Factor analysis of risk variables associated with metabolic syndrome in adult Asian Indians

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ABSTRACT

Background: Several studies hinted about the clustering of risk variables of the metabolic syndrome (MS) and suggested that the underlying genetic polymorphisms could be responsible for the increasing incidence of coronary heart disease (CHD) in people of Indian origin. Therefore, identification of the components of the MS along with the genetic factors could be one of the aspects to make an attempt to prevent the increasing incidence of CHD. **Materials and Methods:** Principal component factor analysis (PCFA) was undertaken to identify the components or factors of the MS among the adult ($\geq$30 years) Asian Indians living in and around Calcutta, India. The study comprised 350 adult Asian Indians. Anthropometric measurements were taken, and lipid profiles, blood pressure and fasting blood glucose were measured for each participant. Two genetic polymorphisms, namely, angiotensin converting enzyme (ACE) gene polymorphism (insertion/deletion [I/D]) or ACE (I/D) and apolipoproteinE (Hha I) were also studied. **Results:** PCFA revealed 3 factors that cumulatively explained 65.39% of the observed variance of the MS by measured variables. The 3 factors identified were lipids and lipoprotein (Factor 1), centripetal fat and blood pressure (Factor 2), and ACE (I/D) polymorphism with blood pressure (Factor 3). Moreover, the first 2 factors, that is, lipids, lipoprotein, centripetal fat, and blood pressures cumulatively explained ~46% (45.94%) of the observed variance of MS in this population. **Conclusions:** Since more than 1 factor was identified for the MS phenotype, more than 1 physiogenetic mechanism could be accounted for MS in the Asian Indian population.

Key words: Asian Indians, factors, gene polymorphism, metabolic syndrome, obesity

INTRODUCTION

The prevalence of coronary heart disease (CHD) is known to be very high among Indians, both in India and abroad. Moreover, among Indians, CHD occurs at least a decade or 2 earlier compared with Europeans.[1,2] The reason for the increased susceptibility of Indians to CHD is yet to be completely understood. However, several studies have hinted that the clustering of risk variables (mechanism of which is still unknown) of metabolic syndrome (MS) could be responsible for the increasing incidence of CHD among Indians. This includes central obesity, hypertriglyceridemia, less levels of high-density lipoprotein cholesterol, high blood pressure, and high levels of fasting blood glucose,[1-4]

along with certain genetic factors (genetic polymorphisms) that adversely affect the levels of such variables, for example, angiotensin converting enzyme (ACE) gene polymorphism (insertion/deletion [I/D]) or ACE (I/D) and ApolipoproteinE gene (ApoE) polymorphisms.[5]

Throughout the Asia-Pacific region, there are differences in obesity prevalence as well as in body fat distribution[6] In Asian populations, morbidity and mortality from cardiovascular diseases (CVD) is occurring also in people with lower body mass index (BMI) and smaller waist circumference.[7,8] Thus, they tend to accumulate intra-abdominal visceral fat without developing generalized obesity.[1,7-9] South Asians have a more centralized

distribution of body fat and markedly higher mean waist–hip ratio for a given level of BMI compared with Europeans and Americans.[5-9] The MS, which can be defined as the constellation of CVD risk factors, is one of the growing public health burdens in the Asia-Pacific region, although people of this region are no more overweight than Europeans and Americans.[6,9]

Several statistical techniques could be applied to identify the components of the MS. Principal component factor analysis (PCFA) is one such approach that groups quantitatively measured variables into clusters known as factors, on the basis of the correlation between variables.[10] PCFA was used to identify the domains of the risk variables of the MS. For example, if there is a single underlying cause for the clustering of the risk variables of the MS, then factor analysis should produce only 1 major factor or component. Therefore, identification of component(s) of the MS (considered to be the leading cause of CHD) is most essential for the etiology of CHD[7] However, a very few studies have so far been undertaken to identify the components of the MS in Asian Indian population[7-9,11-15] These studies suggested that there existed no single or central etiological factor for the clustering of MS phenotypes.[7,8] Therefore, it seems reasonable to argue that several underlying abnormalities do exist that might have relatively greater genetic basis.[7,8]

However, to the best of the authors' knowledge, no study has been undertaken on Asian Indians incorporating the genetic polymorphism(s), lipids, blood glucose, blood pressure, and body fat patterns simultaneously to identify the components of MS in this ethnic group. Keeping this view in mind, the present investigation is an attempt to find out the *physiogenetic* factors responsible for the observed variation of MS in the Asian Indian population living in the eastern part of India.

MATERIALS AND METHODS

Study population

The present community-based cross-sectional study comprised adult (≥30 years) Asian Indians living in and around Calcutta, India. A total of 350 (male = 184 and female = 166) individuals participated in the study. Pregnant women, women undergoing hormone therapy, as well as individuals with known illnesses, such as ischemic heart disease, type 2 diabetes mellitus, and hypertension were not included in the study. Prior to participation, public advertisement was given about the study with the help

of the local officials. Individuals who responded to the advertisement were selected randomly. It is noteworthy that only unrelated adults from a household were included as participants to avoid the effects of intra-household clusters of CVD risk factors. The Institutional Ethics Committee (IEC) of the "Human Genetic Engineering Research Center" (HGERC), Calcutta, India, has approved the study. Written consent from the participants was also obtained prior to the actual commencement of the study.

Anthropometric measurements

Anthropometric measurements, namely, height, weight, waist circumference, and subcutaneous skinfold were obtained using standard techniques.[16] Height and weight (in light clothing) were measured to the nearest 0.1 cm and 0.5 kg, respectively. Waist circumference (WC) was measured to the nearest 0.1 cm using an inelastic tape. The minimum WC was measured at the level of natural waist, which was the narrowest part of the torso. Subcutaneous skinfolds at biceps, triceps, suprailiac and subscapular sides were measured and the sum of the 4 skinfolds was computed subsequently.

Blood pressure

Left arm systolic and diastolic blood pressure measurements were taken twice using sphygmomanometer and stethoscope and were averaged for analyses. A third measurement was taken only when the difference between the 2 measurements was >5 mmHg. Previous medical records for blood pressure were also taken into consideration.

Metabolic profiles

A fasting blood sample (~7 mL) was collected from each subject for determining the metabolic profiles. All the subjects maintained an overnight fast of ≥12 h prior to blood collection. Estimation of total cholesterol (TC), triglycerides (TG), high-density lipoprotein (HDL), and fasting blood glucose was carried out on separated serum by means of a semi-auto analyzer. All biochemical analyses were estimated in mg/dL (mg%) unit.

Genotyping

Two genetic polymorphisms, namely, ACE (I/D) and ApoE (Hha I) polymorphisms were studied in 138 participants. To study ACE (I/D) and ApoE (Hha I) polymorphisms, DNA samples of participants belonging to the highest (90th) and lowest (10th) percentiles of blood pressure centiles (percentiles) and/or lipids were considered. The

detailed procedures of genotyping have been mentioned elsewhere.[17,18]

Statistical analyses

Descriptive statistics, such as mean and standard deviation (SD), of all the variables were calculated. Frequencies (%) of different alleles of ACE (I/D) and ApoE (HhaI) polymorphisms were also calculated. Factor analysis was undertaken to group quantitatively measured variables into clusters known as *factors*. It was done in 3 steps: computation of a correlation matrix for all variables included; factor extraction; and orthogonal rotation to make factors readily interpretable. The factors were extracted by PCFA in which the linear combinations of the variables were formed with the first component accounting for the largest amount of variance in the sample. Varimax rotation, an orthogonal rotation in which the factors are assumed to act independently (maximum likelihood), was used in the study. The components were all uncorrelated. Variables with a factor loading of at least 0.3 have generally been considered for interpretation, although it is suggested that only loading ≥0.4, which therefore shares at least 15% of the variance with a factor, should be used in the interpretation.[19] A factor loading of ≥0.4 was used to interpret the factors in the study. Previous studies have also used a factor loading of ≥0.4 to interpret the final rotated factor pattern.[7,8,19-24]

All statistical analyses were performed using SPSS (PC+ version 10). A *P* value of < 0.05 (two-tailed) was considered as statistically significant.

RESULTS

The distribution of 184 males and 166 females by age groups and sex is presented in Table 1. It was observed that the participants were distributed more or less equally across the age groups and sex.

The mean and standard deviation (SD) of anthropometric, lipids profile, blood glucose, and blood pressure measures are presented in Table 2. The mean ± SD WC in the study population was 89.38 ± 9.87. The mean (SD) triglyceride in the study was 141.95 (25.30). When the known South Asians' specific cutoffs were taken into consideration, the prevalence of MS in the study was 31.4%.

The frequency of ACE (I/D) and ApoE (Hha I) gene polymorphisms is presented in Table 3. The frequency (%) of Insertion/Insertion (I/I) polymorphism for ACE gene
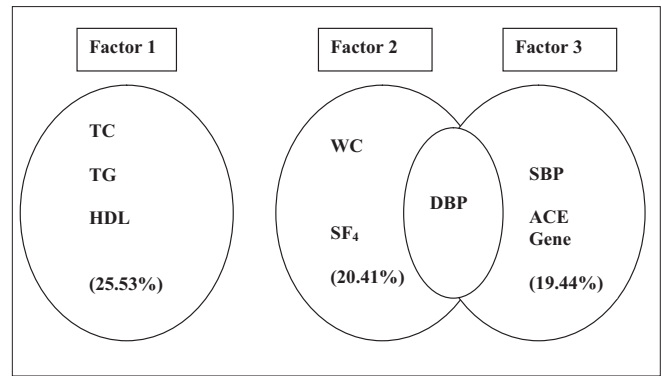

Figure 1: Clustering patterns of cardiometabolic risk variables in the study

Table 1: Distribution of study population by age group and sex

Age group (years)	Male	Female
30–39	20	39
40–49	47	48
50–59	63	43
≥60	57	36

Table 2: Descriptive statistics of study population (n = 350)

Variables	Mean	SD
Waist circumference (cm)	89.38	9.87
Sum of four skinfolds (mm)	97.09	26.58
Total cholesterol (mg%)	202.55	25.76
Triglyceride (mg%)	141.95	25.30
High-density lipoprotein (mg%)	44.35	4.72
Fasting blood glucose (mg%)	90.98	20.73
Systolic blood pressure (mmHg)	134.98	24.31
Diastolic blood pressure (mmHg)	82.82	11.01

was found to be the highest (37%) in the study. On the other hand, epsillion 3/ epsillion 3 for ApoE gene (Hha I) was the most frequent (60.9%) in the study population.

The factor-loading pattern of the 3 factors (components) identified in the study is presented in Table 4. Only variables with loading ≥0.4 were considered for interpretation. The loading of individual risk variable varied from 0.413 to 0.915. The factor 1 (lipids, 25.53%); factor 2 (centripetal fat with blood pressure, 20.41%) and factor 3 (ACE gene along with blood pressure, 19.44%) cumulatively explained 65.39% of the total variation of MS in the study [Figure 1]. Most importantly, the first two factors (lipids, centripetal fat along with blood pressure) cumulatively explained ~46% (45.94%) of the total variation of MS in the study population.

Table 3: Frequency of ACE and ApoE genotypes (n = 138)

Gene	Polymorphic type	n (%)
ACE	Insertion/Insertion (I/I)	51 (37.0)
	Insertion/Deletion (I/D)	47 (34.0)
	Deletion/Deletion (D/D)	40 (29.0)
ApoE	epsillion 2/ epsillion 3	23 (16.7)
	epsillion 2/ epsillion 4	09 (6.5)
	epsillion 3/ epsillion 3	84 (60.9)
	epsillion 3/ epsillion 4	18 (13.0)
	epsillion 4/ epsillion 4	04 (2.9)

ACE, angiotensin converting enzyme; ApoE, apolipoproteinE.

DISCUSSION

The association of central obesity, glucose intolerance, hypertension, dyslipidemia, and hyperinsulinemia known as MS, has been observed in a number of ethnic groups worldwide. Studies across populations demonstrate that MS plays a pivotal role in the occurrence of CVD, including CHD. Therefore, identification of the components of the MS, including the genetic factors would be helpful in understanding the etiology of CHD. A very few studies have so far been undertaken to identify the underlying factors of MS in the Asian Indian population.[7-9,11-15] However, virtually no study has been undertaken on Asian Indians incorporating the genetic polymorphism(s), lipids, blood glucose, blood pressure, and body fat patterns simultaneously to identify the components of MS in this ethnic group. The present investigation was aimed at identifying the *physiogenetic* factors responsible for the observed variation of MS in Asian Indian population living in the eastern part of India.

PCFA had identified 3 factors with 65.39% that explained variance of the MS among the adult Asian Indians of Calcutta. Neither of the variables loaded on all the 3 components. These 3 factors could be identified as lipid (factor 1), centripetal fat with blood pressure (factor 3), and ACE gene along with blood pressure (factor 3). The first 2 factors, that is, lipids, centripetal fat and blood pressure cumulatively explained ~47% of the total variance of the MS in the study population. Except diastolic blood pressure, no overlapping of variables on more than 1 factor indicated that more than 1 variable is responsible for the ultimate phenotype of the MS. The present factor analysis confirmed the general findings from other factor analyses of the MS on different ethnic groups that had 3–4 factors identified [Table 5].

Table 4: Factor loading pattern of cardiometabolic risk factors

	Factors		
Variables	Factor 1	Factor 2	Factor 3
Waist circumference	0.196	0.868*	0.207
Sum of 4 skinfolds	0.108	0.915a	0.060
Total cholesterol	0.824*	−0.069	0.002
Triglyceride	0.898*	0.251	0.090
High-density lipoprotein	−0.867*	−0.233	0.051
Fasting blood glucose	0.314	0.018	0.197
Systolic blood pressure	−0.114	0.281	0.866*
Diastolic blood pressure	−0.028	0.413*	0.808*
ACE gene polymorphism	0.280	−0.283	0.588a
ApoE gene polymorphism	0.275	0.000	0.316
Variance explained	25.53(%)	20.41	19.44
Cumulative variance	25.53(%)	45.94	65.39

ACE, angiotensin converting enzyme; ApoE, apolipoproteinE. a Loading with absolute value ≥ 0.4.

The major limitation of this study is that it was performed on a relatively small sample size, and therefore is not representative of the Asian Indian population. Owing to considerable ethnic and cultural heterogeneity in the Asian Indian population, it is necessary to study other ethnic groups to see if the trends observed here also exist among them. However, it is noteworthy that results from different factor analysis are limited by differences in the ethnic group, sex, and age composition of the study samples, in the number of risk variables included, sample size, and cutoff points of loadings set by the investigators.[7] At the same time, to the best of our knowledge, no PCFA of MS has been undertaken so far, incorporating data on the angiotensin gene and the apolipoproteinE gene, along with the other confounding factors related to the MS in this part of the world. As Indian Diaspora offers a unique opportunity to study the "gene–environment" interaction involved in the etiology of CHD, further comparative studies between Indians living in India and Indians settled elsewhere could yield valuable information on the reasons behind the ethnic susceptibility to CHD among Indians.[7]

This model suggests that the clustering of the variables in MS is a result of multiple factors, including genetic polymorphisms with centripetal fat, lipids, and blood pressure playing key roles. Moreover, all the loaded risk variables, apart from the genetic polymorphism, are modifiable in nature. Therefore, it seems reasonable to argue that early prevention and proper intervention strategies to promote a healthy lifestyle could reduce the burden of MS in this part of the world.

Table 5: Factors of cardiometabolic risk variables across the ethnic groups

Author(s)	Population	Findings
Bhagat *et al.*, (2010)[25]	Adult Asian Indian (women)	Four factors in pre- and postmenopausal women were found and the factors were uncorrelated. It was suggested that a single risk axis for clustering of cardiometabolic phenotypes was highly unlikely.
Oliveira *et al.*, (2010)[26]	Portugal (men and women)	Three factors were identified suggesting that more than one physiological mechanism is associated with high-sensitivity C-reactive protein in both men and women
Deshmukh *et al.*, (2009) [27]	Bogalusa Heart Study (U.S. blacks, white men and women)	Effect of western dietary pattern (WDP) rich in refined grains, high-fat, dairy products, meat and sweets, and PDP consisted of whole grain, legumes, vegetables, fruits etc., were analyzed. Unlike WDP, diet rich in PDP had had inverse association with WC, triceps skinfold, plasma insulin, and MS.
Wu *et al.*, (2008)[28]	Chinese (normal; IGT; type 2 diabetes mellitus)	Three factors were identified: I – blood pressure, II – insulin resistance III – adiposity/glucose. Therefore, it was considered that MS was not unified by a single underlying etiology, that is, insulin resistance.
Harriss *et al.*, (2007)[29]	Australians (native and nonnative)	Dietary pattern and cardiovascular mortality; four dietary factors were identified: I – Mediterranean factor; II and III were vegetables and fruits, respectively; and IV – meat factor not associated with CVD mortality. It was suggested that traditional Mediterranean foods were associated with reduced cardiovascular mortality.
Ghosh (2005)[7]	Adult Asian Indian (men)	Four uncorrelated factors were identified: I – central obesity; II – centralized subcutaneous fat; III – lipid profile, blood glucose; IV – blood pressure. Since no observed variable loaded on all the 4 factors, it was suggested that more than one physiological mechanism could be accounted for risk variables of the MS.
Hanley *et al.*, (2004)[30]	Adult U.S. (African-American, Hispanic, and non-Hispanic whites)	Three factors were identified underlying among a group of inflammation and MS variables: I – metabolic factor; II – inflammation factor; III – blood pressure factor. Insulin sensitivity was loaded on both the metabolic and inflammation variable clusters. Each factor significantly predicted diabetes and therefore it was supported by the emerging hypothesis that chronic subclinical inflammation is associated with insulin resistance and comprises a component of the MS.
Howard *et al.*, (2003)[31]	Adult Women (white, black, Hispanic, Asian/Pacific islander women)	Four factors were identified: I – obesity factor; II – dyslipidemia factor; III – TC and LDL; and IV – blood pressure. It indicated that the components of insulin resistance syndrome was associated with CVD in postmenopausal women, although the magnitude of these relationships differed by ethnicity.
Lehto *et al.*, (2000)[32]	Finland (adult men and women with type II diabetes)	The hyperinsulinemia cluster (a factor having high-positive loadings for BMI, TG, and insulin; and a high-negative loading for HDL) was predictive of death from CHD in patients with type 2 diabetes. Hence, it was mentioned that CVD risk factors clustering with endogenous hyperinsulinemia increase the risk of death from CHD in patients with type II diabetes not treated with insulin.

BMI, body mass index; CVD, cardiovascular diseases; CHD, coronary heart disease; HDL, high-density lipoprotein; LDL, low-density lipoprotein; TC, total cholesterol; TG, triglycerides; WDP, western dietary pattern; PDP, prudent dietary pattern; WC, waist circumference; IGT, impaired glucose tolerance; MS, metabolic syndrome.

ACKNOWLEDGMENTS

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