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# Effect of obesity on cardiovascular morphofunctional phenotype

## Study of Mendelian randomization

Xiaoyu Jiang, MD[a], Longqing Yu, MD[a], Jingyi Li, MD[a], Xizhuang Gao, MD[a], Jinlin Wang, MD[a], Guangyi Qu, MD[a], Cheng Shen, PhD[b,c], Lijun Gan, PhD[b,c,*]

**Abstracts**

**Background:** Obesity is an independent factor for cardiovascular diseases, impacting health across different age groups. cardiovascular magnetic resonance (CMR) imaging is considered the gold standard for noninvasive assessment of cardiovascular structure and function. We conducted a Mendelian randomization (MR) study to explore the associations between obesity-related traits and the clinical pre-phenotype of cardiac and aortic structure and function.

**Methods:** Independent genetic variations significantly correlated with adult body mass index, adult waist-to-hip ratio, birth weight, child body mass index, and excess visceral fat were selected as instrumental variables. Eighty-two CMR imaging features were obtained from the UK Biobank Genome-Wide Association Study. These features served as clinical pre-phenotypes, providing early indications of the structure and function of the 4 cardiac chambers and 2 aortic slices. Preliminary analyses were conducted using MR and inverse variance-weighted methods. Causal directions were determined through Steiger filtering and testing, achieving confirmation. Sensitivity analyses were performed using weighted median, MR-Egger, and MR-PRESSO methods.

**Results:** Adult BMI was positively correlated with left ventricular end-systolic volume, right ventricular end-diastolic volume, right ventricular end-systolic volume, and right ventricular volume per beat. The adult waist-to-hip ratio was inversely proportional to right atrial volume per beat, right atrial maximum volume, right atrial minimum volume, partial regional longitudinal strain, regional peak circumferential strain, and regional radial strain, and positively proportional to partial regional peak circumferential strain and partial end-diastolic local myocardial wall thickness characteristics. Birth weight was positively correlated with maximum right atrial volume, minimum right atrial volume, right atrial volume per beat, right ventricular end-diastolic volume, right ventricular output per beat, maximum area of the ascending aorta, minimum area of the ascending aorta, and negatively correlated with longitudinal strain in some regions. Body mass index in children is positively correlated with left ventricular end-diastolic volume, left ventricular end-systolic volume, left atrial volume per beat, right ventricular end-diastolic volume, and right ventricular volume per beat.

**Conclusion:** This study suggests that obesity may lead to myocardial hypertrophy and dilation of the cardiac chambers and aorta, thereby exerting adverse effects on the cardiovascular system and increasing the susceptibility to HF.

**Abbreviations:** AAo = ascending aorta, AHA = American Heart Association, BMI = body mass index, CMR = Cardiovascular magnetic resonance imaging, DAo = descending aorta, Ecc AHA = regional peak circumferential strain, Ell = longitudinal strain, Err = radial strain, FFMI = fat-free mass index, FMI = fat mass index, GWAS = genome-wide association studies, HF = heart failure, HFpEF = heart failure with preserved ejection fraction, IVW = inverse variance-weighted, LA = left atrium, LAEF = left atrium ejection fraction, LASV = left atrium stroke volume, LAV = left atrium volume, LV = left ventricle, LVCO = left ventricular cardiac output, LVEDV = left ventricular end-diastolic volume, LVEDV = left ventricular end-diastolic volume, LVEF = left ventricular ejection fraction, LVESV = left ventricular end-systolic volume, LVM = left ventricular myocardial mass, LVSV = left ventricular stroke volume, MR = Mendelian randomization, RA = right atrium, RAEF = right atrium ejection fraction, RASV = right atrium stroke volume, RAV_max = right atrium maximum volume, RAV_min = right atrium minimum volume, RV = right ventricle, RVEDV = right ventricular end-diastolic volume, RVESV = right ventricular end-systolic volume, RVSV = right ventricular stroke volume, SNPs = single nucleotide polymorphisms, WHR = waist-to-hip ratio, WT AHA = regional myocardial-wall thicknesses at end-diastole, WT_global = global myocardial-wall thickness at end-diastole.

**Keyword:** adults and children, cardiovascular magnetic resonance, Mendelian randomization, obesity

*XJ and LY contributed to this article equally.*

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*All data generated or analyzed during this study are included in this published article [and its supplementary information files].*

*The summary-level data of GWAS studies involved in the present research are all publicly available and ethical approvals were gained in all original papers.*

*Supplemental Digital Content is available for this article.*

## 1. Introduction

As is well known, obesity is an independent factor for cardiovascular diseases.[1,2] Many obese individuals may develop metabolic syndrome, accompanied by downstream cardiovascular diseases.[3] Obesity has sharply increased in the past few decades, characterized by the excessive accumulation of adipose tissue, leading to elevated risks of cardiovascular metabolic factors such as hyperglycemia, lipid abnormalities, and insulin resistance.[4] Health across different age groups is affected by obesity, and at a younger age, there is an increasing incidence of hypertension in children, making it a public health concern.[5] The relationship between higher body mass index (BMI) values in adolescents and hypertension has been confirmed in other studies.[6–9] Simultaneously, school-age children who are overweight or obese are associated with a low level of cardiorespiratory fitness, posing adverse cardiovascular metabolic risks.[10] However, currently, there is no research associating obesity-related indicators with cardiovascular morphological features.

The structure of the heart and aorta forms the foundation of physiological function and may exhibit abnormalities even before the onset of apparent disease symptoms. Cardiovascular magnetic resonance imaging (CMR) is widely acknowledged as the gold-standard modality for noninvasive evaluation of the structure and function of the cardiovascular system.[11] CMR can integrate multiparametric anatomical and functional information with detailed characterization of soft tissues.[12] Its derived traits are recognized phenotypes, serving as risk biomarkers and imaging surrogate endpoints in clinical trials.[13,14] The feasibility of large-scale genome-wide association studies (GWAS) has been made possible due to the progress in artificial intelligence and the appearance of biobanks. These studies significantly deepen our genetic understanding of the reshaping of cardiac and aortic structure and function during the development of diseases.

In this research, the analysis was carried out on 82 CMR features obtained from 6 GWAS studies, comprising 64 left ventricular, 4 right ventricular, 4 left atrial, 4 right atrial, 3 ascending aortic, and 3 descending aortic features.[13] By making use of Mendelian randomization (MR) with the genetic variations unearthed from GWAS acting as instrumental variables, we delved into the causal associations between obesity-related traits-namely adult BMI, adult waist-to-hip ratio (WHR), birth weight, childhood BMI, and the presence of excessive visceral fat – and the CMR features under scrutiny. The elucidation of these causal relationships holds paramount importance in the assessment and management of cardiovascular risks within the obese demographic. It enables us to gain a more profound comprehension of the mechanisms through which these factors influence the initiation and development of cardiovascular diseases. This, in turn, paves the path for progress in the fields of early-stage detection, treatment modalities, and comprehensive intervention strategies.

## 2. Research design

This study conducted MR analysis based on 3 main assumptions: reliable associations with the investigated risk factors (correlation assumption); no involvement of any known or unknown confounding factors (independence assumption); influencing the outcomes solely through the risk factors and not through any direct causal pathways (exclusion restriction assumption).[15] The study aims to explore the individual causal relationships between obesity in adults and children and 82 cardiovascular morphofunctional phenotypes. Researchers can access the summary-level data from the GWAS studies utilized here through open science platforms, and all original papers have obtained ethical approval.

### 2.1. Genetic instrument selection

The genetic associations with birth weight and childhood BMI are extracted from the Early Growth Genetics Consortium, including birth weight data from 298,142 Europeans and childhood BMI data from 35,668 European children aged 2 to 10 years.[16,17] For adult phenotypes, genetic associations with BMI and WHR come from a GWAS involving up to 806,834 individuals of European ancestry.[18] Summary data on visceral obesity are derived from a GWAS involving 396,220 European individuals. The level of visceral obesity was estimated using machine learning methods, with a training dataset consisting of 4198 European individuals measured for visceral fat tissue using dual-energy X-ray absorptiometry.[19] Bioelectrical impedance was employed to measure fat and fat-free mass, and corresponding genetic associations were obtained from the UK Biobank study, encompassing 331,291 individuals.[20] The calculation method for Fat Mass Index (FMI) and fat-free mass index involves dividing the fat mass or fat-free mass by the square of height.[20] We extracted single nucleotide polymorphisms (SNPs) significantly associated with birth weight, childhood BMI, adult BMI, adult WHR, visceral obesity, and related traits at the genome-wide significance level ($P < 5 \times 10^{-8}$) from the mentioned GWAS. Linkage disequilibrium for selected SNPs for each trait was estimated based on a European reference panel of 1000 genomes. Independent SNPs, after removing linkage disequilibrium ($r^2 \geq 0.001$), were used as instrumental variables for MR analysis. For information about the genetic instrument, see Table S1, Supplemental Digital Content, http://links.lww.com/MD/O517.

### 2.2. Outcome data sources

This study includes 82 CMR features, comprising 64 left ventricular, 4 right ventricular, 4 left atrial, 4 right atrial, 3 ascending aortic, and 3 descending aortic features. The summary-level data associated with these CMR features are sourced from research projects founded on the UK Biobank., with a study population exceeding 40,000 participants.[13] For information about the outcome data, see Table S1, Supplemental Digital Content, http://links.lww.com/MD/O517.

[a] Department of Clinical Medicine, Affiliated Hospital of Jining Medical University, Jining Medical University, Jining, Shandong Province, China, [b] Department of Cardiology, Jining Key Laboratory for Diagnosis and Treatment of Cardiovascular Diseases, Affiliated Hospital of Jining Medical University, Jining, Shandong Province, China, [c] Shandong Provincial Key Medical and Health Discipline of Cardiology (Affiliated Hospital of Jining Medical University), Jining, Shandong Province, China.

* Correspondence: Lijun Gan, Department of Cardiology, Jining Key Laboratory for Diagnosis and Treatment of Cardiovascular Diseases, Affiliated Hospital of Jining Medical University, Jining 272000, Shandong Province, China (e-mail: jyfydoctor@email.cn).



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### 2.3. Statistical analysis

Before conducting MR analysis, exposure and outcome data were harmonized to remove palindromic SNPs. To avoid potential horizontal pleiotropy, SNPs directly correlated with outcome data were further removed, and the directionality of SNPs was tested. Specifically, SNPs reaching genome-wide significance ($P < 5 \times 10^{-8}$) were initially removed from the outcome, and then Steiger filtering was used to test the directionality of the remaining instrumental variables' association with the outcome. Any instrumental variables marked as FALSE through Steiger filtering, indicating that the SNP-explained outcome variance is greater than the exposure variance, were excluded from the MR analysis. For the MR analysis, the inverse variance-weighted (IVW) method was chosen as the primary statistical approach. The present methodology operates under the assumption that all SNPs are valid instrumental variables, providing the most accurate estimates. In this study, the presence of heterogeneity was initially evaluated using Cochran *Q* test. A *P*-value exceeding .05 indicates the absence of significant heterogeneity, prompting the application of the fixed-effects inverse-variance-weighted (IVW) method. Conversely, if the *P*-value is <.05, the random-effects IVW method is employed to account for heterogeneity. Given the susceptibility of the IVW method to horizontal pleiotropy, additional sensitivity analyses were conducted using the Weighted Median and MR-Egger regression methods. The Weighted Median method operates under the premise that a valid causal estimate can be derived if at least 50% of the instrumental variables' weights are free from pleiotropic effects.

The MR-Egger regression intercept can be utilized to assess the potential presence of horizontal pleiotropy. Notably, this analytical approach maintains capability to generate causal effect estimates even under scenarios where all genetic instruments exhibit violations of validity assumptions, though accompanied by increased estimation uncertainty. While both Weighted Median and MR-Egger methodologies demonstrate inferior statistical power compared to the inverse-variance-weighted (IVW) approach, consistent directional agreement among these 3 analytical frameworks significantly enhances confidence in the robustness of causal estimates derived from the principal analytical strategy. All statistical computations were executed through R statistical environment (v4.2.1) employing specialized genetic epidemiology packages, specifically TwoSampleMR (v0.5.7) and MR (v0.9.0), following established protocols for bidirectional MR analysis. MR estimates were represented by effect sizes (β) and 95% confidence intervals (CI). For single-trait MR analysis, FDR correction was applied with a corrected *P*-value threshold of .05, and associations with *P*-values < .05 were considered suggestive. In the case of MVMR analysis, associations with *P*-values < .05 were deemed statistically significant.

## 3. Results

This study includes 82 CMR features, comprising 64 left ventricular, 4 right ventricular, 4 left atrial, 4 right atrial, 3 ascending aortic, and 3 descending aortic features. The summary-level data for these CMR features primarily come from research based on the UK Biobank, with a participant count exceeding 40,000 individuals. Positive results are detailed in Table S2, Supplemental Digital Content, http://links.lww.com/MD/O518 of the additional document and are shown in Figure 1.

The adult BMI is positively correlated with left ventricular end-systolic volume (β = 0.050; 95% CI = 0.020–0.081; *q* = 0.027), positively correlated with right ventricular end-diastolic volume (β = 0.044; 95% CI = 0.015–0.074; *q* = 0.047), positively correlated with right ventricular end-systolic volume (β = 0.049; 95% CI = 0.018–0.080; *q* = 0.034), and positively correlated with right ventricular stroke volume (β = 0.056; 95% CI = 0.022–0.091; *q* = 0.027).The adult WHR is inversely proportional to the right atrial stroke volume (β = –0.116; 95% CI = –0.169 to –0.063; *q* = 0.002), inversely proportional to the right atrial maximum volume (β = –0.100; 95% CI = –0.150 to –0.051; *q* = 0.004), inversely proportional to the right atrial minimum volume (β = –0.091; 95% CI = –0.140 to –0.042; *q* = 0.008), and negatively correlated with the regional longitudinal strain of Ell_2 trait (β = –0.087; 95% CI = –0.142 to –0.032; *q* = 0.032). The adult WHR is positively correlated with the regional peak circumferential strain of Ecc_AHA_2 trait (β = 0.101; 95% CI = 0.054–0.148; *q* = 0.002) and inversely proportional to the regional peak circumferential strain of Ecc_AHA_9 trait (β = –0.081; 95% CI = –0.134 to –0.028; *q* = 0.042). It is inversely proportional to 2 regional radial strain traits, with specific values for Err_AHA_3 (β = –0.116; 95% CI = –0.169 to –0.063; *q* = 0.001) and Err_AHA_4 (β = –0.103; 95% CI = –0.154 to –0.063; *q* = 0.001). The adult WHR is positively correlated with the end-diastolic local myocardial wall thickness traits of 7 pre-defined American Heart Association (AHA) segments, with specific values as follows: WT_AHA_7 (β = 0.070; 95% CI = 0.028–0.112; *q* = 0.023), WT_AHA_8 (β = 0.067; 95% CI = 0.023–0.111; *q* = 0.042), WT_AHA_10 (β = 0.091; 95% CI = 0.050–0.132; *q* = 0.001), WT_AHA_11 (β = 0.110; 95% CI = 0.068–0.150; $q = 4.72 \times 10^{-05}$), WT_AHA_13 (β = 0.065; 95% CI = 0.022–0.107; *q* = 0.045), WT_AHA_15 (β = 0.097; 95% CI = 0.055–0.139; *q* = 0.001), WT_AHA_16 (β = 0.069; 95% CI = 0.026–0.112; *q* = 0.029). The birth weight is positively correlated with the right atrial maximum volume (β = 0.121; 95% CI = 0.063–0.180; *q* = 0.003), positively correlated with the right atrial minimum volume (β = 0.112; 95% CI = 0.054–0.169; *q* = 0.006), positively correlated with the right atrial stroke volume (β = 0.119; 95% CI = 0.056–0.182; *q* = 0.007), positively correlated with the right ventricular end-diastolic volume (β = 0.068; 95% CI = 0.023–0.113; *q* = 0.047), positively correlated with the right ventricular stroke volume (β = 0.081; 95% CI = 0.029–0.133; *q* = 0.036), positively correlated with the maximum area of the ascending aorta (β = 0.139; 95% CI = 0.078–0.199; *q* = 0.001), positively correlated with the minimum area of the ascending aorta (β = 0.125; 95% CI = 0.064–0.186; *q* = 0.003), and negatively correlated with the regional longitudinal strain of Ell_5 trait (β = –0.101; 95% CI = –0.165 to –0.037; *q* = 0.034) and negatively correlated with the regional longitudinal strain of Ell_6 trait (β = –0.098; 95% CI = –0.161 to –0.036; *q* = 0.034).

The BMI in children is positively correlated with the left ventricular end-diastolic volume (β = 0.107; 95% CI = 0.051–0.163; *q* = 0.006), positively correlated with the left ventricular end-systolic volume (β = 0.115; 95% CI = 0.055–0.175; *q* = 0.006), positively correlated with the left atrial stroke volume (β = 0.127; 95% CI = 0.054–0.199; *q* = 0.016), positively correlated with the right ventricular end-diastolic volume (β = 0.107; 95% CI = 0.054 to –0.037; *q* = 0.160), and positively correlated with the right ventricular stroke volume (β = 0.102; 95% CI = 0.040–0.164; *q* = 0.027).

In sensitivity analysis, the associations between most obesity traits and CMR traits remained consistent, and they showed a similarity in the relationship with diabetes and CMR traits. Most results indicated no evidence of heterogeneity or horizontal pleiotropy.

## 4. Discussion

The results of this study are significant and insightful, summarized in the Figure 2. In this research, we utilized the latest large-scale GWAS summary-level data to assess the genetic relationships between 5 obesity traits and 82 CMR traits. These CMR features were derived from 6 GWAS studies, encompassing 64 left ventricular, 4 right ventricular, 4 left atrial, 4 right atrial, 3 ascending aortic, and 3 descending aortic characteristics. To our knowledge, this is the most comprehensive MR

| Exposure | Outcome | nsnp | Beta (95% CI) | P value |
|---|---|---|---|---|
| Adulthood BMI | | | | |
| | LVEDV | 726 | 0.050 (0.020 , 0.081) | 0.027 |
| | RVEDV | 704 | 0.044 (0.015 , 0.074) | 0.048 |
| | RVESV | 701 | 0.049 (0.018 , 0.080) | 0.034 |
| | RVSV | 710 | 0.056 (0.022 , 0.091) | 0.027 |
| Adulthood WHR | | | | |
| | RAV_max | 405 | -0.100 (-0.150 , -0.051) | 0.004 |
| | RAV_min | 421 | -0.091 (-0.140 , -0.042) | 0.008 |
| | RASV | 422 | -0.116 (-0.169 , -0.063) | 0.002 |
| | Ell_2 | 419 | -0.087 (-0.142 , -0.032) | 0.032 |
| | Ecc_AHA_2 | 413 | 0.101 (0.054 , 0.148) | 0.002 |
| | Ecc_AHA_9 | 432 | -0.081 (-0.134 , -0.028) | 0.042 |
| | Err_AHA_3 | 416 | -0.116 (-0.169 , -0.063) | 0.001 |
| | Err_AHA_4 | 437 | -0.103 (-0.154 , -0.051) | 0.004 |
| | WT_AHA_7 | 414 | 0.070 (0.028 , 0.112) | 0.023 |
| | WT_AHA_8 | 408 | 0.067 (0.023 , 0.111) | 0.042 |
| | WT_AHA_10 | 381 | 0.091 (0.050 , 0.132) | 0.001 |
| | WT_AHA_11 | 395 | 0.110 (0.068 , 0.151) | 0.000 |
| | WT_AHA_13 | 433 | 0.065 (0.022 , 0.107) | 0.045 |
| | WT_AHA_15 | 425 | 0.097 (0.055 , 0.139) | 0.001 |
| | WT_AHA_16 | 432 | 0.069 (0.026 , 0.112) | 0.029 |
| Birth weight | | | | |
| | RVEDV | 161 | 0.068 (0.023 , 0.113) | 0.047 |
| | RVSV | 166 | 0.081 (0.029 , 0.133) | 0.036 |
| | RAV_max | 158 | 0.121 (0.063 , 0.180) | 0.003 |
| | RAV_min | 161 | 0.112 (0.054 , 0.169) | 0.006 |
| | RASV | 165 | 0.119 (0.056 , 0.182) | 0.007 |
| | AAo_max_area | 149 | 0.139 (0.078 , 0.199) | 0.001 |
| | AAo_min_area | 147 | 0.125 (0.064 , 0.186) | 0.003 |
| | Ell_5 | 169 | -0.101 (-0.165 , -0.037) | 0.034 |
| | Ell_6 | 162 | -0.098 (-0.161 , -0.036) | 0.034 |
| Childhood BMI | | | | |
| | LVEDV | 14 | 0.107 (0.051 , 0.163) | 0.006 |
| | LVESV | 14 | 0.115 (0.055 , 0.175) | 0.006 |
| | LASV | 14 | 0.127 (0.054 , 0.199) | 0.016 |
| | RVEDV | 14 | 0.107 (0.054 , 0.160) | 0.004 |
| | RVSV | 14 | 0.102 (0.040 , 0.164) | 0.027 |

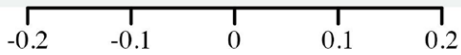


**Figure 1.** Significant associations of obesity with cardiovascular magnetic resonance traits. AAo = ascending aorta, Adulthood BMI = adulthood body mass index, Adulthood WHR = adulthood waist-to-hip ratio, AHA = American Heart Association, childhood BMI = childhood body mass index, LASV, left atrium stroke volume, LVEDV = left ventricular end-diastolic volume, RVEDV = right ventricular end-diastolic volume, RVESV = right ventricular end-systolic volume, RVSV = right ventricular stroke volume, RAV_max = right atrium maximum volume, RAV_min = right atrium minimum volume, RASV = right atrium stroke volume. Ell, longitudinal strain; Ecc AHA, regional peak circumferential strain, segment 2, 9of the 16 predefined segments by the AHA; Err, radial strain; WT AHA, regional myocardial-wall thicknesses at end-diastole, segments 7, 8, 10, 11, 13, 15, and 16 of the 16 predefined segments by the AHA.

study exploring the causal relationships between obesity and the structure and function of the heart and aorta.

The main findings of our study indicate that obesity traits significantly influence the phenotypes of the aorta and left ventricle. The results are as follows: Adult BMI is positively correlated with left ventricular end-systolic volume, right ventricular end-diastolic volume, right ventricular end-systolic volume, and right ventricular stroke volume. Adult waist-to-hip ratio is positively correlated with regional peak circumferential strain characteristic of Ecc_AHA_2, end-diastolic local myocardial wall thickness characteristics of 7 predefined AHA segments, and right atrial stroke volume, right atrial maximum volume, right atrial minimum volume, regional longitudinal strain of Ell_2, regional peak circumferential strain characteristic of Ecc_AHA_9, and negatively correlated with 2 regional radial strain characteristics. Birth weight is positively correlated with right

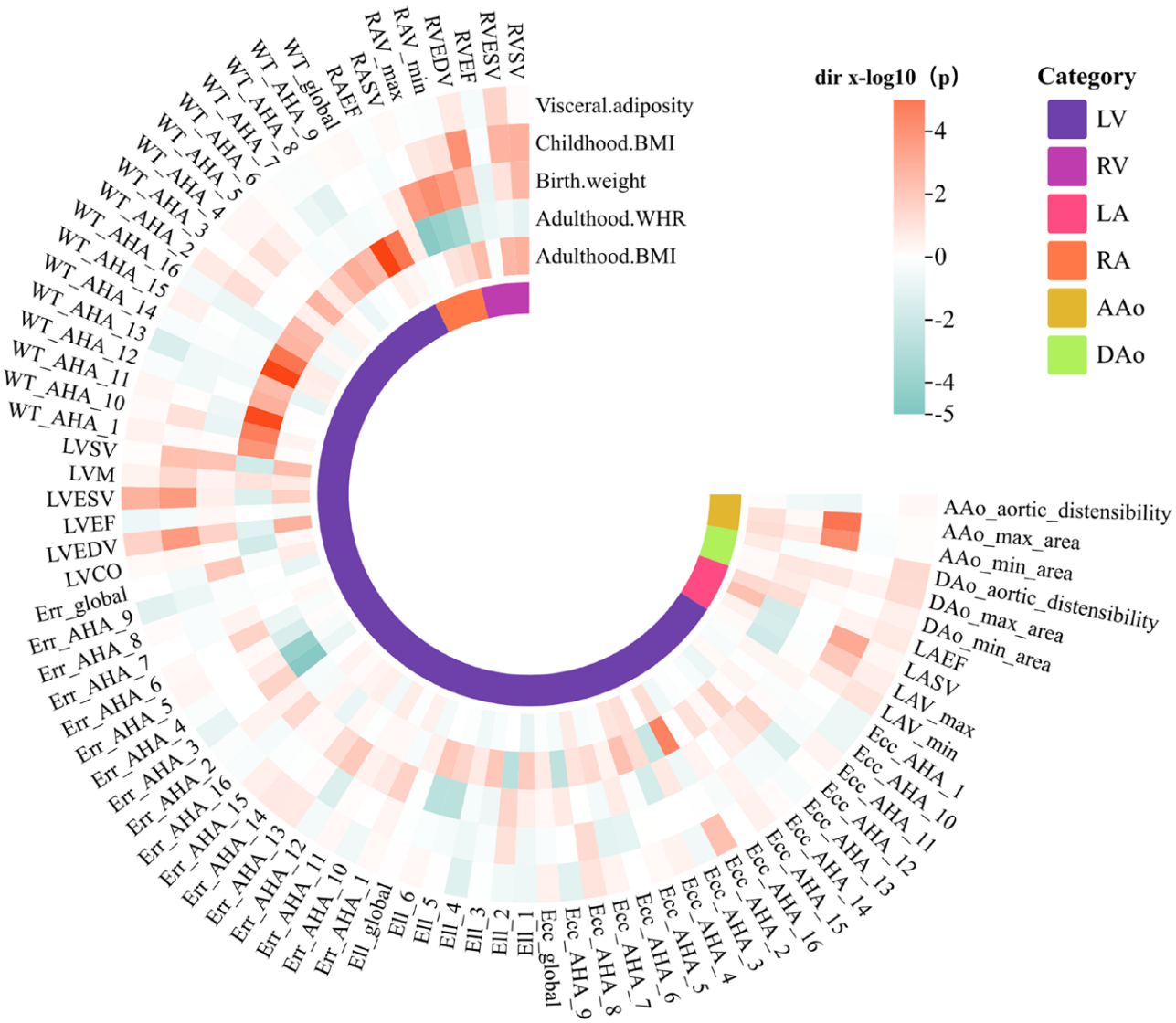


**Figure 2.** All associations with $P < .05$ were clustered based on CMR trait categories, $P$ values were multiplied by – log10 ($P$-values), and was color-coded according to the direction of effect. AAo = ascending aorta, Adulthood BMI = Adulthood body mass index, Adulthood WHR = adulthood waist-to-hip ratio, childhood BMI = childhood body mass index, DAo = descending aorta, Ecc AHA = regional peak circumferential strain, Ell = longitudinal strain, Err = radial strain, LA = left atrium, LAEF = left atrium ejection fraction, LASV = left atrium stroke volume, LAV = left atrium volume, LV = left ventricle, LVCO = left ventricular cardiac output, LVEDV = left ventricular end-diastolic volume, LVEF = left ventricular ejection fraction, LVESV, left ventricular end-systolic volume, LVM = left ventricular myocardial mass, LVSV, left ventricular stroke volume, RA = right atrium, RAEF = right atrium ejection fraction, RASV = right atrium stroke volume, RAV_max = right atrium maximum volume, RAV_min = right atrium minimum volume, RV = right ventricle, RVEDV = right ventricular end-diastolic volume, RVESV = right ventricular end-systolic volume, RVSV = right ventricular stroke volume, WT AHA = regional myocardial-wall thicknesses at end-diastole, WT_global = global myocardial-wall thickness at end-diastole.

atrial maximum volume, right atrial minimum volume, right atrial stroke volume, right ventricular end-diastolic volume, right ventricular stroke volume, maximum area of the ascending aorta, and minimum area of the ascending aorta. It is negatively correlated with regional longitudinal strain characteristics of Ell_5 and Ell_6. Childhood BMI is positively correlated with left ventricular end-diastolic volume, left ventricular end-systolic volume, left atrial stroke volume, right ventricular end-diastolic volume, and right ventricular stroke volume.

Examining the relationship between quantitative imaging phenotypes and modifiable risk factors reveals results of crucial clinical significance. Obesity, characterized by excessive accumulation of adipose tissue, has sharply increased over the past few decades.[4] Adipose tissue is a highly active metabolic organ involved in cross-talk between various systems. As adipose tissue is not merely a passive repository for fat but also an endocrine organ, it can synthesize various important peptides and non-peptidic compounds and release them into the bloodstream. These peptides and compounds may play a role in cardiovascular homeostasis.[21] Therefore, prolonged obesity may be accompanied by changes in cardiovascular morphology and function. Currently, the probability of elderly individuals developing cardiovascular diseases is relatively high, and the risk of cardiovascular diseases in younger people is also increasing. This underscores the need for a primary focus on the primary prevention of cardiovascular diseases. The reliability and consistency of CMR make it an ideal choice for monitoring the effectiveness of intensive glycemic control, aiding in the assessment of the effectiveness of primary prevention of cardiovascular diseases.

The structure and function of the heart and arteries are closely related to cardiovascular diseases, with the left ventricle being the most crucial. A larger left ventricular mass is associated with a higher risk of hypertension and heart disease.

Moreover, larger chamber volumes are linked to an increased risk of heart disease.[22] In obese individuals, the characteristics of the heart include hypertrophy of myocardial cells, infiltration of fat into the extracellular matrix (lipomatosis), and the accumulation of triglycerides in the contractile elements. All these factors can impact the geometric shape of the left ventricle.[23] The mechanisms by which obesity affects the geometric structure and function of the left ventricle include:1.Internal fat distribution and secretory products.2.Elevated insulin levels and insulin resistance and their growth-stimulating effects.3.Increased blood pressure and its cumulative effect on myocardial remodeling4.Sleep apnea and its impact on nighttime blood pressure, adrenergic stimulation, and chronic hypoxemia.[24] Obesity not only predisposes to volume overload and associated hypertension,[25,26] but also induces a low-grade systemic inflammatory response, leading to elevated inflammatory mediators such as CRP, tumor necrosis factor-α, amyloid A, white blood cell count, and interleukin-6.[27] Therefore, obesity can have adverse effects on cardiovascular morphology and function, making individuals more susceptible to cardiovascular-related diseases, ultimately leading to heart failure (HF).

HF is characterized by impairment in the contraction function and/or relaxation function of the heart. In the early stages, it is typically asymptomatic but may involve isolated diastolic dysfunction.[28] Impairment in left ventricular diastolic function is a key factor in the clinical presentation of HF and forms the basis for HF with preserved ejection fraction (HFpEF). In addition to the left ventricle, increasing evidence suggests that assessing the volumes and function of the right ventricle and left atrium using CMR can contribute to a deeper understanding and characterization of HF phenotypes.[29] Regardless of the left ventricular ejection fraction, the right ventricular ejection fraction is closely associated with increased mortality and hospitalization rates for HF.[30] Additionally,[31] right ventricular strain injury is also linked to adverse outcomes in HF.[31,32] In a prospective multicenter cohort study involving 121 suspected HFpEF patients, CMR measurements of left atrial volume index, left atrial reservoir strain, and left atrial area index were identified as the optimal discriminators between HFpEF and non-HFpEF.[33,34] Our research indicates that obesity is associated with an increase in end-diastolic local myocardial wall thickness in segments of the left ventricle, a decrease in regional peak circumferential strain, and a reduction in regional radial strain. This is accompanied by an enlargement of the right ventricle and right atrium volumes, suggesting that obese patients are prone to HF. These findings align with previous studies.[35–39]

The main advantages of this study can be summarized as follows: First, through MR analysis, we systematically revealed the potential causal relationship between obesity and 82 cardiometabolic risk (CMR) characteristics, providing a new research perspective in this field. Secondly, the MR study design effectively reduces the interference of residual confounding factors that are common in traditional observational studies, so as to obtain more convincing causal evidence. Thirdly, in view of the possible bias of reverse causality in MR analysis, we used the Steiger directivity test to screen SNPs, and verified the correct direction of causality through the directivity test to ensure the rationality of the research hypothesis. Fourthly, by integrating multi-source GWAS data resources and conducting confirmatory analysis in different independent datasets, the study not only found previously neglected associations, but also significantly enhanced the credibility of causal inference through the consistency of results. Finally, the analysis based on the pooled data of the European population minimizes the potential risk of bias that may be caused by differences in population structure, which provides an important guarantee for the reliability of the research conclusions.

This study has several limitations. Due to the limitations of summary-level data in GWAS, additional private databases, as well as databases for different ethnic groups, lifestyle habits, and more cardiac-related image types, could be included for more detailed analysis and validation in future studies. Although MR provides evidence for causality, more research, including randomized controlled trials, is needed to confirm the causality identified in this study.

## 5. Conclusion

In conclusion, this study suggests that obesity may lead to myocardial hypertrophy and dilation of the cardiac chambers and aorta, thereby exerting adverse effects on the cardiovascular system and increasing the susceptibility to HF. Obesity is a risk factor influencing cardiac and arterial remodeling, enhancing our understanding of how obesity contributes to the onset and progression of cardiovascular diseases. It highlights the detrimental effects of excessive obesity, providing new insights for early non-pharmacological treatments and intervention strategies for cardiovascular diseases.

## Author contributions

**Writing – original draft:** Xiaoyu Jiang.
**Writing – review & editing:** Longqing Yu, Jingyi Li, Xizhuang Gao, Jinlin Wang, Guangyi Qu, Cheng Shen, Lijun Gan.

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