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**Assessing genetic and environmental influences on epicardial and abdominal adipose tissue quantities: a classical twin study**

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**Conflict of interest**

Gyorgy Jermendy received a research grant from New Horizons Programme of the European Foundation for the Study of Diabetes (EFSD). Szilard Voros is a shareholder in Global Genomics Group, LLC, and receives salary from Global Genomics Group, LLC.). The study was supported by the National Research, Development and Innovation Office of Hungary (NKFIA; NVKP-16-1-2016-0017). No other potential conflict of interest was reported.

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Heritability of different fat compartments

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**BACKGROUND/OBJECTIVE:** Various adipose tissue compartments play an important role in the development of cardiometabolic diseases. The quantity of different fat compartments is influenced by genetic and environmental factors. The aim of our study was to evaluate the magnitude of genetic and environmental effects on epicardial, subcutaneous and visceral adipose tissue (EAT, SAT and VAT) quantities in a cohort of adult twin pairs.

**SUBJECTS/METHODS:** In this cross-sectional study we investigated adult twins (57 monozygotic [MZ] and 33 dizygotic [DZ] same-gender twin pairs; 180 twin subjects). We measured EAT volume using ECG-gated native CT scan of the heart, and abdominal SAT and VAT areas were quantified between the third and fourth lumbar vertebra on native CT images. We calculated genetic and environmental impact on the size of various adipose tissue compartments by analyzing co-twin correlations in MZ and DZ pairs separately, furthermore by using genetic structural equation models.

**RESULTS:** In co-twin analysis, MZ twins had stronger correlations than DZ twins for EAT ( $r_{MZ} = 0.81$ ,  $r_{DZ} = 0.32$ ), similarly to SAT and VAT quantities ( $r_{MZ} = 0.80$ ,  $r_{DZ} = 0.68$  and  $r_{MZ} = 0.79$ ,  $r_{DZ} = 0.48$ , respectively). In multi-trait model fitting analysis, the overall contribution of genetic factors to EAT, SAT and VAT volumes were 80%, 78% and 70% whereas environmental factors were 20%, 22% and 30%, respectively. Common pathway model analyses indicated that none of the EAT, SAT and VAT phenotypes was independent of the other two.

**CONCLUSIONS:** Genetic factors have substantial influence, while environmental factors have only a modest impact on EAT volume, abdominal SAT and VAT quantities. There is a considerable amount of common genetic background influencing the quantities of all three adipose tissue compartments.

**INTRODUCTION**

Obesity, especially an increase in abdominal visceral adipose tissue quantity may play an important role in the development of cardiometabolic disease.<sup>1, 2, 3</sup> During the last couple of years, a special attention was paid to another fat compartment, namely the epicardial adipose tissue (EAT), as its proximity to the myocardium and coronary arteries might also be of pathophysiological importance.<sup>4, 5, 6</sup> Recently, it has been suggested that EAT is a source of inflammatory mediators affecting the myocardium and coronary arteries, and clinical studies suggested that EAT – through paracrine and vasocrine effects – might have an impact on the development and progression of coronary atherosclerosis.<sup>6</sup>

Fat compartments may differ in embryogenetic origin, physiological and pathophysiological functions.<sup>7</sup> Their accumulation leads to local or systemic adiposity and increase of their quantity is influenced by genetic and environmental factors. Classical twin studies compare monozygotic (MZ) and dizygotic (DZ) same-gender twin pairs to help to evaluate the degree of genetic and environmental influences on body composition.<sup>8, 9</sup> Earlier studies demonstrated a predominant genetic effect on body mass index (BMI) and on central abdominal obesity as measured by dual-energy x-ray absorptiometry.<sup>10, 11, 12</sup> In the Framingham Heart Study Offspring and Third-Generation Study cohorts it has been shown by computed tomography (CT) imaging that abdominal subcutaneous adipose tissue (SAT) and visceral adipose tissue (VAT) quantities have a heritability of 57% and 36%, respectively.<sup>13</sup> However, no data are available whether EAT compartment quantity depends predominantly on genetic or environmental factors. Furthermore, data regarding the heritability of abdominal adipose tissue compartment sizes are scarce and the findings are based on family studies and on measurement methods with limited accuracy.

Therefore, we sought to evaluate the magnitude of genetic and environmental impact on the EAT quantity in a cohort of adult twin pairs using standardized measurements by CT imaging. In addition, we sought to assess the degree of common genetic background of EAT, abdominal SAT and VAT quantities in the same twin pairs.

## PATIENTS AND METHODS

### *Study population*

This study was a prospective, single-center, classical twin study involving MZ and DZ same-gender twin subjects of self-reported Caucasian ethnicity. The investigation was part of the BUDAPEST-GLOBAL (Burden of atherosclerotic plaques study in twins - Genetic Loci and the Burden of Atherosclerotic Lesions) clinical study; the participants had been co-enrolled with the large, international, multicenter Genetic Loci and the Burden of Atherosclerotic Lesions (GLOBAL) clinical study (<http://www.ClinicalTrials.gov>: NCT01738828).<sup>14</sup> Detailed study description and enrollment criteria were published previously.<sup>15</sup> The total study population consisted of 202 adult twin subjects (101 twin pairs) who were recruited from the Hungarian Twin Registry<sup>16</sup>, of whom 122 were MZ and 80 were same-gender DZ twin subjects. All subjects provided written informed consent. The study was approved by the National Scientific and Ethics Committee (institutional review board number: ETT TUKEB 58401/2012/EKU [828/PI/12], Amendment-1: 12292/2013/EKU [165/2013] and was carried out according to the principles stated in the Declaration of Helsinki.

In the current study we included 180 twin subjects (90 twin pairs; 63.3% female; 57 MZ and 33 DZ same-gender twin pairs); we excluded 11 twin pairs from the original cohort.

Twin pairs were excluded when either of them had inadequate image quality or insufficient anatomical CT coverage of any of the investigated fat compartments.

#### *Computed tomography (CT) scanning protocol*

Every subject underwent a non-contrast enhanced CT scan of the heart using a 256-slice CT scanner (Philips Brilliance iCT, Philips Healthcare, Best, The Netherlands; 120 kVp with tube current of 20 to 50 mAs depending on BMI, gantry rotation time 270 ms). Furthermore, a single 5 mm thick slice of the abdomen was acquired at the level of the L3/L4 vertebrae for assessing abdominal SAT and VAT (120 kVp, 200 mAs, gantry rotation time 270 ms).<sup>17</sup> Further details of the study protocol were reported previously.<sup>15</sup> Importantly, the native CT of the heart and abdomen resulted in a small ( $0.70 \pm 0.16$  mSv) radiation dose.

#### *Evaluation of EAT, abdominal SAT and VAT compartments*

Semi-automated volumetric EAT quantification was performed on a dedicated workstation (CT-viewer, Intellispace Portal Client, Philips Healthcare, Best, The Netherlands). The pericardial layer was manually traced in every slice of the cardiac CT dataset between the level of the right pulmonary artery and the diaphragm. Adipose tissue attenuation was defined between -195 and -45 Hounsfield Units (HU). EAT quantity was assessed with the volumetric reconstruction of any fat tissue between the myocardial surface and the visceral layer of the pericardium. Abdominal fat compartments were identified and their areas were quantified on the abdominal cross sectional images using a semi-automated software (FAT assessment, Extended Brilliance Workspace, Philips, Best, The Netherlands).<sup>18</sup> The measurements of different fat compartments are illustrated by **Figure 1** and **Figure 2**.

#### *Anthropometric data, medical history and laboratory analysis*

Basic anthropometric parameters (weight, height, waist circumference) of every subject were recorded. Brachial blood pressure was measured prior to the CT exam. Questionnaires regarding past medical history and current lifestyle, smoking and dietary habits were recorded for every participant. Fasting peripheral blood draw was performed before the CT examination.

Laboratory parameters were investigated by using standard methods in certified laboratory.

### *Statistical analysis*

Continuous variables are expressed as mean  $\pm$  standard deviation (SD), whereas categorical variables are expressed as numbers and percentages. MZ and DZ twins were compared using Student's t-tests and Chi-square tests. Correlations were calculated using Pearson correlation coefficients. Intra-reader and inter-reader reproducibility of CT based fat measurements was assessed by two experienced readers in the field (ALJ: 5 years, ZDD: 3 years of experience) based on 10 randomly selected MZ twin pairs and 10 randomly selected DZ twin pairs images using the intra-class correlation coefficient. Coefficient values are interpreted as: 1.00 – 0.81: excellent; 0.80 - 0.61: good; 0.60 - 0.41: moderate; 0.40 - 0.21: fair; 0.20 – 0.00: poor.<sup>19</sup> Descriptive statistics, correlations and reproducibility measurements were calculated using IBM SPSS Statistics version 23 (IBM, Armonk, NY, USA).

Heritability was assessed in two steps; first, co-twin correlations between the siblings were analysed in MZ and DZ pairs separately. Next, genetic structural equation models were used to model the magnitude of genetic and environmental factors influencing the different fat compartments. All phenotypes are caused by genetic and environmental factors. MZ twins share nearly 100% of their genome, while DZ twins only share half. Genetic similarity is caused by additive genetic components (A). While MZ twins share almost 100% of A, DZ twins only share 50% of A. Environmental components are grouped as common factors (C)



i.e. same early childhood, education in the same school, living in the same town, etc. which equally effect the siblings, and unique factors (E) such as specific eating and drinking habits, different physical activity and lifestyle, etc. which cause differences within families. In our study, both MZ and DZ twins shared 100% of their C factors and none of their E factors. Covariance between the siblings can be decomposed into A, C and E latent variables using genetic structural equation models.<sup>20</sup> The likelihood ratio test was used to assess the fit of submodels compared to the full model. If the fit did not decrease significantly by removing one of the parameters, then the more parsimonious submodel was selected. Furthermore, multivariate genetic models can be used to further decompose the results of the heritability estimates into common and unique genetic and environmental factors. Common genetic factors refer to genes that are driving the heritability of all three fat components simultaneously ( $A_c$ ), while common ( $C_c$ ) and unique ( $E_c$ ) environmental factors refer to circumstantial factors that affect the heritability of all three phenotypes. The remaining variance then can be attributed to genetic ( $A_s$ ), common ( $C_s$ ) and unique ( $E_s$ ) environmental factors specific of a given phenotype, which are independent of the other phenotypes. Therefore, the heritability of the fat compartments was decomposed to common ( $A_c$ ,  $C_c$ ,  $E_c$ ) and specific ( $A_s$ ,  $C_s$ ,  $E_s$ ) genetic and environmental factors. Independent and common pathway models were used to find the most parsimonious model best describing our data. All calculations were adjusted for age and sex. Log likelihood-based 95% confidence intervals (CI) were calculated for all estimated parameters. All calculations were performed using R version 3.2.5.<sup>21</sup> Twin modelling was performed using OpenMx version 2.5.2.<sup>22</sup> A  $p$  value lower than 0.05 was considered significant.

## RESULTS

Overall, 180 twins (57 MZ twin pairs, 33 DZ twin pairs) were included from the BUDAPEST-GLOBAL study. Our study population represents a middle-aged, slightly overweight Caucasian population (**Table 1**).

Intra-reader agreement showed excellent reproducibility for all CT based fat measurements ( $ICC_{EAT} = 0.99$ ;  $ICC_{SAT} = 0.98$ ;  $ICC_{VAT} = 0.99$ ). We also found excellent reproducibility regarding inter-reader variability ( $ICC_{EAT} = 0.98$ ;  $ICC_{SAT} = 0.99$ ;  $ICC_{VAT} = 0.99$ ).

Co-twin correlations between the siblings showed that for all three parameters, MZ twins have stronger correlations than DZ twins, suggesting prominent genetic effects (EAT:  $r_{MZ} = 0.81$ ,  $r_{DZ} = 0.32$ ; SAT:  $r_{MZ} = 0.80$ ,  $r_{DZ} = 0.68$ ; VAT:  $r_{MZ} = 0.79$ ,  $r_{DZ} = 0.48$ ).

For all three fat compartments AE model excluding common environmental factors proved to be best fitting [EAT: A: 73% (95% CI = 56%-83%), E: 27% (95% CI = 16-44%); SAT: A: 77% (95% CI = 64%-85%), E: 23% (95% CI = 15%-35%); VAT: 56% (95% CI = 35%-71%), E: 44% (95% CI = 29%-65%)]. Detailed results can be found in **Supplementary information Table 1**.

In multi-trait model fitting analysis (for details see **Supplementary information**), overall contribution of genetic factors to EAT, SAT and VAT was 80%, 78% and 70%, whereas that of environmental factors was 20%, 22% and 30%, respectively (**Table 2**). Results of the multi-variate analysis suggest that a common latent phenotype is associated with the tissue compartments investigated. Based on our results, 98% (95% CI = 77%-100%) of VAT heritability can be accounted by this common latent phenotype which also effects SAT and EAT heritability. This common latent phenotype accounts for 26% (95% CI = 13%-42%) of SAT and 49% (95% CI = 32%-72%) of EAT heritability. This common latent phenotype is influenced by genetics in 71% (95% CI = 54%-81%) and environmental effects

in 29% (95% CI = 19%-46%). Accordingly, the proportion of common and specific genetic and environmental factors contributing to the adipose tissue quantities may differ from each other, for example in case of EAT heritability is caused by 35% common genetic, 45% specific genetic, 14% common environmental, and 6% specific environmental factors. The stronger relationship between VAT and EAT, as compared to between VAT and SAT was reflected by the correlation values between these adipose tissue compartments (0.761 and 0.415, respectively, both  $p=0.01$ ). The path diagram of the model is illustrated by **Figure 3**, and detailed contribution of common and specific genetic and environmental factors for all three fat compartments can be found in **Table 2**. In addition, our results suggest that none of the phenotypes are independent of the other two (**Table 3**), thus the heritability of EAT or SAT or VAT phenotype is associated with the remaining two phenotypes (see **Supplementary information**).

## DISCUSSION

In this classical twin study, we demonstrated that genetics have substantial, while environmental factors have only a modest influence on EAT, SAT and VAT volumes. Our findings show that common and specific genetic effects both play an important role in developing these phenotypes. None of the phenotypic appearance of EAT, SAT and VAT proved to be completely independent of the other two. To the best of our knowledge, this is the first clinical study to evaluate the genetic and environmental dependence of EAT quantity and assessed simultaneously the joint heritability of EAT, SAT and VAT in twin pairs.

In the total cohort, SAT quantity was higher (217.9 mm<sup>2</sup>) than VAT quantity (156.6 mm<sup>2</sup>), however their ratio was similar to other previously published data.<sup>18</sup> The mean volume

of EAT (97.1 cm<sup>3</sup>) was in the range of middle-aged healthy subjects.<sup>6</sup> It is of note, that SAT and VAT was planimetrically, whereas EAT was volumetrically measured in our cohort. Importantly, there was no significant difference in the assessed fat volumes comparing MZ to DZ subjects.

We used advanced statistical methods to decipher the ratio of genetic and environmental effects on EAT, SAT and VAT quantities. In addition to single trait analysis, we performed multi-trait models to explore the complex interactions of multiple quantitative traits. This method has been recently used to dissect genetic mechanisms underlying complex diseases such as obesity.<sup>23, 24</sup> We demonstrated that common genetic effects predominated over common environmental influences on the latent phenotype (71% versus 29%). On the other hand, while the latent phenotype markedly influenced VAT (98%), its effect was minimal on SAT (26%) and its impact on EAT was intermediate (49%). This relationship was reflected by the stronger phenotypic correlation between VAT and EAT, than between VAT and SAT. Latent phenotype could be related to BMI, obesity or total fat depot. However, the co-linearity between BMI (which represents all fat compartments) and specific adipose tissue quantities precludes the independent analysis of BMI in our multi-trait models. Regarding the whole distribution of variance of CT-based fat measurements it seems that the phenotypic appearance of EAT, SAT and VAT quantities are driven by common and specific genetic and environmental factors (**Figure 1, Table 2**). Finally, in Model 6-8 analyses (**Supplementary information**) we found that none of the fat compartments' heritability was independent of the other two. Taken together, an interplay between common and specific genetic effects and environmental influences may be hypothesized, but the magnitude of their relative impact on different adipose tissue compartments varies.

We demonstrated a relatively strong genetic dependence of EAT, which has not been described previously. The genetic dependence of anthropometric parameters (weight, height,

BMI) has been well documented in former twin studies.<sup>25, 26, 27</sup> Heritability of different ectopic fat compartments (hepatic lipid accumulation) was also investigated in twins, and in this case environmental factors predominated over genetic influences.<sup>28</sup> Hence, heritability of different adipose tissue compartments and that of ectopic fats may vary.

The presence of strong genetic predisposition does not automatically translate to the development of clinical disease phenotype. Considering this fact, early and continuous preventive efforts should be implemented. In case of obesity, intervention should be initiated as early as possible and all modifiable risk factors should be addressed with diet, physical activity and behavioral interventions starting as early as preschool age.<sup>29, 30</sup> Importantly, weight loss and exercise training may reduce EAT and abdominal adipose tissue volumes in adult subjects with obesity.<sup>31, 32</sup>

Non-contrast enhanced CT scan was used to evaluate quantities of various fat compartments, although other non-invasive methods (echocardiography, magnetic resonance imaging [MRI]) have been used previously. Echocardiography has several disadvantages including poor reproducibility and high dependence of investigator's experience.<sup>33</sup> MRI provides accurate area measurements but is not as widely available in routine clinical practice as CT. Furthermore, it is more expensive and has poorer spatial resolution compared to CT.<sup>34</sup> The CT-based volumetric measurements in our study were highly reproducible. In addition, it is important to note that to the best of our knowledge, our study represents the first investigation using CT phenotyping of fat compartments in twins.

Our results have to be interpreted within the context of their limitations. The sample size was modest but comparable to that of other classical twin studies.<sup>35, 36</sup> The zygosity in our twin cohort was classified according to validated questionnaires. Nevertheless, this method is widely accepted in clinical studies.<sup>37</sup> Our results were derived from a healthy twin Caucasian

population, therefore, the generalizability of our findings is limited. There was a small albeit significant difference in age of MZ versus DZ pairs, however all parameters were age- and gender-adjusted in our genetic analyses. Nevertheless, an over-estimation of heritability might occur if twin-twin correlations would decline with age in DZ pairs. Importantly, this age difference between the MZ and DZ pairs was small, therefore no substantial effect can be expected. The strengths of our study are worth mentioning. The study was performed at an institution with vast experience in cardiac CT imaging and in conducting twin studies. Furthermore, all CT scans were performed by the same trained investigators (ALJ, PMH). The reliability of CT scan measurements proved to be excellent. The use of structural equation model for evaluating heritability was not restricted to univariate analysis only. The predominant genetic effect on EAT, SAT and VAT was demonstrated not only in single trait but in multi-trait analyses; the latter is considered a more robust method.

In summary, results of this classical twin study indicate that genetic effects predominate over environmental influences in contributing to the phenotype of EAT quantity, similarly to abdominal SAT and VAT volumes. Furthermore, common and specific genetic effects may be involved in the heritability of all three adipose tissue quantities. Our results should stimulate further studies, especially epigenetic investigations in this field.

#### **Conflict of interest**

Gyorgy Jermendy received a research grant from New Horizons Programme of the European Foundation for the Study of Diabetes (EFSD). Szilard Voros is a shareholder in Global Genomics Group, LLC, and receives salary from Global Genomics Group, LLC.). The study was supported by the National Research, Development and Innovation Office of Hungary (NKFI; NVKP-16-1-2016-0017). No other potential conflict of interest was reported.

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**Figure legends****Figure 1. Measurement of epicardial adipose tissue quantity**

- a) Axial CT image of the heart, the pericardial layer is outlined with blue, the epicardial fat is marked with orange colour.
- b) Volume rendered reconstruction of the epicardial fat volume.

**Figure 2. Abdominal subcutaneous and visceral adipose tissue compartments in monozygotic twin pairs**

- a-b) Axial images of the abdomen at the level of the L3/L4 vertebrae. Subcutaneous fat (orange colour) is predominant in this monozygotic twin pair.
- c-d) Axial images of the abdomen at the level of the L3/L4 vertebrae. Visceral fat (blue colour) is more prominent in this monozygotic twin pair.

**Figure 3. Proportion of phenotypic variance of CT-based fat measurements**

Image shows squared standardized path coefficients of best fitting model 5. The common pathway model calculating with only common genetic and environmental factors proved to be the best. Residual variances were decomposed to specific genetic and environmental factors. In case of VAT only specific environmental factors were considered.  $A_c$ : common additive genetic factor,  $A_s$ : specific additive genetic factor  $E_c$ : common environmental factor,  $E_s$ : specific environmental factor, EAT: epicardial adipose tissue, SAT: subcutaneous adipose tissue, VAT: visceral adipose tissue

**Table 1. Demographics, clinical-laboratory data and quantity of fat compartments measured in twins**

Variables	Total <i>n</i> = 180		MZ <i>n</i> = 114		DZ <i>n</i> = 66		<i>p</i>
<b>Demographic, basic hemodynamic characteristics and medical history</b>							
Female (n, %)	114	(63.3%)	68	(59.6%)	46	(69.7%)	0.52
Age (years)	55.8	± 9.6	54.3	± 9.7	58.4	± 8.6	<0.01
Height (cm)	166.4	± 9.6	166.7	± 10.1	165.9	± 8.8	0.63
Weight (kg)	77.2	± 17.5	77.6	± 18.3	76.4	± 16.2	0.67
BMI (kg/m <sup>2</sup> )	27.7	± 5.2	27.7	± 5.1	27.8	± 5.4	0.98
Waist (cm)	96.9	± 14.2	96.8	± 14.6	96.9	± 13.6	0.96
Hypertension (n, %)	76	(42.2%)	42	(36.8%)	34	(51.5%)	0.84
Diabetes mellitus (n, %)	15	(8.3%)	9	(7.9%)	6	(9.1%)	0.89
Dyslipidemia (n, %)	80	(44.4%)	46	(40.4%)	34	(51.5%)	0.48
Current smoker (n, %)	28	(15.6%)	17	(14.9%)	11	(16.7%)	0.88
<b>Laboratory parameters</b>							
Fasting blood glucose (mmol/L)	5.35	± 1.34	5.31	± 1.48	5.41	± 1.06	0.66
HbA1c (%)	5.5	± 0.9	5.5	± 0.9	5.3	± 0.9	0.13
Serum total cholesterol (mmol/L)	5.56	± 1.09	5.63	± 1.11	5.42	± 1.07	0.21
Serum LDL-cholesterol (mmol/L)	3.47	± 0.99	3.52	± 1.04	3.37	± 0.89	0.32
Serum HDL-cholesterol (mmol/L)	1.62	± 0.39	1.61	± 0.41	1.65	± 0.35	0.56
Triglycerides (mmol/L)	1.57	± 1.09	1.62	± 1.23	1.47	± 0.77	0.36
Serum creatinine (μmol/L)	80.0	± 9.0	80.0	± 9.0	80.0	± 9.0	0.41
Serum CRP (mg/L)	2.9	± 4.5	2.7	± 2.9	3.3	± 6.5	0.37
Serum leptin (ng/mL)	18.4	± 17.9	16.2	± 13.5	22.4	± 23.6	0.06
<b>CT-based fat measurements</b>							
Epicardial fat (mm <sup>3</sup> )	97.1	± 45.4	94.9	± 43.2	101.0	± 49.2	0.38
Subcutaneous fat (mm <sup>2</sup> )	217.9	± 97.4	218.6	± 90.1	216.7	± 109.4	0.90
Visceral fat (mm <sup>2</sup> )	156.6	± 87.9	158.9	± 89.2	152.6	± 86.0	0.64

Continuous variables are presented as mean ± SD, while categorical as n (%). P values represent two-sided p values for independent t-tests done between the monozygotic (MZ) and dizygotic (DZ) twin groups. BMI: body mass index, CRP: C-reactive protein, HbA1c: hemoglobinA1c, HDL: high-density lipoprotein, LDL: low-density lipoprotein.

**Table 2. Proportion of common and specific genetic and environmental factors contributing to the phenotypic quantity of CT based fat measurements**

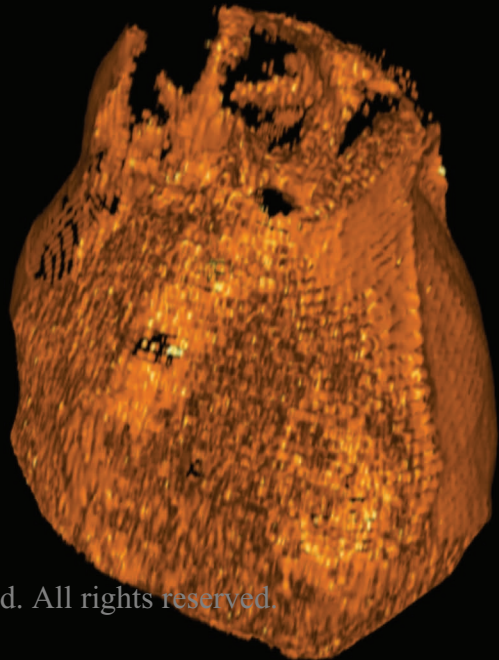
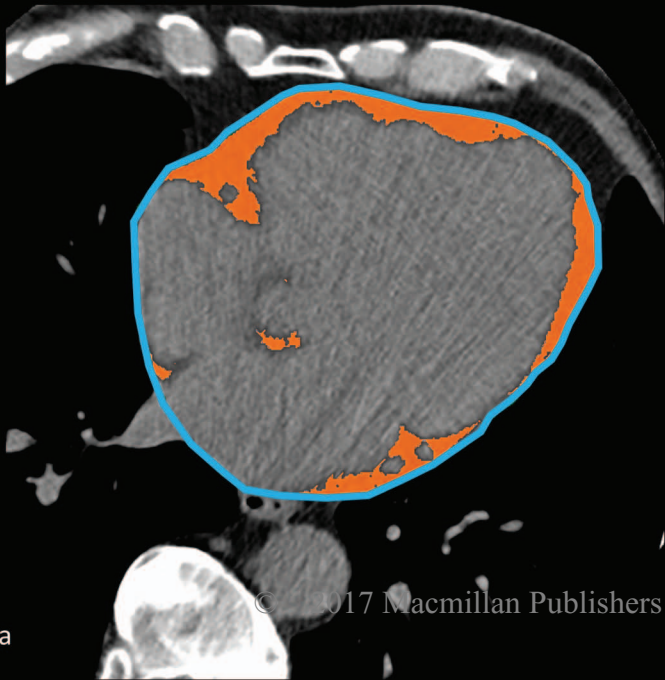
<b>Variable</b>	<b>Epicardial fat</b>	<b>Subcutaneous fat</b>	<b>Visceral fat</b>
<b><i>Common genetic and environmental factors</i></b>			
genetic factors ( $A_C$ )	35%	18%	70%
environmental factors ( $E_C$ )	14%	8%	28%
<b><i>Specific genetic and environmental factors</i></b>			
genetic factors ( $A_S$ )	45%	60%	0%
environmental factors ( $E_S$ )	6%	14%	2%
<b><i>Overall contribution of genetic and environmental factors</i></b>			
genetic factors (A)	80%	78%	70%
environmental factors (E)	20%	22%	30%



**Table 3. Detailed model information regarding multi-trait classical twin models of CT-based fat measurements**

Model number	Model name	Estimated parameters	Model -2LL	Model df	AIC	BIC	Difference to Saturated model -2LL	Difference to Saturated model df	Difference to Saturated model p	Difference to Full model -2LL	Difference to Full model -df	Difference to Full model p
1	Cholesky ACE	24	1047.78	516	15.78	-1274.12	31.38	30	0.40			
2	Cholesky AE	18	1050.47	522	6.47	-1298.43	34.08	36	0.56	2.69	6	0.85
3	Independent pathway AE	18	1050.54	522	6.54	-1298.36	34.15	36	0.56	2.76	6	0.84
4	Common pathway AE 1	17	1052.57	524	4.57	-1305.33	36.18	38	0.55	4.79	8	0.78
5	Common pathway AE 2	16	1052.57	525	2.57	-1309.83	36.18	39	0.60	4.79	9	0.85
6	Common pathway AE SAT-VAT	16	1189.06	525	139.06	-1173.34	172.67	39	9.66*10 <sup>-19</sup>	141.28	9	5.61*10 <sup>-26</sup>
7	Common pathway AE VAT-EAT	16	1110.53	525	60.53	-1251.86	94.14	39	1.86*10 <sup>-6</sup>	62.75	9	3.94*10 <sup>-10</sup>
8	Common pathway AE SAT-EAT	16	1219.96	525	169.95	-1142.44	203.57	39	3.81*10 <sup>-24</sup>	172.18	9	2.17*10 <sup>-32</sup>

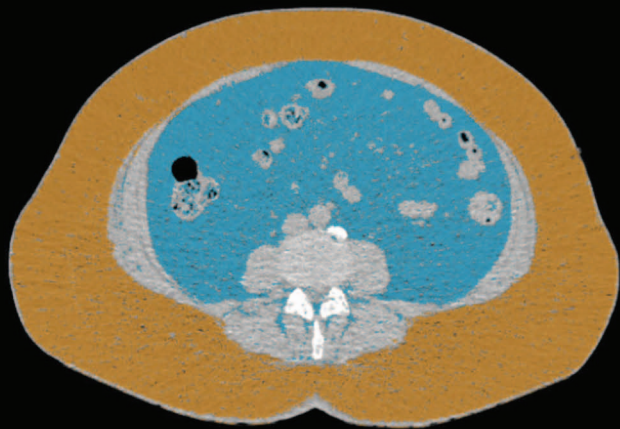
Detailed results of calculated multi-trait structure equation models. -2LL: minus 2 log-likelihood value; AIC: Akaike information criterion; BIC: Bayesian information criterion; df: degrees of freedom  
SAT: subcutaneous adipose tissue; VAT: visceral adipose tissue; EAT: epicardial adipose tissue



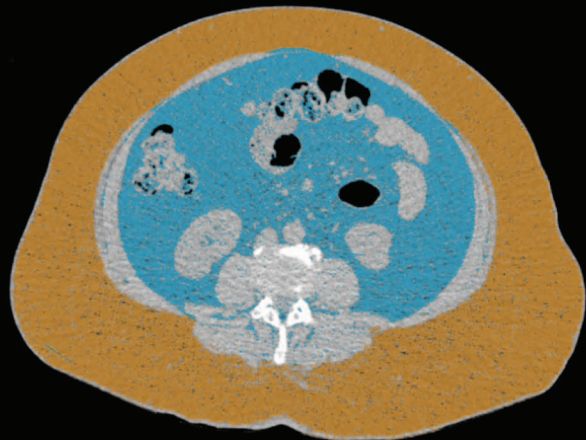
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a

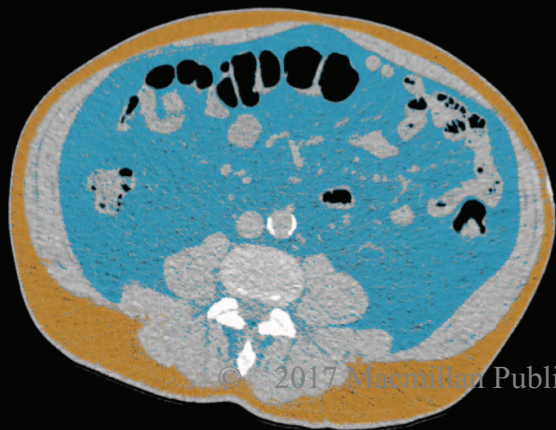
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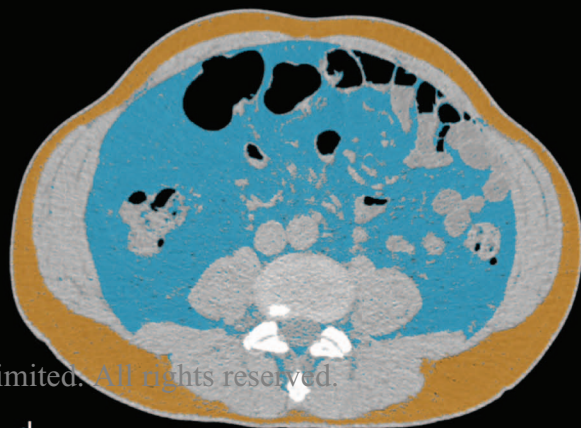
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b



c



d

