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Clustering of insulin resistance, total and central abdominal fat: same genes or same environment?

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Obesity, insulin resistance and disturbed glucose metabolism cluster within the Insulin Resistance Syndrome (IRS). Whether this reflects shared genetic or environmental factors detectable in 'normal' populations (not selected for IRS features) is unknown. This study estimated (i) genetic influences on IRS traits and (ii) shared and specific genetic and environmental factors on the relationships between these traits in healthy female twins. Fasting insulin, glucose, total and central fat were measured in 59 monozygotic (MZ) and 51 dizygotic (DZ) female twin pairs aged (± SD) 52 ± 13 years. Body fat was measured by dual-energy X-ray absorptiometry, insulin resistance and secretion by a modified homeostasis model assessment. Using intraclass correlation coefficients and univariate model-fitting analyses, genetic influences were found in total fat, central fat, insulin resistance, fasting glucose and insulin secretion, with genetic factors explaining 64, 57, 59, 75 and 68% of their variance, respectively, using the latter technique. In matched analysis intra-pair differences in total and central fat related to intra-pair differences in insulin resistance ($r^2 = 0.19$, $P < 0.001$). Multivariate model-fitting showed a close genetic relationship between total and central fat ($r = 0.88$). The genetic correlation between IR and central fat (0.41) was significantly greater than that for total fat (0.24), suggesting that central fat is not only a predictor of, but shares considerable genetic influence with, insulin resistance. In Cholesky analysis, these genetic influences were separate from those shared between central and total fat. In conclusion, both shared and specific genetic factors regulate components of the IRS in healthy females. However, there were discrete genetic influences on β-cell insulin secretion, not shared with other IRS components, suggesting that a separate genetic propensity exists for Type 2 diabetes. These findings suggest we may understand the genetic and environmental influences on IRS from the study of the normal population.

Keywords: twins, insulin, insulin resistance, glucose, genetic epidemiology, fat, visceral fat, abdominal fat, DXA

Introduction

Central abdominal obesity is a pivotal component of the Insulin Resistance Syndrome (IRS)[1–4] and predicts cardiovascular disease,[5–7] Type 2 diabetes mellitus[8,9] and death.[10] Central adiposity relates closely to other metabolic components of IRS, particularly hyperinsulinaemia and insulin resistance,[11–15] which also predict the development of Type 2 diabetes.[1,16]

Genetic factors are implicated in insulin resistance: familial aggregation has been found for hyperinsulinaemia[17–22] and for various measures of insulin resistance.[23–25] Estimates of the heritability of fasting insulin and insulin resistance have ranged between 35 and 60%.[20–23,25] However, these reports have focused on cohorts with a strong genetic susceptibility to Type 2 diabetes (Pima Indians or families with identified probands)[23,25] or have included subjects with diabetes[20–22] and as such may not reflect genetic influences on insulin resistance or the IRS phenotype in the wide 'low incidence' population.

Genetic factors are known to influence total body and central abdominal fat, explaining approximately 50–60% of the population variance.[26] Importantly, we have previously reported the presence of genetic influence on central abdominal fat independent of that on total fat.[26] Genetic factors have also been implicated in determining fasting glucose, explaining 27–39% of population variance.[27,28]

While the clustering of insulin resistance, Type 2 diabetes mellitus, obesity and central adiposity

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within IRS and their close interrelationships, may be due to shared genetic pathways,[29,30] this has not been established in 'normal' populations.

This study aimed to (a) estimate the relative contribution of genetic and environmental factors to several components of the IRS (fasting glucose, insulin resistance, β-cell insulin secretion, central abdominal fat and total fat mass) in healthy, normoglycaemic Caucasian female and (b) determine whether the inter-relationships between these traits are due to shared genetic and/or environmental influences.

Materials and methods

Subjects

Subjects were female twins participating in a study of osteoporosis,[31] volunteers recruited through the National Health and Medical Research Council Twin Registry and a media campaign. The study was approved by the St Vincent's Hospital Research and Ethics Committee. Twin pairs with a history of diabetes (n = 1) or a fasting glucose above 7.0 mmol/L were excluded from the analyses (recommendations of the Expert Committee on the diagnosis and classification of diabetes mellitus from the American Diabetes Association).[32]

Measurements

Total body fat was measured using dual energy X-ray absorptiometry (DXA) (Lunar DPXL, Madison WI, USA). Central abdominal fat mass was determined from the body composition scan. The central fat depot was manually marked out by a single trained technician, as previously described.[26]

The homeostasis model assessment (HOMA) allows estimates of insulin action and β-cell insulin secretion from fasting glucose and insulin values[33] and has been used effectively in large populations.[34] A modification of the HOMA approach was used to reduce misclassification bias without reducing the precision of the estimates.[35]

Fasting insulin and glucose levels were obtained between 8 am and 10 am on the day of DXA scanning, following an overnight fast commencing at 10 pm. Glucose levels were assayed using the hexokinase method (Boehringer Mannheim) and were normally distributed. Subjects with fasting glucose ≥ 7.0 mmol/L were excluded. Fasting insulin levels were measured by an in-house double-antibody radioimmunoassay (intra-assay CV = 6%; inter-assay CV = 7% at 5 mIU/L) and were normally distributed after natural logarithmic transformation.

Analyses

Statistical analyses addressed three issues:

(i) the relationship between body fat, insulin resistance and β-cell insulin secretion;

(ii) the relative contribution of genetic and environmental factors to the variation of each trait; and

(iii) the relative contribution of genes and environment to the covariance between total and central abdominal fat and insulin resistance

As total fat and central fat were highly related, central fat was adjusted for total fat in a simple linear regression model and the standardised residual was used as adjusted central fat. Insulin resistance normally distributed after natural logarithmic transformation. All data were corrected for age in a linear regression model, where each trait was fitted against age. Studentised residuals from this model were used as adjusted values.

The associations between total and central abdominal fat and insulin resistance were assessed and lipid variables were assessed in two ways. First, MZ twin pair analysis was used to examine the influence of higher insulin resistance on other components of the IRS, controlling for genetic factors. Within each MZ pair, twins were designated as having the higher or lower insulin resistance and other variables compared by paired t tests. Second, linear regression analysis was used to examine whether the inter-relationships between IRS traits are present in normal populations not selected for any of these traits. As such, the data were examined in matched and unmatched analyses. In the matched analysis (consisting of both paired MZ and DZ data) intrapair differences in insulin resistance were regressed against intrapair differences in total and central fat measurements and the iteratively weighted least squares method[36] used to estimate the model parameters. In the unmatched (cross-sectional) analysis, each twin within a pair was treated as an individual. Multiple regression analysis was applied with total and adjusted central fat as independent variables and insulin resistance as the dependent variable.

As phenotypic variables in twins are not independent, the estimated error terms of regression parameters tend to be correlated within pairs, with underestimation of standard errors and overstated statistical significance. To overcome this, generalised least square method[36] was used with iterative adjustment for the correlation of errors within pairs. In both matched and unmatched analyses assessment of model adequacy and verification of regression assumptions were based on residual analysis.

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To estimate the relative contribution of genetic and environmental factors to each trait, the data were analysed in two steps: examination of resemblance and estimation of heritability. Resemblance for a variable trait was assessed for MZ and DZ pairs separately by the intraclass correlation coefficient. In this method the total variation of a trait was partitioned into two sources: between pairs (B) and within pairs (W). The correlation was estimated as the difference between the two sources over their sum, ie (B – W)/(B + W). Test for significant difference between the coefficients of MZ and DZ pairs was based on the modified Fisher's z transformation procedure.[37]

The data were further analysed by using the classical twin model,[38] with the aim of partitioning total variance of a trait into genetic and environmental components. Genetic variance may be due to additive (A) or dominant (D) genetic factors; environmental variance to environmental factors shared by twin pairs (C) or specific to each twin (E). Additive genetic factors are the effects of genes taken singly and added over multiple loci; dominant genetic factors represent genetic interaction with loci. This model assumes:

(i) perfect correlation of additive genetic factors and dominant genetic factors in MZ pairs, whilst DZ pairs share half of additive and one quarter of dominant genetic effects;

(ii) shared environmental effects are perfectly correlated in MZ and DZ pairs;

(iii) there are negligible effects of assortive mating, epistasis, negligible genotype–environmental interaction

The amount of variance due to A, C, D and E are derived from variance–covariance matrices subject to analyses specified by five possible models incorporating different combinations of these factors (CE, AE, ACE and ADE). The maximum likelihood method was used to estimate model parameters. The most parsimonious model was selected based on the following criteria: non-significant χ^2 goodness-of-fit test and the minimum value of the Akaike Information Criterion (AIC) which is equal to χ^2 minus twice the number of degrees of freedom. The index of heritability was obtained as the square of parameter A from the most parsimonious model of best fit.

To test the hypothesis that the same set of genes or environmental factors is involved in the clustering of IRS traits, the contribution of genetic and environmental factors to the covariances between traits was examined in three different models: the independent pathway, common pathway and Cholesky models.[39] Only the Cholesky model provided an adequate data fit and was adopted as the best representation of the data. The Cholesky model can test whether there are separate sets of genes for each variable trait, or whether there is at least one set of genes which affects all variable traits simultaneously. If specific genetic factors regulate the traits independently, the genetic correlation between traits is close to zero (or non-significant). If shared genetic factors exist, the genetic correlation is close to 1 (or significant).

The relative contribution of genetic and environmental factors to the genetic and environmental variance of related traits was estimated using the Cholesky model of decomposition.[39] Factor effects were fitted to the variance–covariance matrices. All model parameters were estimated by the method of maximum likelihood using the Mx program.[40]

Results

Two hundred and twenty female twins (59 MZ and 51 DZ pairs) were studied, aged 52 ± 13 years (mean ± SD). The two zygosities were similar for all variables measured (Table 1). Increasing age was significantly related to increased central fat ($r = 0.35$, $P < 0.0001$). Fasting insulin was related to total fat ($r = 0.45$, $P < 0.0001$), central abdominal fat ($r = 0.52$, $P < 0.0001$) and glucose ($r = 0.36$, $P < 0.0001$). Insulin resistance (estimated by modified HOMA) was related to total fat ($r = 0.37$, $P = 0.001$) and central abdominal fat ($r = 0.47$, $P < 0.0001$). Beta-cell secretion (estimated by modified HOMA) was related to total fat ($r = 0.15$, $P = 0.03$) and central abdominal fat ($r = 0.16$, $P = 0.02$).

Table 1 Clinical and metabolic characteristics of healthy normoglycaemic female twin subjects

Variable	Monozygotic twins (n = 59 pairs)	Dizygotic twins (n = 51 pairs)
Age (yrs)	53.7 (14.1)	50.4 (13.2)
Weight (kg)	64.8 (10.3)	66.4 (11.9)
Height (cm)	160.9 (6.0)	161.7 (7.3)
BMI (kg/m^2)	25.2 (4.3)	25.4 (4.0)
Total fat (kg)	25.2 (8.6)	25.4 (8.8)
Central fat (kg)	1.44 (0.58)	1.49 (0.55)
Glucose (mmol/L)	4.8 (0.6)	4.9 (0.7)
Insulin (mIU/L)	7.4 (5.2)	7.1 (4.7)
Ln Insulin Resistance (HOMA′)[a]	3.96 (0.15)	3.98 (0.17)
β-cell Insulin Secretion (HOMA′)[a]	1.37 (0.17)	1.34 (0.19)

Values are mean ± SD; MZ and DZ means were not significantly different, tested by generalised least square method with iterative adjustment for the correlation within pairs; [a]HOMA′: Modified Homeostasis Model Assessment

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Associations between insulin resistance and total and central abdominal fat

(i) Monozygotic twin pair analysis Within genetically identical twin pairs, the twin with the higher insulin resistance had significantly higher total body fat, central abdominal fat mass and fasting glucose insulin, with similar β-cell insulin secretion (Table 2).

(ii) Regression analyses The relationships between insulin resistance and body fat were further examined in matched (both MZ and DZ twin pairs) and unmatched (cross-sectional) analyses (Table 3). In the matched analysis, the intra-pair difference in total fat related to the intra-pair difference in central abdominal fat ($r = 0.95$; $P < 0.0001$), thus central abdominal fat adjusted for total fat was used in the multiple regression model. In this model, both total body fat mass and adjusted central abdominal fat mass were significantly associated with insulin resistance, collectively accounting for 19% of its total variance (Table 3). Each standard deviation of total and central fat mass was associated with 2.4 and 1.8 unit increases in insulin resistance. Similarly in the unmatched analysis, both total fat and adjusted central abdominal fat were independently associated with insulin resistance (Table 3). This highlights that even in normal, unselected populations, previously demonstrated inter-relationships between IRS traits are found.

Table 2 Monozygotic twin pair analysis in healthy normoglycaemic female twins: total body fat, central abdominal fat and fasting glucose are higher in the twin with the higher insulin resistance

	Higher IR twin	Lower IR twin	Intra-pair difference (±SD)
Insulin resistance (IR)	4.01	3.90[c]	0.11±0.01[d]
Total body fat mass (kg)	26.91	23.41[b]	3.50±0.85[d]
Central abdominal fat mass (kg)	1.57	1.32[b]	0.26±0.06[d]
Fasting glucose (mmol/L)	4.9	4.6[c]	0.3± 0.04[d]
Beta-cell insulin secretion	0.32	0.30	0.02±0.01

n = 59 monozygotic pairs; insulin resistance and beta-cell insulin secretion estimated using a modified Homeostasis Model Assessment; [a]High IR twins vs low IR twin, using paired t-test: [b]$P<0.0005$, [c]$P<0.0001$; [d]Significantly different from 0 at $P<0.01$ level

Univariate genetic analysis

Monozygotic twins were more similar for total fat, central abdominal fat, insulin resistance and fasting glucose as intraclass correlation coefficients for total fat, central fat, fasting glucose, insulin resistance and β-cell insulin secretion were significantly higher in MZ than DZ pairs (Table 4). Intraclass correlations for fasting insulin, however, were similar in MZ and DZ pairs (Table 4). Models containing additive genetic and specific environmental factors fitted the data best for all parameters, except for fasting insulin where a model containing shared and specific environmental factors provided the best fit (Table 5). From estimates in these models, 64% and 57% of total variance of total fat and central fat, respectively, was attributable to additive genetic factors. Significant genetic influences on fasting glucose (heritability 75%), insulin resistance (59%) and beta cell secretion (68%) were also found (Table 4). For all traits, there was no significant effect of dominant genetic (D) factors, as the goodness-of-fit of models containing D were not significantly better than those with ACE or AE (data not shown).

Multivariate genetic analysis

Multivariate model-fitting was used to determine whether the inter-relationships between insulin resistance, total and central abdominal fat were attributable to shared genetic or environmental factors. The genetic correlation between total and central abdominal fat was 0.88, comparable to the environmental correlation ($r = 0.91$) (Table 6). Significant genetic ($r = 0.41$) and environmental ($r = 0.52$) correlations were found between central abdominal fat and insulin resistance, which explain

Table 3 Relationships between insulin resistance and total fat and central abdominal fat in healthy normoglycaemic female twins: results from matched (MZ and DZ pairs) and unmatched (cross-sectional) multiple regression analyses

Design	Independent variable	Slope (SE)	Standardised slope	Standard deviation[a]	R^2
Matched (paired) analysis					
Intra-pair difference	Total fat	0.007 (0.002)[c]	0.387	8.65	
	Central fat[b]	0.041 (0.014)[c]	0.257	0.62	0.19
Unmatched analysis					
	Total fat	0.006 (0.001)[c]	0.320	8.71	
	Central fat[b]	0.051 (0.009)[c]	0.331	1.00	0.23

[a]Standard deviation of the measurement (in the intra-pair analysis SDs are in kg; in the cross-sectional analysis total fat SD is in kg); [b]Central fat adjusted for total fat; [c]Statistically significantly different from zero at $P<0.001$ level

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Table 4 Age-adjusted intra-class correlation coefficients for total fat, central fat, fasting glucose and insulin, insulin resistance and β-cell insulin secretion in healthy normoglycaemic female twins with estimation of heritability[a]

	Intraclass correlation coefficients ±SE		Heritability[a]
	rMZ	rDZ	
Total fat	0.66±0.08[b]	0.29±0.13	0.64
Central fat	0.58±0.09[b]	0.31±0.13	0.57
Fasting insulin	0.30±0.12	0.37±0.14	–
Fasting glucose	0.70±0.07[b]	0.28±0.13	0.75
Insulin resistance[c]	0.53±0.10[b]	0.28±0.13	0.59
Beta-cell secretion[c]	0.64±0.08[b]	0.36±0.13	0.68

[a]Heritability estimates derived from the genetic variance component of the model-of-best-fit from univariate model-fitting; [b]rMZ is significantly greater than rDZ based on the modified Fisher's z transformation procedure;[36] [c]insulin resistance and β-cell secretion were estimated using a modified Homeostasis Model Assessment

the close interrelationship between central abdominal fat and insulin resistance (Table 6). No significant genetic correlation between total fat and insulin resistance was found, however, a significant environmental correlation was present (r = 0.49) (Table 6). There was no genetic relationship between β-cell secretion and total or central abdominal fat (data not shown).

Preliminary univariate analyses suggested a model with A and E factors fit the data adequately. Independent pathway and common pathway models did not fit the data (χ^2 = 146.8, P < 0.0001 and χ^2 = 157.4, P < 0.0001, respectively). Therefore a Cholesky model of decomposition including additive genetic effects (A) and non-shared environmental effects (E) was fitted to the variance–covariance matrices. The degree of genetic and environmental sharing is graphically presented in Figure 1. Genetic factors shared with total fat accounted for approximately 80% (42.2/53.2) of the genetic variance of central abdominal fat (Table 7). A separate genetic factor also influenced central abdominal fat (accounting for 18% of the genetic variance) and was shared with insulin resistance (Table 7, Figure 1). Additional specific genetic factors not shared with total or central abdominal fat also influenced insulin resistance (Table 7).

Discussion

In populations at high risk for Type 2 diabetes genetic factors regulate fasting insulin levels and insulin resistance.[17–19,24] In an unselected population of healthy weight female twins, we have previously reported that genetic factors are the major determinant of one IRS component, central abdominal fat.[26] In high risk and affected populations there is evidence of common genetic pathways for the clustering of insulin resistance, total and central adiposity.[29,30] In populations not selected for IRS features, evidence is sparse: one study found genetic effects on different components of the IRS but lacked any evaluation for genetic sharing.[41] Importantly, the nature of the genetic relationships between these traits has only been examined using surrogate estimates of body fatness.

This is the first study to examine the genetic architecture of components of the IRS in a population of healthy, normoglycaemic female twins utilising direct measures of total body and central abdominal adiposity. We found that genetic factors strongly influence insulin resistance, total and central fat, fasting glucose and β-cell insulin secretion, explaining the majority of the population variance of these traits in a normal population. This study also found evidence for a shared genetic basis for the interrelationships between insulin resistance and central abdominal fat in healthy Caucasian females, but no evidence for sharing with genetic or environmental factors governing β-cell insulin secretion.

Our finding of genetic effects on insulin resistance in a 'normal' population, concurs with findings in studies of 'high-risk' populations. The heritability estimate for insulin resistance in this study cannot be directly compared with prior reports, however, due to differences in populations studied, statistical methodology (twin vs family studies) and differences in the measures of insulin resistance.

This study confirms strong shared genetic influences on central abdominal and total body fat mass, together with independent genetic effects on central abdominal fat, as previously reported in healthy postmenopausal English females.[26] Fasting glucose and β-cell insulin secretion are also strongly genetically regulated; these factors may be involved in regulation of stimulation–secretion coupling in the β-cell. Family studies of normoglycaemic subjects have previously found genetic effects on fasting glucose, reporting lesser heritability estimates however (27–39%).[27,28] Our measure of β-cell insulin secretion using a modified Homeostasis Model Assessment has some limitations, but more invasive techniques such as the intravenous glucose tolerance test with frequent sampling are difficult in the larger study cohorts suitable for genetic epidemiological techniques.

This study also dissected the genetic structure of the observed covariance between aspects of IRS the into shared or specific genetic and environmental influences, using direct measures of body fat, in contrast to previous studies. Moreover, bias and inaccuracy were minimised by exclusion of subjects with fasting glucose exceeding 7.0 mmol/L, as the

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Table 5 Contribution of genetic and environmental factors to total fat mass, central abdominal fat mass, fasting insulin, insulin resistance, fasting glucose and insulin secretion in healthy normoglycaemic female twins: a summary of univariate model-fitting analyses

Parameter	Model	Squared standardised coefficients[a]			Adjusted for age		
		A	C	E	χ^2	P value	AIC
Total fat	ACE	0.639	0.000	0.361	3.72	0.29	–2.28
	AE[b]	0.640	–	0.360	3.72	0.45	–4.28
	CE	–	0.480	0.520	10.33	0.04	2.33
Central fat	ACE	0.574	0.000	0.426	2.24	0.52	–3.76
	AE[b]	0.574	–	0.426	2.24	0.69	–0.74
	CE	–	0.435	0.565	7.26	0.12	–0.74
Ln Insulin	ACE	0.064	0.265	0.671	2.42	0.49	–3.53
	AE	0.368	–	0.632	3.65	0.46	–4.35
	CE[b]	–	0.313	0.687	2.56	0.63	–5.44
Insulin resistance	ACE	0.486	0.094	0.420	6.25	0.10	0.25
	AE[b]	0.589	–	0.411	6.29	0.18	–1.71
	CE	–	0.450	0.550	11.14	0.03	3.14
Fasting glucose	ACE	0.756	0.000	0.244	4.20	0.24	–1.80
	AE[b]	0.756	–	0.244	4.20	0.38	–3.80
	CE	–	0.525	0.475	18.91	0.001	10.91
Beta-cell secretion	ACE	0.526	0.144	0.330	5.10	0.16	–0.89
	AE[b]	0.678	–	0.322	5.46	0.24	–2.54
	CE	–	0.542	0.458	9.83	0.04	1.83

[a]Squared standardised coefficients derived from unadjusted data; [b]Model of best fit; A: additive genetics; C: common environment; E: specific environment; Insulin resistance and beta-cell secretion were estimated using a modified Homeostasis Model Assessment

Table 6 Genetic and environmental correlations between insulin resistance, total fat and central abdominal fat in healthy normoglycaemic female twins

	Total fat	Central fat	Insulin resistance
Total fat		0.88[a]	0.24
Central fat	0.91[a]		0.41[a]
Insulin resistance	0.49[a]	0.52[a]	

Values in upper diagonal (bold) are genetic correlations, whilst values in lower diagonal are environmental correlations; data presented are based on age-adjusted analysis; insulin resistance estimated by a modified Homeostasis Model Assessment; [a]Significantly different from zero at P<0.01 level

presence of even mild hyperglycaemia (and 'glucotoxicity') may alter the relationships between the β-cell secretion and insulin resistance. The study demonstrated that the close relationship between total body and central abdominal fat is due, in part, to a degree of genetic sharing. On the other hand, the relationship between total body fat and insulin resistance can be attributed to shared environmental influences. The relationship between insulin resistance and central abdominal fat is in part due to genetic sharing (consistent with other reports, albeit using surrogate measures of body fat). Genetic relationships have been reported between fasting insulin and waist circumference[30] and a single common genetic factor underlying the IRS was suggested in another study relying solely on body mass index without any central abdominal fat

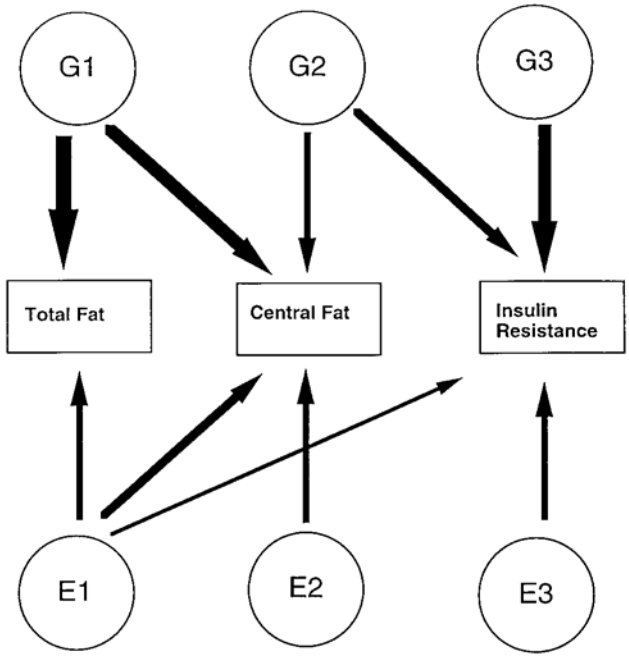

Figure 1 Cholesky factor decomposition. The path diagram depicts the shared and specific factors for genetic and environmental sources of covariance for total fat, central abdominal fat and insulin resistance. There are three genetic factors (G1, G2, G3) and three environmental factors (E1, E2, E3). Arrows represent 10% or more contribution of the factor to the variance of the corresponding trait

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Table 7 Contribution of shared and specific genetic and environmental factors to the variance of total fat, central abdominal fat and insulin resistance in healthy normoglycaemic female twins: Cholesky factor analysis

	Total fat	Central fat	Insulin resistance
Genetic factors			
G1	62.5	42.2	4.3
G2		11.0	11.5
G3			47.6
H^2	62.5	53.2	63.4
Environmental factors			
E1	37.5	36.1	13.7
E2		9.7	4.8
E3			18.1
E^2	37.5	46.8	36.6

G1, G2 and G3 are genetic factors; H^2 is the proportion of the total population variance of each trait attributable to genetic factors. E1, E2 and E3 are environmental factors; E^2 is the proportion of the total population variance of each trait attributable to environmental factors. Insulin resistance estimated by a modified Homeostasis Model Assessment; data presented are based on age-adjusted analysis

assessment.[42] The current study is unique in decomposing specific genetic influences for central abdominal fat (with no impact on total fat) and for insulin resistance (with no impact on central abdominal fat), further clarifying the genetic relationships between body fat and insulin resistance. These results accord with a study reporting that insulin resistance in the offspring of diabetic probands was not solely accounted for by increased total or central abdominal adiposity.[43] Our findings suggest greater complexity to the genetic basis of the IRS (made possible by use of a more detailed and specific phenotype) and that genetic influences on IRS parameters can be studied in normal populations not selected for IRS traits.

Finally, this study found that shared environmental factors also contribute to the close interrelationships between insulin resistance, total and central abdominal fat, consistent with clinical experience, for example, physical activity[44] (which is known to influence insulin resistance, total and central fat mass[45]) and the effect of smoking on total and central fat.[46]

In summary, in healthy normoglycaemic females the clustering of insulin resistance and total and central adiposity is explained by shared and specific genetic factors. Whereas central abdominal and total body fat are influenced by shared and specific genetic factors, this study detects a genetic factor shared between central abdominal fat and insulin resistance which is exclusive of those influencing total fat. Shared environment appears to be responsible for the relationship between total fat and insulin resistance. These findings suggest we can understand the genetic and environmental influences on IRS from the study of the normal population.

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