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DIABETIC Medicine

RESEARCH ARTICLE

Genetic scores associated with favourable and unfavourable adiposity have consistent effect on metabolic profile and disease risk across diverse ethnic groups

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Abstract

Aim: This study aims to investigate the associations between genetic risk scores (GRS) for favourable and unfavourable adiposity and a wide range of adiposity-related outcomes across diverse populations.

Methods: We utilised previously identified variants associated with favourable (36 variants) and unfavourable (38 variants) adiposity to create GRS for each adiposity phenotype. We used summary statistics from 39 outcomes generated by the Pan-UKB genome-wide association studies Version 0.3, incorporating covariates such as age, sex and principal components in six populations: European ($n = 420{,}531$), African (6636), American (980), Central/South Asian (8876), East Asian (2709) and Middle Eastern (1599).

Results: The favourable adiposity GRS was associated with a healthy metabolic profile, including lower risk of type 2 diabetes, lower liver enzyme levels, lower blood pressure, higher HDL-cholesterol, lower triglycerides, higher apolipoprotein A, lower apolipoprotein B, higher testosterone, lower calcium and lower insulin-like growth factor 1 generally consistently across all the populations. In contrast, the unfavourable adiposity GRS was associated with an adverse metabolic profile, including higher risk of type 2 diabetes, higher random glucose levels, higher HbA1c, lower HDL-cholesterol, higher triglycerides, higher liver enzyme levels, lower testosterone, and higher C-reactive protein generally consistently across all the populations.

Conclusion: The study provides evidence that the genetic scores associated with favourable and unfavourable adiposity have consistent effects on metabolic profiles and disease risk across diverse ethnic groups. These findings deepen our understanding of distinct adiposity subtypes and their impact on metabolic health.

KEYWORDS

cardiometabolic risk, favourable adiposity, genetic risk score, type 2 diabetes, unfavourable adiposity

1 | INTRODUCTION

Recent large-scale genome-wide association studies (GWASs) have revealed two distinct types of adiposity with unique genetic and metabolic features.[1] 'Unfavourable adiposity' is characterised by 38 genetic variants and is associated with higher adiposity and increased risk of cardiometabolic disease. In contrast, 'favourable adiposity' is characterised by 36 genetic variants and is also associated with higher adiposity but a healthier metabolic profile, including a lower risk of type 2 diabetes, heart disease and hypertension.

Analyses of MRI-based imaging data have shown that individuals with unfavourable adiposity tend to store fat internally and subcutaneously throughout the body, while those with favourable adiposity preferentially store extra fat as subcutaneous adipose tissue, which protects against ectopic fat deposition in metabolically critical organs like the liver. This indicates that effective storage of fat in subcutaneous adipose tissue may help prevent harmful fat deposition in metabolically vital organs. The 'adipose tissue expandability' hypothesis[2] explains these associations, suggesting that the genetic predisposition for adipose tissue expandability and fat storage capacity plays a role. Individuals capable of expanding their subcutaneous adipose tissue are protected, to some extent, against the adverse effects of higher adiposity and maintain a normal metabolic profile despite increased adipose tissue mass.

The question arises as to whether the genetic variants linked to favourable and unfavourable adiposity among Europeans exhibit a similar paradoxical association with adiposity and diabetes risk in other ethnic groups. Understanding the generalisability of these associations across diverse populations is crucial for unravelling the complex interplay between genetics, adiposity and metabolic health.

This study aims to address this question by assessing the impact of these genetic variants on metabolic profiles and disease risk in different ethnic groups. We used data from six continental ancestry groups, including Europeans, Central/South Asians, East Asians, Africans, Middle Eastern and Americans from the pan-ancestry genetic analysis[3] of the UK Biobank study.[4,5] We created genetic risk scores (GRS) for both favourable and unfavourable adiposity in each population and compared the effects on measures of adiposity, metabolic biomarkers and risk of type 2 diabetes across ethnicities. We additionally characterised the metabolic profile of these two different adiposity phenotypes by estimating their genetic effects on an extended list of biomarkers.

What's new?

- We validated previous findings in Europeans by analysing favourable and unfavourable adiposity genetic risk scores across five non-European populations and demonstarted consistent associations with various health outcomes.
- Novel association between adiposity subtypes and growth hormones, kidney function markers emerged from this study.

2 | METHODS

2.1 | Data sources

We used GWAS summary statistics from the Pan-UKB GWAS Version 0.3 (released 17 March 2022).[3] This data includes genetic analysis of the UK Biobank participants in different populations for different outcomes. We used summary statistics from 39 GWAS in six main populations: European (EUR; $n = 420{,}531$), Central/South Asians (CSA; 8876), East Asian (EAS; 2709), African (AFR; 6636), Middle Eastern (MID; 1599) and admixed American (AMR; 980). Definition of continental population was determined based on the degree of genetic similarity between each participant's ancestry and the populations represented in the reference panels (namely the 1000 Genomes Project[6] and Human Genome Diversity Project [HGDP]).[7] Each GWAS was performed using SAIGE and included the following covariates in the model: Age, Sex, Age*Sex, Age2, Age2*Sex, and the first 10 PCs (Principal Components).[3] The Pan-UKB research has been conducted using the UK Biobank Resource (project ID 31063).

2.2 | Favourable and unfavourable adiposity

We used 36 genetic variants associated with favourable adiposity and 38 variants associated with unfavourable adiposity.[1] These variants were discovered through a two-step process. Initially, they were found to be significantly associated (at a significance level of $p < 5 \times 10^{-8}$) with body fat percentage and a composite metabolic phenotype that includes body fat percentage, HDL-cholesterol, triglycerides, SHBG, alanine aminotransferase and aspartate aminotransferase. Subsequently, a k-means clustering approach was employed, where these variants formed two distinct clusters. One cluster collectively exhibited higher levels of HDL-cholesterol and SHBG, as well as lower

levels of triglycerides and liver enzymes (favourable adiposity) and the other cluster of variants exhibited lower levels of HDL-cholesterol and SHBG, as well as higher levels of triglycerides and liver enzymes (unfavourable adiposity).[1]

2.3 | Genetic risk score analysis

To calculate genetic risk score effect, we used published GWAS summary statistics from each ethnic group. For each genetic variant, we extracted the effect size estimates (beta) and its corresponding standard error (SE) from the GWAS summary statistics of each trait. All favourable and unfavourable adiposity variants were available in all six populations. We aligned all effects for the adiposity-increasing alleles. We performed a random-effect meta-analyses approach using the rma function in R package metafor[8] to calculate the effect of each genetic risk score as previously described.[9]

3 | RESULTS

We analysed the effect of favourable and unfavourable adiposity genetic risk scores against 38 continuous traits and the risk of type 2 diabetes in six different populations. Both favourable (Table S1) and unfavourable (Table S2) adiposity genetic risk scores were associated with 26 and 23 out of 39 outcomes, respectively, in Europeans (FDR < 0.05), while the effect size varied among other ethnic groups.

In all the populations consistently the favourable adiposity GRS was associated ($p < 0.05$) with higher body fat percentage, higher BMI (p_{AMR} and $p_{EAS} > 0.05$) (Figures 1 and 2), higher waist circumference ($p_{AMR} > 0.05$), higher hip circumference and higher whole-body fat mass ($p_{EAS} > 0.05$) (Figures S1–S3). The favourable adiposity GRS was not associated with standing height or whole-body fat-free mass (Figures S4 and S5) in any populations except in AFR where the favourable adiposity GRS was associated with higher whole-body fat-free mass.

The paradoxical association between favourable and unfavourable adiposity and risk of type 2 diabetes and metabolic biomarkers was evident in all the populations. The favourable adiposity GRS was associated with lower risk of type 2 diabetes, with odds ratio [95% confidence intervals] per one additional favourable adiposity allele as follows: EUR 0.97 [0.96, 0.98], AFR 0.97 [0.95, 1.00], CSA 0.97 [0.96, 0.99], EAS 0.96 [0.91, 1.01], MID 0.93 [0.90, 0.98] (Figure 3). On the other hand, the unfavourable adiposity GRS was associated with higher risk of type 2 diabetes as follows: EUR 1.04 [1.03, 1.04], AFR 1.02 [1.00, 1.05], CSA 1.02 [1.01, 1.04], MID 1.04 [0.99, 1.09] but not in EAS 0.99 [0.92, 1.05] (Figure 3). The favourable adiposity GRS was associated with lower diastolic blood pressure in EUR, with same direction of effect in AFR and EAS. Similar pattern of association was observed with systolic blood pressure in all populations except CSA. In contrast, the unfavourable adiposity GRS was associated with higher diastolic and systolic blood pressure in EUR and CSA and same direction of effect in AFR, EAS and MID (Figures S6 and S7).

The favourable adiposity GRS was associated with a healthier metabolic profile in generally all the populations (but with wider confidence intervals in populations with smaller sample size), including lower random glucose levels (Figure S8), lower HbA1c, higher HDL-cholesterol, lower triglycerides, lower levels of alanine aminotransferase, lower levels of aspartate aminotransferase, higher levels of sex hormone-binding globulin (SHBG) (Figures 4–9), lower levels of gamma-glutamyl transferase (Figure S9), while no evidence of association observed with alkaline phosphatase (Figure S10). The unfavourable adiposity

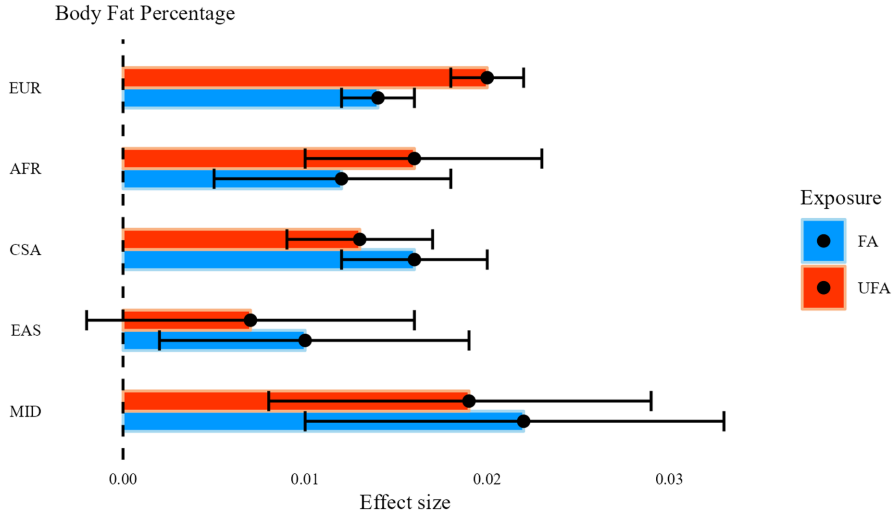

FIGURE 1 The effects on body fat percentage. The X-axis shows the effect size and 95% confidence interval for the association between genetic risk score (GRS) of favourable adiposity (blue) and unfavourable adiposity (red) with body fat percentage across six different populations.

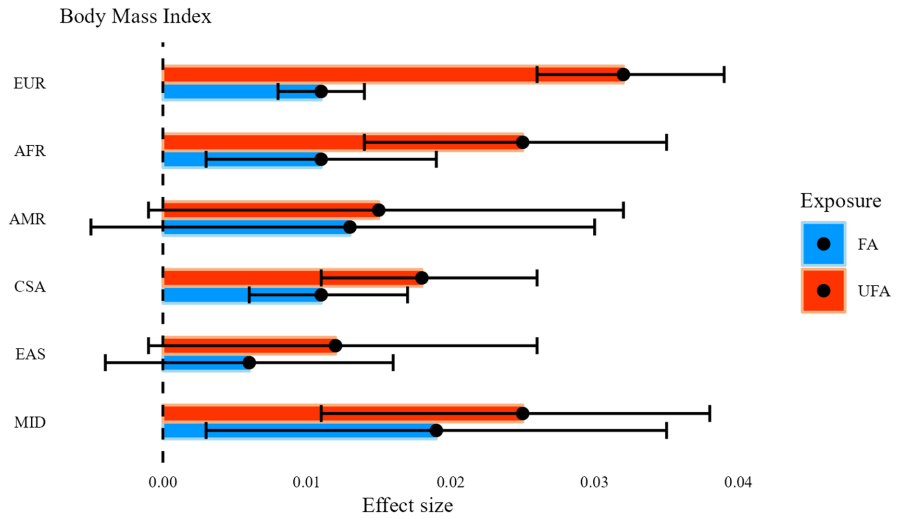

FIGURE 2 The effects on body mass index. The X-axis shows the effect size and 95% confidence interval for the association between genetic risk score (GRS) of favourable adiposity (blue) and unfavourable adiposity (red) with body mass index across six different populations.

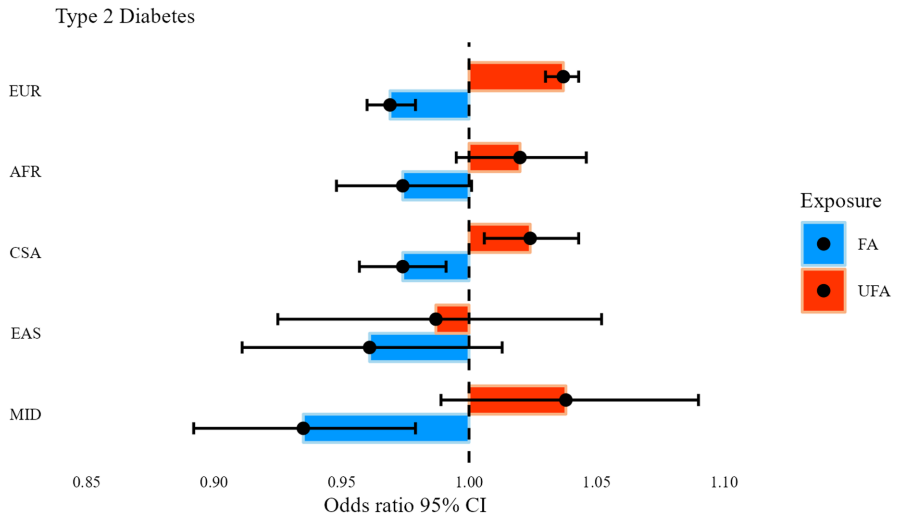

FIGURE 3 The effects on body mass index. The X-axis shows the odds ratio and 95% confidence interval for the association between genetic risk score (GRS) of favourable adiposity (blue) and unfavourable adiposity (red) with type 2 diabetes across six different populations.

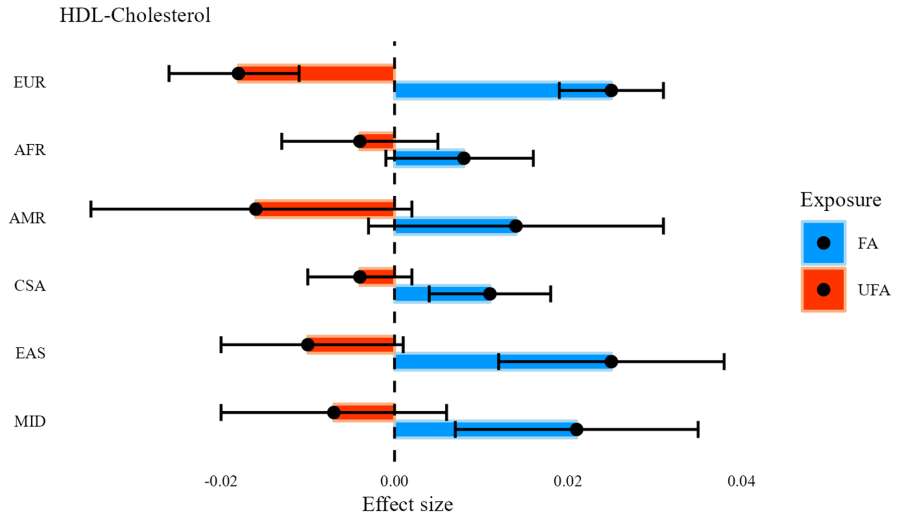

FIGURE 4 The effects on HDL-cholesterol. The X-axis shows the effect size and 95% confidence interval for the association between genetic risk score (GRS) of favourable adiposity (blue) and unfavourable adiposity (red) with HDL-cholesterol across six different populations.

GRS was associated with an adverse metabolic profile including high random glucose levels (except in AMR and EAS) (Figure S8), higher HbA1c, lower HDL-cholesterol, higher triglycerides, higher levels of alanine aminotransferase, higher levels of aspartate aminotransferase (except in AMR and CSA), lower levels of SHBG (Figures 4–9),

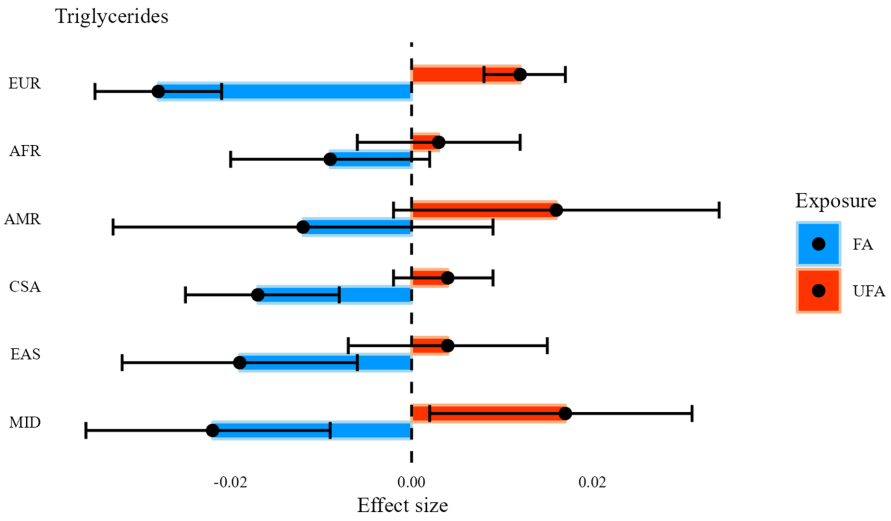

FIGURE 5 The effects on triglycerides. The X-axis shows the effect size and 95% confidence interval for the association between genetic risk score (GRS) of favourable adiposity (blue) and unfavourable adiposity (red) with triglycerides across six different populations.

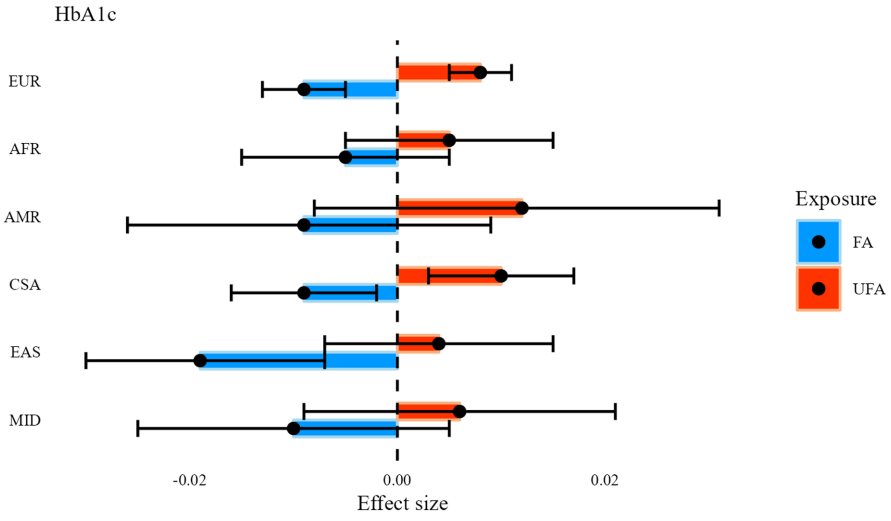

FIGURE 6 The effects on HbA1c. The X-axis shows the effect size and 95% confidence interval for the association between genetic risk score (GRS) of favourable adiposity (blue) and unfavourable adiposity (red) with HbA1c across six different populations.

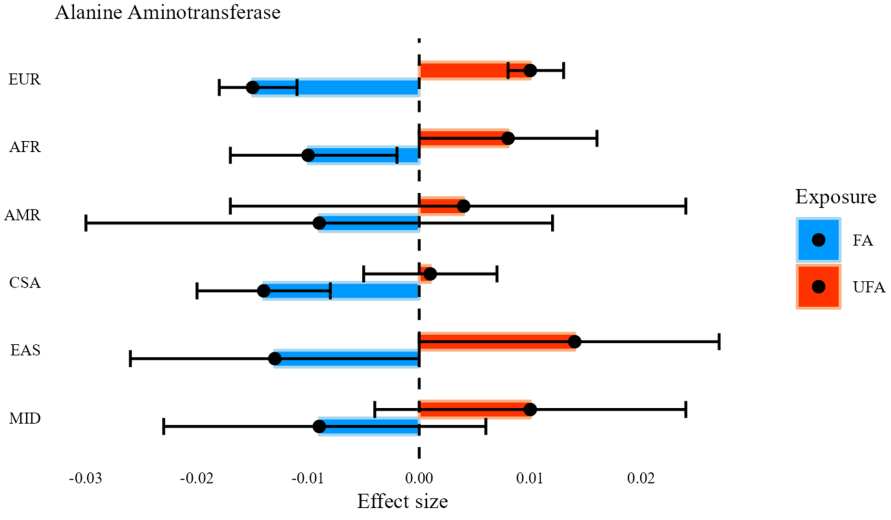

FIGURE 7 The effects on alanine aminotransferase. The X-axis shows the effect size and 95% confidence interval for the association between genetic risk score (GRS) of favourable adiposity (blue) and unfavourable adiposity (red) with alanine aminotransferase across six different populations.

higher levels of gamma-glutamyl transferase (Figure S9), higher levels of alkaline phosphatase (except CSA) (Figure S10).

We additionally looked at other metabolic biomarkers. The favourable and unfavourable adiposity had consistent direction of effect but with wider confidence intervals in

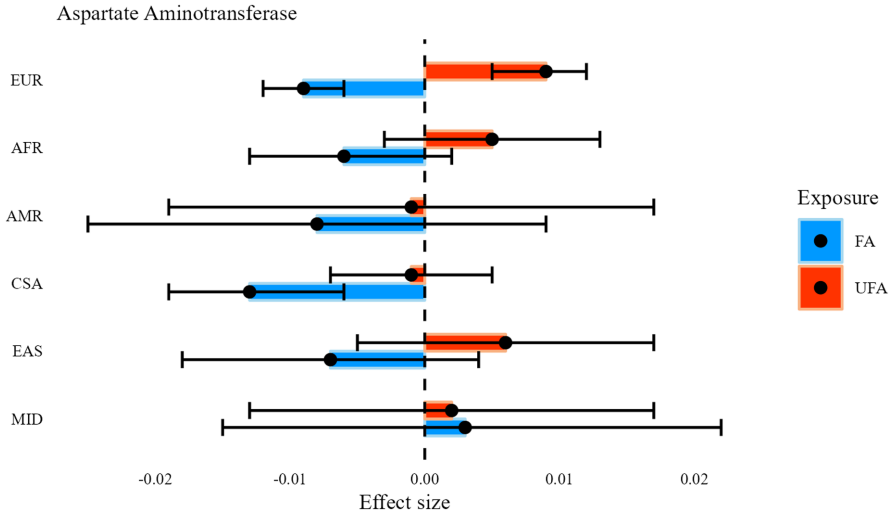

FIGURE 8 The effects on aspartate aminotransferase. The X-axis shows the effect size and 95% confidence interval for the association between genetic risk score (GRS) of favourable adiposity (blue) and unfavourable adiposity (red) with aspartate aminotransferase across six different populations.

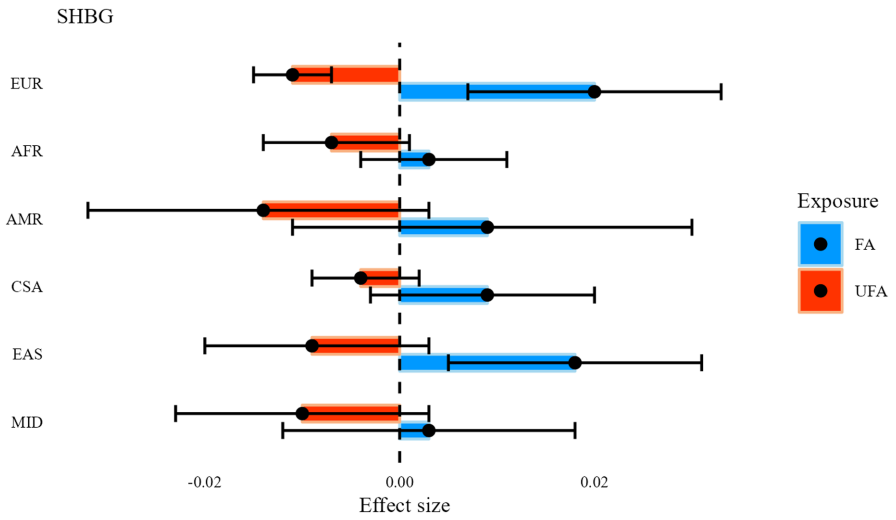

FIGURE 9 The effects on SHBG. The X-axis shows the effect size and 95% confidence interval for the association between genetic risk score (GRS) of favourable adiposity (blue) and unfavourable adiposity (red) with SHBG across six different populations.

smaller populations (Figures S11–S30). The favourable adiposity GRS was associated with higher apolipoprotein A and lower apolipoprotein B (except in AFR and CSA), higher lipoprotein A (except in EAS and MID), higher testosterone (except in MID), higher C-Reactive protein (except in EAS), lower calcium (except in EAS), lower insulin-like growth factor 1 (IGF-1), lower total protein (except in MID), lower albumin, higher cystatin C (except in EAS), lower urate (except in AFR, AMR and MID), while no evidence of association was observed between the favourable adiposity GRS and phosphate, oestradiol, rheumatoid factor, total bilirubin, creatinine, urea, vitamin D or the basal metabolic rate. On the other hand, the unfavourable adiposity GRS was associated with lower apolipoprotein A, lower testosterone (except in EAS), higher C-Reactive protein, higher cystatin C (except in EAS and MID), higher urate (except in EAS), lower total bilirubin (except AMR), lower vitamin D (except in EAS), higher basal metabolic rate, while no evidence of association was observed with oestradiol, calcium, direct bilirubin, IGF-1, phosphate, rheumatoid factor, total protein, albumin or creatinine.

4 | DISCUSSION

We performed a multi-ancestry analysis of favourable and unfavourable adiposity using pan-ancestry genetic analysis of the UK Biobank (Pan-UKB). Our results demonstrated that the genetic scores associated with favourable and unfavourable adiposity have consistent effects on metabolic profiles and disease risk across diverse ethnic groups. Genetic score for favourable adiposity was associated with higher body fat percentage and higher BMI but healthier metabolic profile and lower risk of type 2 diabetes in all ethnic groups. Genetic score for unfavourable adiposity was associated with higher measures of body fat and an adverse metabolic profile and higher disease risk, again with consistent effects across diverse ethnic groups.

Since the discovery of favourable and unfavourable adiposity genetic variants was in Europeans, it was crucial to assess the generalisability of these associations across diverse populations. By analysing data from different non-European populations, including Central/South Asians, East Asians, Africans, Americans and

Middle Easterns, we validated our findings and showed the genetic variants linked to favourable and unfavourable adiposity exhibit similar metabolic profile in various ethnic backgrounds. The consistent effects observed across these populations suggest that the genetic scores associated with these two types of adiposity have robust and universal implications for metabolic health. The inclusion of diverse populations enhances the representativeness of the findings and contributes to a broader understanding of the interplay between genetics, adiposity and metabolic health.

We previously showed in Europeans that individuals who have higher genetic score for unfavourable adiposity tend to store fat internally and subcutaneously throughout the body. On the other hand, those with higher genetic score for favourable adiposity preferentially store extra fat as subcutaneous adipose tissue, which acts as a protective mechanism against ectopic fat deposition in metabolically critical organs like the liver.[1,10] The 'adipose tissue expandability' hypothesis offers a potential explanation for these associations. According to this hypothesis, individuals capable of expanding their subcutaneous adipose tissue are somewhat protected against the adverse effects of higher adiposity, maintaining a normal metabolic profile despite an increased adipose tissue mass. This highlights the importance of understanding the genetic factors underlying adipose tissue expandability and its potential implications for metabolic health.[11–13]

Our results also provided evidence of an improved glucose homeostasis and insulin sensitivity exhibited by the consistent association of favourable adiposity GRS with lower levels of random glucose, HbA1c and insulin-like growth factor 1 (IGF-1) across the different populations. IGF-1 is a hormone that plays a role in regulating cell growth, metabolism and insulin sensitivity. Higher levels of IGF-1 have been associated with increased insulin resistance and an elevated risk of developing type 2 diabetes.[14,15] The observed lower levels of IGF-1 in individuals with the favourable adiposity GRS suggest a potential mechanism by which the genetic predisposition for favourable adiposity may contribute to improved insulin sensitivity and metabolic health. The relationship between ectopic fat and IGF-1 is more complex and multifactorial. Insulin resistance can lead to compensatory hyperinsulinaemia, which can stimulate the production of IGF-1 in the liver. Elevated IGF-1 levels may then promote adipogenesis and lipid accumulation, potentially contributing to the development and progression of ectopic fat deposition.[16] Additionally, some studies suggest that ectopic fat can indirectly influence IGF-1 levels through its impact on adipokines, cytokines secreted by adipose tissue.[17] However, the precise mechanisms underlying the interaction between ectopic fat and IGF-1 are not fully understood and require further investigation.

The paradoxical association of favourable and unfavourable adiposity GRS with SHBG and testosterone implies that there may be distinct metabolic and hormonal profiles associated with different types of adiposity. Sex hormones play a crucial role in regulating adipose tissue metabolism, energy balance and body composition.[6] In our study, the favourable adiposity GRS was found to be associated with higher SHBG, which is known to reduce the bioavailability of sex hormones like testosterone. On the other hand, the unfavourable adiposity GRS was associated with lower SHBG levels. These findings suggest that favourable adiposity may be linked to a hormonal profile that promotes metabolic health. Higher SHBG levels in individuals with higher favourable adiposity GRS may contribute to a more balanced hormonal environment, potentially protecting against the adverse metabolic effects of excess adiposity. Previous Mendelian randomisation studies have provided evidence for a causal role of higher SHBG and lower testosterone in protection from cardiometabolic diseases.[18]

The favourable adiposity GRS was associated with higher levels of apolipoprotein A, which is an indicator of healthy lipid profile and a lower risk of cardiovascular disease,[19] across all populations. The favourable adiposity GRS also showed an association with lower levels of apolipoprotein B, which associates with an adverse lipid profile,[20] except in African and Central/South Asian populations, which can be attributed to lack of power.

The association between both favourable and unfavourable adiposity GRS with higher cystatin C levels suggests a potential link between adiposity and kidney function. Cystatin C is a marker of kidney function and is used to estimate the glomerular filtration rate (GFR), which reflects how well the kidneys are filtering waste from the blood. Elevated cystatin C levels indicate impaired kidney function and reduced renal filtration. The observed association between both favourable and unfavourable adiposity GRS and higher cystatin C levels suggests that adiposity, regardless of its type, may have a detrimental effect on kidney function. It is important to note that the specific mechanisms underlying this association are not fully understood and require further investigation.

The paradoxical association of favourable and unfavourable adiposity GRS with urate suggest that favourable adiposity has a protective effect against hyperuricemia and gout. Urate is an end product from the metabolic breakdown of purine nucleotides. These results are consistent with previous ones showing that genetically higher favourable adiposity is associated with lower risk of gout

while genetically higher unfavourable adiposity is associated with higher risk.[10] In line with our finding, it has been previously shown that visceral adiposity is associated with higher hyperuricemia, independently of BMI, waist circumference and neck circumference among middle-aged and elderly adults.[10,21]

The unfavourable adiposity GRS was associated with lower vitamin D, while no evidence of association was observed with the favourable adiposity GRS. Vitamin D is a multifunctional prohormone, which contributes to various processes across various cells and tissues.[22] Mendelian randomisation studies have previously linked vitamin D to BMI. They have reported that higher BMI is causally associated with lower vitamin D levels, while there is no evidence for vitamin D to causally influence BMI.[23] Another study investigated the association of BMI with vitamin D and reported that BMI causally lower vitamin D levels.[24] Observational studies have also indicated an inverse association between vitamin D and obesity, particularly in individuals with visceral adiposity.[22,25,26] However, the precise mechanism underlying this causal association remains unclear.

Given the significant variations in adiposity and the risk of type 2 diabetes and cardiovascular diseases among different ethnic groups, it is crucial to study diverse populations. The prevalence and age of onset of type 2 diabetes vary considerably across ethnic groups. In the United States, for instance, the prevalence ranges from 17.7% in white Europeans to 22.5% in Asians, 30.6% in Hispanics and Africans and notably high rates of 45.2% in American Indians/Alaska Natives among adults aged 75 years and above.[27] These disparities are further evident within ethnic subgroups, with Indians having the highest disease risk (38.8%) among Asians and Mexicans exhibiting the highest prevalence (33.4%) among Hispanics.[28] It is also noteworthy that type 2 diabetes tends to manifest at a younger age and lower BMI thresholds in Africans and Asians compared to white Europeans.[29] By studying diverse populations, we can gain valuable insights into the underlying factors contributing to these variations. Such knowledge can help identify the specific risk factors and distinct mechanisms linking adiposity to type 2 diabetes and its cardiovascular complications in various populations, which can lead to more personalised approaches in prevention and treatment worldwide.

Our study had several limitations that should be acknowledged. First, the sample sizes for non-European populations, particularly Americans, Middle Eastern and East Asians, were smaller compared to Europeans, ranging from 980 to 2790 individuals. This smaller sample size may have resulted in reduced statistical power and imprecise estimation of effect sizes and associations within these populations. However, by utilising a single study to generate the genetic risk scores and compare their effects across diverse populations, we minimised potential methodological differences in measurements and technical biases across different ethnic groups. Second, it is important to note that the genetic variants associated with favourable and unfavourable adiposity were primarily discovered in European populations. While our findings suggest consistent effects of these variants in non-European populations, it is possible that there may exist novel and undetected genetic variants associated with favourable adiposity specifically in other populations. Future studies focused on non-European populations are needed to identify and investigate these potential variants associated with favourable adiposity. Third, the reliance on summary statistics from GWAS studies limits the availability of detailed individual-level data for more comprehensive analyses. Additionally, the inclusion of additional ethnic groups beyond the ones examined in this study would further enhance the generalisability of the findings.

In conclusion, this study provides evidence that the genetic scores associated with favourable and unfavourable adiposity have consistent effects on metabolic profiles and disease risk across diverse ethnic groups. Understanding the genetic underpinnings of adiposity and its implications for metabolic health contributes to our knowledge of the complex interplay between genetics, adiposity and disease risk. Further research, incorporating larger and more diverse datasets, is warranted to explore additional genetic factors and their interactions with environmental and lifestyle factors in identifying different subtypes of adiposity and their role in shaping metabolic health outcomes.

AUTHOR CONTRIBUTIONS

A.A. and S.J. analysed the data. H.Y. designed the study. A.A., S.J. and H.Y. wrote the manuscript. H.Y. 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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CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest.

DATA AVAILABILITY STATEMENT

All data used in this paper are accessible through https://pan.ukbb.broadinstitute.org/downloads.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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