

Factor Analysis of Metabolic Syndrome Using Directly Measured Insulin Sensitivity

The Insulin Resistance Atherosclerosis Study

Anthony J.G. Hanley,^{1,2} Andrew J. Karter,³ Andreas Festa,¹ Ralph D'Agostino, Jr.,⁴ Lynne E. Wagenknecht,⁴ Peter Savage,⁵ Russell P. Tracy,⁶ Mohammed F. Saad,⁷ and Steven Haffner¹

Factor analysis, a multivariate correlation technique, has been used to provide insight into the underlying structure of metabolic syndrome, which is characterized by physiological complexity and strong statistical intercorrelation among its key variables. The majority of previous factor analyses, however, have used only surrogate measures of insulin sensitivity. In addition, few have included members of multiple ethnic groups, and only one has presented results separately for subjects with impaired glucose tolerance. The objective of this study was to investigate, using factor analysis, the clustering of physiologic variables using data from 1,087 nondiabetic participants in the Insulin Resistance Atherosclerosis Study (IRAS). This study includes information on the directly measured insulin sensitivity index (S_I) from intravenous glucose tolerance testing among African-American, Hispanic, and non-Hispanic white subjects aged 40–69 years at various stages of glucose tolerance. Principal factor analysis identified two factors that explained 28 and 9% of the variance in the dataset, respectively. These factors were interpreted as 1) a “metabolic” factor, with positive loadings of BMI, waist, fasting and 2-h glucose, and triglyceride and inverse loadings of $\log(S_I+1)$ and HDL; and 2) a “blood pressure” factor, with positive loadings of systolic and diastolic blood pressure. The results were unchanged

when surrogate measures of insulin resistance were used in place of $\log(S_I+1)$. In addition, the results were similar within strata of sex, glucose tolerance status, and ethnicity. In conclusion, factor analysis identified two underlying factors among a group of metabolic syndrome variables in this dataset. Analyses using surrogate measures of insulin resistance suggested that these variables provide adequate information to explore the underlying intercorrelational structure of metabolic syndrome. Additional clarification of the physiologic characteristics of metabolic syndrome is required as individuals with this condition are increasingly being considered candidates for behavioral and pharmacologic intervention. *Diabetes* 51:2642–2647, 2002

The relationships among type 2 diabetes, insulin resistance, and associated metabolic abnormalities are both physiologically and statistically complex (1,2). Regarding physiology, the multiple feedback mechanisms involved in the maintenance of glucose and lipid homeostasis make it difficult to establish primary events that lead to the subsequent cascade of disorders that characterize metabolic disease (1). Regarding statistics, strong intercorrelation among the variables that are considered to be central features of metabolic syndrome raises complexities in the interpretation of independent associations in multivariate statistical models (2).

Factor analysis has been proposed as an approach that might address some of these challenges (2,3). This multivariate statistical technique reduces a large number of intercorrelated variables to a smaller set of latent or underlying independent factors (2,4). Over the past 7 years, there have been several publications reporting factor analyses of the metabolic syndrome in various populations (2,3,5–19). As reviewed by Meigs (2), a number of common findings have emerged from these studies, including 1) the identification of between two and four factors; 2) the loading of insulin on more than one factor, including those that have been interpreted as “glycemia,” “obesity,” and “dyslipidemia;” and 3) a separate factor for blood pressure. In addition, studies conducted in the Framingham Offspring and Bogalusa cohorts have reported that factor patterns appear to be relatively stable

From the ¹Division of Clinical Epidemiology, University of Texas Health Sciences Center at San Antonio, San Antonio, Texas; the ²Division of Epidemiology and Biostatistics, Samuel Lunenfeld Research Institute, Mt. Sinai Hospital, Toronto, Canada; the ³Division of Research, Kaiser Permanente, Oakland, California; the ⁴Department of Public Health Sciences, Wake Forest University School of Medicine, Winston Salem, North Carolina; the ⁵Division of Epidemiology and Clinical Applications, National Heart, Lung and Blood Institute, Bethesda, Maryland; the ⁶Departments of Pathology and Biochemistry, College of Medicine, University of Vermont, Burlington, Vermont; and the ⁷Department of Medicine, University of Southern California School of Medicine, Los Angeles, California.

Address correspondence and reprint requests to Dr. Steven Haffner, Division of Clinical Epidemiology, University of Texas Health Science Center at San Antonio, mail code 7873, 7703 Floyd Curl Dr., San Antonio, TX 78229-3900. E-mail: haffner@uthscsa.edu.

Received for publication 6 January 2002 and accepted in revised form 9 May 2002.

R.P.T. has been on advisory panels for Monsanto/Seale, Bio-Tek, and Dade/Behring; holds stock in COR Therapeutics and Haematologic Technologies; has received honoraria and/or consulting fees from Genentech, Pfizer, Merck, Parke-Davis, Bristol-Myers Squibb, Wyeth-Ayerst, Organon, Diagnostic Products, and Diagnostica Stago; and has received grant/research support from Eli Lilly, Genentech, Bristol-Myers Squibb, Unilever, and Pfizer.

FSIGTT, frequently sampled intravenous glucose tolerance test; HOMA-IR, homeostasis model assessment index of insulin resistance; IGT, impaired glucose tolerance; IRAS, Insulin Resistance Atherosclerosis Study; NGT, normal glucose tolerance; S_I , insulin sensitivity index.

TABLE 1
Baseline anthropometric and metabolic characteristics of nondiabetic subjects in the IRAS ($n = 1087$)

Variable	
Age (years)	54.8 ± 8.4 (40–69)
BMI (kg/m ²)	28.5 ± 5.7 (14.2–63.3)
Waist circumference (cm)	90.6 ± 12.9 (58.9–167.0)
Fasting glucose (mg/dl)	98.8 ± 11.4 (74.0–139.0)
2-h glucose (mg/dl)	125.2 ± 34.3 (33.0–199.0)
Fasting insulin (μU/ml)	15.8 ± 14.6 (1.0–255.0)
2-h insulin (μU/ml)	100.0 ± 93.3 (2.0–900.0)
HOMA-IR	4.0 ± 4.0 (0.2–73.7)
$S_1 \times 10^{-4}$ (min ⁻¹ · UU ⁻¹ · ml ⁻¹)	2.2 ± 2.0 (0.0–19.4)
Triglyceride (mg/dl)	134.8 ± 86.9 (16.0–712.0)
LDL cholesterol (mg/dl)	141.6 ± 34.7 (37.0–299.0)
HDL cholesterol (mg/dl)	47.1 ± 15.3 (11.0–125.0)
Systolic blood pressure (mmHg)	122.4 ± 17.0 (85.0–219.0)
Diastolic blood pressure (mmHg)	77.7 ± 9.3 (41.0–119.0)
Albumin/creatinine ratio (mg/mmol)	14.64 ± 40.6 (1.1–643.1)
Sex (% female)	56.4
Non-Hispanic white/African-American/Hispanic American (%)	40.0/26.5/33.5
IGT (%)	34.0
Hypertensive (%)	32.0
Never/former/current smoker (%)	45.3/38.3/16.5
Premenopausal/perimenopausal/postmenopausal (%)	20.1/26.5/33.5

Data are means ± SD (range) or proportions.

across demographic, metabolic, and lifestyle risk factor subgroups (5,9).

There are, however, a number of gaps in the existing literature on factor analysis of metabolic syndrome. First, there have been only two studies conducted to date that have used direct measures of insulin sensitivity (7,17), and the sample sizes of both of these studies were small ($n = 50$ and 74 , respectively). Second, few published studies have included members of multiple ethnic groups, and none, to our knowledge, have included Hispanic Americans, a population at high risk for type 2 diabetes. Finally, little information is available on whether factor patterns differ between subjects with normal glucose tolerance (NGT) and impaired glucose tolerance (IGT) (5).

The objective of the present study was to investigate, using factor analysis, the clustering of anthropometric and metabolic variables using data from the Insulin Resistance Atherosclerosis Study (IRAS). This observational epidemiologic study includes a multiethnic cohort of middle-aged individuals at various stages of glucose tolerance and has used direct measures of insulin sensitivity (insulin sensitivity index [S_1]) from the frequently sampled intravenous glucose tolerance test (FSIGTT).

RESEARCH DESIGN AND METHODS

Study subjects. The IRAS is a multicenter observational epidemiologic study of the relationships among insulin resistance, cardiovascular disease and its known risk factors in different ethnic groups, and varying states of glucose tolerance. The design and methods of this study have been described in detail in previous publications (20,21). Briefly, the study was conducted at four clinical centers. At centers in Oakland and Los Angeles, CA, non-Hispanic white and African-American subjects were recruited from Kaiser Permanente, a nonprofit health maintenance organization. Centers in San Antonio, TX, and San Luis Valley, CO, recruited non-Hispanic white and Hispanic American subjects from two ongoing population-based studies (the San Antonio Heart Study and the San Luis Valley Diabetes Study) (20). A total of 1,625 individuals participated in the baseline IRAS examination (56% women), which occurred between October 1992 and April 1994. The IRAS protocol was approved by local institutional review committees, and all participants provided written

informed consent. The present report includes information on 1,087 individuals who were free of diabetes at baseline and for whom information was available on metabolic variables of interest (Table 1).

Clinical measurements and procedures. The IRAS protocol required two visits, 1 week apart, of ~4 h each. Subjects were asked before each visit to fast for 12 h, to abstain from heavy exercise and alcohol for 24 h, and to refrain from smoking the morning of the examination. During the first visit, a 75-g oral glucose tolerance test was administered, with glucose tolerance status determined using World Health Organization criteria (22). During the second visit, insulin sensitivity and insulin secretion were determined using an FSIGTT with two modifications to the original protocol (23). First, an injection of regular insulin, rather than tolbutamide, was used to ensure adequate plasma insulin levels for the accurate computation of insulin sensitivity across a broad range of glucose tolerance (24). Second, a reduced sampling protocol (with 12 rather than 30 samples) was used for efficiency because of the large number of participants (25). Insulin sensitivity, expressed as S_1 , was calculated using mathematical modeling methods (MINMOD version 3.0) (26). The repeatability of S_1 has been demonstrated in a subsample of the IRAS cohort (27), and the estimate of S_1 from this modified protocol has been validated against gold-standard measures of insulin resistance from the hyperinsulinemic-euglycemic clamp technique ($r = 0.95$) (28).

Height and weight were measured to the nearest 0.5 cm and 0.1 kg, respectively. BMI (kg/m²) was used as an estimate of overall adiposity. Waist circumference, a validated estimate of visceral adiposity (29), was measured to the nearest 0.5 cm using a steel tape. Duplicate measures were made following a standardized protocol, and averages were used in the analysis. Resting blood pressure (systolic and fifth-phase diastolic) was recorded with a standard mercury sphygmomanometer after a 5-min rest. The average of the second and third measurements was used. Ethnicity was assessed by self-report.

Laboratory procedures. Glucose concentration was determined using standard methods as previously described (20). Insulin levels were measured using the dextran-charcoal radioimmunoassay (30), which has a 19% external coefficient of variation. This assay displays a high degree of cross-reactivity with proinsulin. The homeostasis model assessment index of insulin resistance (HOMA-IR) was calculated as described by Matthews et al. (31). Plasma lipid and lipoprotein concentrations were determined from fasting plasma samples at the central IRAS laboratory (Medlantic Research Institute, Washington, DC) using the Lipid Research Clinics methodology. Urinary albumin and creatinine concentrations were assessed in a random morning spot urine sample using procedures described previously (32).

Statistical analyses. Means, SDs, and ranges, or proportions, were presented for subjects in the study. Associations between baseline anthropometric and metabolic variables were determined using Spearman correlation analysis.

TABLE 2
Spearman correlation analysis of baseline variables among nondiabetic subjects in the IRAS

	Waist	Fasting glucose	2-h glucose	Fasting insulin	2-h insulin	HOMA-IR	S ₁	Triglyceride	HDL	Systolic BP	Diastolic BP	ACR
BMI	0.78	0.33	0.31	0.53	0.38	0.55	-0.54	0.21	-0.22	0.25	0.20	0.08
Waist		0.42	0.32	0.52	0.36	0.55	-0.54	0.30	-0.38	0.27	0.24	0.02
Fasting glucose			0.43	0.37	0.26	0.52	-0.34	0.15	-0.18	0.24	0.15	-0.04
2-h glucose				0.32	0.53	0.37	-0.50	0.28	-0.13	0.22	0.07	0.03
Fasting insulin					0.66	0.98	-0.68	0.34	-0.33	0.20	0.19	0.05
2-h insulin						0.65	-0.67	0.32	-0.26	0.22	0.15	0.08
HOMA-IR							-0.68	0.33	-0.33	0.23	0.20	0.04
S ₁								-0.30	0.29	-0.25	-0.16	-0.08
Triglyceride									-0.44	0.07	0.06	-0.01
HDL cholesterol										0.06	-0.05	0.06
Systolic BP											0.57	0.18
Diastolic BP												0.04

P < 0.0001 for r > 0.12; P > 0.05 for r < 0.06. ACR, albumin/creatinine ratio; BP, blood pressure.

The distributions of continuous variables were assessed, and log transformations of skewed variables were used in subsequent analyses, as appropriate. Given that some subjects had S₁ = 0, we used log(S₁+1) as the transformation for the insulin sensitivity variable. Analyses using the rank transformation of S₁ yielded identical results (data not shown). Factor analysis was conducted using the FACTOR procedure of SAS. Principle factor analysis was used to identify the initial set of uncorrelated factors. The number of components to be retained was based on Scree plot analysis (factors above the break in the curve were retained) and eigenvalue criteria (0.9), both of which have been described and recommended elsewhere (2,4,5). Varimax (orthogonal) rotation was used to obtain a set of independent interpretable factors. The resulting factor pattern was interpreted using factor loadings of ≥0.4. The analysis was initially conducted with a set of core variables that are considered central features of metabolic syndrome, including adiposity, fasting and postchallenge glucose concentrations log(S₁+1), blood pressure, lipid concentrations, and microalbuminuria. The log(S₁+1) variable was then replaced with HOMA-IR (or fasting and 2-h insulin concentrations) to assess the effect of using surrogate measures of insulin resistance on the factor pattern. These analyses were initially carried out with all nondiabetic subjects pooled. We then re-ran the analysis within strata of sex, glucose tolerance (NGT versus IGT), and ethnicity (non-Hispanic white, African-American, and Hispanic American) to assess the role of these potential effect-modifying variables. Coefficients of congruence (2,4) were calculated to evaluate similarities among loadings on the same factor stratified by these variables.

RESULTS

Table 1 presents baseline anthropometric and metabolic characteristics of nondiabetic subjects in the IRAS. The

TABLE 3
Results of factor analysis of anthropometric and metabolic variables, including directly measured insulin sensitivity from the FSIGTT among nondiabetic subjects in the IRAS

Variable	Factor	
	Metabolic	Blood pressure
BMI	0.71	0.24
Waist	0.81	0.22
Fasting glucose	0.44	0.24
2-h glucose	0.51	0.18
Log(S ₁ +1)	-0.67	-0.19
Log triglyceride	0.44	-0.09
HDL cholesterol	-0.46	0.15
Systolic BP	0.12	0.71
Diastolic BP	0.09	0.61
Log albumin/creatinine ratio	0.01	0.25
% Total variance	28.1	8.8
% Cumulative variance	28.1	36.9

Loadings ≥0.40 in bold type. BP, blood pressure.

results of Spearman correlation analyses of baseline variables are presented in Table 2. Fasting insulin and HOMA-IR were significantly associated with S₁ (both r = -0.68, P < 0.0001). In addition, fasting insulin, HOMA-IR, and S₁ were each moderately to strongly associated with BMI, waist, and insulin and glucose concentrations.

Table 3 displays the results of factor analysis of core metabolic variables among nondiabetic subjects in the IRAS. A two-factor solution, which was supported by the retention criteria described in RESEARCH DESIGN AND METHODS, explained 37% of the total variance (28% factor 1 and 9% factor 2), and 96% of the common variance in the dataset (73% factor 1 and 23% factor 2). These factors were interpreted as a 1) “metabolic” factor, with positive loadings of BMI, waist, fasting and 2-h glucose, and log triglyceride and inverse loadings of log(S₁+1) and HDL; and 2) a “blood pressure” factor, with positive loadings of systolic and diastolic blood pressure. The results were unchanged when HOMA-IR was substituted for log(S₁+1) (Table 4) or when fasting and 2-h insulin concentrations were substituted for log(S₁+1) (data not shown). In these analyses, HOMA-IR and fasting and 2-h insulin had positive loadings on factor 1. We also explored the possibility of a three-factor solution; however, this conclusion was rejected because it did not meet any of the evaluation

TABLE 4
Results of factor analysis of anthropometric and metabolic variables among nondiabetic subjects in IRAS

Variable	Factor	
	Metabolic	Blood pressure
BMI	0.72	0.23
Waist	0.82	0.21
Fasting glucose	0.51	0.23
2-h glucose	0.46	0.16
Log HOMA-IR	0.66	0.19
Log triglyceride	0.44	-0.08
HDL cholesterol	-0.46	0.15
Systolic BP	0.12	0.70
Diastolic BP	0.11	0.62
Log albumin/creatinine ratio	0.01	0.23
% Total variance	28.4	8.6
% Cumulative variance	28.4	37.0

Loadings ≥0.40 in bold type. BP, blood pressure.

TABLE 5

Results of factor analysis of anthropometric and metabolic variables, including directly measured insulin sensitivity from the FSIGTT, among nondiabetic subjects in the IRAS within strata of sex, glucose tolerance, and ethnicity

Variable	Factor													
	Sex				Glucose tolerance				Ethnicity					
	Men		Women		NGT		IGT		NHW		AA		HA	
	M	BP	M	BP	M	BP	M	BP	M	BP	M	BP	M	BP
BMI	0.78	0.23	0.79	0.25	0.70	0.25	0.71	0.37	0.72	0.20	0.71	0.28	0.78	0.05
Waist	0.84	0.22	0.84	0.25	0.82	0.27	0.79	0.31	0.84	0.18	0.79	0.27	0.85	0.10
Fasting glucose	0.32	0.25	0.48	0.24	0.28	0.29	0.31	0.17	0.53	0.07	0.40	0.30	0.44	0.30
2-h glucose	0.41	0.23	0.58	0.15	0.31	0.27	0.22	0.01	0.52	0.06	0.49	0.32	0.50	0.17
Log (S_1+1)	-0.63	-0.18	-0.68	-0.27	-0.57	-0.28	-0.59	-0.13	-0.69	-0.10	-0.59	-0.26	-0.70	-0.20
Log triglyceride	0.47	-0.13	0.39	-0.03	0.43	-0.05	0.31	-0.13	0.48	-0.09	0.39	-0.04	0.40	0.10
HDL cholesterol	-0.42	0.23	-0.43	0.08	-0.52	0.12	-0.44	0.11	-0.49	0.20	-0.43	0.05	-0.37	-0.02
Systolic BP	0.04	0.76	0.15	0.68	0.07	0.74	-0.05	0.66	0.17	0.68	0.05	0.71	0.18	0.74
Diastolic BP	0.07	0.64	0.04	0.63	0.08	0.62	0.02	0.60	0.13	0.58	0.03	0.59	0.09	0.72
Log albumin/creatinine ratio	0.06	0.30	0.03	0.19	0.01	0.26	0.09	0.25	-0.07	0.23	0.13	0.32	0.04	0.26
% Total variance	26.5	11.2	31.1	7.8	25.7	9.3	22.2	8.7	28.8	8.7	27.9	8.1	29.4	10.0
% Cumulative variance	26.5	37.7	31.1	38.9	25.7	35.0	22.2	30.9	28.8	37.5	27.9	36.0	29.4	39.4

Loadings ≥ 0.40 in bold type. AA, African-American; BP, blood pressure; HA, Hispanic American; M, metabolic factor; NHW, non-Hispanic white.

criteria described in RESEARCH DESIGN AND METHODS (eigenvalue for third factor, 0.50).

The factor patterns were stable in separate analyses among men and women and among subjects with NGT and IGT, although, in the latter case, positive loadings of fasting and 2-h glucose on factor 1 fell below the 0.40 threshold (Table 5). The factor pattern was also remarkably consistent in separate analyses among non-Hispanic whites, African-Americans, and Hispanics (Table 5). Coefficients of congruence for these subgroup analyses are presented in Table 6 and reflect the similar factor loadings by sex, glucose tolerance status, and ethnicity.

DISCUSSION

In the present study, we used factor analysis to investigate the clustering of variables that are thought to be important components of metabolic syndrome. Two factors emerged (metabolic and blood pressure), and these factors were consistent across sex, glucose tolerance, and ethnic subgroups. These findings have made two major contributions to the literature. First, no other large factor analysis study has included information on directly measured S_1 . Despite the fact that surrogate measures of insulin resistance

(such as HOMA-IR and fasting insulin) correlate only moderately with S_1 , our study demonstrates that they yield factor analysis results that are very similar to those using direct measures. This observation is of substantial importance for large epidemiologic and clinical studies in which surrogate measures are the only option. Second, the IRAS included non-Hispanic whites, African-Americans, and Hispanics. These latter two ethnic groups experience high rates of metabolic syndrome and type 2 diabetes; however, less is known about the epidemiology and pathogenesis of the disease in these individuals.

Our analyses yielded only two factors, which is unusual but not unprecedented in the literature. The majority of studies of core metabolic variables have reported three to four factors, although three reports have reported two factors (9,17,18). There do not appear to be any design or demographic characteristics that distinguish these two-factor studies from the others, although there is some evidence to suggest a modest positive association between the number of factors and mean age of the study subjects. Our results are highly consistent with the literature in the identification of a separate blood pressure factor (2). Although the microalbuminuria variable did not load clearly on either of the two factors identified in the present analysis, it did have borderline loadings (>0.30) on the blood pressure factor among men and African-Americans in subgroup analyses. Thus, the presence of microalbuminuria in the metabolic syndrome phenotype may differ by sex and ethnicity.

As reviewed by Meigs (2), the identification of only one underlying factor in a factor analysis of metabolic variables might be interpreted as support for the "unity hypothesis," which suggests that a single pathophysiologic process (in this case insulin resistance) accounts for the observed risk variable clustering. Identification of two or more factors would suggest the rejection of this hypothesis. Our results imply that at least two pathophysiologic processes are operating and that reduced insulin sensitivity is an important component of the anthropometric, dysglycemic, and dyslipidemic aspects of metabolic syn-

TABLE 6

Similarity of factor loading patterns among subgroups of sex, glucose tolerance, and ethnicity

Subgroups	Coefficient of congruence	
	Metabolic factor	Blood pressure factor
Men vs. women	0.99	0.98
NGT vs. IGT	0.99	0.95
NHW vs. HA	0.99	0.92
NHW vs. AA	0.98	0.93
HA vs. AA	0.99	0.94

Measures are coefficients of congruence (see refs. 2 and 4) that range from 0 to 1 and can be interpreted in a similar fashion as correlation coefficients (1 = perfect agreement among subgroups; 0 = no agreement). AA, African American; HA, Hispanic American; NHW, non-Hispanic white.

drome. The loading pattern of our first factor (anthropometry, glucose, insulin sensitivity, and lipids) is similar to some (9,18), but not all, previous studies. Those that reported three or four factors tended to have separate factors for body mass, lipids, and insulin/glucose (3,6,16).

The present study is the largest of only three published to date to have used a direct measure of insulin sensitivity (7,17). S_1 loaded strongly on the first factor together with measures of glucose, lipids, and adiposity, all of which are well-established components of the insulin resistance syndrome. We found that factor patterns in our study were similar when either HOMA-IR or fasting and 2-h insulin concentrations were substituted for S_1 . Similarly, Donahue et al. (17) reported that the addition of the M value from a euglycemic-hyperinsulinemic clamp to their analysis (which included fasting insulin) did not markedly change the resulting factor patterns. These findings lend additional support to evidence from studies examining correlations with direct measures, suggesting that fasting insulin concentration and the HOMA-IR index are reasonable surrogate measures of insulin resistance for use in large epidemiologic studies among nondiabetic subjects (33,34).

Very few previous studies reporting results of factor analysis have included individuals from multiple ethnic groups (9,14,17). To our knowledge, this is the first investigation to have included Hispanic Americans, a population known to be at high risk for type 2 diabetes and associated metabolic disorders (35). We found that the factor patterns among Hispanic Americans were similar to those in non-Hispanic whites and African-Americans. In addition, factor patterns among African-Americans were similar to those in the other two ethnic groups. Two previous factor analysis studies from the Bogalusa Heart Study reported factor patterns that were generally similar among black and white children, adolescents, and young adults (9,14). Minor ethnic differences in these studies included slightly lower loadings of glucose, insulin, and ponderal index on the blood pressure factor among blacks, as well as no loading of renin with the insulin resistance factor in this ethnic group.

Previous studies have reported differences in factor patterns between diabetic and nondiabetic subjects (6,8). However, only one previous study of nondiabetic subjects has presented results separately for those with NGT and IGT (5). An understanding of metabolic clustering among individuals with IGT is of interest given the outcomes of recent clinical trials demonstrating that progression from IGT to diabetes was markedly reduced among subjects in intensive lifestyle or pharmacologic intervention groups (36–38). Factor patterns in the present study were very similar in a separate analysis of subjects with NGT and IGT, suggesting that differences in metabolic clustering (as reflected in the factor loading patterns) do not become apparent until diabetes has fully developed.

In conclusion, factor analysis identified two underlying factors among a group of metabolic syndrome variables, including directly measured S_1 , in a multiethnic cohort of nondiabetic middle-aged subjects. These factors appeared to be stable across sex, glucose tolerance, and ethnic subgroups. The findings were very similar using indirect measures of insulin resistance, which suggests that these surrogate measures provide adequate information to ex-

plore the underlying intercorrelational structure of metabolic syndrome. These findings suggest that metabolic syndrome is likely comprised of two distinct pathophysiologic factors, the dominant one accounting for 30% of the total variance and the subordinate one ~10% of the variance. The dominant “metabolic” factor is comprised of anthropometric and metabolic variables and the subordinate “blood pressure” factor includes systolic and diastolic blood pressure. Although a correlate of the dominating “metabolic” factor, blood pressure may be only a secondary player that is correlated with the metabolic and anthropometric variables without sharing a common pathology.

Patients with metabolic syndrome who are free of clinical disease are increasingly being considered candidates for behavioral interventions and newer generation therapies targeting insulin resistance. Specifying a robust parsimonious case definition for metabolic syndrome is critical to these evolving interventions and to subsequent measurement of treatment effects on metabolic syndrome.

ACKNOWLEDGMENTS

This study was supported by National Heart, Lung, and Blood Institute contracts U01-HL47887, U01-HL47889, U01-HL47892, U01-HL47902, DK-29867, and RO1 58329 (to R.P.T.). A.J.G.H. was supported by a Post-Doctoral Fellowship from the Canadian Institutes of Health Research.

REFERENCES

- Ferrannini E: Insulin resistance versus insulin deficiency in non-insulin-dependent diabetes mellitus: problems and prospects. *Endocr Rev* 19:477–490, 1998
- Meigs JB: Invited commentary: insulin resistance syndrome? Syndrome X? Multiple metabolic syndrome? A syndrome at all? Factor analysis reveals patterns in the fabric of correlated metabolic risk factors. *Am J Epidemiol* 152:908–911, 2000
- Edwards KL, Austin MA, Newman B, Mayer E, Krauss RM, Selby JV: Multivariate analysis of the insulin resistance syndrome in women. *Arterioscler Thromb* 14:1940–1945, 1994
- Cureton EE, D’Agostino RB: *Factor Analysis: An Applied Approach*. Hillsdale, NJ, Lawrence Erlbaum, 1983
- Meigs JB, D’Agostino RB Sr, Wilson PW, Cupples LA, Nathan DM, Singer DE: Risk variable clustering in the insulin resistance syndrome: the Framingham Offspring Study. *Diabetes* 46:1594–600, 1997
- 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
- Leyva F, Godsland IF, Ghatei M, Prouder AJ, Aldis S, Walton C, Bloom S, Stevenson JC: Hyperleptinemia as a component of a metabolic syndrome of cardiovascular risk. *Arterioscler Thromb Vasc Biol* 18:928–933, 1998
- Gray RS, Fabsitz RR, Cowan LD, Lee ET, Howard BV, Savage PJ: Risk factor clustering in the insulin resistance syndrome: the Strong Heart Study. *Am J Epidemiol* 148:869–878, 1998
- Chen W, Srinivasan SR, Elkasabany A, Berenson GS: Cardiovascular risk factors clustering features of insulin resistance syndrome (Syndrome X) in a biracial (Black-White) population of children, adolescents, and young adults: the Bogalusa Heart Study. *Am J Epidemiol* 150:667–674, 1999
- Snehalatha C, Sivasankari S, Satyavani K, Vijay V, Ramachandran A: Insulin resistance alone does not explain the clustering of cardiovascular risk factors in southern India. *Diabet Med* 17:152–157, 2000
- Chen CH, Lin KC, Tsai ST, Chou P: Different association of hypertension and insulin-related metabolic syndrome between men and women in 8437 nondiabetic Chinese. *Am J Hypertens* 13:846–853, 2000
- Sakkinen PA, Wahl P, Cushman M, Lewis MR, Tracy RP: Clustering of procoagulation, inflammation, and fibrinolysis variables with metabolic factors in insulin resistance syndrome. *Am J Epidemiol* 152:897–907, 2000
- Shmulewitz D, Auerbach SB, Lehner T, Blundell ML, Winick JD, Youngman LD, Skilling V, Heath SC, Ott J, Stoffel M, Breslow JL, Friedman JM: Epidemiology and factor analysis of obesity, type II diabetes, hyperten-

- sion, and dyslipidemia (syndrome X) on the Island of Kosrae, Federated States of Micronesia. *Hum Hered* 51:8–19, 2001
14. Chen W, Srinivasan SR, Berenson GS: Plasma renin activity and insulin resistance in African American and white children: the Bogalusa Heart Study. *Am J Hypertens* 14:212–217, 2001
 15. Pyorala M, Miettinen H, Halonen P, Laakso M, Pyorala K: Insulin resistance syndrome predicts the risk of coronary heart disease and stroke in healthy middle-aged men: the 22-year follow-up results of the Helsinki Policemen Study. *Arterioscler Thromb Vasc Biol* 20:538–544, 2000
 16. Lempiainen P, Mykkanen L, Pyorala K, Laakso M, Kuusisto J: Insulin resistance syndrome predicts coronary heart disease events in elderly nondiabetic men. *Circulation* 100:123–128, 1999
 17. Donahue RP, Bean JA, Donahue RD, Goldberg RB, Prineas RJ: Does insulin resistance unite the separate components of the insulin resistance syndrome? Evidence from the Miami Community Health Study. *Arterioscler Thromb Vasc Biol* 17:2413–2417, 1997
 18. Godsland IF, Leyva F, Walton C, Worthington M, Stevenson JC: Associations of smoking, alcohol and physical activity with risk factors for coronary heart disease and diabetes in the first follow-up cohort of the Heart Disease and Diabetes Risk Indicators in a Screened Cohort study (HDDRISC-1). *J Intern Med* 224:33–41, 1998
 19. Kekalainen P, Sarlund H, Pyorala K, Laakso M: Hyperinsulinemia cluster predicts the development of type 2 diabetes independently of family history of diabetes. *Diabetes Care* 22:86–92, 1999
 20. Wagenknecht LE, Mayer EJ, Rewers M, Haffner S, Selby J, Borok GM, Henkin L, Howard G, Savage PJ, Saad MF, Bergman RN, Hamman R: The Insulin Resistance Atherosclerosis Study: design, objectives and recruitment results. *Ann Epidemiol* 5:464–472, 1995
 21. Haffner SM, D'Agostino Jr R, Saad MF, Rewers M, Mykkanen L, Selby J, Howard G, Savage PJ, Hamman RF, Wagenknecht LE, Bergman RE: Increased insulin resistance and insulin secretion in non-diabetic African Americans and Hispanics compared with non-Hispanic whites: the Insulin Resistance Atherosclerosis Study. *Diabetes* 45:742–748, 1996
 22. World Health Organization: *Diabetes Mellitus: Report of a WHO Study Group*. Geneva, World Health Org., 1985 (Tech. Rep. Ser., no. 727)
 23. Bergman RN, Finegood DT, Ader M: Assessment of insulin sensitivity in vivo. *Endocr Rev* 6:45–86, 1985
 24. Welch S, Gebhart SSP, Bergman RN, Phillips LS: Minimal model analysis of intravenous glucose tolerance test derived insulin sensitivity in diabetic subjects. *J Clin Endocrinol Metab* 71:1508–1518, 1990
 25. Steil GM, Volund A, Kahn SE, Bergman RN: Reduced sample number for calculation of insulin sensitivity and glucose effectiveness from the minimal model: suitability for use in population studies. *Diabetes* 42:250–256, 1993
 26. Pacini G, Bergman RN: MINMOD: a computer program to calculate insulin sensitivity and pancreatic responsiveness from the frequently sampled intravenous glucose tolerance test. *Comput Methods Programs Biomed* 23:113–122, 1986
 27. Zaccaro DJ, D'Agostino RB Jr, Karter A, Bergman R, Wagenknecht LE: A comparison of the repeatability of insulin sensitivity with other cardiovascular disease risk factors (Abstract). *Can J Cardiol* 13 (Suppl. B):197B, 1997
 28. Saad MF, Anderson RL, Laws A, Watanabe RM, Kades WW, Chen YD, Sands RE, Pei D, Savage PJ, Bergman RN: A comparison between the minimal model and the glucose clamp in the assessment of insulin sensitivity across the spectrum of glucose tolerance. *Diabetes* 43:1114–1121, 1994
 29. Lemieux S, Prud'homme D, Bouchard C, Tremblay A, Despres J-P: A single threshold value of waist girth identifies normal weight and overweight subjects with excess visceral adipose tissue. *Am J Clin Nutr* 64:685–693, 1996
 30. Herbert V, Lau K, Gottlieb C, Bleicher S: Coated charcoal immunoassay of insulin. *J Clin Endocrinol Metab* 25:1375–1384, 1965
 31. Matthews DR, Hosker JP, Rudenski AS, Naylor BA, Treacher DF, Turner RC: Homeostasis model assessment: insulin resistance and β -cell function from fasting plasma glucose and insulin concentrations in man. *Diabetologia* 28:412–419, 1985
 32. Festa A, D'Agostino R, Howard G, Mykkanen L, Tracy RP, Haffner SM: Inflammation and microalbuminuria in nondiabetic and type 2 diabetic subjects: the Insulin Resistance Atherosclerosis Study. *Kidney Int* 58:1703–1710, 2000
 33. Laakso M: How good a marker is insulin level for insulin resistance. *Am J Epidemiol* 137:959–956, 1993
 34. Anderson RL, Hamman RF, Savage PJ, Saad MF, Laws A, Kades WW, Sands RE, Cefalu W: Exploration of simple insulin sensitivity measures derived from frequently sampled intravenous glucose tolerance (FSIGT) tests: the Insulin Resistance Atherosclerosis Study. *Am J Epidemiol* 142:724–732, 1995
 35. Burke JP, Williams K, Haffner SM, Villalpando CG, Stern MP: Elevated incidence of type 2 diabetes in San Antonio, Texas, compared with that of Mexico City, Mexico. *Diabetes Care* 24:1573–1578, 2001
 36. Chiasson JL, Gomis R, Hanefeld M, Josse RG, Karasik A, Laakso M. The STOP-NIDDM Trial: an international study on the efficacy of an alpha-glucosidase inhibitor to prevent type 2 diabetes in a population with impaired glucose tolerance: rationale, design, and preliminary screening data: Study to Prevent Non-Insulin-Dependent Diabetes Mellitus. *Diabetes Care* 21: 1720–5, 1999
 37. Diabetes Prevention Program Investigators: The Diabetes Prevention Program: design and methods for a clinical trial in the prevention of type 2 diabetes. *Diabetes Care* 22:623–634, 1999
 38. Tuomilehto J, Lindstrom J, Eriksson JG, Valle TT, Hamalainen H, Ilanne-Parikka P, Keinanen-Kiukkaanniemi S, Laakso M, Louheranta A, Rastas M, Salminen V, Uusitupa M, the Finnish Diabetes Prevention Study Group: Prevention of type 2 diabetes mellitus by changes in lifestyle among subjects with impaired glucose tolerance. *N Engl J Med* 344:1343–1350, 2001