

# Familial Clustering for Features of the Metabolic Syndrome

The National Heart, Lung, and Blood Institute (NHLBI) Family Heart Study

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**OBJECTIVE** — Metabolic syndrome–related traits (obesity, glucose intolerance/insulin resistance, dyslipidemia, and hypertension) have been shown to be genetically correlated. It is less clear, however, if the genetic correlation extends to novel risk factors associated with inflammation, impaired fibrinolytic activity, and hyperuricemia. We present a bivariate genetic analysis of MetS-related traits including both traditional and novel risk factors.

**RESEARCH DESIGN AND METHODS** — Genetic correlations were estimated using a variance components procedure in 1,940 nondiabetic white individuals from 445 families in the National Heart, Lung, and Blood Institute (NHLBI) Family Heart Study. Twelve MetS-related traits, including BMI, waist circumference, blood pressure, white blood cell count, fasting serum triglycerides, HDL cholesterol, insulin, glucose, plasminogen activator inhibitor-1 antigen, uric acid, and C-reactive protein, were measured and adjusted for covariates, including lifestyle variables.

**RESULTS** — Significant genetic correlations were detected among BMI, waist circumference, HDL cholesterol, triglycerides, insulin, and plasminogen activator inhibitor-1 antigen and between uric acid and all of the above variables except insulin. C-reactive protein and white blood cell count were genetically correlated with each other, and both showed significant genetic correlations with waist circumference and insulin. Fasting glucose was not significantly genetically correlated with any of the other traits.

**CONCLUSIONS** — These results suggest that pleiotropic effects of genes or shared family environment contribute to the familial clustering of MetS-related traits.

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**Abbreviations:** CRP, C-reactive protein; dBp, diastolic blood pressure; FHS, Family Heart Study; NHLBI, National Heart, Lung, and Blood Institute; PAI-1, plasminogen activator inhibitor 1; sBP, systolic blood pressure; WBC, white blood cell count.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

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**M**etabolic syndrome describes a constellation of cardiovascular disease risk factors related to metabolic, vascular, inflammatory, fibrinolytic, and coagulatory abnormalities (1–3). Among them, insulin resistance and obesity are hypothesized to be two of the major contributors to the manifestations of the syndrome (1,2). Emerging evidence suggests that there are other causal factors that may act through obesity, insulin resistance, or biological pathways independent of them (4–6). For example, inflammation has been found to predict weight gain (4) and worsening of insulin sensitivity (5), and hyperuricemia also predicted progression of hyperinsulinemia (6).

Abundant evidence from twin and family studies has demonstrated genetic influence for familial clustering of MetS-related traits including obesity, insulin resistance, dyslipidemia, and hypertension (7–10). It is currently less clear whether the genetic correlation extends to novel risk factors associated with inflammation, impaired fibrinolytic activity, and hyperuricemia. Only a few studies have partly addressed this issue (11–15). In this study, we present a bivariate genetic analysis of a comprehensive list of MetS-related traits ranging from traditional cardiovascular disease risk factors that include BMI, waist circumference, fasting insulin and glucose, triglycerides, HDL cholesterol, systolic blood pressure (sBP), and diastolic blood pressure (dBp) to novel risk factors that include C-reactive protein (CRP), white blood cell count (WBC), plasminogen activator inhibitor 1 (PAI-1), and serum uric acid. Using this approach, we identified pairs of the MetS-related traits sharing common genetic/familial influences.

## RESEARCH DESIGN AND METHODS

The National Heart, Lung, and Blood Institute (NHLBI) Family Heart Study (FHS) is a multicenter population-based family study to investigate the genetic and nongenetic determinants of coronary heart disease, pre-

clinical atherosclerosis, and cardiovascular disease risk factors (16). Proband for the NHLBI FHS included a random sample and a second sample with a family history of coronary heart disease. Both samples were recruited through probands in the Framingham Heart Study (Framingham, MA), the Utah Health Family Tree Study (Salt Lake City, UT), and the Atherosclerosis Risk in Communities Study (Minneapolis, MN, and Forsyth County, NC). Proband's family members who were >25 years of age were invited to participate.

In this study, we only included individuals from randomly ascertained families to obtain estimates of genetic parameters of the general population because it is difficult to perform an appropriate ascertainment correction to obtain unbiased estimates. African Americans were not included in this report because of the limited number of African Americans in the NHLBI FHS. In the FHS, there were 535 random families containing 2,647 white individuals. Subjects meeting any of the following criteria were excluded from the analysis: missing information on one or more of the core MetS variables (waist circumference, HDL cholesterol, triglycerides, fasting glucose, and blood pressures) ( $n = 357$ ), missing information on covariates ( $n = 100$ ), prevalent diabetes ( $n = 175$ ), or from singleton families ( $n = 75$ ). As a result, a total of 1,940 white participants from 445 families remained in the study. The distribution of family size in the final sample is as follows [family size (number of families)]: 2 (100), 3 (86), 4 (85), 5 (58), 6 (47), 7 (26), 8 (18), 9 (13), 10 (6), 11 (5), and 12 (1). Among these families, 218 were sibships or nuclear families and the remaining 227 were more complex pedigrees. A total of 3,526 relative pairs contributed to the analysis, including parent-offspring (1,038), full siblings (1,544), grandparent-grandchild (61), avuncular (785), half-siblings (58), half avuncular (36), and first cousins (4). Subjects who were on antihypertensive medications ( $n = 301$ ) were set to missing for their blood pressure, subjects who were on cholesterol-lowering drugs ( $n = 130$ ) were set to missing for their HDL cholesterol and triglycerides, and subjects who were on anticoagulant therapy ( $n = 137$ ) were set to missing for PAI-1.

All blood assays except CRP were measured in the entire sample; CRP was measured in a subset of 702 individuals (349 families) who were from the largest

Table 1—Phenotypic characteristics

	Women	Men
Age (years)	52.0 ± 13.8 (1,029)	50.9 ± 14.2 (911)
BMI (kg/m <sup>2</sup> )	26.9 ± 5.8 (1,029)	27.6 ± 4.3 (911)
Waist circumference (cm)	93.2 ± 16.0 (1,029)	99.8 ± 12.1 (911)
HDL cholesterol (mg/dl)	57.2 ± 14.7 (965)	44.1 ± 11.2 (845)
Triglycerides (mg/dl)	127.1 ± 76.3 (965)	147.8 ± 103.7 (845)
Fasting insulin (mU/l)	9.09 ± 5.93 (1,029)	10.7 ± 6.79 (911)
Fasting glucose (mmol/l)	5.09 ± 0.50 (1,029)	5.35 ± 0.51 (911)
sBP (mmHg)	111.2 ± 16.3 (880)	116.2 ± 14.4 (758)
dBp (mmHg)	65.9 ± 9.3 (880)	70.0 ± 9.6 (758)
Serum uric acid (mg/dl)	4.64 ± 1.21 (1,029)	6.14 ± 1.26 (911)
PAI-1 (ng/ml)	22.6 ± 33.1 (972)	32.7 ± 37.7 (802)
CRP (mg/l)	2.92 ± 3.60 (369)	1.73 ± 2.26 (333)
WBC (× 10 <sup>3</sup> /mm <sup>3</sup> )	6.01 ± 1.61 (1018)	6.05 ± 1.57 (904)
Metabolic syndrome (%)	22.5 (1,029)	24.5 (911)
Hypertension (%)	22.3 (1,029)	26.5 (906)
Coronary heart disease (%)	1.8 (1,029)	8.5 (909)

Data are means ± SD ( $n$ ) or prevalence ( $n$ ).

pedigrees or had increased risk for coronary heart disease. Details on the sampling selection for CRP measurement has been described elsewhere (17).

### Measurements of phenotypes

The clinical examination of each study participant was performed according to a standardized protocol. Participants were asked to fast for 12 h before the clinical examination, during which blood was drawn for laboratory tests. Information on lifestyle variables, medical history, and medication use were obtained by a standardized interview during the clinic visit. Details on measurements of phenotypes and definition of coronary heart disease are provided in an online appendix (available at <http://care.diabetesjournals.org>).

Hypertension was defined as sBP ≥140 mmHg, dBp ≥90 mmHg, or treatment for hypertension. Diabetes was defined by the American Diabetes Association criteria (fasting glucose ≥126 mg/dl or use of hypoglycemic medication). Metabolic syndrome was defined by the National Cholesterol Education Program Adult Treatment Panel III criteria as the presence of at least three of the following abnormalities: abdominal obesity, hypertriglyceridemia, low HDL cholesterol, high blood pressure, and hyperglycemia (18).

### Statistical analysis

Heritability of the MetS-related quantitative traits and bivariate genetic correlations among these traits were estimated with a maximum likelihood-based vari-

ance components approach implemented in SOLAR version 2.1.3 (19). Heritability is computed as the proportion of phenotypic variance due to additive effects of genes. In bivariate genetic analysis, we work with two traits measured on pairs of relatives. This provides several types of covariances. We have a covariance for the pair of traits for individual subjects (the phenotypic covariance), one covariance for each trait for pairs of relatives, and a "cross-covariance" for each trait in the first relative with the other trait in the second relative. These covariances, and corresponding correlations, can be modeled in terms of genetic and environmental parameters including heritability, genetic variance, environmental variance, and genetic and environmental correlation. For example, the phenotypic correlation (standardized phenotypic covariance) can be expressed as:

$$\rho_p = \rho_g \sqrt{h_1^2 h_2^2} + \rho_e \sqrt{(1 - h_1^2)(1 - h_2^2)},$$

where  $\rho_p$  is the phenotypic correlation,  $\rho_g$  is the additive genetic correlation,  $\rho_e$  is the environmental correlation, and  $h_1^2$  and  $h_2^2$  are heritability for traits 1 and 2, respectively. For a pair of traits, the proportion of total additive genetic variance that is due to the shared genes is estimated by squaring the genetic correlation between two traits. Because the genetic correlation is modeled based on the extent of similarity between a pair of traits in different family members in proportion to kinship coefficients, it may contain a contribution from shared environment as well. Signifi-

Table 2—Phenotypic correlation coefficients  $\pm$  SE among the metabolic syndrome-related variables before (above the diagonal) and after (below the diagonal) adjustment for covariates

	BMI	Waist circumference	HDL cholesterol	Triglycerides	Insulin	Glucose	sBP	DBP	Serum uric acid	PAI-1	CRP	WBC
BMI	0.87 $\pm$ 0.01	-0.30 $\pm$ 0.02	0.34 $\pm$ 0.02	0.58 $\pm$ 0.01	0.34 $\pm$ 0.02	0.27 $\pm$ 0.02	0.27 $\pm$ 0.02	0.27 $\pm$ 0.02	0.37 $\pm$ 0.02	0.51 $\pm$ 0.02	0.31 $\pm$ 0.03	0.18 $\pm$ 0.02
Waist circumference	0.88 $\pm$ 0.01	-0.32 $\pm$ 0.02	0.37 $\pm$ 0.02	0.57 $\pm$ 0.01	0.39 $\pm$ 0.02	0.33 $\pm$ 0.02	0.29 $\pm$ 0.02	0.45 $\pm$ 0.02	0.55 $\pm$ 0.02	0.27 $\pm$ 0.03	0.27 $\pm$ 0.03	0.19 $\pm$ 0.02
HDL cholesterol	-0.29 $\pm$ 0.02	-0.28 $\pm$ 0.02	-0.46 $\pm$ 0.02	-0.40 $\pm$ 0.02	-0.36 $\pm$ 0.02	-0.22 $\pm$ 0.02	-0.07 $\pm$ 0.03	-0.11 $\pm$ 0.03	-0.39 $\pm$ 0.02	-0.42 $\pm$ 0.02	-0.05 $\pm$ 0.04*	-0.11 $\pm$ 0.02
Triglycerides	0.30 $\pm$ 0.02	0.31 $\pm$ 0.02	-0.31 $\pm$ 0.02	0.37 $\pm$ 0.02	0.39 $\pm$ 0.02	0.24 $\pm$ 0.02	0.27 $\pm$ 0.02	0.25 $\pm$ 0.02	0.34 $\pm$ 0.02	0.43 $\pm$ 0.02	0.21 $\pm$ 0.04	0.19 $\pm$ 0.02
Insulin	0.54 $\pm$ 0.02	0.53 $\pm$ 0.02	-0.20 $\pm$ 0.02	0.18 $\pm$ 0.02	0.33 $\pm$ 0.02	0.36 $\pm$ 0.02	0.21 $\pm$ 0.02	0.23 $\pm$ 0.02	0.35 $\pm$ 0.02	0.53 $\pm$ 0.02	0.22 $\pm$ 0.03	0.21 $\pm$ 0.02
Glucose	0.30 $\pm$ 0.02	0.27 $\pm$ 0.02	-0.05 $\pm$ 0.03*	0.20 $\pm$ 0.02	0.19 $\pm$ 0.02	0.22 $\pm$ 0.03	0.21 $\pm$ 0.02	0.25 $\pm$ 0.02	0.37 $\pm$ 0.02	0.40 $\pm$ 0.02	0.05 $\pm$ 0.04*	0.08 $\pm$ 0.02
sBP	0.24 $\pm$ 0.03	0.21 $\pm$ 0.03	-0.06 $\pm$ 0.03	0.20 $\pm$ 0.02	0.18 $\pm$ 0.02	0.18 $\pm$ 0.02	0.18 $\pm$ 0.02	0.15 $\pm$ 0.03	0.26 $\pm$ 0.02	0.24 $\pm$ 0.02	0.13 $\pm$ 0.04	0.11 $\pm$ 0.03
DBP	0.23 $\pm$ 0.03	0.22 $\pm$ 0.03	-0.06 $\pm$ 0.03	0.20 $\pm$ 0.02	0.21 $\pm$ 0.02	0.18 $\pm$ 0.02	0.15 $\pm$ 0.03	0.12 $\pm$ 0.02	0.24 $\pm$ 0.02	0.27 $\pm$ 0.02	0.04 $\pm$ 0.04*	0.08 $\pm$ 0.03
Serum uric acid	0.36 $\pm$ 0.02	0.35 $\pm$ 0.02	-0.25 $\pm$ 0.02	0.31 $\pm$ 0.02	0.31 $\pm$ 0.02	0.25 $\pm$ 0.02	0.15 $\pm$ 0.03	0.12 $\pm$ 0.02	0.43 $\pm$ 0.02	0.49 $\pm$ 0.02	0.10 $\pm$ 0.04	0.15 $\pm$ 0.02
PAI-1	0.48 $\pm$ 0.02	0.50 $\pm$ 0.02	-0.36 $\pm$ 0.02	0.43 $\pm$ 0.02	0.49 $\pm$ 0.02	0.33 $\pm$ 0.02	0.18 $\pm$ 0.03	0.22 $\pm$ 0.02	0.23 $\pm$ 0.03	0.22 $\pm$ 0.04	0.17 $\pm$ 0.04	0.18 $\pm$ 0.02
CRP	0.33 $\pm$ 0.03	0.32 $\pm$ 0.03	-0.18 $\pm$ 0.04	0.19 $\pm$ 0.04	0.25 $\pm$ 0.03	0.09 $\pm$ 0.04	0.16 $\pm$ 0.04	0.10 $\pm$ 0.03	0.23 $\pm$ 0.03	0.22 $\pm$ 0.04	0.37 $\pm$ 0.03	0.32 $\pm$ 0.03
WBC	0.19 $\pm$ 0.02	0.19 $\pm$ 0.02	-0.10 $\pm$ 0.02	0.18 $\pm$ 0.02	0.22 $\pm$ 0.02	0.08 $\pm$ 0.02	0.12 $\pm$ 0.03	0.10 $\pm$ 0.03	0.18 $\pm$ 0.02	0.16 $\pm$ 0.02		

Data are adjusted for age, age squared, sex, field center, hormone replacement therapy, smoking (cigarettes/day), alcohol intake (g/day), energy intake (kcal/day), dietary fat (%), physical activity index (metabolic equivalent min/week), and sedentary behavior (television hours/day). \*Not significantly different from 0 at  $P < 0.05$ .

ificance testing of bivariate genetic and environmental correlations was made against the null hypothesis,  $\rho_g = 0$  and  $\rho_e = 0$ , respectively, by using likelihood ratio tests. Covariates were modeled in SOLAR as fixed effects. The following covariates were included: age, age squared, sex, field center, hormone replacement therapy, current smoking (cigarettes/day), alcohol intake (g/day), energy intake (kcal/day), dietary fat (%), physical activity index (metabolic equivalent min/week), and sedentary behavior (hours of television watched/day). Five variables (triglycerides, glucose, insulin, PAI-1, and CRP) were natural log transformed to remove skewness of the distributions before the genetic analysis. In addition, a tdist option was turned on in SOLAR to obtain robust estimation of mean and variance when trait distributions significantly deviated from multivariate normality (even after the log transformation). The tdist method models the pedigree phenotypic vectors using a multivariate  $t$  distribution instead of a multivariate normal distribution (20). By introducing an additional parameter that is primarily a function of the kurtosis of phenotype distribution, the influence of outliers is reduced (20).

**RESULTS**— Table 1 shows phenotypic characteristics of subjects by sex. After adjustment for age, age squared, sex, field center, hormone replacement therapy, current smoking and alcohol intake, energy intake, dietary fat, physical activity, and sedentary behavior, all of the 12 traits were significantly correlated with each other within individuals, with the exception of HDL cholesterol with sBP (Table 2). Before the adjustment, the correlation between HDL cholesterol and sBP was significant and that of CRP with HDL cholesterol, glucose, and DBP non-significant. Table 3 shows heritability (diagonal elements), bivariate genetic correlations (below diagonal elements), and environmental correlations (above diagonal elements) for the MetS-related traits after adjustment for the above covariates. All traits were significantly heritable. There were significant pairwise genetic correlations among BMI, waist circumference, HDL cholesterol, triglycerides, and insulin. There was no significant genetic correlation between glucose and any of the other variables. sBP was only significantly genetically correlated with DBP and CRP, and DBP was only genetically associated with insulin and sBP.

Uric acid and PAI-1 were significantly genetically correlated with each other and with BMI, waist circumference, HDL cholesterol, and triglycerides. Uric acid also showed a significant genetic correlation with WBC, and PAI-1 additionally exhibited significant genetic correlations with insulin and CRP. CRP and WBC were significantly genetically correlated with each other and with waist circumference and insulin. Moreover, CRP had significant genetic correlations with BMI. The proportion of total additive genetic variance that is due to the shared genes was estimated to range from 3.6% for uric acid–HDL cholesterol to 79.2% for BMI–waist circumference.

There were significant environmental correlations among most of the traits, with few exceptions (Table 3). For example, significant environmental correlations were detected between PAI-1 and all traits except CRP. In contrast, CRP was only significantly environmentally correlated with uric acid and WBC.

To test the sensitivity of the results, previously excluded subjects who were on antihypertensive, cholesterol-lowering, or anticoagulant therapy were included on a reanalysis for blood pressure, HDL cholesterol, triglycerides, and PAI-1, with and without further adjustment for corresponding medication use. In either adjustment model, heritability and bivariate genetic correlations did not change materially except for insulin–dBP. The genetic correlations between insulin and dBP decreased from 0.25 to 0.15 (not adjusted for antihypertensive medication) and 0.16 (adjusted for antihypertensive medication), which were no longer significantly different from zero.

**CONCLUSIONS**— We found significant genetic correlations among BMI, waist circumference, HDL cholesterol, triglycerides, insulin, and PAI-1 and significant genetic correlations between uric acid and the above variables except insulin. CRP and WBC were genetically correlated with each other, and both showed signifi-

Table 3—Heritability  $\pm$  SE (diagonal elements, shaded cells), bivariate genetic correlation  $\pm$  SE (cells below shaded diagonal), and bivariate environmental correlation  $\pm$  SE (cells above shaded diagonal) for the metabolic syndrome-related variables

	BMI	Waist circumference	HDL cholesterol	Triglycerides	Insulin	Glucose	sBP	dBp	Serum uric acid	PAI-1	CRP	WBC
BMI	<b>0.46 <math>\pm</math> 0.05</b>	0.88 $\pm$ 0.01	-0.38 $\pm$ 0.07	0.37 $\pm$ 0.06	0.62 $\pm$ 0.03	0.39 $\pm$ 0.05	0.30 $\pm$ 0.06	0.29 $\pm$ 0.06	0.37 $\pm$ 0.05	0.49 $\pm$ 0.04	0.15 $\pm$ 0.09	0.19 $\pm$ 0.05
Waist circumference	0.89 $\pm$ 0.02	<b>0.42 <math>\pm</math> 0.05</b>	-0.36 $\pm$ 0.07	0.35 $\pm$ 0.05	0.53 $\pm$ 0.04	0.35 $\pm$ 0.05	0.24 $\pm$ 0.06	0.26 $\pm$ 0.06	0.39 $\pm$ 0.05	0.44 $\pm$ 0.04	0.13 $\pm$ 0.09	0.18 $\pm$ 0.05
HDL cholesterol	-0.23 $\pm$ 0.08	-0.22 $\pm$ 0.08	<b>0.63 <math>\pm</math> 0.05</b>	-0.41 $\pm$ 0.06	-0.38 $\pm$ 0.05	-0.32 $\pm$ 0.07	-0.14 $\pm$ 0.08	-0.16 $\pm$ 0.07	-0.33 $\pm$ 0.06	-0.39 $\pm$ 0.06	-0.17 $\pm$ 0.12	-0.12 $\pm$ 0.07
Triglycerides	0.23 $\pm$ 0.08	0.28 $\pm$ 0.08	-0.51 $\pm$ 0.06	<b>0.48 <math>\pm</math> 0.05</b>	0.37 $\pm$ 0.05	0.28 $\pm$ 0.06	0.22 $\pm$ 0.06	0.27 $\pm$ 0.06	0.24 $\pm$ 0.06	0.38 $\pm$ 0.05	0.12 $\pm$ 0.10	0.23 $\pm$ 0.06
Insulin	0.44 $\pm$ 0.08	0.54 $\pm$ 0.07	-0.27 $\pm$ 0.08	0.37 $\pm$ 0.09	<b>0.29 <math>\pm</math> 0.04</b>	0.42 $\pm$ 0.04	0.20 $\pm$ 0.05	0.19 $\pm$ 0.05	0.37 $\pm$ 0.04	0.47 $\pm$ 0.04	0.13 $\pm$ 0.08	0.22 $\pm$ 0.05
Glucose	0.17 $\pm$ 0.09	0.14 $\pm$ 0.10	-0.09 $\pm$ 0.09	0.05 $\pm$ 0.10	0.13 $\pm$ 0.11	<b>0.37 <math>\pm</math> 0.05</b>	0.25 $\pm$ 0.06	0.22 $\pm$ 0.06	0.29 $\pm$ 0.05	0.44 $\pm$ 0.04	0.15 $\pm$ 0.09	0.16 $\pm$ 0.05
sBP	0.15 $\pm$ 0.10	0.16 $\pm$ 0.11	0.03 $\pm$ 0.10	0.17 $\pm$ 0.11	0.18 $\pm$ 0.11	0.18 $\pm$ 0.11	<b>0.34 <math>\pm</math> 0.06</b>	0.57 $\pm$ 0.04	0.17 $\pm$ 0.06	0.26 $\pm$ 0.05	0.03 $\pm$ 0.09	0.10 $\pm$ 0.06
dBp	0.13 $\pm$ 0.11	0.14 $\pm$ 0.11	0.03 $\pm$ 0.10	0.12 $\pm$ 0.11	0.25 $\pm$ 0.12	0.11 $\pm$ 0.12	0.82 $\pm$ 0.05	<b>0.33 <math>\pm</math> 0.06</b>	0.08 $\pm$ 0.06	0.22 $\pm$ 0.05	0.01 $\pm$ 0.09	0.06 $\pm$ 0.06
Serum uric acid	0.36 $\pm$ 0.09	0.30 $\pm$ 0.09	-0.19 $\pm$ 0.09	0.42 $\pm$ 0.09	0.19 $\pm$ 0.11	0.17 $\pm$ 0.10	0.12 $\pm$ 0.12	0.22 $\pm$ 0.12	<b>0.36 <math>\pm</math> 0.05</b>	0.40 $\pm$ 0.04	0.24 $\pm$ 0.09	0.12 $\pm$ 0.05
PAI-1	0.49 $\pm$ 0.09	0.62 $\pm$ 0.08	-0.37 $\pm$ 0.09	0.54 $\pm$ 0.08	0.56 $\pm$ 0.09	0.07 $\pm$ 0.12	0.01 $\pm$ 0.13	0.21 $\pm$ 0.13	0.48 $\pm$ 0.10	<b>0.27 <math>\pm</math> 0.05</b>	0.15 $\pm$ 0.08	0.17 $\pm$ 0.05
CRP	0.54 $\pm$ 0.11	0.57 $\pm$ 0.11	-0.20 $\pm$ 0.12	0.26 $\pm$ 0.13	0.50 $\pm$ 0.13	-0.05 $\pm$ 0.15	0.39 $\pm$ 0.17	0.24 $\pm$ 0.16	0.23 $\pm$ 0.14	0.35 $\pm$ 0.18	<b>0.43 <math>\pm</math> 0.11</b>	0.35 $\pm$ 0.08
WBC	0.18 $\pm$ 0.09	0.21 $\pm$ 0.09	-0.08 $\pm$ 0.09	0.11 $\pm$ 0.09	0.22 $\pm$ 0.10	0.06 $\pm$ 0.10	0.18 $\pm$ 0.11	0.17 $\pm$ 0.12	0.28 $\pm$ 0.10	0.16 $\pm$ 0.11	0.41 $\pm$ 0.12	<b>0.38 <math>\pm</math> 0.05</b>

Data are adjusted for age, age squared, sex, field center, hormone replacement therapy, smoking (cigarettes/day), alcohol intake (g/day), energy intake (kcal/day), dietary fat (%), physical activity index (metabolic equivalent min/week), and sedentary behavior (television hours/day). Data in bold are significantly different from 0 at  $P < 0.05$ .

cant genetic correlations with waist circumference and insulin. The major strengths of this study are inclusion of novel risk factors such as PAI-1, uric acid, CRP, and WBC and adjustment for a comprehensive list of lifestyle/behavioral variables. Our adjustment for the lifestyle variables was designed to remove the influence of familial environment as much as possible. However, it is possible that there were still residual effects from those covariates that were not fully captured by the statistical adjustment. In addition, there were other potentially important environmental factors that were not considered or measured in the study. For example, impaired fetal growth, which is associated with maternal undernutrition and/or poor intrauterine environment, has been identified as an important contributor to insulin resistance and other MetS-related traits (21). Accordingly, the rate of fetal growth may contribute to sibling correlations of MetS-related traits, since siblings have been exposed to the same uterus. Moreover, shared household effects during childhood and adulthood were not considered in the study. Therefore, the estimated heritability and genetic correlations may have been influenced by familial environmental determinants. The overall pattern of bivariate genetic correlations obtained in our study is comparable with that of most previous reports (7–13,15,22) using similar or different methods, as summarized in the online appendix. However, there are also discrepancies. In contrast to findings from other studies where significant genetic/familial influences common to BMI/blood pressure (10,13,22), BMI/glucose (22), and PAI-1/sBP (13) were detected, we could not reproduce these results. The discrepancies may be caused by differences in population characteristics and adjustment schemes. In addition, chance may play a role because multiple pairs of traits were analyzed. The biological mechanisms underlying the association among obesity, hyperinsulinemia, dyslipidemia, impaired fibrinolytic activity, and hyperuricemia are not fully understood. Insulin resistance in adipose tissue is believed to be an originating factor for the overall insulin resistance syndrome associated with obesity (23,24). The presence of insulin resistance or limited storage capacity in adipose tissue results in increased release of free fatty acids to non-adipose tissue such as liver and skeletal muscle, leading to hyperinsulinemia, glucose intolerance (24), and increased VLDL, with the latter leading to hypertriglyceridemia and low HDL cholesterol (23). Several factors that include in-

sulin, triglycerides, and free fatty acids can stimulate PAI-1 expression by adipocytes, hepatocytes, and endothelial cells (23,25–27). The association of hyperuricemia with MetS has been attributed to reduced renal clearance of uric acid due to hyperinsulinemia (28). In addition, increased production of uric acid was postulated to play a role. Matsuura et al. (29) reported that 44% of subjects with visceral fat obesity and hyperuricemia showed increased 24-h urinary urate excretion, indicating an overproduction of uric acid. The association of WBC with uric acid may reflect a causative relationship between increased proliferation of white blood cells and increased purine synthesis and degradation (30).

How do the bivariate genetic correlations we observed fit in the above mechanisms? It is possible that underlying genetic/familial factors directly affect the initiating traits (e.g., obesity and/or insulin resistance), influencing the other genetically correlated traits via pathways mediated by those traits. However, it is also possible that the responsible genetic/familial factors act upon each of the traits directly. The genetic mechanism in the first situation has been termed by Hadorn (cited by Rieger et al. [31]) as relational pleiotropy and that in the second situation as mosaic pleiotropy. These two mechanisms are not easily distinguished by study of trait correlations in family members, as is the case in our study. Ultimately, it will require gene discovery and genotype-phenotype studies to determine the biological relationships between the underlying genes and the MetS-related traits. Among the 31 trait pairs that exhibited significant genetic correlations, 2 trait pairs showed strong genetic correlations ( $\rho_g > 0.70$ ), 13 trait pairs showed modest genetic correlations ( $0.7 \geq \rho_g > 0.4$ ), and the remaining 16 pairs showed genetic correlations of  $<0.4$ . Whereas pairs of traits with modest genetic correlations may still share common genetic determinants, it is important to note that, for those traits, shared genetic factors do not likely contribute as much to their additive genetic variation as do genetic factors unique to each trait. However, this does not rule out the importance of identifying modest genetic correlations in gene discovery studies. Because MetS-related traits are complex in nature, it is likely that each trait is influenced by multiple genes, with a few of the genes for one trait being common to one or some of the other traits, resulting in modest genetic correlations. Therefore,

genomic regions that are identified for one trait should be evaluated for other genetically correlated traits. This may present as an effective strategy for linkage studies to locate genomic regions that are linked to a cluster of traits. Identifying responsible genes in those regions may lead to new insights into the biochemical pathways that constitute pathophysiological mechanisms underlying the MetS.

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