Risk Factor Clustering in the Insulin Resistance Syndrome and its Relationship to Cardiovascular Disease in Postmenopausal White, Black, Hispanic, and Asian/Pacific Islander Women

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The aim of this study was to examine how major components of the insulin resistance (IR) syndrome relate to each other and to cardiovascular disease (CVD) in postmenopausal women in 4 ethnic groups. Baseline data from the Women's Health Initiative (WHI) on 3,083 50- to 79-year-old women (1,635 white, 802 black, 390 Hispanic, and 256 Asian/Pacific Islander) were examined. Participants underwent a personal interview and a physical examination, blood samples were drawn, and a detailed cardiovascular history was ascertained. Factor analysis was used to assess the clustering and interdependence of groups of CVD-related IR syndrome variables. Four factors were identified. An obesity factor included IR in all groups and had a significant association with CVD in white ($P = .0001$) and Hispanic ($P = .0024$) women. A dyslipidemia factor (high-density lipoprotein [HDL], triglycerides, and HDL_2: total HDL ratio) also included insulin and IR and was significantly correlated with CVD in black ($P = .0006$) and Hispanic ($P = .0217$) women and had a borderline association in white women ($P = .068$). Total and low-density lipoprotein (LDL) cholesterol did not relate to CVD in any group. Blood pressure was related weakly to CVD in white women ($P = .0434$) and strongly in black women ($P = .0095$). Components of the IR syndrome appear to be associated with CVD in postmenopausal women, although the magnitude of these relationships differed by ethnicity.

THE INSULIN RESISTANCE (IR), or metabolic, syndrome, has been proposed to include a set of metabolic characteristics, of which central obesity, hyperinsulinemia, glucose intolerance, hypertriglyceridemia, and a reduced concentration of high-density lipoprotein (HDL) cholesterol are the predominant components.[1] Other manifestations that have been proposed include hypertension; a preponderance of small, dense low-density lipoprotein (LDL); albuminuria; elevated plasminogen activator inhibitor 1 (PAI-1), and increased uric acid concentrations.[2] It is important to understand IR and its metabolic components because it is a precursor of both diabetes and cardiovascular disease (CVD).[3-5] Not all of the features of the IR syndrome are necessarily expressed in any one individual. There may be ethnic differences in the expression of components in this syndrome. For example, hypertension has been consistently associated with IR in whites, but not in American Indians or African Americans.[6]

CVD is the leading cause of death in women, and CVD risk increases steadily with age.[7,8] This increase may be explained, in part, by the menopausal decline in estrogen, a hormone which increases HDL, lowers LDL, and may reduce central fat distribution.[9-11] IR is associated with lower estrogen concentrations[12] and therefore increases after menopause. IR is associated with hypertension, dyslipidemia, and other abnormalities in risk factors that greatly increase CVD risk. It is therefore important to examine IR, its associated metabolic changes, and its relationship to CVD in postmenopausal women.

Traditional analyses have examined the relationship between insulin and each of the risk factors individually associated with CVD, because many of these metabolic abnormalities correlate with each other. However, it is of value to identify and quantify the interrelationships among these metabolic changes to determine how they relate to subsequent disease development. An understanding of how these metabolic components interrelate within populations or different age groups may further our understanding of how and why the IR syndrome predicts atherosclerosis and to what extent it is important.

One statistical method that can be used to evaluate the interdependence of variables is factor analysis.[13,14] This technique is used to reduce the number of variables and to quantify the relationships between variables. Factor analysis has been applied to constituents of the IR syndrome in several age/gender/ethnic groups, but little information is available for postmenopausal women. Factor analysis of IR was used in studies of a small population of white women in California,[15] middle-aged white men and women from the Framingham and Kuopio studies,[16-18] American Indian men and women from the Strong Heart Study,[19] elderly white men and women from the Cardiovascular Health Study,[20] men from the Risk Indicators in a Screened Cohort (RISC) studies,[21-23] Honolulu Heart Study Japanese,[24] black and white young people from the Bogalusa Heart Study,[25] and men and women from Mauritius,[26] Micro-

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Submitted July 3, 2002; accepted September 24, 2002.

Supported by Contract No. N01-WH-4-2123 from the National Heart, Lung, and Blood Institute, National Institutes of Health.

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0026-0495/03/5203-0015$30.00/0

doi:10.1053/meta.2003.50057

nesia,[27] southern India,[28] and Kinmen, China.[29] None of these, however, focused on IR in menopause. The Women's Health Initiative (WHI) affords the unique opportunity to examine IR and its manifestations in a large group of postmenopausal women from 4 ethnic groups. We therefore have examined the data from the baseline examination of the WHI, using factor analysis, to consider how the major components of the IR syndrome associate with one another and with CVD in postmenopausal white, black, Hispanic, and Asian/Pacific Islander women. Although there was no direct measure of IR, fasting glucose and insulin values were used to estimate IR using the homeostasis model assessment (HOMA).

MATERIALS AND METHODS

Study Population

Participants in this study were those enrolled in the WHI clinical trials of diet modification and hormone replacement therapy. These trials were approved by an institutional review committee, and all participants gave informed consent. The study protocol conformed to the ethical guidelines of the 1975 Declaration of Helsinki. The WHI is an ongoing study of major health issues in postmenopausal women. A more detailed description of the overall study and experimental design has been published previously.[30] A total of 68,135 women are enrolled in one or both of the clinical trials. Participants ranged in age from 50 to 79 years and were recruited from 40 clinical centers throughout the United States. Exclusion criteria for the hormone trial included history of breast cancer, an acute cardiovascular event in the previous 6 months, invasive cancer in the past 10 years, current use of hormone replacement therapy or oral corticosteroids, and mental illness or other factors that would preclude informed consent. Exclusion criteria for the diet trial included eating $\geq$ 10 meals per week outside the home, previous diagnosis of breast or colon cancer, type 1 diabetes, gastrointestinal conditions that contraindicated a high-fiber diet, and current consumption of a diet containing $<$ 32% of energy from fat.

Sample Selection

Six percent of women who enrolled in the clinical trial components were randomly selected to have their blood analyzed for lipids, glucose, insulin, fibrinogen, and other dietary analytes. The sampling procedure was random and stratified by clinical center, age, hysterectomy status, and ethnicity to over-sample minority women. For this analysis, women with a self-reported history of a diagnosis of diabetes or women taking insulin or oral hypoglycemic agents were excluded. The data set for analysis included 1,635 white women, 802 black women, 390 Hispanic women, and 256 Asian/Pacific Islander women (total 3,083). There was an insufficient number of American Indian women (42) to include in the analysis.

Clinical Examinations

The WHI baseline examinations included interviewer- and self-administered questionnaires, physical measurements, and a fasting blood sample. Clinical measurements included weight and height. Body mass index (BMI) was calculated as weight in kilograms divided by height in meters squared (weight [kg]/height [m]^2). Overweight was defined as BMI $\geq$ 25 kg/m^2 and obesity was defined as BMI $\geq$ 30 kg/m^2. Waist circumference was measured, with the participant standing, at the natural waist or narrowest part of the torso; hip circumference was measured at the maximal circumference. A blood sample was collected after a 12-hour fast. Participants were asked not to take aspirin or nonsteroidal anti-inflammatory drugs for 48 hours before the visit, to refrain from smoking at least 1 hour before the blood draw, and not to perform any vigorous physical activity for at least 12 hours before the blood draw. Blood was processed at each clinical center, and plasma and serum aliquots frozen at -70° F within 2 hours.

Two consecutive measurements of blood pressure using the first and fifth Korotkoff sounds were performed with the participants seated, after 5 minutes of rest, on the right arm using the appropriate size cuff with a mercury sphygmomanometer. The mean of the 2 measurements was used to estimate blood pressure.

Self-report questionnaires included assessment of demographic factors, medical and reproductive history, and health habits. Information on the use and dose of all current medications, including hormones, was ascertained by an interviewer-administered questionnaire. Use of vitamins and supplements was also assessed.

Participants were designated as having had a myocardial infarction (MI) if they had a positive response to the question, "Has a doctor said that you have had a heart attack?" or if their baseline 12 lead electrocardiogram, which was evaluated using Minnesota coding at a central reading center, showed major or moderate Q waves, minor Q waves with ST-T abnormalities, or isolated profound or major ST-T abnormalities. Presence of CVD was ascertained if the participant had had an MI, was taking pills for angina, or reported a doctor's confirmation of stroke, cardiac arrest, congestive heart failure, coronary bypass operation, angioplasty of the coronary arteries, or carotid endarterectomy.

Blood specimens were analyzed by Medical Research Laboratories (Highland Heights, KY). Cholesterol and triglycerides were analyzed by enzymatic methods on a Hitachi 747 analyzer (Boehringer Mannheim Diagnostics, Indianapolis, IN) as previously described.[31] HDL cholesterol was isolated using heparin/manganese chloride.[32] HDL_2 and HDL_3 were determined using a dextran sulfate/$MgCl_2$ precipitation procedure.[33] Lipid assays were certified by the National Heart, Lung, and Blood Institute (NHLBI) Centers for Disease Control (CDC) control part III program.[34] Glucose was measured using the hexokinase method[35,36] on the Hitachi 747 analyzer; interassay coefficients of variation were $<$ 2%. Insulin was measured using a stepwise sandwich enzyme-linked immunosorbent assay (ELISA) procedure;[37] interassay coefficients of variation were 3.2% to 9.5%. Fibrinogen was measured using a turbidimetric assay;[38] coefficients of variation were 2.3% to 3.6%. Factor VII activity was measured using a turbidometric assay;[39] coefficients of variation were 4% to 7.8%.

Statistical Analyses

IR was estimated using the HOMA, which uses fasting insulin and glucose measures.[40] IR was calculated as fasting insulin (μU/mL) $\times$ fasting glucose (mmol/L)/22.5. A ratio of HDL_2/total HDL was used as a measure of HDL size distribution.

All analyses were restricted to participants with known measurements of BMI, hip circumference, waist circumference, systolic and diastolic blood pressure, insulin, glucose, fibrinogen, HDL cholesterol, HDL_2, LDL cholesterol, and factor VII activity. This resulted in 1,635 white women, 802 black women, 390 Hispanic women, and 256 Asian/Pacific Islander women for a total of 3,083 of the 3,446 women available for analyses. Frequencies and means before restricting the dataset were all similar to the complete case, except for prevalence of CVD, which was about 8% higher in the unrestricted dataset.

Descriptive analyses, in the form of means and cross-tabulations, were performed to examine the association between ethnicity and demographic, medication use, and metabolic characteristics in the clinical trial blood analyte subsample. Triglyceride, HDL cholesterol, glucose, insulin, and IR values were all log transformed for analyses because their distribution was skewed.

Age-adjusted Pearson correlations by ethnicity were performed for initial assessment of association between variables. These relationships

Table 1. Demographic and Metabolic Characteristics by Ethnicity

Characteristic	White (n = 1,635)		Black (n = 802)		Hispanic/Latino (n = 390)		Asian/Pacific Islander (n = 256)		Total (N = 3,083)	
	%/Mean	SD	%/Mean	SD	%/Mean	SD	%/Mean	SD	%/Mean	SD
Age at screening (yr)	63.1	6.9	61.0	6.9	60.2	6.4	62.7	7.2	62.1	7.0
BMI (kg/m^2)	28.5	5.6	31.6	6.5	29.7	5.4	25.6	4.5	29.2	6.0
Waist (cm)	88	13.7	92	13.1	88	12.2	80	10.5	88	13.5
Hip (cm)	108	11.7	112	12.9	107	12.2	97	9.3	108	12.5
Hormone use										
Never	43.3		49.9		46.8		41.4		45.4	
Past	28.7		31.0		28.1		26.6		29.0	
Current	28.0		19.1		25.2		32.0		25.6	
History of MI	8.0		10.2		8.5		8.5		8.7	
History of CVD	12.7		14.6		10.6		11.1		12.8	
Family history of MI	49.8		42.5		43.4		37.1		46.1	
Blood pressure (mm Hg)										
Systolic	127	17.8	131	17.5	125	16.1	128	17.6	128	17.6
Diastolic	75	9.1	78	8.8	75	8.9	77	9.4	76	9.1
Triglyceride (mg/dL)*	136	59.0	107	44.2	145	58.7	142	60.7	129	56.9
LDL cholesterol (mg/dL)	136	34.6	139	38.6	135	33.4	130	33.1	136	35.5
Total cholesterol (mg/dL)*	225	37.2	222	41.3	221	35.5	221	34.1	223	37.9
HDL cholesterol (mg/dL)*	57	14.6	57	13.8	53	12.1	58	14.2	57	14.1
HDL distribution, HDL_2/HDL-C	0.31	0.1	0.31	0.1	0.29	0.1	0.31	0.1	0.31	0.1
Glucose (mg/dL)*	94.9	12.2	96.4	15.2	96.9	17.5	98.5	14.3	95.9	14.0
Insulin (μU/mL)*	9.3	4.4	11.6	5.5	11.2	5.6	8.8	4.1	10.1	4.9
Fibrinogen (mg/dL)	301	57.5	319	63.1	312	67.1	294	55.8	306	60.7
Factor VI activity, antigen (%)	130	31.8	113	26.5	123	27.8	127	27.7	124	30.5
Insulin resistance*†	2.2	1.2	2.8	1.5	2.7	1.6	2.1	1.2	2.4	1.3

NOTE. SI conversion factors: 0.02586 for cholesterol, 0.01129 for triglycerides, 0.05551 for glucose, 7.175 for insulin, and 0.01 for fibrinogen.

Abbreviations: BMI, body mass index; MI, myocardial infarction; CVD, cardiovascular disease, includes prior history of MI, an ECG with Novacodes 5.1-5.6 (abnormality), stroke, cardiac arrest, congestive heart failure, coronary bypass surgery, angioplasty, carotid endarterectomy or taking pills for angina; LDL, low-density lipoprotein; HDL, high-density lipoprotein.

*Means and standard deviations were computed on the log scale with back-transformed values reported here.

†Insulin resistance was calculated using the HOMA (fasting insulin μU/mL; fasting glucose mmol/L/22.5).

were assessed to determine appropriateness of inclusion in the factor analysis.

Factor analysis, within ethnic groups, was used to identify relationships among several correlated variables in terms of a smaller number of conceptually meaningful, relatively independent factors. The method of principal components (from the Proc Factor procedure within SAS, version 6.12, SAS Institute, Cary, NC) was used for the analysis to obtain orthogonal factors that are linear combinations of the original variables. Factors were then selected based on the criterion of the eigenvalue >1.0 (the Kaiser criterion). Because, within each ethnicity, $N > 250$ and the mean communality (amount of variance on a variable accounted for by the set of factors) is ≥ 0.60, this criterion is accurate for use in selection. This method of factor selection picks the factors that account for large and distinct amounts of variation. After the number of important factors was selected, a Varimax rotation was implemented to simplify the structure of the factors and provide more meaningful solutions. The Varimax rotation is an orthogonal rotation that maintains the independence of the factors and forces each factor to load high on a smaller number of variables and low or very low on the other variables. Rotated factor loadings (see Tables 2 through 5) were examined to determine which variables are most important within each factor. Factor loadings can be interpreted as the Pearson correlation (r) between the original variables and the corresponding factor. A variable that shared $\geq 15\%$ of its variance with the factor was used to help name it (ie, $r^2 \geq 15\%$). This corresponds with selecting variables with loadings greater in absolute value than $r = \sqrt{(0.15)} = 0.4$.

Factor scores were then computed for each factor using Proc Score in SAS to assess associations of the factors with CVD. Factor scores are a weighted sum of the standardized values of the variables used in the factor analysis, where the factor loadings for the associated factor are used as the weights. That is, the standardized values of the variables for each participant are multiplied by the factor loadings and summed to create a factor score for each participant and each factor. The association of the factor scores with CVD within each ethnic group was tested for statistical significance using t tests comparing those with CVD versus those without CVD. All analyses were conducted using the SAS System for Windows version 6.12 (SAS Institute).

RESULTS

Demographic Characteristics

Table 1 shows demographic and metabolic characteristics by ethnic group. Average age was similar in all 4 groups. White, black, and Hispanic women tended to be overweight, with black women having higher BMI and central obesity. Mean BMI and waist circumference for the Asian/Pacific Islander women were at normal levels. Prevalence of MI and CVD were highest in black women.

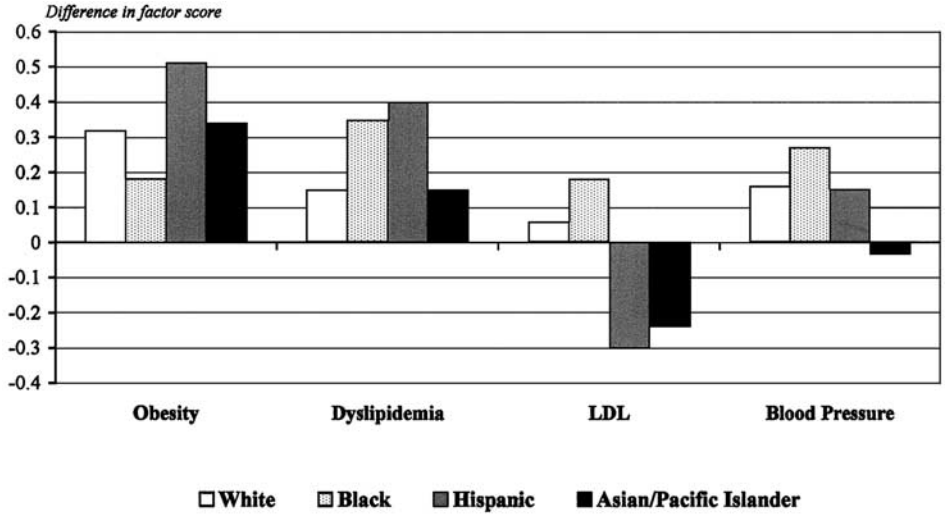

Fig 1. Difference in mean factor scores: Women with CVD *v* women without CVC. Variation in the association of factor scores with CVD, indicated by the difference between scores in women with and without CVD. Significance of the differences are shown in Tables 2 through 5. Data are from 1,635 white, 802 black, 390 Hispanic, and 256 Asian/Pacific Islander women.

Metabolic Characteristics

Blood pressure was highest in black women and lowest in Hispanics. Triglycerides were lowest in black women and HDL lowest in Hispanic women. Total and LDL cholesterol were lower in Asians/Pacific Islanders and Hispanics and highest in blacks. Glucose concentrations were similar in all 4 groups, whereas fasting insulin concentrations and the HOMA estimates of IR were higher in black and Hispanic women.

Analyses of relationships of medication use with IR indicated correlations between IR and the use of antihypertensive medications and estrogen, but not with thyroid, antianginal, or hypolipidemic medications. When individuals on antihypertensive medications, hypolipidemic agents, or estrogen were eliminated from the analysis, no substantive changes occurred (data not shown).

Factor Analysis

Factors and factor headings for white, black, Hispanic, and Asian/Pacific Islander women are shown in Tables 2 through 5. Relationships of factor scores with CVD and MI by ethnic group are also shown in the tables. Differences in factor score between those with or without CVD for each factor by ethnicity is plotted in Fig 1.

White women. Results of the factor analysis for white women are shown in Table 2. An obesity factor was characterized by positive correlations with BMI, waist and hip circumferences, and insulin and IR. The factor accounted for 43.9% of the total variance of all the variables considered, and it was positively associated with evidence of CVD ($P = .0001$). A dyslipidemia factor was characterized by correlations with HDL and its distribution, insulin and IR, and glucose, and negative correlations with triglycerides. This factor accounted for 18.7% of the variance and had only a borderline significant association with CVD ($P = .068$). The LDL factor consisted primarily of total and LDL cholesterol. It accounted for 11.5% of the variance and was not significantly associated with CVD. A blood pressure factor (systolic plus diastolic) accounted for 10.1% of the variance and differed weakly across levels of CVD ($P = .0434$).

Black women. Factor distribution in black women is shown in Table 3. The obesity factor was associated with fibrinogen; this factor accounted for 38.9% of the variance and was not significantly related to CVD. The dyslipidemia factor, which included glucose, accounted for 20.4% of the variance and was strongly associated with CVD ($P = .0006$). The LDL factor accounted for 14.3% of the variance and was not related to CVD. The blood pressure factor accounted for 11.4% of the variance and was significantly associated with CVD ($P = .0095$)

Hispanic women. The factor analysis for Hispanic women is shown in Table 4. The obesity factor accounted for 38.2% of the variance and was significantly related to CVD ($P = .0024$); this factor, however, did not include glucose. The dyslipidemia factor, which included glucose, accounted for 20.1% of the variance and was related to CVD ($P = .0217$). The LDL factor explained 13.6% of the variance, but was not related to CVD. The blood pressure factor accounted for 11.7% of the variance and was not associated with CVD.

Asian/Pacific Islander Women. Factor distribution in Asian/Pacific Islander women, shown in Table 5, was similar to that of Hispanic women except that none were significantly related to CVD. Variation in the association of the factor scores with CVD as indicated by the difference between scores in those with and without CVD is shown in Fig 1. Obesity score was least important in blacks. The dyslipidemia score was most important in blacks and Hispanics, and blood pressure was most important in blacks.

DISCUSSION

Because both CVD and IR increase after menopause, examination of the IR syndrome in postmenopausal women is critically important. Although principal components analysis has been used to evaluate IR in several different populations and age groups,[15-29] this is the first study in which it has been used

Table 2. Age-Adjusted Rotated Factor Loadings for WHI CT Participants in the Blood Analyte Subsample: Whites

	Factors (N = 1,635)			
	Obesity	Dyslipidemia	LDL	Blood Pressure
% Variance explained	43.9	18.7	11.5	10.1
Factor variables				
BMI (kg/m^2)	0.88651	0.07855	0.04175	0.1826
Hip (cm)	0.88361	−0.00806	0.01518	0.14029
Waist (cm)	0.85987	0.15764	0.06411	0.14723
Log insulin resistance	0.66461	0.52643	0.01477	0.01821
Log insulin (μU/mL)	0.64592	0.50257	0.01446	0.02676
Log glucose (mg/dL)	0.40637	0.35475	0.00864	−0.02177
Fibrinogen (mg/dL)	0.32133	0.09845	0.00515	−0.02712
Log HDL cholesterol (mg/dL)	−0.23697	−0.76511	0.03026	0.02155
HDL distribution	−0.0823	−0.74875	0.00201	−0.09119
Log triglyceride (mg/dL)	0.13415	0.68337	0.35007	0.19158
Total cholesterol (mg/dL)	−0.03531	−0.0179	0.98727	0.04015
LDL cholesterol (mg/dL)	0.02337	0.0625	0.93035	−0.03875
Factor VII activity, antigen (%)	0.15405	0.20959	0.28372	0.2353
Blood pressure				
Systolic (mm Hg)	0.07168	0.06338	0.03886	0.86988
Diastolic (mm Hg)	0.0961	0.05434	0.00361	0.8687
Mean Factor Score				
By CVD				
No	11.8	−1.7	6.8	6.7
Yes	12.1	−1.8	6.8	6.9
Δ*	0.32	0.15	0.06	0.16
P value†	.0001	.0680	.4312	.0434
By MI				
No	11.8	−1.6	6.8	6.7
Yes	12.2	−1.8	6.8	6.9
Δ*	0.33	0.20	0.01	0.17
P value†	.0005	.0321	.9154	.0673

NOTE. Highlighted areas show variables with factor loadings > .4. SI conversion factors: 7.175 for insulin, 0.05551 for glucose, 0.01 for fibrinogen, 0.02586 for cholesterol, and 0.01129 for triglycerides.

*Difference in mean factor scores (women with CVD minus women without CVD).

†*P* value from a *t* test of differences in factor scores by CVD or MI status.

to evaluate the IR syndrome and its components in postmenopausal black, Hispanic, or Asian-American women and to compare the results of such an analysis in the 4 major US ethnic groups. Factor analysis contributes in several ways to our understanding of this complex syndrome. It helps with the interpretation of multiple variables by reducing their number, aids in the examination of the interrelationships among related variables, and can facilitate comparison of these variables to diseases of interest.

Four factors were found in all racial groups that accounted for at least 84% of the total variation. The first factor was an obesity factor, which included BMI and waist and hip circumferences. The obesity factor was closely related to insulin concentrations and IR in all ethnic groups. In studies of younger individuals, IR has been closely related to obesity and especially the presence of abdominal fat as reflected by waist measurement.[41-43] These data suggest that body weight and central body fat are also linked to IR in older women. The obesity factor was significantly related to the presence of CVD in white and Hispanic women, but not in black and Asian/Pacific Islander women. A number of previous studies have suggested that obesity might be less strongly related to CVD in blacks[44,45] and American Indians[46] than in whites. The current data are consistent with the previous reports in black women. There were not enough American Indian women in WHI to include in the current analyses, but in similar analysis of American Indian women in the Strong Heart Study, obesity was not related to CVD.[47] For Asian/Pacific Islander women, the lack of association between obesity and CVD may be because there was less obesity in this group. In Hispanics and Asians/Pacific Islanders, fibrinogen concentrations were also found to cluster with this factor. Previous studies have suggested that fibrinogen increases with obesity,[48-50] and the current data suggest that obesity may be related to prothrombotic tendency in some women. This factor included glucose concentration only in whites. Hyperglycemia is caused by IR and β-cell dysfunction. It is possible that IR may play a more predominant role in postmenopausal white women than in other ethnic groups. This possibility must be examined further in metabolic studies.

The second factor is a dyslipidemia factor that comprises HDL concentration, triglyceride concentration, and the ratio of HDL_2 to total HDL. The latter was chosen as an index of HDL size distribution. This factor also included insulin and IR. The

Table 3. Age-Adjusted Rotated Factor Loadings for WHI CT Participants in the Blood Analyte Subsample: Blacks

	Factors (N = 802)			
	Obesity	Dyslipidemia	LDL	Blood Pressure
% Variance Explained	38.9	20.4	14.3	11.4
Factor Variables				
BMI (kg/m^2)	0.91120	0.15798	−0.00259	0.07873
Hip (cm)	0.90231	0.06252	−0.01721	0.06495
Waist (cm)	0.85142	0.28211	0.02817	0.08170
Fibrinogen (mg/dL)	0.45934	−0.03313	−0.01995	−0.06648
Log insulin resistance	0.40449	0.75812	0.09152	0.13095
Log insulin (μU/mL)	0.43539	0.69433	0.06555	0.12473
Log triglyceride (mg/dL)	−0.05797	0.64004	0.37609	0.06816
Log glucose (mg/dL)	0.11405	0.58357	0.12597	0.08621
HDL distribution	0.02935	−0.69425	0.08976	0.03135
Log HDL cholesterol (mg/dL)	−0.02442	−0.71497	0.09409	0.06441
Total cholesterol (mg/dL)	−0.07511	−0.03693	0.98557	0.05003
LDL cholesterol (mg/dL)	−0.04722	0.04865	0.92857	0.00932
Factor VII activity, antigen (%)	0.19719	0.11731	0.24675	−0.06749
Blood pressure				
Systolic (mm Hg)	−0.01096	0.05040	0.00128	0.88855
Diastolic (mm Hg)	0.06337	0.06545	0.00019	0.88840
Mean Factor Score				
By CVD				
No	7.8	3.9	8.9	10.8
Yes	8.0	4.2	9.1	11.1
Δ*	0.18	0.35	0.18	0.27
P value†	.0901	.0006	.1128	.0095
By MI				
No	7.8	3.9	8.9	10.8
Yes	8.0	4.3	9.2	11.1
Δ*	0.20	0.40	0.22	0.34
P value†	.0877	.0007	.0702	.0043

NOTE. Highlighted areas show variables with factor loadings > .4. SI conversion factors: 0.01 for fibrinogen, 7.175 for insulin, 0.01129 for triglycerides, 0.05551 for glucose, and 0.02586 for cholesterol.

*Difference in mean factor scores (women with CVD minus women without CVD).

†*P* value from a *t* test of differences in factor scores by CVD or MI status.

triad of higher triglycerides, reduced HDL, and small dense LDL has been referred to as metabolic dyslipidemia, and this constellation of lipid disorders occurs in individuals with IR and diabetes. It is thought that these lipid disorders have a common metabolic origin.[51] Elevation of very–low-density lipoprotein (VLDL) triglycerides, usually a result of impaired clearance, leads to exchange of triglyceride between VLDL and LDL and HDL. When the latter are acted upon by hepatic lipase, the triglyceride is hydrolyzed, leaving smaller, denser, cholesterol-depleted particles. Thus, the ratio of HDL_2 to total HDL in this analysis may be a reflection of small dense LDL as well. This factor was most strongly related to CVD in blacks and Hispanics, but in whites and Asians/Pacific Islanders, there was a much smaller relationship. This constellation of lipoprotein disorders is related to atherogenesis in several ways. HDL is responsible for reverse cholesterol transport, the process by which cholesterol is transferred from peripheral cells and the vessel wall to the liver for excretion; thus, low concentrations have been consistently associated with increased risk for atherosclerosis.[52,53] Small dense LDL has been linked to the atherosclerotic process because it is more susceptible to oxidation and glycation and more prone to evoke an inflammatory response.[54,55]

Total and LDL cholesterol clustered together as a third factor, which did not relate to the obesity factor, the dyslipidemia factor, or to insulin or IR. This is consistent with other studies and a considerable body of metabolic data that indicate that total cholesterol levels are largely determined by LDL cholesterol concentrations, which, in turn, are determined by both the level of LDL receptor activity and the rate of apolipoprotein B production.[56] The cholesterol factor did not relate to the prevalence of MI or CVD in any of the ethnic groups. The lack of a significant association between the LDL factor and CVD was somewhat surprising. However, some previous prospective epidemiologic studies have suggested that in terms of relative risk, LDL cholesterol is a weaker predictor of subsequent CVD events in women than in men. In the Lipid Research Clinics follow-up study, the relative risk of CVD death per 0.78 mmol/L (30 mg/dL) of LDL cholesterol was 1.48 and highly significant in men.[57] In contrast, in women, the relative risk was only 1.12 and not significant. In a recent Framingham update, in relative terms compared with an LDL

Table 4. Age-Adjusted Rotated Factor Loadings for WHI CT Participants in the Blood Analyte Subsample: Hispanic/Latino

	Factors (N = 390)			
	Obesity	Dyslipidemia	LDL	Blood Pressure
% Variance Explained	38.2	20.1	13.6	11.7
Factor Variables				
BMI (kg/m^2)	0.82908	0.02838	−0.09678	0.18626
Waist (cm)	0.80374	0.17964	−0.05689	0.10709
Hip (cm)	0.80232	−0.03329	−0.05423	0.14694
Log insulin resistance	0.65777	0.55433	−0.09828	−0.03698
Log insulin (μU/mL)	0.64583	0.51197	−0.09304	−0.01697
Fibrinogen (mg/dL)	0.37021	−0.16136	0.16654	−0.08606
Log triglyceride (mg/dL)	−0.06327	0.75035	0.21345	0.14666
Log glucose (mg/dL)	0.37643	0.40714	−0.06588	−0.07498
Factor VII activity, antigen (%)	−0.1662	0.21394	0.18903	0.05759
HDL distribution	−0.03056	−0.69483	0.01195	−0.05507
Log HDL cholesterol (mg/dL)	−0.14572	−0.74249	0.01644	0.00576
Total cholesterol (mg/dL)	−0.07139	0.03283	0.9764	0.03453
LDL cholesterol (mg/dL)	0.01033	0.02816	0.95783	−0.01938
Blood pressure				
Systolic (mm Hg)	0.07398	0.01364	0.05411	0.89373
Diastolic (mm Hg)	0.11822	0.10514	−0.02195	0.87664
Mean Factor Score				
By CVD				
No	11.0	0.8	6.9	7.1
Yes	11.6	1.2	6.6	7.2
Δ*	0.51	0.39	−0.30	0.15
P value†	.0024	.0217	.0785	.3733
By MI				
No	11.1	0.8	6.8	7.1
Yes	11.4	1.2	6.6	7.1
Δ*	0.37	0.40	−0.23	0.05
P value†	.0420	.0314	.2074	.7795

NOTE. Highlighted areas show variables with factor loadings > .4. SI conversion factors: 7.175 for insulin, 0.01 for fibrinogen, 0.01129 for triglycerides, 0.05551 for glucose, and 0.02586 for cholesterol.

*Difference in mean factor scores (women with CVD minus women without CVD).

†*P* value from a *t* test of differences in factor scores by CVD or MI status.

cholesterol level of 2.59 to 3.34 mmol/L (100 to 129 mg/dL), an LDL cholesterol level < 2.59 mmol/L (< 100 mg/dL) was less protective in women than in men, and an LDL cholesterol level > 4.91 mmol/L (> 190 mg/dL) posed less risk in women than in men.[58] An alternative explanation is that the present analysis is cross-sectional.

A final factor in all racial groups was the blood pressure factor. Systolic and diastolic blood pressures were related to each other, but not to insulin concentrations or IR. There have been several reports of an association between hypertension and IR, but most of these studies were of younger, white individuals.[59,60] The association of IR with blood pressure has rarely been observed in blacks[6] and is not seen in American Indians.[61] This factor strongly relates to CVD in blacks and least strongly in Asians/Pacific Islanders. Thus, blood pressure may not be primarily determined by IR in postmenopausal women, but appears to be most strongly related to CVD in black women.

This analysis has a number of limitations. Although the WHI cohort is large and diverse in geography and socioeconomic status, it is not a population-based sample, and prevalence of CVD was low. Thus, ethnic comparisons must be interpreted with caution. We did not have measures of inflammation such as C-reactive protein (CRP) or lipoprotein (a) [Lp(a)], and thus could not evaluate these as potential covariates. Another limitation was that the HOMA index is not a direct measure of IR, and thus comparisons may be weakened or skewed. We did not have sufficient sample sizes to present the factor analyses in estrogen users, but a repeat of the analysis in nonusers did not change the relationship. Finally, this is a cross-sectional analysis; assessment of the observed factors as predictors of CVD must await the conclusion of the WHI trials.

In summary, these data show that IR and the components of the IR syndrome, dyslipidemia, and central obesity appear to have an important relationship with CVD in postmenopausal women of all racial groups. Distribution of factors was similar in the 4 ethnic groups, confirming the common metabolic determinants; however, there were differences in the strength of the associations with CVD, with obesity being a stronger correlate in white and Hispanic women, whereas dyslipidemia and blood pressure were stronger in blacks. There appears to be a dissociation of blood pressure and IR, suggesting that other determinants may be more predominant in women in this age group. Efforts to increase physical activity and control weight

Table 5. Age-Adjusted Rotated Factor Loadings for WHI CT Participants in the Blood Analyte Subsample: Asian/Pacific Islander

	Factors (N = 256)			
	Obesity	Dyslipidemia	LDL	Blood Pressure
% Variance Explained	45.5	17.6	11.6	9.8
Factor Variables				
Hip (cm)	0.88953	0.11191	−0.07314	0.13648
Waist (cm)	0.85707	0.29242	−0.03545	0.17096
BMI (kg/m^2)	0.85239	0.22012	−0.02501	0.18120
Log insulin (μU/mL)	0.65902	0.53747	0.07722	−0.01142
Log insulin resistance	0.64594	0.59242	0.07805	−0.02406
Fibrinogen (mg/dL)	0.42271	−0.09507	0.17697	−0.01212
Log triglyceride (mg/dL)	0.05249	0.69063	0.21171	0.24000
Log glucose (mg/dL)	0.32892	0.5206	0.04761	−0.05520
HDL distribution	−0.04897	−0.72081	0.10679	−0.13029
Log HDL cholesterol (mg/dL)	−0.13816	−0.77124	0.02192	−0.14075
Total cholesterol (mg/dL)	0.00876	0.00484	0.9804	0.07964
LDL cholesterol (mg/dL)	0.05804	0.06479	0.93172	0.03884
Blood pressure				
Systolic (mm Hg)	0.07728	0.13817	−0.03348	0.86394
Diastolic (mm Hg)	0.07248	0.05154	0.05898	0.85754
Factor VII activity, antigen (%)	0.13717	0.19981	0.18548	0.30653
Mean Factor Score				
By CVD				
No	11.6	0.5	7.1	5.0
Yes	11.9	0.7	6.8	5.0
Δ*	0.34	0.15	−0.24	−0.03
P value†	.098	.466	.2487	.8785
By MI				
No	11.6	0.5	7.1	5.0
Yes	11.9	0.8	6.9	5.1
Δ*	0.38	0.28	−0.19	0.11
P value†	.1051	.2406	.4085	.6365

NOTE. Highlighted areas show variables with factor loadings > .4. SI conversion factors: 7.175 for insulin, 0.01 for fibrinogen, 0.01129 for triglycerides, 0.05551 for glucose, and 0.02586 for cholesterol.

*Difference in mean factor scores (women with CVD minus women without CVD).

†*P* value from a *t* test of differences in factor scores by CVD or MI status.

may favorably influence IR and its associated CVD risk factors and thus play an important role in preventing CVD in postmenopausal women of all races.

ACKNOWLEDGMENT

The authors thank the clinic staffs and participants at the 40 Women's Health Initiative sites.

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