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Genetic loci implicated in meta-analysis of body shape in Africans

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Abstract *Background and aims:* Obesity is one of the leading causes of non-communicable diseases (NCD). Thus, NCD risk varies in obese individuals based on the location of their fat depots; while subcutaneous adiposity is protective, visceral adiposity increases NCD risk. Although, previously anthropometric traits have been used to quantify body shape in low-income settings, there is no consensus on how it should be assessed. Hence, there is a growing interest to evaluate body shape derived from the principal component analysis (PCA) of anthropometric traits; however, this is yet to be explored in individuals of African ancestry whose body shape is different from those of Europeans. We set out to capture body shape in its multidimensional structure and examine the association between genetic variants and body shape in individuals of African ancestry.

Method and results: We performed a genome-wide association study (GWAS) for body shape derived from PCA analysis of anthropometric traits in the Ugandan General Population Cohort (GPC, $n = 6407$) and the South African Zulu Cohort (SZC, $n = 2595$), followed by a GWAS meta-analysis to assess the genetic variants associated with body shape. We identified variants in *FGF12*, *GRM8*, *TLX1NB* and *TRAP1* to be associated with body shape. These genes were different from the genes been associated with BMI, height, weight, WC and waist-hip ration in continental Africans. Notably, we also observed that a standard deviation change in body shape was associated with an increase in blood pressure and blood lipids.

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Conclusion: Variants associated with body shape, as a composite variable might be different for those of individual anthropometric traits. Larger studies are required to further explore these phenomena.

1. Introduction

The prevalence of obesity has tripled since 1975, accounting for over 650 million obese individuals, globally. It is now one of the leading causes of non-communicable diseases, such as cardiovascular diseases (CVDs), metabolic diseases and cancer [1,2]. Anthropometric traits provide information about an individual's obesity through body shape, size and adiposity [3]. Body shape indicates body fat distribution and different types of adiposity that can reveal an individual risk of developing certain diseases [4]. The gold standard methods of measuring adiposity include dual-energy X-ray absorptiometry (DXA) and magnetic resonance imaging (MRI) [5]. However, these methods are often not available in most low-income clinical settings and are also expensive to run. Whereas inexpensive methods of measuring body fat include the use of anthropometric traits such as weight, height, body mass index (BMI), waist circumference (WC), hip circumference (HC), waist to hip ratio (WHR) and a body shape index (ABSI), derived from weight, height, and WC.

Although inexpensive measures of body fat are readily available in most clinical settings from lower-to-high income and even rural-to-urban, these measures are often not robust enough to differentiate between fat and muscle mass, nor visceral adiposity and peripheral adiposity; therefore, poorly predicting body shape as an index for obesity. Thus, there is a growing interest to evaluate body shape derived from the principal component analysis (PCA) of anthropometric traits in large diverse datasets of uncorrelated variables that are combined to denote body shape. Only a few studies have applied a PCA approach to investigate genetic loci associated with a complex trait like body shape, predominately in Europeans [6–8]. However, due to the history of steatopygia and its elevated prevalence in Africans, a PCA approach assessing body shape as an index of obesity is needed in continental Africans.

To capture body shape in its multidimensional structure and to identify genetic loci associated with body shape in individuals of African ancestry, we applied PCA to several anthropometric traits, including weight, height, BMI, WC, HC and WHR. Herein, we performed a GWAS meta-analysis from two African cohorts to identify genetic loci associated with body shape as an index of obesity in individuals of African ancestry.

2. Results

Overall, our study had 6407 Ugandans from the general population cohort (GPC) and 2598 South African Zulu cohort (SZC). The majority of our study participants were females in both the GPC (57.1%) and SZC (73.8%) datasets (Table 1). The median age of our study participants was 29.8 years in the Ugandan GPC and 52.0 years in the SZC, indicating SZC was predominately made up of older women. Moreover, we observed SZC had a higher median BMI, height, weight, WHR, HC, and WC compared with the Ugandans (Table 1).

2.1. PCA and body shape

In the Ugandans, our first PC explained 61.93% of the variation for all anthropometric traits. We noted that the first PC has high loadings for BMI, weight, HC and WC, thus capturing body fatness among Ugandans from GPC and we named it "weight driven body shape" (Fig. 1). In the SZC, our first PC explained 56.41% of the variation and had high loadings for BMI, weight, HC and WC (Fig. 2). This PC also driven by weight, BMI, HC and WC, among the SZC and it was also named "weight driven body shape" to match with the one retained for the Ugandans. Based on the Kaiser rule, which chooses only PCs with eigenvalues >1 (to retain only PCs that explain more than one variable) [9], we chose to retain the first and second PCs after PCA. We used the first PC of both Ugandans and Zulus, because of the similar anthropometric variables that were driving these principal components, which are the proxy for body shape in our

Table 1 Participant characteristics.

Variables	**Ugandan study (n = 6407)** median (IQR)	**South African Zulu (n = 2595)** median (IQR)
Female, n (%)	3660 (57.1)	1919 (73.8)
Age, years	29.8 (17.8–46.1)	52.0 (39.0–60.0)
BMI, kg/m^2	20.7 (18.8–23.0)	31.4 (26.1–36.9)
Height, m^2	1.57 (1.51–1.63)	1.60 (1.55–1.65)
Weight, kg	52.0 (45.0–60.0)	80.0 (67.5–93.6)
WHR	0.84 (0.80–0.88)	0.92 (0.85–1.00)
HC, cm	89.0 (83.5–94.5)	109 (100–120)
WC, cm	74.0 (69.1–79.5)	103 (91.0–113)

IQR; interquartile range, BMI; body mass index, WHR; waist-hip-ratio, HC; hip circumference, WC; weight circumference.

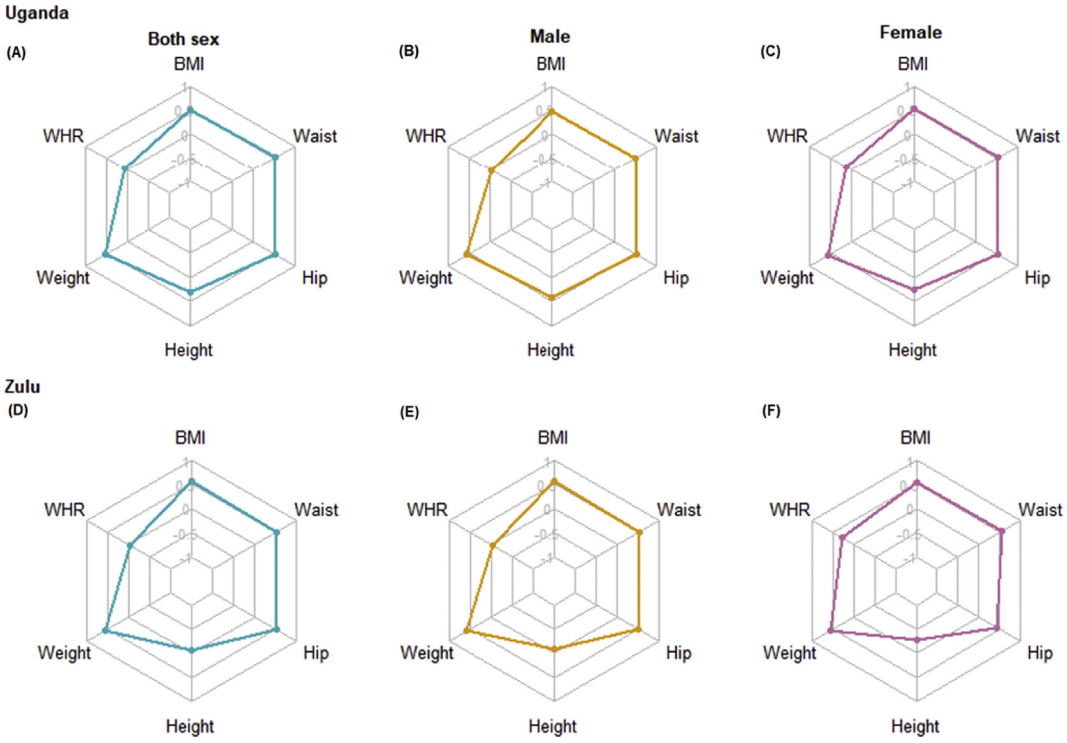

Figure 1 First PC was used to capture body shape in its multidimensional structure showing loadings for Ugandan and Zulu cohorts. (A) Loading for all participants in the Ugandan cohort, (B) loadings for male-Ugandan cohort (C) loading for female Ugandans. (D) Loading for all participants in the South African Zulu cohort, (E) loadings for male Zulus (F) loadings for female Zulus.

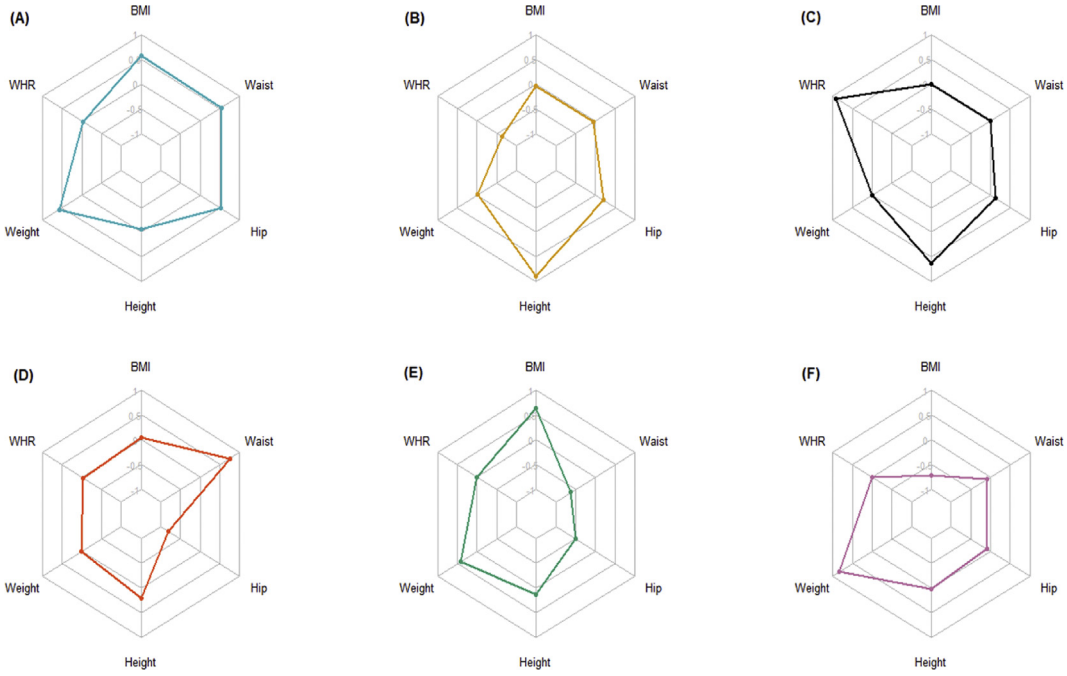

Figure 2 PC loadings for Zulu in South Africa using six anthropometric traits to capture body shape in its multidimensional structure. **(A)** The first PC shows high loading for weight, BMI, WC and HC, **(B)** The second PC shows high loading for height, **(C)** The third PC shows high loading for WHR and height, **(D)** The fourth PC shows high loading WC, but opposite loading for HC, **(E)** The fifth PC shows high loading for BMI and opposite loadings for WC and HC **(F)** The sixth PC shows high loading for weight but opposite loading for BMI.

analysis (Table S1, Fig S1). We then averaged loadings of first PC for Ugandans and Zulus to generate the PC which is representative of the most common body shape in Uganda and South African Zulu (Fig.S1). This first PC explained 60% of the variation for all anthropometric traits and had high loadings for weight, BMI, HC and WC; highlighting weight,

BMI, HC and WC, as the main drivers of body shape in this context. The same approach was repeated for the sex stratified analysis. The male PC1 body shape was similar that of the combined analysis, while the female pc1 body shape, had increased loadings in the for waist-hip ration compared to the male and the combined PC1 body shape (Fig. 1).

2.2. Body shape association with cardiometabolic traits

We performed a linear regression to assess whether any changes in body shape in both the Ugandans and Zulus were associated with blood pressure (systolic and diastolic) and blood lipids (low-density lipoprotein cholesterol, triglycerides, total cholesterol, and high-density lipoprotein cholesterol) traits in individuals of African ancestry. In our analysis, we observed that body shape changes were positively associated with blood pressure and blood lipids traits in Ugandans after adjusting for age and sex (Table.S2). Similarly, in the Zulus, the body shape was also positively associated with blood pressure traits, however, for blood lipid traits, the body shape was only positively associated with low-density lipoprotein cholesterol (Table.S2).

2.3. Discovery of body shape genetic loci

We then performed genome-wide association analyses for body shape in Ugandans and Zulus and meta-analysed the summary statistics to identify genetic loci associated with body shape, as an index of obesity in both cohorts (Methods). Furthermore, we performed a meta-analysis using the summary statistics from the Ugandans and Zulus to identify additional genetic loci associated with body shape. We identified rs150717769 to be associated with body shape at genome-wide significance, P-value = 4.01e-09 (Table 2). The Manhattan and QQ plot for the meta-analysis of body shape in individuals of African ancestry is shown in Fig. 3. Moreover, rs150717769 is mapped onto the intron in the *TRAP1* gene (Table 2). For the sex stratified meta-analysis we found four variants that were significant associated ($p < 5e-08$) with body shape in women and one in men. These were rs111783937 (*TRAP1*), rs17867127 (*FGF12*), rs17867127 (*GRM8*), rs75156321 (*FGF12*), rs17126580 (*RNU4ATAC*) in females and rs7089940 (*TLX1NB*) in men. These variants and their related genes were different from those identified for the individual traits (Fig. S4). We explored other traits these SNPs had been associated with in the Europeans using a PHEWAS approach and the TRAP1 variant was associated with anthropometric trails. This variant based on the Diabetes Epigenome atlas was is involved in regulatory activities as an enhancer in the adipose tissues. The other variants were involved in the regulation of the central nervous system as enhancers and binding sites in the mammary glands (Table 2) (see Fig. 4).

3. Discussion

In this study, we performed a GWASs of PC derived body shape in two different African populations, as well as a meta-analysis of the most similar PCs, which presented several novel genetic loci associated with body shape in individuals of African ancestry. BMI, weight, WC and HC contributed the most in driving body shape patterns and they explained most of the variances for all the six anthropometric traits measured. We identified *HNRNPC* and *GBE1* genetic loci to be associated with body shape in Ugandans and Zulus, respectively. Overall, our meta-analysis of the Ugandan and Zulu

Table 2 Genetic loci associated with body shape composite phenotype in individuals of African ancestry.

SNP	Annotation/ tissue	Effect Allele	Non-Effect Allele	EAF	Nearest Gene	Zulu		UGR		Meta-analysis		
						Beta	P	Beta	P	Beta	P	Direction
Combined												
rs150717769	Intron/ Enhancer/ Adipose Tissue	A	G	0.73	*TRAP1*	−0.58	2.50e-03	−0.58	4.96e-07	0.58	4.01e-09	++
Females												
rs111783937	Inron/Enhancer/ Central Nervous Tissue	A	G	0.73	*FGF12*	−0.43	1.17e-02	−0.12	7.41e-07	−0.21	4.32e-08	−−
rs17867127	Intron/ Enhancer/Stem Cell	A	G	0.14	*GRM8*	0.21	3.14e-03	0.14	1.12e-07	0.12	1.74e-09	++
rs75156321	Intron	A	G	0.73	*FGF12*	−0.32	1.42e-02	−0.31	4.32e-07	−0.25	3.43e-08	−−
rs17126580	Intron/ Enhancer/ central nervous system	T	C	0.02	*RNU4ATAC*	0.24	7.33e-04	0.18	1.40e-05	0.25	3.79e-08	++
Males												
rs7089940	Intron/Binding site/Mammary gland	A	G	0.12	*TLX1NB*	0.18	1.34e-02	0.09	8.03e-07	0.29	3.43e-08	++

CHR; chromosome, SNP; single nucleotide polymorphisms, BP; base pair position, MAF; minor allele frequency, SE; standard error, P; p-value, UGR; Uganda Cohort, Zulu; South African Zulu Study. Annotation based in the Diabetes Epigenome Atlas.

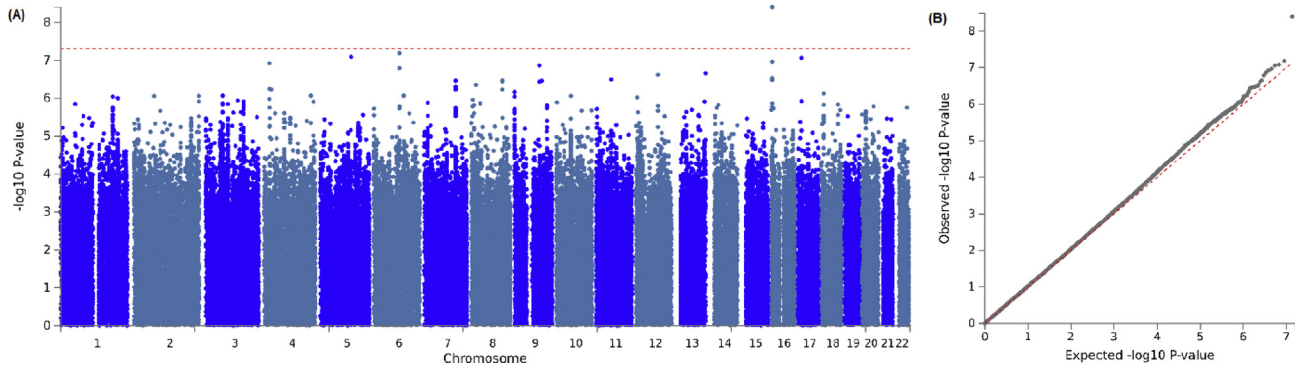

Figure 3 Meta-analysis association between genetic variants and body shape in individuals of African ancestry. **(A)** Manhattan plot, **(B)** QQ plot.

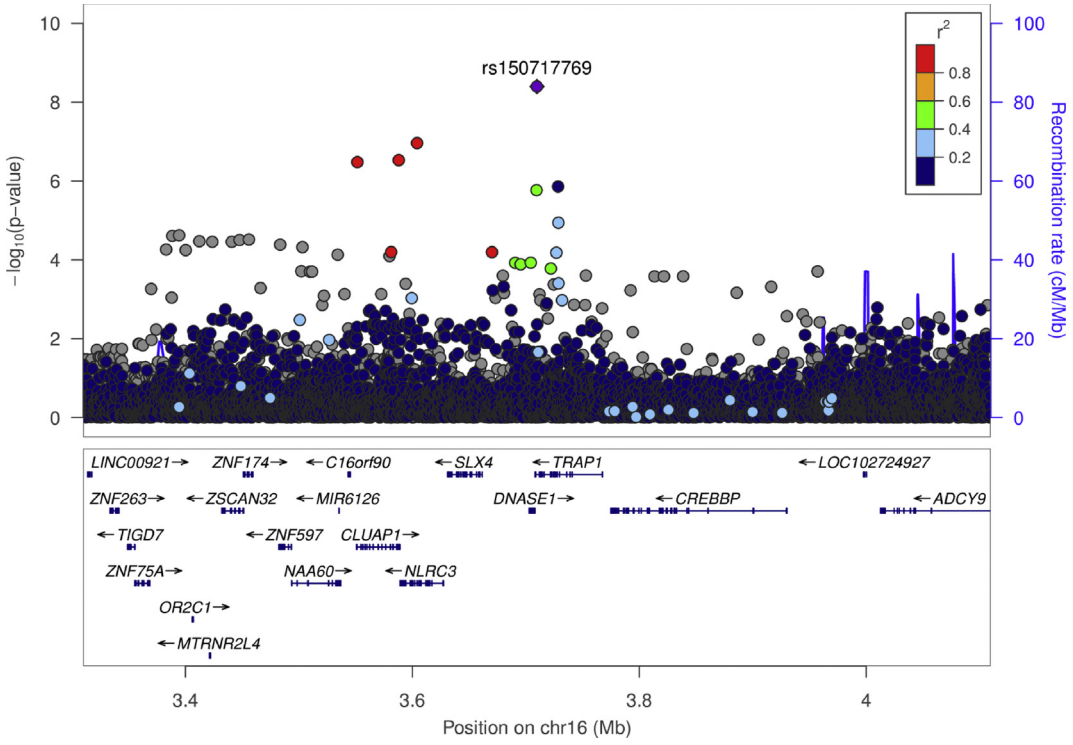

Figure 4 Locus zoom plot for meta-analysis association between genetic variants and body shape showing rs150717769 mapped within the intergenic region between *TRAP1* and *DNASE1*.

GWASs identified *TRAP1* as a mutual, additional genetic locus associated with body shape, using the average loadings of the first PC for our six anthropometric traits.

Using average PC from 20 studies, Reid et al. (2016) reported body shape characterised by high loadings for all traits (weight, BMI, WC, WHR, and HC), except height in individuals of European ancestry [6]. Subsequently, in our analysis of continental Africans, we observed that the PC1 had high loadings for weight, BMI, WC and HC, and not in height nor WHR, thus, overall adiposity/body fatness in body shape in Africans is mostly driven by the former four traits. The loadings are in the same direction; meaning that the average PC1 captures inter-individual variation in either increased or decreased BMI, weight, WHR, HC and WC. Interestingly, we observed that the first PC loadings in both Ugandans and Zulus were consistent in weight, BMI, WC and HC, even though the exact variances were different. This observation suggests that the body shape as an index of adiposity has predominantly common measures and features with variability in individuals of African ancestry residing in southern and eastern parts of Africa, as well as Europeans.

On the other hand, the notable differences between Reid et al. (2016), and our meta-analysis in the average PC1 are the low loadings of WHR in individuals of African ancestry. Since the majority of our study participants were women, hence, the observed differences those are probably true for women of African ancestry, as they often tend to have wider hips, a lower WHR, and a higher prevalence of steatopygia, than women of European ancestry [10,11].

Furthermore, we also observed that both the WHR and height in both Ugandans and South African Zulus had low loadings in opposite directions, suggesting the average PC1 does not capture inter-individual variation in either increased or decreased WHR/height. However, the cause is not clear. For example, our second PCs in Ugandans and South African Zulus were driven more by WHR (and then height) and height (and then WHR, both in the opposite direction), respectively, compared to other anthropometric traits, Thus, our individual cohort loadings for our second to sixth PCs were not consistent between Ugandans and South African Zulus to use for meta-analyses.

After linear regression, with blood pressure and blood lipids traits in individuals of African ancestry in Uganda, our first PC was positively associated with adiposity derived body shape. However, in the Zulus, our PC1 was positively associated with blood pressure traits and only LDL; whereas, HDL exerted a protective effect. The observed differences in cardiometabolic trait prediction using PC1 between Ugandans and Zulus may be due to genetic and some environmental exposure differences between these cohorts [12–14] and future studies are needed to examine this association further.

.Using PC GWAS meta-analysis we identified rs150717769 ($p = 4.01e-09$) to be associated with body shape in individuals of African ancestry. This variant is mapped in the intergenic region between *TRAP1* (Table 2). *TRAP1* acts as a key regulator of mitochondrial homeostasis, bioenergetics and metabolism, thus contributing to the regulation of the body shape. Moreover, *TRAP1* have been previously identified to be associated with BMI in individuals of diverse ancestry population [17]; and *TRAP1* was also associated with height in individuals of European ancestry [18]. Using the GTEx Portal, we observed that *TRAP1* is strongly expressed in visceral and subcutaneous adipose tissue, supporting our findings that the average PC1 captures largely adiposity in both Ugandans and South African Zulu. The other variants associated with sex stratified body shape located in *GRM8, TLX1NB, FGF12* were noted to be involved in the regulatory activities in the central nervous system as enhancers. This is similar to what has been reported in related anthropometric GWAS where variants with function in the central nervous system have been implicated with obesity.

The main strength of this study is that our PC1 which explains much of anthropometric traits variation was associated with cardiometabolic traits including blood pressure and blood lipids traits in individuals of African ancestry. However, our study was limited by a few SNPs reaching genome-wide significance in both cohorts and our analyses were limited to PC1. Nevertheless, the other PCs have loadings similar to the single-trait GWASs and they do not explain much of the variation for anthropometric traits.

In summary, we identified five genomic loci to be associated with body shape in individuals of African ancestry that are different from those identified for individual traits in this population group. Our findings suggest that the body shape assessed by PCs provide more detailed information about an individual's body shape, size and adiposity that is not fully captured by individual anthropometric traits. If applied to other highly correlated phenotypes, PCA might reveal novel genetic loci and pathways that have not been identified in single-trait GWAS.

4. Methods

4.1. Study population

The Medical Research Council (MRC) United Kingdom, together with the Uganda Virus Research Institute (UVRI) launched the General Population Cohort in the 1980s with the primary aim of investigating the epidemiology of Human Immunodeficiency Virus (HIV) infection in Uganda's. In 2011, the University of Cambridge, Wellcome Sanger Institute (WSI), in collaboration with the MRC/UVRI began the GPC round 22 studies to investigate the genetics and epidemiology of communicable and non-communicable diseases in Uganda's, using both populations' genetic and epidemiological approaches. A total of 4778 Uganda's from the GPC round 22 study and 1629 individuals from the Uganda 2000 Genomes project (UG2G) [19,20], making up a total of 6407 individuals were used as the discovery cohort.

The South African Zulu study, is a combination of the Durban Diabetes Study (DDS) and the Durban Case-Control Study (DCC) in KwaZulu-Natal, South Africa. DDS is a population-based cross-sectional study of individuals aged >18 years residing in the urban black communities in Durban, KwaZulu-Natal, South Africa. DCC is a case−control study of individuals aged >40 years with diabetes recruited from tertiary hospitals in Durban. Data collection was conducted from 2009 to 2013 for the DCC and from 2013 to 2014 for the DDS. The survey questionnaire included socioeconomic factors, health information, lifestyle factors, anthropometric measurements (including height, weight, systolic blood pressure, diastolic blood pressure, and hip and waist circumferences), biomarkers for communicable and non-communicable diseases, and genetic data. Of the 2804 individuals surveyed, 1204 were from the DDS and 1600 were from the DCC; more detailed information on the study design and quality controls have been published previously [21]. The DDS was approved by the University of KwaZulu-Natal Biomedical Research Ethics Committee (UKZN BREC) (BF030/12) and the UK National Research Ethics Service (14/WM/); the DCC was approved by UKZN BREC (BF078/08) and the UK National Research Ethics Service (11/H0305/6). All study participants in the GPC Ugandan and Zulu cohorts had anthropometric measurements and provided written informed consent to participate in the studies.

4.2. Anthropometric traits measurements

At recruitment anthropometric traits including height, weight, WC and HC were measured from all the study participants. Height and weight were measured using the Leicester stadiometer and the Seca 761 class III mechanical

flat scales, respectively [19]. WC and HCs were measured using the non-stretch Seca 201 ergonomic circumference measuring tape. WC was measured at the mid-point between the lower costal margin and the level of the anterior superior iliac crests. HC was measured at the greater trochanter of the femur as previously described [19]. BMI values were derived from weight over height whilst WHR was derived from WC values over HC values.

4.3. Genotype data

Information on sample collection, genotyping, imputation and quality control procedures were described in detail by previous studies [8,19] Participant samples from the Uganda GPC were genotyped on the Illumina Human Omni 2.5M Bead Chip array at the Wellcome Trust Sanger Institute (WTSI). The samples were chosen as a subset of the survey population with the most complete phenotype data on the traits measured. Samples from the South African Zulu study were genotyped on the consortium-driven Illumina HumanOmni Multi-Ethnic GWAS/Exome Array (MEGA pre-commercial v1) using the Infinium Assay. Quality control was carried out collectively, with sample QC including filtering for called proportion (<97%), heterozygosity (>4SD from mean), sex check fails (F statistic <0.8 for men, and >0.2 for women). Sample QC was followed by SNP QC, including filtering for called proportion (<97%), Hardy Weinberg disequilibrium ($p < 1e-06$), and relatedness (IBD >0.90). Samples and variants that did not pass the quality thresholds for the SNP and samples quality control were excluded. Principal Component Analysis (PCA) was carried out to correct for population/ancestry outliers. Following quality control, phasing and imputation for both cohorts were carried out with SHAPEIT2 using default parameters and IMPUTE2 respectively. Transformation of traits was carried out uniformly for each cohort to make effect sizes comparable across cohorts, allowing meta-analyses of summary results.

4.4. Estimation of PCs loadings and association testing

To capture body shape in its multidimensional structure, we carried out PCA on six anthropometric traits. For each study, we performed a PCA on the standardized residuals of the anthropometric traits and adjusted for age and sex for the Uganda study. Diabetes status in addition to age and sex were corrected for in the South African Zulu study in the combined analysis. In the sex stratified analysis age and diabetes status were corrected for. The standardized residuals were decomposed into six principal components (PCs) according to eigenvectors, and principal loadings. The six resulting PCs is an aggregate and an orthogonal linear representation of individual PCs of the six anthropometric traits. In our analysis loadings is used to describe the weight of each PCs. The loadings and explained variances were comparable between Uganda's and Zulu from South Africa. The association between genetic variants and body shape was tested using the linear mixed model implemented in genome-wide efficient mixed-model analysis (GEMMA) [22]. In our analysis, we used PC1 as the phenotype of interest in both Uganda's and Zulu. Furthermore, we adjusted for cryptic relatedness by including a kinship matrix in the model. The kinship matrix was estimated using genetic variants with MAF >1% and pruned to an r2 threshold of 0.5.

4.5. Meta-analysis and annotation of genetic variants

Meta-analyses of 8769 participants was performed on the summary statistics of the PC1 of the Ugandan GPC ($N = 6178$) and South African Zulu cohort ($N = 2591$), using the inverse variance weighted fixed-effects model as implemented in Metal. We also lated conducted meta-analysis in men and women for the PC1 body shape.This is a free, efficient, and open-source meta-analysis software tool for GWASs analysis [23]. We used FUMA [24], to annotate, prioritize, visualize, and interpret GWASs results for body shape. Genetic variants with $p < 5 \times 10^{-8}$ were selected as signals with genome-wide significance. The SNP2GENE function within FUMA takes GWAS summary statistics as an input and provides extensive functional annotation in genomic areas identified by lead SNPs, while the GENE2FUNC annotates genes in a biological context [24].

4.6. Body shape and cardiometabolic traits

Based on the Kaiser rule, we chose to retain the first and second PCs after PCA. However, in our analysis, we focused on the first PC in Ugandans as it was similar to the first PC in the South African Zulu dataset. We further evaluated whether our PC1 in both cohorts are associated with cardiometabolic traits, we then performed a linear regression analysis in both Ugandans and South African Zulu. In both cohorts, we adjusted for age and sex. We further adjusted for T2D in the South African Zulu dataset. In this analysis, our cardiometabolic traits were blood pressure (systolic and diastolic) and blood lipids (low-density lipoprotein cholesterol, triglycerides, total cholesterol, and high-density lipoprotein cholesterol) traits. The linear regression analysis was performed using the generalised linear model (GLM) and all statistical analyses were performed using the R language [25].

Contribution statement

SF and TC conceptualized the study. MN, OS, TM, TC and SF performed the data analyses. ABK validated the analyses. MN and OS wrote the first draft. ABK, TM, TC, SF reviewed the first draft. SF and TC supervised the project. All the authors read and provided critical feedback on the paper.

Declaration of competing interest

None.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.numecd.2022.03.010.

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