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ORIGINAL ARTICLE

Common familial influences on clustering of metabolic syndrome traits with central obesity and insulin resistance: the Kiel obesity prevention study

A Bosy-Westphal[1], S Onur[1], C Geisler[1], A Wolf[2], O Korth[1], M Pfeuffer[3], J Schrezenmeir[3], M Krawczak[2] and MJ Müller[1]

[1]*Institut für Humanernährung und Lebensmittelkunde, Christian-Albrechts-Universität, Kiel, Germany;* [2]*Institut für Medizinische Informatik und Statistik, Universitätsklinikum Schleswig Holstein, Kiel, Germany and* [3]*Bundesforschungsanstalt für Ernährung und Lebensmittel, Kiel, Germany*

Objective: The phenotypic heterogeneity of metabolic syndrome (MSX) suggests heterogeneity of the underlying genotype. The aim of the present study was to examine the common genetic background that contributes to the clustering between the two main features (insulin resistance, central obesity) and different MSX component traits.
Methods: In all, 492 individuals from 90 families were investigated in a three-generation family path study as part of the Kiel Obesity Prevention Study (KOPS, 162 grandparents, 66.1 ± 6.7 years, 173 parents, 41.3 ± 5.4 years and 157 children, 10.8 ± 3.4 years). Overall heritability was estimated and common familial (genetic and environmental) influences on insulin resistance (HOMA-IR) or central obesity (elevated waist circumference, WC), respectively, and different MSX traits were compared in a bivariate cross-trait correlation model.
Results: Prevalence of MSX (according to NCEP criteria) was 27.2% (f) and 27.8% (m) in adults and 3.5% (f) and 8.5% (m) in children and adolescents, respectively. MSX phenotype was found to be highly variable, comprising 16 subtypes of component trait combinations. Within-trait heritability was 38.5% for HOMA-IR and 53.5% for WC, cross-trait heritability was 53.4%. As much as 6–18% and 3–10% of the shared variance between different MSX component traits (lipid profile, blood pressure) and WC or HOMA-IR, respectively, may be genetic. With the exception of HDL-C, the shared genetic variance between MSX component traits and WC was higher than the genetic variance shared with HOMA-IR.
Conclusion: A common genetic background contributes to the clustering of different MSX component traits and central obesity or insulin resistance. Common genetic influences favour central obesity as a major characteristic linking these traits.
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Keywords: metabolic syndrome; insulin resistance; cross-trait heritability

Introduction

Metabolic syndrome (MSX) is defined by the simultaneous occurrence of obesity, insulin resistance, hypertension and dyslipidemia. Originally, MSX was believed to be attributable to insulin resistance, as was expressed by the use of the alternative term 'insulin resistance syndrome'.[1] Accordingly, MSX definitions by the World Health Organization (WHO) and the European Group for the study of Insulin Resistance (EGIR) regard insulin resistance as a necessary condition.[2,3] There is, however, controversy about whether insulin resistance is the central feature of MSX. Thus, the National Cholesterol Education Program Adult Treatment Panel III (NCEP ATP III) definition weights all MSX traits equally and defines a 'MSX' rather than an 'insulin resistance syndrome'.[4] Only recently, the International Diabetes Federation (IDF) introduced a new MSX definition assuming central obesity to be the primary cause of the syndrome.[5]

Today both views are supported by a large body of epidemiological as well as functional metabolic data (insulin resistance[1,6–11] and for central obesity[9,12–15]). It is therefore unclear whether insulin resistance or abdominal obesity is the central feature of MSX.

Genetic epidemiology adds yet another facet to this controversy. Genetic factors are major contributors to

Correspondence: Professor Dr MJ Müller, Institut für Humanernährung und Lebensmittelkunde, Agrar- und Ernährungswissenschaftliche Fakultät, Christian-Albrechts-Universität zu Kiel, Düsternbrooker Weg 17-19, D-24105 Kiel, Germany E-mail: mmueller@nutrfoodsc.uni-kiel.de
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the manifestation of MSX and to its incident morbidity (i.e. diabetes mellitus, cardiovascular disease).[16–18] The co-inheritance of different MSX component traits may therefore partly explain the association of different risk factors observed at the population level. Calculation of cross-trait heritability may improve our understanding of common genetic and environmental influences (pleiotropy) upon either *insulin resistance* or *central obesity*, and MSX component traits.

Previous studies have revealed everything from low to substantial commonality in the genetic influence on measures of insulin resistance and adiposity.[19–23] Apart from differences in the parameters used for phenotype characterization, these discrepant findings may be explicable in terms of different study designs (e.g. number of generations studied, family or twin studies), sample sources (e.g. with respect to ethnicity, age-range and morbidity) and statistical methodology, all of which may render a direct comparison of the obtained heritability estimates impossible. Thus, a direct comparison between the proportion of total genetic variance shared by MSX traits and either *insulin resistance* or *central obesity* is only possible within one and the same study, and the results should be interpreted in relative rather than absolute terms.

The aim of the present three-generation family path study, which is part of the Kiel Obesity Prevention Study (KOPS),[24,25] was to (i) investigate the variability of the MSX phenotype between children, parents and grandparents, (ii) to estimate the heritability of individual MSX component traits and (iii) to compare the commonality of the familial (genetic and environmental) influence upon *insulin resistance* and MSX component traits to that on *central obesity* and MSX component traits.

Subjects and methods

Study population and design

Between July 2003 and December 2004, 90 families were recruited through the KOPS.[24,25] The main objective of this three-generation trial was to assess the contribution of genetic factors to obesity and MSX. The 492 study subjects (age range: 4–84 years) comprised 162 grandparents (mean age 66.1 ± 6.7 years), 173 parents (41.3 ± 5.4 years) and 157 children (10.8 ± 3.4 years). All were recruited by advertisements in local newspapers, by notice-board postings and by writing to families who are continuously followed-up in a KOPS sub-cohort. Inclusion criteria for study participation were at least one overweight or obese family member and at least two grandparents taking part as well. All participants were white Northern-Europeans. The study protocol was approved by the ethics committee of the Christian-Albrechts-Universität, Kiel. Each subject provided informed written consent before participation. Parents assented for underage children.

Anthropometric measurements and body composition analysis

Body weight was measured to the nearest 0.1 kg on an electronic scale coupled to the BOD-POD Body Composition System (Life Measurement Instruments., Concord, CA, USA). Height was measured on a stadiometer to the nearest 0.5 cm. Underweight, normal weight, overweight and obesity were determined by use of corresponding actual German BMI percentiles (<10, >90 and >97P, respectively) for children and adolescents[26] and by WHO criteria for adults.[27] Waist circumference (WC) was measured to the nearest 0.5 cm half way between the lowest rib and the iliac crest while the subject was at minimal respiration. Air-displacement plethysmography was performed using the BOD-POD device as described in detail elsewhere.[28] Briefly, subjects were measured in tight fitting underwear and a swimming cap. Two repeated measurements of body volume were performed and averaged. Measured thoracic lung volume was subtracted from body volume. The BOD-POD software was used to calculate body density as body weight divided by body volume, and fat mass (FM) % using Siri's equation.[29] Child-specific corrections of air-displacement plethysmography results were used.[30] FFM (kg) was calculated accordingly as weight (kg) – FM (kg).

Clinical and metabolic variables

Blood pressure measurements were obtained while the subject was in a seated position, using a standard manual sphygmomanometer. Blood samples were obtained after 8 h overnight fast and analyzed following standard procedures. Briefly, plasma glucose was assayed using a hexokinase enzymatic method. Triacylglycerol concentrations were measured enzymatically by hydrolyzing cholesterol ester and triacylglcerol to cholesterol and glycerol, respectively. HDL cholesterol (HDL-C) was measured in the supernatant after precipitation of lipoproteins (kits and standards by Konelab-Cooperation, Espoo, Finland). Plasma insulin was measured by RIA showing no cross-reactivity with C-peptide and only 14% with proinsulin (Adaltis, Rome, Italy). The homeostasis model assessment[31] was used to calculate insulin resistance (IR) as insulin resistance by homeostasis model assessment (HOMA-IR) = fasting insulin (μU/ml) × fasting glucose (mmol/l)/22.5. Subjects were classified as having IR if this value exceeded 2.61.[31] The HOMA-IR was not calculated for subjects who had fasting glucose level >7.0 mmol/l or were on insulin treatment or oral antidiabetics. As a result of the distorting effects of pubertal stage on plasma insulin concentrations the prevalence of elevated insulin and HOMA-IR in children was assessed using age- and gender-specific reference percentiles.[32] HOMA-IR values from 62 children between 11 and 15 years were not used for correlation analysis and the calculation of heritability for HOMA-IR, respectively. MSX was defined according to the NCEP Adult Treatment Panel III report definition of MSX[4,33] as presence of three or more of the following characteristics: (1) hypertriglyceridemia: ⩾150 mg/dl (⩾1.69 mmol/l), (2) low HDL-C: <40 mg/dl (<1.04 mmol/l) in men or <50 mg/dl (<1.29 mmol/l) in women, (3) high blood pressure: ⩾130/85 mm Hg, (4) high fasting plasma glucose: ⩾110 mg/dl

($\geqslant$6.1 mmol/l) and (5) abdominal obesity: WC $>$88 cm in women, and $>$102 cm in men. For children and adolescents, child specific reference values for blood pressure and WC were used.[34,32] Participants who reported a history of physician-diagnosed diabetes, hypertension or hyperlipidemia, and who were taking antihypertensive (14.8%), antidiabetic (insulin or oral agents) (2.7%) or lipid lowering drugs (5.4%) were defined as hypertensive, hyperglycemic or hyperlipidaemic, respectively. Data from these subjects were excluded from the descriptive statistics as well as from the analyses of continuous variables.

Statistical analyses

Means$\pm$s.d. and age-adjusted means$\pm$s.e. were used as descriptive statistics. Mean differences between sexes were assessed for statistical significance using a Mann–Whitney *U*-test. A mixed-model ANOVA followed by a Bonferroni *post hoc* test was conducted to compare means between generations. In this analysis 'family identity' was used as a random factor to take into account the correlation within pedigrees. ANCOVA was used to adjust means of metabolic risk factors for age. Relationships between variables were analyzed using Pearson's product-moment correlation coefficients. Plasma levels of triglycerides (TG), insulin, systolic blood pressure (BPsys) and HOMA-IR were log-transformed for correlation analysis. Partial correlation coefficients adjusted for age and sex were used to compare the relationships between HOMA-IR and WC and components of the NCEP-MSX definition. A *P*-value <0.05 was considered statistically significant. All analyses were performed using SPSS for Windows (SPSS Inc., Chicago, LA, USA).

Univariate and bivariate genetic analyses were carried out using SOLAR (Sequential Oligogenic Linkage Analysis Routines; 23). A total of 86 families, ranging in size from three to 10 individuals, were included in the heritability estimation. The samples comprised 498 pairs of first-degree relatives (414 parent offspring pairs and 84 sibling pairs), and 206 grandparent–grandchild pairs. The heritability H^2 is defined as the proportion V_G of the observed phenotypic variance V_P of a particular trait that is attributable to genetic causes, that is $H^2 = V_G/V_P$. Mean univariate $H^2 \pm$s.e. were calculated from *Z*-transformed trait values in order to adjust for age and sex effects.

The variance component method employed in the above calculations is based on the fact that relatives share a certain amount of genes identical-by-descent (IBD). For example, siblings and grandparent–grandchild pairs share 50 and 25% of their genes, respectively. The expected genetic variance is then specified as a function of the IBD relationship between relatives, whereas phenotypic variances are calculated from the data. The statistical significance of the estimated heritabilities was assessed by means of a likelihood ratio test comparing the log likelihood with the estimated genetic variance to the log likelihood with the additive genetic variance component constrained to zero.

As a multivariate extension of the univariate case, bivariate genetic analysis estimates the effects of linked genes, or of a single major gene controlling more than one trait, or of shared environmental factors on the phenotypic covariance of a pair of traits. To this end, inter- and intraindividual cross-trait correlations, for example the cross-trait correlations between obesity and hypertension between mothers and daughters, as well as intraindividual cross-trait correlations within mothers and daughters, were calculated. The significance of these cross-trait correlations was determined by comparing the likelihood with the estimated correlations to the likelihood of a submodel in which the correlations were fixed at zero. The proportion of common genetic or environmental variance in a pair of traits was estimated from the square of the genetic correlation (P_G) and the environmental correlation (P_E), respectively.

Results

Characterization of study population

Means of age, nutritional status, metabolic and cardiovascular risk factors, stratified by sex and generation, are given in Table 1. In comparison to males, females had a higher percentage of body FM and a lower WC. This sex difference was independent of the generation studied. Mean BMI, BPsys, plasma TG and glucose concentrations were higher in parents than in children. HDL-C was lower in men than in women. A sex difference for plasma glucose level was also observed in children. When comparing different generations, increases in BMI, percentage FM, WC, systolic blood pressure, HOMA-IR and all metabolic variables were observed with increasing age, except for HDL-C concentrations. Overall, the prevalence of the different MSX traits was found to vary considerably, ranging from 9.4% for hyperglycemia in females to 48.7% for central obesity in females. Approximately 40–50% of the adult population had elevated HOMA-IR. The prevalence of MSX ranged from 12.5% in mothers and 25.9% in fathers to 30.5% in grandfathers and 39.8% in grandmothers, respectively. MSX was already prevalent in 8.1% of girls and 7.0% of boys from the children generation, respectively.

Comparing the age-adjusted values of nutritional status and metabolic risk factors in 243 adult subjects without MSX and in 92 subjects with MSX, those who suffered from MSX were generally older and had higher mean BMI, % FM and WC (data not shown). In this MSX group, the prevalence of insulin resistance was 67.5% for males and 55.8% for females. The prevalence of central obesity, as assessed by elevated WC, was 80.0% in male and 96.2% in female subjects with MSX.

Patterns of MSX cluster

Regarding the heterogeneity of the MSX phenotype, the different combinations of NCEP-MSX components revealed a

Table 1 Characterization of the study population

	Grandparents		*Parents*		*Children*	
	♂ ($n=59$)	♀ ($n=103$)	♂ ($n=85$)	♀ ($n=88$)	♂ ($n=71$)	♀ ($n=86$)
Age (years)	67.4±6.0[a]	65.3±7.0*[a]	42.5±5.6[c]	40.1±5.0[c]**	10.8±2.8[b]	10.7±3.9[b]
BMI (kg/m^2)	27.5±3.7	28.7±5.0	27.9±4.4[c]	26.9±5.9[c]*	20.0±5.6[b]	20.3±6.0[b]
FM (%)	29.3±6.4	42.9±6.2***[a]	27.3±8.1	36.1±7.9[c]***	25.9±10.3	30.3±10.1*[b]
WC (cm)	101.0±10.8	94.3±14.2**[a]	97.1±11.8[c]	86.7±13.8[c]***	70.4±15.9[b]	67.5±13.9[b]
sys.BP (mm Hg)	142.1±20.8[a]	141.0±22.8[a]	131.8±17.9[c]	119.9±12.7[c]***	109.4±10.1[b]	110.7±12.1[b]
dias.BP (mm Hg)	84.7±10.1	85.8±9.6[a]	82.6±9.5[c]	78.1±9.0[c]***	69.1±8.1[b]	70.3±9.2[b]
TG (mg/dl)	116.9±67.9	135.9±65.6*[a]	123.7±74.2[c]	86.7±35.2***	83.1±47.2[b]	73.6±33.9[b]
TC (mg/dl)	223.0±31.7	236.7±50.5[a]	209.2±37.7[c]	196.6±31.0[c]	166.7±29.7[b]	174.8±27.4[b]
LDL-C (mg/dl)	142.8±26.1	153.4±41.8[a]	133.8±31.2[c]	117.8±30.3***[c]	96.5±27.1[b]	103.6±26.5[b]
HDL-C (mg/dl)	51.5±15.4	54.4±14.7	45.4±13.0[c]	56.9±15.2***	52.5±12.6	53.8±11.4
Glucose (mmol/l)	5.70±1.01	5.72±1.43[a]	5.54±1.14[c]	4.97±0.45***	4.86±0.39[b]	4.67±0.58*[b]
Insulin (μU/ml)	14.6±10.0	16.4±12.2	14.2±10.3	13.4±10.4	12.3±6.7	14.4±11.4
HOMA-IR (μU/ml × mmol/l)	3.11±1.72	4.05±3.08[a]	3.48±3.07[c]	3.06±2.77	2.33±1.60 ($n=32$)	2.36±1.33[b] ($n=43$)

Abbreviations: FM, fat mass; HDL-C, HDL-cholesterol; LDL-C, LDL-cholesterol; syst.BP, systolic blood pressure; TC, total cholesterol; TG, triglycerides; WC, waist circumference. Data are presented as means±s.d. ($n=481$). *$P<0.05$; **$P<0.01$, ***$P<0.001$ significant differences within generations and between sexes (Mann–Whitney *U*-Test). a b c significant difference within sex and between generations ([a] grandparents vs parents; [b] grandparents vs children; [c] parents vs children) $P<0.05$ ANOVA (Bonferroni *post hoc* test);

total of 16 MSX phenotype clusters. Up to 41% of all MSX cases could be summarized into three types of MSX, each including increased WC and blood pressure at concomitantly low HDL-C. The highest prevalence (18%) was observed for a phenotype combining elevated WC, blood pressure, triglyceride and glucose levels with a low HDL-C. By contrast, the lowest prevalence of only 1% was found for two phenotypes either combining elevated blood pressure, triglyceride and glucose levels with low HDL-C and a normal WC, or combining a normal HDL-C level and a normal blood pressure with elevated WC, triglyceride and glucose concentrations. The prevalence for the remaining 11 MSX-subtypes ranged between 2 and 10%.

Relationship between central obesity, insulin resistance and MSX components

In adults, WC and log-transformed HOMA-IR both showed a significant positive age- and sex-adjusted correlation with log sysBP and log TG concentrations. A negative correlation was observed with HDL-C level (Table 2). In children, similar age- and sex-adjusted partial correlation coefficients were observed with log HOMA-IR (vs log sysBP: $r=0.26$, $P<0.05$; vs log TG: $r=0.46$, $P<0.001$; vs HDL-C: $r=-0.25$, $P<0.05$) and WC (vs log sysBP: $r=0.48$, $P<0.001$; vs log TG: $r=0.33$, $P<0.001$; vs HDL-C: $r=-0.35$, $P<0.001$). logHOMA-IR and WC were significantly correlated in both adults and children (age- and sex-adjusted partial correlation coefficients: $r=0.60$, $P<0.001$ in adults, $r=0.38$, $P=0.001$ in children).

Heritability of MSX traits

Univariate heritabilities (H^2) of MSX traits, that is the proportion of the phenotypic variance that is due to genetic sources, are given in Table 3. These 'within trait' H^2 values ranged from moderate (e.g. 18.0% for systolic BP and 30.6% for glucose levels) to a particularly large estimate of 53.5% for WC. All were significantly different from zero. The H^2 estimate for HOMA-IR (38.5%) was 15% lower than for WC.

Table 2 Partial correlation, adjusted for age and sex, between HOMA-Index (HOMA-IR) or WC and $_{log}$sys.BP $_{log}$TG and HDL-C for adults ($n=335$)

	$_{log}$HOMA-IR	*WC*
WC	0.60***	—
$_{log}$sys.BP	0.18**	0.23***
$_{log}$dias.BP	0.29***	0.25***
$_{log}$TG	0.53***	0.45***
HDL-C	−0.34***	−0.41***
Glucose	—	0.30***

Abbreviations: HDL-C, high-density lipoprotein-cholesterol; $_{log}$sys.BP, systolic blood pressure; $_{log}$TG, triglycerides; WC, waist circumference. **, ***significant correlations at **$P<0.01$ and ***$P<0.001$.

Common familial influences of WC, HOMA-IR and MSX traits

Table 4 shows cross-trait heritabilities (P_G) and the shared environment influences (P_E) for WC or HOMA-IR, respectively, and different MSX traits. The genetic correlation with systolic and diastolic BP and TG concentrations was higher for WC than for HOMA-IR. By contrast, the genetic correlation between WC and HDL-C was less pronounced than between HOMA-IR and HDL-C. Additive genetic components underlying WC and HOMA-IR were highly but not completely correlated ($P_G=0.731$). Based on the data in Tables 3 and 4, it can be estimated that 53.4% (i.e. 0.731^2) of the heritability of either HOMA-IR or WC is due to genetic influences shared with the other trait. Likewise, genetic

variation underlying HOMA-IR also explained 6.2% ($0.586^2 \times 0.180$) and 3.2% ($0.345^2 \times 0.271$) of the phenotypic variance in sysBP and diasPB, respectively, and 9.9% ($0.567^2 \times 0.308$) and 9.8% ($-0.502^2 \times 0.390$) of the phenotypic variance in TG and HDL-C concentrations, respectively. Similarly, 18.0 and 10.2% of the variance in sysBP and diasPB, respectively, and 11.3 and 6.2% of the variance in TG and HDL-C concentrations, respectively, are determined by genetic variation that also influences WC.

When the shared environmental variances between traits are compared, a higher proportion of joint environmental influence upon TG levels was observed for HOMA-IR ($0.474^2 = 22.5\%$) than for WC ($0.268^2 = 7.2\%$, Table 4). The environmental correlation between HOMA-IR and WC was 0.352, indicating that 12.4% of the covariance in these traits is explained by a shared environment.

Discussion

Heterogeneity of the MSX phenotype

The definition of MSX is based upon different component traits. From the pathophysiological point of view, patients with MSX represent a heterogeneous group comprising multiple subtypes of the MSXs. In fact, looking for factor combinations, we found a total of 16 MSX subtypes. The co-occurrence of MSX traits may be explained either by familial factors (common genetic causes in close linkage, or a shared major gene effect, or shared environmental effects such as life style factors including nutrition, physical activity and smoking) or in terms of the pathophysiology (insulin resistance with hyperinsulinemia, for example, contributes to an elevated VLDL-TG synthesis in the liver and to increased renal sodium retention, thereby contributing to hypertriglyceridemia as well as hypertension). Summarizing different traits into a syndrome may be justified if the syndrome purports to factors involved in a unique pathological process. However, instead of providing a physiological construct, the MSX definitions proposed by WHO, EGIR, NCEP or IDF aim at providing a means of clinical diagnosis, to be of prognostic value, and to identify individuals at risk. The WHO and the NCEP definition of MSX were both shown to be predictive of a health risk in different populations (for review, see Eckel *et al*.[35]) whereas the predictive value of the new IDF definition, that focuses on abdominal obesity, has not been investigated in longitudinal trials.

Table 3 Univariate heritability estimates (H^2) for different components of the metabolic syndrome and HOMA-index (HOMA-IR)

	H^2	P-*value*	n
WC	0.54±0.08	0.0000	431
sys.BP	0.18±0.10	0.0247	393
dias.BP	0.27±0.10	0.0010	393
Triglycerides	0.31±0.11	0.0014	393
HDL-cholesterol	0.39±0.11	0.0002	394
Glucose	0.31±0.10	0.0004	384
HOMA-IR	0.39±0.12	0.0007	316

Abbreviations: HDL-C, high-density lipoprotein-cholesterol; sys.BP, systolic blood pressure; WC, waist circumference.

Heritability estimates of individual MSX component traits

Using phenotype and genotype data from the Framingham Heart Study, heritability estimates were found to be high for the overall covariate-adjusted trait (i.e. 61% for the composite trait MSX) but variable for the individual traits (i.e. 39–62%, 18). These heritability estimates were slightly higher than observed in our study (Table 3). However, lower heritabilities of MSX features (e.g. 43% for serum TG concentrations) have been reported in analyses of a two generation path study of healthy families before.[36] Some heritability estimates may be inflated in families with an increased susceptibility to type 2 diabetes mellitus (36; e.g. fasting glucose concentration had a heritability of 72[37] vs 30.6% in our study or 21% in 34). Other component traits, in contrast, (e.g. HDL-C, 52 vs 39 or 44%) as well as insulin sensitivity (29 vs 38.5 or 31%) showed only minor differences in H^2. Familial clustering of insulin levels and abdominal visceral fat was investigated in the HERITAGE family study.[23] These authors found lower within-trait heritabilities of insulin (21%) and visceral fat (42%) than were estimated in our study for HOMA-IR (38.5%) and WC (53.5%). However, a direct comparison of the heritability estimates obtained in the two studies may be problematic owing to differences between the study samples (more

Table 4 Genetic (P_G) and environmental (P_E) correlations (±s.e.) between HOMA-index (HOMA-IR) or WC and single NCEP criteria

	WC			*HOMA-IR*		
	P_G	P_E	n	P_G	P_E	n
WC	—	—	—	+0.73±0.12***	+0.35±0.10**	432
sys.BP	+1.00±0.00***	+0.19±0.10	432	+0.59±0.29*	+0.06±0.10	420
dias.BP	+0.61±0.16***	+0.12±0.11	432	+0.35±0.23	+0.19±0.09	420
Triglycerides	+0.61±0.13***	+0.27±0.10*	432	+0.57±0.21*	+0.47 ±0.09***	402
HDL-cholesterol	−0.40±0.15*	−0.28±0.11*	432	−0.50±0.26*	−0.18±0.13	402
Glucose	+0.44±0.15**	+0.15±0.11	432	—	—	—

Abbreviations: HDL-C, High-density lipoprotein-cholesterol; $_{log}$sys.BP, systolic blood pressure; $_{log}$TG, Triglycerides; WC, waist circumference. *$P<0.05$; **$P<0.01$; ***$P<0.001$.

healthy and younger subjects in the HERITAGE study) and between the parameters chosen to assess insulin resistance or central obesity. Nevertheless, similar to our results, the HERITAGE study also found a higher genetic contribution to central obesity than to insulin resistance. On the other hand, type 2 diabetes, hypertension and cardiovascular disease all become more frequent with age. As these diseases may entail a higher genetic susceptibility *per se*, it is not surprising that the heritability estimates for the different risk factors in our study were higher than, for instance, in the HERITAGE study, where the authors excluded subjects bearing these conditions.[23]

Common familial influence upon insulin resistance, obesity and different MSX component traits

Our comparison of shared familial influences on HOMA-IR and MSX traits with those on WC and MSX partly explains the observed clustering of MSX traits with obesity and insulin resistance. By comparing the common familial (genetic and environmental) background of these two risk factors with blood pressure, HDL-C and triglyceride concentrations, we found that considerable proportions of the variance in these MSX traits is explained by the same genetic influences that partly explain the variance in WC and HOMA-IR, respectively. With the exception of HDL-C, the genetic correlation of NCEP criteria was higher with WC than with HOMA-IR, implicating a considerable genetic relationship between central obesity and elevated blood pressure or TG concentrations. In agreement with the lower within-trait heritability, results from the HERITAGE study showed a considerably lower cross-trait heritability between insulin resistance and abdominal obesity, which was only 6% compared to 53.4% in our study.[23]

The environmental correlation P_E was lower than the genetic correlation P_G for all pairs of traits investigated in our study (Table 4). This finding indicates that the phenotypic correlation between traits might have been primarily due to the pleitropic action of shared genes.

In conclusion, the MSX phenotype was found in our study to exhibit a high variance of component trait combinations. Clustering of MSX traits with insulin resistance and central obesity was partly explained by a low to moderate genetic correlation. Genetic influences on blood pressure and triglyceride concentrations, common with WC, were stronger than those common with HOMA-IR, implying that central obesity might be the major phenotype linking these MSX traits together at the genetic level.

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