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A New Look at the Genetic and Environmental Coherence of Metabolic Syndrome Components

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Abstract

Objective—Metabolic syndrome, a clustering of risk factors including insulin resistance, dyslipidemia, central obesity and hypertension, increases risk for cardiovascular disease and cognitive decline. The etiology of the risk factors' cohesion remains unclear. We examined how genetic and environmental influences explained co-occurrence of metabolic syndrome components.

Methods—Continuous measures of body mass index (BMI), waist circumference, blood pressure (BP), fasting insulin and glucose, high-density-lipoprotein cholesterol (HDL) and triglycerides from 1193 middle-aged twin men participating in the Vietnam Era Twin Study of Aging at average age 62 (range 56-67) were analyzed using multivariate biometrical modeling.

Results—We found four heritable factors: adiposity (BMI, waist circumference), insulin resistance (glucose, insulin), lipids (HDL, triglycerides), and BP (systolic, diastolic). Heritabilities were .42-.68. In the best-fitting model, insulin resistance, lipids, and adiposity comprised a higher-order latent genetic factor. Adiposity and BP shared genetic influences independent of the latent genetic factor. All factors aggregated on a latent unique environmental factor.

Conclusions—Metabolic syndrome components form the equivalent of two genetic factors. BP was genetically unrelated to insulin resistance and lipids. Adiposity was the only characteristic genetically and environmentally related to all other factors. These results inform strategies for gene discovery and prediction of health outcomes.

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Keywords

(3-6) metabolic syndrome; obesity; individual differences; VETSA

Introduction

Metabolic syndrome (MetS) is a powerful risk factor for cardiovascular disease and related conditions in older adults. Adults with MetS are three times more likely to have heart attacks or strokes, twice as likely to die from these events, and five times more likely to develop type 2 diabetes than adults without MetS¹. MetS and its components also contribute to risk for cognitive decline and accelerated neurodegeneration²⁻⁴. Over a quarter of the world's adults are estimated to have MetS, thus contributing to significant public health burden¹. A World Health Organization (WHO) report recommended that researchers focus on elucidating common metabolic pathways underlying MetS components because improved understanding of MetS pathogenesis can inform strategies to reverse or modify its risks⁵.

A WHO consensus panel identified five common criteria for MetS: abdominal obesity, elevated blood pressure (BP), elevated triglycerides, reduced high density lipoprotein cholesterol (HDL), and elevated fasting glucose as well as surrogate measures such as drug treatment^{1,6}. These components do not necessarily have the same etiology or pathophysiology. Co-occurrence may be due to factors ranging from shared genes to shared behaviors, partially overlapping pathophysiologies, as well as lifestyle and environmental factors. The mechanisms linking these conditions are poorly understood.

Twin studies provide a unique, but complementary approach to molecular genetics for testing predictions of existing theory and contributing to specification of underlying etiologies⁷. A review of twin/family studies reported moderate to strong genetic and environmental influences on individual MetS components⁸. However, only four twin/family studies, to our knowledge, examined the genetic architecture underlying the coherence of all MetS components simultaneously, with inconsistent results⁹⁻¹². Some had very wide age ranges, which can be problematic because the prevalence of MetS, and the level and variability of MetS components are very different in younger and older adults. Studies often excluded people with diabetes or cardiovascular disease, which makes sense for some risk prediction studies but doing so in genetic analyses excludes people likely to be enriched for “risk” genes. Moreover, exclusion results in a very select group with respect to older adults and survival bias. Few studies accounted for effects of medication on component measures.

Given the importance of MetS components as risk factors for health and mortality and the limitations of previous studies, we examined the etiology of the coherence of MetS components in a large sample of middle-aged twins. If the genetic and environmental structure closely approximates the phenotypic structure of MetS, a single latent factor should emerge¹³ (Figure 1A) that would support a higher-order factor in which all components share a metabolic pathway. However, no single etiology or pathophysiology has yet been identified¹⁴. As suggested by previous twin studies, there are likely to be independent genetic and environmental influences on at least some of the observed relationships among MetS components (Figure 1B). Identifying different combinations of MetS components that

are genetically and/or environmentally related to each other would help to elucidate metabolic/biologic pathways for sets of risk factors.

Methods

Participants

This study is based on 1193 participants (330 monozygotic [MZ] pairs, 233 dizygotic [DZ] pairs, 67 unpaired twins) from wave 2 of the Vietnam Era Twin Study of Aging (VETSA)¹⁵. VETSA is a longitudinal study of midlife risk and protective influences on cognitive aging in a community-dwelling sample¹⁶. At baseline, 1237 individual twins were randomly recruited from twin pairs in the nationally representative Vietnam Era Twin Registry, an all-male registry¹⁷. At wave 2, twins were on average 61.7 years old (SD 2.4; range 56-66.9). The sample is predominantly of European descent. Although participants were all veterans, nearly 80% reported no combat exposure. Health and lifestyle characteristics are comparable to American men in this age group¹⁸.

Zygosity was primarily determined by 25 microsatellite markers; for 8% of the sample zygosity was determined by questionnaires and blood group, with 95% agreement with DNA-based results. Participants underwent medical history interviews which elicited information about prescription medications. Written informed consent was obtained from all participants. Metabolic syndrome measures.

After removing shoes and heavy outer clothing, participants were weighed to the nearest half pound on a digital scale and height was assessed with a stadiometer. Body mass index (BMI) was calculated as: Weight (kg)/Height² (m²). Waist circumference was measured as the smallest horizontal circumference between the 12th rib and the iliac crest.

Morning and afternoon systolic and diastolic BP (SBP, DBP) measurements were obtained in a seated position using automated sphygmomanometers. After waiting quietly for five minutes, BP was measured twice with one-minute breaks between readings. SBP and DBP scores were averages of the four readings. Triglycerides and HDL (mmol/L), insulin (pmol/L), and glucose (mmol/L) were assayed from fasting blood samples at certified laboratories (Nichols Institute/Quest Diagnostics, San Juan Capistrano, CA).

Medications were categorized and organized by RLH, KK*, MS, and CEF according to mechanism of action and indication. Medication adjustments for BP were based on previous work showing that taking into account drug class, number of antihypertensive drugs, and ethnicity was optimal; depending on these characteristics, values added to SBP/DBP measures ranged from 14-38/9-27mmHg, respectively¹⁹. Based on Wu et al,²⁰, HDL and triglycerides were adjusted by drug class, ethnicity, and number of statin or fibrate drugs taken.

To account for skewness and effects of diabetes-related medications, ordinal measures were created for insulin and glucose to approximate normal distributions. Glucose was divided into 10 categories. The first seven represented glucose levels in individuals not taking diabetes-related medications; the last three represented individuals who were taking

medication. Insulin level was divided into five categories. The first four represented individuals not taking diabetes-related medication. Many individuals had the lowest detectable value; thus, more insulin categories could not be created. All diabetes was type 2 as those with type 1 diabetes were not inducted into the military.

Statistical analysis—In classical twin design, variance of any phenotype is partitioned into components attributable to additive genetic influences (A), common environmental influences (C, i.e., environmental factors that make twins similar to one another), and individual-specific or unique environmental factors (E, i.e., environmental factors that make twins different from one another, including measurement error), called the “ACE” model²¹. Additive genetic influences are assumed to correlate 1.0 between MZ twins because they share 100% of their genes. DZ twins on average share 50% of their segregating genes, and are assumed to correlate .50. Common environmental influences are assumed to correlate 1.0 between members of a twin pair regardless of zygosity. By definition, unique environmental influences are uncorrelated within pairs. When two phenotypes are correlated, multivariate extensions of the ACE model decompose the covariance between phenotypes into genetic and environmental components thereby revealing the extent and sources of overlap. This allows for estimation of genetic and environmental correlations (representing the degree of shared genetic and environmental variance, respectively), as well as testing of genetically-informative factor models.

We first fit a Cholesky decomposition to the data. The Cholesky provides the most saturated representation of the genetic and environmental relationships among the variables and offers a summary of the data prior to imposing structure. Then, using two indicators for each physiological system, we fit a series of multi-strata (higher-order) independent and common pathways models²² to the data in order to determine the genetic and environmental factor structure. In these models measurement error is largely restricted to the level of the observed variables, thus genetic and environmental influences of the latent phenotypes can be more clearly elucidated.

We first fit a four-correlated-factors common pathways model to estimate the phenotypic, genetic, and environmental covariance among latent phenotypes. This provided a reference against which all subsequent models could be compared. The higher-order common pathway model (Figure 1A) assumes that the covariance among the physiological domains is accounted for by a single, higher-order latent phenotype and that the genetic and environmental covariance among the domains is accounted for by genetic and environmental influences operating through that phenotype²². The higher-order independent pathways model (Figure 1B) assumes that the covariance among the physiological measures is accounted for by independent, higher-order genetic (A_L) and environmental (E_L) factors, while residual genetic and environmental influences are allowed at the level of the domains and the measured variables. The model does not require an overarching latent phenotype; it can account for the covariance via separate genetic and environmental factors that are independent of one another, and whose loadings do not have to be colinear. The model also allows for genetic and environmental factor structures to be tested separately from one another, thus remaining agnostic as to whether genetic and environmental influences adhere to the same covariance structure²². In all models the common environmental covariance was

freely estimated at the level of the observed variables. Doing so allowed us to establish estimates of the genetic variance and covariance that were unbiased by the small, but nevertheless nontrivial, common environmental effects (see Results).

Analyses were performed using OpenMx software²³. When necessary, variables were transformed in order to normalize their distributions. Evaluation of model fit was performed using the likelihood-ratio chi-square test (LRT), i.e., the difference in the $-2 \log$ -likelihood ($-2LL$) of a model relative to that of a comparison model. The Bayesian Information Criterion (BIC) served as a secondary indicator of model fit^{24,25}. More negative values indicate a better balance between goodness-of-fit and parsimony.

Results

Descriptive analyses

Sample characteristics are presented in Table 1. The strongest phenotypic correlations were between measures within the same physiological domain, ranging from $-.60$ for HDL-triglycerides to $.90$ for BMI-waist circumference (Table 2). The weakest cross-domain correlations were between BP and other measures. With the exception of the SBP-HDL correlation ($r = -.06$) all other cross-measure correlations were significant.

All measures had significant genetic influences, with heritabilities ranging from $.43$ for triglycerides to $.67$ for HDL (Table 3). Results in Table 3 are based on the full ACE Cholesky which provides the best description of the interrelationships among the measures before imposing structure on the genetic and environmental covariance. Unique environmental influences were also significant for all measures, ranging from $.32$ for BMI and HDL to $.54$ for SBP. Only waist circumference ($c^2 = .12$), and BMI ($c^2 = .13$) had significant, albeit small, common environmental estimates. Within-domain genetic correlations ranged from $-.75$ to $.90$ indicating substantial shared genetic variance.

Multivariate model-fitting

The four-correlated factors common pathways model had a good fit relative to the Cholesky (see Table 4, Model 2 relative to Model 1). We refer to these latent factors as insulin resistance (glucose, insulin levels), adiposity (BMI, waist circumference), lipids (triglycerides, HDL), and BP (SBP, DBP). Each latent factor was significantly heritable, with estimates of $.67$ for insulin resistance, $.68$ for lipids, $.62$ for adiposity, and $.42$ for BP (see Supplemental Table 1; Supplemental Table 2 shows phenotypic, genetic, and environmental correlations among the four latent physiological factors).

At the phenotypic level, all four factors were significantly correlated, ranging from $.16$ for BP-lipids to $.57$ for insulin resistance-lipids. At the genetic level, BP shared significant genetic influences with adiposity ($r_g = .49$) but not with insulin resistance ($r_g = .17$, ns) or lipids ($r_g = .17$, ns). Insulin resistance, lipids, and adiposity all shared significant genetic influences with each other. For the unique environmental correlations, all four factors were significantly correlated. This pattern suggested that a higher-order common pathways model was unlikely to fit the data.

The higher-order common pathways model resulted in a significant reduction in fit relative to the correlated factors model (Table 4, fit of Model 3 relative to Model 2). This effectively rejects the view that a single latent factor accounts for the coherence in MetS components. We then systematically tested alternative structures of the genetic and environmental covariance using various independent pathway models.

The final best-fitting model was achieved when a modified higher-order genetic factor was combined with a higher-order unique environmental factor (Table 4, Model 9; & Figure 2). Based on examination of the genetic correlations observed among the physiological domains in the four-correlated factors model, we allowed for an additional covariance parameter between the factor specific genetic influences for adiposity and BP (we refer to this as the Modified Higher-Order IP Model). The inclusion of this parameter resulted in an improvement in model fit. As shown in Figure 2, insulin resistance, adiposity, and lipids loaded on a genetic latent factor dominated by insulin resistance and lipids. This latent factor did not account for all of the genetic influences. An additional parameter accounted for significant genetic influences shared by adiposity and BP. A separate latent factor accounted for unique environmental influences on all four physiological factors. The inclusion of a similar correlation parameter among residual environmental influences for adiposity and BP did not improve model fit. It should also be noted that adiposity and BP had significant specific genetic influences, not accounted for by the higher-order factors, and the physiological factors had additional specific unique environmental influences.

Discussion

We found four heritable physiological factors: insulin resistance (glucose, insulin), adiposity (BMI, waist circumference), lipids (HDL, triglycerides), and BP (systolic, diastolic) underlying MetS components. Insulin resistance, lipids, and adiposity shared genetic influences, comprising a higher-order genetic factor. We also detected genetic influences that were shared between adiposity and BP but not with insulin resistance or lipids. Some research suggests that insulin resistance and/or central obesity are the most likely causative factors underlying MetS^{1,5,6}; however, there are longitudinal data indicating that a large waist circumference precedes changes in other MetS components, but not the reverse⁶. Although we cannot be certain, those longitudinal findings plus the fact that adiposity was the only component genetically linked with all other components in our data are consistent with the view that genetic influences on adiposity might account for or “drive” overlapping pathophysiologies in MetS components. All components aggregated on a single latent unique environmental factor, suggesting similar underlying environmental influences, which might include individual behaviors such as diet and exercise.

Importantly for the discovery of pathogenic mechanisms and their biomarkers that predict risk for cognitive impairment and eventual dementia, a recent study found that genes regulating BMI are highly enriched in the hippocampus and limbic system, which control memory, learning and emotion²⁶. Moreover, brain-specific genes regulating glutamate receptor signaling and trafficking, synaptic plasticity, and other neuronal responses involved in cognitive functioning are genetically linked to BMI regulation²⁶. The central role of adiposity would also be consistent with work by Peeters et al¹² in younger twins, as well

with our earlier work in a different sample of VET Registry twins showing that age 20 BMI predicted diabetes but not hypertension at age 48; age 48 BMI, however, was associated with both diabetes and hypertension²⁷.

The finding of different genetic influences for different MetS components is also supported by recent genome-wide association studies (GWAS) that found significant single-nucleotide polymorphism (SNP)-based heritability for each of the components, and varying degrees of genetic overlap²⁸⁻³⁰. A SNP-based study of pleiotropy also strongly supports our findings: SNPs associated with SBP were significantly enriched as a function of their association with BMI, waist-hip ratio, and diabetes, but not with type 2 diabetes, HDL, or triglycerides³¹. Avery et al³² found aggregation of glucose intolerance, dyslipidemia, and adiposity in adults of European descent and identified rs4420638 (in the region of APOE and APOC genes) as well as loci in the region of BRAP and PLGC1 as accounting for these associations. Recent studies of obesity-induced hypertension identified some distinct biological pathways linking obesity with BP through renal sympathetic nerve activity and the melanocortin/renin-angiotension system compared with lumbar sympathetic mechanisms linking obesity, insulin resistance and dyslipidemia³³⁻³⁶. Similarly, the low genetic correlation between HDL and BP found in this study parallels that found in some forms of lipodystrophy³⁷.

Although the twin method cannot identify specific genes, it does account for the influences of all genes. Thus, it can provide convergent validation with GWAS as well as a priori hypotheses regarding associations in GWAS (e.g., what phenotypes will or will not have pleiotropic effects), all before knowing what the specific genes are. It is also worth noting that these GWAS and studies of linked biological pathways examined associations between pairs of MetS components separately. In contrast, our multivariate analysis addressed the interrelationships among multiple MetS components simultaneously.

A limitation of our study is that it largely comprises non-Hispanic men of European origin. Thus, its generalizability to women and other ethnic/racial groups is unclear. GWAS have identified different SNPs by gender, race, and ethnicity³⁸, but the consistency of those findings remains to be determined. Prior twin studies did not find sex differences but were underpowered to do so.

Our findings, placed in the context of previous twin studies, highlight the potential importance of age when examining co-occurrence of MetS components: little association among components in younger participants,^{11,12} and greater coherence in older participants⁹. The mean ages in two of the twin studies were 38¹¹ and 66⁹, but they had 49- and 35-year age ranges, respectively. In the study of younger twins¹¹, genetic associations among MetS measures were weak (though insulin resistance measures adjusted for BMI which would reduce that cross-domain association). However, another study found small but significant common sources of genetic and environmental variance in young adult twins ages 18-34 across six MetS measures that loaded heavily on waist circumference¹². Unlike VETSA, there was additional covariation between lipids and BP; most of the variance, however, was measure specific. A study of older twins ages 52-86 found one genetic factor and one environmental factor linking five MetS components⁹. Similar to our results, obesity was related to all other measures; a variation of the model similar to ours was not tested,

perhaps because of limited computing resources at the time of that study. Finally, in monozygotic twins ages 18-76, two latent factors emerged, one a separate lipids factor¹⁰. That small study included only healthy individuals at all ages, making the older portion of the sample atypical and underpowered. Across studies, BP has low associations with other MetS components.

Our study also has multiple strengths. In contrast to some previous studies we used continuous measures for all MetS components. The sample was a large national sample in a narrow age range in which prevalence rates of MetS related conditions increase rapidly. Thus, the considerable differences in MetS in older versus younger adults was not a factor. We also included adults with type 2 diabetes or cardiovascular disease; exclusion of these conditions from genetic studies of middle-aged and older adults effectively create samples that are enriched for genes that predispose to healthy aging, i.e., reduced risk of diabetes or cardiovascular disease. On the other hand, it would have little effect on young adults in whom these conditions are rare. Without excluding particular conditions, we had many participants who were taking various medications. We accounted for the influence of medication based on the best available published data of the effects of the medications in different ethnic groups. Despite evidence for the validity of such adjustments, they are still imperfect. However, we believe they are preferable to not taking medications into account or excluding participants taking medications, which would result in misleading values that did not fully reflect genetic influences.

Conclusion

The results supported pleiotropy underlying some MetS components in late middle-aged men and provide strong evidence that common metabolic pathways only partially explain the coherence in MetS components. The common thread was that adiposity was the sole component that was genetically related to all others. The two different sets of shared genetic influences may partially underlie the link from obesity to development of other MetS components. Our multivariate twin analyses elucidate the underlying genetic architecture of MetS components in a way that simple associations between pairs of components cannot. Our results were supported by some recent GWAS, and may be informative for future GWAS. Through a better understanding of the genetic and environmental influences underlying MetS components, some treatments and interventions could be developed that more efficiently affect multiple components, while other components will need more targeted interventions. This approach could lead to developing personalized pharmacotherapies, lifestyle modifications, and other interventions to delay or curtail development of cognitive impairment, cardiometabolic-related disorders and other pathologies^{39,40}. The U.S. Surgeon General targeted obesity and its role in over 100,000 deaths per year in the U.S as a major public health challenge⁴⁰. The importance of this issue is borne out in the present sample in which there was a shift from 75-80% with normal BMI at age 20 to 75-80% with midlife BMI in the overweight or obese range²⁷.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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What is already known about this subject?

- Metabolic syndrome components (i.e. obesity, hypertension, dyslipidemia, and insulin resistance) independently and as a unit comprise powerful risk factors for cardiovascular disease, diabetes, and early mortality.
- Studies find low to moderate correlations between metabolic syndrome components.
- Mechanisms underlying the coherence of metabolic syndrome are understudied.

What does this study contribute to this subject?

- Multivariate twin analyses can elucidate the mechanisms underlying metabolic syndrome in ways that simple associations between components cannot.
- Adiposity, insulin resistance, and lipids shared genetic influences but adiposity and blood pressure had genetic influences in common that were independent of the other components.
- Adiposity, as the only component common to both sets of genetic influences, may play a central role in metabolic syndrome in middle age men.

Figure 1.

Common pathway (A) and higher-order independent pathway (B) models of the components of metabolic syndrome. Rectangles represent observed (measured) variables, ellipses represent latent phenotypes, and circles represent latent genetic and environmental variance components. For simplicity, shared/common environmental influences are not presented. Genetic and environmental influences for the higher-order factors are designated by the subscript “L”, whereas genetic and environmental influences for the physiological domains have numerical subscripts. Genetic and environmental influences that are specific to the observed variables are designated with the subscript “s”. BMI = body mass index. HDL = high density lipoprotein.

FIGURE 2.

Standardized variance components for best-fitting model of latent metabolic syndrome components (Model 9 in Table 4). For simplicity of presentation, observed variables, variable-specific genetic and environmental influences, as well as common environmental influences are not shown. 95% confidence intervals are presented in parentheses underneath each estimate. Genetic and environmental influences for the higher-order factors are designated by the subscript “L”.

Table 1

Characteristics of the VETSA sample

	Mean (SD)	Range
Age (years)	61.7 (2.4)	56.0 to 66.9
Education (years)	13.8 (2.1)	5.0 to 20.0
Ethnicity		
Caucasian (%)	89.10%	--
African American (%)	5.50%	--
Hispanic (%)	3.00%	--
Other (%)	2.40%	--
Fasting Glucose (mmol/L)	6.01 (1.8)	3.3 to 20.1
Fasting Insulin (pmol/L)	65.28 (96.53)	6.9 to >2000
Height (cm)	175.5 (6.9)	157 to 198
Weight (kg)	92.8 (17.7)	52.5 to 171.5
Waist Circumference (cm)	103.9 (13.2)	73 to 160
Body Mass Index	29.9 (5.4)	18 to 53
High Density Lipoprotein Cholesterol (mmol/L)	1.24 (.37)	.54 to 2.8
Triglycerides (mmol/L)	1.56 (1.02)	.33 to 11.2
Medication Corrected HDL Cholesterol (mmol/L)	1.2 (.38)	.36 to 2.8
Medication Corrected Triglycerides (mmol/L)	1.69 (1.01)	.33 to 11.2
Average Systolic BP (mmHg)	127.9 (15.8)	77.0 to 194.5
Average Diastolic BP (mmHg)	78.33 (8.9)	51.8 to 115.5
Medication Corrected Systolic BP (mmHg)	138.7 (18.8)	93.0 to 225.8
Medication Corrected Diastolic BP (mmHg)	85.9 (10.9)	55.8 to 131.9
Self-Report Hypertension (% yes)	55.10%	--
Self-Report High Cholesterol (% yes)	57.00%	--
Self-Report Diabetes (% yes)	18.20%	--
Taking Anti-Hypertension Medication (% yes)	57.30%	--
Taking Cholesterol-Related Medication (% yes)	49.60%	--
Taking Diabetes-Related Medication (% yes)	16.80%	--

Table 2

Phenotypic correlations among the observed variables

Phenotype	1	2	3	4	5	6	7	8
1. Fasting Glucose	1.0							
2. Fasting Insulin	.67 (.63; .70)	1.0						
3. Body Mass Index	.31 (.25; .37)	.46 (.40; .51)	1.0					
4. Waist Circumference	.32 (.25; .37)	.46 (.41; .51)	.90 (.89; .91)	1.0				
5. HDL Cholesterol	-.26 (-.32; -.20)	-.41 (-.46; -.35)	-.33 (-.39; -.27)	-.32 (-.38; -.26)	1.0			
6. Triglycerides	.27 (.21; .33)	.38 (.32; .43)	.29 (.22; .35)	.30 (.24; .36)	-.60 (-.64; -.55)	1.0		
7. Systolic Blood Pressure	.20 (.14; .26)	.17 (.11; .24)	.26 (.20; .32)	.24 (.18; .30)	-.06 (NS)	.17 (.10; .23)	1.0	
8. Diastolic Blood Pressure	.17 (.11; .23)	.18 (.11; .24)	.29 (.23; .35)	.28 (.22; .34)	-.08 (-.14; -.01)	.19 (.12; .25)	.82 (.80; .84)	1.0

NS indicates that the correlation is not statistically significant at the $p < .05$ level. 95% confidence intervals are presented in the parentheses. Results are derived from the multivariate ACE Cholesky model.

Table 3

Genetic and environmental influences of the observed variables

	1.	2.	3.	4.	5.	6.	7.	8.
<u>Genetic Influences</u>								
1. Fasting Glucose	.52 (.35; .64)							
2. Fasting Insulin	.74 (.62; .84)	.54 (.38; .66)						
3. Body Mass Index	.15 (NS)	.39 (.19; .54)	.55 (.38; .69)					
4. Waist Circumference	.17 (NS)	.42 (.22; .59)	.90 (.85; .94)	.50 (.33; .64)				
5. HDL Cholesterol	-.39 (-.60; -.24)	-.54 (-.71; -.40)	-.35 (-.52; -.19)	-.36 (-.54; -.19)	.67 (.55; .73)			
6. Triglycerides	.34 (.04; .64)	.48 (.21; .75)	.31 (.01; .59)	.32 (.01; .61)	-.75 (-.98; -.59)	.43 (.20; .61)		
7. Systolic Blood Pressure	.18 (NS)	.08 (NS)	.27 (.00; .53)	.25 (NS)	-.06 (NS)	.24 (NS)	.45 (.22; .53)	
8. Diastolic Blood Pressure	.21 (NS)	.17 (NS)	.40 (.17; .65)	.37 (.13; .64)	-.09 (NS)	.25 (NS)	.87 (.76; .94)	.48 (.28; .55)
<u>Common Environment Influences</u>								
1. Fasting Glucose	.08 (NS)							
2. Fasting Insulin	1.0 (NS)	.08 (NS)						
3. Body Mass Index	.99 (.07; 1.0)	.99 (.14; 1.0)	.13 (.01; .28)					
4. Waist Circumference	.99 (.01; 1.0)	.99 (.05; 1.0)	.99 (.74; 1.0)	.12 (.01; .27)				
5. HDL Cholesterol	.96 (NS)	.96 (NS)	.98 (NS)	.96 (NS)	.01 (NS)			
6. Triglycerides	.19 (NS)	.18 (NS)	.09 (NS)	.18 (NS)	-.09 (NS)	.11 (NS)		
7. Systolic Blood Pressure	.82 (NS)	.82 (NS)	.87 (NS)	.82 (NS)	.94 (NS)	-.41 (NS)	.01 (NS)	
8. Diastolic Blood Pressure	-.33 (NS)	-.32 (NS)	-.23 (NS)	-.32 (NS)	-.06 (NS)	-.99 (NS)	.28 (NS)	.00 (NS)
<u>Unique Environment Influences</u>								
1. Fasting Glucose	.40 (.33; .47)							
2. Fasting Insulin	.51 (.42; .59)	.38 (.32; .45)						
3. Body Mass Index	.36 (.25; .45)	.41 (.31; .50)	.32 (.27; .38)					
4. Waist Circumference	.34 (.24; .44)	.38 (.28; .47)	.87 (.84; .89)	.38 (.32; .45)				
5. HDL Cholesterol	-.16 (-.27; -.05)	-.32 (-.42; -.22)	-.47 (-.55; -.37)	-.41 (-.50; -.31)	.32 (.27; .39)			
6. Triglycerides	.21 (.10; .32)	.31 (.21; .41)	.32 (.22; .42)	.31 (.20; .41)	-.50 (-.58; -.41)	.46 (.38; .53)		
7. Systolic Blood Pressure	.19 (.08; .30)	.24 (.14; .34)	.22 (.11; .32)	.20 (.09; .30)	-.09 (NS)	.16 (.05; .26)	.54 (.46; .63)	
8. Diastolic Blood Pressure	.15 (.04; .26)	.21 (.11; .32)	.21 (.11; .31)	.22 (.12; .32)	-.07 (NS)	.17 (.06; .28)	.78 (.74; .82)	.52 (.45; .61)

Note: HDL=High Density Lipoprotein. Standardized variance components appear in **bold** on the diagonal. Correlations appear on the off-diagonal in *italics*. 95% confidence intervals are presented in the parentheses. *NS* indicates that the value is not statistically significant at the $p < .05$ level. Results are derived from the multivariate ACE Cholesky model.

Table 4**Multivariate Model Fitting Results**

Model	–2LL	df	BIC	LRT	df	p
1. ACE Cholesky	19644.78	8981	–38244.23	--	--	--
2. Correlated Factors CP*	19686.01	9013	–38409.26	41.23	32	.1271
3. Higher-Order CP	19706.28	9020	–38434.11	20.27	7	.0050
4. Higher-Order IP A & E	19699.31	9017	–38421.75	13.30	4	.0099
5. Higher-Order IP A	19694.12	9015	–38413.97	8.11	2	.0173
6. Modified Higher-Order IP A	19686.04	9014	–38415.68	0.03	1	0.8625
7. Higher-Order IP E	19691.01	9015	–38417.16	5.00	2	.0821
8. Modified Higher-Order IP E	19690.97	9014	–38410.75	4.96	1	.0259
9. Modified Higher-Order IP A & Higher-Order IP E	19691.95	9016	–38422.67	5.94	3	.1146

–2LL = –2 log likelihood; df = degrees of freedom; BIC = Bayesian information criterion; LRT = likelihood ratio test; df = change in degrees of freedom; p = significance of LRT; CP = Common Pathway Model; IP = Independent Pathways Model; A = Additive genetic influences; E = Unique environmental influences. Modified Higher-Order IP models include an additional covariance parameter between adiposity and blood pressure. Best-fitting model is in bold.

* The fit of Model 2 is tested relative to Model 1. For all subsequent models (3 through 9), the fit is determined relative to Model 2. For all models common environmental influences (C) are estimated as a Cholesky structure.