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Cross-Trait Familial Resemblance for Body Fat and Blood Pressure: Familial Correlations in the Québec Family Study

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Summary

Cross-trait resemblance between body fat and blood pressure (BP) was examined among families in the Québec Family Study by using a bivariate familial correlation model assessing both intraindividual (e.g., comparison of father's body fat with his own BP) and interindividual (e.g., comparison of father's body fat with son's BP) cross-trait correlations. Each of six body-fat measures—(i) percent body fat, (ii) body-mass index , (iii) the sum of six skinfolds, (iv) the ratio of the sum of six skinfolds to total fat mass, (v) the ratio of the trunk skinfold sum to the extremity skinfold sum, and (vi) the regression of the trunk-extremity skinfold ratio on the sum of six skinfolds—was analyzed separately with systolic BP and with diastolic BP. Results showed that (1) upper-body fat was the strongest interindividual correlate of BP (especially the correlation of trunk-extremity ratio with diastolic BP), suggesting shared pleiotropic genetic and/or common familial environmental effects; (2) summary body-fat measures either were inconsistent (in the case of both percent body fat and sum of six skinfolds) or gave no evidence of interindividual cross-trait resemblance with BP (in the case of body-mass index); and (3) intraindividual resemblance between the sum of six skinfolds and BP largely vanished once the skinfold sum was adjusted for fat mass, suggesting that the intraindividual association may be mediated largely by the absolute amount of subcutaneous fat rather than by the subcutaneous proportion. Finally, the magnitude of the spouse resemblance for the trunk-extremity ratio with diastolic BP suggests that a significant proportion of the resemblance may be due to environmental influences. In summary, our investigation confirms a heritable link between BP and truncal-abdominal fat as predicted by the metabolic-syndrome hypothesis. That this result is obtained in primarily normotensive, nonobese families, suggests the connection involves normal metabolic paths.

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Introduction

Obesity is a heterogeneous phenotype, with one form in particular (truncal/abdominal, or android) being associated with a cluster of metabolic conditions that can lead to increased risk for cardiovascular disease, stroke, and non–insulin-dependent diabetes mellitus. This metabolic cluster—including obesity, upper-body fat, insulin resistance, hyperinsulinemia, decreased glucose tolerance, and hypertension—is referred to as "syndrome X," by Reaven (1988), and, more recently, as "metabolic syndrome," by Björntorp (1992). The specific metabolic mechanisms connecting blood pressure (BP) with truncal/abdominal fat are believed to center around insulin resistance, compensatory hyperinsulinemia, the sympathetic nervous system (SNS), and dietary pathways (for a review, see Landsberg 1986). In summary, increased insulin levels (as observed in hypertensives) stimulate renal sodium reabsorption. Increased renal perfusion pressure is accompanied by increased arterial pressure, in order to maintain comparable reabsorption and excretion amounts. Hyperinsulinemia also activates the SNS, raising noradrenaline levels, which in turn enhances sodium reabsorption and increases arterial pressure. Diet also activates the SNS; high carbohydrate and fat levels and low protein levels increase SNS activity and thus the noradrenaline-sodium-arterial pressure progression.

A considerable body of work has established the association of these traits within individuals (for review, see Sims and Berchtold 1982) and, indeed, has guided the formulation of the metabolic-syndrome hypothesis. Genetic pleiotropy is implied among traits that presumably share common metabolic paths. Dietary factors also imply transmissible environmental effects and gene × environment interactions. However, previous work relies primarily on the correlation of traits within individuals. Those intraindividual correlations do not necessarily provide evidence for shared genetic or environmental components, since traits may be correlated via specific factors that are not shared among family members and so are not heritable. In fact, relatively little is known about whether the heritable factors that underlie these traits are related to each other.

This study represents the first component in a series of investigations screening for cross-trait heritabilities among some of the factors in the metabolic syndrome. A simple

and quick screening of whether there are common genetic factors among the various conditions in this syndrome involves assessing the bivariate familial relationships, by using quantitative genetic methods. Familial correlations underlie most of these methods, involve few assumptions, and can lead to certain genetic and environmental inferences simply by inspection of the correlational patterns. For example, significant correlations among siblings and between parents and offspring (but not between spouses) suggest a genetic heritability. Significant spouse correlations, in addition to sibling and parent-offspring correlations, suggest that at least some of the heritability may be due to shared environments. Similarly, the pattern of cross-trait familial correlations leads to the same type of genetic and environmental inferences. A pattern of significant cross-trait correlations between parents' BP and offspring's body fat and between siblings (i.e., BP in one sib and body fat in the other), but not between spouses, suggests that a common gene(s) influences both traits (i.e., genetic pleiotropy).

Here, we specifically examine the familial correlations, for each of two BP phenotypes (systolic and diastolic), with each of six body-fat phenotypes. Three of the body-fat variables represent summary measures: the percent of body fat (%BF) is derived from underwater weighing techniques; the body-mass index (BMI) is based on height and weight measures; and total subcutaneous fat is measured as the sum of six skinfolds (SF6). The SF6 is also adjusted for total fat mass (FM), by the ratio SF6/FM, approximating the percent of fat that is subcutaneous. The distributional pattern of the subcutaneous fat is assessed as the ratio of trunk-skinfold sum to extremity-skinfold sum (trunk/extremity ratio [TER]). High scores for TER indicate greater truncal than extremity fat deposition. Finally, TER is also adjusted for total subcutaneous fat, by means of regression analysis (TER-sf). The TER-sf indexes the preferential deposition of fat on the upper-body areas (vs. that in the extremities), for a given level of fatness. The latter two body-fat variables are expected to show the largest relationship with BP, since they assess components of truncal/abdominal adiposity, as specifically predicted in the metabolic-syndrome hypothesis.

Subjects and Methods

Sample

The Québec Family Study (QFS) consists of families of French descent living within 80 km around Quebec City who were recruited through the media during the years 1978–81 for a study of the genetic effects on several physiological and biochemical traits. A total of 1,630 individuals, constituting 375 families, were ascertained. Individuals in the parental generation (N = 727) were 30.2–59.5 years old, while the offspring (N = 903) were 8.4–25.7 years old.

Table 1

Measures and Raw Units of Measurement

Variable	Measurement
BMI	Weight (kg)/height (m^2)
SF6	Suprailiac + subscapular + abdominal + medial calf + biceps + triceps (mm)
TER	(suprailiac + subscapular + abdominal)/(medial calf + biceps + triceps)
TER-sf	Regression of polynomial in SF6 on TER
SBP	mmHg
DBP	mmHg

Socioeconomic status (SES) of the families was rated on the basis of occupation, by means of the Blishen and McRoberts (1976) index. The average (±SD) SES rating for the fathers in this study is 54.1 ± 14.19 (range 23.0–75.3), which is comparable to that of the general French Canadian population (Blishen 1970).

The sample includes nuclear families consisting of parents and singleton offspring, as well as families with twin and/or adopted offspring, step-parents, or cousins. For the purposes of data adjustments (i.e., age and sex corrections described below), the complete sample was used. However, for the familial correlation analyses, only traditional nuclear families consisting of parents and their singleton biological offspring were retained. Sample sizes used in the familial analyses are given below.

Measures

A wide variety of physiological and behavioral measurements was obtained during a 1-d visit of the families to the laboratory. Measures relating to body fat include height, weight, %BF, and skinfold thicknesses (see table 1). Height and weight were used to compute the BMI. %BF was assessed by an underwater weighing technique (Himes and Bouchard 1985). Further details regarding measurement and reliability of the %BF have been published elsewhere (Bouchard 1985; Himes and Bouchard 1985).

Six measures of skinfold thicknesses (see table 1) on the left side of the body were obtained with a Harpenden skinfold caliper, according to the procedures recommended by the International Biological Programme (Weiner and Lourie 1969). Further details regarding measurement and reliability of the skinfolds may be found elsewhere (Bouchard 1985; Himes and Bouchard 1985). Two variables were extracted from the six skinfolds: SF6 and TER.

Additionally, SF6 was adjusted for FM (computed from %BF and body weight) by using the ratio SF6/FM. (Note that FM is not reported here, since it is highly correlated with %BF within individuals, and since the familial correlation results are almost identical to those for %BF.) Finally, TER-sf was determined by regression analysis. In

summary, the regression analysis consisted of a stepwise procedure, extracting the standardized residual from the regression of TER, up to a cubic polynomial in SF6. The same procedure as is described later for age and sex correction of the variables was used, and the regressions were performed separately in four sex × generation groups. In fathers, a linear and squared term in SF6 accounted for 19.1% of the variance, and in mothers a linear term in SF6 accounted for 15% of the variance. In both offspring groups, all three SF6 terms (linear, squared, and cubed) were required, with 14.3% (sons) and 11.7% (daughters) of the mean variation accounted for. No heteroscedastistic effects were noted (i.e., there were no SF6 effects in the variability of the TER).

BP was measured with a mercury sphygmomanometer (Baumanometer) and a stethoscope, according to the recommendations of the American Heart Association (Kirkendall et al. 1967). The subjects were in a supine position. A first reading was taken after a 10-min rest, followed by a second reading after a 2-min delay. The mean of two consecutive measurements that were <10 mm Hg apart was used; <1% of the individuals required multiple readings in order to meet the criteria. SBP was determined at the point at which the Korotkoff sounds became audible, whereas DBP was measured at the complete cessation of the Korotkoff sounds (phase V in the American Heart Association protocol). Further details regarding BP measurement may be found in the work of Després et al. (1988) and Pérusse et al. (1989).

Table 2 gives the means and SDs of the unadjusted variables, separately, in four sex × generation groups (fathers, mothers, sons, and daughters). On the basis of a comparison of standard errors, there are generation differences for all variables. The general trend is for higher values in parents than in offspring, except that SF6/FM is in the opposite direction (i.e., there are higher means in the offspring groups). There are also sex differences for most variables. The exceptions are for BMI and DBP in offspring, which show no sex differences in the mean levels. The sample statistics given in table 2 represent the subsample used in the familial correlation analyses (see footnote to table 2).

Data Adjustments

Each of the six body-fat and two BP variables was adjusted for the effects of age. These data adjustments were carried out separately in the four sex × generation groups, since mean differences had been noted previously. In summary, extreme outliers (>4 SD from the mean) were temporarily set aside so that the regression models would not be unduly influenced by extreme observations. A given measure was regressed on up to a cubic polynomial in age in a stepwise manner, retaining terms significant at the 5% level. The residual variance was also examined for age effects (heteroscedasticity) by regressing the squared residual from the aforementioned age regression (or the log of the squared residual) on another polynomial in age in a stepwise manner and retaining terms significant at the 5% level. The final phenotypes were computed for all individuals (including the extreme observations) by using the best regression models.

Age regression results for SF6 and TER may be found in the work of Rice et al. (1992); %BF and BMI in the work of Borecki et al. (1991); and SBP and DBP in the work of Pérusse et al. (1989). In general, ≤5% of the variance was accounted for by age effects, with a few exceptions, as follows. Age accounted for a noticeable percentage of the variance in the TER offspring subsamples (a full cubic polynomial in age accounted for 47% in sons and 10% in daughters) and in the BMI offspring subsamples (a full quadratic polynomial in age accounted for 40% in sons and 26% in daughters). For the %BF, age accounted for an appreciable percentage of the variance in fathers (age^3 term 12%), mothers (age^3 term 15%) and sons (a full cubic polynomial accounted for 15%). The only variables for which no age effects were noted were SF6 in fathers and sons and BMI in fathers.

The variables SF6/FM and TER-sf are the only measures for which data adjustments have not been previously reported. For SF6/FM, mean age effects were found only for fathers (the age^2 term accounted for 6.3%) and daughters (the linear age term accounted for 17.4%). Heteroscedasticity was noted only in daughters, with a linear term in age accounting for 4.9% of the variance. For TER-sf, no age effects were found, as expected, since age-sex–corrected TER and SF6 phenotypes were used to construct the variable.

Table 3 gives the intraindividual correlations among the body-fat phenotypes, separately in four sex × generation groups. Mothers are on the upper diagonal, and fathers are on the lower diagonal, of the first matrix; daughters are on the upper diagonal, and sons are on the lower diagonal, of the second matrix. The correlations between SF6 and SF6/FM are low (in parents) to nonsignificant (in offspring). Much higher intraindividual correlations are noted among the three summary measures (%BF, BMI, and SF6, range ~.6–.8). A notable exception is for %BF-BMI in sons, which is somewhat lower (.45) but still significant. We include all three summary measures because %BF may represent a more precise measure of adiposity whereas BMI and SF6 are more accessible to most researchers. High (.87–.94) correlations are also noted between TER and TER-sf. Both are included because one, TER, assesses the overall pattern of fat distribution whereas the other takes into consideration the total level of fatness. In general, correlations of TER and TER-sf with the remaining variables are low to nonsignificant. SF6/FM is either nonsignificant or negatively correlated with the other variables. FM, the fat-mass measure that was used to correct

Table 2

Sample Statistics for Raw Variables, by Sex and Generation Groups

	Males			Females		
Group and Variable	*n*	Mean	SD	*n*	Mean	SD
Parents:						
%BF	139	23.33	6.79	135	31.85	7.12
BMI	283	25.40	3.07	300	23.34	3.59
SF6	283	73.37	26.99	300	100.39	35.60
SF6/FM	139	4.29	1.12	135	5.29	1.20
TER	283	2.25	.60	300	1.16	.38
SBP	283	120.53	13.05	300	114.79	13.44
DBP	283	78.22	10.12	300	73.67	9.87
Offspring:						
%BF	179	13.26	6.96	160	20.15	6.60
BMI	355	19.11	2.71	301	19.22[a]	2.82
SF6	355	45.49	21.26	301	66.91	26.94
SF6/FM	179	9.68	11.27	160	7.20	2.43
TER	355	1.20	.45	301	1.01	.26
SBP	355	111.04	11.10	301	108.30	9.27
DBP	355	63.67	9.79	301	64.62[a]	9.15

NOTE.—Sample sizes involving the %BF (or FM) are approximately half those of the other variables, since underwater weighting was conducted only in the second half of the data-collection phase of the QFS. For variables involving the %BF, there are 174 families (613 individuals), and for the remaining variables there are 309 families (1,239 individuals).

[a] On the basis of a comparison of standard errors, sex differences in the offspring generation are *not* significant (all other group comparisons—i.e., sex within generation and generation within sex—are significant).

the SF6, is highly correlated with %BF (.90–.93), SF6 (.76–.87), and BMI (.64–.83).

Familial Correlations

The model.—A multivariate familial correlation model may be conceptualized as a simple extension of the univariate case using matrix notation. In the univariate familial correlation model involving four types of individuals (F = fathers; M = mothers; S = sons; and D = daughters), there are eight correlations: one spouse (FM), four parent-offspring (FS, FD, MS, and MD), and three sibling (SS, DD, and SD). All eight of these correlations are interindividual;

Table 3

Intraindividual Correlations among Body-Fat Variables

	%BF	BMI	SF6	SF6/FM	TER-sf	TER
Parents:						
%BF		.62	.72	−.29	−.14*	.16
BMI	.63		.81	−.04*	−.04*	.28
SF6	.67	.75		.32	−.03*	.36
SF6/FM	−.49	−.16	.18		.13*	.25
TER-sf	−.23	.04*	.02*	.29		.92
TER	.08*	.32	.38	.33	.91	
Offspring:						
%BF		.62	.77	−.54	−.05*	.15
BMI	.45		.82	−.15	.13	.30
SF6	.71	.73		−.05*	.14	.35
SF6/FM	−.39	−.12*	−.11*		.07*	.05*
TER-sf	−.02*	.23	.31	.06*		.94
TER	.14	.38	.41	.02*	.87	

NOTE.—Data for parents are given in the upper matrix, and data for offspring are given in the lower matrix; in each matrix, data for females are given above the diagonal, and data for males are given below the diagonal.

* $P \geq .05$.

Table 4

Bivariate Familial Correlation Model

	F	M	S	D
F	$\mathbf{R_F}$	FM	FS	FD
M		$\mathbf{R_M}$	MS	MD
S			$\mathbf{R_S}$ and SS	SD
D				$\mathbf{R_D}$ and DD

NOTE.—In element notation the matrices are defined as follows, where the subscript "1" denotes a body-fat measure and the subscript "2" reflects a BP measure.

Interindividual-intergroup (full rank) matrices:

$$\mathbf{FM} = \begin{matrix} f_1m_1 & f_1m_2 \\ f_2m_1 & f_2m_2 \end{matrix} \quad \mathbf{FS} = \begin{matrix} f_1s_1 & f_1s_2 \\ f_2s_1 & f_2s_2 \end{matrix} \quad \mathbf{FD} = \begin{matrix} f_1d_1 & f_1d_2 \\ f_2d_1 & f_2d_2 \end{matrix}$$

$$\mathbf{MS} = \begin{matrix} m_1s_1 & m_1s_2 \\ m_2s_1 & m_2s_2 \end{matrix} \quad \mathbf{MD} = \begin{matrix} m_1d_1 & m_1d_2 \\ m_2d_1 & m_2d_2 \end{matrix} \quad \mathbf{SD} = \begin{matrix} s_1d_1 & s_1d_2 \\ s_2d_1 & s_2d_2 \end{matrix}$$

Interindividual-intragroup (diagonal) matrices:

$$\mathbf{SS} = \begin{matrix} s_1s_1 & s_1s_2 \\ & s_2s_2 \end{matrix} \quad \mathbf{DD} = \begin{matrix} d_1d_1 & d_1d_2 \\ & d_2d_2 \end{matrix}$$

Intraindividual (correlational) matrices:

$$\mathbf{R_F} = \begin{matrix} 1 & f_{12} \\ & 1 \end{matrix} \quad \mathbf{R_M} = \begin{matrix} 1 & m_{12} \\ & 1 \end{matrix} \quad \mathbf{R_S} = \begin{matrix} 1 & s_{12} \\ & 1 \end{matrix} \quad \mathbf{R_D} = \begin{matrix} 1 & d_{12} \\ & 1 \end{matrix}$$

The blank elements (lower off-diagonals in the latter six matrices) are equated with their respective upper off-diagonal elements (e.g., $s_2s_1 = s_1s_2$). The number of cross-trait correlations (all off-diagonal elements) is 18 and constitutes the primary focus of this study.

six (FM, FS, FD, MS, MD, and SD) are intergroup while the remaining two (SS and DD) are intragroup. In expanding to a multivariate case, each of the eight single correlations becomes a matrix of correlations (see table 4), with the size of each matrix depending on the number of multiple variables (n) and the type of individuals in the comparison. For the six interindividual-intergroup comparisons (**FM, FS, FD, MS, MD,** and **SD**), the matrices are of full rank, with n^2 elements each. For the two interindividual-intragroup comparisons (**SS** and **DD**), the matrices are diagonal, with $[n+n(n-1)/2]$ elements each. Finally, four additional intraindividual matrices are needed to describe the correlation patterns among variables within each of the four types of individuals. These four additional matrices ($\mathbf{R_F}$, $\mathbf{R_M}$, $\mathbf{R_S}$, and $\mathbf{R_D}$) are correlational, with $[n(n-1)/2]$ elements each.

For a bivariate case (i.e., two measures in each individual), the total number of estimated correlations is 34. The means and variances for the two offspring groups are also estimated, leading to an additional eight parameters. The eight means and variances in the parents are fixed at their observed values.

The cross-trait correlations are the primary focus of this study. There are 18 cross-trait correlations: 2 in each of **FM, FS, FD, MS, MD,** and **SD** (interindividual-intergroup); 1 in each of **SS** and **DD** (interindividual-intragroup); and 1 in each of $\mathbf{R_F}$, $\mathbf{R_M}$, $\mathbf{R_S}$, and $\mathbf{R_D}$ (intraindividual). Element notation (see footnote to table 4) is used in presenting the cross-trait correlations and hypotheses tested. For example, the term f_1m_2 denotes the cross-trait correlation between fathers' body fat and mothers' BP, f_1s_2 denotes correlation between fathers' body fat and sons' BP, and f_{12} denotes the body-fat–BP intraindividual correlation within fathers.

The computer program SEGPATH (Province and Rao 1992, and in press) was used to estimate the familial correlations, by maximum likelihood methods. SEGPATH is a general purpose program that can be used to generate any linear model for analyzing pedigree data and is based on flexible, model-specification syntax. Here, the statistical method of analysis fits the model directly to the family data, under the assumption that the phenotypes in a family follow jointly a multivariate normal distribution. The total log-likelihood function for the entire sample of families is expressed as a function of the 34 correlations and the 16 means and variances and is maximized by ALMINI/GEMINI.

Hypotheses.—A general model is estimated for each bivariate pair of variables, as is a series of reduced models, in order to test certain sex-specific and cross-trait hypotheses. Hypotheses are tested using the likelihood-ratio test, which is minus twice the difference in the log-likelihoods obtained under two different (nested) models. The likelihood ratio is distributed as a χ^2, with the df being the difference in the number of parameters estimated in the two competing hypotheses.

For each pair of variables, at least 12 alternate models are estimated, as detailed in table 5. In addition to the general model (model 1), there are three hypotheses concerning sex differences and seven hypotheses regarding cross-trait resemblance. Under model 2, no sex differences in offspring are allowed by equating correlations involving sons and daughters. This reduction affects 7 sibling correlations, 8 parent-offspring correlations, and 1 intraindividual correlation, leading to a total reduction of 16 correlations. In model 3, no sex differences in either parents or offspring are allowed, leading to a reduction of 22 correlations (7 sibling, 12 parent-offspring, 1 spouse, and 2 intraindividual). In model 4, no sex or generation differences are allowed, leading to a reduction of 27 correlations (23 parent-offspring and sibling, 1 spouse, and 3 intraindividual).

Tests of cross-trait hypotheses are listed in models 5–11. In model 5, the cross-trait correlations in the sibling matrices are fixed at zero, reducing the parameter set by four (i.e., $s_1s_2 = d_1d_2 = s_1d_2 = s_2d_1 = 0$). The next model (model 6) tests whether there are cross-trait correlations in the parent-offspring matrices (df = 8), and in model 7 no cross-trait correlations are allowed in either the sibling or the parent-offspring correlations (df = 12). Cross-trait cor-

Table 5

Summary of Sex and Cross-Trait Hypotheses

Model	df	Parameter Reductions
1. General	. . .	All 34 correlations estimated
2. No sex differences in offspring	16	$s_1s_1 = d_1d_1 = s_1d_1, s_1s_2 = d_1d_2 = s_1d_2 = s_2d_1, s_2s_2 = d_2d_2 = s_2d_2,$ $f_1s_1 = f_1d_1, f_1s_2 = f_1d_2, f_2s_1 = f_2d_1, f_2s_2 = f_2d_2,$ $m_1s_1 = m_1d_1, m_1s_2 = m_1d_2, m_2s_1 = m_2d_1, m_2s_2 = m_2d_2,$ $s_{12} = d_{12}$
3. No sex differences in offspring or parents	22	$s_1s_1 = d_1d_1 = s_1d_1, s_1s_2 = d_1d_2 = s_1d_2 = s_2d_1, s_2s_2 = d_2d_2 = s_2d_2,$ $f_1s_1 = f_1d_1 = m_1s_1 = m_1d_1, f_1s_2 = f_1d_2 = m_1s_2 = m_1d_2, f_2s_1 = f_2d_1 = m_2s_1 = m_2d_1,$ $f_2s_2 = f_2d_2 = m_2s_2 = m_2d_2,$ $f_1m_2 = f_2m_1,$ $f_{12} = m_{12}, s_{12} = d_{12}$
4. No sex or generation differences	27	$f_1s_1 = f_1d_1 = m_1s_1 = m_1d_1 = s_1s_1 = d_1d_1 = s_1d_1,$ $f_1s_2 = f_1d_2 = m_1s_2 = m_1d_2 = f_2s_1 = f_2d_1 = m_2s_1 = m_2d_1 = s_1s_2 = d_1d_2 = s_1d_2 = s_2d_1,$ $f_2s_2 = f_2d_2 = m_2s_2 = m_2d_2 = s_2s_2 = d_2d_2 = s_2d_2,$ $f_1m_2 = f_2m_1,$ $f_{12} = m_{12} = s_{12} = d_{12}$
5. No cross-trait in siblings	4	$s_1s_2 = d_1d_2 = s_1d_2 = s_2d_1 = 0$
6. No cross-trait in parent-offspring	8	$f_1s_2 = f_2s_1 = f_1d_2 = f_2d_1 = m_1s_2 = m_2s_1 = m_1d_2 = m_2d_1 = 0$
7. No cross-trait in siblings or parent-offspring	12	$s_1s_2 = d_1d_2 = s_1d_2 = s_2d_1 = 0,$ $f_1s_2 = f_2s_1 = f_1d_2 = f_2d_1 = m_1s_2 = m_2s_1 = m_1d_2 = m_2d_1 = 0$
8. No cross-trait in spouse	2	$f_1m_2 = f_2m_1 = 0$
9. No cross-trait in intraindividual	4	$f_{12} = m_{12} = s_{12} = d_{12} = 0$
10. No cross-trait in interindividual	14	$s_1s_2 = d_1d_2 = s_1d_2 = s_2d_1 = 0,$ $f_1s_2 = f_2s_1 = f_1d_2 = f_2d_1 = m_1s_2 = m_2s_1 = m_1d_2 = m_2d_1 = 0,$ $f_1m_2 = f_2m_1 = 0$
11. No cross-trait at all	18	$s_1s_2 = d_1d_2 = s_1d_2 = s_2d_1 = 0,$ $f_1s_2 = f_2s_1 = f_1d_2 = f_2d_1 = m_1s_2 = m_2s_1 = m_1d_2 = m_2d_1 = 0,$ $f_1m_2 = f_2m_1 = 0,$ $f_{12} = m_{12} = s_{12} = d_{12} = 0$
12. Most parsimonious		Combination of all nonrejected hypotheses above

relations are also tested for both the spouse (model 8; df = 2) and the intraindividual matrices (model 9; df = 4). Model 10 examines cross-trait resemblance in all of the interindividual matrices simultaneously (sibling, parent-offspring, and spouse; with 14 df), and model 11 examines all matrices simultaneously (sibling, parent-offspring, spouse, and intraindividual; with 18 df). Finally, the most parsimonious model is obtained by combining all nonrejected hypotheses into a single test (model 12). If the combined test fails to fit the data, then the hypothesis having the smallest P value is added back into the parsimonious model until an acceptable fit is obtained.

Results

Table 6 gives the P values associated with each of the models described above, for each of the 12 sets of bivariate analyses. The six body-fat variables are listed across the top, and the alternative hypotheses are listed along the side. The first set of P values denotes associations between each body-fat phenotype and SBP, and the second set of P values denotes associations between each body-fat phenotype and DBP.

The only pairs of variables that are suggestive of familial cross-trait resemblance (as evidenced by significant interindividual cross-trait resemblance in model 10) are TER with DBP ($P < .001$), SF6 with DBP ($P = .011$), and TER-sf with both SBP ($P = .020$) and DBP ($P = .002$). For the latter three pairs, however, the tests of individual matrices suggest that, whereas the parent-offspring cross-trait correlations (model 6) are significant, the sibling cross-trait correlations (model 5) are borderline nonsignificant ($P = .057$ for SF6-DBP; $P = .156$ for TER-sf-SBP; and $P = .063$ for TER-sf–DBP). For two other pairs of variables, there is an inconsistent pattern of interindividual cross-trait resemblance, where some individual matrices evidence cross-trait resemblance, but, on the basis of the overall test (model 10), cross-trait resemblance is nonsignificant. Specifically, for TER-SBP, significant parent-offspring cross-trait resemblance is observed (model 6; $P = .021$), with borderline sibling cross-trait resemblance (model 5; $P = .095$) and borderline overall resemblance (model 10; $P =$

Table 6

Summary of *P* Values for Each Sex and Cross-Trait Hypothesis Test

Model	n_c[a]	df[b]	%BF	BMI	SF6	SF6/FM	TER-sf	TER
SBP:								
1. General	34	. . .						
2. No sex differences in offspring	18	16	.053	.502	.059	.007	.045	.055
3. No sex differences in offspring or parents	12	22	.120[c]	.675	.108[c]	.008	.099	.197[c]
4. No sex nor generation differences	7	27	.012	.092[c]	.110	.002	.002	.015
5. No cross-trait in siblings	30	4	.412	.163	.140	.869	.156[c]	.095[c]
6. No cross-trait in parent-offspring	26	8	.284	.783	.259	.369	.003	.021
7. No cross-trait in siblings or parent-offspring	22	12	.276	.519	.241	.523	.011	.056
8. No cross-trait in spouse	32	2	.751	.163	.462	.619	.093[c]	.270[c]
9. No cross-trait in intraindividual	30	4	<.001	<.001	<.001	.104	<.001	<.001
10. No cross-trait in interindividual	20	14	.360[c]	.294[c]	.140[c]	.625	.020	.099
11. No cross-trait at all	16	18	<.001	<.001	<.001	.194[c]	.009	<.001
12. Most parsimonious[d]			(26) .135	(29) .040	(26) .021	(18) .194	(6) .106	(24) .052
13. Revised most parsimonious[d]				(26)[e] .726	(14)[f] .140			
DBP:								
1. General	34	. . .						
2. No sex differences in offspring	18	16	.026	.165	<.001	.034	.023	.040
3. No sex differences in offspring or parents	12	22	.063	.330[c]	<.001	.076	.090	.181
4. No sex nor generation differences	7	27	.002	<.001	<.001	.001	<.001	<.001
5. No cross-trait in siblings	30	4	.025	.152	.057[c]	.648	.063[c]	.002
6. No cross-trait in parent-offspring	26	8	.529[c]	.311	.016	.624	<.001	<.001
7. No cross-trait in siblings or parent-offspring	22	12	.160	.174	.013	.690	.001	<.001
8. No cross-trait in spouse	32	2	.681[c]	.564	.805[c]	.248	.005	.012
9. No cross-trait in intraindividual	30	4	<.001	<.001	<.001	.659	<.001	<.001
10. No cross-trait in interindividual	20	14	.237	.193[c]	.011	.674	.002	<.001
11. No cross-trait at all	16	18	<.001	<.001	<.001	.729[c]	<.001	<.001
12. Most parsimonious[d]			(10) .657	(26) .191	(6) .132	(18) .729	(4) .063	General model

[a] No. of estimated correlations.
[b] No. of reduced correlations.
[c] Hypotheses are included in the most parsimonious model.
[d] Nos. in parentheses are no. of reduced correlations, or df.
[e] The most parsimonious model did not fit, model 4 was removed, and model 3 was added to model 10 as parsimonious.
[f] The most parsimonious model did not fit, and model 3 was removed, leaving model 10 only as the most parsimonious.

.099). For %BF-DBP, the sibling cross-trait resemblance is significant ($P = .025$), but there is no parent-offspring cross-trait resemblance ($P = .529$).

There is no evidence for interindividual cross-trait resemblance (model 10) between BMI and either SBP ($P = .294$) or DBP ($P = .193$) or between SBP and either %BF ($P = .360$) or SF6 ($P = .140$), although each of these pairs of measures is strongly intercorrelated within individuals (model 9). Finally, there is no evidence for any cross-trait resemblance (neither inter- nor intraindividual) between SF6/FM and either of the BP measures (model 11).

In general, sex differences are either significant or borderline for all pairs of measures, except for BMI with each of the BPs. Generation differences are significant for all comparisons.

The cross-trait parameter estimates and standard errors under both the general and the most parsimonious models are given in table 7 (comparison of six body-fat measures, with SBP and with DBP). On the basis of a comparison of standard errors, several cross-trait correlations in table 7 are zero in the parsimonious models but are apparently significant under the general model. For example, for sibling BMI-SBP the daughter-daughter cross-trait correlation is significant ($d_1d_2 = .17 \pm .07$). However, when this single correlation is tested in conjunction with the other three cross-trait sibling correlations (s_1s_2, s_1d_2, and s_2d_1), its overall effect is nonsignificant ($P = .163$).

Several other isolated cross-trait correlations are also significant on the basis of a standard-error comparison but are nonsignificant on basis of the likelihood-ratio tests. Four of these are of particular interest: the son-son cross-correlation (s_1s_2) for SF6-DBP ($.16 \pm .06$), TER-sf–DBP ($.15 \pm .07$), TER-sf–SBP ($.17 \pm .07$), and TER-SBP ($.17 \pm .07$). In all four cases, there is evidence for significant parent-offspring cross-trait correlations, but the results of the tests for sibling cross-trait correlations are borderline nonsignificant ($P = .057$, .063, .156, and .095, respectively). Since familial factors are already implied (via the parent-

Table 7

Maximum-Likelihood Estimates of Cross-Trait Correlations ± Standard Errors, under the General (Gen) and Most Parsimonious (Par) Models

	%BF		BMI		SF6		SF6/FM		TER-sf		TER	
CORRELATION	Gen	Par	Gen	Par	Gen	Par	Gen	Par	Gen	Par	Gen	Par
SBP:												
Spouse:												
f_1m_2	−.05 ± .11	[0]	−.11 ± .06	[0]	−.07 ± .06	[0]	.08 ± .10	[0]	.11 ± .06	[0]	.07 ± .06	[0]
f_2m_1	−.05 ± .09	[0]	−.02 ± .06	[0]	.02 ± .06	[0]	.04 ± .09	[0]	.07 ± .06	[0]	.06 ± .06	[0]
Parent-offspring:												
f_1s_2	−.06 ± .09	[0]	.09 ± .06	[0]	.10 ± .06	[0]	.02 ± .08	[0]	.13 ± .06	.06 ± .05	.14 ± .06	.02 ± .03
f_2s_1	.23 ± .09	[0]	−.00 ± .06	[0]	.09 ± .06	[0]	−.16 ± .09	[0]	.15 ± .07	.10 ± .06	.16 ± .06	.06 ± .03
f_1d_2	−.07 ± .09	[0]	.01 ± .06	[0]	.04 ± .06	[0]	.02 ± .09	[0]	.06 ± .06	.01 ± .06	.06 ± .06	[.02]
f_2d_1	−.03 ± .09	[0]	−.03 ± .06	[0]	−.01 ± .06	[0]	.15 ± .09	[0]	.04 ± .06	−.00 ± .05	.02 ± .06	[.06]
m_1s_2	−.03 ± .09	[0]	.07 ± .06	[0]	.06 ± .06	[0]	.14 ± .09	[0]	.03 ± .06	−.00 ± .05	.05 ± .05	[.02]
m_2s_1	.07 ± .08	[0]	−.01 ± .06	[0]	.12 ± .05	[0]	−.02 ± .08	[0]	.14 ± .06	.08 ± .05	.10 ± .06	[.06]
m_1d_2	.12 ± .09	[0]	.06 ± .06	[0]	.06 ± .06	[0]	.10 ± .10	[0]	.04 ± .07	.01 ± .06	.05 ± .07	[.02]
m_2d_1	−.09 ± .11	[0]	.01 ± .06	[0]	−.00 ± .06	[0]	−.00 ± .11	[0]	.23 ± .06	.20 ± .06	.15 ± .06	[.06]
Sibs:												
s_1s_2	.05 ± .09	[0]	.04 ± .07	[0]	.07 ± .07	[0]	−.02 ± .08	[0]	.17 ± .07	[0]	.17 ± .07	[0]
d_1d_2	.14 ± .10	[0]	.17 ± .07	[0]	.14 ± .07	[0]	−.01 ± .10	[0]	.03 ± .06	[0]	.05 ± .07	[0]
s_1d_2	.14 ± .10	[0]	.07 ± .07	[0]	.11 ± .07	[0]	.06 ± .08	[0]	.11 ± .07	[0]	.13 ± .07	[0]
s_2d_1	.12 ± .09	[0]	.08 ± .06	[0]	.09 ± .06	[0]	−.06 ± .11	[0]	.05 ± .06	[0]	.06 ± .06	[0]
Intraindividual:												
f_{12}	.26 ± .08	.26 ± .05	.28 ± .05	.26 ± .03	.19 ± .06	.18 ± .05	−.17 ± .08	[0]	.13 ± .06	.10 ± .06	.21 ± .06	.19 ± .04
m_{12}	.28 ± .08	[.26]	.24 ± .05	[.26]	.29 ± .06	.27 ± .05	.07 ± .09	[0]	.14 ± .06	.12 ± .07	.22 ± .05	[.19]
s_{12}	.12 ± .07	.13 ± .05	.31 ± .05	.24 ± .03	.27 ± .05	.20 ± .05	.09 ± .07	[0]	.16 ± .05	.07 ± .05	.25 ± .05	.12 ± .03
d_{12}	.23 ± .08	[.13]	.27 ± .06	[.24]	.25 ± .06	.17 ± .04	−.10 ± .09	[0]	.13 ± .06	.10 ± .04	.14 ± .06	[.12]
DBP:												
Spouse:												
f_1m_2	−.03 + .10	[0]	−.06 ± .06	[0]	−.03 ± .06	[0]	.12 ± .10	[0]	.14 ± .06	.13 ± .06	.12 ± .06	.12 ± .06
f_2m_1	−.08 ± .09	[0]	−.02 ± .06	[0]	.02 ± .06	[0]	.11 ± .10	[0]	.13 ± .06	.11 ± .06	.14 ± .06	.14 ± .06
Parent-offspring:												
f_1s_2	.12 ± .09	[0]	.13 ± .06	[0]	.14 ± .06	.11 ± .06	−.07 ± .09	[0]	.15 ± .06	.10 ± .06	.18 ± .06	.18 ± .06
f_2s_1	.12 ± .10	[0]	.05 ± .06	[0]	.11 ± .06	.06 ± .06	−.07 ± .09	[0]	.19 ± .06	.14 ± .06	.21 ± .06	.21 ± .06
f_1d_2	.05 ± .09	[0]	.06 ± .06	[0]	.11 ± .06	.09 ± .06	.01 ± .09	[0]	.13 ± .06	.09 ± .06	.12 ± .06	.12 ± .06
f_2d_1	−.10 ± .09	[0]	−.02 ± .06	[0]	−.03 ± .06	−.06 ± .06	.14 ± .10	[0]	.11 ± .06	.07 ± .06	.09 ± .06	.09 ± .06
m_1s_2	−.03 ± .09	[0]	.07 ± .06	[0]	.07 ± .06	.04 ± .06	.14 ± .09	[0]	.17 ± .06	.12 ± .05	.19 ± .06	.19 ± .06
m_2s_1	.06 ± .09	[0]	−.00 ± .05	[0]	.14 ± .05	.11 ± .05	−.02 ± .08	[0]	.11 ± .06	.07 ± .05	.12 ± .06	.12 ± .06
m_1d_2	−.09 ± .09	[0]	−.00 ± .06	[0]	−.01 ± .06	−.04 ± .06	.03 ± .10	[0]	.06 ± .07	.02 ± .06	.05 ± .06	.05 ± .06
m_2d_1	−.14 ± .10	[0]	−.10 ± .06	[0]	−.11 ± .06	−.13 ± .06	.02 ± .11	[0]	.21 ± .06	.18 ± .06	.16 ± .06	.16 ± .06
Sibs:												
s_1s_2	.25 ± .09	.21 ± .09	.12 ± .06	[0]	.16 ± .06	[0]	−.09 ± .08	[0]	.15 ± .07	[0]	.23 ± .06	.23 ± .06
d_1d_2	.11 ± .10	.13 ± .10	.12 ± .07	[0]	.12 ± .07	[0]	−.03 ± .10	[0]	.08 ± .06	[0]	.10 ± .06	.10 ± .06
s_1d_2	−.06 ± .10	−.07 ± .10	.04 ± .07	[0]	.08 ± .07	[0]	.04 ± .08	[0]	.13 ± .07	[0]	.18 ± .06	.18 ± .06
s_2d_1	−.04 ± .10	−.05 ± .10	.04 ± .07	[0]	.05 ± .07	[0]	−.04 ± .12	[0]	.13 ± .07	[0]	.14 ± .07	.14 ± .07
Intraindividual:												
f_{12}	.20 ± .08	.19 ± .07	.28 ± .05	.27 ± .03	.20 ± .06	.20 ± .05	−.10 ± .08	[0]	.23 ± .05	.22 ± .06	.29 ± .05	.29 ± .05
m_{12}	.26 ± .08	.29 ± .07	.26 ± .05	[.27]	.31 ± .05	.30 ± .05	.03 ± .09	[0]	.15 ± .06	.14 ± .06	.26 ± .05	.26 ± .05
s_{12}	.17 ± .08	.13 ± .07	.21 ± .05	.15 ± .03	.21 ± .05	.13 ± .04	−.08 ± .08	[0]	.24 ± .05	.13 ± .04	.29 ± .05	.29 ± .05
d_{12}	.16 ± .08	.18 ± .08	.19 ± .06	[.15]	.20 ± .06	.13 ± .04	−.03 ± .09	[0]	.10 ± .06	.02 ± .04	.13 ± .06	.13 ± .06

Table 8

Summary of Cross-Trait Resemblance

Type of Cross-Trait	%BF	BMI	SF6	SF6/FM	TER-sf	TER
SBP:						
Intraindividual	Yes	Yes	Yes	No	Yes	Yes
Interindividual	No	No	No	No	Some	Some
DBP:						
Intraindividual	Yes	Yes	Yes	No	Yes	Yes
Interindividual	Some	No	Some	No	Some	Yes

NOTE.—Cross-trait resemblance is separately defined for intraindividual and interindividual: "Yes" designates significant correlations, "No" designates nonsignificance, and "Some" designates that at least some of the correlations (spouses, parent-offspring, and sibs) are significant.

offspring comparisons), these suggestive correlations tend to strengthen the genetic hypothesis for these pairs of measures.

Discussion

Although the primary purpose of this study was to delineate which phenotypes may have cross-trait familial resemblance, the negative results also are revealing. Table 8 summarizes the cross-trait resemblance and highlights an important distinction between intraindividual and interindividual differences, in the context of genetic analyses. That is, significant cross-trait correlations within individuals do not imply familial factors; rather, they may reflect specific environmental factors that are unique to each individual. For example, table 8 implies that, although the BMI is significantly correlated with BP within individuals, BMI and BP may share relatively few genetic or common environmental factors, since the interindividual cross-trait correlations are all zero. This suggests that the factors that make BMI and BP covary are specific to each individual. Also, table 8 shows that adjusting SF6 for FM (i.e., the ratio SF6/FM) reduces its intraindividual cross-trait resemblance with BP. This suggests that the SF6-BP relationship within individuals may be mediated by the absolute amount of subcutaneous fat and not by the proportion of total fat that is stored subcutaneously. Clearly, more research is needed to clarify this association.

Concerning significant interindividual resemblance in this study, which alone is capable of suggesting common genetic and/or familial environmental factors, the clearest case is TER-DBP. The evidence is suggestive also for TER-SBP, TER-sf with both BPs, SF6-DBP, and %BF-DBP. If it is assumed that all such resemblance is due only to common genetic factors, the magnitude of the cross-trait heritability may be approximated by doubling the average sibling correlation. This yields the largest cross-trait heritability estimate, 33%, for TER-DBP. That is, as much as 33% of the variation in each of the two traits (i.e., TER and DBP) may be due to shared genes. In comparison, path analysis of the TER (Bouchard et al. 1991) yields a univariate heritability of ~30%. Support for a major gene for TER (Borecki et al., in press) is also found, with a putative major locus accounting for >35% of the variance and with an additional nearly 30% being due to a multifactorial (polygenic and/or environmental) background. For DBP in this French Canadian sample, Pérusse et al. (1989) report a higher genetic heritability in offspring (~50%) than in parents (<10%), with additional environmental heritability as well (~40%). Thus, the bivariate (TER-DBP) heritability estimate of ~33% in the current study (when only a genetic etiology is assumed) is certainly within range of each of the univariate estimates, suggesting that a substantial percentage of the genes that affect TER may also affect BP.

The present study also reveals significant spouse correlations for TER-DBP. In general, if assortative mating is assumed, spousal resemblance is due to common environmental factors. However, if mating is not at random, then the resemblance may also include genetic factors or even gene × environment interactions. The metabolic-syndrome hypothesis predicts that a pertinent environmental source of variance is dietary, and results from Bouchard et al. (1990) further suggest that the component may involve a genotype × environment interaction. In overfeeding experiments in MZ twins, intrapair-weight, body-fat, and fat-distribution changes in response to overfeeding were more similar among brothers of the same MZ pairs (who share all genes in common) than among members of different MZ pairs (who do not share genes by descent). This suggests that individuals with similar genotypes metabolically and morphologically respond to food more similarly than do individuals who are genetically unrelated.

To our knowledge, only one study has examined pleiotropic effects of BP and body mass (Schork et al. 1994). These investigators used a bivariate variance-components analysis of family data, partitioning the covariances among

relatives into several components, including (in part) bivariate additive genetic and bivariate environmental factors. Weight and BMI represented the body-mass measures, while various other cardiovascular factors—e.g., mean arterial BP (MBP) and several measures of sodium—were also examined. None of the additive genetic covariances with MBP exceeded 1% of the variance—except for weight, which reached just over 3%. Pleiotropy between MBP and BMI was significant but, again, accounted for <1% of the covariance. Additionally, several variables—including red-blood-cell sodium, sodium creatinine levels, sodium potassium, and BMI— shared environmental covariance with MBP (each accounting for <1%). Schork et al. concluded that pleiotropic genes, while small in magnitude, may be important when considered collectively.

The results of Schork et al. (1994) support the metabolic-syndrome hypothesis, since significant pleiotropy (albeit small) was detected between BP and body-mass measures. Additionally, significant MBP covariance with the various sodium measures is also predicted by the metabolic-syndrome hypothesis, as reviewed earlier. However, the low magnitude of the Schork et al. (1994) effects may relate to two factors not considered by the authors. First, the study did not specifically assess body fat or upper-body-fat mass but, rather, looked at total weight and the BMI. Previous research (for a review, see Landsberg 1986) indicates that the cluster of diseases is associated more with upper-body obesity than with other measures of body fat. Second, MBP was considered, not the two important measurements of SBP and DBP. Both of these considerations could contribute to the low magnitude of effects reported in the Schork et al. sample, since secondary (or correlated) phenotypes were used, perhaps leading to only a partial assessment of covariances. This correlated-phenotype explanation also applies to the inconsistent results (%BF and SF6) or nonsignificant results (BMI) with BP that are found in the current study; that is, %BF and SF6 are measures of total body fat, not measures of upper-body fat specifically, and thus are correlated measures. This suggests that there are many more genetic effects on BP and overall body composition that are not shared than there are shared factors.

Sex differences are an additional complication in this syndrome. There is the well-known sexual dimorphism in the regional depots of body fat (Vague 1956). Truncal/abdominal fat (vs. lower-body fat) is called "android," since it is found primarily in men, while femoral fat (vs. upper-body fat) is called "gynoid," since it occurs primarily in women. As reviewed by Bouchard et al. (1991), sex hormones do not fully explain the sex differences in regional distributions. While higher plasma testosterone and estradiol levels and lower sex hormone–binding globulin (SHBG) levels are found in women with upper-body fat (vs. lower-body fat), in men with upper-body fat the SHBG and testosterone levels are lower than those in men with lower-body fat. Sex differences also have been reported by Després et al. (1988), who found that the significance of the TER-BP association varied not only by BP phenotype but also by sex. The present study also suggests sex differences in the body-fat–BP association. Significant sex differences in both the sibling and the parent-offspring cross-trait correlations for TER-DBP suggest that the magnitude of the body-fat–BP covariation increases as the number of sons in the comparison increases; e.g., $r_{SS} > r_{SD} > r_{DD}$. This is a typical pattern for inferring sex dimorphism in genetic effects. Also, the greater effect of males (compared with females) is consistent with the finding of greater truncal/abdominal fat in men than in women (Bouchard et al. 1991).

In summary, familial cross-trait correlations are simple and effective methods for screening pairs of measures for possible pleiotropic effects. This component of our investigation confirms a heritable (genetic and/or common environment) link between BP and body-fat distribution, as predicted by the metabolic-syndrome hypothesis. The propensity for preferential fat deposition in the truncal/abdominal area (vs. the lower-body area) is particularly associated with DBP. Evidence is also found for a link between upper-body fat and both SBP and DBP, even after adjustment for the amount of subcutaneous fat, a finding that reemphasizes the important and specific role of fat topography in the metabolic alterations mediated by body-fat content or obesity. Furthermore, these results are obtained from primarily normotensive, nonobese families, suggesting that the connection between the metabolic conditions and body-fat distribution derives from normal metabolic pathways. Other factors that should be considered in future investigations include the familial associations between insulin, glucose, lipid, and sex-hormone levels with body fat, especially the truncal/abdominal and abdominal/visceral forms.

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