA of β-cell function; HOMA%S, HOMA of insulin sensitivity; NCEP ATP III, National Cholesterol Education Program Adult Treatment Panel III; SWAN, Study of Women's Health Across the Nation.

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

Decreased β-cell function and decreased insulin sensitivity are the two major risk factors for the development of type 2 diabetes. Insulin sensitivity varies widely among individuals who have normal glucose tolerance (1). The β-cell's ability to compensate for a decrease in insulin sensitivity enables these individuals to maintain normal glucose levels. The fundamental pathological sequence leading to type 2 diabetes is presumed to be the development of obesity-induced decrease in insulin sensitivity followed by hyperglycemia when the β-cell can no longer compensate (2). However, it is still unknown whether β-cell dysfunction (3), decreased insulin sensitivity (4), or a combination of both defects are the primary abnormalities leading to type 2 diabetes (5). Although the risk factors for type 2 diabetes are similar among ethnically diverse populations, ethnic differences in insulin sensitivity and β-cell function exist among groups at high risk for type 2 diabetes. Understanding how differences in insulin sensitivity and β-cell function vary between ethnic groups will become important as ethnic-specific type 2 diabetes prevention strategies are developed.

It is well known that African Americans are less insulin sensitive and have greater β-cell function than non-Hispanic whites, whereas Mexican Americans are less insulin sensitive but have similar β-cell function as non-Hispanic whites, after correcting for differences in insulin sensitivity (6). Population-based studies assessing potential differences in insulin sensitivity and β-cell function among other ethnic populations residing in the U.S. are limited. Because of this, results from Mexican-American Latinos and Japanese Americans are often extrapolated onto non–Mexican-American Latino and Asian populations, respectively. These

groups represent 42% of Latinos and 38% of the Asian population in the U.S. (7).

We used the baseline data of the 3,302 premenopausal and early perimenopausal women enrolled in the Study of Women's Health Across the Nation (SWAN) to examine ethnic differences in insulin resistance and β-cell function between non-Hispanic whites and African-American, Chinese-American, Japanese-American, and non–Mexican-American Latino women residing in the U.S. SWAN is a multicenter, multiethnic, community-based, longitudinal study of premenopausal and early perimenopausal women designed to characterize the biological and psychosocial changes that occur during the menopausal transition and their effect on women's health.

RESEARCH DESIGN AND METHODS

— The design, sampling strategy, cohort recruitment, and enrollment of SWAN have been described in detail elsewhere (8). In brief, participants were enrolled at seven clinical sites. Recruitment techniques were designed to generate a representative sample of women at each of the seven sites. All seven sites enrolled non-Hispanic whites, and each site also enrolled women belonging to one prespecified minority ethnic group. African-American women were enrolled in Boston, Chicago, Detroit, and Pittsburgh. Japanese-American, Chinese-American, and Latino women were enrolled in Los Angeles and Oakland, California, and in Hudson County, New Jersey, respectively. Eligibility criteria for entry into the SWAN longitudinal cohort were as follows: aged 42–52 years, presence of a uterus and at least one ovary, no current use of estrogens or other medications known to affect ovarian function, at least one menstrual period in the 3 months before screening, and self-identification as a member of one of the five eligible ethnic groups. A total of 3,302 women were enrolled. The cohort consists of 1,550 non-Hispanic whites, 935 African Americans, 281 Japanese Americans, 250 Chinese Americans, and 286 Latinos.

We performed this analysis from the baseline data from SWAN. Women with a history of diabetes, with fasting plasma glucose level ≥7.0 mmol/l, and those who were missing a key variable (insulin, glucose, waist circumference, or BMI) were excluded. A total of 2,789 women (1,359 non-Hispanic whites, 746 African Americans, 219 Latinos, 210 Chinese Americans, and 255 Japanese Americans) were studied. The Latino cohort consisted of 37 Cubans, 43 Puerto Ricans, 31 Dominicans, 24 Central Americans, and 83 women of South American, Spanish, or other Latino descent. The one Mexican-American participant was excluded from this analysis. The Institutional Review Board at each SWAN center approved the study. All women provided written informed consent before enrollment into the study.

Questionnaires and physical measurements

Demographic information, history of hypertension or diabetes, smoking status, perceived stress, physical activity, race/origin, and menopausal status were obtained using standardized questionnaires. Primary race/ethnicity was self-defined as Black or African American, non-Hispanic white, Chinese or Chinese American, Japanese or Japanese American, or Latino.

Nutrient intake was assessed using the NCI (Block) food frequency questionnaire, which was enhanced to accommodate the ethnic diversity in SWAN (9). Information on alcohol consumption was derived from the food frequency questionnaire and categorized based on amount of alcohol consumption (10). Standardized protocols were used to measure height, weight, waist circumference, and blood pressure.

Biochemical measurements

Blood samples were collected on days 2–7 of the follicular phase in 86.7% of women and after an 8-h fast in 96.2% of all women. Serum insulin level was measured using a solid-phase radioimmunoassay (DPC Coat-A-Count Insulin RIA; Diagnostic Products, Los Angeles, CA). All lipids were analyzed on EDTA-treated plasma. Triglycerides were analyzed by enzymatic methods using a Hitachi 747 analyzer (Boehringer Mannheim Diagnostics, Indianapolis, IN). HDL cholesterol was isolated using heparin-2M manganese chloride. Glucose levels were measured using a hexokinase-coupled reaction (Boehringer Mannheim Diagnostics, Indianapolis, IN). Estradiol levels were measured using the ACS-180 automated analyzer (Bayer Diagnostics, Norwood, MA).

The homeostasis model assessment (HOMA) models were used to estimate the insulin sensitivity (HOMA%S) and β-cell function (HOMA%β) in this study. The HOMA models are reasonable substitutes for more sophisticated measures of insulin sensitivity and β-cell function that are suitable for large epidemiologic studies (11,12). Since their original publication, there have been modifications to the mathematical structure of the HOMA models to provide a more accurate physiological representation (13,14). The new HOMA%S model provides similar information on insulin sensitivity and β-cell function across a range of glucose tolerance, as does a frequently sampled intravenous glucose tolerance test with minimal modeling across a range of glucose tolerance (HOMA%S $R^2 = 0.88$, HOMA%β $R^2 = 0.73$) (15,16). These revised computer models were used to estimate insulin sensitivity and β-cell function in this cohort from their baseline insulin and glucose measurements (17).

Statistical analysis

Descriptive statistics on the outcome variables and covariates were obtained within ethnic groups. Alcohol consumption and tobacco use were converted to categorical variables before analysis (10). Univariate ANOVA was used to compare the means of ethnic groups on descriptive characteristics using 0.01 and Sidak's correction for pairwise multiple comparisons. χ^2 and categorical models were used to compare proportions.

HOMA%S, HOMA%β, estradiol, and triglycerides were log-transformed to accommodate skewing of the distributions. Non-Hispanic whites were the reference population in this analysis. Separate stepwise multivariable ethnic-specific analysis of covariance models were developed to compare HOMA%S and HOMA%β between each of the four ethnic groups and the non-Hispanic whites from the same site (or sites). For each such ethnic comparison, covariates were entered as blocks in a preselected order into a series of models. Blocks were formed to separate the components of the metabolic syndrome, as defined by the National Cholesterol Education Program Adult Treatment Panel III (NCEP ATP III), i.e., waist circumference, serum triglycerides, HDL, blood pressure, and impaired fasting glucose (18), from other potential confounders. These blocks were then added

Table 1—*Descriptive characteristics by ethnic group*

	Non-Hispanic whites	African Americans	Non–Mexican-American Latinos	Chinese Americans	Japanese Americans
n	1,359	746	218	210	255
Age*	46 ± 2.7	46 ± 2.7	46 ± 2.8	46 ± 2.7	47 ± 2.7
Household income (per year)					
<$20,000	2%[a]	10%[b]	28%[c]	1%[a]	2%[a]
$20–35,000	4%	10%	31%	3%	1%
>$35,000	94%	80%	42%	96%	97%
Level of education					
Less than High school	1%[a]	5%[b]	46.5%[c]	12%[b]	1%[a,b]
High school	14%	22%	28.0%	14%	18%
More than High school	85%	73%	25.5%	74%	81%
BMI (kg/m^2)	27.3 ± 6.5[a]	30.8 ± 7.0[c]	28.7 ± 5.6[a]	23.1 ± 3.8[b]	22.8 ± 3.6[b]
Waist circumference (cm)	84 ± 15[a]	91 ± 15[c]	87 ± 13[a]	77 ± 10[b]	73 ± 9[b]
Systolic blood pressure (mmHg)	113 ± 14[a]	125 ± 21[b]	123 ± 11[b]	112 ± 15[a]	114 ± 14[a]
Diastolic blood pressure (mmHg)	73 ± 9[a,b]	77 ± 12[c]	82 ± 7[d]	73 ± 11[a]	76 ± 10[b,c]
Insulin (uIU/ml)	7.5 (2.5–86.6)[a]	10.4 (2.0–129.4)[b]	10.6 (3.6–115.1)[b]	7.1 (2.9–33.6)[a,c]	6.6 (2.6–26.7)[c]
Glucose (mmol/l)	5.1 ± 0.5[a]	5.2 ± 0.5[b]	5.1 ± 0.6[a,b]	5.2 ± 0.4[a,b]	5.1 ± 0.4[a,b]
Prevalence of impaired fasting glucose (%)	4.0%[a]	7.8%[b]	5.5%[a,b]	4.3%[a,b]	2.8%[a]
HDL (mmol/l)	1.46 ± 0.37[a]	1.46 ± 0.39[a]	1.32 ± 0.29[c]	1.57 ± 0.34[b]	1.58 ± 0.38[b]
Triglycerides (mmol/l)	1.0 (0.4–9.9)[a,b]	0.9 (0.4–5.9)[a]	1.2 (0.5–9.4)[c]	1.1 (0.3–5.1)[a,b]	1.0 (0.4–12.2)[b]
Estradiol (pmol/l)	206 (18–5,470)[a]	202 (22–1,982)[a]	217 (22–1,982)[a,b]	180 (37–1,358)[b]	191 (22–1,065)[a,b]
Dietary fat (g/day)	67 ± 30[a,b]	75 ± 43[a]	62 ± 25[b,c]	58 ± 27[c]	61 ± 24[b,c]
Calories from fat (%)	33 ± 7[a]	34 ± 7[a]	33 ± 7[a]	29 ± 7[b]	30 ± 7[b]
Dietary fiber (g/day)	12 ± 6.0[a]	12 ± 6.1[a]	12 ± 5.3[a]	15 ± 6.9[b]	13 ± 6.4[a]
Alcohol consumption					
None	38%[a]	56%[b]	47%[b]	79%[c]	56%[b]
0.1–5 g/day	26%	20%	32%	14%	21%
>5.0 g/day	36%	24%	22%	7%	23%
Tobacco use					
Never	52%[a]	53%[a]	66%[b]	94%[c]	71%[b]
Previous smokers	33%	23%	13%	4%	19%
Active smokers	15%	24%	21%	2%	10%
Physical activity indexes					
Household/caregiving	2.8 ± 0.9[a]	2.8 ± 0.8[a]	2.2 ± 0.8[b]	2.3 ± 0.8[a]	2.8 ± 0.8[a]
Active living	2.5 ± 0.8[a]	2.2 ± 0.8[b]	2.6 ± 0.9[a]	2.4 ± 0.7[a]	2.4 ± 0.7[a]
Sports	2.9 ± 1.1[a]	2.5 ± 0.9[b]	2.0 ± 0.8[c]	2.5 ± 1.0[b]	2.8 ± 1.1[a]
Perceived stress	8.4 ± 2.9[a]	8.4 ± 3.0[a]	10.0 ± 3.0[b]	8.2 ± 2.4[a]	8.8 ± 2.7[a]

Data are means ± SD or median (range) unless otherwise indicated. Group differences evaluated by univariate ANOVA or χ^2 tests at $P < 0.01$ were found across the ethnic groups in all of the descriptive characteristics except for age. In pairwise comparisons, ethnic groups marked with the same superscript letter are not significantly different. *$P > 0.05$; † comparisons of means were performed on logarithmic scale.

sequentially as follows: *1*) age, waist circumference, BMI; *2*) presence of impaired fasting glucose defined as a plasma glucose level of 110–125 mg/dl; *3*) estradiol, triglycerides, and HDL; *4*) systolic blood pressure and diastolic blood pressure; *5*) smoking history; *6*) dietary fat, fiber, and alcohol intake; *7*) indexes of sports activity, general leisure activity, and household and childcare activity; *8*) self-perceived stress and cynicism scale; and *9*) education level and income categories. At each entry stage, a covariate within the block was retained if its partial *F* test *P* value was <0.05. Addition of covariates terminated when ethnicity was no longer a statistically significant factor. Statistical models presented are stratified by the number of factors (<3 or ≥3), which characterize the metabolic syndrome as defined by the NCEP ATP III. The models for African Americans were adjusted for site as a factor and tested for site-ethnicity interaction to allow for possibly inconsistent differences between African Americans and non-Hispanic whites at the four sites where African Americans were the target ethnicity. Ethnic differences in HOMA%β were analyzed following the same procedure. Analyses were performed using SAS version 8.02 (SAS Institute, Cary, NC).

RESULTS

Clinical descriptive characteristics

The mean age of the cohort of 2,789 women was 46 years and did not differ among ethnic groups (Table 1). On average, non–Mexican-American Latinos had lower income and were less educated. Japanese-American and Chinese-

American women had lower BMI and waist circumference. Systolic blood pressure was highest in African Americans and non–Mexican-American Latinos, whereas diastolic blood pressure was highest only in non–Mexican-American Latinos.

Fasting insulin levels were highest in African Americans and non–Mexican-American Latinos. Although fasting plasma glucose levels were similar among all of the minority ethnic groups, the prevalence of impaired fasting glucose was similar among non-Hispanic whites, non–Mexican-American Latinos, Chinese Americans, and Japanese Americans. HDL levels were highest among Japanese-American and Chinese-American women, whereas triglyceride levels were highest in non–Mexican-American Latinos. Estradiol levels were similar among non-Hispanic whites, African Americans, non–Mexican-American Latinos, and Japanese Americans.

On average, all groups consumed >55 g of fat per day. The percent of calories from fat was lowest in Chinese Americans and Japanese Americans. Chinese-American women consumed the largest amount of dietary fiber and were most likely to abstain from use of alcohol and tobacco. The physical activity index of sports was lowest in non–Mexican-American Latinos. Active living scores were lowest in African Americans, and the household caregiving score were lowest in non–Mexican-American Latinos and Chinese Americans. Non–Mexican-American Latino women had the highest perceived stress scores.

Insulin sensitivity

Ethnic-specific models were used to gain a better understanding of differences in HOMA%S between non-Hispanic whites and each of the four ethnic groups (Table 2). The models presented are stratified by the number of factors comprising the metabolic syndrome. African Americans had lower HOMA%S than non-Hispanic whites after correcting for waist circumference, presence of impaired fasting glucose, triglycerides, HDL, smoking status, alcohol consumption, and sports index in the final model (76.8 vs. 88.6%, $P < 0.0001$). HOMA%S values in non–Mexican-American Latinos did not differ from those in non-Hispanic whites, either before or after adjustment for differences in waist circumference and BMI. In unadjusted models, Chinese Americans and Japanese Americans had similar levels of HOMA%S as non-Hispanic whites. However, after correcting for the large differences in waist circumference and presence of impaired fasting glucose in the first model presented in Table 2, Japanese Americans and Chinese Americans were less insulin sensitive than their site-matched non-Hispanic whites (104.1 vs. 116.5%, $P = 0.0012$ and 94.2 vs. 101.8%, $P = 0.045$, respectively). The observed ethnic difference for Japanese Americans disappeared after adjusting for triglyceride levels. The difference for Chinese Americans disappeared after adjusting for estradiol and triglycerides. Estradiol was not a significant covariate in any of the other ethnic group comparisons.

β-Cell function

Ethnic-specific models were used to gain a better understanding of differences in HOMA%β between non-Hispanic whites and each of the four ethnic groups (Table 3). African Americans had higher levels of HOMA%β when compared with non-Hispanic whites after controlling for site, alcohol consumption, and factors used to define the metabolic syndrome: waist circumference, prevalence of impaired fasting glucose, and triglycerides (108.2 vs. 99.9%, $P < 0.0001$). Chinese Americans and Japanese Americans had lower levels of HOMA%β than non-Hispanic whites after controlling for waist circumference, prevalence of impaired fasting glucose, triglycerides, and amount of alcohol consumed (89.0 vs. 98.3%, $P = 0.0011$ and 84.0 vs. 91.2%, $P = 0.0025$, respectively). No difference in HOMA%β was observed between non–Mexican-American Latino and non-Hispanic white women. Estradiol was not a significant covariate in any of the ethnic group comparisons.

CONCLUSIONS — This large multiethnic community representative cohort of premenopausal and early perimenopausal women demonstrates that ethnic differences in insulin sensitivity and β-cell function exist between non-Hispanic whites and Chinese-American, Japanese-American, and African-American women. Chinese-American, Japanese-American, and African-American women have decreased insulin sensitivity when compared with non-Hispanic white women. To maintain normoglycemia in the presence of this decrease in insulin sensitivity, African-American women have a compensatory increase in β-cell function, whereas Chinese Americans and Japanese Americans do not. Non–Mexican-American Latino women had similar levels of insulin sensitivity and β-cell function as non-Hispanic white women. These data suggest that initial type 2 diabetes prevention strategies for African-American women should target their decreased insulin sensitivity, whereas strategies for Japanese-American and Chinese-American women may need to initially target both decreased insulin sensitivity and β-cell function. Progressive loss of β-cell function in the phase of decreased insulin sensitivity among these ethnic groups will put them at higher risk for type 2 diabetes over time. Previous studies of Mexican-American populations may not be applicable to non–Mexican-American Latino women.

Few studies have assessed ethnic differences in insulin sensitivity and β-cell function between Asian-American populations and non-Hispanic whites. Two non–population-based studies assessing ethnic differences in insulin sensitivity found conflicting results (19,20). In agreement with our study, Chiu's study demonstrated that Asians were less insulin sensitive than non-Hispanic whites by directly measuring insulin sensitivity using a hyperglycemic clamp (19,21). However, opposite results were found in the Japanese-American population enrolled in the Genetics of Non-Insulin Dependent Diabetes Mellitus (GENNID) Study. The cohort of 66 nondiabetic first-degree relatives of subjects with type 2 diabetes was found to be more insulin sensitive than non-Hispanic whites as assessed by the original HOMA model (20). The lack of agreement with our study may be due to the differences in the composition of the Japanese cohort. Unlike the GENNID study, our cohort is a community representative sample of premenopausal and early perimenopausal women that seem to be younger (46 vs. 54 years) and leaner (23 vs. 25 kg/m^2) than the GENNID cohort (20,22). At the present time, we are unaware of any other population-based study assessing ethnic differences in insulin sensitivity between Chinese Americans and non-Hispanic whites.

The difference in insulin sensitivity between Japanese Americans, Chinese

Table 2—*Ethnic-specific ANCOVA models for HOMA%S*

Ethnic comparison of adjusted HOMA%S (mean with 95% CI)			Variables in model	*P*	R^2
African Americans		Non-Hispanic whites			
76.6 (74.2–79.0)	vs.	84.7 (82.3–87.1)	<3 factors	<0.0001	0.39
			Ethnicity	0.0004	
			Site	<0.0001	
			Waist circumference	<0.0001	
			Presence of impaired fasting glucose		
76.8 (74.3–79.4)	vs.	88.6 (86.0–91.3)	≥3 factors		
			Ethnicity	<0.0001	0.45
			Site	0.0002	
			Waist circumference	<0.0001	
			Presence of impaired fasting glucose	<0.0001	
			log Triglycerides	<0.0001	
			HDL	0.0196	
			Smoking status	<0.0001	
			Alcohol	0.0017	
			Sports index	0.0197	
Non–Mexican-American Latinos		Non-Hispanic whites			
66.6 (61.7–72.0)	vs.	70.6 (63.5–78.6)	<3 factors		
			Ethnicity	0.39	0.21
			Waist circumference	<0.0001	
			BMI	0.0098	
Japanese Americans		Non-Hispanic whites			
104.1 (99.6–108.7)	vs.	116.5 (110.8–122.6)	<3 factors	0.0012	0.35
			Ethnicity	<0.0001	
			Waist circumference	0.046	
			Presence of impaired fasting glucose		
107.0 (102.5–111.7)	vs.	113.8 (108.2–119.9)	≥3 factors		0.39
			Ethnicity	0.084	
			Waist circumference	<0.0001	
			Presence of impaired fasting glucose	0.042	
			log Triglycerides	<0.0001	
Chinese Americans		Non-Hispanic whites			
94.2 (89.6–99.3)	vs.	101.8 (99.6–107.4)	<3 factors	0.045	0.38
			Ethnicity	<0.0001	
			Waist circumference	0.0100	
			Presence of impaired fasting glucose		
95.8 (91.2–100.7)	vs.	99.7 (94.5–105.2)	≥3 factors		0.41
			Ethnicity	0.30	
			Waist circumference	<0.0001	
			Presence of impaired fasting glucose	0.031	
			log triglycerides	0.0001	
			Estradiol	0.0066	

Ethnic-specific models were generated. Variables in the model were added sequentially and addition terminated when ethnicity was no longer significant. The models presented are stratified by the number of factors characterizing the metabolic syndrome (<3 or ≥3) included in the model.

Americans, and non-Hispanic whites persisted after correcting for waist circumference and the presence of impaired fasting glucose. In Japanese-American women, this difference was lost after serum triglycerides were added to the model. In Chinese-American women, differences in insulin sensitivity were lost after the inclusion of triglycerides and estradiol. Decreased insulin sensitivity is known to increase hepatic VLDL production, thus leading to an increase in serum triglycerides (23,24). HOMA%S and serum triglycerides were significantly correlated in our study ($R = -0.39$). The inclusion of serum triglycerides into the model indirectly corrected for differences in insulin sensitivity between the two groups. This led to the loss of ethnic differences and suggests that decreased insulin sensitivity may be an integral part of the metabolic syndrome in these populations (25).

β-Cell function varies quantitatively as a function of insulin resistance; hence,

Table 3—*Ethnic-specific ANCOVA for HOMA%β*

Ethnic comparison of adjusted HOMA%β			Variables in model	*P*	R^2
African Americans		Non-Hispanic whites			
108.2 (105.8–110.7)	vs.	99.9 (97.8–101.9)	Ethnicity	<0.0001	0.24
			Site	0.097	
			Waist circumference	<0.0001	
			Presence of impaired fasting glucose	<0.0001	
			log Triglycerides	<0.0001	
			Alcohol consumption	<0.0001	
Non–Mexican-American Latinos		Non-Hispanic whites			
124.8 (118.1–131.7)	vs.	120.5 (111.7–129.9)	Ethnicity	0.46	0.11
			Waist circumference	<0.0001	
Japanese Americans		Non-Hispanic whites			
84.0 (81.3–86.9)	vs.	91.2 (87.8–94.8)	Ethnicity	0.0025	0.25
			Waist circumference	<0.0001	
			Presence of impaired fasting glucose	0.0001	
			log Triglycerides	0.0002	
			Alcohol consumption	0.0013	
Chinese Americans		Non-Hispanic whites			
89.0 (85.2–92.9)	vs.	98.3 (94.7–102.1)	Ethnicity	0.0011	0.31
			Age	0.0042	
			Waist circumference	<0.0001	
			Presence of impaired fasting glucose	<0.0001	
			log Triglycerides	0.0091	
			Alcohol consumption	0.0190	

Data are means (95% CI). Ethnic-specific models were generated. Variables in the model were added sequentially and addition terminated when ethnicity was no longer significant.

low insulin sensitivity is associated with a compensatory increase in β-cell function to maintain normoglycemia. Our Asian cohorts, despite having lower levels of insulin sensitivity, maintained normoglycemia with lower levels of β-cell function. In contrast to our findings, both the GENNID study and the study by Chiu et al. (19) failed to demonstrate a difference in β-cell function between their Asian cohorts and the non-Hispanic white control subjects. Both of these studies directly measured β-cell function and corrected for differences in insulin sensitivity between the groups. Correcting for differences in insulin sensitivity between groups is important in assessing potential differences in β cell-function (26). We could not adjust β-cell function for insulin sensitivity because the fasting glucose and insulin values used to calculate HOMA%β were the same as those used to calculate HOMA%S. Although we could not correct for differences in insulin sensitivity, the expected compensatory increase in β-cell function observed in our African-American cohort was not seen in either Chinese-American or Japanese-American women. The differences in β-cell function we observed persisted after correcting for components of the metabolic syndrome that have been correlated with decreased insulin sensitivity. Therefore, our findings of decreased insulin sensitivity, combined with the lack of compensatory increase in β-cell function, may help explain why Asians are at an increased risk for type 2 diabetes at lower levels of obesity than non-Hispanic whites (27,28). In these Asian populations, the β-cells may lose their ability to compensate for the decrease in insulin sensitivity seen with the development of central adiposity. Loss of β-cell function has been demonstrated to appear before the development of the obesity-induced decreased insulin sensitivity among subpopulations of Japanese and Japanese Americans who develop type 2 diabetes (29,30). However, the technical and/or physiological basis for the observed difference in our Asian cohort remain to be explored.

Differences in insulin sensitivity and β-cell function between non-Hispanic whites and various Latino subgroups remain to be determined. Our findings suggest that data obtained from previous studies may not be applicable to other Latinos as a group, particularly the findings that Latinos of Mexican (San Antonio, TX) and Spanish (San Luis Valley, CO) origin are less insulin sensitive than non-Hispanic whites (31,32). These findings may have been inappropriately extrapolated to other non–Mexican-American Latino subgroups, as studies in other Latino subgroups are limited. A single community-based study of Cubans (Dade County, FL) suggested that they were less insulin sensitive than non-Hispanic whites (33). Unlike Mexican Americans, the non–Mexican-American Latinos in our cohort had similar levels of β-cell function to non-Hispanic whites. It is unclear whether potential differences in β-cell function truly exist between the San Luis Valley Latinos of Spanish descent and non-Hispanic whites, because the original studies did not take into account differences in insulin sensitivity between the two groups (32). Our inability to find differences in insulin sensitivity and β-cell function between the non-Hispanic whites and non–Mexican-American Latinos suggests that our cohorts were not different.

The characterization of Latinos as a single population has been criticized for being an oversimplification of a large heterogeneous group. Their grouping of Latinos into a single category may mask substantial differences between subgroups (34). Data from the Hispanic Health and Nutrition Examination Survey 1982–1984 suggest that differences in the prevalence of diabetes between Cubans and Puerto Ricans/Mexican Americans exist (35). For the group aged 45–74 years, the total weighted age- and sex-adjusted prevalence (prevalence with 95% CIs) of diabetes for Cubans (15.8% [10.5–21.1]) was similar to that of the non-Hispanic whites (12.0% [10.7–13.2]). However, the prevalence in Cubans was significantly lower than that in both Puerto Ricans (26.1% [22.1–30.1]) and Mexican Americans (23.9% [20.8–27.1]), in whom prevalence was similar. Further studies assessing potential differences between non-Hispanic whites and each Latino subgroup must be performed before definitive conclusions for each specific group could be made.

African Americans have been previously reported to be less insulin sensitive and have greater β-cell function than non-Hispanic whites. Our findings agree with these previous studies, even after correcting for multiple confounders. The persisting difference in insulin sensitivity after correcting for triglycerides suggests that unlike Japanese American and Chinese Americans, African Americans may have other inherent differences in insulin sensitivity that cannot be accounted for by the metabolic syndrome or modifiable risk factors (36). Differences in β-cell function also persisted after correcting for factors associated with the metabolic syndrome and alcohol consumption. These findings suggest that, despite our limitations in correcting β-cell function for insulin sensitivity, the observed β-cell function differences with greater HOMA%β are likely to be valid.

Serum estradiol levels and differences in menopausal status did not seem to confound our results. Serum estradiol level was not a significant covariate in any of the HOMA%β models. It was only significant in one HOMA%S model (Chinese versus non-Hispanic whites). In that comparison, when estradiol was included in the model, all of the factors retained their relative significance. When assessing for differences in the proportion of premenopausal and early perimenopausal women during ethnic-specific comparisons, the only site noted to have a difference was in the Japanese versus non-Hispanic white comparisons (data not shown). In that model, estradiol variation was not significant.

Type 2 diabetes can be prevented or delayed with lifestyle modification (37,38) and pharmacologic therapy (38). Although the risk factors for type 2 diabetes are similar among ethnically diverse populations (39,40), ethnic differences in insulin sensitivity and β-cell function among individuals without type 2 diabetes are important because they will influence diabetes prevention strategies.

Acknowledgments— SWAN was funded by the National Institute on Aging, the National Institute of Nursing Research, and the Office of Research on Women's Health of the National Institutes of Health. Supplemental funding was received from the National Institute of Mental Health, the National Institute on Child and Human Development, the National Center on Complementary and Alternative Medicine, and the Office of AIDS Research (U01-AG12546, U01-AG12553, U01-NR04061, U01-AG12531, U01-AG12505, U01-AG12554, U01-A12539, U01-AG12535, U01-AG12546). J.I.T. was supported by NIH Grant HD-01457 as a BIRCWH Scholar.

We thank the study staff at each site and all the women who participated in SWAN. We also thank Dr. Jonathan Levey and Dr. David Matthews, from the Oxford Centre of Diabetes, Endocrinology and Metabolism at the Radcliffe Infirmary in Oxford, U.K., for providing the software for the HOMA calculations and for giving advice on the limitations of the model.

References

1. Bergman RN: Lilly lecture 1989: toward physiological understanding of glucose tolerance: minimal-model approach. *Diabetes* 38:1512–1527, 1989
2. Saad MF, Knowler WC, Pettitt DJ, Nelson RG, Charles MA, Bennett PH: A two-step model for development of non-insulin-dependent diabetes. *Am J Med* 90:229–235, 1991
3. Pimenta W, Korytkowski M, Mitrakou A, Jenssen T, Yki-Jarvinen H, Evron W, Dailey G, Gerich J: Pancreatic beta-cell dysfunction as the primary genetic lesion in NIDDM: evidence from studies in normal glucose-tolerant individuals with a first-degree NIDDM relative. *JAMA* 273:1855–1861, 1995
4. Eriksson J, Franssila-Kallunki A, Ekstrand A, Saloranta C, Widen E, Schalin C, Groop L: Early metabolic defects in persons at increased risk for non-insulin-dependent diabetes mellitus. *N Engl J Med* 321:337–343, 1989
5. Haffner SM, Miettinen H, Gaskill SP, Stern MP: Decreased insulin secretion and increased insulin resistance are independently related to the 7-year risk of NIDDM in Mexican-Americans. *Diabetes* 44:1386–1391, 1995
6. Haffner SM, D'Agostino R, Saad MF, Rewers M, Mykkanen L, Selby J, Howard G, Savage PJ, Hamman RF, Wagenknecht LE, Bergman RN: Increased insulin resistance and insulin secretion in nondiabetic African-Americans and Hispanics compared with non-Hispanic whites: the Insulin Resistance Atherosclerosis Study. *Diabetes* 45:742–748, 1996
7. U.S. Census Bureau Census 2000 Summary File 1 [article online]. Available from http://factfinder.census.gov/servlet/QTTable?ds_name=D&geo_id=D&qr_name=DEC_2000_SF1_U_QTP3&_lang=en. Accessed March 2003
8. Sowers MF, Crawford SL, Sternfeld B, Morganstein D, Gold EB, Greendale G, Evans D, Neer R, Matthews K, Sherman S, Lo A, Weiss F, Kelsey J: SWAN: a multicenter, multi-ethnic, community-based cohort study of women and the menopausal transition. In *Menopause: Biology and Pathobiology*. Lobo RA, Kelsey J, Marcus R, Eds. San Diego, Academic Press, 2000, p. 175–188
9. Huang MH, Schocken M, Block G, Sowers M, Gold E, Sternfeld B, Seeman T, Greendale GA: Variation in nutrient intakes by ethnicity: results from the Study of Women's Health Across the Nation (SWAN). *Menopause* 9:309–319, 2002
10. Hu FB, Manson JE, Stampfer MJ, Colditz G, Liu S, Solomon CG, Willett WC: Diet, lifestyle, and the risk of type 2 diabetes mellitus in women. *N Engl J Med* 345:790–797, 2001
11. Hanson RL, Pratley RE, Bogardus C, Narayan KM, Roumain JM, Imperatore G, Fagot-Campagna A, Pettitt DJ, Bennett PH, Knowler WC: Evaluation of simple indices of insulin sensitivity and insulin secretion for use in epidemiologic studies. *Am J Epidemiol* 151:190–198, 2000
12. Bonora E, Targher G, Alberiche M, Bonadonna RC, Saggiani F, Zenere MB, Monauni T, Muggeo M: Homeostasis model assessment closely mirrors the glucose clamp technique in the assessment of insulin sensitivity: studies in subjects with various degrees of glucose tolerance and insulin sensitivity. *Diabetes Care* 23:57–63, 2000
13. Rudenski AS, Matthews DR, Levy JC, Turner RC: Understanding "insulin resis-

tance": both glucose resistance and insulin resistance are required to model human diabetes. *Metabolism* 40:908–917, 1991
14. Rudenski AS, Hosker JP, Burnett MA, Matthews DR, Turner RC: The beta cell glucose stimulus-response curve in normal humans assessed by insulin and C-peptide secretion rates. *Metabolism* 37: 526–534, 1988
15. Hermans MP, Levy JC, Morris RJ, Turner RC: Comparison of tests of beta-cell function across a range of glucose tolerance from normal to diabetes. *Diabetes* 48: 1779–1786, 1999
16. Hermans MP, Levy JC, Morris RJ, Turner RC: Comparison of insulin sensitivity tests across a range of glucose tolerance from normal to diabetes. *Diabetologia* 42: 678–687, 1999
17. Levy JC, Matthews DR, Hermans MP: Correct homeostasis model assessment (HOMA) evaluation uses the computer program. *Diabetes Care* 21:2191–2192, 1998
18. Executive Summary of The Third Report of The National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol In Adults (Adult Treatment Panel III). *JAMA* 285:2486–2497, 2001
19. Chiu KC, Cohan P, Lee NP, Chuang LM: Insulin sensitivity differs among ethnic groups with a compensatory response in β-cell function. *Diabetes Care* 23:1353–1358, 2000
20. Jensen CC, Cnop M, Hull RL, Fujimoto WY, Kahn SE: β-Cell function is a major contributor to oral glucose tolerance in high-risk relatives of four ethnic groups in the U.S. *Diabetes* 51:2170–2178, 2002
21. Chiu KC, Chuang LM, Yoon C: Comparison of measured and estimated indices of insulin sensitivity and beta cell function: impact of ethnicity on insulin sensitivity and beta cell function in glucose-tolerant and normotensive subjects. *J Endocrinol Metab* 86:1620–1625, 2001
22. Raffel LJ, Robbins DC, Norris JM, Boerwinkle E, DeFronzo RA, Elbein SC, Fujimoto W, Hanis CL, Kahn SE, Permutt MA, Chiu KC, Cruz J, Ehrmann DA, Robertson RP, Rotter JI, Buse J: The GENNID study: a resource for mapping the genes that cause NIDDM. *Diabetes Care* 19: 864–872, 1996
23. Ruotolo G, Howard BV: Dyslipidemia of the metabolic syndrome. *Curr Cardiol Rep* 4:494–500, 2002
24. Adeli K, Taghibiglou C, Van Iderstine SC, Lewis GF: Mechanisms of hepatic very low-density lipoprotein overproduction in insulin resistance. *Trends Cardiovasc Med* 11:170–176, 2001
25. World Health Organization: *Definition, Diagnosis and Classification of Diabetes Mellitus and its Complications: Report of a WHO Consultation*. Geneva, World Health Org. (WHO/NCD/99.2), 1999
26. Bergman RN, Ader M, Huecking K, Van Citters G: Accurate assessment of β-cell function: the hyperbolic correction. *Diabetes* 51 (Suppl. 1):S212–S220, 2002
27. Ko GT, Chan JC, Cockram CS, Woo J: Prediction of hypertension, diabetes, dyslipidaemia or albuminuria using simple anthropometric indexes in Hong Kong Chinese. *Int J Obes Relat Metab Disord* 23: 1136–1142, 1999
28. Deurenberg-Yap M, Yian TB, Kai CS, Deurenberg P, van Staveren WA: Manifestation of cardiovascular risk factors at low levels of body mass index and waist-to-hip ratio in Singaporean Chinese. *Asia Pac J Clin Nutr* 8:177–183, 1999
29. Yoshinaga H, Kosaka K: Heterogeneous relationship of early insulin response and fasting insulin level with development of non-insulin-dependent diabetes mellitus in non-diabetic Japanese subjects with or without obesity. *Diabetes Res Clin Pract* 44:129–136, 1999
30. Chen KW, Boyko EJ, Bergstrom RW, Leonetti DL, Newell-Morris L, Wahl PW, Fujimoto WY: Earlier appearance of impaired insulin secretion than of visceral adiposity in the pathogenesis of NIDDM: 5-year follow-up of initially nondiabetic Japanese-American men. *Diabetes Care* 18:747–753, 1995
31. Haffner SM, Stern MP, Watanabe RM, Bergman RN: Relationship of insulin clearance and secretion to insulin sensitivity in non-diabetic Mexican Americans. *Eur J Clin Invest* 22:147–153, 1992
32. Boyko EJ, Keane EM, Marshall JA, Hamman RF: Higher insulin and C-peptide concentrations in Hispanic population at high risk for NIDDM: San Luis Valley Diabetes Study. *Diabetes* 40:509–515, 1991
33. Donahue RP, Bean JA, Donahue RA, Goldberg RB, Prineas RJ: Insulin response in a triethnic population: effects of sex, ethnic origin, and body fat Miami Community Health Study. *Diabetes Care* 20: 1670–1676, 1997
34. Hajat A, Lucas JB, Kington R: Health outcomes among Hispanic subgroups: data from the National Health Interview Survey, 1992–95. *Adv Data* 25:1–14, 2000
35. Flegal KM, Ezzati TM, Harris MI, Haynes SG, Juarez RZ, Knowler WC, Perez-Stable EJ, Stern MP: Prevalence of diabetes in Mexican Americans, Cubans, and Puerto Ricans from the Hispanic Health and Nutrition Examination Survey, 1982–1984. *Diabetes Care* 14:628–638, 1991
36. Brancati FL, Kao WH, Folsom AR, Watson RL, Szklo M: Incident type 2 diabetes mellitus in African American and white adults: the Atherosclerosis Risk in Communities Study. *JAMA* 283:2253–2259, 2000
37. Tuomilehto J, Lindstrom J, Eriksson JG, Valle TT, Hamalainen H, Ilanne-Parikka P, Keinanen-Kiukaanniemi S, Laakso M, Louheranta A, Rastas M, Salminen V, Uusitupa M: Prevention of type 2 diabetes mellitus by changes in lifestyle among subjects with impaired glucose tolerance. *N Engl J Med* 344:1343–1350, 2001
38. Knowler WC, Barrett-Connor E, Fowler SE, Hamman RF, Lachin JM, Walker EA, Nathan DM: Reduction in the incidence of type 2 diabetes with lifestyle intervention or metformin. *N Engl J Med* 346:393–403, 2002
39. Haffner SM, Miettinen H, Stern MP: Are risk factors for conversion to NIDDM similar in high and low risk populations? *Diabetologia* 40:62–66, 1997
40. Edwards KL, Burchfiel CM, Sharp DS, Curb JD, Rodriguez BL, Fujimoto WY, LaCroix AZ, Vitiello MV, Austin MA: Factors of the insulin resistance syndrome in nondiabetic and diabetic elderly Japanese-American men. *Am J Epidemiol* 147:441–447, 1998