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ORIGINAL CONTRIBUTIONS

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

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Recently, independent factors representing different features of insulin resistance syndrome (Syndrome X) have been identified by factor analysis in middle-aged and elderly adult populations. In this study, factor analysis was applied to the clustering characteristics of Syndrome X in a biracial (Black-White) community-based population of 4,522 children (ages 5–11 years), adolescents (ages 12–17 years), and young adults (ages 18–38 years) from the Bogalusa Heart Study who were screened during 1988–1996. Ponderal index (weight (kg)/height (m)^3), levels of insulin, glucose, triglycerides, and high density lipoprotein cholesterol, and systolic and diastolic blood pressure were used as measures of components of Syndrome X. No evidence was found to support a one-factor hypothesis for this syndrome, but factor analysis yielded two uncorrelated factors (factor 1: insulin/lipids/glucose/ponderal index; factor 2: insulin/blood pressure). These two factors explained 54.6% of the total variance in the entire sample. The factor loading patterns were very similar in all race and age groups, based on high values of coefficients of congruence (0.89–1.0). These results suggest that Syndrome X is characterized by the linking of a metabolic entity (hyperinsulinemia/insulin resistance, dyslipidemia, and obesity) to a hemodynamic factor (hypertension) through shared correlation with hyperinsulinemia/insulin resistance, and that the clustering features are independent of sex and age in both Black and White populations. *Am J Epidemiol* 1999;150:667–74.

blacks; cardiovascular diseases; factor analysis, statistical; insulin resistance; metabolism; Syndrome X; whites

Insulin resistance syndrome or "Syndrome X" has been defined as clustering of cardiovascular disease risk factors, including hyperinsulinemia/insulin resistance, hypertension, dyslipidemia, obesity, and glucose intolerance (1–3). The clustering of risk variables in Syndrome X may reflect interrelations among risk variables or manifestation of a dominant underlying common factor. The coexistence of cardiovascular risk variables related to Syndrome X has been well documented in epidemiologic studies of adults and children (4–11). Although the underlying mechanism(s) of the syndrome is not completely understood, the findings of prospective studies suggest that hyperinsulinemia/insulin resistance may play a role in the development of Syndrome X (3, 5, 7).

While associations between risk variables related to Syndrome X have long been established, strong intercorrelations among these variables make it difficult to determine which variable(s), if any, plays the dominant pathophysiologic role in this disorder. The technique of factor analysis, which resolves highly interrelated variables into a set of composite factors unrelated to each other (12, 13), is particularly useful for examining the multifaceted nature of Syndrome X.

Recently, in an attempt to define a basic phenotype underlying Syndrome X for use in epidemiologic studies, factor analysis has been conducted in middle-aged and elderly adult populations composed mainly of Whites, Japanese Americans, and American Indians (9, 14–17). These studies showed more than one independent pathophysiologic process underlying risk factors clustering in Syndrome X in relatively older adults. However, to our knowledge, results of factor analysis of the components of Syndrome X in children and adolescents have not been reported so far. Furthermore, body fat mass and fat pattern as well as insulin sensitivity change markedly during periods of growth and

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Abbreviation: HDL, high density lipoprotein.

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maturation (18–20). Thus, we performed factor analysis to characterize the clustering features of Syndrome X in a biracial (Black-White) community-based population of children, adolescents, and young adults.

MATERIALS AND METHODS

Study subjects

The Bogalusa Heart Study is a long term epidemiologic study of cardiovascular disease risk factors in children and young adults from birth through 38 years of age in a biracial community (65 percent White, 35 percent Black) in Bogalusa, Louisiana (21). Young adults aged 18–38 years (n = 2,571) were examined in 1988–1991 and 1995–1996. Children and adolescents aged 5–17 years (n = 3,262) were screened during the 1991–1993 school years. After removal of individuals with nonfasting blood samples or missing values for study variables, the final sample size of children, adolescents, and young adults for the current analyses was 4,522 (63.7 percent White, 36.3 percent Black).

Examination procedures

Standardized protocols were used in all examinations, and data were collected by trained staff (21). Informed consent had been obtained before screening. Subjects had been instructed to fast for 12–14 hours, and compliance regarding fasting was determined by interview on the morning of examination. Measurements of height (to ±0.1 cm) and weight (to ±0.1 kg) were performed according to specified protocols (21). Ponderal index (weight (kg)/height $(m)^3$) was used as an indicator of obesity in this study because, unlike body mass index (weight (kg)/height $(m)^2$), it does not relate to height in children and adolescents. Blood pressure measurements were made on the right arm in seated, relaxed subjects. For both systolic and diastolic blood pressure, the average of six replicate mercury readings taken by two randomly assigned trained nurses was used in these analyses.

Laboratory analyses

Cholesterol and triglyceride levels were measured using enzymatic procedures on the Abbott VP instrument (Abbott Laboratories, North Chicago, Illinois) (22, 23). Serum lipoprotein cholesterol levels were analyzed by a combination of heparin-calcium precipitation and agar-agarose gel electrophoresis procedures (24). The laboratory used is monitored by the Lipid Standardization and Surveillance Program of the Centers for Disease Control and Prevention (Atlanta, Georgia). A commercial radioimmunoassay kit was used for measuring plasma immunoreactive insulin level (Padebas Pharmacia, Piscataway, New Jersey). Plasma glucose level was measured by an enzymatic method using the Beckman Instant Glucose Analyzer (Beckman Instruments, Palo Alto, California).

Statistical methods

All data analyses were performed using SAS (25). To improve the normality of the data distributions, we log-transformed triglyceride and insulin levels for significance tests, correlation analysis, and factor analysis. Associations between individual pairs of risk variables were examined using partial Pearson's correlation coefficients. All statistical analyses were carried out separately for Whites and Blacks and for three age groups: children (ages 5–11 years), adolescents (ages 12–17 years), and young adults (ages 18–38 years). One hundred and two young adults who were taking antihypertensive medication at the time of examination were excluded from factor analysis. None were taking cholesterol-lowering medications. The disorders of high blood pressure, obesity, hyperinsulinemia, and dyslipidemia were defined as having values in the race-, sex-, and age-specific extreme quartiles of elevated systolic and/or diastolic blood pressure, ponderal index, insulin level, and triglyceride level and/or decreased high density lipoprotein (HDL) cholesterol level, respectively. Subjects taking antihypertensive medications were considered to have high blood pressure regardless of their measured blood pressure levels.

Factor analysis was performed using principal-components analysis with varimax rotation to condense highly intercorrelated risk variables to a few hypothetical underlying "factors." Data were stratified with respect to race and three age groups. R-mode factor analyses, methods for studying the interrelations among variables, were carried out with adjustment for sex and age within each age group in Blacks and Whites. We performed factor analysis using the principal-components option of the SAS FACTOR procedure. The factor analysis process consists of the following three steps (12, 13).

Principal-components analysis. Principal-components analysis transforms the original variables into a new set of components which are independent of each other; i.e., they are uncorrelated or orthogonal. These components are linear combinations that account for the maximum amount of total variance in the original data. The minimum number of components was identified on the basis of eigenvalues, although there may be as many principal components as the original variables. Eigenvalues are the sum of the squared factor loadings, and they represent the amount of variance attributable to each component. The default cutoff

point for eigenvalues is set to 1.0 in the SAS FACTOR procedure.

Rotation of principal components. After they were identified, the components were rotated using a varimax rotation method to produce interpretable factors. This orthogonal rotation is a transformation of the original components that produces factors unrelated to each other but highly correlated with unique subsets of the original risk variables. With the varimax rotation method, the loading coefficients were made large or small so that some variables had high loadings on a small number of factors. The amount of variance explained by each factor had to be recalculated after rotation, since the proportions of variance had been reallocated by rotation.

Interpretation of factors. Factor loading coefficients are equivalent to correlation coefficients between the factors and the original independent risk variables and can be used to interpret the factors. Through assessment of the magnitude of loading coefficients, factors are named based on the risk variables loading highly on these derived factors. Only variables with loadings greater than or equal to 0.3 were considered for interpretation in the present study.

Coefficients of congruence were calculated to examine the extent of agreement between corresponding factor loadings in selected subgroups of the sample with respect to race, sex, and age. The coefficient of congruence can range in value from 1 for perfect agreement to 0 for no agreement. We used the maximum likelihood factor analysis option in SAS FACTOR to conduct the significance test for the number of common factors. This method gave a statistic with an approximately χ^2 distribution. The null hypothesis, H_0, is the hypothesis that m factors are sufficient to explain the majority of the variance, and the alternative hypothesis, H_A, is that some larger number of factors may be assumed to explain the observed correlations.

RESULTS

Risk variables

Table 1 shows the mean levels (and standard deviations) of risk variables included in the factor analysis, by race and age group. Sex differences were significant for triglycerides (females > males in children and adolescents; males > females in adults) and glucose (males > females), and racial differences were significant for triglycerides (Whites > Blacks), HDL cholesterol (Blacks > Whites), and insulin (Blacks > Whites). Sex and race differences in other variables were not consistent across the three age groups. The prevalence of Syndrome X, consisting of high blood pressure, dyslipidemia (high triglycerides and/or low HDL cho-

TABLE 1. Levels of risk variables and prevalence of insulin resistance syndrome (Syndrome X), by race and age group, Bogalusa Heart Study, 1988–1996

Variable	Children (ages 5–11 years) (n = 1,088)				Adolescents (ages 12–17 years) (n = 1,427)				Young adults (ages 18–38 years) (n = 2,007)			
	Whites		Blacks		Whites		Blacks		Whites		Blacks	
	Mean	SD†	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Systolic blood pressure (mmHg)	98.1	8.7	97.8	8.3	105.4	8.8	106.9**	9.3	109.4	9.6	112.7***	10.7
Diastolic blood pressure (mmHg)	58.1	8.2	57.3	8.6	65.4	7.5	65.6	7.6	72.1	7.9	72.6**	8.8
Triglycerides (mg/dl)	80.7	39.4	67.7***	28.5	96.7	51.8	70.6***	27.6	118.2	90.1	88.5***	62.5
HDL† cholesterol (mg/dl)	51.8	10.6	59.3***	12.3	48.4	10.2	55.9***	13.3	48.0	12.3	54.9***	14.2
Glucose (mg/dl)	79.1	6.3	77.7**	7.9	81.6	7.0	80.8	7.9	80.3	14.3	80.2	10.4
Insulin (μU/ml)	8.8	5.9	9.5***	6.0	12.5	7.9	13.7*	9.7	11.2	7.5	13.6***	13.1
Ponderal index‡	13.8	2.4	13.6	2.5	13.7	3.0	13.7	3.1	15.3	3.5	16.4***	4.5
Prevalence of Syndrome X§ (%)	4.8		3.7		3.0		2.7		3.6		2.4	

* $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$ (racial difference, adjusted for sex and age).
† SD, standard deviation; HDL, high density lipoprotein.
‡ Weight (kg)/height (m)^3.
§ Components of Syndrome X: high blood pressure, dyslipidemia (elevated triglycerides and/or decreased HDL cholesterol), hyperinsulinemia, and obesity, defined as extreme quartiles specific for race, sex, and age. For high blood pressure, subjects on antihypertensive medication were also included regardless of their blood pressure levels.

lesterol), hyperinsulinemia, and obesity without hyperglycemia, ranged from 2.4 percent to 4.8 percent. The observed prevalence rates were 8–37 times those expected for Syndrome X. No significant race difference was observed in the prevalence rates of Syndrome X by age group.

Correlation analysis

Table 2 gives partial Pearson correlation coefficients, adjusted for sex and age, between risk variables, by race and age group. All correlation coefficients shown in table 2 were significant ($p < 0.01$). In general, correlations were stronger in Whites than in Blacks and numbers of significant correlations were more common in adults than in children and adolescents. HDL cholesterol was always negatively correlated with other variables.

Factor analysis

The hypothesis that one common factor underlies Syndrome X was tested in all six race- and age-specific groups. The null hypothesis that one factor was sufficient to explain the majority of the variance was rejected ($p < 0.001$). The alternative hypothesis that more factors are needed to explain a significant proportion of the total variance was accepted. Two factors were generated for all groups that fitted the criterion of an eigenvalue greater than 1.0.

The factor loading patterns of the two factors generated are presented in table 3, by race and age group. Triglycerides, fasting insulin, and ponderal index loaded positively on factor 1, and HDL cholesterol loaded negatively on this factor in all race-age groups. Fasting glucose was included in factor 1 with positive loading in adults and Black adolescents, whereas its loadings were low on factor 1 in White children and adolescents. While systolic and diastolic blood pressure consistently had high positive loadings on factor 2 in all race-age groups, other risk factors showed no consistent correlation with factor 2 among the race-age groups. These two factors explained 49.7–58.6 percent of the total variance in the six groups.

We calculated coefficients of congruence, a measure of the degree of similarity in factor patterns, to compare factor loading patterns between race-sex-age groups. High coefficients of congruence ranging from 0.89 to 1.0 were noted in all race-sex-age groups. All of the race-sex-age groups were pooled, based on the similarity of the factor patterns. Table 4 shows the factor loadings of the entire sample. The one-factor hypothesis was rejected at the significance level of $p < 0.001$, and two factors were identified. Triglycerides, HDL cholesterol, fasting insulin, fasting glucose, and ponderal index loaded on factor 1, with high loading values. Blood pressure and fasting insulin loaded on factor 2. The loading of ponderal index on factor 2 was much smaller than the loading of fasting insulin. The variance explained by these two factors was 54.6 percent of the total variance in the entire sample.

A graphic illustration of the factor loading pattern based on the entire sample is presented in figure 1. As was noted above, only variables with loadings greater than or equal to 0.3 were considered for interpretation. Five metabolic variables—triglycerides, HDL cholesterol, glucose, insulin, and ponderal index—were linked to factor 1. Factor 2 was characterized by blood pressure and insulin levels. Factors 1 and 2 were unified by a shared correlation with fasting insulin.

DISCUSSION

The uniformity of Syndrome X and the possibility of a single underlying etiologic basis for Syndrome X have been challenged in epidemiologic studies (9, 14–16, 26), although a common genetic influence on the components of Syndrome X has been suggested in several genetic studies (27–30). In the present study, factor analysis was used to characterize Syndrome X among Black and White children, adolescents, and young adults in a large, biracial community-based sample from the Bogalusa Heart Study. The large sample provided us with a unique opportunity to compare the clustering features of the risk variables in terms of factor patterns among children, adolescents, and young adults, as well as Blacks and Whites. In the current analysis, seven cardiovascular risk variables were reduced to two independent composite factors in all six race-age groups and in the entire sample, suggesting that a one-factor model could not explain sufficiently the clustering of components of Syndrome X. These two factors, which explained 50–59 percent of the total variance, were interpreted as 1) insulin/lipids/glucose/obesity and 2) insulin/blood pressure factors. Earlier studies of factor analysis of Syndrome X found 2–4 uncorrelated factors characterizing this syndrome. In general, factors of insulin/lipids/obesity, blood pressure/obesity, blood pressure/obesity/insulin, glucose/insulin, and obesity/insulin have been reported (9, 14–17). These studies and the present one used an eigenvalue greater than or equal to 1 as the criterion for defining the factor in the SAS FACTOR procedure (25). Note that comparison of results from different factor analyses is limited by differences in the race, sex, and age composition of the study samples, the number of risk variables included, sample sizes, and the cutoff points of loadings set by the investigators.

TABLE 2. Age- and sex-adjusted Pearson correlations among risk variables, by race and age group, Bogalusa Heart Study, 1988–1996

Variable	Diastolic blood pressure		Log triglycerides		High density lipoprotein cholesterol		Glucose		Log insulin		Ponderal index	
	Blacks	Whites	Blacks	Whites	Blacks	Whites	Blacks	Whites	Blacks	Whites	Blacks	Whites
Children (ages 5–11 years)												
Systolic blood pressure	0.54	0.61	0.16	0.32	—*	–0.12	0.17	0.33	0.32	0.42	0.28	0.43
Diastolic blood pressure			—	0.24	—	–0.12	—	0.21	0.21	0.29	0.20	0.34
Log triglycerides					–0.22	–0.41	—	0.17	0.42	0.43	0.29	0.39
High density lipoprotein cholesterol							—	—	–0.17	–0.23	–0.22	–0.28
Glucose									0.33	0.35	—	0.16
Log insulin											0.44	0.57
Adolescents (ages 12–17 years)												
Systolic blood pressure	0.41	0.52	—	0.14	—	—	—	0.15	0.20	0.25	0.12	0.20
Diastolic blood pressure			—	0.10	—	—	—	0.12	—	0.20	—	0.20
Log triglycerides					–0.28	–0.42	—	—	0.33	0.44	0.25	0.40
High density lipoprotein cholesterol							–0.13	—	–0.26	–0.30	–0.33	–0.30
Glucose									0.19	0.34	0.13	0.10
Log insulin											0.45	0.61
Young adults (ages 18–38 years)												
Systolic blood pressure	0.66	0.70	0.12	0.25	—	—	0.11	0.09	0.22	0.28	0.24	0.29
Diastolic blood pressure			0.12	0.24	—	–0.07	—	0.11	0.21	0.27	0.23	0.30
Log triglycerides					–0.26	–0.38	—	0.14	0.36	0.49	0.23	0.39
High density lipoprotein cholesterol							–0.16	–0.09	–0.36	–0.29	–0.31	–0.28
Glucose									0.38	0.27	0.26	0.19
Log insulin											0.59	0.63

* Correlation coefficient with $p > 0.01$.

TABLE 3. Factor loadings of risk variables for Syndrome X after varimax rotation, by race and age group, Bogalusa Heart Study, 1988–1996*

Variable	Blacks		Whites	
	Factor 1	Factor 2	Factor 1	Factor 2
Children (ages 5–11 years)				
Systolic blood pressure	0.11	0.85†	0.19	0.82†
Diastolic blood pressure	–0.01	0.84†	0.10	0.75†
Log triglycerides	0.74†	0.03	0.76†	0.21
High density lipoprotein cholesterol	–0.57†	0.07	–0.81†	0.12
Glucose	0.24	0.31†	0.02	0.60†
Log insulin	0.70†	0.37†	0.54†	0.54†
Ponderal index	0.63†	0.29	0.59†	0.47†
Variance explained (%)	26.2	25.0	27.4	31.1
Cumulative variance (%)	26.2	51.2	27.4	58.5
Adolescents (ages 12–17 years)				
Systolic blood pressure	0.16	0.82†	0.06	0.84†
Diastolic blood pressure	–0.09	0.84†	0.02	0.84†
Log triglycerides	0.63†	–0.10	0.76†	0.04
High density lipoprotein cholesterol	–0.65†	0.09	–0.69†	0.06
Glucose	0.34†	0.05	0.20	0.35†
Log insulin	0.74†	0.17	0.75†	0.33†
Ponderal index	0.73†	0.09	0.73†	0.25
Variance explained (%)	29.2	20.5	31.3	24.4
Cumulative variance (%)	29.2	49.7	31.3	55.7
Young adults (ages 18–38 years)				
Systolic blood pressure	0.10	0.89†	0.12	0.91†
Diastolic blood pressure	0.07	0.90†	0.14	0.89†
Log triglycerides	0.53†	0.09	0.72†	0.17
High density lipoprotein cholesterol	–0.67†	0.18	–0.67†	0.16
Glucose	0.53†	0.03	0.39†	0.06
Log insulin	0.82†	0.20	0.78†	0.25
Ponderal index	0.72†	0.26	0.72†	0.28
Variance explained (%)	31.8	24.9	32.6	26.0
Cumulative variance (%)	31.8	56.7	32.6	58.6

* Data represent factor loading, the correlation between the individual variable and each factor.
† Loadings with absolute values ≥0.3.

TABLE 4. Factor loadings of risk variables for Syndrome X after varimax rotation in the total sample (n = 4,522), Bogalusa Heart Study, 1988–1996

Variable	Factor 1	Factor 2
Systolic blood pressure	0.16	0.88†
Diastolic blood pressure	0.11	0.89†
Log triglycerides	0.70†	0.08
High density lipoprotein cholesterol	–0.66†	0.09
Glucose	0.38†	0.14
Log insulin	0.76†	0.30†
Ponderal index	0.70†	0.17
Variance explained (%)	30.1	24.5
Cumulative variance (%)	30.1	54.6

* Data represent factor loading, the correlation between the individual variable and each factor.
† Loadings with absolute values ≥0.3.

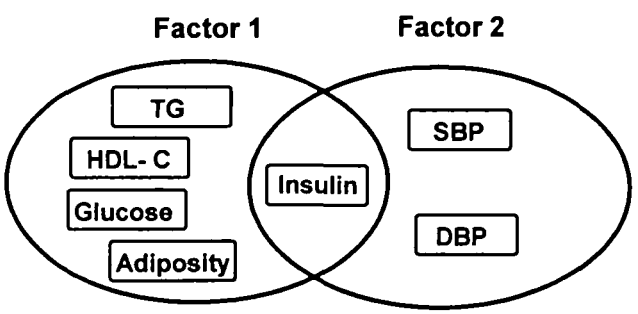

FIGURE 1. The factor loading pattern of risk variables related to insulin resistance syndrome (Syndrome X) in a factor analysis of 4,522 subjects aged 5–38 years, Bogalusa Heart Study, 1988–1996. The small boxes represent seven risk variables included in the analysis; the large circles represent two factors characterizing two distinct features of Syndrome X. The two features are linked by the shared correlations with hyperinsulinemia. Variables loaded on each factor were interpreted with loadings greater than or equal to 0.3. TG, triglycerides; HDL-C, high density lipoprotein cholesterol; SBP, systolic blood pressure; DBP, diastolic blood pressure.

The high coefficients of congruence (0.89–1.0) of the two factors noted in the present study indicate that the factor patterns were similar among Whites and Blacks and males and females, as well as among children, adolescents, and young adults. The similarity of factor patterns among males and females in this study is consistent with the findings of the Framingham Offspring Study (9) and the Strong Heart Study (17) regarding the lipids/obesity factor and the blood pressure factor. The consistency and similarity of the factor patterns among the race-sex-age groups suggest that factors characterizing the clustering of risk variables are independent of sex and age in both Black and White populations. Despite the similarity of factor patterns as a whole in Black and White subjects based on high coefficients of congruence, loadings of glucose (0.05), insulin (0.17), and ponderal index (0.09) on factor 2 in Black adolescents were much lower than those in their White counterparts (table 3). The differences in loadings may reflect a different correlation structure of blood pressure, insulin, and obesity during periods of growth and maturation in Black adolescents. Longitudinal data from the same population showed marked changes in cardiovascular risk profiles from childhood to adulthood, especially for the insulin-resistant state in Black girls (4).

Fasting insulin level, an indicator of insulin resistance (31), loaded highest within factor 1 in the total study population. Factor loading for insulin was also high in individual race-age groups, except Black adolescents. In agreement with earlier reports (9, 14, 17), the present study demonstrates that hyperinsulinemia/insulin resistance, dyslipidemia, and obesity form a closely interrelated physiologic entity. The fact that insulin was loaded along with blood pressure in factor 2 to form a distinct physiologic entity suggests that hypertension was linked to other components of Syndrome X through hyperinsulinemia/insulin resistance. These findings support the concept that hyperinsulinemia/insulin resistance plays a pivotal role in risk variable clustering (3, 5, 7, 32).

Although an interrelation between hyperinsulinemia/insulin resistance, dyslipidemia, and obesity is well established (4, 6, 10, 11), the evidence for an association of hypertension with hyperinsulinemia/insulin resistance and dyslipidemia is not consistent (9, 14–16). Obesity has been shown to be associated with dyslipidemia, hypertension, and hyperinsulinemia/insulin resistance in both children and adults (5, 6, 11, 32–36). In this study, correlation analysis showed that ponderal index correlated with other risk factor variables as highly as fasting insulin did. In factor analysis, loading for ponderal index in factor 2 was very close to the cutoff point of 0.3 in all race-age groups except Black adolescents. However, the loading was reduced to just 0.17 in the entire sample. Therefore, it is not clear whether hyperinsulinemia/insulin resistance plays a role in linking hypertension to other components of Syndrome X through its shared association with obesity. Furthermore, conclusions regarding causal relations between variables cannot be drawn from factor analysis using cross-sectional data. Confirmation of the causal relation between hyperinsulinemia/insulin resistance and the clustering of risk variables will require longitudinal data and a better understanding of other mechanisms influenced by these variables.

In summary, factor analysis showed the presence of two distinct physiologic processes characterizing the clustering of risk variables related to Syndrome X. The occurrence of a distinct metabolic entity characterized by hyperinsulinemia/insulin resistance, dyslipidemia, and obesity which is linked to hypertension through hyperinsulinemia/insulin resistance provides an alternative means of examining the association between risk variables and coronary heart disease in terms of uncorrelated factors measured by factor scores rather than as individual variables.

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