Metabolic and Inflammation Variable Clusters and Prediction of Type 2 Diabetes

Factor Analysis Using Directly Measured Insulin Sensitivity

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Factor analysis, a multivariate correlation technique, has been used to provide insight into the underlying structure of the metabolic syndrome. The majority of previous factor analyses, however, have used only surrogate measures of insulin sensitivity; very few have included nontraditional cardiovascular disease (CVD) risk factors such as plasminogen activator inhibitor (PAI)-1, fibrinogen, and C-reactive protein (CRP); and only a limited number have assessed the ability of factors to predict type 2 diabetes. The objective of this study was to investigate, using factor analysis, the clustering of metabolic and inflammation variables using data from 1,087 nondiabetic participants in the Insulin Resistance Atherosclerosis Study (IRAS) and to determine the association of these clusters with risk of type 2 diabetes at follow-up. This study includes information on directly measured insulin sensitivity (S_i) from the frequently sampled intravenous glucose tolerance test among African-American, Hispanic, and non-Hispanic white subjects aged 40–69 years. Principal factor analysis of data from nondiabetic subjects at baseline (1992–1994) identified three factors, which explained 28.4, 7.4, and 6% of the total variance in the dataset, respectively. Based on factor loadings of ≥ 0.40 , these factors were interpreted as *1*) a "metabolic" factor, with positive loadings of BMI, waist circumference, 2-h glucose, log triglyceride, and log PAI-1 and inverse loadings of log S_i + 1 and HDL; *2*) an "inflammation" factor, with positive loadings of BMI, waist circumference, fibrinogen, and log CRP and an inverse loading of log S_i + 1; and *3*) a "blood pressure" factor, with positive loadings of systolic and diastolic blood pressure. The results were similar within strata of ethnicity, and there were only subtle differences in sex-specific analyses. In a prospective analysis, each of the factors was a significant predictor of diabetes after a median follow-up period of 5.2 years, and each factor remained significant in a multivariate model that included all three factors, although this three-factor model was not significantly more predictive than models using either impaired glucose tolerance or conventional CVD risk factors. Factor analysis identified three underlying factors among a group of inflammation and metabolic syndrome variables, with insulin sensitivity loading on both the metabolic and inflammation variable clusters. Each factor significantly predicted diabetes in multivariate analysis. The findings support the emerging hypothesis that chronic subclinical inflammation is associated with insulin resistance and comprises a component of the metabolic syndrome. *Diabetes* 53: 1773–1781, 2004

Type 2 diabetes is a global health problem of increasing magnitude (1). Despite significant advances in strategies to delay the onset of diabetic complications, the disease is progressive and sequelae frequently develop over the course of the illness. Primary prevention thus remains a desirable goal, and, in this context, a number of approaches to identify predictors of type 2 diabetes have been explored (2–5).

It has been recognized for many years that clusters of cardiovascular disease (CVD) risk factors, including abdominal adiposity, dyslipidemia, and hypertension, also characterize and predict type 2 diabetes (6). Stern and colleagues (5,7) have reported that better prediction of CVD and type 2 diabetes can be achieved using combinations of conventional clinically available measures such as lipids, blood pressure, BMI, and family history compared with measures from an oral glucose tolerance test. This cluster of risk factors has been variably referred to as syndrome X, the insulin resistance syndrome, or the metabolic syndrome (8,9). Recently, evidence has been accumulating to suggest that a number of nontraditional risk factors for CVD, including C-reactive protein (CRP), plasminogen activator inhibitor (PAI)-1, fibrinogen, and other markers of inflammation and fibrinolysis are com-

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AA, African American; AROC, area under the receiver operating characteristic; CHS, Cardiovascular Health Study; CRP, C-reactive protein; CVD, cardiovascular disease; HA, Hispanic American; HS, Hispanic; IGT, impaired glucose tolerance; IRAS, Insulin Resistance Atherosclerosis Study; NHW, non-Hispanic white; PAI, plasminogen activator inhibitor.

TABLE 1
Baseline characteristics of nondiabetic subjects in the IRAS (n = 1,087)

	Mean or median	SD or interquartile range	Range	%
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	74–139	
2-h glucose (mg/dl)	125.2	34.3	33–199	
Fasting insulin (μU/ml)	13	9–19	1–255	
2-h insulin (μU/ml)	79	37–126	2–900	
$S_i \times 10^{-4}$ ($min^{-1} \cdot UU^{-1} \cdot ml^{-1}$)	1.6	0.9–2.9	0.0–19.4	
Triglycerides (mg/dl)	112	79–163	16–712	
HDL cholesterol (mg/dl)	47.1	15.3	11–125	
Systolic blood pressure (mmHg)	122.4	17.0	85–219	
Diastolic blood pressure (mmHg)	77.7	9.3	41–119	
Fibrinogen (mg/dl)	276.8	56.6	72–595	
PAI-1 (ng/ml)	17	10–28	1–322	
CRP (mg/l)	1.8	0.8–3.7	0.1–67.8	
Sex (% female)	—	—	—	56.4
NHW/AA/HA	—	—	—	40.0/26.5/33.5
IGT	—	—	—	34.0

Sample sizes vary slightly because of occasional missing values. Differences were assessed using t tests or χ^2 tests.

ponents of this cluster (10,11) and add independently to the prediction of CVD and diabetes (12,13).

However, the physiological and statistical complexity of the associations between these variables has made elucidation of the underlying etiological relationships difficult. Factor analysis has been proposed as a complementary approach that might aid in the interpretation of the underlying physiological and statistical structure of the metabolic syndrome (14,15). This multivariate statistical technique reduces a large number of intercorrelated variables to a smaller set of latent or underlying orthogonal (uncorrelated) independent factors (14–16). Several publications have reported factor analyses of conventional metabolic syndrome variables in various populations (14,15,17–32). Only a limited number, however, have used direct measures of insulin sensitivity (19,29,32), and only two have included nontraditional cardiovascular risk factors, including the inflammatory measures PAI-1, fibrinogen, CRP, and white cell count (24,30). Furthermore, although the ability of metabolic syndrome factors to predict incident CVD has been assessed in a number of publications (27,28,33–35), less information is available regarding factors and the prediction of type 2 diabetes (36,37) or how this prediction compares to that from models containing conventional risk factors or impaired glucose tolerance (IGT).

The objective of this study was to investigate, using factor analysis, the clustering of CVD risk factors, inflammation variables, and insulin resistance using data from 1,087 nondiabetic participants in the Insulin Resistance Atherosclerosis Study (IRAS) and to determine whether these clusters predict the development of type 2 diabetes over time. This study includes information on traditional and nontraditional risk factors for CVD and type 2 diabetes, as well as directly measured insulin sensitivity (S_i) from the frequently sampled intravenous glucose tolerance test (FSIGT) among middle-aged African-American (AA), Hispanic (HS), and non-Hispanic white (NHW) subjects.

RESEARCH DESIGN AND METHODS

The IRAS is a multicenter observational epidemiologic study of the relationships between insulin resistance, CVD, 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 (38,39). Briefly, the study was conducted at four clinical centers. At centers in Oakland and Los Angeles, California, NHW and AA subjects were recruited from Kaiser Permanente, a nonprofit health maintenance organization. Centers in San Antonio, Texas, and San Luis Valley, Colorado, recruited NHW and Hispanic-American (HA) subjects from two ongoing population-based studies (the San Antonio Heart Study and the San Luis Valley diabetes study) (38). A total of 1,625 individuals participated in the baseline IRAS examination (56% women), which occurred between October 1992 and April 1994. After an average of 5.2 years (range 4.5–6.6), follow-up examinations of this cohort were conducted using the protocol used at baseline. The response rate was 81%, and individuals who attended the follow-up examination were similar to those who did not attend in terms of ethnicity, sex, baseline glucose tolerance status (normal glucose tolerance vs. IGT), and BMI (all comparisons, $P > 0.32$). 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 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 (40). During the second visit, insulin sensitivity and insulin secretion were determined using a frequently sampled intravenous glucose tolerance test, with two modifications to the original protocol (41). 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 (42). Second, a reduced sampling protocol (with 12 rather than 30 samples) was used for efficiency given the large number of participants (43). Insulin sensitivity, expressed as the insulin sensitivity index (S_i), was calculated using mathematical modeling methods (MINMOD version 3.0, 1994) (44). The repeatability of S_i has been demonstrated in a subsample of the IRAS cohort (45), and the estimate of S_i from this modified protocol has been validated against gold standard measures of insulin resistance from the hyperinsulinemic-euglycemic clamp technique (r = 0.95) (46).

Height and weight were measured to the nearest 0.5 cm and 0.1 kg, respectively. BMI was calculated as weight/height^2 (kg/m^2) and was used as an estimate of overall adiposity. Waist circumference, a validated estimate of visceral adiposity (47), 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

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

	BMI	Waist	Fasting glucose	Fasting insulin	S_i	Triglyceride	HDL cholesterol	Systolic blood pressure	Diastolic blood pressure	Fibrinogen	PAI-1	CRP
Age	−0.03	0.03	0.07	−0.04	−0.07	0.09	0.08	0.32	−0.06	0.12	−0.02	0.08
BMI		0.78	0.33	0.53	−0.54	0.21	−0.22	0.25	0.20	0.27	0.34	0.43
Waist			0.42	0.52	−0.54	0.30	−0.38	0.27	0.24	0.20	0.39	0.33
Fasting glucose				0.37	−0.34	0.15	−0.18	0.24	0.15	0.06	0.23	0.14
Fasting insulin					−0.68	0.34	−0.33	0.20	0.19	0.19	0.43	0.34
S_i						−0.30	0.29	−0.25	−0.16	−0.21	−0.38	−0.39
Triglyceride							−0.44	0.07	0.06	0.00	0.36	0.20
HDL cholesterol								0.06	−0.05	−0.05	−0.33	−0.04
Systolic blood pressure									0.57	0.17	0.09	0.22
Diastolic blood pressure										0.07	0.18	0.12
Fibrinogen											0.13	0.52
PAI-1												0.24

See Table 1 for units. $P < 0.0001$ for $r > 0.12$; $P > 0.05$ for $r < 0.06$.

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, smoking, and parental or sibling history of diabetes were assessed by self-report.

Laboratory procedures. Glucose concentration was determined using standard methods as described previously (38). Insulin levels were measured using the dextran-charcoal radioimmunoassay (48), which has a 19% external coefficient of variation (CV). This assay displays a high degree of cross-reactivity with proinsulin. 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. The determination of CRP, fibrinogen, and PAI-1 has been described in detail previously (11,49). Briefly, CRP was measured using an in-house ultrasensitive competitive immunoassay (antibodies and antigens from Calbiochem, La Jolla, CA), with an interassay CV of 8.9% (50). Fibrinogen was measured in citrated plasma with a modified clot-rate assay using the Diagnostica STAGO ST4 instrument (51). This procedure was based on the original method of Clauss (52), with a CV of 3.0%. PAI-1 was determined in citrated plasma using a two-site immunoassay that is sensitive to free PAI-1 but not to PAI-1 complexed with tissue plasminogen activator; the CV was 14% (53,54).

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

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 an $S_i = 0$, we used $\log(S_i + 1)$ as the transformation for the insulin sensitivity variable. Principal factor analysis was conducted using the FACTOR procedure of SAS. The number of factors to be retained was based on scree plot analysis (factors above the break in the curve were retained), proportion of common variance explained (>10%), and factor interpretability criteria, which have been described and recommended elsewhere (14,16). The often-cited Kaiser criterion (retain factors with eigenvalues >1) is more appropriate for principal components analysis and may be relaxed for common factor analysis, depending on the number of variables (16). 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. We report both the common variance (proportion of a variance in a variable shared with the common factors) and total variance (common variance plus specific variance plus error variance) explained by the factors. These analyses were initially carried out with all nondiabetic subjects pooled. We then reran the analysis within strata of ethnicity (NHW, AA, and HA) and sex to assess the role of these potential effect-modifying variables. Coefficients of congruence (16,17) were calculated to evaluate similarities between loadings on the same factor stratified by these variables. Additional detail regarding factor analysis in the current study is included in an online appendix at http://diabetes.diabetesjournals.org.

Factor scores were calculated for each subject. These scores represent the subjects' predicted values for each factor and are calculated using the factor weights and the original variable values. The association of factor scores with risk of incident diabetes at the follow-up examination was assessed using logistic regression analysis. Factor scores were modeled as continuous independent variables, with odds ratios referring to risk of diabetes per 1 SD difference. Both univariate (assessing the association with diabetes for each factor separately) and multivariate (all factors with covariates including age, sex, and smoking status) models were constructed. In addition, the multivariate factor model (with covariates age, sex, clinical site, and ethnicity) was compared with models containing either *1*) IGT and covariates or *2*) a clinical model adapted from the work of Stern et al. (5), including age, sex, fasting glucose, systolic blood pressure, HDL, BMI, and parental or sibling history of diabetes and covariates (clinical site and ethnicity). The area under the receiver operating characteristic (AROC) curve for each of these models was calculated. The AROC curve is a measure of how well a variable is able to predict the outcome of interest. AROC curves of the models were formally compared using the DeLong algorithm (55).

RESULTS

Table 1 presents baseline anthropometric and metabolic characteristics of nondiabetic subjects in the IRAS. The results of Spearman correlation analyses of baseline variables are presented in Table 2. BMI and waist circumference showed moderate and statistically significant positive correlations with fasting insulin, PAI-1, and CRP (correlation coefficient range 0.33–0.53, $P < 0.0001$) and significant inverse correlations with S_i ($r = -0.54$, $P < 0.0001$ for both). Both insulin and S_i were significantly and moderately correlated with PAI-1 and CRP (insulin: $r = 0.43$, $r = 0.34$, respectively, both $P < 0.0001$; S_i: $r = -0.38$, $r = -0.39$, respectively, both $P < 0.0001$). Fibrinogen most strongly associated with CRP ($r = 0.52$, $P < 0.0001$) but demonstrated more modest correlations with measures of adiposity and insulin sensitivity.

Table 3 displays the results of factor analysis of metabolic and inflammation variables among nondiabetic subjects in the IRAS. A three-factor solution, which was supported by the retention criteria described in RESEARCH DESIGN AND METHODS, explained 41.8% of the total variance (28.4% factor 1, 7.4% factor 2, 6.0% factor 3) and 101% of the common variance in the dataset (68.7% factor 1, 18.0% factor 2, 14.4% factor 3). These factors were interpreted as *1*) a "metabolic" factor, with positive loadings of BMI, waist circumference, 2-h glucose, log triglyceride, and log PAI-1 and inverse loadings of log $S_i + 1$ and HDL; *2*) an "inflammation" factor, with positive loadings of BMI, waist circumference, fibrinogen, and log CRP and an inverse loading of log $S_i + 1$; and *3*) a "blood pressure" factor, with positive loadings of systolic and diastolic blood pressure.

TABLE 3
Results of factor analysis of anthropometric, metabolic, and inflammation variables, including directly measured insulin sensitivity from the frequently sampled intravenous glucose tolerance test, among nondiabetic subjects in the IRAS

	Factor		
	Metabolic	Inflammation	Blood pressure
BMI	**0.45**	**0.62**	0.14
Waist	**0.63**	**0.49**	0.19
Log (S_i + 1)	**−0.53**	**−0.42**	−0.19
Fasting glucose	0.37	0.17	0.28
2-h glucose	**0.40**	0.30	0.20
Log triglyceride	**0.55**	−0.01	0.02
HDL cholesterol	**−0.57**	0.03	0.05
Systolic blood pressure	0.03	0.17	**0.69**
Diastolic blood pressure	0.09	0.04	**0.66**
Fibrinogen (mg/dl)	−0.03	**0.58**	0.05
Log PAI-1 (ng/ml)	**0.52**	0.17	0.11
Log CRP (mg/l)	0.12	**0.66**	0.11
% Total variance	28.4	7.4	6.0
% Cumulative total variance	28.4	35.8	41.8

Loadings ≥0.40 are in bold.

We also explored the possibility of four- and five-factor solutions; however, these solutions were rejected because they did not meet any of the evaluation criteria described in RESEARCH DESIGN AND METHODS. The results were unchanged when we substituted the log of fasting insulin concentration for log S_i + 1 (data presented in an online appendix).

The results were essentially similar within strata of ethnicity, although the loading of log S_i + 1 on the inflammation factor was slightly weaker in all ethnic subgroups, and waist circumference demonstrated a weaker loading on the inflammation factor among both NHW and HS (Table 4). There were subtle factor pattern differences in separate analyses of males and females (Table 5). Among males, PAI-1 loaded with both the metabolic and inflammation factors, and adiposity measures loaded only on the metabolic factor. Among females, factor loading patterns were generally similar to the pooled analysis, although the inflammation factor (high BMI, waist, fibrinogen, and CRP and low insulin sensitivity) explained a larger amount of total variance than the metabolic factor (high 2-h glucose, triglyceride, and PAI-1 and low insulin sensitivity and HDL). Coefficients of congruence, which provide a formal assessment of the similarity of factor loading patterns between subgroups of sex and ethnicity, were calculated. The modest sex and ethnic differences (HA vs. AA subjects) in loading patterns on the inflammation factor are reflected in the coefficients (males vs. females: metabolic, 0.81; inflammation, 0.69; blood pressure, 0.89; NHW vs. HA subjects: metabolic, 0.99; inflammation, 0.97; blood pressure, 0.92; NHW vs. AA subjects: metabolic, 0.99; inflammation, 0.94; blood pressure, 0.93; HA vs. AA subjects: metabolic, 0.97; inflammation, 0.87; blood pressure, 0.92).

The association of factor scores with prospective risk of diabetes development was assessed using logistic regression (Table 6). In separate univariate analyses, each factor significantly predicted diabetes (metabolic factor: odds ratio [OR] 2.26, 95% CI 1.82–2.80; inflammation factor: 1.57, 1.32–1.87; blood pressure factor: 1.44, 1.20–1.73, all $P <$ 0.0001) (Table 6, models 1–3). These associations were essentially unchanged with adjustment for age, sex, and smoking status (data presented in an online appendix). In a multivariate model including all three factors, there was modest attenuation in the magnitude of the associations, although each factor continued to be a significant predictor (Table 6, model 4). The results were generally similar in separate analyses by sex and ethnicity (Table 7), and there were no significant statistical interactions of sex or ethnicity with the three factors on risk of diabetes (all $P >$ 0.14). There were some notable univariate subgroup differences, however, including no significant association of the blood pressure factor with incident diabetes among male, NHW, or HA subjects and no significant prediction of diabetes with the inflammation factor among AA subjects.

Finally, we compared how the multivariate factor model

TABLE 4
Results of factor analysis of anthropometric, metabolic, and inflammation variables, including directly measured insulin sensitivity from the frequently sampled intravenous glucose tolerance test, among nondiabetic subjects in the IRAS within strata of ethnicity

	NHW			AA			HA		
	Metabolic	Inflammation	Blood pressure	Metabolic	Inflammation	Blood pressure	Metabolic	Inflammation	Blood pressure
BMI	**0.61**	**0.42**	0.18	**0.46**	**0.66**	0.15	**0.70**	0.36	−0.02
Waist	**0.77**	0.26	0.24	**0.60**	**0.54**	0.15	**0.81**	0.24	0.06
Log (S_i + 1)	**−0.64**	−0.32	−0.10	**−0.53**	−0.31	−0.19	**−0.64**	−0.29	−0.19
Fasting glucose	**0.54**	0.01	0.14	**0.52**	−0.07	0.36	**0.42**	0.18	0.30
2-h glucose	**0.46**	0.23	0.06	**0.54**	0.08	0.34	**0.42**	0.32	0.18
Log triglyceride	**0.48**	0.09	−0.01	**0.49**	0.02	−0.06	**0.45**	−0.05	0.18
HDL cholesterol	**−0.55**	0.05	0.09	**−0.46**	−0.10	0.09	**−0.45**	0.17	−0.07
Systolic blood pressure	0.07	0.17	**0.65**	0.06	0.17	**0.66**	0.15	0.17	**0.73**
Diastolic blood pressure	0.09	0.06	**0.64**	0.05	0.11	**0.59**	0.13	−0.03	**0.73**
Fibrinogen	0.08	**0.57**	0.09	−0.02	**0.58**	0.07	0.02	**0.62**	0.03
Log PAI-1	**0.52**	0.17	0.18	**0.50**	0.20	0.20	**0.46**	0.15	0.11
Log CRP	0.18	**0.69**	0.13	0.13	**0.63**	0.14	0.23	**0.68**	0.08
% Total variance	29.7	7.5	5.0	28.1	6.9	6.5	28.9	8.3	6.5
% Cumulative total variance	29.7	37.2	42.2	28.1	35.0	41.5	28.9	37.2	43.7

Loadings ≥0.40 are in bold. Coefficients of congruence: NHW vs. HA: metabolic, 0.99; inflammation, 0.97; blood pressure, 0.92; NHW vs. AA: metabolic, 0.99; inflammation, 0.94; blood pressure, 0.93; HA vs. AA: metabolic, 0.97; inflammation, 0.87; blood pressure, 0.92.

TABLE 5
Results of factor analysis of anthropometric, metabolic, and inflammation variables, including directly measured insulin sensitivity from the frequently sampled intravenous glucose tolerance test, among nondiabetic subjects in IRAS within strata of sex.

	Males			Females		
	Metabolic	Inflammation	Blood pressure	Metabolic	Inflammation	Blood pressure
BMI	**0.86**	0.07	0.12	0.28	**0.85**	0.10
Waist	**0.87**	0.20	0.08	0.38	**0.82**	0.11
Log (S_i + 1)	**−0.53**	**−0.41**	−0.03	**−0.58**	**−0.41**	−0.24
Fasting glucose	0.28	0.21	0.16	0.37	0.28	0.26
2-h glucose	0.29	**0.43**	0.13	**0.56**	0.22	0.22
Log triglyceride	0.31	0.37	−0.28	**0.58**	0.01	0.03
HDL cholesterol	−0.29	−0.24	0.35	**−0.51**	−0.16	0.09
Systolic blood pressure	0.11	0.20	**0.70**	0.10	0.17	**0.66**
Diastolic blood pressure	0.16	0.16	**0.59**	0.02	0.12	**0.61**
Fibrinogen	0.02	**0.51**	0.14	0.04	**0.46**	0.14
Log PAI-1	**0.40**	**0.43**	−0.07	**0.46**	0.24	0.06
Log CRP	0.17	**0.59**	0.14	0.25	**0.51**	0.23
% Total variance	26.9	9.2	5.6	6.7	31.7	5.5
% Cumulative total variance	26.9	36.1	41.7	6.7	38.4	43.9

Loadings ≥0.40 are in bold. Coefficients of congruence: metabolic, 0.81; inflammation, 0.69; blood pressure, 0.89.

predicted diabetes compared with two other commonly used strategies: a model with IGT and covariates or a clinical model including age, sex, fasting glucose, systolic blood pressure, HDL, BMI, and parental or sibling history of diabetes and covariates. The AROC curve for the multivariate factor model was 76.5%, which was similar to that from the model containing clinical variables (78.5%, $P = 0.25$) and greater than that from the model containing IGT, although this difference was of borderline statistical significance (72.0%, $P = 0.06$).

DISCUSSION

In the present study, factor analysis was used to investigate the clustering of metabolic and inflammation variables that have been proposed as important features of the metabolic syndrome. Factor analysis has been suggested as a useful complementary approach to increase our understanding of the underlying structure of the metabolic syndrome, which is characterized by physiological complexity and a high degree of statistical intercorrelation among its core variables (14). Three factors emerged in the present analysis of nondiabetic subjects, which were interpreted as "metabolic," "inflammation," and "blood pressure" factors. These factors were generally consistent across sex and ethnic subgroups, and each factor was found to be significantly associated with progression to diabetes over the follow-up period. The major contribution of this study is the inclusion of a detailed measure of insulin sensitivity in addition to several markers of inflammation, as well as the examination of prospective associations between factor scores and incident diabetes. A limited number of previous studies have contained information on either inflammatory markers (24,30) or direct measures of insulin sensitivity (19,29,32), but to our knowledge, these two physiological domains have not previously been factor-analyzed together. In addition, although two previous studies (36,37) have examined the prospective association between factors and risk of diabetes, these studies were conducted in individual ethnic groups and neither included the detailed metabolic and inflammation variables that were available in the present study. These characteristics represent an important extension of the literature given emerging evidence suggesting that inflammation may represent a component of the metabolic syndrome and indicate increased risk for diabetes development (10,11,56–59). Despite the availability of a direct measure of insulin sensitivity in the current study, it should be pointed out that both total and abdominal adiposity were estimated using indirect measures (BMI and waist circumference, respectively). This limitation has potential implications for the study given emerging evidence indicating a central role for the adipocyte in metabolic regulation.

Two previous articles have presented factor analyses of markers of inflammation and other nontraditional CVD risk factors (24,30). Using data from a cohort study of company health program participants, Godsland et al. (30) reported that two factors explained 32.6% of the variance in this dataset. Conventional metabolic variables (including adiposity, insulin, glucose, and lipids) loaded on the first factor, whereas lifestyle variables, hemoglobin, and white cell count loaded on the second. A recent article by Sakkinen et al. (24) included information on a large number of procoagulation, inflammation, and fibrinolysis measures in elderly participants in the Cardiovascular Health Study (CHS). Factor analysis of these data returned

TABLE 6
Logistic regression analysis of associations of factor scores from the baseline IRAS examination (1992–1994) with risk of incident diabetes at the follow-up examination (median follow-up, 5.2 years)

	OR*	95% CI
Univariate models		
1. Metabolic factor	2.26	1.82–2.80†
2. Inflammation factor	1.57	1.32–1.87†
3. Blood pressure factor	1.44	1.20–1.73†
Multivariate model		
4. Metabolic factor	2.09	1.67–2.60†
Inflammation factor	1.38	1.14–1.67‡
Blood pressure factor	1.41	1.16–1.72‡

*ORs per SD difference in factor score. †$P < 0.0001$; ‡$P < 0.001$.

TABLE 7
Logistic regression analysis of associations of factor scores from the baseline IRAS examination (1992–1994) with risk of incident diabetes at the follow-up examination (median follow-up, 5.2 years): separate analyses by sex and ethnicity

	Sex subgroups		Ethnic subgroups		
	Male	Female	NHW	AA	HA
Univariate models					
1. Metabolic factor	1.71 (1.29–2.26)*	3.59 (2.55–5.05)†	3.18 (2.16–4.68)†	2.56 (1.68–3.91)†	1.87 (1.34–2.60)*
2. Inflammation factor	1.79 (1.32–2.43)*	1.42 (1.14–1.79)‡	1.45 (1.09–1.93)§	1.15 (0.80–1.66)	1.42 (1.06–1.92)§
3. Blood pressure factor	1.24 (0.94–1.64)	1.49 (1.17–1.89)‡	1.32 (0.98–1.77)	2.38 (1.54–3.69)†	1.14 (0.82–1.54)
Multivariate model					
4. Metabolic factor	1.59 (1.20–2.10)‡	3.59 (2.51–5.12)†	2.97 (2.01–4.38)†	2.74 (1.72–4.36)†	1.78 (1.27–2.49)*
Inflammation factor	1.69 (1.22–2.34)‡	1.29 (1.01–1.66)§	1.21 (0.87–1.66)	0.92 (0.61–1.38)	1.31 (0.96–1.78)
Blood pressure factor	1.17 (0.88–1.55)	1.57 (1.19–2.07)‡	1.21 (0.86–1.70)	2.58 (1.61–4.13)†	1.14 (0.83–1.55)

Data are ORs (95% CI). ORs are per SD difference in factor score. *$P < 0.001$; †$P < 0.0001$; ‡P 0.01; §$P < 0.05$.

seven factors that explained 65.9% of the total variance. These factors were interpreted as "body mass," "inflammation," "vitamin K–dependent proteins," "insulin/glucose," "procoagulation," "blood pressure," and "lipids."

Our observation that PAI-1 loaded with insulin sensitivity, body mass, and waist circumference in the "metabolic" factor rather than with CRP and fibrinogen in the separate "inflammation" factor was somewhat unexpected because PAI-1 is considered to be an acute-phase protein (10). This finding, however, is consistent with that of Sakkinen et al. (24), who found that PAI-1 loaded with waist circumference, body weight, and insulin in a "body mass" factor. It is conceivable that excess visceral adipose tissue, represented in these studies by elevated waist circumference, may explain this observation. Visceral adipose tissue may cause elevated PAI-1 either directly (although this is controversial) or indirectly by way of increased synthesis of proinflammatory cytokines such as tumor necrosis factor-α (24,60,61).

Although our factor analysis revealed separate "metabolic" (including adiposity, S_i, lipids, and PAI-1) and "inflammation" (including adiposity, S_i, fibrinogen, and CRP) factors, we found that BMI, waist circumference, and directly measured insulin sensitivity loaded on both of these factors. The observation suggests that adiposity and/or insulin resistance may play a central role in the hyperglycemia, dyslipidemia, and inflammation that characterizes the metabolic syndrome and related conditions (10,62). This notion is supported by the results of previous analyses of the IRAS baseline cohort using more conventional statistical approaches (11,49). Festa et al. (11,49) reported that both BMI and S_i were independently associated with PAI-1, fibrinogen, and CRP in separate models after adjustment for other metabolic variables such as proinsulin concentration and blood pressure. This finding differs from that of Sakkinen et al. (24), who found that adiposity and insulin loaded only with PAI-1 in the "body mass" factor and not with CRP and fibrinogen in the "inflammation" factor. This divergent result may be related to the differences in ethnicity and age structure between the two cohorts; IRAS subjects were multiethnic and middle-aged, whereas CHS participants were elderly and 96.3% were white. Alternatively, the inconsistency may be related to the use of different measures of insulin sensitivity; the CHS used indirect measures including fasting and 2-h insulin, whereas the IRAS used a direct measure of insulin sensitivity from the frequently sampled intravenous glucose tolerance test. Finally, a broader set of variables was available in the CHS, including markers of vitamin K–dependent proteins as well as more markers related to inflammation and procoagulation, which may have resulted in differences in the factor loading pattern.

Factor patterns were remarkably similar in separate analyses of AA, HS, and NHW subjects, suggesting that the underlying mechanisms that cause the clustering of metabolic and inflammation variables are not modified to a large degree by ethnicity. This observation is consistent with the findings of a recent prospective study of IRAS participants, which suggested that the prospective associations of baseline PAI-1, CRP, and fibrinogen with incident diabetes were consistent across these ethnic groups (63). These results notwithstanding, relatively little information is available regarding ethnic differences in measures of inflammation and their relationship to metabolic syndrome variables; thus, additional studies are warranted.

The factor analysis findings presented in this article are based on cross-sectional data, and therefore they are not able to directly contribute to an understanding of the temporal relationship between inflammation and insulin resistance. Although it is possible that the elevated levels of inflammation markers in diabetes and insulin resistance are epiphenomenal events, a recent article by Vozarova et al. (64) reported that an elevated baseline white blood cell count was prospectively associated with worsening directly measured insulin sensitivity.

The significant prospective association between both the metabolic and inflammation factors and risk of diabetes is in line with results of epidemiological studies reporting that individual components of these factors, including adiposity, reduced insulin sensitivity, dyslipidemia, and elevated CRP and PAI-1, are significant predictors of diabetes (56–59,65,66). The absence of an association between the inflammation factor and risk of diabetes among AA subjects is consistent with recent findings from the Atherosclerosis Risk in Communities study (67). Obvious pathophysiological mechanisms to explain this inconsistency between ethnic groups do not immediately come to mind, and the result should primarily be interpreted as a hypothesis-generating observation. The significant association between the blood pressure factor and risk of diabetes is also difficult to interpret. This association appeared to be restricted to females and AA subjects, the latter population known to experience a heavy burden of hypertension (68). Whereas the finding for AA subjects

is consistent with previous studies, including a recent analysis from the Atherosclerosis Risk in Communities group (69), the mechanism for this association is unclear. It is of interest to note that both fasting and 2-h glucose had stronger loadings on the blood pressure factor (0.36 and 0.34, respectively) among AA subjects compared with the other ethnic groups, suggesting the possibility that early impaired glucose regulation may partially explain this association. It is also possible that blood pressure is reflecting some unmeasured risk factor for diabetes in AA subjects. Clinical trial results demonstrating lower diabetes incidence in subjects treated with ACE inhibitors or angiotensin II antagonists raise the possibility that pathophysiological mechanisms underlying hypertension may also influence glucose tolerance via effects on insulin sensitivity or secretion (70,71). Two previous studies have examined prospective associations between metabolic syndrome factors and risk of diabetes (36,37). Kekäläinen et al. (36) reported that the first of four identified factors was significantly predictive of diabetes in a univariate analysis of Finnish subjects with and without a family history of diabetes. This "hyperinsulinemia" factor was characterized by loadings of age, BMI, hypertension, HDL, triglyceride, and glucose and insulin areas. In Pima Indian subjects, Hanson et al. (37) found that three factors, interpreted as insulinemia, body size, and lipids, were significantly associated with risk of diabetes, whereas a fourth blood pressure factor was not predictive. Finally, it was recently reported that the National Cholesterol Education Program definition of metabolic syndrome (which includes abdominal obesity, dyslipidemia, hypertension, and hyperglycemia) was significantly associated with incident diabetes in a population-based study of Hispanics and non-Hispanic whites (3).

In the present study, a multivariate logistic model containing the three factors with covariates was comparable in terms of diabetes prediction to a model containing clinical variables and somewhat more predictive than a model with IGT. Although these results, together with those from a previous article (37), do not support the superiority of factor scores in predicting diabetes, the orthogonal nature of the factors may offer advantages in understanding disease etiology. The present analysis, for example, extends the evidence for separate independent effects of a metabolic variable cluster, inflammation, and hypertension on diabetes risk in a more parsimonious model. The significant association with the blood pressure factor in AA subjects suggests that slightly different prediction strategies might be used in this group.

In conclusion, factor analysis of a group of inflammation and metabolic syndrome variables identified three underlying factors, interpreted as "metabolic," "inflammation," and "blood pressure" factors, all of which were significant predictors of diabetes development. The findings support the emerging hypothesis that chronic subclinical inflammation is associated with insulin resistance and comprises a component of the metabolic syndrome (10–13). Low insulin sensitivity and elevated BMI and waist circumference loaded on both the "metabolic" and "inflammation" factors, indicating a central role for adiposity or insulin resistance (or both) in explaining the clustering of these conventional and emerging CVD risk factors in nondiabetic individuals. The results suggest that strategies to encourage weight loss and improve insulin sensitivity (including lifestyle and pharmacological intervention) may have beneficial effects on both traditional and nontraditional risk factors for type 2 diabetes and CVD.

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