Original Article
EPIDEMIOLOGY/GENETICS

Obesity

Genetic Determination of Body Fat Distribution and the Attributive Influence on Metabolism

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Objective: Genome-wide association studies (GWAS) have identified single-nucleotide polymorphisms (SNPs) associated with estimates of body fat distribution. Using predefined risk allele scores, the correlation of these scores with precisely quantified body fat distribution assessed by magnetic resonance (MR) imaging techniques and with metabolic traits was investigated.
Methods: Data from 4,944 MR scans from 915 subjects of European ancestry were analyzed. Body fat distribution was determined by MR imaging and liver fat content by ^{1}H-MR spectroscopy. All subjects underwent a five-point 75-g oral glucose tolerance test. A total of 65 SNPs with reported genome-wide significant associations regarding estimates of body fat distribution were genotyped. Four genetic risk scores were created by summation of risk alleles.
Results: A higher allelic load of waist-to-hip ratio SNPs was associated with lower insulin sensitivity, higher postchallenge glucose levels, and more visceral and less subcutaneous fat mass.
Conclusions: GWAS-derived polymorphisms estimating body fat distribution are associated with distinct patterns of body fat distribution exactly measured by MR. Only the risk score associated with the waist-to-hip ratio in GWAS showed an unhealthy pattern of metabolism and body fat distribution. This score might be useful for predicting diseases associated with genetically determined, unhealthy obesity.

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Introduction

The prevalence of obesity is increasing globally, leading to substantial metabolic and cardiovascular morbidity (1,2). However, obesity itself does not necessarily cause cardiovascular morbidity, while accumulation of fat in specific depots does (3,4). In particular, increased visceral adipose tissue (VAT) mass and an elevated liver fat content represent profound cardiometabolic risk factors and have been found to be associated with increased mortality independent of overall obesity (5-7). In contrast, subcutaneous adipose tissue (SCAT) mass is less consistently associated with cardiovascular morbidity and is therefore believed to cause less adverse effects (8). Furthermore, organ-attributed fat depots such as perivascular fat (9,10), renal sinus fat (11), pericardial fat (12), and ectopic lipid deposition in the liver (13) could each have a specific impact on metabolic disease and organ function (14,15).

There are several methods for quantification of adipose tissue within the body. Body fat distribution is easily estimated by clinical anthropometric measurements, including waist circumference, hip circumference, and waist-to-hip ratio (WHR). Because these measurements are relatively imprecise and influenced by several confounders, the gold standard for determination of body composition is tomographic imaging. Different fat depots can be accurately distinguished, and their volumes can be calculated with appropriately weighted magnetic resonance imaging (MRI) or computed tomography (16-18).

The pathogenesis of obesity is mainly driven by complex interactions between environmental and genetic determinants. Heritability estimates for body fat distribution range from 36% to 56% for VAT and 42% to 57% for SCAT (19,20). However, fat distribution follows a complex polygenic inheritance. With genome-wide association studies (GWAS), hundreds of thousands of common genetic variants have

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been investigated. This unbiased approach searches for statistically significant associations of single-nucleotide polymorphisms (SNPs) with anthropometric traits that allow estimation of body fat distribution. Using data from several meta-analyses, the Genetic Investigation of Anthropometric Traits consortium identified 1 and 14 WHR-associated loci, respectively, reaching genome-wide significance (21,22). More recently, 36 additional SNPs were found to be associated with WHR in a large-scale meta-analysis, mostly involving participants of European ancestry (23). Many of the discovered loci showed sexual dimorphisms, with larger effects in females for most of the polymorphisms (23).

Some of the SNPs associated with anthropometric traits also are associated with fasting insulin or adiponectin levels. Pathway analyses have suggested adipogenesis, angiogenesis, transcriptional regulation, and insulin resistance as potential underlying mechanisms (23). Nevertheless, the biology behind the identified variants that associate with estimates of body fat distribution remains largely unknown.

We investigated how variants associated with anthropometric estimates in GWAS correlate with precisely quantified body fat distribution and ectopic lipid deposition in the liver as assessed by MRI and ^{1}H-MR spectroscopy. We also analyzed the associations of SNPs with metabolic traits determined during the oral glucose tolerance test (OGTT).

Methods

Participants

We retrospectively analyzed data from 2,774 individuals of European ancestry who were enrolled in the Tübingen Family, Tübingen Lifestyle Intervention, and Nutritional Prevention of Diabetes studies. Of these, 915 subjects underwent MRI measurements. Some of these individuals participated in an ongoing prospective follow-up study with repeated visits every 2 to 4 years. Including all follow-up visits that were not within 1 year after a lifestyle intervention, a total of 4,825 participant visits for metabolic traits and 4,944 participant visits for MR phenotypes were available. Details of the study population are presented in Supporting Information Table S1. Informed written consent was obtained from all subjects, and the local Ethics Committee of the Medical Faculty of the Eberhard Karls University of Tübingen, Germany, approved the protocol.

Measurements and analytical procedures

Height, weight, waist circumference, and hip circumference were measured at every visit. Waist circumference was measured at the narrowest point of the waist between the hip and rib bones in the standing, undressed participant after light exhalation. Hip circumference was measured at the widest gluteal protuberance. A stretch-resistant tape measure was wrapped around the hip and waist line parallel to the ground.

Whole-body fat percentage was measured by bioelectrical impedance (BIA-101; RJL Systems, Detroit, Michigan). Body fat distribution variables, i.e., total adipose tissue, VAT, and SCAT, were determined by whole-body T1-weighted MRI and liver fat content by volume selective ^{1}H-MR spectroscopy (16,24). To estimate the relative proportion of body fat depots, volumes were measured in liters and adjusted for the total adipose tissue volume.

All participants underwent a standardized 75-g OGTT with sampling at fasting and 30, 60, 90, and 120 minutes after the OGTT was started. The glucose-oxidase method was used to determine plasma glucose (Yellow Springs Instrument Co., Inc., Yellow Springs, Ohio). Plasma insulin was measured by a chemiluminescence assay for ADVIA Centaur (Siemens Medical Solutions, Erlangen, Germany). The insulin sensitivity index was calculated as proposed by Matsuda and DeFronzo (25).

Genotyping

We selected 65 SNPs that showed genome-wide significant associations with estimated body fat distribution in GWAS (Supporting Information Table S2). DNA was extracted from peripheral blood by cell lysis, protein precipitation, and a washing protocol. All SNPs were genotyped using the MassARRAY platform (Sequenom, San Diego, California). Four SNPs (DCST2, MSC, NKX2-6, PDXDC1) were excluded from the analysis, as they were not in Hardy-Weinberg equilibrium ($P < 0.05$).

Calculations and statistical analyses

Two approaches were employed to detect genotype-phenotype associations. In the first approach, we used linear regression models for cross-sectional data, taking the first measurements when multiple measurements were available. In the second approach, taking repeated measurements into account, we employed linear mixed models, as proposed by Fan et al. (26). In brief, single measurement variation and correlations between multiple measurements were modeled with a variance-covariance structure based on the elapsed time between measurements. All models were adjusted for sex and age. Metabolic traits were additionally adjusted for BMI.

In addition to separate tests for each SNP, genetic risk scores (GRS) were calculated based on the aggregate number of risk alleles associated with the given trait. We clustered the 65 genotyped SNPs into groups according to their discovery phenotype. Four scores were created: the hip circumference score (including SNPs associated with hip circumference and hip circumference adjusted for BMI), the waist circumference score (including SNPs associated with waist circumference and waist circumference adjusted for BMI), the WHR score, and a score with SNPs associated with WHR adjusted for BMI (Figure 1). Missing SNPs in the GRS were imputed from mean genotype values. As a sensitivity analysis, we then performed a GRS analysis including only participants with complete genotyping (Supporting Information Tables S3 and S4).

For the individual SNPs, $P < 0.0008$ was considered statistically significant, and for the scores, $P < 0.05$ was considered statistically significant. Because the tested phenotypes were predefined according to our biological hypothesis and several of the traits are correlated, we did not perform further correction on the number of investigated phenotypes. All P values are shown uncorrected throughout the paper.

Calculations were performed with R version 3.2.2 (The R Foundation, https://www.r-project.org/) and JMP 12 (SAS Institute, Cary, North Carolina).

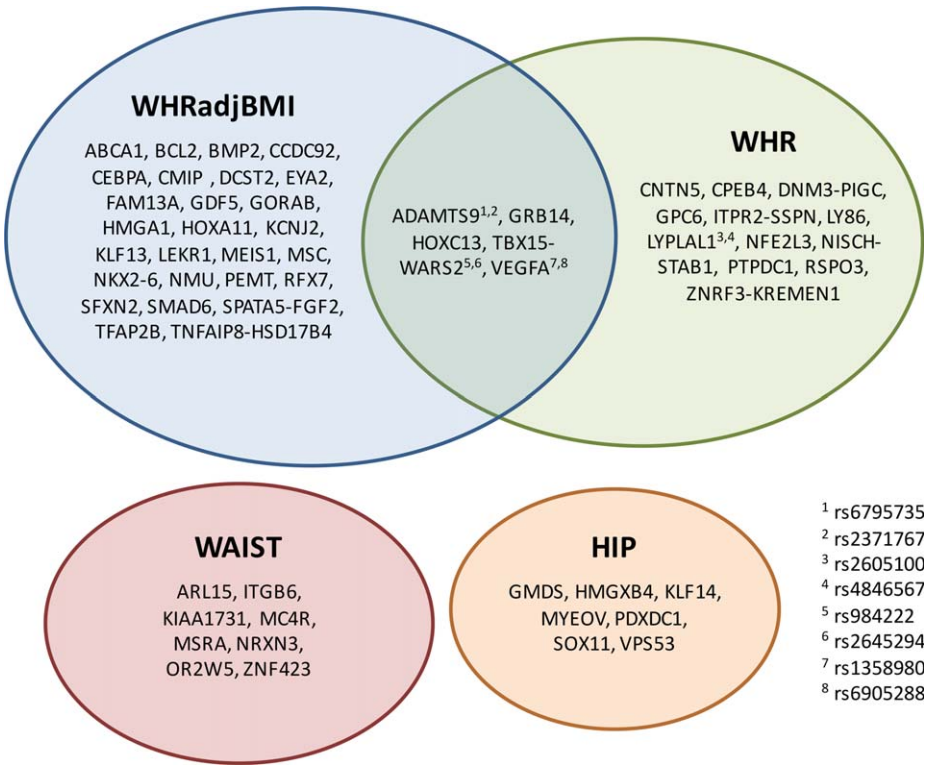

Figure 1 Assignment of single-nucleotide polymorphisms (SNPs) to genetic risk scores. The four genetic risk scores are depicted as circles containing the names of the assigned SNPs, each represented by the name of the nearest gene. Each depicted SNP was assigned to at least one of the four scores. Five SNPs were concomitantly assigned to the WHR-adj-BMI and the WHR scores. Abbreviations: WAIST, waist circumference score; HIP, hip circumference score; WHR, waist-to-hip ratio; WHR-adj-BMI, WHR adjusted for BMI.

Results

First, each SNP was evaluated independently. For the risk alleles described in the GWAS, no statistically significant association with waist circumference, hip circumference, WHR, or MR-derived body fat distribution was detected after correction for multiple testing (all $P \geq 6 \times 10^{-5}$) (Supporting Information Table S5).

We next created genetic risk scores through summation of the risk alleles (Figure 1). Based on the respective GWAS results, we computed four distinct scores: hip circumference score (hip score), waist circumference score (waist score), WHR score, and WHR adjusted for BMI score (WHR-adj-BMI score).

We next assessed the association of these scores with MR-derived body fat distribution from 915 individual participants (cross-sectional) and from 4,944 MRI measurements using a mixed-model approach on repeated measurements. We analyzed these scores' relationships with glucose and lipid metabolism (Tables 1 and 2).

The waist score showed a significant correlation only with liver fat content ($P = 0.006$ in the cross-sectional analysis, $P = 0.01$ in the mixed model). A higher number of waist circumference risk alleles were associated with elevated liver fat content. Further evaluation revealed an interaction with gender ($P = 0.02$) (Table S6); the association of the waist score was present in females but not in males (Figure 2). The waist score was not associated with insulin sensitivity or any of the other investigated metabolic traits in females or males.

For the hip score, an association with lower SCAT mass was detected (cross-sectional $P = 0.04$, mixed model $P = 0.04$). Again, no significant associations of the hip score with metabolic traits were present.

The WHR score was associated with more VAT mass (cross-sectional $P = 0.01$, mixed model $P = 0.03$) and less SCAT mass (cross-sectional $P = 0.02$, mixed model $P = 0.1$), resulting in an elevated VAT-to-SCAT ratio (cross sectional $P = 0.001$, mixed model $P = 0.0009$). The WHR score was also associated with lower insulin sensitivity (cross-sectional $P = 0.05$, mixed model $P = 0.002$), and with higher fasting (cross-sectional $P = 0.01$, mixed model $P = 0.01$) and postchallenge glucose levels during the OGTT (cross-sectional $P = 0.2$, mixed model $P = 0.0004$). It also was associated with increased cholesterol (cross-sectional $P = 0.04$, mixed model $P = 0.4$) and decreased high-density lipoprotein cholesterol levels (cross-sectional $P = 0.6$, mixed model $P = 0.003$).

In terms of body fat distribution, the WHR-adj-BMI score was associated with higher WHR adjusted for BMI (cross-sectional $P = 0.01$, mixed model $P = 0.1$). An inverse association of the WHR-adj-BMI score with SCAT mass was detected ($P = 0.005$, mixed model $P = 0.01$), while a positive association was seen for the VAT-to-SCAT

TABLE 1 Cross-sectional results

Genetic risk score	Trait	Estimate ± SE	β	*P* value
Waist SNPs	Waist circumference (cm)	0.208 ± 0.267	0.026	0.4
	VAT (L)	−0.033 ± 0.027	−0.024	0.2
	Liver fat content (%)	0.378 ± 0.136	0.092	**0.006**
	SCAT (L)	−0.047 ± 0.044	−0.015	0.3
	VAT-to-SCAT ratio	−0.001 ± 0.003	−0.008	0.7
	OGTT-derived insulin sensitivity index (AU)	0.056 ± 0.117	0.015	0.6
	Fasting glucose (mmol/L)	−0.004 ± 0.011	−0.011	0.7
	Glucose 120 min (mmol/L)	0.064 ± 0.038	0.058	0.1
	Cholesterol (mg/dL)	0.329 ± 0.722	0.016	0.6
	LDL cholesterol (mg/dL)	0.967 ± 0.654	0.052	0.1
	HDL cholesterol (mg/dL)	−0.264 ± 0.232	−0.036	0.3
	Fasting triglycerides (mg/dL)	−2.543 ± 1.649	−0.053	0.1
Hip SNPs	Hip circumference (cm)	−0.164 ± 0.355	−0.017	0.6
	VAT (L)	−0.002 ± 0.040	−0.001	1.0
	Liver fat content (%)	0.308 ± 0.199	0.052	0.1
	SCAT (L)	−0.130 ± 0.064	−0.028	**0.04**
	VAT-to-SCAT ratio	0.004 ± 0.004	0.021	0.4
	OGTT-derived insulin sensitivity index (AU)	−0.239 ± 0.171	−0.045	0.2
	Fasting glucose (mmol/L)	0.018 ± 0.017	0.036	0.3
	Glucose 120 min (mmol/L)	0.106 ± 0.056	0.066	0.1
	Cholesterol (mg/dL)	−1.138 ± 1.061	−0.037	0.3
	LDL cholesterol (mg/dL)	−0.746 ± 0.962	−0.027	0.4
	HDL cholesterol (mg/dL)	0.111 ± 0.342	0.010	0.7
	Fasting triglycerides (mg/dL)	−2.671 ± 2.427	−0.038	0.3
WHR SNPs	WHR	0.001 ± 0.001	0.041	0.1
	VAT (L)	0.045 ± 0.018	0.048	**0.01**
	Liver fat content (%)	0.011 ± 0.092	0.004	0.9
	SCAT (L)	−0.066 ± 0.029	−0.031	**0.02**
	VAT-to-SCAT ratio	0.006 ± 0.002	0.074	**0.001**
	OGTT-derived insulin sensitivity index (AU)	−0.157 ± 0.078	−0.064	0.05
	Fasting glucose (mmol/L)	0.019 ± 0.008	0.081	**0.01**
	Glucose 120 min (mmol/L)	0.031 ± 0.026	0.042	0.2
	Cholesterol (mg/dL)	0.976 ± 0.486	0.069	**0.04**
	LDL cholesterol (mg/dL)	0.506 ± 0.442	0.040	0.3
	HDL cholesterol (mg/dL)	−0.081 ± 0.157	−0.016	0.6
	Fasting triglycerides (mg/dL)	1.487 ± 1.113	0.046	0.2
WHR-adj-BMI SNPs	WHR-adj-BMI	0.002 ± 0.001	0.059	**0.01**
	VAT (L)	0.028 ± 0.015	0.037	0.1
	Liver fat content (%)	0.095 ± 0.076	0.042	0.2
	SCAT (L)	−0.06 ± 0.024	−0.039	**0.005**
	VAT-to-SCAT ratio	0.004 ± 0.002	0.050	**0.03**
	OGTT-derived insulin sensitivity index (AU)	−0.064 ± 0.065	−0.031	0.3
	Fasting glucose (mmol/L)	0.009 ± 0.006	0.045	0.2
	Glucose 120 min (mmol/L)	0.014 ± 0.021	0.023	0.5
	Cholesterol (mg/dL)	0.515 ± 0.404	0.044	0.2
	LDL cholesterol (mg/dL)	0.479 ± 0.367	0.046	0.2
	HDL cholesterol (mg/dL)	0.002 ± 0.130	0.001	1.0
	Fasting triglycerides (mg/dL)	−0.373 ± 0.926	−0.014	0.7

Statistically significant *P* values are in bold.
Abbreviations: AU, arbitrary units; HDL, high-density lipoprotein, LDL, low-density lipoprotein; OGTT, oral glucose tolerance test; SCAT, subcutaneous adipose tissue; SE, standard error; SNP, single-nucleotide polymorphism; VAT, visceral adipose tissue; WHR, waist-to-hip ratio; WHR-adj-BMI, WHR adjusted for BMI.

TABLE 2 Repeated measures results (mixed model)

Genetic risk score	Trait	Estimate ± SE	β	*P* value
Waist SNPs	Waist circumference (cm)	0.040 ± 0.405	0.002	0.9
	VAT (L)	−0.012 ± 0.024	−0.009	0.6
	Liver fat content (%)	0.270 ± 0.106	0.072	**0.01**
	SCAT (L)	−0.062 ± 0.038	−0.020	0.1
	VAT-to-SCAT ratio	0.002 ± 0.003	0.013	0.5
	OGTT-derived insulin sensitivity index (AU)	0.020 ± 0.075	0.004	0.8
	Fasting glucose (mmol/L)	−0.001 ± 0.007	−0.003	0.8
	Glucose 120 min (mmol/L)	0.004 ± 0.019	0.004	0.8
	Cholesterol (mg/dL)	0.025 ± 0.376	0.001	0.9
	LDL cholesterol (mg/dL)	0.345 ± 0.330	0.019	0.3
	HDL cholesterol (mg/dL)	0.017 ± 0.127	0.002	0.9
	Fasting triglycerides (mg/dL)	−1.609 ± 1.361	−0.024	0.2
Hip SNPs	Hip circumference (cm)	0.262 ± 0.419	0.012	0.5
	VAT (L)	−0.013 ± 0.035	−0.007	0.7
	Liver fat content (%)	0.167 ± 0.154	0.030	0.3
	SCAT (L)	−0.112 ± 0.056	−0.025	**0.04**
	VAT-to-SCAT ratio	0.004 ± 0.004	0.021	0.3
	OGTT-derived insulin sensitivity index (AU)	0.112 ± 0.113	0.015	0.3
	Fasting glucose (mmol/L)	−0.007 ± 0.010	−0.012	0.5
	Glucose 120 min (mmol/L)	0.015 ± 0.028	0.009	0.6
	Cholesterol (mg/dL)	−0.396 ± 0.566	−0.012	0.5
	LDL cholesterol (mg/dL)	−0.495 ± 0.497	−0.018	0.3
	HDL cholesterol (mg/dL)	0.283 ± 0.191	0.025	0.1
	Fasting triglycerides (mg/dL)	−1.870 ± 2.052	−0.018	0.4
WHR SNPs	WHR	0.001 ± 0.009	0.001	0.9
	VAT (L)	0.035 ± 0.016	0.040	**0.03**
	Liver fat content (%)	0.041 ± 0.070	0.017	0.6
	SCAT (L)	−0.045 ± 0.025	−0.023	0.1
	VAT-to-SCAT ratio	0.005 ± 0.002	0.067	**0.0009**
	OGTT-derived insulin sensitivity index (AU)	−0.146 ± 0.046	−0.049	**0.002**
	Fasting glucose (mmol/L)	0.011 ± 0.004	0.043	**0.01**
	Glucose 120 min (mmol/L)	0.041 ± 0.012	0.059	**0.0004**
	Cholesterol (mg/dL)	0.181 ± 0.233	0.014	0.4
	LDL cholesterol (mg/dL)	0.264 ± 0.204	0.023	0.2
	HDL cholesterol (mg/dL)	−0.236 ± 0.079	−0.050	**0.003**
	Fasting triglycerides (mg/dL)	0.690 ± 0.844	0.016	0.4
WHR-adj-BMI SNPs	WHR adjusted for BMI	0.014 ± 0.008	0.029	0.1
	VAT (L)	0.024 ± 0.013	0.031	0.1
	Liver fat content (%)	0.060 ± 0.059	0.029	0.3
	SCAT (L)	−0.054 ± 0.021	−0.031	**0.01**
	VAT-to-SCAT ratio	0.003 ± 0.001	0.042	**0.03**
	OGTT-derived insulin sensitivity index (AU)	−0.077 ± 0.042	−0.028	0.1
	Fasting glucose (mmol/L)	0.005 ± 0.004	0.022	0.2
	Glucose 120 min (mmol/L)	0.016 ± 0.010	0.026	0.1
	Cholesterol (mg/dL)	0.226 ± 0.211	0.019	0.3
	LDL cholesterol (mg/dL)	0.241 ± 0.185	0.023	0.2
	HDL cholesterol (mg/dL)	−0.102 ± 0.071	−0.024	0.2
	Fasting triglycerides (mg/dL)	0.832 ± 0.765	0.022	0.3

Statistically significant *P* values are in bold.
Abbreviations: AU, arbitrary units; HDL, high-density lipoprotein; LDL, low-density lipoprotein; OGTT, oral glucose tolerance test; SCAT, subcutaneous adipose tissue; SE, standard error; SNP, single-nucleotide polymorphism; VAT, visceral adipose tissue; WHR, waist-to-hip ratio; WHR-adj-BMI, WHR adjusted for BMI.

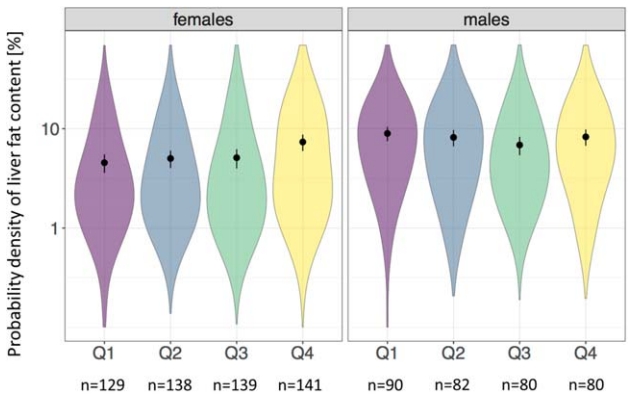

Figure 2 Liver fat content in males and females of the cohort. Violin plots showing the distribution of liver fat content (%, log scale) stratified by sex and quartiles of genetic waist circumference score. The number of participants per quartile is presented below the figure.

ratio (cross-sectional $P = 0.03$, mixed model $P = 0.03$). For the other fat depots, no significant associations were present. The score also did not associate with any of the analyzed metabolic traits.

In addition, MR-derived body fat distribution traits correlated with the OGTT-derived insulin sensitivity index. VAT mass ($P = 3 \times 10^{-22}$), liver fat content ($P = 1 \times 10^{-24}$), and the VAT-to-SCAT ratio ($P = 4 \times 10^{-16}$), all adjusted for total adipose tissue mass, gender, and age, were negatively associated with insulin sensitivity, whereas adjusted SCAT mass was positively associated with insulin sensitivity ($P = 8 \times 10^{-15}$) (Supporting Information Table S7).

Discussion

When investigating genetic variants associated with estimates of body fat distribution in GWAS (21-23), we identified differential associations of these SNPs with MR-derived body fat distribution. While none of the investigated SNPs showed statistically significant correlations with fat distribution patterns when tested alone (after correction for multiple testing), the summation of alleles into genetic risk scores indeed revealed such associations. For most of the scores, those associations were not as expected from the GWAS results. In particular, the genetic risk scores composed of SNPs associated with waist circumference and WHR adjusted for BMI were not statistically significantly associated with the expected fat compartment, i.e., VAT volume. On the other hand, increased liver fat content was detected in subjects with a higher waist circumference score. Of note, elevated liver fat content is known to result in a larger liver volume (27,28) that might then be detected as a larger waist circumference. Despite this, while increased liver fat content generally associates with impaired glucose metabolism (29), no association of the waist circumference score with any of the investigated metabolic traits was detected. This is in line with recent data indicating that increased liver fat content is not always associated with impaired glucose metabolism. Under some conditions, hepatic steatosis appears to be metabolically inert (30). This appears to be the case with the rs738409 C>G p.I148M variation in the PNPLA3 gene (31,32). Hence, genetic variants that behave this way could be enriched among the SNPs included in the waist circumference score, potentially explaining why the waist circumference score was associated with liver fat content but not with insulin sensitivity. This appears to be gender specific, with genetic background having a stronger effect on liver fat accumulation in women. While sexual dimorphisms have previously been detected for several of the tested polymorphisms (23), the underlying biology is still unclear and needs further research.

No correlation of the hip score with any other fat compartment was present in our study. In contrast to most other fat compartments, subcutaneous fat is generally believed to represent a healthy fat depot with preventive effects on obesity-related diseases (33). The lack of an association of the genetic hip score with metabolic traits in the present study suggests that such effects, at least if genetically determined, may be small.

The results of the WHR score point toward an association with an adverse body fat distribution pattern also yielding signals for expected metabolic correlates such as insulin resistance and lower high-density lipoprotein cholesterol. Thus, the genetic variants included in this score may indeed predispose individuals to diabetes and related diseases by promoting unhealthy body fat distribution.

Of note, there was only very limited overlap between the SNPs that are GWAS-derived risk variants for WHR (unadjusted) and those identified in GWAS investigating WHR adjusted for BMI (see also Figure 1). This suggests that both strategies detect distinct phenotypes. In line with this, our WHR adjusted for BMI genetic risk score was associated with SCAT mass but not with any other fat depot or metabolic trait. Therefore, in contrast to the SNPs included in the WHR score that were associated with unfavorable fat accumulation, these variants seem not to have a major impact on adverse fat distribution or metabolism.

While easy to obtain anthropometric measurements such as waist or hip circumference are established predictors for individual cardiometabolic risk (34), our results underscore that they are not necessarily precise measures to assess body fat distribution and related metabolic traits. For example, the genetic variants associated with waist circumference in the GWAS did not determine the amount of VAT mass as expected, but rather were associated with liver fat content. Thus, further studies on genetic determinants of body fat distribution should focus on a more precise quantification thereof, preferably using imaging techniques for phenotyping.

Limitations of our current work include the sample size of 915 subjects, which is much smaller than GWAS discovery populations. Presumably, a small effect size of individual SNPs precluded a detection of associations between individual SNPs and phenotypes in our cohort. Therefore, the use of these polymorphisms for individual risk prediction does not seem to be feasible. The small effects of the single polymorphisms also impeded the identification of the SNPs that contributed most to the observed effects. Such variants would be candidates for experimental follow-up studies aiming to dissect the underlying pathomechanisms. As we only studied individuals of Caucasian origin, we cannot exclude different relationships in other populations.

In conclusion, we detected associations of GWAS-derived risk polymorphisms with distinct patterns of body fat distribution in healthy

humans. Single genetic risk variants that associated with waist circumference, hip circumference, and WHR adjusted for BMI in larger GWAS studies did not associate with precisely quantified fat depots in our study. The genetic risk score for WHR was associated with an unhealthy body fat distribution pattern with elevated VAT mass and metabolic disturbances, including insulin resistance and impaired glucose tolerance. This score might therefore be useful for predicting diseases associated with genetically determined unhealthy obesity.O

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