Cardiovascular Diabetology

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Independent association of leg-height ratio with 15 cardiometabolic diseases

Ran Zhao[1], Wenyan Xian[1], Valerio Napolioni[2], Zhiyi Wang[3], Zhiyan Ding[4], Patrick W C Lau[5], Xiao-Li Tian[6], Andre Franke[7] and Jie Huang[1*]

Abstract

Background The association between adult height and coronary artery disease (CAD) was established a decade ago. Accumulating evidence has since linked adult height to a variety of cardiometabolic diseases (CMD). As waist-hip ratio (WHR) has become an increasingly important independent risk factor in addition to body mass index, we aim to assess whether leg-height ratio (LHR) could also be a risk factor independent of overall height.

Methods LHR was defined as the ratio of leg length to standing height and further adjusted for overall height by regression. Using data from UK Biobank, we first performed genome-wide association study (GWAS) of LHR and height, then assessed their associations with 15 major CMD at phenotypic and genetic levels. Mediation and colocalization analyses were conducted to identify mediators and shared variants.

Results We identified 747 genome-wide significant variants of LHR after stepwise conditional and joint analysis. SNP-based heritability was estimated at 24% for LHR, versus 47% for height. A low LHR (bottom 20%) was associated with a substantially higher risk of CAD than a medium (middle 60%) or high (top 20%) LHR, regardless of the height category. This pattern is pronounced for type 2 diabetes (T2D), where tall individuals with low LHR exhibit higher risk (HR = 1.39 [1.29–1.49], $P = 2.7 \times 10^{-20}$) than individuals of short or medium height with higher LHR. Lipids (especially high-density lipoprotein cholesterol) primarily mediated the protective effect of LHR on CMD, whereas inflammatory markers (especially neutrophils) mainly mediated the effect of height on CMD. Colocalization analyses revealed LHR-specific variants shared with CMD, including notable colocalization with T2D at the *JAZF1* locus.

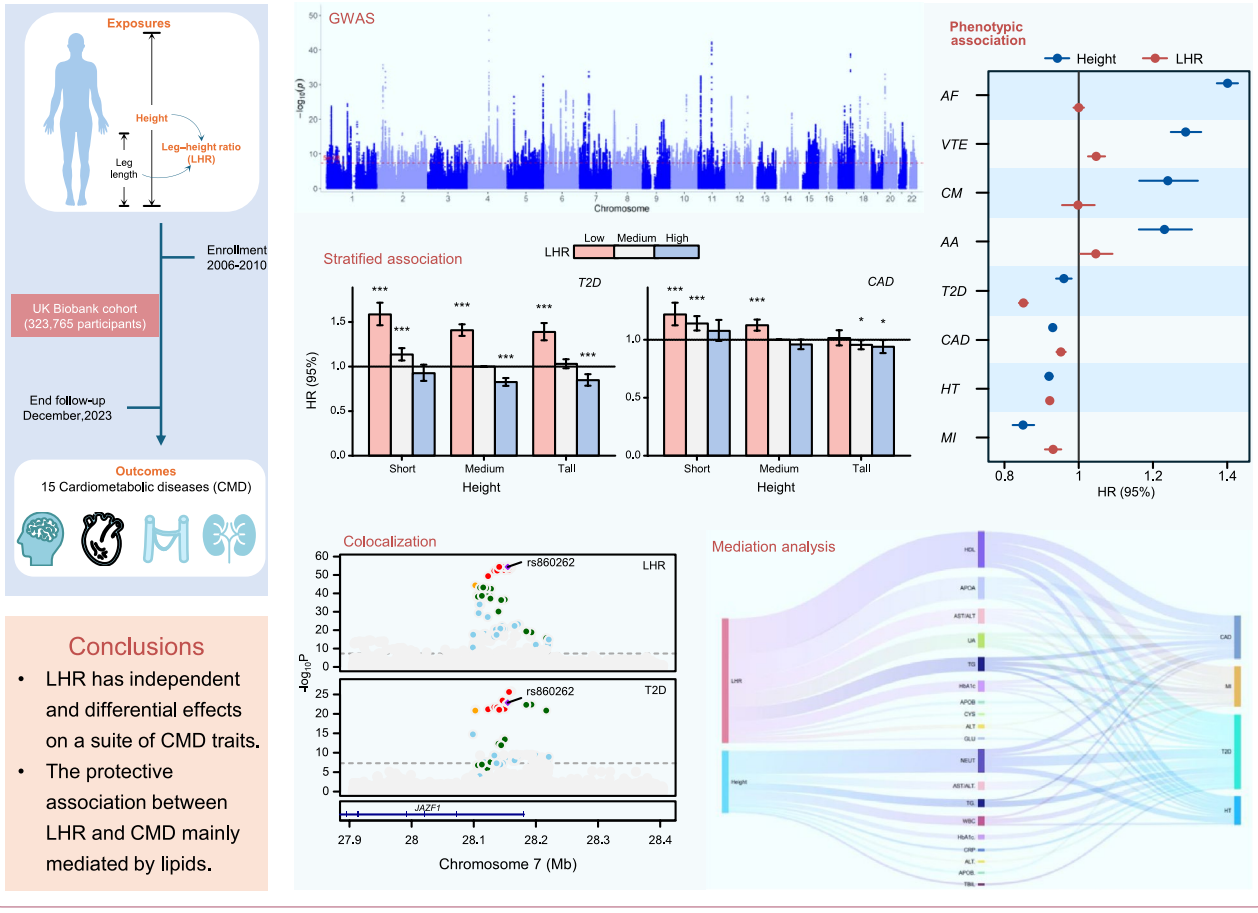
Conclusions LHR has independent and differential effects on a suite of CMD traits. The protective association between LHR and CMD is mainly mediated by lipids, and genes shared between LHR and these outcomes are predominantly enriched in development and differentiation of skeletal and embryonic tissues.

Keywords Leg-height ratio, Height, Cardiometabolic diseases, GWAS, Phenotypic association, Genetic association

*Correspondence:
Jie Huang
huangj@sustech.edu.cn

Full list of author information is available at the end of the article

Graphical abstract



Research insights

What is currently known about this topic?

Shorter height is associated with an increased risk of cardiometabolic diseases (CMD), such as coronary artery disease (CAD), myocardial infarction (MI), and type 2 diabetes (T2D). Some studies suggest that leg length may be dominantly attributed to these associations.

What is the key research question?

Is leg-height ratio (LHR) independently associated with 15 CMD at phenotypic and genetic levels?

What is new?

LHR is a highly polygenic trait with a SNP-based heritability of 24%.

LHR, adjusted for overall height, is independently associated with a lower risk of several CMD, including T2D, CAD, hypertension (HT), and MI. The protective effect of LHR on CMD was mainly mediated by lipids.

LHR colocalized with T2D at GCKR, JAZF1, and MC4R loci, and colocalized with CAD at the MTMR11 and OTUD7B loci.

How might this study influence clinical practice?

The findings of this study suggest that LHR is a clinically significant factor that should be considered alongside traditional measures like height and BMI in risk assessments for CMD. While height remains a known risk factor, this research emphasizes that LHR provides additional, independent predictive value, particularly in diseases like T2D and CAD.

Introduction

Body shape not only influences aesthetic perceptions but also significantly impacts health. While body size and adiposity measures such as body mass index (BMI), waist circumference, and fat mass are established as causative factors in the rising incidence of cardiometabolic diseases (CMD), adult height has emerged as an intriguing independent predictor [1].

Generally, height is studied as a component of BMI, yet it is also related to major CMD. A decade ago, genetically determined shorter stature was found to cause an increased risk of coronary artery disease (CAD), which was partly explained by the association between shorter height and an adverse lipid profile [2]. A more recent

study showed varied degrees of associations between body height and cardiovascular risk factors at different time points in Norway [3]. Epidemiological and genetic studies have also confirmed that adult height is inversely associated with the incidence of CAD, myocardial infarction (MI), and type 2 diabetes (T2D) [4–6], while positively associated with risk of atrial fibrillation (AF) and venous thromboembolism (VTE) [7, 8].

BMI alone, however, inadequately captures differences in body shape distribution, thus necessitating additional metrics like waist-hip ratio (WHR) to distinguish between pear-shaped and apple-shaped obesity, which carry different cardiometabolic risks [9, 10]. Analogously, examining body proportions, particularly the leg-height ratio (LHR), may provide distinct insights beyond overall height alone. Existing observational evidence indicates that the inverse associations of height with CMD, particularly CAD and T2D, are mainly attributable to leg length rather than sitting height. Sitting height generally exhibits minimal independent effects after adjustment for confounding factors [5, 11]. Thus, separately evaluating leg length and sitting height can yield clearer mechanistic insights. For example, individuals with normal height but disproportionately long legs and narrow thoracic cavities might experience increased cardiopulmonary stress, potentially heightening risks for cardiovascular complications, including deep vein thrombosis (DVT) [12, 13]. However, despite such plausible mechanistic links, the independent effect of LHR on CMD remains understudied, representing a significant gap in current research.

In this study, we investigated the genetic and phenotypic associations of height and LHR with 15 CMD using data from the prospective UK biobank cohort, which includes deep individual-level phenotypic and genetic data for about 0.5 million men and women participants. We created a new variable, LHR, and performed all analyses for LHR in parallel with those for overall height. We first performed genome-wide association analyses and used linkage disequilibrium score regression (LDSC) to estimate heritability and genetic correlations. Then we examined phenotypic associations and conducted mediation analyses to explore potential intermediate pathways. Colocalization was applied to explore shared causal variants. Finally, we carried out pathway enrichment analyses to characterize the biological functions underlying the identified signals.

Methods

Samples

We used individual-level genotype and phenotype data from the UK Biobank, a large population-based cohort comprising approximately 500,000 participants aged 37–73 years at recruitment [14]. We restricted our analysis to participants classified as European ancestry by the UK Biobank genetic quality-control pipeline. UK Biobank defined genetically homogeneous ancestry groups by projecting participants onto the 1000 Genomes reference principal component space and applying a distance-based clustering algorithm [14]. Individuals with sex mismatch, high genotype missingness (> 2%), or withdrawn consent were excluded. After quality control, a total of 457,384 European ancestry individuals were included in the genome-wide association study (GWAS) of height and LHR (Supplementary Fig. 7a).

Height and LHR

Height, seated height, and seating box height were measured using a Seca 202 device. Sitting height, defined as the distance from the rump to the crown in a seated position, was calculated as the difference between seated height and seating box height. Leg length was calculated by subtracting sitting height from total height. Because height may confound the relationship between body proportion and clinical outcomes, we defined LHR as the ratio of leg length to standing height and further adjusted for height. Adjustment for height in the regression model allows separation of the effects of height (body size) and LHR (body proportion). The standardized residual after regression represents the height-adjusted LHR and was used as the phenotype in the GWAS of LHR.

Genotyping, imputation, and quality control

Genotyping was performed by UK Biobank using the UK BiLEVE (49,950 participants) and UK Biobank Axiom arrays (438,427 participants). Genotype imputation was carried out centrally using the Haplotype Reference Consortium panel and the combined UK10K/1000 Genomes Phase 3 reference panel [14]. We applied variant-level quality control using the following criteria: (1) Minor allele frequency (MAF) ≥ 0.01; (2) Imputation INFO score ≥ 0.8; (3) Hardy–Weinberg equilibrium p-value ≥ 1×10^{-6}; (4) Missing call rate < 2%. Only autosomal variants passing these filters were retained for association testing.

GWAS and conditional analyses

Genome-wide association analyses for height and LHR were performed using REGENIE (v4.1.1) [15], a whole-genome regression method for biobank-scale data that accounts for sample relatedness and population structure. REGENIE was run in two steps: in step 1, ridge regression was fitted on LD-pruned genotyped variants to obtain trait predictions; in step 2, association tests were carried out for imputed variant dosages using the step-1 predictions as offset. For each trait we assumed an additive genetic model and adjusted for age at assessment, sex, assessment center, and first five genetic principal components provided by UK Biobank. We used

the standard genome-wide significance threshold of $P < 5 \times 10^{-8}$ to identify significant SNPs.

To identify independent genome-wide significant lead variants of height and LHR, we performed a stepwise conditional and joint analysis using GCTA-COJO (GCTA software v1.94.1) [16, 17], and applied the default COJO settings (genome-wide significance threshold of $P < 5 \times 10^{-8}$, a 10-Mb window assumption for linkage equilibrium between distant variants, collinearity control at $R^2 < 0.9$, and exclusion of variants with large allele-frequency discrepancies between the summary statistics and the LD reference). For reporting, we defined a locus using a distance-based rule as a 10-Mb region (± 5 Mb) centered on each COJO-identified lead variant, and merged overlapping regions into a single locus.

To evaluate the local clustering of association signals across the genome, we calculated the signal density for each lead SNP by counting the number of other conditionally independent SNPs located within a ± 1 Mb window. This metric was used to characterize the degree of genomic aggregation of independent locus, and to explore whether certain regions harbor unusually dense association signals. We used "gwaslab" to calculate the signal density and draw density plots for GWAS [18].

Genetic correlation and heritability estimation

LD score regression (LDSC) [19] was used to compute heritability of height and LHR, and genome-wide genetic correlations between height, LHR, and 15 CMD. LDSC uses only GWAS summary statistics to estimate genetic correlation (r_g) without bias due to sample overlap. By regressing the statistical effect size of each variant against its LD score, LDSC distinguishes true polygenic genetic signals from potential confounders, thus estimating the genetic correlation between two traits. The estimates r_g ranges from −1 (perfect negative correlation) to 1 (perfect positive correlation). We also used LDSC applied to specifically expressed genes (LDSC-SEG) [20] to estimate the heritability enrichment of height, LHR and genetic correlations between traits in functional categories [21] and GTEx tissues [22]. SNPs from the HapMap3 European ancestry panel were annotated for every functional category of tissue, and the LD scores were calculated. FDR correction applied for multiple testing and considered $P < 0.05$ as significant after correcting.

Phenotypic associations

At the phenotypic level, individual phenotypic data from UK Biobank were used to analyze the associations between height and LHR with 15 CMD, including AF, aortic aneurysm (AA), cardiomyopathy (CM), heart failure (HF), CAD, MI, VTE, peripheral artery disease (PAD), hypertension (HT), ischemic stroke (IS), hemorrhagic stroke (HS), transient ischemic attack (TIA), any stroke (AS), T2D, and chronic kidney disease (CKD). Participants who were hospitalized with any of these conditions during follow-up were considered as the incidence of an outcome event, determined based on ICD-10 codes. The specific diagnostic codes can be found in Supplementary Table 5. Self-reported diseases were not considered as outcome events since the follow-up period began at each participant's date of enrollment in the UK Biobank. The "first occurrence date" field was used to define the date of occurrence for each outcome.

Covariates: Age, sex, total annual household income, and education level were self-reported at the time of recruitment into the UK Biobank. The Townsend deprivation index was calculated immediately prior to participant attendance. Waist-to-hip ratio, an important potential confounder influencing outcomes [23, 24], was calculated using waist and hip circumference from the initial measurement. The body mass index was not included as a covariate since it is directly derived from the exposure. Smoking and drinking statuses were categorized as current, previous, or never, based on participants' self-reports. Physical activity was assessed by questionnaire as the number of days per week participants engaged in moderate physical activity lasting 10 min or more. Additionally, the first five genetic principal components were included to control for confounding due to population structure and genetic background.

Follow-up time was defined as the period from the date of recruitment until the end of follow-up. The follow-up period was censored based on the following conditions: (1) occurrence of an outcome event, with follow-up ending at the date when any CMD was first recorded; (2) death from a cause other than any CMD outcome, if the linked death registries indicated a date prior to any outcome event; (3) loss to follow-up, defined as participant withdrawal or loss of contact during the follow-up period without experiencing any of the above events, in which case follow-up ended on the date of last contact; and (4) reaching the end date of the study period (December 31, 2023) for participants without documented outcomes, death, or loss to follow-up.

The Cox proportional hazards model was used to estimate the prospective associations of height, LHR with CMD. The effects estimation of exposures was reported as 1 SD increase. Age, sex, household income, education level, Townsend deprivation index, WHR, weekly moderate physical activity days, smoking status, drinking status, and first five principal components were included in all models as covariates. To explore potential joint effects, participants were categorized into nine groups based on 20th and 80th percentiles of height (short [bottom 20%], medium [middle 60%], and tall [top 20%]) and LHR (low [bottom 20%], medium [middle 60%], high [top 20%]). Stratified Cox models were then applied to estimate

CMD risk across the 3 × 3 joint exposure groups, using participants with both medium height and medium LHR as the reference group. In a complementary analysis, participants were divided into quintiles based on SD units of height or LHR. Using the SD = 0 group (mean-centered) as the reference, we assessed linear trends across exposure levels to examine dose–response relationships between the two traits and CMD outcomes. For sensitivity analysis, we included lipid traits, including high-density lipoprotein cholesterol (HDL-c), low-density lipoprotein cholesterol (LDL-c), total cholesterol (TC), and TG (triglycerides) as additional covariates and repeated main analyses stratified by sex. FDR corrected $P < 0.05$ considered as significance. The Schoenfeld residuals test was used to check the proportional hazards assumption. Variance inflation factors across all models indicated acceptable levels of low multicollinearity (VIF < 1.8).

Mediation analyses

To explore whether the height- and LHR-CMD associations are mediated by different factors, we included 28 blood-based biomarkers—covering lipid and glucose metabolism, liver and kidney function, and inflammatory—as potential mediators. These included lipids, glycated hemoglobin (HbA1c), AST (aspartate aminotransferase), creatinine (CRE), WBC (white blood cells), C-reactive protein (CRP), among others. A full list of biomarkers is provided in Supplementary Table 6. Causal mediation analyses were conducted using the R package "mediation". The exposure–mediator relationship was modeled using linear regression, while the mediator–outcome relationship was modeled using survival regression. For each model, we estimated the direct effect of height on CMD, the indirect effect through each mediator, and the proportion mediated. All *P* values were adjusted using the FDR method to account for multiple comparisons.

Colocalization

For CMD that showed significant phenotypic and genetic associations with height or LHR, colocalization analyses were conducted using R package "coloc" to determine whether these CMD and height/LHR share common causal genetic variants. SNPs that were independent lead variants were retained as index SNPs. For each index SNP, we extracted all SNPs within ± 500 kb window to define the region for colocalization testing to calculate the PP.H4. Only SNPs present in both datasets, with matched alleles and positions, were included in the analysis. PP.H4 > 0.9 was considered as evidence supporting colocalization.

Tissue and cell-type enrichment

First, we conducted gene-base analysis using MAGMA (Multi-marker Analysis of GenoMic Annotation) [25] to identify associated genes of height/LHR and genes share by height or LHR trait pairs with CMD. European ancestry panel in the 1000 Genomes Project (Phase 3) used as the LD reference. *P* value threshold was adjusted by Bonferroni correction.

To evaluate tissue-specific expression enrichment of the identified gene sets, we used the GENE2FUNC module in the FUMA platform [26], which performs hypergeometric tests of overrepresentation using RNA-seq data from 54 major tissue types in GTEx v8. A gene was defined as tissue-specific if its expression in a given tissue was significantly higher than in all other tissues (Bonferroni-corrected $P < 0.05$).

To further investigate cell-type specificity, we conducted cell-type-specific expression enrichment analysis using the WebCSEA [27] platform, which leverages single-cell transcriptomic datasets across multiple human tissues and cell populations. Genes associated with height, LHR, and their shared CMD trait pairs were analyzed for overrepresentation in cell-type-specific gene expression profiles. Enrichment significance was determined by FDR correction.

Over-representation enrichment

GO (Gene Ontology)and KEGG (Kyoto Encyclopedia of Genes and Genomes) enrichment analyses were conducted using "clusterProfiler" [28] to identify overrepresented biological functions among significant genes, with FDR adjusted $P < 0.05$ indicating significance.

Results

Genome-wide association

We conducted genome-wide association studies (GWAS) for both height and leg-height ratio (LHR) using genotype data from 457,384 individuals of European ancestry in the UK Biobank. To minimize the confounding influence of overall height on LHR, we derived residuals from a linear regression of LHR on height and used these residuals as the phenotype in the LHR GWAS. The Manhattan plot for the height and LHR GWAS is shown in Fig. 1a. Both height and LHR exhibited highly polygenic architectures. Using GCTA-COJO conditional analysis, we identified 1797 and 747 independent genome-wide significant single nucleotide polymorphisms (SNPs) for height and LHR, respectively (Supplementary Table 1 and 2, Supplementary Fig. 1). Of the 747 LHR-associated SNPs, 134 were also independently associated with height (Supplementary Table 2). Among the LHR-associated SNPs, the three most significant signals were located near *SLC39A8* (rs13107325) and *KDM2A* (rs7952436) (Table 1). The regional plots are shown in Supplementary

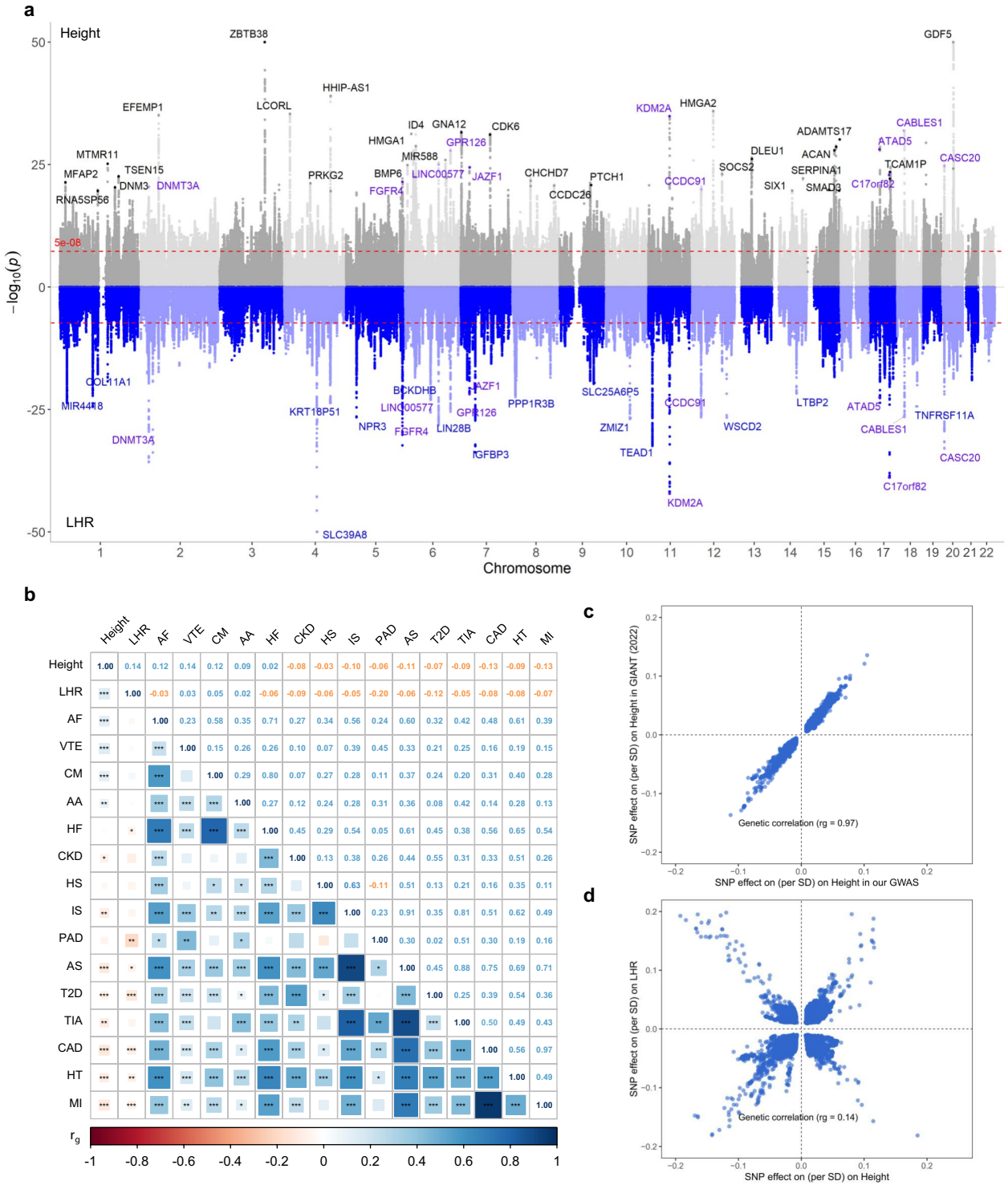


Fig. 1 **a** Manhattan plots of genome-wide association studies for height and LHR. The *p* value was capped at 1×10^{-50} to alleviate the impact of lead SNPs with extreme *p* values. Variants with capped $p<1\times10^{-20}$ that remained independent after COJO analysis were annotated by their nearest genes. Black and blue annotations denote height-specific and LHR-specific signals, respectively, while shared signals are annotated in purple. **b** Heatmap shows genetic correlations between height, LHR, and 15 cardiometabolic diseases. The r_g values range from −1 (perfect negative correlation) to 1 (perfect positive correlation). *FDR-adjusted $P<0.05$, **$P<0.01$, ***$P<0.001$. **c** Comparison of effect sizes of significant SNPs on height from our GWAS and those reported by the GIANT consortium (2022). **d** Effect sizes of significant SNPs on both height and LHR from our GWAS. *LHR* leg-height ratio, *AF* atrial fibrillation, *VTE* venous thromboembolism, *CM* cardiomyopathy, *AA* aortic aneurysm, *HF* heart failure, *CKD* chronic kidney disease, *HS* hemorrhagic stroke, *IS* ischemic stroke, *PAC* peripheral artery calcification, *AS* all types of stroke, *T2D* type 2 diabetes, *TIA* transient ischemic attack, *CAD* coronary artery disease, *HT* hypertension, *MI* myocardial infarction, *SNP* single nucleotide polymorphism

Table 1 Top 20 SNPs that are only independently associated with LHR after conditioned analysis using GCTA-COJO

CHR	SNP	POS	EA	EAF	BETA (COJO)	SE (COJO)	P (COJO)	Nearest gene	Height-related
1	rs3753841	103,379,918	A	0.6116	0.031	0.0023	7.07E-42	COL11A1	NO
4	rs4629389	145,205,246	C	0.5498	0.0336	0.0023	2.13E-47	GYPA	NO
6	rs2050157	142,658,162	A	0.2846	0.0415	0.0023	6.66E-74	GPR126	NO
6	rs9296143	35,115,292	C	0.6739	0.0287	0.0022	1.88E-38	TCP11	NO
7	rs864745	28,180,556	C	0.5059	−0.0334	0.0021	3.01E-59	JAZF1	NO
7	rs3110697	45,955,029	G	0.5778	−0.0357	0.0022	3.34E-58	IGFBP3	NO
7	rs3807947	20,424,889	G	0.3951	−0.0276	0.0021	2.44E-39	ITGB8	NO
9	rs16909898	98,231,008	G	0.0955	−0.0557	0.0036	4.91E-54	PTCH1	NO
11	rs9888258	12,782,716	G	0.4122	0.042	0.0021	2.02E-90	TEAD1	NO
12	rs3764002	108,618,630	T	0.2618	−0.0421	0.0023	7.19E-73	WSCD2	NO
12	rs10771427	28,605,426	A	0.7673	−0.0411	0.0024	2.42E-63	CCDC91	NO
15	rs4842918	84,536,999	C	0.2817	−0.0328	0.0023	3.35E-45	ADAMTSL3	NO
16	rs72766534	4,338,359	C	0.2473	−0.0302	0.0024	7.56E-37	TFAP4	NO
17	rs2942164	43,721,283	C	0.225	0.0353	0.0025	2.51E-46	CRHR1-IT1	NO
17	rs9913611	69,995,886	T	0.3515	−0.0292	0.0021	4.71E-42	LINC01152	NO
18	rs884205	60,054,857	C	0.748	−0.0411	0.0024	8.91E-67	TNFRSF11A	NO
20	rs2145272	6,626,218	A	0.6353	−0.0441	0.0021	1.05E-94	CASC20	NO
20	rs6066103	45,527,902	G	0.3178	−0.0278	0.0022	2.81E-37	EYA2	NO
20	rs1014884	21,844,694	C	0.5988	−0.0265	0.0021	1.15E-36	RPL41P1	NO
20	rs2145272	6,626,218	A	0.6353	−0.0441	0.0021	1.05E-94	CASC20	NO

LHR leg-height ratio, *CHR* chromosome, *SNP* single nucleotide polymorphism, *POS* position, *EA* effect allele, *EAF* effect allele frequency

Fig. 2. We also tested the signal densities of the independent SNPs of height and LHR. Within the range of 1 Mb, the average signal density of height was 3.15, while that of LHR was only 1.16. The signal with the highest density of LHR is located near the *BMP2* gene (Supplementary Fig. 3), which is a member of the transforming growth factor-β superfamily, acts as a pivotal inducer of osteogenesis through SMAD-mediated activation of runt-related transcription factor 2 and is clinically applied to enhance bone regeneration [29].

Genetic correlation and heritability estimation

We used LD score regression (LDSC) to estimate SNP-based heritability for height and LHR, as well as genetic correlations between these traits and 15 major cardiometabolic diseases (CMD). Height showed significant positive genetic correlations with atrial fibrillation (AF) ($r_g = 0.12$), venous thromboembolism (VTE) ($r_g = 0.13$), cardiomyopathy (CM) ($r_g = 0.12$), and aortic aneurysm (AA) ($r_g = 0.09$), whereas no such associations were observed for LHR. Both height and LHR exhibited independent negative genetic correlations with type 2 diabetes (T2D) ($r_g = -0.07$ for height, -0.12 for LHR), coronary artery disease (CAD) ($r_g = -0.13$ for height, -0.08 for LHR), hypertension (HT), and myocardial infarction (MI) (Fig. 1b). We also confirmed a high concordance between our height GWAS and that of the GIANT consortium (2022) [30], with a genetic correlation of $r_g = 0.97$ (Fig. 1c). We also conducted GWAS on leg length (Supplementary Fig. 4a), and the r_g between it and height was 0.93 (Supplementary Fig. 4b), while the genetic correlation between height and LHR was modest ($r_g = 0.14$) (Fig. 1d). SNP-based heritability estimates were 46% for height and 24% for LHR (Supplementary Fig. 5). We further conducted partitioned heritability and genetic correlation analyses [20] using 53 GTEx tissue-specific annotations and 97 gene functional categories from the Roadmap Epigenomics Project [21, 31]. Diseases genetically negatively correlated with height exhibited stronger tissue-specific genetic enrichment in the brain, while diseases positively correlated with height showed no correlation in brain tissue. For LHR, the genetic correlation with T2D was particularly elevated in brain ($r_g = -0.18$ to -0.26) and pancreatic ($r_g = -0.22$) tissues (Supplementary Fig. 5). Yet heritability estimates for both height and LHR were slightly lower in brain tissues compared to other tissues (Supplementary Fig. 5). No substantial differences were observed across functional genomic annotations (Supplementary Fig. 6).

Phenotypic association

We further examined phenotypic associations between height, LHR, and the risk of 15 CMD. The study population was derived from the UK Biobank cohort, comprising a total of 323,765 individuals (mean age at baseline = 55.48; 169,885 females and 153,880 males). Participants who had either recorded or self-reported outcome events prior to baseline were excluded (Supplementary Fig. 7a). Consequently, due to variations in the number of pre-baseline events across different CMD, the final analytical sample sizes varied by CMD, ranging from 281,832 (HT) to 323,507 participants (AA),

and the average follow-up duration ranged from 12.6 to 14.42 years (Supplementary Fig. 7b). The mean height was 169.56 cm (standard deviation [SD] = 9.2 cm). Detailed baseline characteristics were provided in the Supplementary Table 3.

After adjustment for height using linear regression, the residuals of LHR ranged from −0.19 to 0.41. At the phenotypic level, there was almost no correlation between height and LHR (*Pearson* correlation coefficient = 0.01) (Supplementary Fig. 8). As shown in Fig. 2a, each 1 SD increase in height was associated with a 40.1% higher risk of AF (hazard ratio [HR] = 1.401, 95% confidence interval [CI]: 1.372–1.429, $P = 4.21 \times 10^{-231}$), the most pronounced association observed. Height also showed positive associations with VTE, CM, and AA, while LHR exhibited only

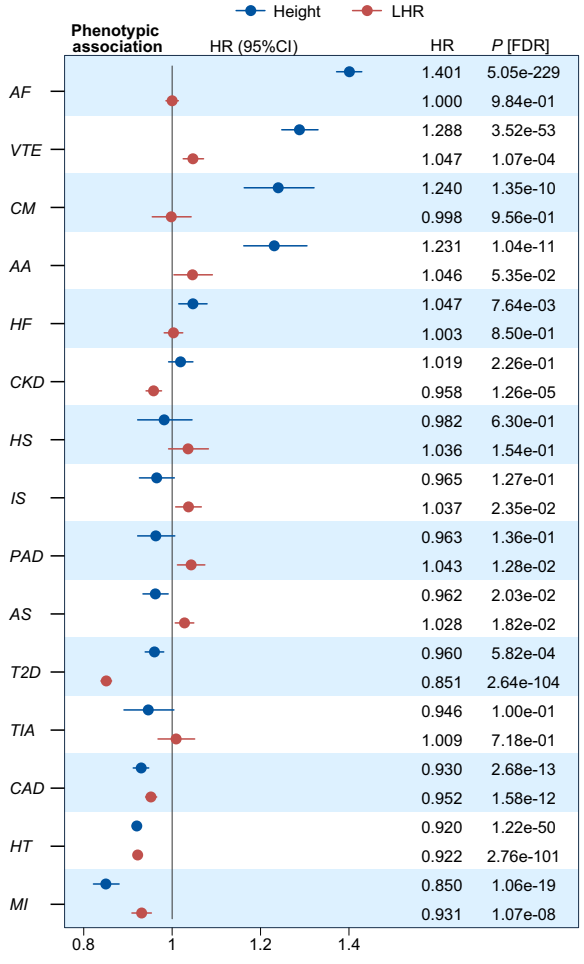


Fig. 2 Phenotypic associations of height and LHR with 15 cardiometabolic diseases in 323,765 individuals from the UK Biobank. Associations with $P < 0.05/120 = 4.17 \times 10^{-4}$ were considered statistically significant after Bonferroni correction. *LHR* leg-height ratio, *AF* atrial fibrillation, *VTE* venous thromboembolism, *CM* cardiomyopathy, *AA* aortic aneurysm, *HF* heart failure, *CKD* chronic kidney disease, *HS* hemorrhagic stroke, *IS* ischemic stroke, *PAD* peripheral artery disease, *AS* all types of stroke, *T2D* type 2 diabetes, *TIA* transient ischemic attack, *CAD* coronary artery disease, *HT* hypertension, *MI* myocardial infarction

a modest positive association with VTE (HR = 1.047, 95% CI: 1.025–1.071, $P = 3.91 \times 10^{-5}$). Both height and LHR were inversely associated with the risk of T2D, CAD, HT, and MI. Notably, 1 SD increase in LHR associated with a 14.9% reduction in T2D risk (HR = 0.851, 95% CI: 0.839–0.863, $P = 8.81 \times 10^{-106}$). Sensitivity and sex stratified analyses results see Supplementary Fig. 9 and 10.

A high LHR (top 20%) was associated with a substantially lower risk of CAD, MI, T2D, and HT than a medium (middle 60%) or low (bottom 20%) LHR, regardless of the height category (Fig. 3). Among medium height individuals, a low LHR was associated with a 6% higher risk of CAD than a medium LHR (HR = 1.06, 95% CI:1.02–1.11, $P = 6.43 \times 10^{-3}$). This pattern is even more pronounced for T2D, where tall individuals with low LHR exhibit higher disease risk (HR = 1.39, 95% CI:1.29–1.49, $P = 2.70 \times 10^{-20}$) than short or medium height individuals with higher LHR. Compared to the medium–medium group, individuals with short height and low LHR had the highest risk of T2D (HR = 1.585, 95% CI: 1.464–1.717, $P = 9.46 \times 10^{-30}$) (Fig. 3).

To further assess risk gradients, participants were stratified by SD of height and LHR residuals. As shown in Supplementary Fig. 11, the risks of AF and VTE increased monotonically with taller height. The inverse association between height and type 2 diabetes (T2D) was attenuated among individuals above the mean height (SD > 0), whereas increasing LHR residuals were consistently associated with lower T2D risk. The associations of both traits with CAD, HT, and MI showed broadly similar trends.

Mediation analyses

We conducted mediation analyses for four CMD—T2D, CAD, MI, and HT—which showed inverse associations with both height and LHR. As shown in Fig. 4, lipid-related biomarkers such as HDL-c, apolipoprotein A, and TG primarily mediated the associations between LHR and these CMD. For example, HDL-c mediated 31% (95% CI: 25.27%–40.13%, $P < 0.0001$) of the association between LHR and CAD. In contrast, the associations between height and these diseases were mainly mediated by inflammatory markers such as NEUT (neutrophils) and WBC. Additionally, the association of both height and LHR with T2D was jointly mediated by the AST/ALT (aspartate aminotransferase to alanine aminotransferase ratio). Detailed results are provided in Supplementary Table 4.

Colocalization

Colocalization analysis revealed multiple loci with high posterior probability (PP.H4 > 0.9) of shared causal variants between height, LHR and significant associated CMD (Fig. 5a). We found that only LHR colocalized with

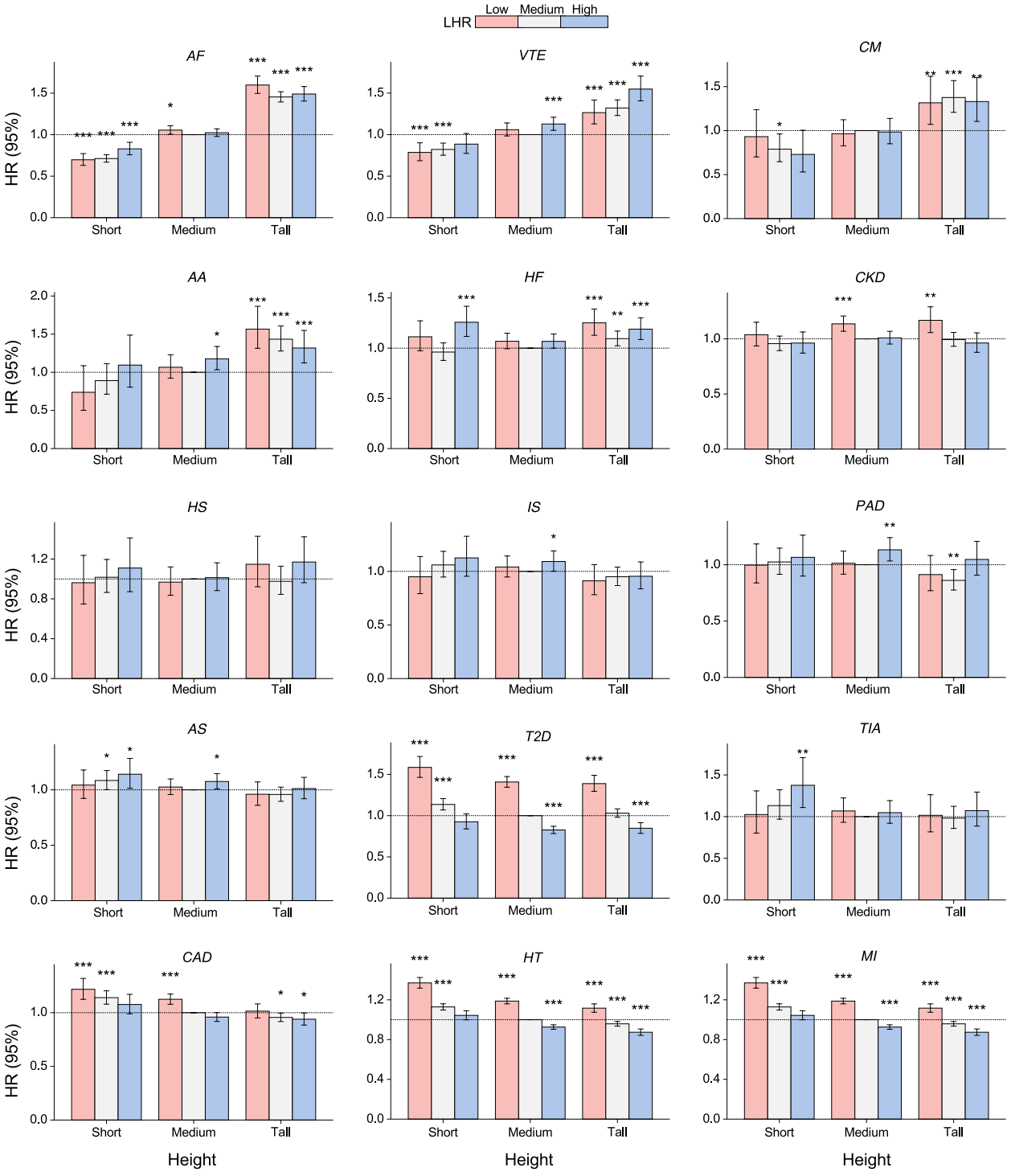


Fig. 3 Joint associations of height and LHR with cardiometabolic diseases. Individuals were stratified into three categories separately for each trait: height was grouped into short (bottom 20%), medium (middle 60%), and tall (top 20%), while LHR was grouped into low (bottom 20%), medium (middle 60%), and high (top 20%). The reference group comprised individuals with both height and LHR in the medium range. * Adjusted $P < 0.05$, ** $P < 0.01$, *** $P < 0.001$. *LHR* leg-height ratio, *AF* atrial fibrillation, *VTE* venous thromboembolism, *CM* cardiomyopathy, *AA* aortic aneurysm, *HF* heart failure, *CKD* chronic kidney disease, *HS* hemorrhagic stroke, *IS* ischemic stroke, *PAD* peripheral artery disease, *AS* all types of stroke, *T2D* type 2 diabetes, *TIA* transient ischemic attack, *CAD* coronary artery disease, *HT* hypertension, *MI* myocardial infarction

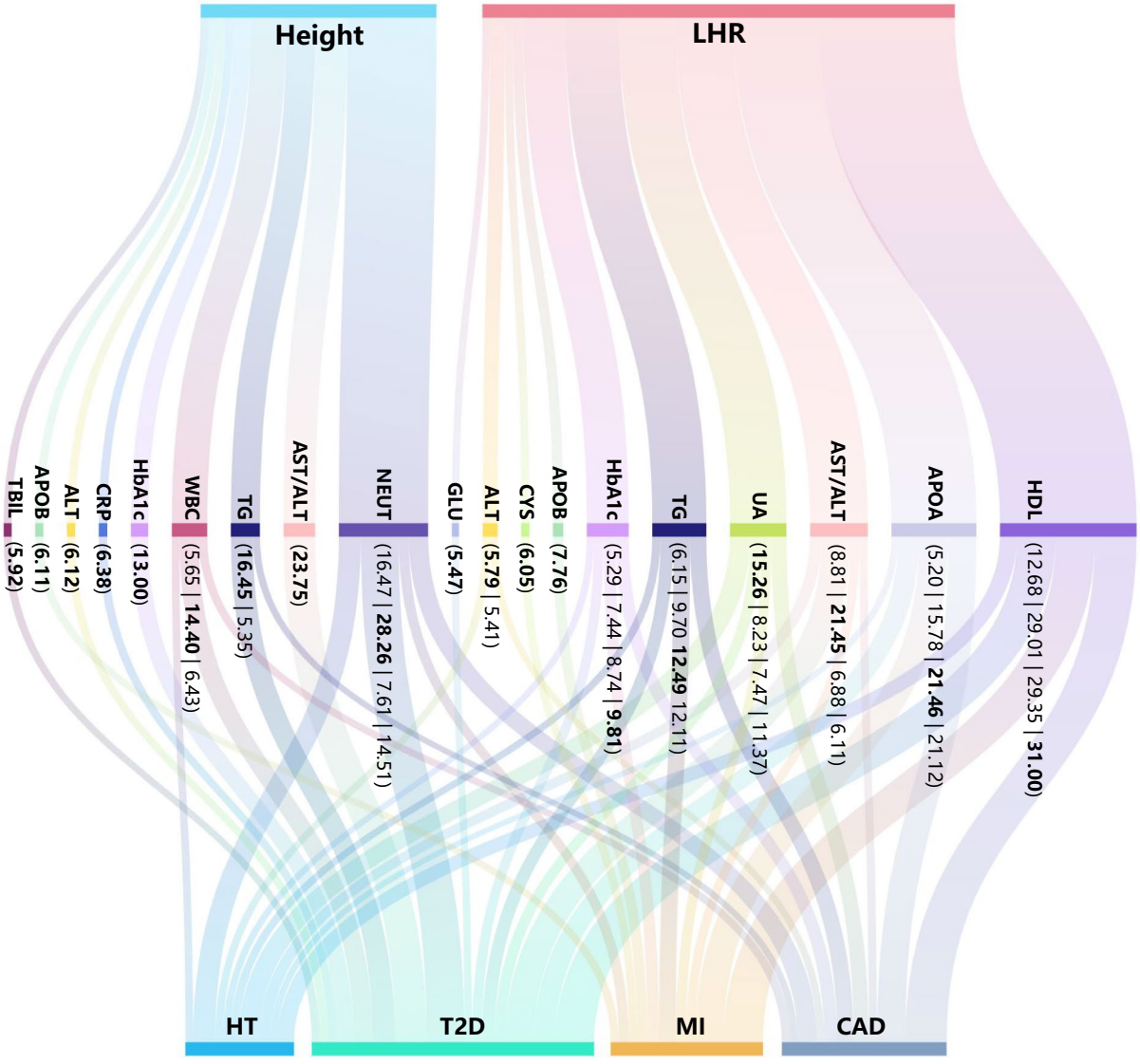


Fig. 4 Mediation analysis results. The Sankey plot illustrates the mediation analysis results of Height and LHR on four cardiometabolic diseases: CAD, MI, T2D, and HT. The numbers represent the mediation proportion (%) of each path from left to right. All mediators shown are statistically significant ($P < 0.0001$) and have a mediation proportion ≥ 5%. *LHR* leg-height ratio, *HDL-c* high-density lipoprotein cholesterol, *APOA* apolipoprotein A, *APOB* apolipoprotein B, *AST/ALT* aspartate aminotransferase to alanine aminotransferase ratio, *ALT* alanine aminotransferase, *TG* triglycerides, *UA* uric acid, *GLU* fasting glucose, *HbA1c* glycated hemoglobin A1c, *CYS* cystatin C, *TBIL* total bilirubin, *NEUT* neutrophils, *WBC* white blood cell count, *CRP* C-reactive protein, *CAD* coronary artery disease, *MI* myocardial infarction, *T2D* type 2 diabetes, *HT* hypertension

T2D at *GCKR* (rs1260326) (Fig. 5b) and *JAZF1* (rs860262, rs1513272) (Fig. 5c), a diabetes susceptibility gene [32]. Strong colocalization was also observed at the *MTMR11* and *OTUD7B* locus (rs11205303, rs12048493) between height, LHR, and CAD (Fig. 5d); at the *MC4R* locus (rs66922415) among height, LHR, and T2D (Fig. 5e); and at the *MMA3* locus (rs2133189) among LHR, CAD, and MI (Fig. 5f). These findings provide locus-specific evidence supporting shared genetic architecture and potential pleiotropy linking growth traits with cardiometabolic outcomes.

Tissue and cell-type enrichment

We used MAGMA gene-based analysis to identify significant genes associated with height, LHR, and 15 CMD, and further inferred genes shared between height or LHR and each CMD. The shared gene number of every paired trait is shown in Supplementary Fig. 12. To explore tissue and cell-type specificity, we assessed the enrichment of these genes from gene expression in GTEx and single-cell transcriptome.

Significant genes for both height and LHR were broadly enriched across multiple tissues, particularly in the heart, pancreas, brain, and liver (Fig. 6a). Similarly, genes

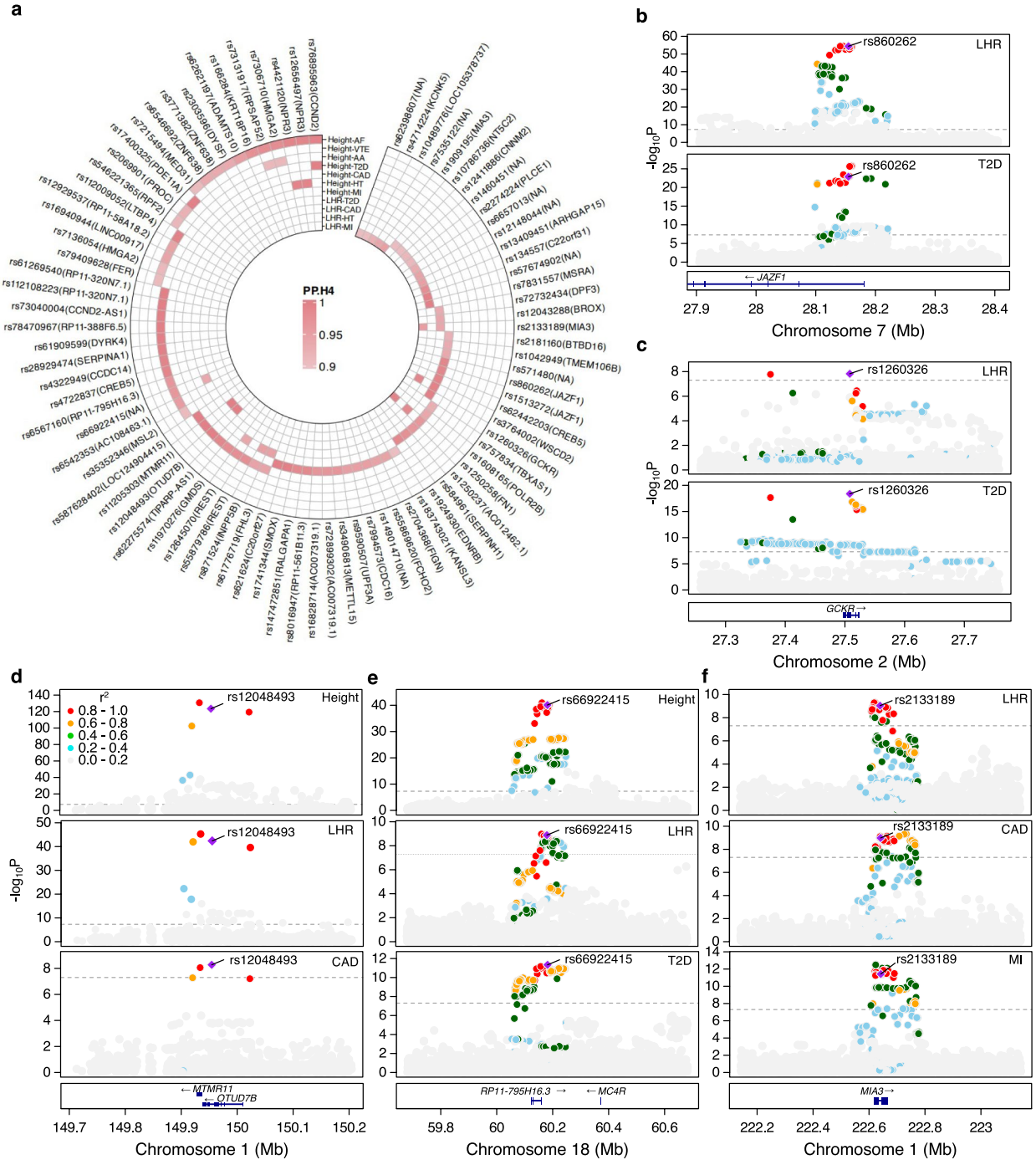


Fig. 5 Colocalization analysis results. **a** Colocalization analysis identified shared genetic variants between height or LHR and cardiometabolic diseases with significant genetic correlations; a posterior probability hypothesis 4 of shared signal (PP.H4) > 0.9 was considered evidence of colocalization. **b**–**f** LocusZoom plots illustrate representative regions of colocalized loci. *LHR* leg-height ratio, *AF* atrial fibrillation, *VTE* venous thromboembolism, *CM* cardiomyopathy, *AA* aortic aneurysm, *T2D* type 2 diabetes, *CAD* coronary artery disease, *HT* hypertension, *MI* myocardial infarction

shared between height/LHR and CMDs also tended to be enriched in these tissues (Fig. 6b).

For cell-type, both height and LHR were strongly enriched in mesenchymal stem cells, glial cells, and fibroblasts. Height-specific genes were more significantly enriched in monocytes and erythroid progenitor cells, while LHR-specific genes were more significantly enriched in endothelial cells and pancreatic stellate cells (Fig. 6c). Shared genes between height or LHR and CMD tend to enrich in endothelial cells, especially for paired traits such as height-MI, height-HT, LHR-T2D, and LHR-HT. Height-AA shared genes were predominantly

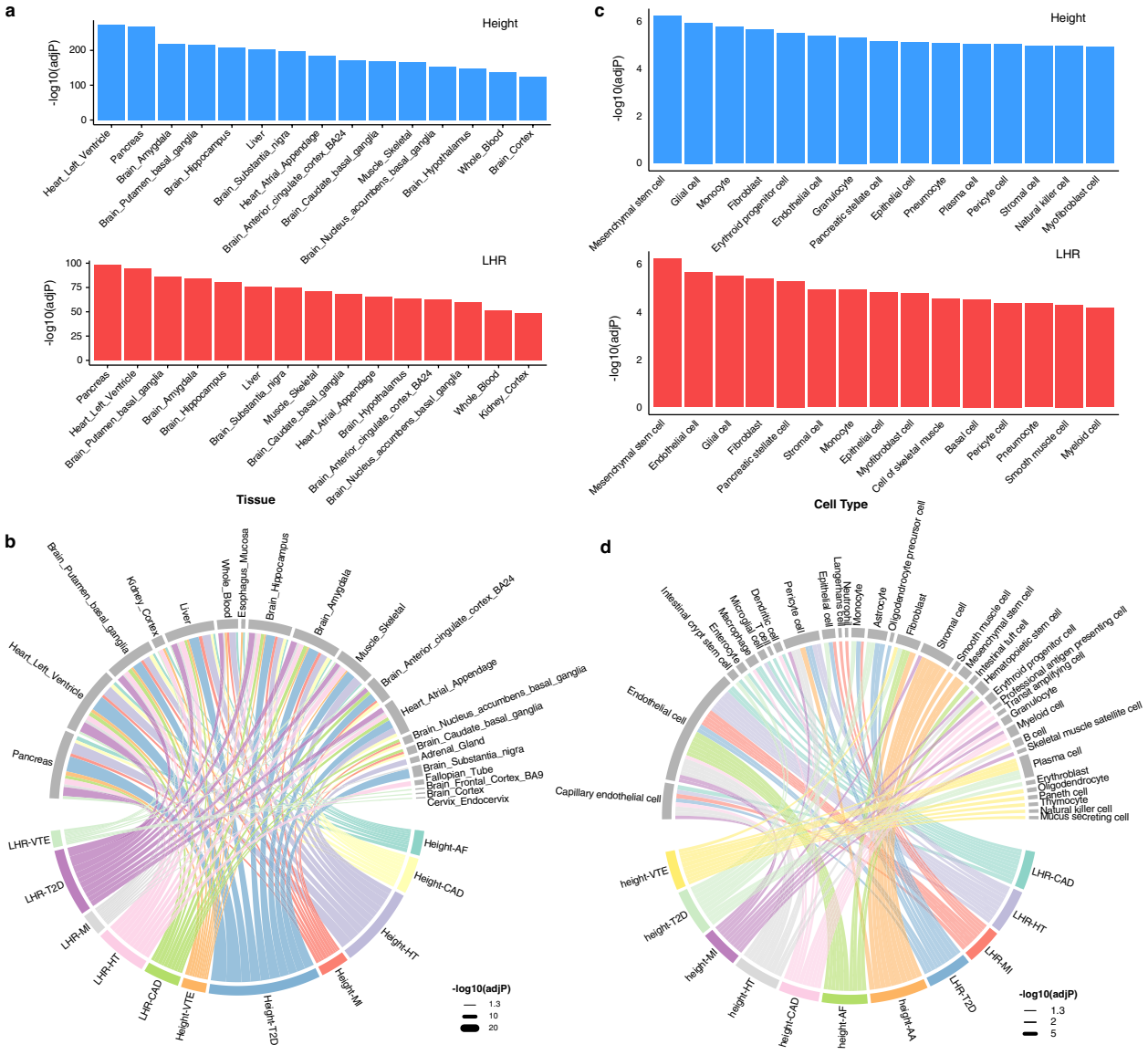


Fig. 6 Tissue and cell-type enrichment analyses results. **a** Bar plot shows top 15 significantly enriched tissues for height and LHR. **b** Chord plot shows tissue enrichment of trait pairs between height or LHR and cardiometabolic diseases. Only display the top 10 significantly enriched tissues for each trait. **c** Bar plot shows top 15 significantly enriched cells for height and LHR. **d** Bar plot shows cell-type enrichment of trait pairs between height or LHR and cardiometabolic diseases. Only display the top 10 significantly enriched cells for each trait. Line thickness in chord plots indicates statistical significance ($-\log_{10}$ adjusted P-value). Tissue enrichment analysis conducted on FUMA and cell-type enrichment analysis conducted on WebCSEA. All analysis based on significant genes retained from gene-based analysis using MAGMA. *LHR* leg-height ratio, *AF* atrial fibrillation, *VTE* venous thromboembolism, *AA* aortic aneurysm, *T2D* type 2 diabetes, *CAD* coronary artery disease, *HT* hypertension, *MI* myocardial infarction

enriched in stromal cells and smooth muscle cells. Height-T2D and LHR-T2D genes showed stronger enrichment in astrocytes. Immune cell enrichment patterns also differed by trait pair. Height-CAD genes were preferentially expressed in myeloid cells, granulocytes, and professional antigen-presenting cells, whereas LHR-CAD genes were more enriched in macrophages, microglia, T cell, and dendritic cell (Fig. 6d).

GO and KEGG enrichment

In the GO enrichment analysis, height-associated genes were primarily involved in skeletal development, cell growth, and morphogenesis, whereas LHR-associated genes were enriched in pattern specification, cell adhesion, and connective tissue development, highlighting distinct biological pathways underlying overall stature and LHR (Supplementary Fig. 13).

Shared genes of height-AF were significantly enriched in biological processes such as skeletal system morphogenesis, cell adhesion, heart contraction, and blood

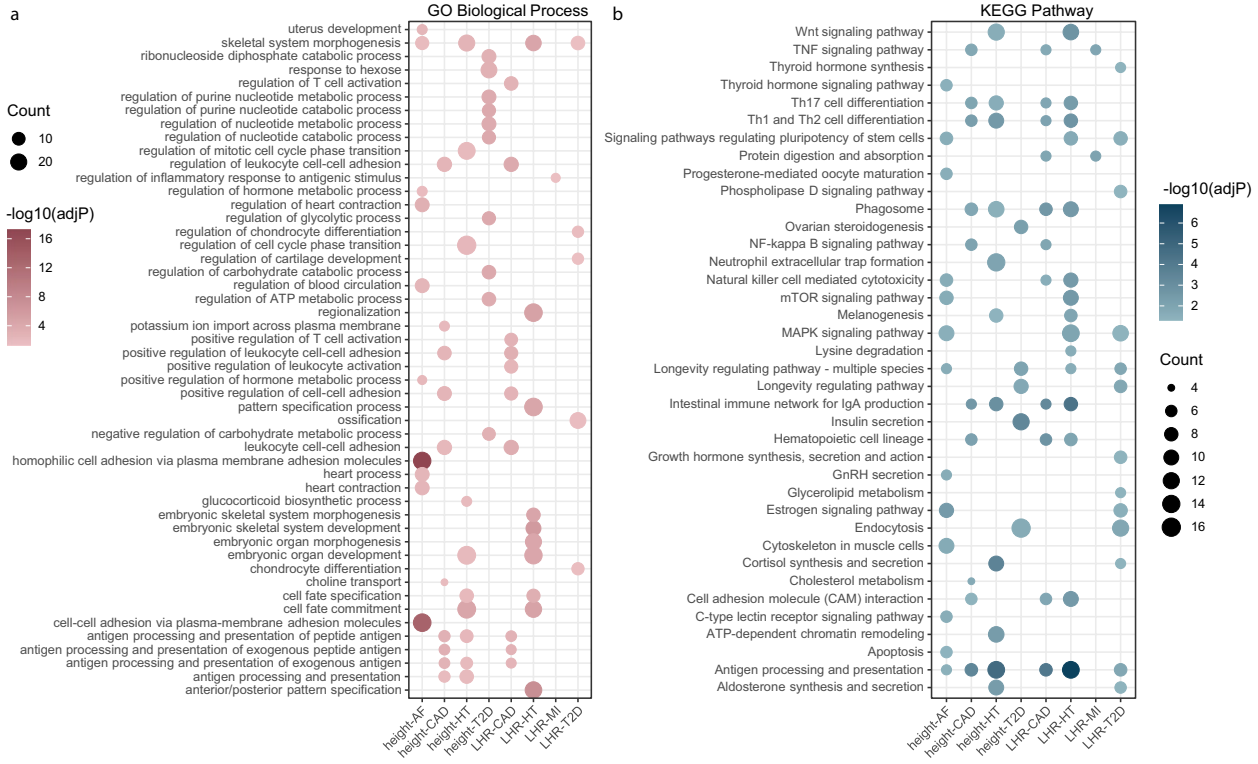


Fig. 7 GO and KEGG enrichment results. **a** Gene Ontology biological process enrichment for shared genes between height or LHR and cardiometabolic disease. **b** Kyoto Encyclopedia of Genes and Genomes pathway enrichment for the same gene sets. *LHR* leg-height ratio, *AF* atrial fibrillation, *T2D* type 2 diabetes, *CAD* coronary artery disease, *HT* hypertension, *MI* myocardial infarction

circulation. Genes shared between height and LHR with CAD and HT were commonly enriched in antigen processing pathways. Notably, both height-HT and LHR-HT showed strong enrichment in processes related to embryonic development and differentiation, while height-T2D and LHR-T2D were more enriched in chondrocyte differentiation and metabolic processes (Fig. 7a).

In the KEGG pathway analysis, genes shared by height or LHR with CAD and HT were enriched in several immune-related pathways, including Th17 cell differentiation and Th1/Th2 cell differentiation. In contrast, LHR-T2D showed stronger enrichment in metabolic and aging-related pathways, such as glycerolipid metabolism and the longevity regulating pathway (Fig. 7b).

Discussion

In this study, we conducted a genome-wide association study of height and LHR in over 450,000 participants from the UK Biobank. We confirmed that LHR is a highly polygenic trait with a SNP-based heritability of 24%. Conditional analysis identified 747 independent SNPs associated with LHR. While LHR was strongly correlated with height, substantial genetic overlap remained even after rigorous adjustment for height, with 134 independent variants jointly influencing both traits.

The GWAS of height and LHR reveals distinct genetic architectures underlying these two anthropometric traits. Height exhibits widespread and highly significant association signals across the genome, with prominent genes such as *ZBTB38*, *HMGA2*, and *HHIP* [33, 34], which are known to be involved in growth factor signaling, embryonic development, and skeletal regulation. In contrast, LHR, a proportional trait reflecting body segment distribution, demonstrates fewer but more localized association signals. These are enriched for genes related to chondrogenesis and limb-specific skeletal development, such as *SLC39A8*, *IGFBP3*, and *TMEM38B* [35–39]. While some loci, such as *KDM2A*, appear in both traits, the overall limited overlap suggests that height and LHR are governed by partially distinct regulatory networks. This divergence underscores the importance of considering biological context—global versus segmental growth—when interpreting GWAS results for anthropometric traits.

The relationship between height and CMD risk has been extensively studied. Consistent with previous findings, we observed a bidirectional pattern: taller stature was associated with increased risks of AF, VTE, CM, and AA [7, 40, 41], but with decreased risks of CAD, HT, and T2D [2, 8, 42, 43]. Prior studies have suggested that such associations are primarily driven by leg length rather

than sitting height [5, 11, 44, 45], yet little attention has been paid to the proportional contribution of leg length relative to overall height. By integrating phenotypic and genetic analyses, we found that a higher LHR independently conferred a lower risk of T2D, CAD, HT, and MI, while slightly increasing VTE risk. These associations closely mirrored those of total height, extending prior findings by suggesting that—at a given height—individuals with higher LHR may experience additional protection of T2D, CAD, HT, MI. The effect was particularly notable for T2D: at the phenotypic level, LHR showed a stronger association with diabetes risk than height, and individuals with lower LHR had a significantly elevated T2D risk even when matched on stature. For the four diseases that are inversely associated with both height and LHR (T2D, CAD, HT, and MI), we found distinct mediation pathways. Lipid biomarkers, particularly HDL-c, primarily mediated the associations between LHR and these diseases, whereas inflammatory markers, especially NEUT, mainly mediated the associations with height. These findings suggest that height and LHR exert protective effects through different biological pathways, which warrant further investigation and validation.

Our refined colocalization analysis revealed divergent genetic architectures linking height and LHR to CMD. For example, rs76895963 (*CCND2*), a variant implicated in regenerative potency of cardiomyocytes [46, 47], showed strong colocalization across height, leg length, and sitting height with AF. Similarly, rs7306710 (*HMGA2*) and rs73131917 (*RPSAP52*, lncRNA antisense for *HMGA2* and overexpression increases HMGA protein levels) [48]—loci widely recognized for their involvement in height determination via growth plate regulation and IGF signaling [34]—were shared between height and AF, underscoring a potential developmental link between skeletal growth and atrial structure. We identified strong colocalization between height or LHR and T2D at genes such as *M4CR*, which can alter diabetes risk through a primary effect on obesity [49]. In contrast, LHR–T2D showed extra signals, notably at *JAZF1*, a diabetes susceptibility gene that regulates ribosome biogenesis and insulin translation. Its dysfunction under metabolic stress impairs protein synthesis and promotes β-cell failure, suggesting that leg proportion may capture unique developmental–metabolic pathways not reflected by total height [32]. Shared loci between Height–CAD and LHR–CAD, such as *MTMR11*, point to common genetic determinants related to lipid regulation and inflammatory signaling [50]. However, height uniquely colocalized at *TIPARP-AS1* and *REST*, while LHR colocalized with *FN1* and *MIA3*, the latter being linked to vascular integrity and coronary disease risk [51, 52].

Given the large number of genes associated with both height and LHR, we observed widespread enrichment across most tissues, with particularly strong signals in the brain, heart, pancreas, and liver, highlighting their broad expression and the multi-organ regulation of these complex traits [53]. Partitioned genetic correlation revealed that several inverse associations—such as height–CAD, height–T2D, and LHR–T2D—showed stronger genetic correlation in brain tissues, whereas positively correlated trait pairs did not exhibit such a pattern. Endothelial cells showed pronounced enrichment across multiple trait pairs, including LHR–CAD, LHR–T2D, and Height–VTE, supporting the notion that endothelial dysfunction represents a critical early event in the pathogenesis of T2D, CAD, and VTE [54, 55]. Although most paired traits exhibited convergent enrichment in cardiovascular and metabolic tissues, notable differences were observed in both tissue preference and cellular specificity. For example, while LHR–T2D and Height–T2D both mapped to pancreas and liver, only LHR–T2D showed strong enrichment in pancreatic stellate and endothelial cells, suggesting a more localized metabolic axis. Similarly, Height–CAD and LHR–CAD both involved immune pathways, but were linked to distinct immune cell types—monocyte, Professional antigen presenting cell, and myeloid cell for height, versus dendritic cell, T cell, microglial cell, and macrophage for LHR—reflecting divergent mechanisms of atherosclerosis susceptibility.

Height–T2D and LHR–T2D both showed enrichment in key metabolic biological processes, such as regulation of glycolytic process, carbohydrate catabolic process, and nucleotide metabolism, underscoring shared metabolic mechanisms. However, LHR–T2D additionally showed strong enrichment in skeletal developmental pathways including ossification, skeletal system morphogenesis, and chondrocyte differentiation, suggesting a developmental component in leg proportion–related diabetes susceptibility. This pattern is consistent with prior evidence that leg length is influenced by early-life skeletal growth and is tightly linked to childhood nutrition and insulin-like growth factor (IGF) signaling [56]. The enrichment in ossification and chondrogenesis terms may reflect genetic effects on endochondral bone development that also impact metabolic programming in peripheral tissues such as pancreas and muscle. It supports the idea that LHR captures a distinct growth trajectory that affects metabolic disease risk via developmental origins [57]. From the KEGG pathway analysis, LHR–T2D was also uniquely enriched in immune-vascular pathways such as NF-kappa B signaling, endocytosis, and natural killer cell–mediated cytotoxicity, which were absent or weaker in Height–T2D. This suggests that inflammation and immune regulation may play a more central role in the link between leg proportion and diabetes, potentially through vascular or islet stress [58, 59].

Our findings highlight LHR as a clinically meaningful anthropometric trait that provides information beyond overall height. Much like WHR refines the clinical interpretation of BMI by distinguishing body fat distribution, LHR captures variation in body proportion—distinguishing individuals with relatively longer legs from those with a more centralized build. Importantly, we show that LHR is independently associated with the risk of CMD, including T2D, CAD, MI, and HT, even after adjusting for height. This suggests that height alone is insufficient to capture relevant skeletal and developmental differences that influence disease susceptibility. Incorporating LHR into routine clinical assessment may offer a simple yet powerful tool for risk stratification, enabling clinicians to identify at-risk individuals who may be overlooked by traditional height or BMI-based evaluations.

This study has limitations. First, the analysis was conducted primarily in individuals of European ancestry from a single large-scale biobank, which may limit the generalizability of our findings to other populations with different growth patterns, body proportions. Second, our observational analyses may still be affected by residual confounding from unmeasured early-life exposures, nutritional status, or hormonal influences. Third, although we identified multiple genetic loci associated with LHR, most of these signals remain to be functionally validated, and the underlying biological mechanisms require further investigation.

In conclusion, LHR is a polygenic trait with hundreds of independent variants. It has independent and differential effects across 15 CMD traits. The protective association between LHR and CMD is mainly mediated by lipids, and genes shared between LHR and these outcomes are predominantly enriched in development and differentiation of skeletal and embryonic. Further studies are warranted to investigate the biological mechanisms by which LHR influences CMD.

Abbreviations

BMI	Body mass index
CMD	Cardiometabolic disease
CAD	Coronary artery disease
MI	Myocardial infarction
T2D	Type 2 diabetes
AF	Atrial fibrillation
VTE	Venous thromboembolism
WHR	Waist-hip ratio
LHR	Leg-height ratio
DVT	Deep vein thrombosis
LDSC	Linkage disequilibrium score regression
GWAS	Genome-wide association study
AA	Aortic aneurysm
CM	Cardiomyopathy
HF	Heart failure
PAD	Peripheral artery disease
HT	Hypertension
IS	Ischemic stroke
HS	Hemorrhagic stroke
TIA	Transient ischemic attack
AS	Any stroke
CKD	Chronic kidney disease
HDL-c	High-density lipoprotein cholesterol
LDL-c	Low-density lipoprotein cholesterol
TC	Total cholesterol
TG	Triglycerides
HbA1c	Hemoglobin A1c
AST	Aspartate aminotransferase
CRE	Creatinine
WBC	White blood cell
CRP	C-reactive protein
MAGMA	Multi-marker analysis of genomic annotation
GO	Gene Ontology
KEGG	Kyoto encyclopedia of genes and genomes
NEUT	Neutrophils

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12933-025-03074-z.

Supplementary material 1.

Supplementary material 2.

Supplementary material 3.

Supplementary material 4.

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Author contributions

All authors meet authorship criteria by contributing to components of research conception, design, and writing. J.H. and R.Z. conceptualized this research, conducted the data analysis, and drafted the initial manuscript. W.Y. and Z.Y. contributed to data analysis and manuscript writing. Z.W. revised the manuscript. V.N., P.W.C.L., A.F. provided input into the study design and revised the manuscript. X.L. interpreted the results and revised the manuscript. All authors reviewed the final manuscript.

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Data availability

All statistical codes for this study are available at https://github.com/zhaoran7/LHR. GWAS summary statistics of height and LHR are available at https://zenodo.org/uploads/15861435. GWAS summary statistics for all 15 outcomes were obtained from https://www.finngen.fi/en/access_results. The UK Biobank data can be accessed upon application at https://www.ukbiobank.ac.uk. Publicly available software was used to perform the analyses, including REGENIE (https://rgcgithub.github.io/regenie/), LDSC (https://github.com/bulik/ldsc), GCTA (https://yanglab.westlake.edu.cn/software/gcta), Coloc (https://github.com/chr1swallace/coloc), MAGMA (https://ctg.cncr.nl/software/magma), FUMA (https://fuma.ctglab.nl/), WebCSEA (https://bioinfo.uth.edu/webcsea), and gwaslab (https://cloufield.github.io/gwaslab/).

Declarations

Ethics approval and consent to participate.

The UK Biobank has received approval from the North West Multicenter Research Ethics Committee (No. 11/NW/0382) and accorded to the Declaration of Helsinki. Participants provided informed consent and data access was granted under approved application protocols.

Consent for publication

Not applicable.

Competing interests
The authors declare no competing interests.

Author details
[1]School of Public Health and Emergency Management, Southern University of Science and Technology, Shenzhen, Guangdong Province, China
[2]School of Biosciences and Veterinary Medicine, University of Camerino, Camerino, Italy
[3]School of Mathematics and Statistics, Nanjing University of Information Science and Technology, Nanjing, Jiangsu, China
[4]International Curriculum Center of RDFZ, Beijing, China
[5]Department of Sport, Physical Education and Health, Hong Kong Baptist University, Kowloon Tong, Hong Kong SAR, China
[6]Aging and Vascular Diseases, Human Aging Research Institute (HARI) and School of Life Science, Nanchang University, Nanchang, Jiangxi, China
[7]Institute of Clinical Molecular Biology (IKMB), Christian-Albrechts-University of Kiel & University Hospital Schleswig-Holstein (UKSH), Kiel, Germany

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