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Heritabilities of the metabolic syndrome and its components in the Northern Manhattan Family Study

H.-F. Lin, **B. Boden-Albala**, **S. H. Juo**, **N. Park**, **T. Rundek**, and **R. L. Sacco**
Genome Center, Columbia University, 1150 Saint Nicholas Avenue, New York, NY 10032, USA.

Department of Neurology, Kaohsiung Medical University, Kaohsiung, Taiwan

Department of Neurology, Columbia University, New York, NY, USA

Department of Sociomedical Science, Columbia University, New York, NY, USA

Department of Epidemiology, Columbia University, New York, NY, USA

Department of Medical Research, Mackay Memorial Hospital, Taipei, Taiwan

Sergievsky Center, Columbia University, New York, NY, USA

Abstract

Aims/hypothesis—Growing evidence suggests that the traits comprising the metabolic syndrome have a genetic basis. However, studies of genetic contributions to the syndrome are sparse. Against this background, we sought to estimate the heritability of the metabolic syndrome and its component traits.

Materials and methods—We investigated 803 subjects from 89 Caribbean-Hispanic families who have enrolled to date in the current Northern Manhattan Family Study and for whom metabolic syndrome information was available. Metabolic syndrome was defined in accordance with the National Cholesterol Education Program Adult Treatment Panel III (NCEP/ATPIII) criteria. Variance component methods were used to estimate age and sex-adjusted heritability of the metabolic syndrome and its components. To obtain the structures underlying the metabolic syndrome, we performed principal component factor analyses using six quantitative phenotypes included in the ATPIII definition.

Results—The heritability for the metabolic syndrome was 24% (p=0.009), and ranged from 16 to 60% for its five components. Factor analysis yielded two independent factors (factor 1: lipids/glucose/obesity; factor 2: blood pressure). Heritability analysis revealed significant genetic effects on both factors (44% for lipids/glucose/obesity, and 20% for blood pressure).

Conclusions/interpretation—In the Caribbean-Hispanic families investigated, we demonstrated moderate and significant heritabilities for the metabolic syndrome itself, as well as for individual components and independent factors of the syndrome. These results provide evidence that could support future tasks of mapping susceptibility loci for this syndrome.

Keywords

Factor analysis; Genetics; Heritability; Metabolic syndrome

e-mail:shj34@columbia.edu, Tel.: +1-212-8515182, Fax: +1-212-8515176.

Abbreviations

MSS: metabolic syndrome score; NCEP/ATPIII: National Cholesterol Education Program Adult Treatment Panel III; NOMAS: Northern Manhattan Study; NOMAFS: Northern Manhattan Family Study; SOLAR: Sequential Oligogenic Linkage Analysis Routines

Introduction

The metabolic syndrome is a highly prevalent constellation of vascular risk factors including elevations of blood pressure, blood glucose, waist circumference and triglycerides, as well as lower levels of HDL-cholesterol. Although several definitions of the metabolic syndrome exist, it has been most frequently defined using the National Cholesterol Education Program Adult Treatment Panel III (NCEP/ATPIII) criteria [1]. The syndrome is also associated with increased risk of cardiovascular disease [2–4], stroke [5,6] and type 2 diabetes [7,8]. Based on the result of a prospective cohort study in a Finnish population [4], the presence of the metabolic syndrome provides a substantial additional cardiovascular risk above and beyond the individual risk factors [9]. Therefore, the syndrome may provide additional information with which to identify patients at high risk.

The prevalence of the metabolic syndrome varies among ethnic groups [10–12]. According to the Third National Health and Nutrition Examination Survey, adult prevalence of the metabolic syndrome was 32% in Hispanic-Americans, 22% in African-Americans and 24% in Caucasian-Americans [11]. Similarly, a prevalence of 24% among white subjects was reported in the Framingham Offspring Study, and a prevalence of 31% was reported among Mexican-American subjects in the San Antonio Heart Study [12]. The reasons for these race/ethnic disparities of prevalence are not clear. Besides variations in environmental factors, an increased genetic susceptibility could explain the observed differences.

Indeed, growing evidence suggests that a genetic basis for the metabolic syndrome and its component traits is probable [13–16]. According to studies in twins, the individual components of the metabolic syndrome, such as obesity, serum lipids, blood pressure and fasting insulin levels, are to some extent influenced by genetic factors [17–20]. Several studies have also provided evidence for genetic influences on the combinations of components that characterise the metabolic syndrome [21,22]. Using factor analysis, a few studies combined these intercorrelated components into fewer independent factor structures to examine their heritability [16,23,24]. However, because the syndrome is associated with a substantially greater risk than the sum of its parts [9], it may be a unique disease entity. Some investigators, moreover, have started to map susceptibility genes to the metabolic syndrome [25,26]. Thus, it is important to know whether this syndrome has appreciable heritability.

In this study, we used two different approaches to understand the genetic architecture of the metabolic syndrome. The first was to estimate the heritability of the metabolic syndrome and its components using the ATPIII definitions among a high-vascular-risk Caribbean-Hispanic population involved in the ongoing Northern Manhattan Family Study (NOMAFS). The second approach was to obtain the structures underlying the metabolic syndrome using principal component factor analysis of the six quantitative phenotypes included in the ATPIII definition, and to calculate the heritability of the factor score for each independent factor.

Subjects and methods

Study subjects

NOMAFS is a cohort of high-risk Caribbean-Hispanic probands and their family members initially identified from the Northern Manhattan Study (NOMAS) stroke-free cohort [27]. A high-risk proband was defined by one of the following criteria: (1) reporting a sibling with a history of myocardial infarction or stroke; (2) having two of three quantitative risk phenotypes (maximal carotid plaque thickness, left ventricle mass divided by the body surface area, or homo-cysteine level) above the 75th percentile in the NOMAS cohort. Eligible high-risk probands were considered for enrolment provided they met one of the above criteria, were cognitively intact and had at least three first-degree relatives willing to participate. An interview was conducted in the proband's native language using structured questionnaires. Probands were asked to call family members to encourage participation in the study. After the proband had made the first contact, we followed this up with the relatives to explain the study and to solicit their participation. Every attempt was made to contact and include all living relatives in the USA and some in the Dominican Republic. Although the lineages are not yet complete, the participation rate is unlikely to be biased by the presence or absence of the metabolic syndrome or any of its components. Most participants are unaware of the definition of the metabolic syndrome and many are less aware of their own blood pressure and glucose or lipid levels in this underserved community.

Family members were recruited to have an in-person baseline assessment. The assessment consisted of fasting blood specimens, anthropometric measurements, high-resolution carotid ultrasound, echocardiography and standardised sociodemographic and medical history questions adapted from the Centers for Disease Control and Prevention Behavioral Risk Factor Surveillance System. The participants were informed and all gave their consent. The study was approved by the Columbia University Medical Center Institutional Review Board.

Definition and assessment of the metabolic syndrome and its components

The NCEP/ATPIII [1] defined metabolic syndrome as consisting of three or more of the following components: waist circumference >40 inch (>102 cm) in men or >35 inch (>89 cm) in women; triglycerides ≥1.7 mmol/l; HDL-cholesterol <1.04 mmol/l in men or <1.3 mmol/l in women; systolic blood pressure ≥130 mmHg or diastolic blood pressure ≥85 mmHg; and fasting glucose ≥6.1 mmol/l. The definition of metabolic syndrome used in our study mostly followed the ATPIII criteria, except that we also included persons who were taking hypertensive and diabetic medications but who had normal blood pressure and glucose values. Glucose was measured after an 8-h fast using a Hitachi 747 automated spectrometer (Boehringer; Indianapolis, IN, USA). Concentrations of HDL-cholesterol were determined using standard enzymatic procedures [28]. Triglycerides were measured in fresh plasma samples using standard enzymatic procedures [29]. The latter two analyses were performed using a Hitachi 912 automated spectrometer (Hitachi, Mito, Japan). A mercury sphygmomanometer was used to measure systolic and diastolic blood pressure, this being done after each subject had been seated for 5 min. Two measurements were taken on the right arm and the average of these two measurements was used for all analyses. Waist measurements were collected using the standard protocols [30].

Statistical analysis

To compare the heritabilities between the metabolic syndrome and its components, we analysed each component as a dichotomised trait as defined in the ATPIII. Quantitative trait analysis does not need an arbitrary cut-off point to define affect status, and it can reduce misclassification of phenotypes. Therefore, we also estimated heritability for quantitative data

of each continuous component of this syndrome with adjustment for covariates and medications.

For factor analysis, continuous traits were first adjusted for age, sex and medication status by a multiple regression model, and standardised residuals were used in the analysis. Factor analysis consisted of principal component analysis, a varimax rotation and identification of the variables to facilitate interpretation. Factor numbers were determined using the Eigen value-one criterion and the Scree test. The latter is a plot of the variance associated with each factor and shows a distinct break between the steep slope of the large factors and the gradual trailing off shown by the others. Items with loadings >0.4 were entered into the factor [31]. Factor scores were weighted by the sum of the values of the phenotypes multiplied by standardised scoring coefficients for that factor. All factor analyses were performed using SPSS version 11.0. Data for fasting glucose, systolic blood pressure and triglycerides were log transformed before analysis because of their skewed distributions.

The heritabilities of continuous traits were calculated using a standard quantitative genetic variance-components model implemented in the Sequential Oligogenic Linkage Analysis Routines (SOLAR) software package (http://www.sfbr.org/solar/index.html; Version 2.1.3) [32]. With this approach, the maximum-likelihood estimation is applied to a mixed-effects model that incorporates fixed covariate effects, additive genetic effects and residual error. The additive genetic effects and residual error are assumed to be normally distributed and to be mutually independent. Heritability is calculated as the proportion of phenotypic variance explained by additive genetic effects after accounting for covariates.

The heritabilities of discrete traits were analysed by a threshold model in SOLAR. The method assumes that an individual belongs to a specific affect status if an underlying genetically determined risk (i.e. liability) exceeds a certain threshold [33]. The correlation in liability between individuals i and j is given by $\rho_{ij}=2\phi_{ij}h^2+I_{ij}e^2$, where ρ_{ij} is the correlation in liability to disease between individuals i and j; ϕ_{ij} is the kinship coefficient for individuals i and j; h^2 is the heritability attributed to additive polygenic effects; I_{ij} is the coefficient for the random environmental component for individuals i and j; and e^2 is equal to $1-h^2$. The null hypothesis of no genetic effect ($h^2=0$) was tested by comparing the likelihood of a restricted model, where h^2 was constrained to zero, with a general model in which the same parameter was estimated. A statistically significant test ($p<0.05$) was considered to be evidence of a non-zero estimate for a given parameter. Ascertainment correction was performed for all heritability analyses by conditioning on the proband in each family. A covariate with a p value <0.05 was considered significant.

Results

The NOMAFS cohort consisted of 803 subjects from 89 Caribbean-Hispanic families who had enrolled to date and for whom information on the metabolic syndrome was available. Family size varied from three to 53 individuals with a mean of nine subjects. The mean age was 47 years (SD=17.8), with a range of 18 to 95 years. Men accounted for 37% of the study subjects. Mean fasting glucose, triglycerides, HDL-cholesterol, waist circumference and systolic and diastolic blood pressures are shown in Table 1. Among family members, 104 subjects were on lipid-lowering medications, 38 subjects were using hypoglycaemic drugs/insulin and 235 subjects were on antihypertensive medications. According to the ATPIII definition of the metabolic syndrome, 26% of these individuals were classified as having the syndrome.

After adjusting for age and sex, the metabolic syndrome had a heritability of 24% ($p=0.009$). When the components were treated as continuous traits, the estimates of heritability varied from 16% for systolic blood pressure to 60% for HDL-cholesterol after adjusting for age, sex

and appropriate medication. When the metabolic syndrome components were analysed as discrete traits according to ATPIII, the estimates of age and sex-adjusted heritability varied from 27% for large waist circumference to 51% for low HDL-cholesterol levels (Table 2). We did not adjust for medication while analysing the dichotomised traits, because patients on medication were recorded as affected.

All components of the metabolic syndrome were significantly correlated with each other except for the pair of diastolic blood pressure and HDL-cholesterol (Table 3). The factors and patterns of factor loadings obtained in this study are shown in Table 4. Two factors were extracted from six continuous traits of the metabolic syndrome. The first factor (factor I), which explained 34.0% of the total variance in the dataset, was dominated by lipids, obesity and blood glucose, whereas the second factor (factor II) was dominated by blood pressure (percentage variance=23.2). The two factors accounted for 57.2% of the total variance in the dataset. The heritability estimations for the two factors were 44% ($p<0.001$) and 20% ($p<0.001$), respectively.

Discussion

In this study we found a significant heritability for the metabolic syndrome and each of its components among Caribbean-Hispanic families in the NOMAFS. To our knowledge, this is the first report of heritability of the metabolic syndrome as defined by ATPIII. Our results confirm that genetic factors contribute to the familial aggregation of the metabolic syndrome and its components. Among the metabolic syndrome components analysed, HDL-cholesterol had the highest heritability estimation of 60%, while systolic blood pressure had the lowest heritability estimation of 16%. Using factor analysis, the heritability of factor I was 44% and that of factor II was 20%. Although the heritability between the metabolic syndrome and factor analysis was not directly comparable because they represent different phenotypes, both approaches suggested appreciable heritability for either phenotype. However, because most clinical and epidemiological studies investigate the consequence of the metabolic syndrome, genetic studies on the syndrome may provide more direct and valuable information to healthcare providers and the general population.

A number of studies have investigated the question of whether the metabolic syndrome truly exists or is just the sum of its risk components. Their results have provided convincing evidence that the components of this syndrome occur simultaneously more often than would be expected by chance [34–36]. This might indicate that co-occurrence of these risk components is the result of a common underlying process. It would, therefore, be of interest to determine whether the metabolic syndrome per se can be inherited, as this would justify the endeavors of gene-mapping projects in this area. Although several papers have discussed genetic influences on the metabolic syndrome, these studies investigated the components of the metabolic syndrome rather than the metabolic syndrome as a whole [13–15,37,38]. Only one previous study has reported an estimate of heritability for the metabolic syndrome; the author defined a novel variable called the metabolic syndrome score (MSS) [39]. In that study, the MSS was generated by adding the values of the four component traits and then subtracting the value of HDL-cholesterol. However, it is not clear whether the MSS can also be highly associated with complications related to the metabolic syndrome. Investigators have already started performing linkage and association studies to discover susceptibility loci for the metabolic syndrome, assuming it has appreciable genetic components. By estimating the heritability of the metabolic syndrome, the present study provides direct support for related gene mapping projects. In particular, our findings justify our future plan to perform genome-wide linkage studies in this population.

Our study of heritability for the metabolic syndrome components is generally consistent with previous similar studies conducted in different Hispanic populations [40,41]. The study of Mexican-Americans in the San Antonio Family Heart Study demonstrated heritabilities of 40% for triglycerides, 46% for HDL-cholesterol, 18% for systolic blood pressure, 42% for body mass index and 18% for blood sugar. All their results were similar to our estimates for Caribbean-Hispanics. A study of North European families analysed the quantitative values of risk components and demonstrated heritabilities of 19% for triglycerides and 37% for body mass index, both of which were lower than our present results [14]. Although the heritability estimation of individual components varied among the populations, these results consistently indicated significant underlying genetic influences on all of the components.

There are different possible explanations for the clustering of the metabolic syndrome components. One is the presence of a common genetic and/or environmental factor underlying the clustering of these components. Indeed studies have demonstrated that common genes exert pleiotropic effects on fasting insulin and body mass index, fasting insulin and triglycerides [38], and also HDL-cholesterol and triglycerides [23,42]. To provide new insights into the underlying pathophysiological mechanisms, some studies used factor analysis to break the related metabolic syndrome components into two [43,44], three [16,23,24,45], or four [4,7,8] factors. Most previous studies included more than the ATPIII-defined variables for factor analysis and thus yielded more factors than our study. It has been suggested that the number of factors will be equal to or less than the number of original variables divided by three [46]. Therefore, our study only had two factors extracted from six ATPIII-defined variables. Regardless of how many factors are extracted, our study shared common patterns with previous studies that indicated glucose, obesity and lipid load are part of the same factor [43,44], and that blood pressure variables load is a separate factor [8,16,47]. Also, the total variance explained by the two factors extracted in this study was 57%, which is similar to values found by previous studies (ranging from 55 to 68%) [24,43,44]. In addition, our heritability estimation of each factor was comparable to those found by previous studies of the Japanese-American population [16] and the Mexican-American population [24].

Our study has strengths and limitations. The strengths include the following: (1) we used data from a high-risk population, where the prevalence of diabetes is significantly higher than in other ethnic groups [48]; (2) the families in the current study will be used for future genome-wide linkage studies to discover susceptibility genes to the metabolic syndrome; and (3) we recruited extended families, which provide a better statistical power to detect genetic signals than nuclear families or sib-pair data. The main limitations of our study are firstly that the heritability estimates might be influenced by shared environmental factors because the variance component approach did not account for these factors among family members. On the other hand, the SOLAR program may underestimate heritability that is caused by the genetic effects because of gene–environment interactions. Secondly, we do not have genotyping data to validate amily relationships. The most likely situation is that participants over-reported a biological kinship. For example, a half-sib was reported as a full-sib. If so, the estimates of heritability could be underestimated.

The public health burden of the metabolic syndrome is considerable. The syndrome is associated with increasing risk of vascular morbidity and mortality [4,49]. Furthermore, in a cross-sectional study, the metabolic syndrome was associated with a history of myocardial infarction and stroke [6]. Within the NOMAS study, we found that the metabolic syndrome accounts for 22% of vascular events, 19% of strokes, 30% of strokes in women and 43% of strokes in Hispanics [50]. Caribbean-Hispanics are one of the two major groups of Hispanics in the USA and are relatively recent immigrants from the Caribbean Islands, including the Dominican Republic and Puerto Rico. Understanding the genetic and environmental factors of the metabolic syndrome among Caribbean-Hispanics may lead to a more comprehensive

understanding of the syndrome and may have important implications for clinical care and public health.

Here, we report a moderate and significant heritability of the metabolic syndrome and its components among Caribbean-Hispanic families. Factor analysis indicated two independent components that also had appreciable heritabilities. The results strongly encourage efforts to identify the underlying susceptibility genes.

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Table 1

Characteristics of the study participants

	All, *n*=803	**Men, *n*=299**	**Women, *n*=504**
Age (years)	46.5±17.8	44.2±17.7	47.8±17.8
Waist circumference (cm)	93.5±14.0	96.3±12.7	91.7±14.5
Fasting glucose (mmol/l)	4.9±1.6	5.1±1.8	4.8±1.5
Triglycerides (mmol/l)	1.4±0.9	1.6±1.0	1.3±0.8
HDL-cholesterol (mmol/l)	1.3±0.4	1.1±0.3	1.3±0.4
Systolic blood pressure (mmHg)	122.0±20.0	123.9±18.0	120.8±20.5
Diastolic blood pressure (mmHg)	76.2±10.0	78.2±10.4	75.0±9.7
Metabolic syndrome (%)	26	21	28
High blood pressure (%)	46	45	46
High triglycerides (%)	24	27	22
Low HDL-cholesterol (%)	47	44	48
High fasting-glucose (%)	14	16	13
High waist circumference (%)	43	25	54

Unless otherwise stated, values are mean±SD. High blood pressure, high triglycerides, low HDL-cholesterol, high fasting-glucose, high waist circumference and the metabolic syndrome were defined according to ATPIII criteria, except that patients on hypertensive and diabetic medication were also included

Table 2

Heritability estimates for the metabolic syndrome and its components treated as continuous and discrete traits

	h^2 (SE)	*p*-value	Covariates	Variation explained by covariates
Metabolic syndrome	0.24 (0.11)	0.009	Age, sex[a]	0.10[b]
Waist				
cm[c]	0.46 (0.08)	<0.001	Age, sex[aa]	0.08
Women >89, men >102[d]	0.27 (0.19)	0.002	Age, sex[aa]	0.09[b]
Fasting glucose				
mmol/l, [ce]	0.24 (0.07)	<0.001	Age[a], sex[a], hypoglycaemic medication[a]	0.19
≥6.1 or on hypoglycaemic medication[d]	0.31 (0.17)	0.020	Age, sex[aa]	0.14[b]
Triglycerides				
mmol/l, [ce]	0.47 (0.07)	<0.001	Age[a], sex[a], lipid-lowering medication[a]	0.13
≥1.7[d]	0.50 (0.11)	<0.001	Age[a], sex[a], lipid-lowering medication	0.03[b]
HDL-cholesterol				
mmol/l[c]	0.60 (0.07)	<0.001	Age[a], sex[a], lipid-lowering medication	0.09
Women <1.3, men <1.04[d]	0.51 (0.10)	<0.001	Age[a], sex, lipid-lowering medication	0.008[b]
Blood pressure				
Systolic, [ce]	0.16 (0.07)	0.005	Age[a], sex[a], antihypertensive medication[a]	0.37
Diastolic[c]	0.21 (0.07)	<0.001	Age[a], sex[a] antihypertensive medication[d]	0.17
Systolic ≥130 or diastolic ≥85 or on antihypertensive medication[b]	0.30 (0.12)	0.005	Age, sex[aa]	0.28[e]

h^2 Heritability

[a] $p<0.05$

[b] Variation explained by covariates as suggested by the Kullback–Leibler *R*-squared value

[c] Treated as continuous traits

[d] Treated as discrete traits

[e] Log transformation

Table 3

Correlation coefficients between variables used in factor analysis

	Diastolic blood pressure	Systolic blood pressure	Triglycerides	HDL-cholesterol	Fasting glucose	Waist
Diastolic blood pressure[a]	1.00					
Systolic blood pressure[a, b]	0.66	1.00				
Triglycerides, [cb]	0.14	0.12	1.00			
HDL-cholesterol[c]	−0.06	−0.09	−0.46	1.00		
Fasting glucose, [bd]	0.09	0.09	0.19	−0.16	1.00	
Waist[e]	0.18	0.18	0.20	−0.24	0.20	1.00

[a] Adjusted for age, sex and antihypertensive medication by regression analysis

[b] Log transformation

[c] Adjusted for age, sex and lipid-lowering medication by regression analysis

[d] Adjusted for age, sex and hypoglycaemic medication by regression analysis

[e] Adjusted for age and sex by regression analysis

Table 4

Results of factor analysis, variance components and heritability estimation

	Factor I: lipids/glucose/obesity	Factor II: blood pressure
Diastolic blood pressure[a]	0.085	0.902
Systolic blood pressure[a, b]	0.092	0.898
Triglycerides, [cdb]	0.767	0.041
HDL-cholesterol[c]	−0.785	0.045
Fasting glucose, [eb]	0.496	0.076
Waist[d]	0.528	0.241
Percentage of variance (%)	33.988	23.241
Heritability	0.44, $p<0.001$	0.20, $p<0.001$

[a] Adjusted for age, sex and antihypertensive medication by regression analysis

[b] Log transformation

[c] Adjusted for age, sex and lipid-lowering medication by regression analysis

[d] Adjusted for age and sex by regression analysis

[e] Adjusted for age, sex and hypoglycaemic medication by regression analysis