

Genetic evidence for different adiposity phenotypes and their opposing influence on ectopic fat and risk of cardiometabolic disease

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Abstract

To understand the causal role of adiposity and ectopic fat in type 2 diabetes and cardiometabolic diseases, we aimed to identify two clusters of adiposity genetic variants, one with 'adverse' metabolic effects (UFA) and the other with, paradoxically, 'favourable' metabolic effects (FA). We performed a multivariate genome-wide association study using body fat percentage and metabolic biomarkers from UK Biobank and identified 38 UFA and 36 FA variants. Adiposity-increasing alleles were associated with an adverse metabolic profile, higher risk of disease, higher CRP, higher fat in subcutaneous and visceral adipose tissue, liver and pancreas for UFA; and a favourable metabolic profile, lower risk of disease, higher CRP, higher subcutaneous adipose tissue but lower liver fat for FA. We detected no sexual dimorphism. The Mendelian randomization studies provided evidence for risk-increasing effect of UFA and protective effect of FA on type 2 diabetes, heart disease, hypertension, stroke, non-alcoholic fatty liver disease and polycystic ovary syndrome. FA is distinct from UFA by its association with lower liver fat, and protection from cardiometabolic diseases; it was not associated with visceral or pancreatic fat. Understanding the difference in FA and UFA may lead to new insights in preventing, predicting and treating of cardiometabolic diseases.

Introduction

Obesity is a significant risk factor for various conditions including type 2 diabetes, heart disease and hypertension – a cluster of events often referred to as the metabolic syndrome (1). However, in the general population, approximately 15-40% of individuals categorized as obese do not present any obesity-related metabolic conditions or diseases, and are ‘metabolically benign’ at the specific timepoint of measurement, supporting the existence of metabolically benign obesity (2; 3).

We have previously shown that a genetic predisposition to storing excess fat in subcutaneous adipose tissue (SAT) is associated with a reduced propensity to store fat in the liver, consequently reducing risk of disease (4). The identification of ‘favourable adiposity’ variants, since their adiposity-increasing alleles were paradoxically associated with lower risk of type 2 diabetes, heart disease and hypertension (4-7), provided genetic evidence for the paradox of metabolically benign obesity. These genetic findings suggest there are at least two types of variants associated with higher adiposity: one with favourable metabolic profile (favourable adiposity, FA) and the other with an unfavourable metabolic profile (unfavourable adiposity, UFA).

Although our previous studies have suggested an important role for liver fat, they have been unable to determine whether pancreatic fat deposition or liver and pancreas volumes were similarly implicated due to lack of data, nor has it been possible to investigate mechanisms imposed by each variant individually. Clarification of the underlying pathophysiologic mechanisms that link adiposity to higher risk of type 2 diabetes and other cardiometabolic

disease is critical to understanding disease progression and remission, especially given the rising prevalence of obesity and the rapid rise in an aging population. The availability of both metabolic markers and MRI scan data in the UK Biobank (8) has enabled us to test in more detail the characteristics of adiposity variants and the role of ectopic fat in disease mechanism.

The focus of this study was to understand how higher adiposity is associated with ectopic fat, metabolic derangements and cardiometabolic risk. Specifically, we aimed to (1) identify distinct clusters of FA and UFA variants; (2) investigate the relation between FA and UFA variants and ectopic fat deposition in the liver and pancreas; (3) examine how FA and UFA variants are associated with circulating markers of inflammation; (4) determine whether sexual dimorphism is a factor in the association between the clusters and metabolic biomarkers, fat distribution and disease risk; and (5) use MR to determine the potential causal role of 'favourable' and 'unfavourable' adiposity on different components of metabolic syndrome.

Method

Discovery data set – UK Biobank

UK Biobank recruited >500,000 individuals aged 37–73 years (99.5% were between 40 and 69 years of age) between 2006 and 2010 from across the UK (**Table S1**) (8). The UK Biobank has approval from the North West Multi-centre Research Ethics Committee (MREC) (<http://www.ukbiobank.ac.uk/ethics/>), and these ethical regulations cover the work in this study. Written informed consent was obtained from all participants.

The steps performed to identify variants associated with adiposity but with different effects on metabolic traits are outlined in **Fig. S1**. And briefly as follows:

Step 1: Genetic variants associated with both body fat percentage and composite metabolic biomarkers.

We performed a multivariate GWAS of relevant metabolic biomarkers that were available in individuals of European ancestry from the UK Biobank, including HDL-cholesterol (HDL; n=392,965), sex hormone-binding globulin (SHBG; n=389,354), triglycerides (n=429,011), aspartate transaminase (AST; n=427,778), and alanine transaminase (ALT; n=429,203), using BOLT-LMM v2.3.4 (9) and metaCCA software (10) as described previously (4). Specifically, metaCCA uses canonical correlation analysis to identify the maximal correlation coefficient between genome-wide genetic variants and a linear combination of the above phenotypes, based on the computed phenotype-phenotype Pearson correlation matrix. We chose these specific metabolic biomarkers to be consistent with our previous approach (4). These biomarkers are used to discriminate between three monogenic forms of insulin resistance:

lipodystrophy (disorders of fat storage), monogenic obesity and insulin signalling defects (6; 11).

We identified 254 variants at $p < 5 \times 10^{-8}$ associated with both our univariate GWAS of body fat percentage ($n=620$ variants previously published (4)) and our composite metabolic phenotype as estimated by the above multivariate GWAS model. This represents an increase in 221 signals compared to the 33 previously reported using a similar approach (4). This increase was largely attributable to the availability of the metabolic biomarkers in 451,099 individuals of European ancestry from UK Biobank, whereas previous studies were limited to smaller separate data (e.g. 100,000 with HDL and triglycerides, 21,800 with SHBG, and 55,500 with ALT).

Step 2: Classification of adiposity variants.

We applied a k-means algorithm on the 254 variants and their effects on the values of the 6 phenotypes from the first step and used the parameter $k=3$ to group them into: (i) 'favourable adiposity' (FA) and (ii) 'unfavourable adiposity' (UFA). We considered a third cluster of 'conflicting' to group any variants that do not belong to the FA or UFA clusters and did not pursue these variants in the rest of the analyses to minimise false discovery. Within UFA and FA clusters, we inspected whether the loci are driven by colocalisation of signals from a combination of traits or whether they represent a strong univariate signal.

Step 3: Validation of FA and UFA variants

To validate FA and UFA variants, we assessed their effects on risk of type 2 diabetes using data from GWAS of 31 studies, excluding UK Biobank, which included 55,005 cases and

400,308 controls of European ancestry (12). We expected to observe adiposity-increasing alleles as associated with lower risk of type 2 diabetes for FA variants and higher risk of type 2 diabetes for UFA variants.

Imaging study

A sub-cohort of 100,000 subjects were selected for the imaging enhancement of the UK Biobank, currently at 49,938. Abdominal MRI scans were obtained using a Siemens Aera 1.5T scanner (Syngo MR D13) (Siemens, Erlangen, Germany) (13). Image-derived phenotypes were generated from the 3D Dixon neck-to-knee acquisition, the high-resolution T1-weighted 3D pancreas acquisition, and liver and pancreas single-slice multi-echo acquisitions. Images for this study were obtained through UK Biobank application 44584. Following automated pre-processing of the different sequences, volumes of organs of interest (including the liver, pancreas, and subcutaneous and visceral adipose tissue) were segmented using convolutional neural networks (14). Fat content of the liver and pancreas were obtained from the multi-echo acquisitions after pre-processing where the proton density fat fraction (PDFF) was estimated (15).

GWAS of imaging derived phenotypes

We used the UK Biobank imputed genotypes v3 (16), excluding SNPs with minor allele frequency < 1% and imputation quality < 0.9. We excluded participants not recorded as Europeans, exhibiting sex chromosome aneuploidy, with a discrepancy between genetic and self-reported sex, heterozygosity outliers, and genotype call rate outliers. We used BOLT-LMM (9) version 2.3.2 to conduct the genetic association study. We included age at imaging visit, age squared, sex, imaging centre, and genotyping batch as fixed-effect covariates, in

addition to scan date scaled and scan time scaled and genetic relatedness derived from genotyped SNPs as a random effect to control for population structure and relatedness. We performed GWAS for visceral adipose tissue (VAT, n=32,859), subcutaneous adipose tissue (SAT, n=32,859), visceral to subcutaneous adipose tissue ratio (VAT:SAT, n=32,859), pancreatic fat (n=24,673), liver fat (n=32,655), pancreas volume (n=31,758) and liver volume (n=32,859) (**Table S1**).

Replication data set

To replicate the effect of FA and UFA variants on measures of adiposity, metabolic biomarkers and C-reactive protein (CRP), we used summary statistics from published GWAS which were independent of UK Biobank (**Table S1**). To replicate the effects on subcutaneous and ectopic fat, we used data from a combined multi-ethnic sample-size weighted fixed-effects meta-analysis of SAT (n=18,247), VAT (n=18,332), VAT:SAT (n= 18,191), and pericardial adipose tissue (n=12,204) measured by CT or MRI (17) (**Table S1**).

Genetic Score Analysis

We studied the association of individual variants and of genetic scores with cardiometabolic traits and diseases in the UK Biobank using our GWAS results. GWAS were performed using BOLT-LMM to account for population structure and relatedness using covariates such as age, sex, genotyping platform and study centre in the model. For genetic score analysis, we used the inverse-variance weighted method assigning a weight of 1 to each variant. This method approximates the association of an unweighted genetic score (18).

Mendelian randomization (MR) studies

We investigated the causal associations between a ‘favourable’ and an ‘unfavourable’ adiposity, using FA and UFA clusters as instruments, and six cardiometabolic disease outcomes (type 2 diabetes, heart disease, hypertension, stroke, NAFLD (non-alcoholic fatty liver disease), and PCOS (polycystic ovary syndrome)) by performing two-sample MR analysis (19). We used the inverse-variance weighted approach (IVW) as our main analysis, and MR-Egger and weighted median as sensitivity analyses in order to detect unidentified pleiotropy of our genetic instruments. We used two sources of data: FinnGen GWAS summary results (20) and published GWAS of the same diseases, excluding UK Biobank to separate it from our discovery dataset and allow us to run two-sample MR (**Table S1**). We performed MR within each data source and then meta-analysed the results across the two datasets using a random-effects model with the R package *metafor*(21). We ran the same models in UK Biobank data for comparison. For more information on definition of diseases and ICD codes, please see the **Supplementary Material**.

Tissue enrichment analyses

We used DEPICT (Data-Driven Expression-Prioritised Integration for Complex Traits) v.1 rel194 beta (22) to identify tissues and cells in which the genes from associated loci are highly expressed. Using 37,427 human Affymetrix HGU133a2.0 platform microarrays, DEPICT assesses whether genes at the relevant loci are highly expressed in any of the 209 tissues, cell types and physiological systems annotated by Medical Subject Headings (MeSH).

Data and resource availability

The datasets analysed during the current study are available from FinnGen (20) and the relevant published GWAS (**Table S1**). The data that support the findings of this study are

available from UK Biobank but restrictions apply to the availability of these data, which were used under licence for the current study (UK Biobank project application numbers 9072, 9055 and 44584) and therefore are not publicly available. No applicable resources were generated or analysed during the current study.

Results

Clusters of adiposity variants

Among 254 variants associated (at $p < 5 \times 10^{-8}$) with both body fat percentage (4) and a composite metabolic phenotype, we identified two distinct clusters of adiposity variants; (a) 38 variants grouped as UFA and (b) 36 variants grouped as FA (**Tables S2-4, Fig. S2**). UFA genetic score was associated with higher body fat percentage and higher BMI and an adverse metabolic profile including lower HDL and SHBG, and higher triglycerides, ALT, and AST. FA genetic score was also associated with higher body fat percentage and BMI, but in contrast a favourable metabolic profile including higher HDL and SHBG and lower triglycerides, ALT and AST (**Table 1, Fig. 1a**). There was no sex difference in the association between FA and UFA genetic scores with adiposity measures or biomarkers at multiple-test-corrected significance threshold ($0.05/44 \text{ tests} = 0.0011$) (**Table S5, Fig. S3**). The association between UFA adiposity-increasing alleles and an adverse metabolic profile and FA adiposity-increasing alleles and a favourable metabolic profile was replicated in independent published GWAS of these biomarkers (**Table S6**).

The mean (SD) UFA and FA genetic scores in the UK Biobank were 36.99 (3.83) and 37.32 (3.75) respectively. The distributions of UFA and FA genetic scores among the UK Biobank participants with and without type 2 diabetes are shown in **Fig. S4**. The UFA and FA variants explained 0.6% and 0.2% variance in body fat percentage in the UK Biobank, respectively.

We used data from the latest GWAS of type 2 diabetes excluding UK Biobank (12) to validate the paradoxical association between the adiposity-increasing alleles at FA and UFA variants

and risk of type 2 diabetes. Among 38 UFA variants, 33 adiposity-increasing alleles were correlated with higher risk of type 2 diabetes ($p_{two-tailed\ binomial}=4E-6$) with 24 at $p<0.05$. Among 36 FA variants, all adiposity-increasing alleles were correlated with lower risk of type 2 diabetes ($p_{two-tailed\ binomial}=3E-11$) including 23 variants at $p<0.05$ (**Fig. 2**). This paradoxical association was consistent with the pattern of association with type 2 diabetes using data from the UK Biobank (**Fig. S5**).

To explore whether the UFA and FA variants represent biologically meaningful entities, we searched whether genes at the relevant loci were enriched for expression in certain tissues or pathways. FA variants were enriched (at FDR < 5%) in adipocyte-related cells and tissues and in physiological systems labelled as 'digestive' (small intestine, oesophagus, pancreas, upper gastrointestinal tract and ileum) and 'cardiovascular' (arteries); while UFA variants were enriched in mesenchymal stem cells and in physiological systems labelled as 'cardiovascular' (aortic valve, heart valves) (**Fig. 3, Tables S7 and 8**).

Association with MRI-derived measures of abdominal fat distribution

To investigate the relation between UFA and FA variants and abdominal fat distribution, we looked at the effect of FA and UFA variants on SAT, VAT and ectopic fat in the liver and pancreas in addition to liver and pancreas volume in 32,859 individuals of European ancestry from the UK Biobank. While both UFA and FA genetic scores were associated with higher SAT with similar effect size, UFA score was associated with higher liver and pancreatic fat, higher VAT, and increased liver volume, but FA score was associated with lower liver fat, smaller liver and pancreas volume and had no effect on pancreatic fat (**Table 1, Fig. 1b**). Both UFA and FA genetic scores were associated with lower VAT:SAT ratio.

We replicated these associations using independent data from the published GWAS of abdominal fat as measured by CT or MRI in up to 18,332 individuals for some of the measured phenotypes. UFA genetic score was associated with higher SAT ($p=3E-8$), higher VAT ($p=6E-7$), and higher pericardial adipose tissue ($p=0.003$) but had no effect on VAT:SAT ratio ($p=0.70$); while FA genetic score was associated with higher SAT ($p=6E-6$), lower VAT:SAT ratio ($p=2E-6$), and had no effect on VAT ($p=0.92$) or pericardial adipose tissue ($p=0.50$) (**Table S6**).

There was no sex difference in the association between FA and UFA clusters and MRI-derived measures of fat distribution at multiple-test-corrected significance threshold except for VAT where FA score was associated with higher VAT in men vs. lower VAT in women ($p_{\text{difference}}=0.0006$, **Table S5, Fig. S3**).

Using the data from the UK Biobank MRI sub-cohort, among 38 UFA variants, adiposity-increasing alleles at 31 variants ($p_{\text{two-tailed binomial}}=0.0001$) were correlated with higher ectopic liver fat, including 7 variants with $p<0.05$ (**Fig. S6**) and 31 adiposity-increasing alleles were correlated with higher pancreatic fat ($p_{\text{two-tailed binomial}}=0.0001$), including 7 variants at $p<0.05$ (**Fig. S7**). Of the 36 FA variants, 29 adiposity-increasing alleles were correlated with lower liver fat ($p_{\text{two-tailed binomial}}=0.0003$), including 9 variants at $p<0.05$ (**Fig. S6**). FA variants had a mixed effect on pancreatic fat as only 14 adiposity-increasing alleles were correlated with lower pancreatic fat ($p_{\text{two-tailed binomial}}=0.24$), including two alleles associated with higher and two with lower pancreatic fat at $p<0.05$ (**Fig. S7**).

Results on interesting individual FA variants with paradoxical effects where adiposity-increasing alleles are associated with lower risk of type 2 diabetes (from UK Biobank-independent GWAS) and lower liver fat (from the UK Biobank) at $p < 0.05$ are illustrated as forest plots in **Fig. S8**. These include 8 variants: rs4684847 (*PPARG*), rs12130231 (*LYPLAL1/SLC30A10*), rs11664106 (*EMILIN2*), rs13389219 (*GRB14/COBLL1*), rs2943653 (*NYAP2/IRS1*), rs30351 (*ANKRD55*), rs4450871 (*CYTL1*), and rs7133378 (*DNAH10*). Among these variants, the FA alleles at only two variants were associated with pancreatic fat at $p < 0.05$; near *GRB14* with lower pancreatic fat and near *PPARG* with higher pancreatic fat.

Association with CRP levels

To understand the role of inflammation in the mechanisms that link higher adiposity to risk of cardiometabolic disease, we looked at the association between FA and UFA variants and CRP levels as an inflammatory marker. In the UK Biobank, both UFA and FA genetic scores were associated with higher CRP (**Table 1, Fig. 1a**). These associations were replicated using an independent GWAS of CRP (27); **Table S6**). There was no sex difference in the association between UFA and FA variants and CRP levels (**Table S5, Fig. S3**). 35 out of 38 UFA adiposity-increasing alleles ($p_{\text{two-tailed binomial}} = 7E-8$) and 27 out of 36 FA adiposity-increasing alleles ($p_{\text{two-tailed binomial}} = 0.004$) were correlated with higher CRP, including 32 and 15 variants with $p < 0.05$, respectively (**Fig. S9**).

Association with cardiometabolic disease risk

Using UK Biobank data, UFA genetic score was associated with higher risk of type 2 diabetes ($p = 6E-16$), heart disease ($p = 2E-7$), hypertension ($p = 4E-8$), stroke ($p = 0.0005$), fatty liver disease ($p = 0.004$), and PCOS ($p = 7E-5$) (**Table 1, Fig. 1c**). In contrast, FA genetic score was

associated with lower risk of type 2 diabetes ($p=2E-9$), heart disease ($p=3E-5$), hypertension ($p=0.0001$), fatty liver disease ($p=0.03$), and PCOS ($p=0.02$) (**Table 1, Fig. 1c**). These findings were replicated using a UK Biobank-independent GWAS data (**Table S6**). There was no sex difference in the association between UFA and FA clusters with risk of disease at multiple-test-corrected significance threshold (**Table S5, Fig. S3**).

To understand the causal nature of these associations, we took an MR approach and used two UK Biobank-independent datasets (published GWAS and FinnGen). A 1-SD higher genetically instrumented unfavourable adiposity was associated with higher risk of type 2 diabetes (IVW odds ratio: 5.50 [95%CI: 4.29, 7.05]; $p=4E-41$), heart disease (1.66 [1.08, 2.54]; $p=0.02$), hypertension (3.03 [2.18, 4.22]; $p=5E-11$), stroke (1.43 [1.23, 1.67]; $p=3E-6$), NAFLD (3.70 [1.22, 11.17]; $p=0.02$) and PCOS (7.13 [3.66, 13.90]; $p=8E-9$) (**Table 2, Fig. 3, Table S9**). In contrast, a 1-SD higher genetically instrumented favourable adiposity was associated with lower risk of type 2 diabetes (0.11 [0.08, 0.16]; $p=4E-33$), heart disease (0.34 [0.25, 0.47]; $p=2E-11$), hypertension (0.34 [0.21, 0.55]; $p=1E-5$), stroke (0.65 [0.52, 0.83]; $p=0.0004$), and NAFLD (0.14 [0.03, 0.79]; $p=0.03$). There was a trend towards an association with lower odds of PCOS (0.51 [0.21, 1.23]; $p=0.13$) but with wider confidence intervals due to smaller samples size in the UK Biobank-independent GWAS (**Table 2, Fig. 3, Table S8**).

Discussion

In this study, we have used a unique genetic approach to understand the role of body adiposity, in relation to the fat content and volumes of the liver and pancreas, as well as pathogenicity of cardiometabolic disease. We have identified two distinct clusters of variants associated with higher adiposity, one with a favourable metabolic profile referred to as 'favourable adiposity' or FA, consisting of 36 variants, and the other with an unfavourable metabolic profile and referred to as 'unfavourable adiposity' or UFA which included 38 variants. Although the adiposity-increasing alleles in both clusters are associated with increased SAT, the FA alleles are specifically associated with a lower liver fat and appear to provide protection against risk of cardiometabolic diseases; whereas the UFA alleles are associated with higher deposition of all fat depots including liver, pancreas and visceral fat and are associated with higher risk of cardiometabolic disease.

The results of our genetic analysis support the observations from phenotyping studies that have proposed different obesity phenotypes related to the distribution of body fat (28; 29). The two adiposity phenotypes we have described in the present study highlight the role of SAT as a metabolic sink in obesity. In FA, this metabolic sink can accommodate excess triglycerides to specifically protect the liver from ectopic fat accumulation and prevent or delay pathogenic processes; in UFA, the excess triglycerides appears to exceed the capacity of the SAT metabolic sink, consequently being deposited in alternate sites, including the VAT depot, liver, pancreas and pericardial adipose tissue (30).

Our data, consistent with previous findings, provide evidence that accumulation of fat in the liver, which is an integral organ to glucose, insulin and metabolism, directly contributes to the development of metabolic derangements associated with higher adiposity (31; 32). Using a small subset of FA variants and a limited sample size with MRI scans (n=9,510), we previously showed that FA alleles were associated with lower ectopic liver fat in women but not men (4). The availability of MRI scans of liver fat in 32,859 UK Biobank participants allowed us to demonstrate that there is no sex-specific association with liver fat. However, both FA and UFA variants had a bigger overall effect on liver fat in women than men, which could indicate the confounding effects of other factors in the measured liver fat in men. The association of both FA and UFA clusters with, respectively, smaller and bigger liver size is most likely biased by the accumulation of liver fat (33).

The pattern of association between FA and UFA variants and MRI-derived measures of ectopic fat can help understand the role of each ectopic fat depot in the pathophysiology of cardiometabolic diseases. While the FA cluster is associated with lower ectopic liver fat, it has no effect on VAT. This is consistent with previous studies showing the effect of thiazolidinediones, a class of medicines that improve insulin sensitivity, on promoting differentiation of new adipocytes in SAT without changing VAT (34). In the light of strong association between VAT and development of metabolic dysfunction (35), our data suggest that VAT may reflect the ectopic fat deposition in the liver (r between the two measures=0.5 (14)) but itself may not be causally related to the development of cardiometabolic diseases. The sex-specific association between the FA cluster and lower VAT in women and higher VAT in men is also consistent with more general sex-specific pattern of VAT distribution as previously shown by genetic studies of waist-to-hip ratio (36). Furthermore, while FA alleles

are associated with lower VAT in women and higher VAT in men, they are associated with protection from cardiometabolic diseases with similar effect size between men and women.

Although the UFA cluster was associated with higher pancreatic fat; we did not detect any association between the FA cluster and this fat depot. FA variants individually had a mixed effect on pancreatic fat with the FA allele near *PPARG*, which is the most prominent example of FA variants mimicking the effect of thiazolidinediones, being associated with higher pancreatic fat. The role of pancreatic fat in the pathogenicity of type 2 diabetes is currently not clear-cut. Although many cross-sectional studies have reported higher pancreatic fat in subjects with type 2 diabetes compared with age-matched controls (37-40), there are conflicting views regarding whether pancreatic fat is itself a driver of type 2 diabetes with some studies showing no association between type 2 diabetes and pancreatic fat using either CT or histology at autopsy (41-44). Moreover, a recent study testing the so-called “twin cycle model” (liver and pancreatic fat) before and after the onset of type 2 diabetes, showed that liver fat was the main mediator associated with glycaemic control (45). Furthermore, a recent genetic study of pancreatic fat and liver fat in the UK Biobank showed that genetic variants associated with pancreatic fat did not have a significant impact on metabolic disease(14), suggesting pancreatic fat has no direct role in pathogenicity of type 2 diabetes and other metabolic disease. Longitudinal imaging studies of individuals prior to and after clinical disease onset in addition to MR studies of pancreatic fat in type 2 diabetes and other metabolic diseases will help to unravel the cause and consequence of this relationship.

The FA cluster was associated with a smaller pancreas volume whereas the UFA cluster had no association with pancreas volume. Studies of individuals with type 2 diabetes using CT or

ultrasound have shown 7-33% lower pancreas volume compared to controls (43; 46-48). Given only 1-2% of the adult pancreas is composed of endocrine islets, changes in exocrine cell number may contribute more to lower pancreas volume as shown in the studies of type 1 diabetes (49). Since insulin also acts as a growth stimulation hormone and maintains tissue mass (50; 51), a decline in pancreas size in diabetes could be due to a loss of the trophic effect of insulin on exocrine cells (52; 53). We previously showed variants associated with FA are associated with lower fasting insulin levels (4-6), which could explain why the FA cluster was associated with a smaller pancreas volume.

Subclinical inflammation is another factor that has been shown to be associated with components of metabolic syndrome and vascular disease (54-58). Our data provided no evidence for any direct role of CRP in disease mechanism that link FA and UFA clusters to, respectively, lower and higher risk of disease since both clusters were associated with higher CRP levels consistent with the largest MR study of CRP against risk of metabolic disease (27). The pattern of association between FA and UFA clusters and CRP level in our study could suggest that higher CRP levels are secondary to higher adiposity. Data on other markers of inflammation, including tumour necrosis factor- α and interleukin-6, could clarify more the role of inflammation in cardiometabolic disease mechanism.

Our tissue enrichment analysis provided further evidence that UFA and FA are biologically two different subtypes of adiposity. FA loci were enriched for genes expressed in adipose tissue and adipocytes; while UFA loci were enriched for genes expressed in mesenchymal stem cells. The enrichment of genes in adipose-related tissues and cells was previously shown for loci associated with WHR (23) in contrast to BMI loci enriched in the central nervous

system (24). However, this is the first time mesenchymal stem cells are highlighted in tissue enrichment analysis to be associated with adiposity. Mesenchymal stem cells are major sources of adipocyte generation and, in addition to adipose tissue, they also exist in skeletal muscle, the liver, and pancreas, which could suggest that they are responsible for ectopic fat formation in these organs (25; 26). Further experiments and data are necessary to determine the relationship between mesenchymal stem cells and ectopic lipid accumulation.

There have been few approaches to identify variants associated with favourable and unfavourable adiposity using different combinations of traits. Winkler *et al.* used 159 variants associated with BMI, waist-to-hip ratio (WHR), or WHR adjusted for BMI and described 24 'favourable adiposity' variants as those associated with both lower WHR and higher BMI, and 82 'unfavourable adiposity' variants as those associated with both higher WHR and higher BMI (59). Pigeyre *et al.* used polygenic correlation between BMI and type 2 diabetes to identify genetic regions where BMI-increasing effect was linked to a corresponding increase, decrease, or neutral effect on type 2 diabetes risk (60). Our FA and UFA variants that overlap with these studies are listed in **Table S10**. The main difference between our approach and these two studies is that they have started with variants associated with BMI or WHR as measures of adiposity. Recent studies have demonstrated that BMI is a poor proxy for body adiposity (61), particularly at an individual level, providing limited insight into body fat distribution, VAT or non-adipose deposition of fat (29). For example, only 7/36 and 12/36 FA variants are associated with BMI and WHR, respectively. Similarly, while UFA variants are enriched for BMI variants, 7 variants are not associated with BMI and only 14/38 UFA variants are associated with WHR (**Fig. S10**). Furthermore, using only BMI and type 2 diabetes to identify variants with opposite effects can induce index event bias (62), e.g. *TCF7L2* (60).

There are several limitations to our study. First, we did not have independent studies to replicate the association with liver and pancreas fat and volume measurements. However, we used the largest dataset on MRI phenotypes available from the UK Biobank with 32,859 samples and replicated the association with some fat depots available from a published GWAS (17). Second, our study population was limited to Europeans only; it is unclear how our findings can be generalized to other populations and whether they can explain the excess risk of cardiometabolic disease in non-Europeans (63). Third, we lacked data on ectopic fat accumulation in muscle in our samples; future studies of MRI-derived muscle fat in the UK Biobank will enable the role of this ectopic fat in the pathophysiology of cardiometabolic disease to be investigated. Fourth, lower body subcutaneous fat mass in the gluteofemoral or leg region has previously been associated favourably with obesity-related cardiometabolic diseases (64). It would also have been of interest to study whether the FA cluster is protective of cardiometabolic diseases particularly via increasing gluteofemoral and leg fat mass. Fourth, we used ALT and AST in our discovery pipeline to identify FA and UFA variants which could have biased our findings toward those variants that influence liver fat more than pancreatic fat. Fifth, comparing to our previous study (4), we did not have fasting insulin and adiponectin in our composite metabolic phenotype since these two biomarkers are not measured in the UK Biobank. However, our 36 FA variants include all 14 variants previously identified as 'favourable adiposity' (4) and the comparison of the multivariate GWAS p-values for these variants (**Fig. S11**) indicates additional power gained in the current study largely attributable to the availability of other metabolic biomarkers in 451,099 individuals in a single cohort, the UK Biobank.

One of the major strengths of this study was the unique approach to understand different mechanisms underlying the association between adiposity and risk of cardiometabolic diseases. This unique approach is coupled with gold-standard measurements of organ volume and content from MRI scans to understand the role of different fat depots in pathogenicity. The availability of the UK Biobank made it possible to study the sex-specific effects of our variants against metabolic biomarkers, MRI measures of fat distribution and ectopic fat, and risk of disease. We used the largest published GWAS and FinnGen study and independently replicated our results against risk of disease and performed MR studies. Unlike previous studies which examined the role of ectopic fat and pancreas size in small groups of participants dichotomized by their diabetes status, we investigated the role of these phenotypes in a population-based study of 32,859 participants which minimizes the effect of confounding factors and statistical bias. Finally, our sets of FA and UFA variants provide two important genetic instruments for any MR study to examine the causal role of adiposity on risk of disease uncoupled from its metabolic effect.

Conclusion

This study has provided genetic evidence for two types of adiposity; one coupled with a favourable metabolic profile and the other with an unfavourable profile. Both FA and UFA variants were associated with higher CRP levels. We demonstrated that reduced liver fat, but not VAT or pancreatic fat, is on the pathway that links 'favourable adiposity' to lower risk of diseases related to metabolic syndrome. We determined no sexual dimorphism in the way the FA and UFA variants are associated with metabolic profile, abdominal fat distribution and risk of disease. Future MR, longitudinal and independent studies are required to elucidate

whether higher pancreatic fat and smaller pancreas volume are a consequence of the ongoing pathological processes or causal to cardiometabolic disease outcomes. Better understanding of the difference between FA and UFA may lead to new insights in preventing, predicting and treating people who suffer from cardiometabolic diseases.

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Authors contributions. S.M. performed the statistical analyses. H.Y. and S.M. designed the study and wrote the first draft of the manuscript. N.B., Y.L., B.W., J.D.B., E.L.T. created the MRI derived phenotypes and contributed to the writing of the manuscript. M.C., E.S. performed the GWAS of MRI derived phenotypes. J.T., R.N.B., A.R.W, T.M.F. contributed to the analysis of biomarkers from the UK Biobank.

Guarantor Statement: Dr Yaghootkar is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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Table 1. The sex-combined effects per 1 SD higher body fat percentage as estimated by “favourable adiposity” and “unfavourable adiposity” genetic scores (in UK Biobank) on BMI, biomarkers, MRI-derived measures of fat distribution, and cardiometabolic diseases using data from UK Biobank.

Outcome	Unfavourable adiposity		Favourable adiposity	
	Effect [95% CI]	P-value	Effect [95% CI]	P-value
BMI (SD)	1.27 [1.01, 1.53]	4E-22	0.67 [0.50, 0.84]	3E-15
HDL (SD)	-0.64 [-0.89, -0.40]	2E-7	1.26 [0.96, 1.56]	3E-16
SHBG (SD)	-0.47 [-0.62, -0.32]	1E-9	1.10 [0.44, 1.76]	0.001
Triglycerides (SD)	0.49 [0.34, 0.64]	7E-11	-1.54 [-1.92, -1.15]	4E-15
ALT (SD)	0.45 [0.36, 0.54]	4E-21	-0.90 [-1.12, -0.69]	6E-17
AST (SD)	0.35 [0.19, 0.50]	1E-5	-0.54 [-0.71, -0.36]	2E-9
CRP (SD)	0.52 [0.38, 0.65]	3E-14	0.30 [0.09, 0.51]	0.005
SAT (SD)	1.09 [0.87, 1.31]	1E-22	0.96 [0.74, 1.18]	1E-17
VAT (SD)	0.56 [0.41, 0.72]	2E-12	-0.02 [-0.35, 0.31]	0.92
VAT:SAT (SD)	-0.34 [-0.50, -0.18]	3E-5	-0.85 [-1.16, -0.53]	1E-7
Liver fat (SD)	0.46 [0.30, 0.63]	2E-8	-0.72 [-1.01, -0.43]	9E-7
Pancreas fat (SD)	0.52 [0.36, 0.69]	7E-10	0.16 [-0.20, 0.51]	0.38
Liver volume (SD)	0.64 [0.44, 0.85]	3E-10	-0.43 [-0.73, -0.13]	0.006
Pancreas volume (SD)	0.06 [-0.15, 0.28]	0.57	-0.46 [-0.76, -0.15]	0.003
Type 2 diabetes (OR)	1.06 [1.04, 1.07]	6E-16	0.93 [0.91, 0.96]	2E-9
Heart disease (OR)	1.05 [1.03, 1.07]	2E-7	0.94 [0.92, 0.97]	3E-5
Hypertension (OR)	1.13 [1.08, 1.18]	4E-8	0.90 [0.85, 0.95]	0.0001
Stroke (OR)	1.01 [1.01, 1.02]	0.0005	0.99 [0.98, 1.00]	0.17
Fatty liver disease (OR)	1.01 [1.00, 1.01]	0.004	0.99 [0.98, 0.999]	0.03
PCOS (OR)	1.01 [1.00, 1.01]	7E-5	0.995 [0.99, 0.999]	0.02

CI: confidence intervals; SD: standard deviation; OR: odds ratio; HDL: HDL-cholesterol; SHBG: sex-hormone binding globulin; ALT: alanine transaminase; AST: aspartate transaminase; CRP: C-reactive protein; ASAT: abdominal subcutaneous adipose tissue; VAT: visceral adipose tissue; VATSAT: visceral to subcutaneous adipose tissue ratio; T2D: type 2 diabetes; NAFLD: non-alcoholic fatty liver disease; PCOS: polycystic ovary syndrome.

Table 2. The inverse-variance weighted two-sample MR meta-analysis of cardiometabolic diseases from published GWAS and FinnGen for “favourable adiposity” (FA) and “unfavourable adiposity” (UFA) clusters. OR: odds ratio; 95% CI: 95% confidence interval; P: p-value; NAFLD: non-alcoholic fatty liver disease; PCOS: polycystic ovary syndrome.

Outcome	Favourable adiposity				Unfavourable adiposity			
	OR	Lower 95% CI	Upper 95% CI	P	OR	Lower 95% CI	Upper 95% CI	P
Type 2 diabetes	0.11	0.08	0.16	4E-33	5.50	4.29	7.05	4E-41
Heart disease	0.34	0.25	0.47	2E-11	1.66	1.08	2.54	0.02
Hypertension	0.34	0.21	0.55	1E-05	3.03	2.18	4.22	5E-11
Stroke	0.65	0.52	0.83	0.0004	1.43	1.23	1.67	3E-06
NAFLD	0.14	0.03	0.79	0.03	3.70	1.22	11.17	0.02
PCOS	0.51	0.21	1.23	0.13	7.13	3.66	13.90	8E-09

Fig. 1. The sex-combined and sex-specific effects and 95% confidence intervals per 1 SD higher body fat percentage as estimated by “favourable adiposity” and “unfavourable adiposity” genetic scores for (a) measures of adiposity and biomarkers, (b) MRI-derived measures of fat distribution, and (c) cardiometabolic diseases in UK Biobank. In summary, a 1 SD higher body fat percentage as estimated by UFA genetic score was associated with HDL: HDL-cholesterol; SHBG: sex-hormone binding globulin; ALT: alanine transaminase; AST: aspartate transaminase; CRP: C-reactive protein; ASAT: abdominal subcutaneous adipose tissue; VAT: visceral adipose tissue; VATSAT: VATSAT ratio; T2D: type 2 diabetes; NAFLD: non-alcoholic fatty liver disease; PCOS: polycystic ovary syndrome.

Fig. 2. Adiposity-increasing alleles were correlated with lower risk of type 2 diabetes for all 36 “favourable adiposity” variants, and 33 adiposity-increasing alleles of 38 “unfavourable adiposity” variants were correlated with higher risk of type 2 diabetes using published GWAS. Effects on X are from the GWAS of body fat percentage in UK Biobank and on Y from the GWAS of type 2 diabetes published by Mahajan et al. excluding data from UK Biobank.

Fig. 3. Tissue-specific gene expression for UFA and FA variants using DEPICT. Results with FDR < 0.05 are highlighted in red (for UFA) and blue (for FA). Results are grouped by type and ordered alphabetically by MeSH term within (a) cell types, (b) tissues and (c) specific system (details in Tables S7 and 8).

Fig. 4. The inverse-variance weighted (IVW) two-sample MR meta-analysis of published GWAS and FinnGen and one-sample MR of UK Biobank for “favourable adiposity” (FA) and “unfavourable adiposity” (UFA) clusters for (a) type 2 diabetes; (b) heart disease; (c)

hypertension; (d) stroke; (e) non-alcoholic fatty liver disease (NAFLD); (f) polycystic ovary syndrome (PCOS). The error bars and width of diamonds represent the 95% confidence intervals of the IVW estimates in odds ratio per standard deviation change in genetically determined FA and UFA; I^2 : heterogeneity I^2 -statistic; p: p-value for the test of heterogeneity.

Figure 1a

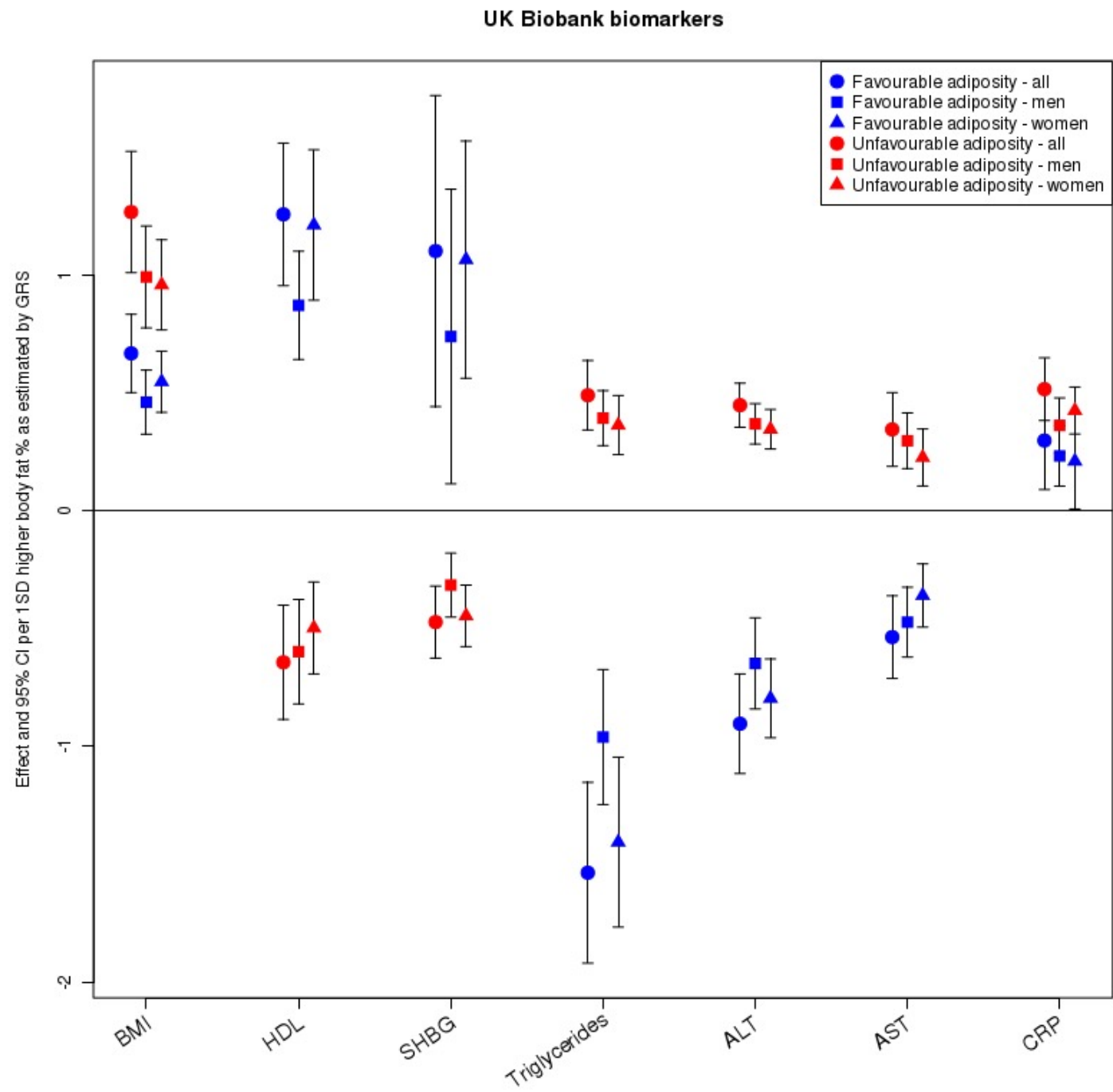


Figure 1b

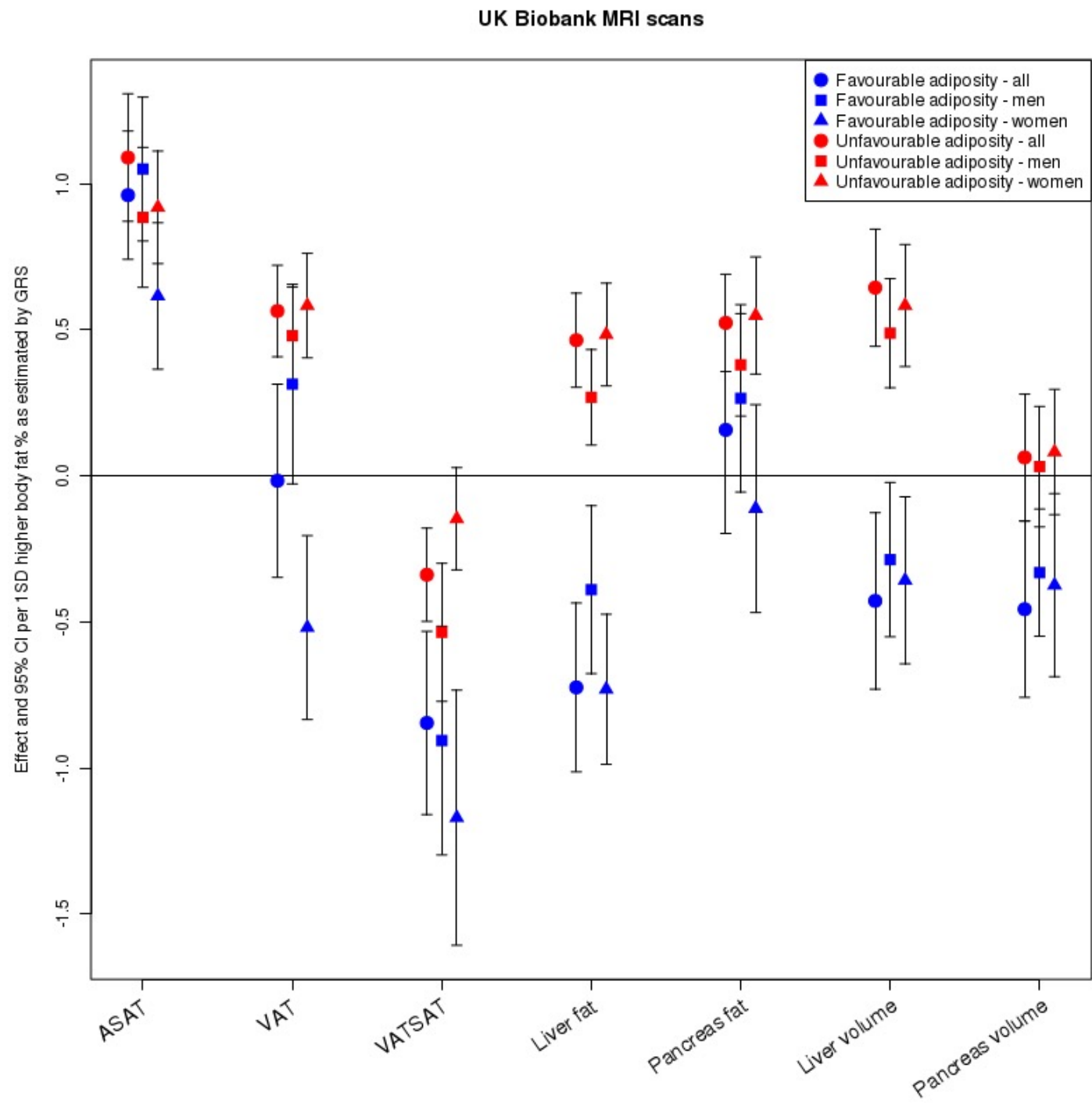


Figure 1c

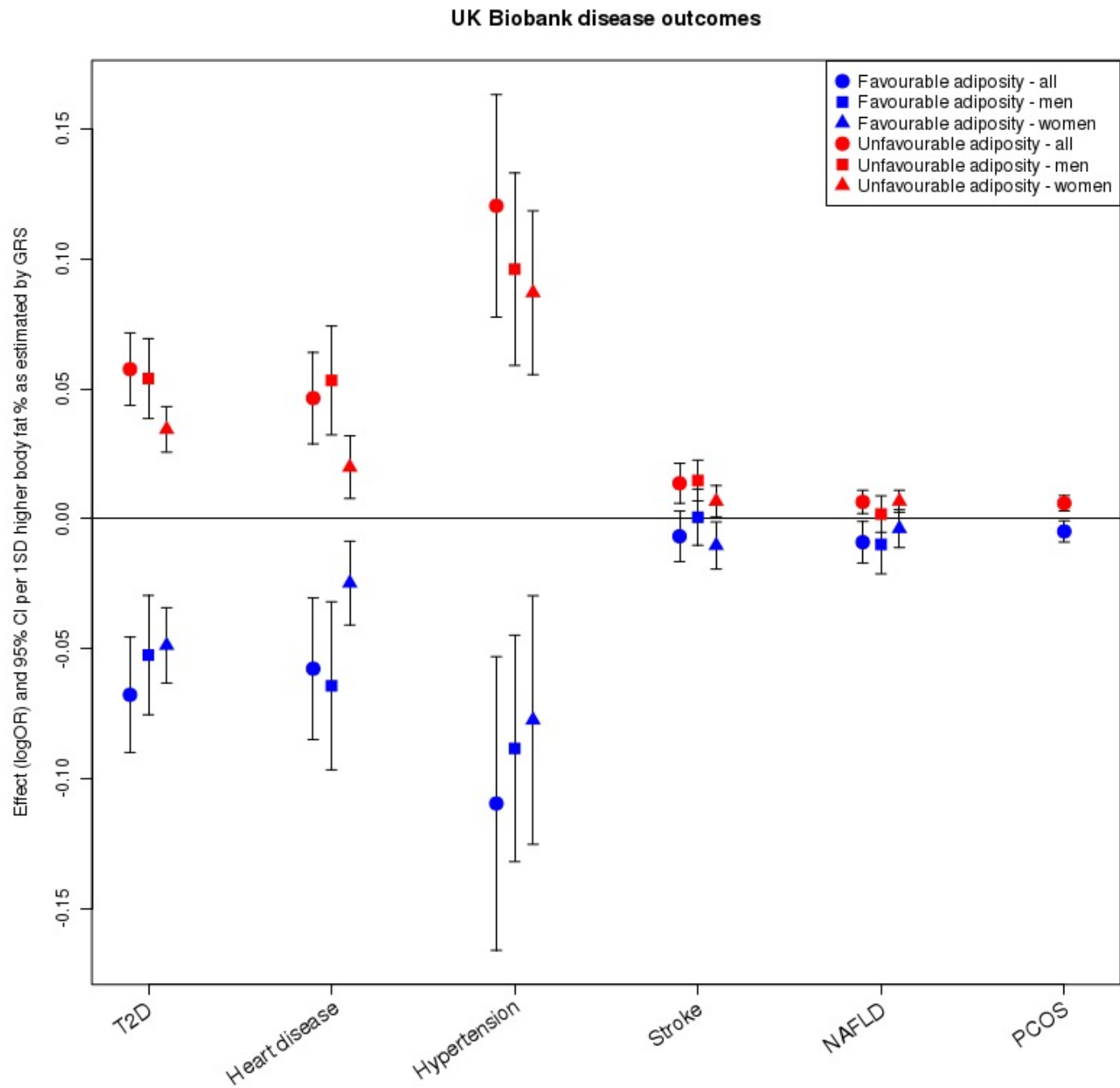


Figure 2

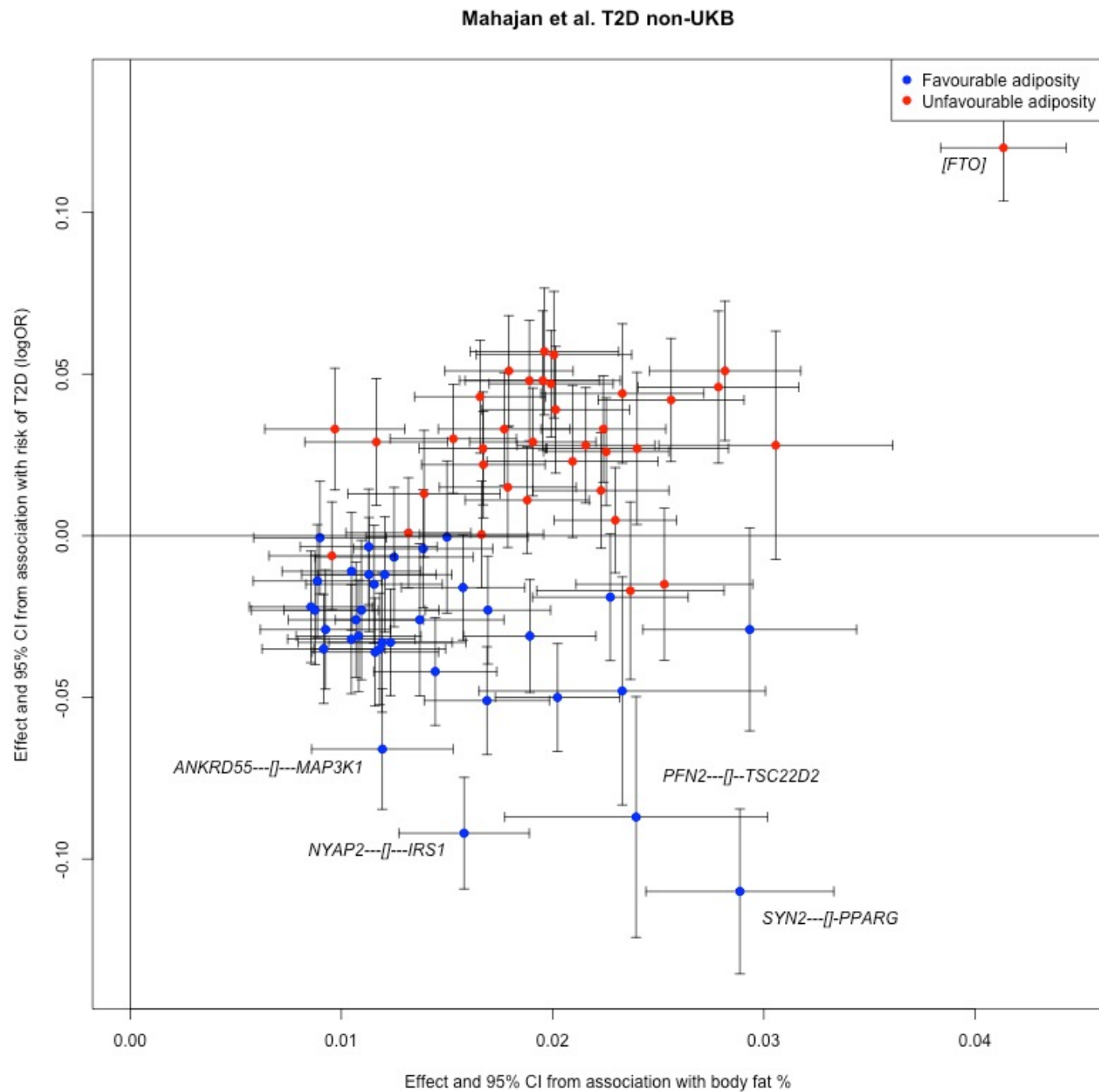
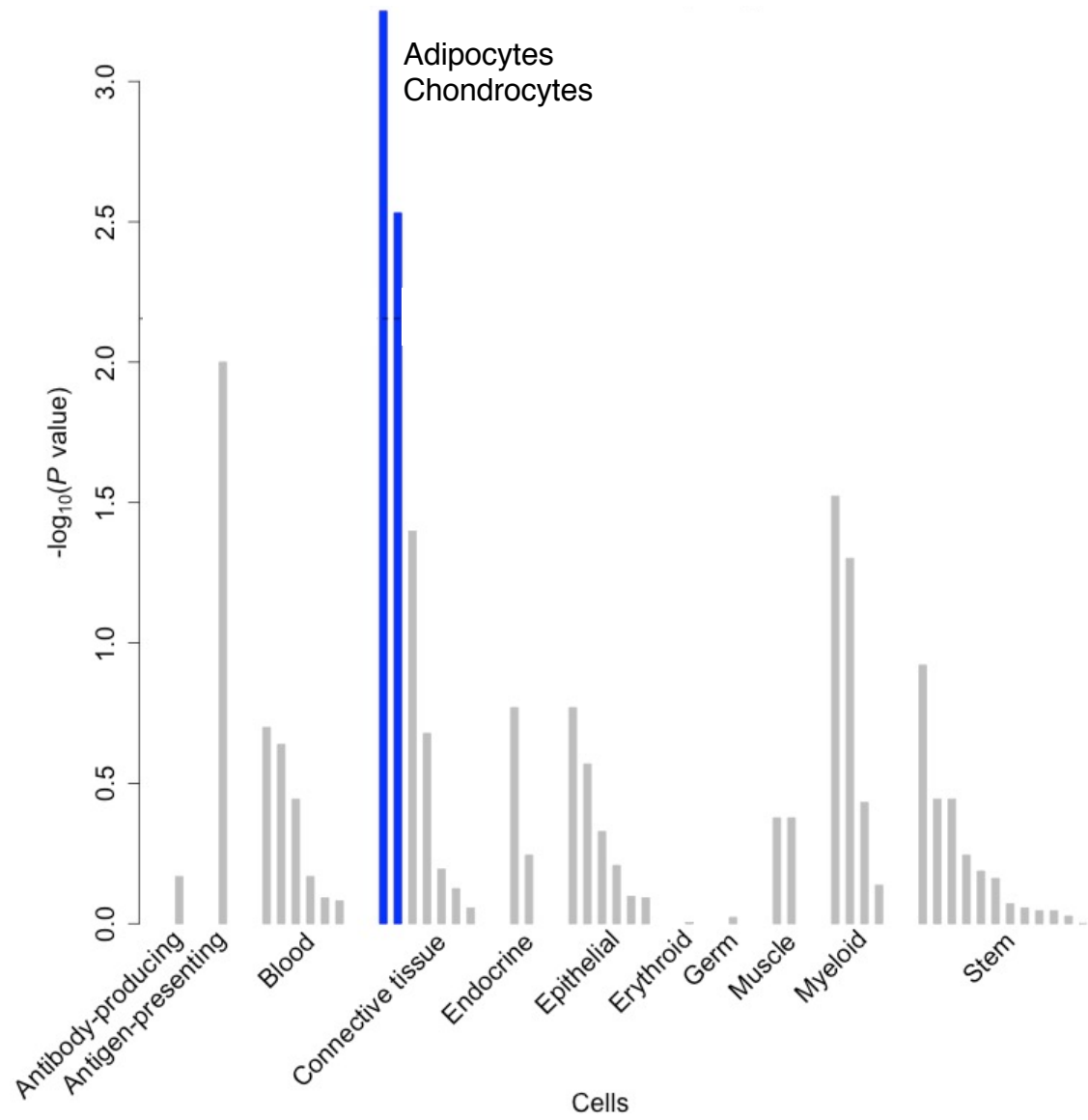


Figure 3a

Favourable adiposity



Unfavourable adiposity

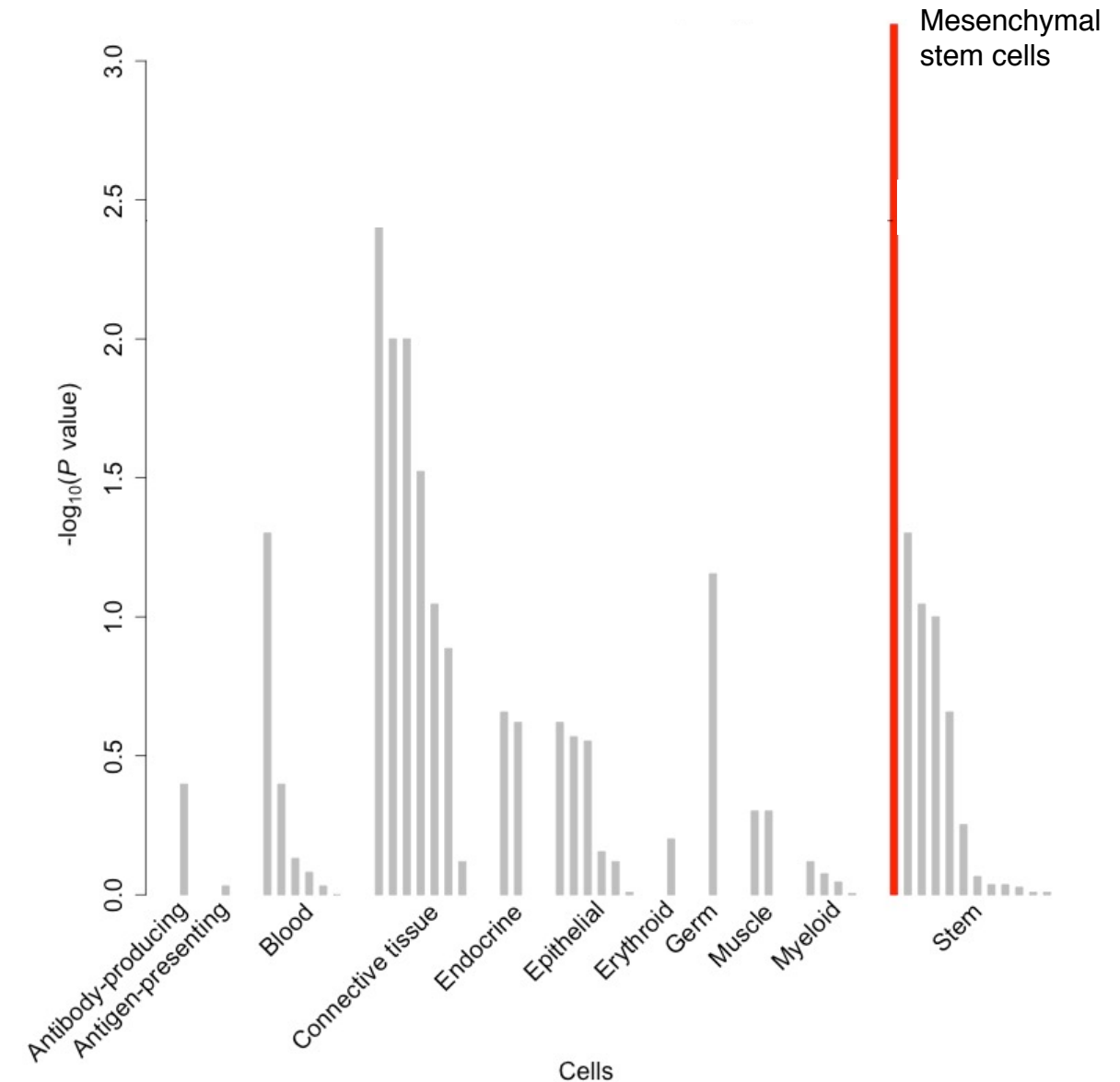
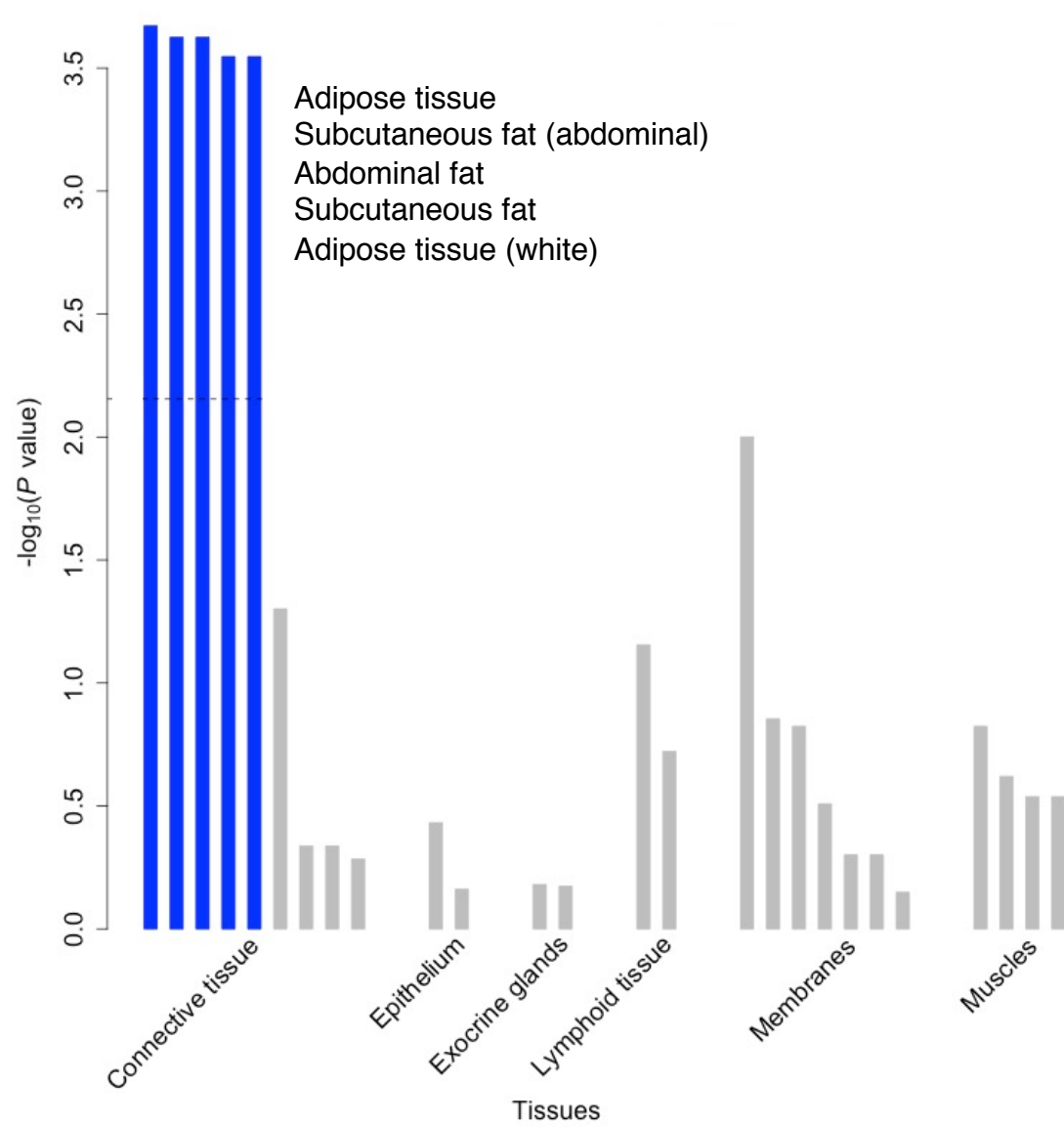


Figure 3b

Favourable adiposity



Unfavourable adiposity

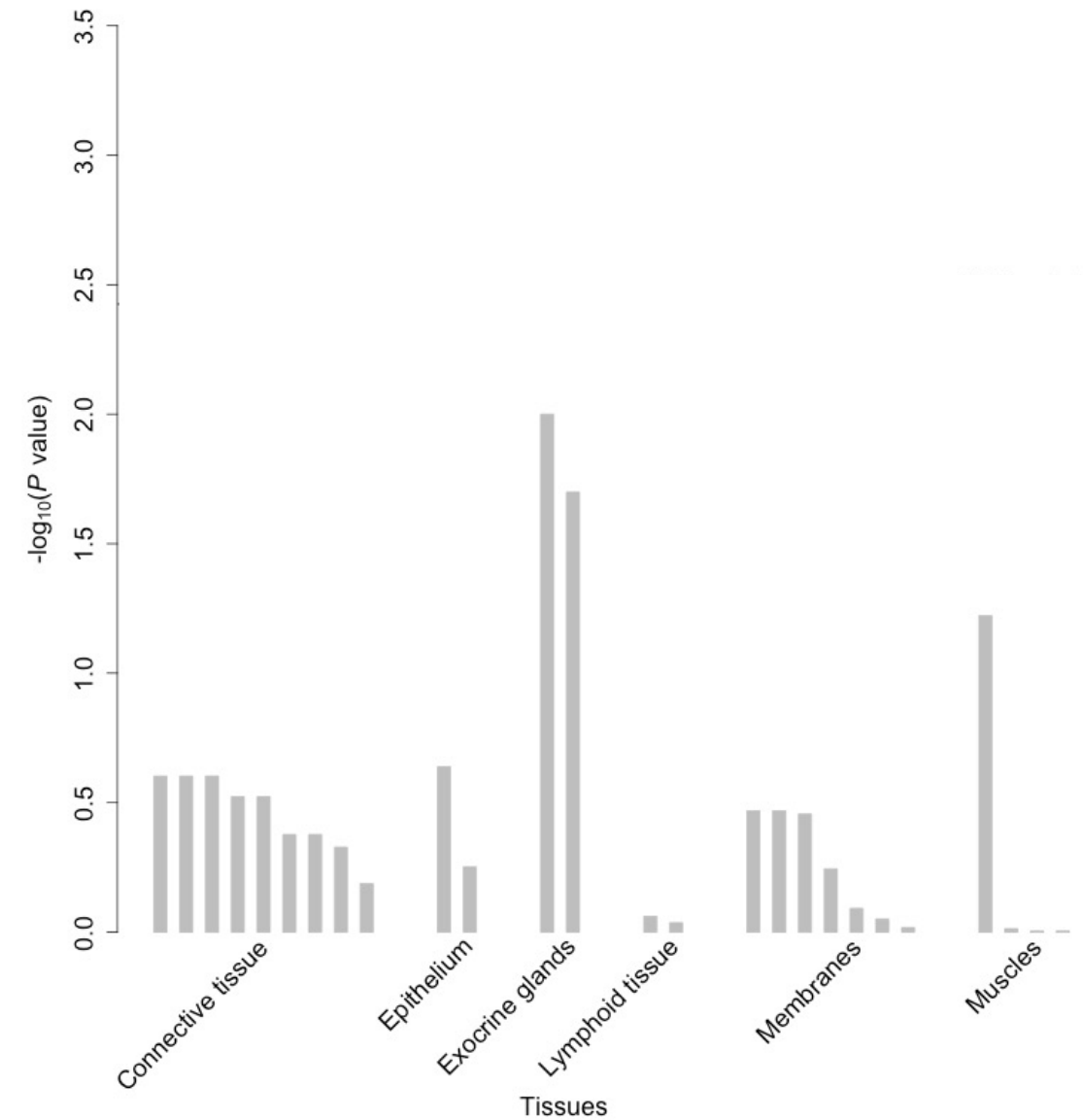
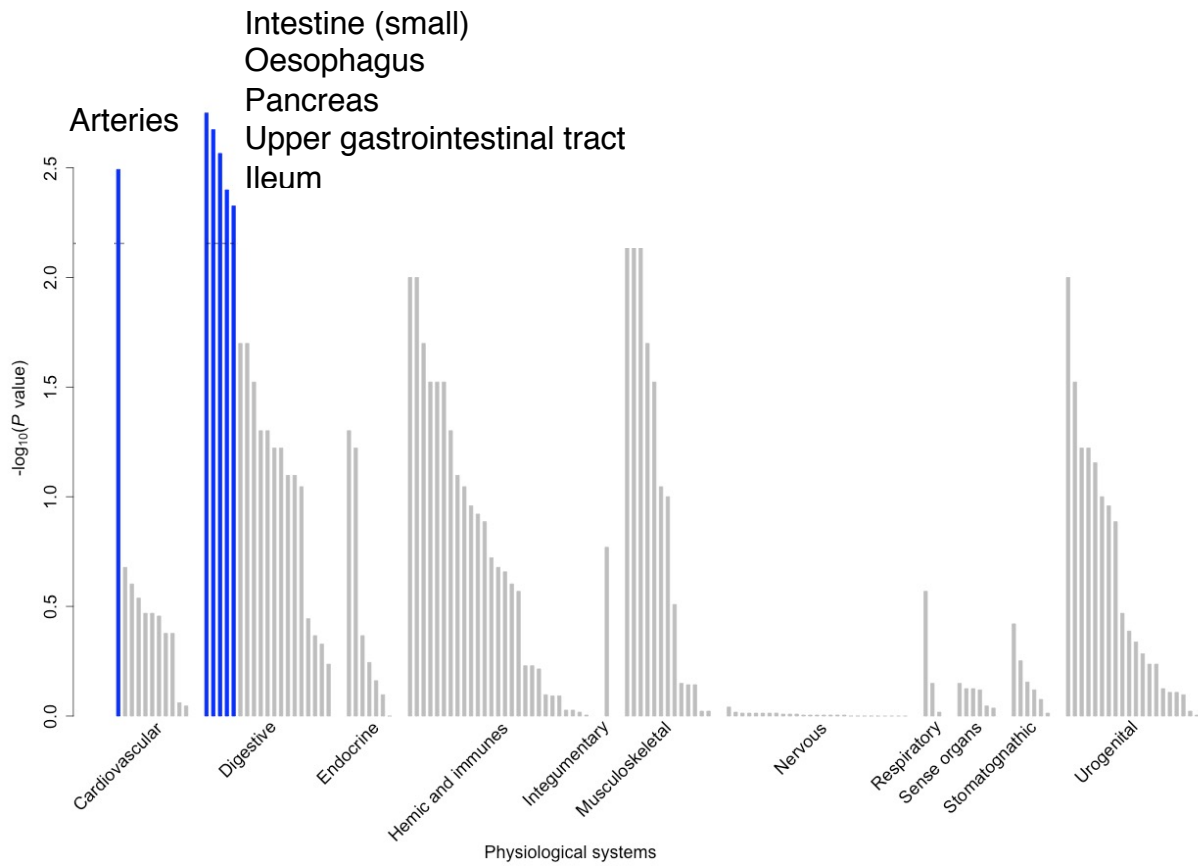


Figure 3c

Favourable adiposity



Unfavourable adiposity

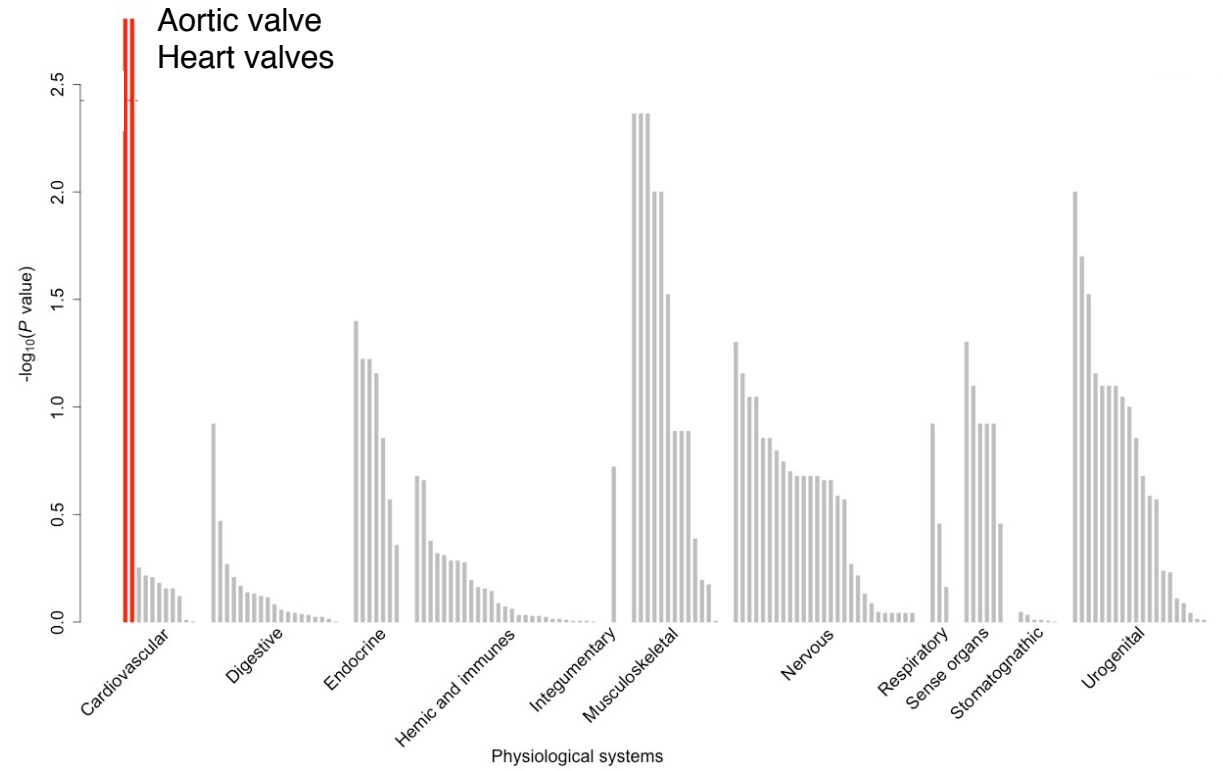


Figure 4a

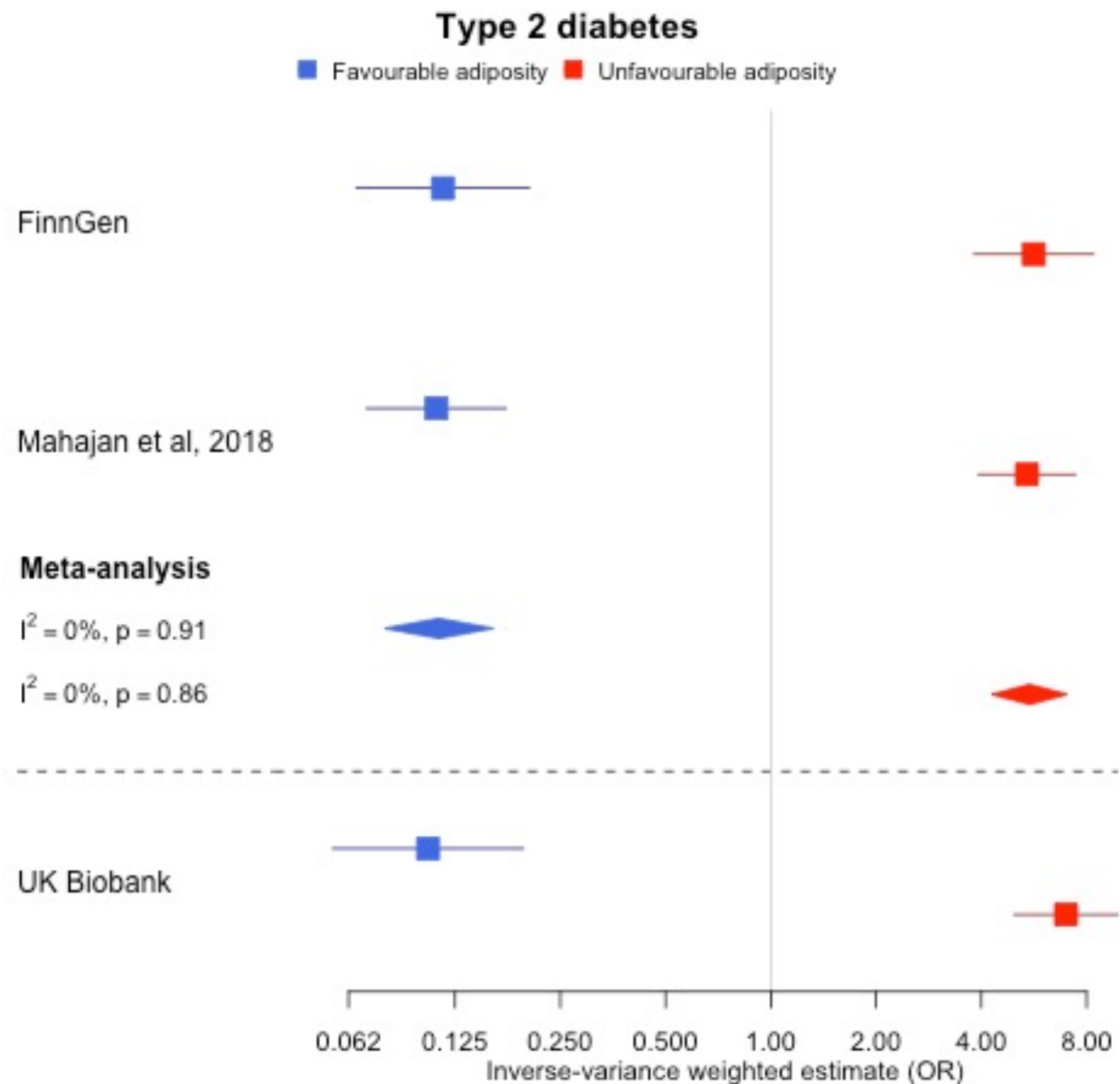


Figure 4b

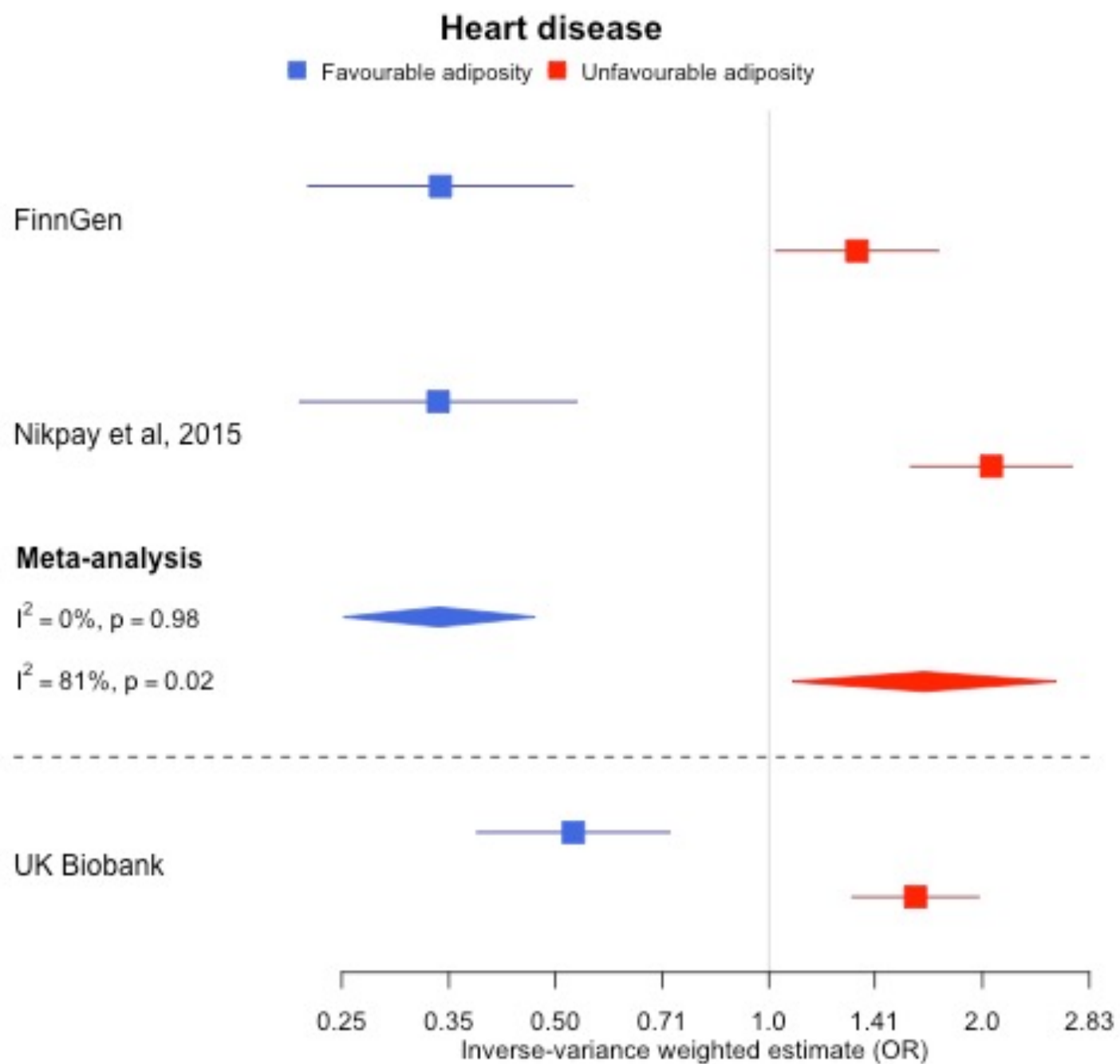


Figure 4c

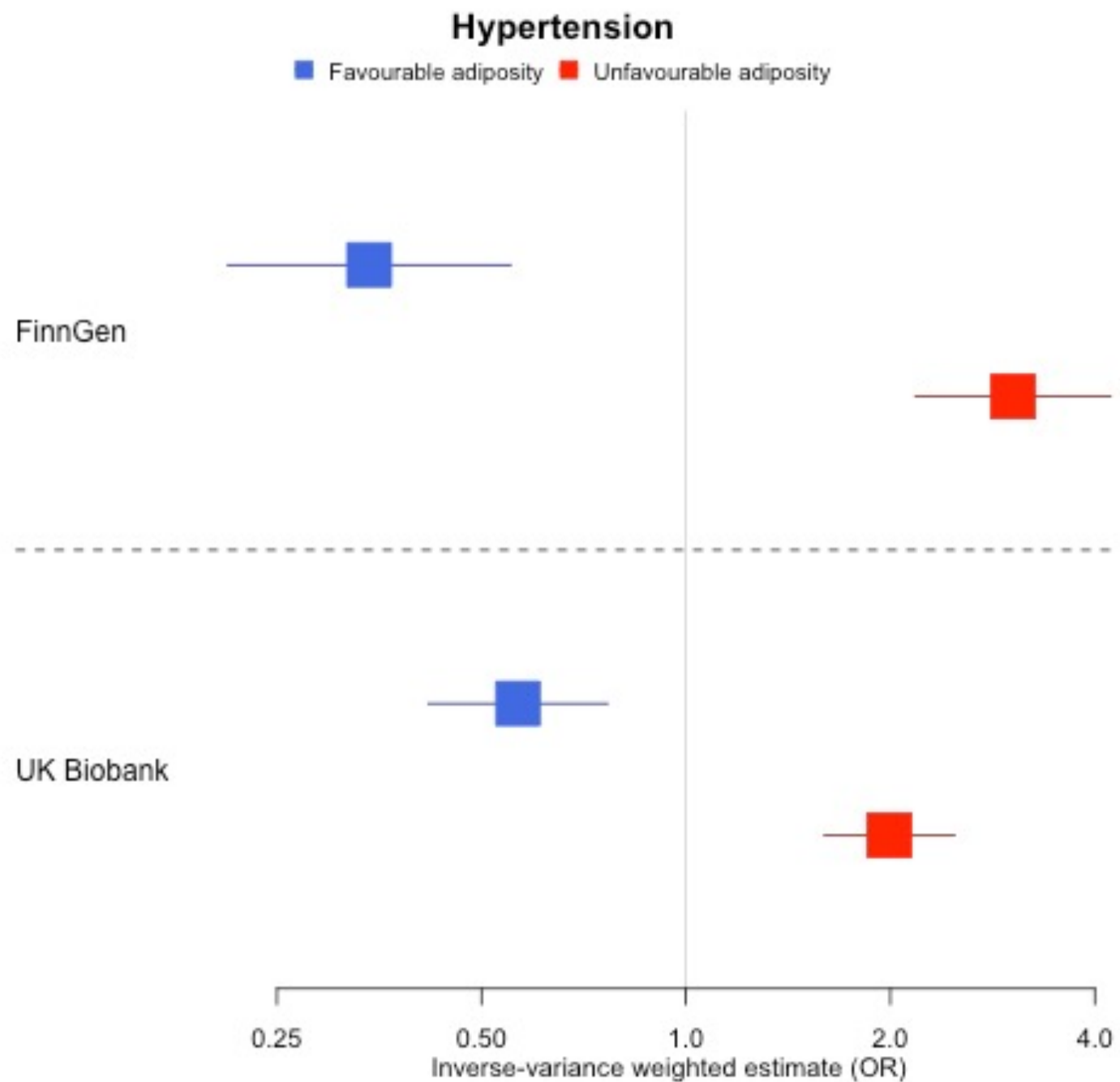


Figure 4d

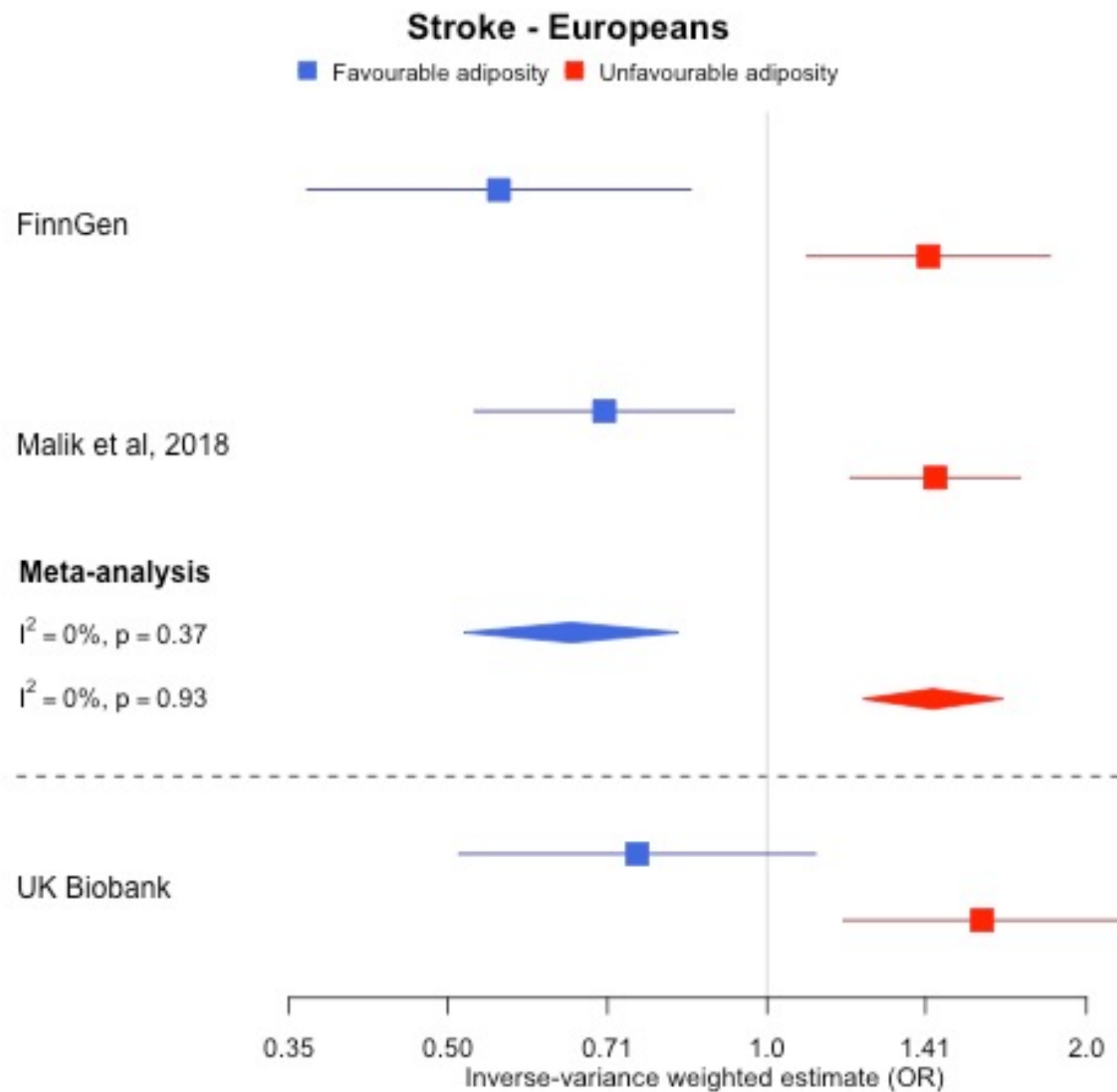


Figure 4e

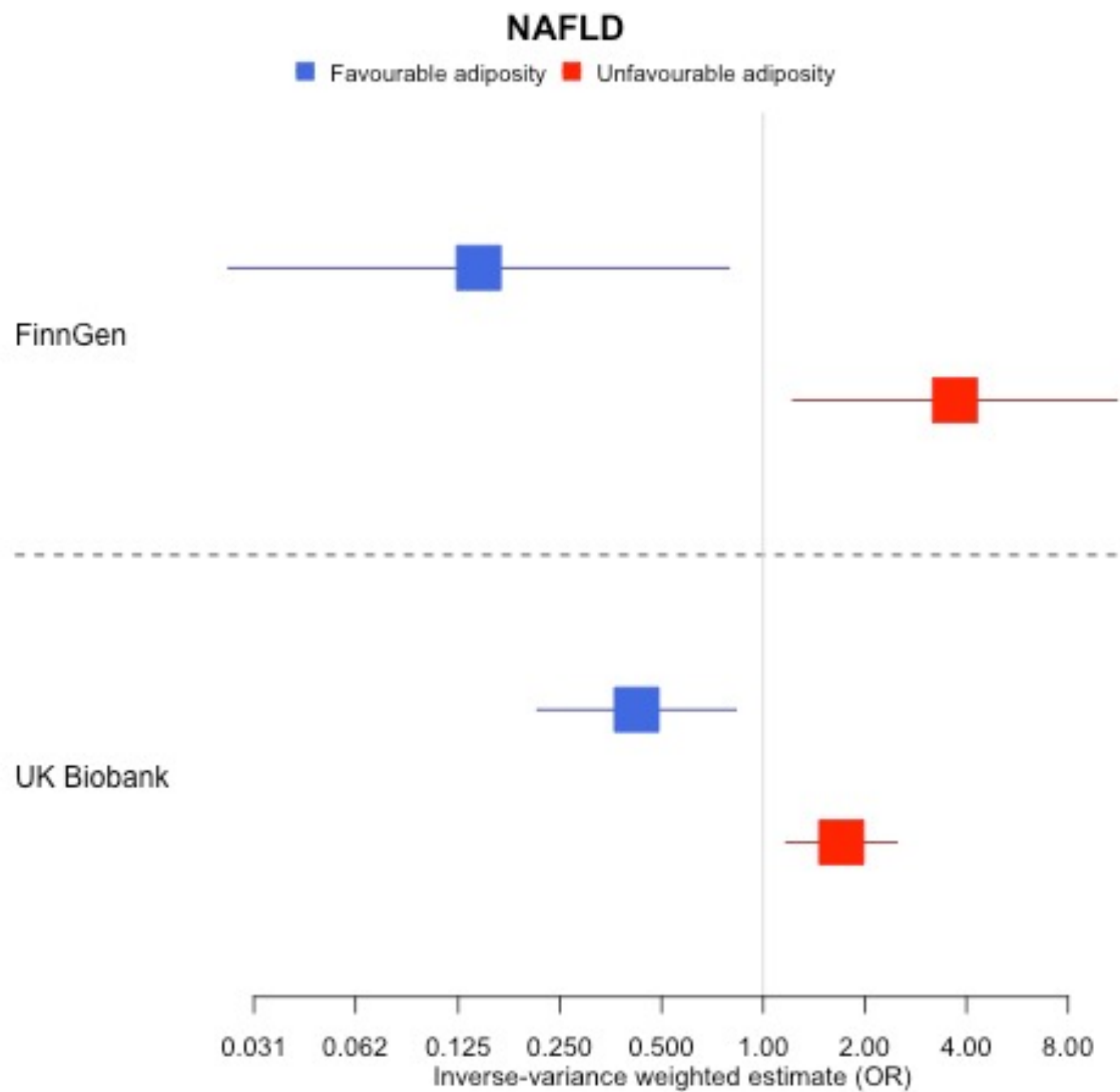


Figure 4f

