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**Genome-wide and abdominal MRI-imaging data provides evidence that a genetically determined favourable adiposity phenotype is characterized by lower ectopic liver fat and lower risk of type 2 diabetes, heart disease and hypertension.**

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## **Abstract (200 words)**

Recent genetic studies have identified alleles associated with opposite effects on adiposity and risk of type 2 diabetes. We aimed to identify more of these variants and test the hypothesis that such “favourable adiposity” alleles are associated with higher subcutaneous fat and lower ectopic fat. We combined magnetic resonance imaging (MRI) data with genome-wide association studies (GWAS) of body fat % and metabolic traits. We report 14 alleles, including 7 newly characterized alleles, associated with higher adiposity, but a favourable metabolic profile. Consistent with previous studies, individuals carrying more “favourable adiposity” alleles had higher body fat % and higher BMI, but lower risk of type 2 diabetes, heart disease and hypertension. These individuals also had higher subcutaneous fat, but lower liver fat and lower visceral-to-subcutaneous adipose tissue ratio. Individual alleles associated with higher body fat % but lower liver fat and lower risk of type 2 diabetes included those in *PPARG*, *GRB14* and *IRS1*, whilst the allele in *ANKRD55* was paradoxically associated with higher visceral fat but lower risk of type 2 diabetes. Most identified “favourable adiposity” alleles are associated with higher subcutaneous and lower liver fat, a mechanism consistent with the beneficial effects of storing excess triglyceride in metabolically low risk depots.

## Introduction

There are many overweight or obese individuals who do not carry the expected metabolic disease risks associated with higher BMI (1; 2) while some lean or normal weight individuals develop diseases like type 2 diabetes(3-5). We(6; 7) and others(8-10) have previously shown that genetic variation is likely to contribute to these differences by increasing adiposity but lowering the risk of type 2 diabetes. We labelled these variants “favourable adiposity” since the alleles associated with higher BMI are associated with a favourable metabolic profile and lower risk of type 2 diabetes. The alternative alleles of the same variants could be characterized as “unfavorable lack of adiposity” or “limited adipose tissue storage capacity”. The identification of these variants differed by study. One study started with a genome-wide association study (GWAS) of body fat % in 76,150 individuals and showed that a common allele near the *IRS1* gene was associated with higher adiposity but lower insulin resistance and risk of disease(8). The remaining studies were limited to genetic variants associated with fasting insulin levels at genome-wide levels of statistical confidence and used a combination of data and approaches to identify genetic scores of between 10 and 53 variants that collectively were associated with opposite effects on BMI and risk of type 2 diabetes(6; 7; 9; 10).

More detailed characterization of these alleles revealed several insights. First, the alleles associated with higher BMI but lower risk of type 2 diabetes were associated with a lower risk of hypertension and heart disease as well as type 2 diabetes(6; 7; 9). Second, most of the alleles associated with higher insulin sensitivity, as identified by GWAS of fasting insulin levels, were associated with higher BMI or a redistribution of fat into the lower body, as estimated by waist-to-hip ratio(6; 7; 9; 10). Third, these

alleles were associated with more refined measures of adipose tissue distribution: the alleles associated with higher BMI but lower risk of disease were also associated with higher adiposity in the lower body (gynoid area and legs) as measured by DEXA(9).

The association of “favourable adiposity” alleles with higher peripheral adiposity in the previous studies proposed that a likely explanation for the mechanism is altered adipose tissue storage capacity(6; 7; 9; 10) consistent with the “adipose tissue expandability” hypothesis(11). To have a clear understanding about the underlying mechanisms associated with “favourable adiposity” in the context of the “adipose tissue expandability” hypothesis, we need to study whether “favourable adiposity” alleles are specifically associated with lower levels of ectopic fat. Furthermore, since men and women have different body fat distribution regulated by sex steroids(12), the study of underlying mechanisms separately in men and women may help elucidate the biology of the cardio-metabolic diseases.

The aim of this study was to identify additional alleles associated with “favourable adiposity” and to combine genetic and MRI data to understand more about the underlying mechanisms. In contrast to most previous studies, that focused on variants associated with surrogate measures of insulin resistance (fasting insulin), we started with variants associated with altered body fat %. We describe an approach that led to the characterization of 14 alleles collectively associated with higher body fat % but lower risk of type 2 diabetes, hypertension and heart disease. We showed that these alleles are associated with lower ectopic fat in the liver, based on MRI data.



## **Method**

**UK Biobank study:** UK Biobank recruited over 500,000 individuals aged 37-73 years (99.5% were between 40 and 69 years) between 2006-2010 from across the UK (**supplementary table 1**). The study has been described in more detail elsewhere(13).

**UK Biobank genetic data:** SNP genotypes underwent extensive central quality control (<http://biobank.ctsu.ox.ac.uk>). We based our study on 451,099 individuals of white European descent as defined by Principal Components Analysis (PCA). Briefly, principal components were generated in the 1000 Genomes Cohort using high-confidence SNPs to obtain their individual loadings. These loadings were then used to project all of the UK Biobank samples into the same principal component space and individuals were clustered using principal components 1-4. We removed 7 participants who withdrew from the study, and 348 individuals whose self-reported sex did not match their genetic sex based on relative intensities of X and Y chromosome SNP probe intensity.

**Measures of disease and disease related traits in UK Biobank:** We used 3 cardio-metabolic diseases: type 2 diabetes, hypertension (also represented by continuous measures of systolic and diastolic blood pressure) and heart disease – all using baseline data and following similar definitions to those used in previous GWASs (**supplementary table 1**).

We defined type 2 diabetes cases using baseline data if 3 criteria were present: i) reports of diabetes at the interview, ii) at least one year gap from diagnosis without requiring insulin, iii) reported age at diagnosis over the age of 35 years to limit the numbers of individuals with slow-progressing autoimmune diabetes or monogenic forms. Individuals not reporting an age of diagnosis were excluded. We also excluded

individuals diagnosed with diabetes within the year prior to the baseline study visit as we were unable to determine whether they were using insulin within the first year. Controls were individuals not fulfilling these criteria.

We defined subjects as hypertensive if systolic blood pressure was  $>140$  mmHg, or a diastolic blood pressure was  $>90$  mmHg, or blood pressure medication was reported. Controls were individuals not fulfilling these criteria. For the analysis of systolic and diastolic blood pressure, we corrected blood pressure measures in people on antihypertensive drugs by adding 15 mmHg to systolic and 10 mmHg to diastolic blood pressure.

We defined heart disease cases if individuals reported angina and/or a heart attack at the interview stage. We defined controls as individuals without these conditions.

### **Identification of genetic variants associated with “favorable adiposity”**

We designed a study in three steps to identify genetic variants associated with “favourable adiposity” (**supplementary figure 1**).

**First, genetic variants associated with adiposity.** We used Bio-impedance measures of body fat % measured by the Tanita BC418MA body composition analyser as measure of adiposity (N = 442,278 individuals from UK Biobank). We used a linear mixed model implemented in BOLT-LMM to account for population structure and relatedness(14). We used age, sex, genotyping platform, study centre and the first 5 principal components as covariates in the model.

**Second, genetic variants associated with a multivariate metabolic outcome:** We used summary statistics from published GWASs (not including UKBiobank) of metabolic biomarkers including body fat % (N = 120,000)(15), HDL-C (99,900)(16),

adiponectin (29,400)(17), sex hormone binding globulin (SHBG, 21,800)(18), triglycerides (96,600)(16), fasting insulin (51,800)(19), and alanine transaminase (55,500)(20). We used these biomarkers to be consistent with our previous approach(7). These biomarkers are used to discriminate monogenic disorders of fat storage (lipodystrophy) from other monogenic conditions where insulin sensitivity and adiposity are affected(7; 21; 22).

Within each GWAS, we standardized the effect sizes to correct for the differences in sample size and the various traits measurement unit across different GWAS:

$$\text{beta}_{\text{standardized}} = \frac{\text{beta}}{\text{se} * \sqrt{n}}$$

We used metaCCA(23) to run a multivariate GWAS. The phenotype-phenotype correlation matrix ( $\Sigma^{\text{YY}}=\text{cov}(Y, Y)$ ) was built according to the Pearson correlation between any pairs of traits across genome-wide genetic variants. Genotype-genotype correlation matrix ( $\Sigma^{\text{XX}}=\text{cov}(X, X)$ ) was computed using reference database from 1000 Genomes. The canonical correlation analysis in metaCCA finds the maximal correlation coefficient  $R_{\text{metaCCA}}$  between genetic variants and linear combination of phenotypes based on phenotype-phenotype correlation matrix. We defined genetic variants associated with a multivariate metabolic outcome if metaCCA  $p < 5 \times 10^{-8}$ .

**Third, genetic variants associated with “favourable adiposity”.** We selected genetic variants associated with both adiposity (step 1) and a multivariate metabolic outcome (step 2) at  $p < 5 \times 10^{-8}$  and used a hierarchical clustering approach to narrow down the list to ones showing a pattern of “favourable adiposity”. We calculated the frequency of times the variants were in the same cluster to identify “favourable adiposity” cluster using the “pvclust” package in R as shown before(7).

## **Genetic score analysis**

We constructed the genetic score of “favorable adiposity” variants as the number of “favorable adiposity” alleles carried by each individual (un-weighted). We used age, sex, genotyping platform, study center and the first 5 ancestry principal components as covariates in the model.

## **Additional studies for replication of the non-imaging findings**

To provide further evidence for the role of “favorable adiposity” alleles, we used 5 cohorts that were not part of the published GWASs used in our discovery stage (**supplementary table 1**): NEO study (The Netherlands Epidemiology of Obesity; 6,671 individuals of white European descent collected from the greater area of Leiden in the West of the Netherlands(24)), EXTEND (Exeter 10,000; 7,340 individuals of white European descent collected from South West England), GS:SFHS (Generation Scotland: Scottish Family Health Study; 20,000 individuals of white European descent collected from Scotland(25)), TÜF (Tübingen Family Study for Type 2 Diabetes; 2,679 individuals of white European descent collected from Southern Germany(26)), and IMI-DIRECT (Diabetes Research on Patient Stratification; 3,029 Caucasian pre-diabetic and Type 2 Diabetes subjects recruited by clinical centers located across Europe(27)).

To further provide evidence for the role of “favorable adiposity” alleles in risk of cardiometabolic diseases, we used published GWAS studies of type 2 diabetes(28), heart disease(29) and blood pressure(30).

**Studies contributed to imaging findings (liver fat, visceral fat and subcutaneous fat):**

**UK Biobank:** We used 5,045 individuals who had available data obtained through UK Biobank Access Application number 9914 and 6569. Participants were MRI scanned as previously described(31). Briefly, a single transverse slice located at the liver was acquired from each subject using multi-echo spoiled-gradient-echo acquisition and analysed as previously described(32). Assessment of abdominal subcutaneous and visceral fat was described previously(33).

**NEO:** Abdominal subcutaneous and visceral fat was assessed in 2,236 participants using MRI and were quantified by a turbo spin echo imaging protocol. At the level of the 5th lumbar vertebra 3 transverse images each with a slice thickness of 10 mm were obtained during a breath-hold. Proton ( $^1\text{H}$ )-MRS of the liver was used to assess hepatic triglyceride content (N = 1,821)(24).

**TÜF:** The TÜF study contributed subcutaneous and visceral adipose tissue measurements from 833 and 906 genotyped individuals, respectively, who underwent whole body magnetic resonance tomography. The two fat depots were quantified by an axial T1-weighted fast spin echo technique with a 1.5 T whole-body imager (Magnetom Sonata, Siemens Healthcare), as previously described(26). Liver fat measurements were available from 911 genotyped individuals who underwent localized  $^1\text{H}$  magnetic resonance spectroscopy, as described(26).

**IMI-DIRECT:** The IMI-DIRECT consortium is a collaboration among investigators from a range of European academic institutions and pharmaceutical companies. Liver fat was assessed on 1,457 subjects using a multi-echo acquisition as previously described(34). Briefly, the liver was identified from a scout abdominal image and axial images were performed during suspended respiration, which were used to position a single slice multi-echo sequence through the liver.

**Published GWAS:** We used published genome-wide association study of subcutaneous and visceral fat distribution as measured by CT scan or MRI(35).

## Results

### *We identified 14 alleles associated with “favourable adiposity”*

Using a 3-step approach, we characterized 14 genetic variants associated with “favourable adiposity”. Of these variants, seven were previously known to be associated with a “favourable adiposity” phenotype - those in/near *PPARG*, *LYPLAL1*, *GRB14*, *IRS1*, *PEPD*, *FAM13A* and *ANKRD55*, five were known to be associated with a relevant trait, but not confirmed as having a “favourable adiposity” phenotype, (those in/near *TRIB1*, *KLF14/MKLN1*, *DNAH10*, *VEGFA/C6orf223* and *AEBP2/PDE3A*) and two were entirely novel (those in/near *MAFF* and *CITED2*) (**supplementary table 2**). Twelve of the 14 variants had not previously been associated with body fat % at genome-wide levels of statistical confidence.

In the first step (**supplementary figure 1**), we performed a GWAS of body fat % in 442,278 individuals in the UK Biobank. We identified 620 variants at  $p < 5 \times 10^{-8}$ . In the second step, we used published GWAS statistics from 7 circulating biomarkers of metabolic health and identified 33 of these 620 variants as associated with a multivariable metabolic phenotype. This approach identifies alleles associated with metabolic traits after accounting for the phenotypic correlation between higher adiposity and these metabolic traits (**supplementary table 3 & 4, supplementary figure 2**). For example, this approach has more power to detect alleles paradoxically associated with higher adiposity but a favourable metabolic profile, because the model accounts for the population level correlation between higher adiposity and an adverse metabolic profile. The resulting 33 alleles also included some alleles associated very strongly with higher BMI and adverse metabolic profile, such as the allele in the *FTO* gene, most likely because adjusting for body fat % in the model

does not fully account for the adverse metabolic effects of lifelong higher adiposity. We therefore undertook a third step where we further refined the phenotypic characteristics of these variants by performing a clustering analysis. This approach led to the clustering of 14 alleles associated with “favourable adiposity” as defined by association with higher body fat %, HDL-C, SHBG and adiponectin levels, and lower triglycerides, alanine transaminase and fasting insulin levels (**supplementary figure 3**). We validated the effect of the 14 “favourable adiposity” alleles together in a genetic score on levels of metabolic biomarkers using 5 independent studies: NEO, EXTEND, GenScotland, TÜF and IMI-DIRECT (**supplementary table 5**).

*A genetic score of “favourable adiposity” alleles was associated with lower risk of cardiometabolic disease outcomes.*

Carrying additional "favourable adiposity" alleles was associated with higher body fat % and higher BMI but lower risk of type 2 diabetes, hypertension and heart disease (**table 1**). For example, the 10% of people carrying the most “favourable adiposity” alleles had approximately 1.04% higher body fat % (95%CI [0.95,1.13],  $p=6 \times 10^{-115}$ ) and 0.4 kg/m<sup>2</sup> higher BMI ([0.32,0.45],  $3 \times 10^{-29}$ ) but 0.66 OR lower risk of type 2 diabetes ([0.61,0.72],  $7 \times 10^{-23}$ ), 0.87 lower risk of hypertension ([0.84,0.90],  $1 \times 10^{-19}$ ) and 0.84 OR lower risk of heart disease ([0.80,0.89],  $6 \times 10^{-10}$ ) compared to the 10% of people carrying the fewest “favourable adiposity” alleles (data from UK Biobank) (**figure 1**). These effects were similar in men and women and when we removed the seven known "favourable adiposity" variants from the analysis (**table 1**). These associations were similar when using data from published GWASs (**supplementary table 6**). For each of the 14 individual variants, the body fat % increasing allele was associated with at least one of lower risk of type 2 diabetes, lower risk of heart disease



or lower diastolic or systolic blood pressure in UK Biobank except the variant at the *AEBP2* locus (**supplementary figure 4**). In published GWAS data the exceptions were the variants at the *AEBP2* and *MAFF* loci (**supplementary table 6**).

*Individual “favourable adiposity” alleles were associated with heterogeneous effects on waist-to-hip ratio.*

Five of the individual 14 variants were previously identified as associated with waist-to-hip ratio(36). Previous studies have pointed out that the disease-protective effect of these alleles is likely to be due to their association with redistribution of the extra fat into the lower body (defined by lower waist-to-hip ratio). We therefore examined the alleles’ association with waist-to-hip ratio in more detail. Carrying more “favourable adiposity” alleles was associated with lower waist circumference ( $p=3.7\times 10^{-5}$ ) but higher hip circumference ( $2.3\times 10^{-109}$ ) in women. However, in men, carrying more “favourable adiposity” alleles was associated with higher waist circumference ( $1.7\times 10^{-40}$ ), higher hip circumference ( $1.8\times 10^{-53}$ ) and no effect on waist-to-hip ratio (**supplementary table 7**). These associations were robust when limiting the variants to the 7 not previously identified as having a “favourable adiposity” phenotype (**supplementary table 7**). The individual variants were associated with heterogeneous effects on waist-to-hip ratio. Most notably, for two variants, those in/near *PPARG* and *ANKRD55*, the “favourable adiposity” allele was not associated with lower waist-to-hip ratio in women, and for *ANKRD55*, it was associated with higher waist-to-hip ratio (**figure 2**).

*“Favourable adiposity” alleles were associated with less liver fat and more abdominal subcutaneous fat.*

We next investigated the associations between the “favourable adiposity” variants and MRI measures of subcutaneous, visceral and liver fat using data from 9,434 individuals and 4 studies – the first wave of UK Biobank imaging data (n=5,045), NEO (2,236), IMI-DIRECT (1,323) and TUF (906). A fifth set of data did not include liver fat and came from a published meta-analysis of 13 studies with abdominal MRI or CT scans of 18,332 individuals(35).

The genetic score of “favourable adiposity” alleles was associated with lower visceral-to-subcutaneous adipose tissue ratio ( $p=2 \times 10^{-14}$ ) in both men and women. This effect was driven by association with more subcutaneous fat ( $p=2 \times 10^{-14}$ ; **table 2, figure 3**). All 14 individual genetic variants were associated with higher subcutaneous adipose tissue, seven at  $p < 0.05$  (in/near *DNAH10*, *FAM13A*, *GRB14*, *KLF14*, *LYPLAL1*, *IRS1* and *PPARG*). Nine individual “favourable adiposity” alleles were associated with lower visceral-to-subcutaneous adipose tissue volume ratio, all at  $p < 0.05$  (in/near *CITED2*, *DNAH10*, *FAM13A*, *KLF14*, *LYPLAL1*, *IRS1*, *PPARG*, *TRIB1* and *VEGFA*; **supplementary figure 4, supplementary table 8**). Paradoxically, the “favourable adiposity” alleles in/near *ANKRD55* and *PEPD* were associated with higher visceral-to-subcutaneous adipose tissue volume ratio ( $p=0.001$  and  $0.02$ , respectively).

The genetic score of “favourable adiposity” was associated with lower liver fat in women ( $p=6.3 \times 10^{-9}$ ) but was not associated with liver fat in men ( $p=0.8$ ; **table 2, figure 3**). These effects were robust when limiting the variants to the 7 not previously identified as having a “favourable adiposity” phenotype (**table 2**). For 11 individual variants, the allele associated with higher subcutaneous fat was associated with lower

liver fat, four with  $p < 0.05$  (in/near *CITED2*, *GRB14*, *PPARG* and *TRIB1* (**supplementary figure 4, supplementary table 8**).

#### *Sensitivity analysis of liver fat.*

We performed three sensitivity analyses to assess whether the effect of “favourable adiposity” alleles on lower liver fat was affected by menopause, inclusion of type 2 diabetes patients or alcohol consumption.

First, menopause leads to a redistribution of adipose tissue towards more central obesity and an android phenotype(37; 38). To study whether or not the association with liver fat in women was influenced by menopausal status, we divided women from the UK Biobank and TÜF studies into pre- and post-menopausal status. The association between “favourable adiposity” alleles and lower liver fat in pre-menopausal women was twice that (-0.258 % [-0.223,-0.293];  $p=0.002$ ;  $n=433$ ) of post-menopausal women (-0.124 % [-0.106,-0.142];  $p=0.002$ ;  $n=2,356$ ) but the difference was not statistically meaningful ( $P_{\text{difference}}=0.14$ ; **supplementary table 9**).

Second, fatty liver disease is very common (>50%) in patients with type 2 diabetes(39). To check whether inclusion of people with type 2 diabetes had affected the association with liver fat, we ran the tests in UK Biobank individuals excluding people diagnosed with type 2 diabetes ( $n=222$ ) from the analysis of liver fat. The association of “favourable adiposity” alleles with liver fat remained similar after exclusion of patients with type 2 diabetes in all, men and women (all  $P_{\text{difference}} > 0.7$ ; **supplementary table 10**).

Third, the most common cause of increased fat in the liver is alcohol consumption which is more prevalent in men(40; 41). To study whether or not the lack of

association with liver fat in men was due to greater alcohol consumption, we assessed the effect of “favourable adiposity” alleles on liver fat in men defined as heavy, moderate and non-drinkers based on self-report alcohol questionnaires. The “favourable adiposity” alleles were not associated with liver fat in any of the three groups (**supplementary table 11**).

## Discussion

We characterized 14 genetic variants associated with “favourable adiposity”. Our study adds to previous studies(6; 7; 9; 10) in several ways. First, we outlined a new approach which leads to the identification of more “favourable adiposity” variants. Second, we provide more clarity about which individual alleles are likely “favourable adiposity” alleles and how they affect metabolic traits and diseases. Third, we used MRI data which strongly suggests these variants have a collective effect on lower liver fat as well as higher subcutaneous fat but they have little detectable effect on visceral fat. Finally, we provide a template for detecting alleles with apparently paradoxical effects on adiposity and disease using a wide variety of publically accessible GWAS data. In addition, our results strengthen previous observations including the “favourable adiposity” effect is not driven by altered body shape in men detectable by waist-to-hip ratio (6).

Of the 14 variants detected, 12 had been associated with at least one metabolic trait, including fasting insulin (those in/near *LYPLALI*, *GRB14*, *IRS1*, *FAM13A*, *ANKRD55* and *PEPD* (42)), lipid levels (those in/near *GRB14*, *IRS1*, *KLF14*, *TRIB1* and *DNAH10* (16)), adiponectin (those in/near *TRIB1*, *DNAH10* and *AEBP2*(17)) and alanine transaminase (*TRIB1*(20)). However, only two were known to be associated with body fat % (those in/near *GRB14* and *IRS1*(15)) at genome-wide levels of statistical confidence. Our data provides several insights about individual variants. First, the alleles at *PPARG*, *GRB14* and *IRS1* are associated with higher body fat % but lower liver fat and lower risk of type 2 diabetes. Second, the allele in *ANKRD55* is paradoxically associated with higher visceral fat but lower risk of type 2 diabetes. In agreement with this finding, this variant is in high linkage disequilibrium ( $R^2= 0.97$ )

with another variant (rs459193) found to associate with lower waist circumference, but higher 2-hour glucose levels(43). Third, the allele in *TRIB1* is associated with higher body fat %, lower visceral fat, lower liver fat and lower risk of heart disease and hypertension but it does not have any detectable effect on type 2 diabetes. Fourth, 4 variants we previously noted as favourable adiposity were not detected in this study. These variants (in or near *PDGFC*, *PEPD*, *RSPO3* and *TET2*) may alter body fat distribution or other aspects of body composition without altering overall body fat %, and hence were not detected at  $p < 5 \times 10^{-8}$  in stage 1.

A key question is whether or not the “favourable adiposity” effect is entirely due to preferential storage of the excess adiposity in the lower body as proposed before(36; 44). We made two general observations. First, despite similar effects on higher body fat % and lower risk of disease in each sex, the protective effect in men was not characterized by preferentially more fat in the lower body, as estimated by waist-to-hip ratio, consistent with our previous observation(6). Second, the individual variants were associated with heterogeneous effects on waist-to-hip ratio even within women. For example the allele in/near *ANKRD55* was associated with “favourable adiposity” but higher waist-to-hip ratio in women.

Having established that the “favourable adiposity” effect is not driven by preferential storage of fat in the lower body, as estimated by waist-to-hip ratio, in men, we examined more detailed measures of fat redistribution using MRI data. The association with lower liver fat was only detected in women. Our sensitivity analyses did not find hormonal differences due to menopause, alcohol consumption or type 2 diabetes as possible explanations for sex differences. We would expect the “favourable adiposity” alleles to be associated with liver fat in non-drinkers or

moderate drinkers if the alcohol intake in men confounded the association. However, the analysis stratified by alcohol intake in men did not show any association. The lack of association with visceral fat suggests that these alleles were not protecting from disease due to lower visceral fat. This observation is consistent with some studies which showed lower ectopic fat accumulation in the liver may be more important than visceral fat in protection from risk of type 2 diabetes(45). A caveat to this conclusion is that we used a marker of liver fat, alanine transaminase, as one of the metabolic biomarkers to identify the variants, and therefore will be biased towards those that affect liver more than visceral fat.

Our approach provides a framework for identifying additional alleles with apparently paradoxical effects on adiposity and disease. A previous study(9) used a simple and effective approach by taking published GWAS data and selecting all variants associated with higher fasting insulin adjusted for BMI, lower HDL-C and higher triglycerides at  $p < 0.005$  for each of the three traits. However, this approach has limitations for two reasons, first it applies an arbitrary cut-off for the three traits, and second, it does not use information from other biomarkers. We combined GWASs of seven metabolic biomarkers and used a multivariate test that does not require individual trait associations to reach a certain statistical threshold. We showed that our method performs well, as it was able to identify the 7 variants previously known to be associated with “favourable adiposity” as well as 7 additional variants that we then validated in independent GWAS data. Furthermore, by including SHBG, adiponectin and ALT in the model, we had more power to detect “favourable adiposity” variants (**supplementary table 12**).

The identification of “favourable adiposity” alleles highlights genes that may be targets for novel insulin-sensitizing agents. The allele in *PPARG* provides an important proof of principle because thiazolidinediones are PPAR- $\gamma$  agonists and appear to lower glucose levels despite increasing the patient’s weight by activating adipocyte differentiation, which redistributes fat away from liver towards an expanded subcutaneous depot(46; 47). The variants identified in our study do not identify which genes they are acting through; however, previous studies suggest some strong candidates. For example, *TRIB1* encodes a protein critical for adipose tissue maintenance and suppression of metabolic disorders(48). Mice lacking Trib1 show diminished adipose tissue mass and increased lipolysis even when on a normal diet(48). GWAS studies in humans have implicated *TRIB1* in lipid metabolism(16) and regulation of hepatic lipogenesis(20). Higher levels of VEGF-A in mice can facilitate healthy expansion of adipose tissue and protect from lipotoxicity and metabolic disease(49). *CITED2* is required for optimal PPAR $\gamma$  activation(50). *FAM13A* encodes a protein enriched in mature adipocytes and plays an important role in the insulin signaling cascade(51) by protecting IRS1 (insulin receptor substrate 1) from degradation(51). The proteins encoded by *IRS1* and *CCDC92* are associated with adipogenesis, lipid accumulation and adipocyte differentiation ability(9; 51). Functional studies suggest *DNAH10* is involved in adipocyte differentiation capacity(9). *KLF14* is a master regulator of gene expression in adipose tissue(52) associated with adipocyte cell size in humans(53). *MAP3K1* regulates expression of *IRS1*(54). *LYPLAL1*, as a triglyceride lipase, is over-expressed in subcutaneous adipocytes of obese people to maintain triglycerides metabolism(55). The regulation of Grb14 expression in adipose tissue may play a physiological role in insulin sensitivity(56). *AEBP2* regulates a gene encoding a fatty acid-binding protein.



Our study had a number of limitations. First, we used 7 metabolic biomarkers from published GWASs in our multivariate analysis. The sample size for each GWAS was different: ranging from 21,800 individuals from GWAS of SHBG to 99,900 from the GWAS of lipids. These differences, caused by using GWAS meta-analysis data from different studies, will have limited our power, and led to less accurate estimates of the correlation between phenotypes compared to having the same sample size for all phenotypes. Second, the published GWASs of biomarkers were performed in men and women together rather than in a sex specific way. As men and women have different body fat distribution, it seems necessary to perform the discovery of “favourable adiposity” variants in men and women separately when data becomes available. Third, we used bio-impedance measures of body fat % as measure of adiposity in the discovery step. This measure of adiposity is an imprecise measure and is not as accurate in calculating body fat % in obese individuals or people with higher muscle mass(57). However, it’s availability in 442,278 individuals meant it represented a powerful dataset from which to start(58). Fourth, individual variants had subtle effect sizes; all variants were associated with at least one disease, with the body fat % increasing allele associated with lower risk except the one at *AEBP2* locus; although this variant had a paradoxical effect on adiposity and metabolic biomarkers with significant association between body fat % increasing allele and higher adiponectin ( $p= 4.76 \times 10^{-8}$ ), higher HDL-C ( $p=2.83 \times 10^{-6}$ ) and lower triglycerides ( $p=0.003$ ; **supplementary table 4**).

To yield a better understanding of how “favourable adiposity” protects against cardiometabolic disease, more studies in future are warranted. First, it will be important to test the association of “favourable adiposity” variants with pancreatic fat as a potential cause of  $\beta$ -cell dysfunction that will inform the associations with type 2

diabetes. Second, there are substantial ethnic differences in diabetes risk by BMI with South Asians having a much higher risk of type 2 diabetes for a given BMI compared to Europeans(59). Study of the genetics of “favourable adiposity” in different ethnic groups may provide important insights into the mechanisms underpinning the significant ethnic differences in diabetes risk.

In summary, our study provides further genetic evidence that the balance of subcutaneous to ectopic liver fat is an important factor for type 2 diabetes, heart disease and hypertension. This finding is consistent with data from monogenic forms of lipodystrophy and the importance of an expandable subcutaneous adipose tissue as a protective disease mechanism and limited adipose storage capacity as a risk mechanism (based on the opposite alleles) as proposed in previous studies(60-62).

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**Tables**

**Table 1.** The effect of “favourable adiposity” genetic score on measures of adiposity and cardiometabolic disease outcome in the UK Biobank study. Effects are per carrying additional adiposity allele. 95% CI: 95% confidence interval; P: p-value; N: number; OR: odds ratio.

Trait/disease	Analysis	14 SNPs			7 “additional” SNPs			N (cases vs. controls)
		Effect	95% CI	P	Effect	95% CI	P	
Body fat %	ALL	0.17	0.169, 0.171	$6 \times 10^{-263}$	0.15	0.149, 0.151	$1 \times 10^{-105}$	443,000
	Women	0.15	0.148, 0.152	$3.5 \times 10^{-116}$	0.14	0.138, 0.142	$8.9 \times 10^{-52}$	240,882
	Men	0.19	0.188, 0.192	$1 \times 10^{-165}$	0.16	0.158, 0.162	$3 \times 10^{-61}$	202,118
BMI (kg/m <sup>2</sup> )	ALL	0.040	0.039, 0.041	$3.6 \times 10^{-45}$	0.045	0.044, 0.047	$4.5 \times 10^{-30}$	449,359
	Women	0.041	0.039, 0.042	$3 \times 10^{-28}$	0.047	0.045, 0.049	$1.9 \times 10^{-19}$	243,797
	Men	0.039	0.038, 0.041	$1.6 \times 10^{-22}$	0.042	0.040, 0.045	$6 \times 10^{-14}$	205,528
Type 2 diabetes (OR)	ALL	0.954	0.948, 0.960	$4 \times 10^{-44}$	0.966	0.957, 0.975	$1.9 \times 10^{-13}$	14,371 vs. 428,017
	Women	0.950	0.939, 0.961	$3 \times 10^{-18}$	0.962	0.946, 0.977	$2 \times 10^{-6}$	4,713 vs. 236,073
	Men	0.960	0.948, 0.964	$5 \times 10^{-26}$	0.966	0.955, 0.978	$1 \times 10^{-8}$	9,076 vs. 192,344
Heart disease (OR)	ALL	0.984	0.980, 0.989	$3 \times 10^{-14}$	0.982	0.976, 0.988	$1.5 \times 10^{-9}$	37,741 vs. 318,892
	Women	0.987	0.980, 0.994	0.0003	0.981	0.971, 0.991	0.0003	12,270 vs. 184,550
	Men	0.982	0.977, 0.987	$2 \times 10^{-11}$	0.983	0.975, 0.990	$2.6 \times 10^{-6}$	25,363 vs. 134,433
Hypertension (OR)	ALL	0.987	0.985, 0.989	$1 \times 10^{-33}$	0.989	0.986, 0.992	$3 \times 10^{-13}$	241,691 vs. 206,525
	Women	0.988	0.985, 0.991	$2 \times 10^{-16}$	0.989	0.985, 0.993	$3 \times 10^{-7}$	114,713 vs. 128,623
	Men	0.985	0.981, 0.988	$1.7 \times 10^{-19}$	0.987	0.983, 0.992	$1.6 \times 10^{-7}$	126,978 vs. 77,902
Systolic blood pressure (mmHg)	ALL	-0.173	-0.174, -0.172	$9 \times 10^{-46}$	-0.139	-0.141, -0.138	$3.6 \times 10^{-16}$	450,075
	Women	-0.163	-0.165, -0.162	$1 \times 10^{-22}$	-0.134	-0.136, -0.132	$1 \times 10^{-8}$	244,183
	Men	-0.206	-0.208, -0.205	$7.9 \times 10^{-27}$	-0.161	-0.163, -0.159	$2 \times 10^{-9}$	205,892
Diastolic	ALL	-0.074	-0.075, -	$7 \times 10^{-24}$	-0.085	-0.087, -0.083	$1 \times 10^{-16}$	449,322

<b>blood pressure (mmHg)</b>	Women	-0.078	0.073 -0.080, -0.077	1.6x10 <sup>-14</sup>	-0.093	-0.095, -0.091	1x10 <sup>-10</sup>	243,732
	Men	-0.073	-0.074, -0.071	1.9x10 <sup>-10</sup>	-0.081	-0.083, -0.079	3.5x10 <sup>-7</sup>	205,590

**Table 2.** The effect of “favourable adiposity” genetic score on (MRI/CT scan) measures of abdominal adipose tissue using data from 5 studies.

Effects are per carrying additional adiposity allele. 95% CI: 95% confidence interval; P het: P of heterogeneity test across the 5 studies.

	<b>Analysis</b>	<b>14 SNPs</b>				<b>7 “additional” SNPs</b>			
		<b>Beta</b>	<b>95% CI</b>	<b>P</b>	<b>P het</b>	<b>Beta</b>	<b>95% CI</b>	<b>P</b>	<b>P het</b>
<b>Subcutaneous adipose tissue (Litres)</b>	<b>All</b>	0.054	0.042, 0.067	2x10 <sup>-14</sup>	0.36	0.048	0.029, 0.067	9.6x10 <sup>-7</sup>	0.38
	<b>Women</b>	0.032	0.016, 0.048	6x10 <sup>-5</sup>	0.55	0.032	0.010, 0.054	3x10 <sup>-3</sup>	0.89
	<b>Men</b>	0.051	0.035, 0.067	2.5x10 <sup>-11</sup>	0.16	0.045	0.022, 0.064	4.9x10 <sup>-5</sup>	0.35
<b>Visceral adipose tissue (Litres)</b>	<b>All</b>	0.005	-0.007, 0.014	0.4	0.69	-0.002	-0.016, 0.011	0.84	0.94
	<b>Women</b>	-0.007	-0.018, 0.005	0.2	0.28	-0.009	-0.025, 0.005	0.21	0.6
	<b>Men</b>	0.011	0.000, 0.020	0.05	0.05	0.007	-0.009, 0.020	0.43	0.34
<b>VATSAT ratio</b>	<b>All</b>	-0.005	-0.007, -0.004	2x10 <sup>-14</sup>	0.15	-0.005	-0.008, -0.004	4x10 <sup>-9</sup>	0.75
	<b>Women</b>	-0.005	-0.007, -0.003	1x10 <sup>-10</sup>	0.46	-0.006	-0.008, -0.004	9x10 <sup>-8</sup>	0.93
	<b>Men</b>	-0.004	-0.005, -0.002	7x10 <sup>-7</sup>	0.03	-0.004	-0.006, -0.002	4x10 <sup>-4</sup>	0.16



<b>Liver fat (%)</b>	<b>All</b>	-0.087	-0.124, -0.051	$5.6 \times 10^{-6}$	0.015	-0.060	-0.115, -0.009	0.02	0.015
	<b>Women</b>	-0.170	-0.225, -0.110	$6.3 \times 10^{-9}$	0.26	-0.133	-0.216, -0.055	$1 \times 10^{-3}$	0.57
	<b>Men</b>	-0.005	-0.055, 0.041	0.8	0.16	0.000	-0.069, 0.069	0.99	0.086

## Figures

**Figure 1.** Carrying more “favourable adiposity” alleles was associated with higher adiposity but lower risk of type 2 diabetes (a), heart disease (b) and hypertension (c). We divided individuals from UK Biobank into 10 centiles based on their “favourable adiposity” genetic score (x vector). The distribution of “favourable adiposity” genetic score is shown in black and the case/control proportion is shown in red per each centile.

**Figure 2.** The individual variants were associated with heterogeneous effects on waist-to-hip ratio. Most notably, for two variants, those in/near *PPARG* and *ANKRD55*, the “favourable adiposity” allele was not associated with lower waist-to-hip ratio in women, and for *ANKRD55*, it was associated with higher waist-to-hip ratio. For eleven variants (those in/near *IRS1*, *TRIB1*, *CITED2*, *FAM13A*, *VEGFA*, *AEBP2*, *KLF14*, *LYPLAL1*, *DNAH10*, *MAFF* and *GRB14*) the “favourable adiposity” allele was associated with lower waist-to-hip ratio in women, whilst for the variant in/near *PEPD* there was no clear association with waist-to-hip ratio in either sex. The x vector illustrates the effect on body fat % in men (right plot) and women (left plot). The y vector illustrates the effect on waist-to-hip ratio. Data is from UK Biobank population.

**Figure 3.** The effect of “favourable adiposity” genetic score on (MRI/CT scan) measures of abdominal adipose tissue using data from 5 studies. The x-axis is the effect size per carrying additional “favourable adiposity” allele.

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