



Genetic and environmental influences on body fat distribution, fasting insulin levels and CVD: are the influences shared?

Tracy L Nelson¹, George P Vogler¹, Nancy L Pedersen^{1,2,3}, Yuling Hong^{2,4} and Toni P Miles⁵

¹Department of Biobehavioral Health and Center for Developmental and Health Genetics, The Pennsylvania State University, PA, USA

²Division of Genetic Epidemiology, Institute of Environmental Medicine, Karolinska Institute, Stockholm, Sweden

³Department of Psychology, University of Southern California, Los Angeles, CA

⁴Division of Biostatistics, Washington University, School of Medicine, St Louis, MO

⁵Department of Family Practice, Division of Geriatrics, University of Texas Health Sciences Center-San Antonio, TX, USA

Central body fat distribution has been shown to be related to hyperinsulinemia, insulin resistance, hypertriglyceridemia, and atherosclerosis to a greater degree than general obesity. There are known to be both genetic and environmental effects on all components of this clustering. Whether these genetic effects are due to one set of genes in common to the components or whether genetic influences on insulin resistance and/or general/abdominal fatness ‘turn on’ other genes that affect other components of the syndrome is not clear. We analyzed data from the Swedish Adoption/Twin Study of Aging (60% female; monozygotic = 116, dizygotic = 202; average age 65 years) to determine whether there were genetic and/or environmental factors shared among general body fat distribution, abdominal body fat distribution, fasting insulin levels and cardiovascular disease. We found additive genetic effects in males to be significantly different from those in females with genetic effects accounting for variance in waist–hip ratio (males = 28%; females = 49%), body mass index (males = 58%; females = 73%), fasting insulin levels (FI) (males = 27%; females = 49%), and cardiovascular disease (CVD) (males = 18%; females = 37%). There were also shared genetic and environmental effects among all the variables except CVD, but a majority of the genetic variance for these measures was trait specific. *Twin Research* (2000) 3, 43–50.

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Introduction

The clustering of obesity, hyperinsulinemia, insulin resistance, hypertriglyceridemia, atherosclerosis, and hypertension has been documented extensively over the past 10 years. The clustering of such disorders has recently been identified as syndrome X or the metabolic syndrome.^{1,2} Central body fat distribution has been shown to be more strongly related to these metabolic disorders than peripheral fat distribution.^{3–7} It is thought that insulin resistance and/or central obesity are the underlying precursors of the other components of the syndrome.^{1,8,9} Genetic and environmental effects are known to influence all the components of the metabolic syndrome.^{10–20} However, whether these genetic effects are due to one set of genes in common

with the components or whether genetic influences on insulin resistance and/or general/abdominal fatness ‘turn on’ other genes that affect other components of the syndrome is not clear. Several studies have given some indication that there may be shared genes. However, to our knowledge there are no studies to elucidate whether one genetic effect precedes the others. Using data from the National Academy of Sciences–National Research Council Twin Registry, a common latent factor was found to explain the clustering of hypertension, diabetes and obesity in male twins;¹⁴ 59% of the variance in this latent factor was genetic and 41% environmental. Using data from the Swedish Adoption/Twin Study of Aging (SATSA), genetic effects shared by body mass index (BMI), insulin resistance, triglycerides, high-density lipoprotein (HDL) cholesterol and systolic blood pressure were found, with BMI and insulin resistance sharing genetic effects to the greatest degree.²⁰ In the San Antonio Family Heart Study, genetic correlations were high between fasting insulin levels and, BMI, HDL level, and waist/hip ratio (WHR), indicating that the same gene or set

Correspondence: Dr Tracy L Nelson, Colorado State University, Department of Health and Exercise Science, 218 F Moby-B Complex, Fort Collins, CO 80523-1582, USA. Tel: (970) 491 6320; Fax: (970) 491 0445; E-mail: tnelson@cahs.colostate.edu
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of genes may influence insulin's relationship to these traits.¹⁶

Environmental effects may influence this clustering as well. A study using women's data from the Kaiser Permanente Twin Registry found BMI to be associated with fasting insulin levels after controlling for genetic influences.¹⁷ They also found a decrease in the correlation coefficient between fasting insulin (FI) levels, triglycerides and hypertension after adjusting for BMI. They hypothesize that non-genetic variation in obesity may influence the other components of the syndrome. Thus, there appear to be genetic and environmental influences shared among most components of the syndrome. The extent to which these influences are shared and the potential for one factor to initiate the others are questions that need clarification.

The purpose of the present study was to continue to look for genetic clustering of components of the metabolic syndrome and to see whether they differed in males and females. We were particularly interested in whether BMI and WHR were related differently to FI levels and/or cardiovascular disease (CVD), and whether gender or age had any effects. Specifically, we analyzed data from SATSA to determine whether there were genetic and/or environmental factors shared among general fat distribution, abdominal fat distribution, FI and CVD among males and females.

Methods

Sample

Data for this study came from the Swedish Adoption/Twin Study of Aging. The SATSA sample was identified through the Swedish Twin Registry, which includes questionnaire responses from almost 25 000 pairs of like-sexed twins born in Sweden during 1886–1958.²¹ The SATSA subregistry was formed in 1984 by contacting monozygotic (MZ) and dizygotic (DZ) twin pairs identified in the Swedish Twin Registry as having been reared apart (MZA and DZA), along with matched pairs reared together (MZT and DZT). The identification and characterization of the SATSA sample has been described in detail elsewhere.^{22,23} Measurements of BMI, WHR and CVD were obtained from a subset of individuals from 318 twin pairs (male pairs MZA = 23, MZT = 27, DZA = 38, DZT = 43; female pairs MZA = 23, MZT = 43, DZA = 73, DZT = 48) who were subjected to physical examinations during in person testing between 1989 and 1991. Fasting insulin levels were obtained in a subset of individuals from 180 twin pairs of the 322 pairs who were subjected to in person testing in 1986–1988. Those persons taking insulin were excluded from the

analysis. The average age of twins used in this analysis was 65 years (range 45–85 years) with 60% female and 40% male.

Measures

Waist measurements were obtained as the circumference around the smallest part of the waist and hip measurements as the circumference around the widest point between the hip and buttock. Waist/hip ratio was then determined by dividing the waist measurement by the hip measurement. Height was measured in (m) and weight in (kg) from subjects dressed in lightweight clothes and not wearing shoes. Body mass index was calculated as (weight in kg/height in m²).

Fasting blood samples were taken for determining insulin levels. Serum insulin was measured using a radioimmunoassay technique (RIA 100, Pharmacia). Fasting insulin levels were used as an indicator of insulin resistance. Cardiovascular disease was assessed from self reports on whether subjects had been diagnosed with or had angina pectoris, high blood pressure, heart insufficiency, heart attack, claudication, phlebitis, circulation problems, thrombosis, stroke, tachycardia, a heart operation, or heart valve problem. If subjects answered yes to any of these questions they were considered as having cardiovascular disease.

Statistical analysis

Descriptive statistics were performed using SAS.²⁴ Log transformations for BMI and FI were used in the analysis because of their skewed distributions. Model-fitting analyses were performed using the structural equation model-fitting program Mx²⁵ to evaluate quantitative distributions of genetic and environmental (shared rearing, correlated and non-shared) components. The assumptions of model-fitting analysis are that MZ twins share 100% of their additive genetic effects and DZ twins share 50% of their additive genetic effects. Twins reared together share similar rearing environmental effects. Because we had available both twins reared together and twins reared apart we were able to model genetic variance as well as three types of environmental variance including: shared rearing environmental variance, correlated environmental variance, and non-shared environmental variance. Shared rearing environmental variance is present when twins (of the same zygosity) reared together are more alike than those reared apart. Correlated environmental variance is present when identical twins are similar to fraternal twins regardless of rearing status. Non-shared environmental variance is that part of the variance not explained by genetic factors, shared

rearing environmental factors, or correlated environmental factors. Such variance is unique to the individual. The following equations can be used to describe the total phenotypic variance (V_p) and its components: additive genetic (V_G), shared rearing environment (V_{Es}), correlated environment (V_{Ec}), and non-shared environment (V_E). The total phenotypic variance is $(V_p) = V_G + V_{Es} + V_{Ec} + V_E$. The covariance of MZ twin pairs reared apart (MZA) is $Cov_p = V_G + V_{Ec}$. The covariance of MZ twin pairs reared together (MZT) is $Cov_p = V_G + V_{Es} + V_{Ec}$; the covariance of DZ twins pairs reared apart (DZA) is $Cov_p = 0.5 \cdot V_G + V_{Ec}$ and for DZ twin pairs reared together (DZT) $Cov_p = 0.5 \cdot V_G + V_{Es} + V_{Ec}$.

In twin studies of aging, there is often missing data. One twin may not have data for a variable being studied and the entire pair will then be discarded from the analysis under conventional pairwise deletion strategies. Discarding twin pairs becomes a particularly acute problem with multivariate analysis. To avoid such problems we used Mx a model-fitting program that allows missing data to be considered in the analysis. Since Mx uses raw data instead of variance–covariance matrices, the program does not give an actual fit statistic (ie χ^2) for the overall model, but does provide a value for the

likelihood. Relative fit of nested models can be evaluated by first determining the maximum likelihood statistic for a general model and then comparing with a more constrained model. The difference between minus twice the log-likelihood of each model is distributed as a χ^2 with degrees of freedom being the difference in the number of parameters estimated in the two different models. So, for example, if shared environmental effects were set to zero and compared with the general model (difference between minus twice the log-likelihoods), a statistically significant χ^2 would mean that shared environmental effects were a significant component of the variance for the variable under consideration.

The genetic or environmental covariance between two traits reflects the extent to which genetic or environmental effects are shared by the two traits. A Cholesky model²⁶ (Figure 1) which permits systematic decomposition of the genetic and environmental covariance among the four measures into independent factors was used in this analysis. In this model, genetic factor1 loads on all the variables, genetic factor 2 loads on all but one of the measures, genetic factor 3 on all but two of the measures and so on. The environmental measures have a similar pattern of

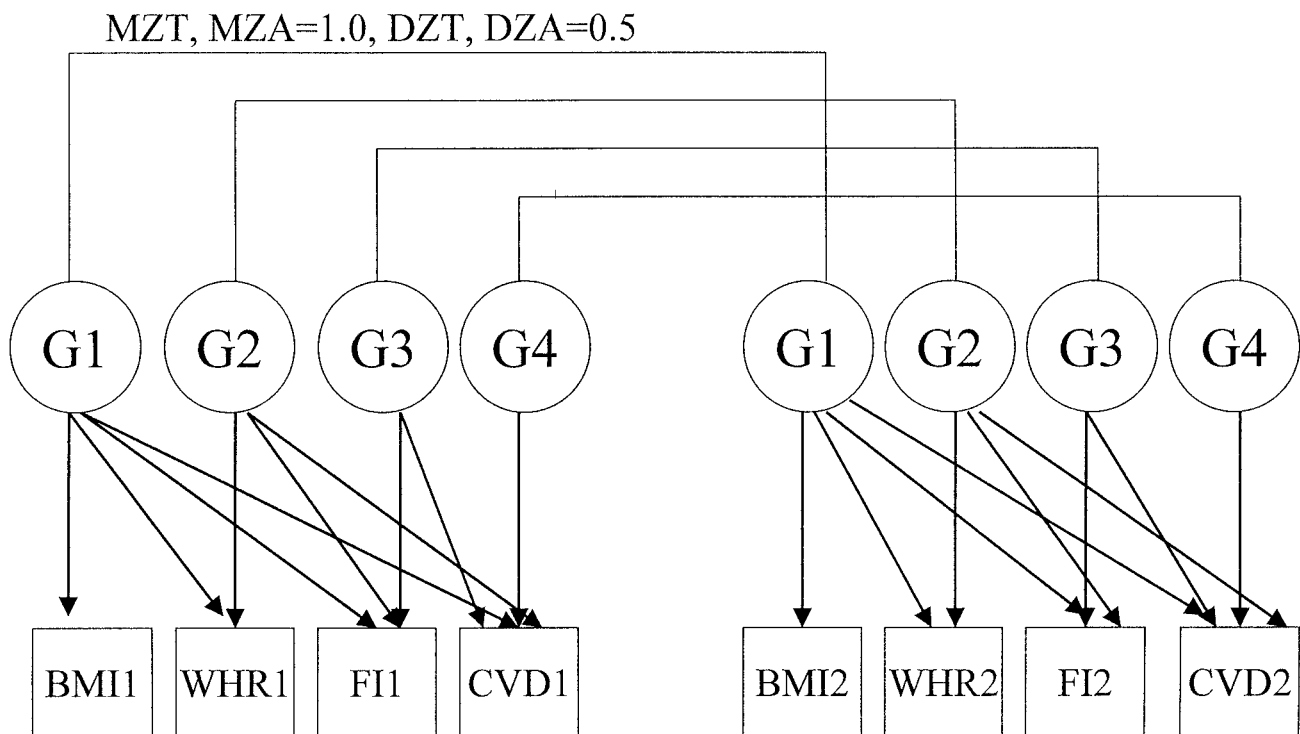


Figure 1 Multivariate Cholesky model for BMI, WHR, fasting insulin levels, and CVD. Path diagram shows genetic effects on body mass index (BMI), waist/hip ratio (WHR) fasting insulin levels (FI), and cardiovascular disease (CVD). BMI1 indicates twin 1 and BMI2 indicates twin 2 etc. MZT indicates monozygotic twins reared together; MZA indicates monozygotic twins reared apart; DZT indicates dizygotic twins reared together; DZA indicates dizygotic twins reared apart. G1 indicates genetic factor 1, G2 genetic factor2 etc. Environmental influences are not shown but are modeled similarly

loadings. Age was also used in these analyses as another covariate so that the genetic and environmental components of variance would not be biased by possible age effects. Gender effects were taken into consideration by estimating models for both males and females separately.

Results

Sample characteristics

At the time of testing in 1989–1991, male subjects were on average 63 ± 8 years of age and female subjects were on average 67 ± 9 years of age. The mean values for each of the variables is listed in Table 1. These values are about average for this age population.

Table 2 shows the intraclass correlations for twins by rearing status, gender and zygosity group. On average MZ (MZA and MZT) correlations were higher than DZ (DZA and DZT) correlations for each of the variables, indicating the importance of genetic influences for each of the variables studied. For BMI in males and WHR in females, twins reared together had greater correlations than twins reared apart, suggesting the importance of shared rearing environment. For BMI in females, there is little difference in

MZ and DZ correlations regardless of rearing status. This finding suggests possible correlated environmental effects such as similar adult lifestyles. The negative correlations might suggest the twins' scores for the relevant variables are in opposite directions; however, these correlations were not significantly different from zero. In traditional genetic analysis, comparison of pairs of correlations limits our ability to assess genetic influences because all the information contained in all groups regarding genetic influences is not used simultaneously. However, we used model-fitting analyses as these are more powerful for detecting genetic effects because information from all the groups is considered jointly in a single comprehensive analysis.

Model fitting analysis

Model fitting analyses indicate genetic effects on WHR, BMI, FI and CVD in males and females. When the model was constrained to be equal across gender the constrained model fit the data less well than the general model ($\chi^2 = 69$, $df = 42$, $P < 0.01$). Subsequently, we estimated parameters separately for males and females. Table 3 shows the goodness-of-fit parameters of the Cholesky model along with the nested models. When all correlated environmental loadings were set to zero there was no significant

Table 1 Mean values, standard deviations, and number of individuals (in parentheses) for waist/hip ratio (WHR), body mass index (BMI), log transformed BMI (lnBMI), fasting insulin levels (FI), log transformed fasting insulin levels (lnFI), and cardiovascular disease (CVD) by gender, rearing status and zygosity

	MZA	MZT	DZA	DZT
Males				
WHR	0.95 ± 0.05 (42)	0.93 ± 0.05 (54)	0.93 ± 0.05 (70)	0.90 ± 0.05 (79)
BMI	25.90 ± 3.0 (42)	26.00 ± 3.0 (54)	25.90 ± 3.0 (70)	24.3 ± 3.0 (79)
lnBMI	3.30 ± 0.11 (42)	3.20 ± 0.13 (54)	3.30 ± 0.11 (70)	3.20 ± 0.11 (79)
FI	13.70 ± 10.0 (29)	14.90 ± 10.0 (30)	11.60 ± 7.0 (35)	11.6 ± 7.0 (56)
lnFI	2.60 ± 0.40 (29)	2.50 ± 0.67 (30)	2.50 ± 0.33 (35)	2.4 ± 0.44 (56)
CVD	0.43 ± 0.50 (42)	0.37 ± 0.49 (54)	0.46 ± 0.50 (70)	0.36 ± 0.48 (79)
Females				
WHR	0.81 ± 0.04 (41)	0.81 ± 0.06 (70)	0.82 ± 0.07 (129)	0.82 ± 0.05 (82)
BMI	25.10 ± 3.3 (41)	25.20 ± 3.0 (70)	26.50 ± 4.8 (129)	26.10 ± 4.4 (82)
lnBMI	3.20 ± 0.16 (41)	3.20 ± 0.11 (70)	3.30 ± 0.17 (129)	3.30 ± 0.16 (82)
FI	12.80 ± 9.0 (27)	14.60 ± 9.0 (46)	12.30 ± 6.0 (89)	11.40 ± 6.0 (50)
lnFI	2.40 ± 0.55 (27)	2.60 ± 0.58 (46)	2.50 ± 0.45 (89)	2.40 ± 0.40 (50)
CVD	0.33 ± 0.48 (41)	0.40 ± 0.50 (70)	0.40 ± 0.50 (129)	0.48 ± 0.50 (82)

MZA = MZ pairs reared apart; MZT = MZ pairs reared together; DZA = DZ pairs reared apart; DZT = DZ pairs reared together.

Table 2 Intraclass correlations and number of twin pairs for waist/hip ratio (WHR), log transformed body mass index (lnBMI), log transformed fasting insulin levels (lnFI), and cardiovascular disease (CVD) by gender, rearing status and zygosity

	Male				Female			
	WHR	lnBMI	lnFI	CVD	WHR	lnBMI	lnFI	CVD
MZA	0.38 (19)	0.55 (19)	0.54 (12)	0.55 (19)	-0.12 (18)	0.67 (18)	0.72 (7)	0.17 (18)
MZT	0.48 (27)	0.67 (27)	0.59 (12)	-0.10 (27)	0.66 (27)	0.65 (27)	0.54 (14)	0.53 (27)
DZA	-0.07 (32)	0.22 (32)	0.02 (13)	-0.04 (32)	0.25 (58)	0.48 (58)	0.35 (34)	0.20 (56)
DZT	-0.12 (36)	0.33 (36)	-0.05 (23)	0.21 (36)	0.34 (34)	0.51 (34)	0.13 (15)	0.06 (34)

MZA = MZ pairs reared apart; MZT = MZ pairs reared together; DZA = DZ pairs reared apart; DZT = DZ pairs reared together; Note: these are only full twin pairs.

loss of fit compared with the full model ($\chi^2 = 4$, $df = 20$), nor was there loss for setting all additive genetic effects to zero ($\chi^2 = 17$, $df = 20$) or setting all shared rearing environmental effects to zero ($\chi^2 = 10$, $df = 20$). However, when we dropped all parameters contributing to familial similarity (ie shared rearing environmental effects, correlated environmental effects and additive genetic effects from the model), we found a significant chi-square ($\chi^2 = 145$, $df = 60$, $P < 0.001$). Testing a model where only correlated environment and shared rearing environmental effects were set to zero resulted in a non-significant change in the chi-square ($\chi^2 = 13$, $df = 40$). After considering the parameter estimates shared between WHR, BMI, FI and CVD we dropped parameters shared between CVD and the other variables due to the extremely small estimates. This constrained model without correlated environmental or shared rearing environmental effects was not significantly worse than the general model ($\chi^2 = 31$, $df = 52$). To ensure that this final model (model 8 in Table 3) was the most parsimonious we computed the Akaike Information Criterion (AIC) ($\chi^2 - 2df$). The model with the lowest AIC value is considered to fit best. As can be seen in Table 3, model 8 was the most parsimonious (AIC = -73).

Using model 8 we found in males, additive genetic effects accounted for 28% of the total variance in WHR, 58% of BMI, 27% of FI and 18% of CVD. In females, we found additive genetic effects accounted for 49% of the total variance in WHR, 73% of BMI, 49% of FI and 37% of CVD. We found genetic effects shared among both males and females for BMI, WHR, and FI. In males, of the total variance for WHR, 28% was due to genetic variance. Three percent of the total variance was in common with BMI, thus the 'trait specific' genetic variance in WHR was 25%. Similarly for FI, 27% of the total variance was genetic, 8% of the total variance was genetic variance in common with WHR and 7% was in common with BMI. In females, genetic variance accounted for 49% of the total variance in WHR, 8% was genetic variance in common with BMI, so the 'trait specific' genetic variance was 41% for WHR.

Similarly 49% of the total variance in FI was due to genetic variance of which 7% was genetic variance in common with WHR and 24% was genetic variance in common with BMI. The environmental effects in common, in males, were very high between BMI and WHR, accounting for almost half the total environmental variance on WHR. In females, the environmental effects in common between BMI and WHR were smaller (8% of the 47% total variance). The environmental effects in common between BMI and FI were almost non-existent among females (1%) and there were no environmental effects in common between WHR and FI in either males or females (Tables 4 and 5).

To describe the nature of the genetic and environmental covariances in another way, we have presented the phenotypic correlations separated into genetic and environmental components (Table 6). The most striking difference between males and females can be seen for the phenotypic correlations between FI and the obesity measures. In males, the correlations are close to the same when insulin is associated with BMI or WHR (BMI-FI = 0.47; WHR-FI = 0.43), whereas in females the correlation coefficient between FI and BMI is slightly larger than that between FI and WHR (BMI-FI = 0.45; WHR-FI = 0.35).

Genetic and environmental covariation can also be expressed as genetic and environmental correlations (Table 7). These correlations may be conceptualized in a simplified manner as an indication of the extent to which genetic (or environmental) influences for two measures are 'the same' or 'overlap'. For example, in males, the genetic correlation between BMI and WHR was 0.34 and the environmental correlation was 0.63, suggesting that about one third of the genetic effects on BMI and WHR are the same. Over half the environmental influences on BMI and WHR are the same. For WHR and FI in males the genetic correlation is 0.64, suggesting that WHR and FI share many of the same genes; and for BMI and FI the correlation is 0.51 suggesting they also share many of the same genes. The females' genetic correlations are very similar to those found in males; for WHR and

Table 3 Test of Cholesky models for log transformed body mass index (lnBMI), waist/hip ratio (WHR), log transformed fasting insulin levels (lnFI), and cardiovascular disease (CVD)

	<i>-2log likelihood</i>	<i>df</i>	<i>Difference</i>		<i>P</i>	<i>AIC</i>
			χ^2	<i>df</i>		
1. Full model	837	2295				
2. Constrained model (males=females)	906	2337	69	42	0.01	-21
3. Constrained model (no Ec)	841	2315	4	20	1.0	-36
4. Constrained model (no Es)	847	2315	10	20	0.97	-30
5. Constrained model (no A)	854	2315	17	20	0.65	-23
6. Constrained model (no A, Ec, Es)	982	2355	145	60	0.001	25
7. Constrained model (no Ec or Es)	850	2335	13	40	1.0	-67
8. Constrained model (no Ec, Es, or shared effects with CVD)	868	2347	31	52	0.99	-73

A = additive genetic effects; Ec = correlated environmental effects; Es = shared environmental effects.

Table 4 Percentage genetic and environmental influence (in parentheses) for log transformed body mass index (lnBMI), waist/hip ratio (WHR), log transformed fasting insulin levels (lnFI), cardiovascular disease (CVD) and age for males

	lnBMI	WHR	lnFI	CVD
lnBMI	58% (42%)	3% (32%)	7% (18%)	—
WHR	—	25% (40%)	8% (—)	—
lnFI	—	—	12% (55%)	—
CVD	—	—	—	18% (82%)
Age	—	—	—	—
Total	58% (42%)	28% (72%)	27% (73%)	18% (82%)

Table 5 Percentage genetic and environmental influence (in parentheses) for log transformed body mass index (lnBMI), waist/hip ratio (WHR), log transformed fasting insulin levels (lnFI), cardiovascular disease (CVD) and age for females

	lnBMI	WHR	lnFI	CVD
lnBMI	73% (27%)	8% (8%)	24% (18%)	—
WHR	—	41% (39%)	7% (—)	—
lnFI	—	—	18% (50%)	—
CVD	—	—	—	37% (63%)
Age	—	4%	—	—
Total	73% (27%)	49% (47%)+4%	49% (51%)	37% (63%)

Table 6 Genetic and environmental components of phenotypic correlations for log transformed body mass index (lnBMI), waist/hip ratio (WHR), log transformed fasting insulin levels (lnFI) for males (lower diagonal) and females (upper diagonal)

	lnBMI	WHR	lnFI
lnBMI	—	0.39 (G = 0.24; E = 0.15)	0.45 (G = 0.41; E = 0.04)
WHR	0.48 (G = 0.13; E = 0.35)	—	0.35 (G = 0.31; E = 0.04)
lnFI	0.47 (G = 0.20; E = 0.27)	0.43 (G = 0.18; E = 0.25)	—

Table 7 Genetic and environmental correlations for log transformed body mass index (lnBMI), waist/hip ratio (WHR), log transformed fasting insulin levels (lnFI) for males (lower diagonal) and females (upper diagonal)

	lnBMI	WHR	lnFI
lnBMI	—	(G = 0.39; E = 0.42)	(G = 0.70; E = 0.11)
WHR	(G = 0.34; E = 0.63)	—	(G = 0.64; E = 0.08)
lnFI	(G = 0.51; E = 0.49)	(G = 0.64; E = 0.35)	—

FI, and BMI and FI, they were 0.64 and 0.70, respectively, suggesting that many of the same genes influence these traits. See the Appendix for a description of the phenotypic correlation calculations.

With regard to age effects, we did not find that age contributed to the variance in males, but in females 4% of the variance in WHR could be attributed to age.

Discussion

The purpose of this study was to continue to look for a genetic clustering of the components of the

metabolic syndrome. We were able to obtain separate estimates for genetic and environmental components of variance for both males and females. We found both males and females to have genetic and environmental effects unique to each of the metabolic components, (ie WHR, BMI, FI and CVD) with genetic effects being greater for females than males for all components. Previous research has found these components to have genetic influences,^{10–12,15–20} but not much has been done in comparing heritability estimates for males and females. Most of the work on WHR has been done in either all male or all female samples. BMI has been studied in males and females with varying results; a study using the Virginia Twin Registry and twins ascertained through the American Association of Retired Persons found females to have higher heritabilities than males (75% vs 69%).²⁶ Stunkard *et al*¹⁰ found males to have heritability estimates of 74% and females 69% using data from the 1984 wave of the SATSA questionnaire data. Heritability was estimated as 0.53 for fasting insulin levels, by Mayer *et al*¹⁷ among female twins, average age 51 years, but little has been done in comparing heritabilities among males and females. Various components of cardiovascular disease have been studied with regard to genetic influences as described below, but it is hard to compare such studies with our use of a global self-reported measure.

We also found genetic and environmental effects in common among BMI, WHR, and FI and differences in the magnitude of these shared effects for each gender. The lack of effects shared between CVD and the other variables may be because CVD was expressed as a simple dichotomy (presence or absence) based on a number of self-reported variables. It may also be that this was based on cross-sectional data, if we had used longitudinal data for cardiovascular disease it may have shown different results. Other studies have found indicators of cardiovascular disease to share genetic and environmental effects with body fat and insulin resistance. In this sample (SATSA), BMI, insulin resistance, triglycerides, HDL and to a lesser extent systolic blood pressure were found to share genetic effects.²⁰ The San Antonio Heart Study found suggestive evidence for genetic effects shared between insulin levels and HDL, triglycerides, BMI and WHR.¹⁶

We found both BMI and WHR have more environmental influences in common than genetic influences, especially in males. Further, the fat distribution measures and FI were found to have more genetic influences on average than environmental influences in common.

The shared genetic effects between WHR and FI as well as between BMI and FI suggest the same gene or set of genes are influencing both obesity measures

and FI. In females, almost half of the variance in fasting insulin levels is accounted for by genetic influences on BMI. This is consistent with several studies that have shown both obesity measures and fasting insulin or insulin resistance to be consistently associated in families with a history of non-insulin dependent diabetes mellitus (NIDDM).^{27,28} For example, Carey *et al*²⁸ found increased levels of central fat and decreased insulin sensitivity in subjects who have first-degree relatives with NIDDM compared with controls (these subjects were matched for age, BMI and percentage body fat). Also, Hong *et al*²⁰ found BMI and insulin resistance to share genetic effects to the greatest extent among BMI, insulin resistance, triglycerides, HDL and systolic blood pressure.

The genetic effect in common to WHR and BMI is not as large as that for WHR and FI or BMI and FI. This suggests that body fat distribution and overall body fat are influenced by trait-specific genetic influences more so than FI and these measures. Rice *et al*²⁹ found that familial influences were shared between BMI and body fat distribution, but the estimate is not large and they suggest there are heritable factors specific to each trait.

Although the genetic effects common to WHR and BMI are not large the environmental effects common to BMI and WHR are substantial, suggesting that environmental influences acting on BMI are similar to those acting on WHR. Such environmental influences may include overeating or lack of physical activity as both have been associated with both BMI and WHR.^{30–32}

In males, WHR and FI have about the same phenotypic correlations as BMI and FI, whereas in females, BMI and FI have a greater phenotypic correlation than WHR and FI. The phenotypic correlations in women were accounted for to a greater extent by genetic covariation than environmental covariation, whereas in males it was the opposite. This result is primarily due to the difference in heritability estimates between males and females since the genetic correlations were very similar for males and females (that is the extent to which the same genes or set of genes influence both obesity measures and FI).

The greater correlations for females between BMI and FI over WHR and FI may reflect the differences in fat accumulation between the sexes. When males gain fat, they tend to put on more in the intra-abdominal adipocytes and subcutaneous adipocytes in the central region, while females tend to put on excess fat in subcutaneous fat deposits throughout the body.⁵ After the menopause females start to put on more fat in the central region but they still do not deposit as much in the visceral adipocytes as males. It is thought that the visceral adipocytes are related

to insulin levels to a greater extent than subcutaneous adipocytes. However, this is still not clear as several studies have shown the importance of the subcutaneous adipocytes in predicting insulin resistance.^{33,34} As females age beyond 65 (the mean of this group), there may be even greater fat deposition in the abdominal area. It would be interesting to see whether the correlations between WHR and FI increase and the correlations between BMI and FI decrease among females in a longitudinal design. This may give more insight into the importance of subcutaneous vs visceral adipocytes in their relationship to insulin resistance. We did find variance in WHR in females to be partially accounted for by age effects (4%).

In conclusion, BMI, WHR and insulin resistance seem to share similar genetic effects as well as have trait-specific genetic effects. We found significant differences between males and females for such estimates. The correlation between WHR and FI in males tended to be of the same magnitude as those between BMI and FI, while the correlation between BMI and FI for females was greater than that for WHR and FI. These correlations were accounted for by shared genetic effects to a greater extent than the relationship between BMI and WHR. Taken together it could be that WHR and BMI are influenced by separate genetic influences and these measures then influence the same genes that influence insulin regulation.

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Appendix. Calculation of phenotypic, genetic and environmental correlations

The following is the equation used to calculate the phenotypic correlations as well as the genetic and environmental components of this phenotypic correlation.

$$R_p = h_x h_y r_{G_{xy}} + e_x e_y r_{E_{xy}}$$

Where r_p = phenotypic correlation between variable x and variable y ; h_x is the square root of the heritability for variable x and h_y is the square root of the heritability for variable y ; $r_{G_{xy}}$ is the genetic correlation between variables x and y . This is calculated as: $\text{Cov}(G_x)(G_y) / \sqrt{V_{G_x} V_{G_y}}$ which is the genetic covariance of x and y divided by the product of the square root of the genetic variance of x and the square root of the genetic variance of y . The environmental correlation is calculated in the same way.