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Pathophysiology

Obesity Phenotypes Causally Affect Cardiac MRI Structure and Induced Non-ischaemic Cardiomyopathy

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Abstract

Background: The growing obesity epidemic highlights the need to understand how various obesity phenotypes affect myocardial structure and increase non-ischaemic cardiomyopathy (NICM) incidence. The aim of this study was to investigate the causal effect of eight obesity-related traits on NICM and 16 cardiac MRI parameters. Potential mediators between obesity and NICM were also investigated. **Methods:** Two-sample Mendelian randomisation was used to explore the causal relationship between eight obesity-related traits and NICM and assess their impact on cardiac MRI indicators. The study also used validation dataset analysis and multivariable Mendelian randomisation to ensure robustness, and mediation Mendelian randomisation analysis to identify metabolic markers as potential mediators. **Results:** All eight obesity-related traits demonstrated a causal relationship with NICM, with the relationship between BMI and NICM persisting after adjustment for LDL cholesterol, urate level and hypertension (HTN). These traits also influenced arterial and cardiac structure and function, especially with regard to left ventricular mass. HTN was identified as a significant mediator, with a mediation effect ratio of 31%. **Conclusion:** There is a robust causal association between obesity and NICM, and with abnormalities in myocardial structure and function. HTN emerges as a pivotal mediator in the obesity–NICM pathway, underscoring the critical role of managing obesity and HTN in preventing NICM progression.

Keywords

Obesity, body mass index, hypertension, non-ischaemic cardiomyopathy, Mendelian randomisation.

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Data availability: The data are sourced from a public database and can be obtained using the data code in *Supplementary Table 1*. More detailed data are available from the corresponding author upon reasonable request.

Authors' contributions: Conceptualisation: YZ, ZX, ZW; data curation: TZ, EQ, BL, SP; methodology: YZ; writing – original draft preparation: LP, YZ, EQ; writing – review & editing: YZ.

Ethics: Each dataset used in this study has already undergone the necessary ethics review. Due to the use of anonymised and de-identified public data, no additional ethics review is required.

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Obesity and overweight pose significant challenges to public health. Over the past three decades, the global prevalence of obesity has continued to rise.[1] In Western countries, this prevalence has reached 25%.[2] In China, nearly half of adults are overweight or obese, and the number of children being overweight or obese is also increasing.[3] These are conditions caused by a combination of genetics and environmental exposure. Epidemiological and cohort studies consistently demonstrate an association between a higher BMI and an increased risk of various cardiovascular diseases (CVDs), including atherosclerosis and heart failure (HF).[4,5] Obesity has a significant impact on the development of HF, and the American College of Cardiology/American Heart Association (ACC/AHA) HF guidelines recognise obesity as a risk factor for HF.[6] Nonetheless, recent investigations have yielded an abundance of evidence suggesting that metabolically healthy obesity (MHO; a subgroup of obesity in which the individual has normal metabolic markers) might not be closely linked to adverse CVD outcomes.[7,8] Meanwhile, some studies suggest that individuals classified as MHO, irrespective of their metabolic status, have diverse cardiovascular risk factors and the term 'MHO' should be avoided because it is misleading.[9,10] Therefore, the causal association between obesity itself and CVD remains controversial and requires further research.

Non-ischaemic cardiomyopathy (NICM), which has been a major contributor to HF and to the need for heart transplants in recent years, is an abnormality of cardiac structure and function caused by factors other than coronary ischaemia.[11–13] However, its aetiology and mechanisms are

complex and have not been fully elucidated, with factors such as genetics, hypertension (HTN), valvular disease and toxin exposure playing a role in myocardial remodelling.[14] These factors contribute to myocardial remodelling in NICM, resulting in a progressive decline in cardiac output, increased cardiomyocyte apoptosis, and heightened fibrosis, ultimately leading to HF. Observational studies found that obesity alone also affects myocardial structure and pump performance.[15,16] The term 'obesity cardiomyopathy' is used to define myocardial disease in individuals with obesity that cannot be explained by other factors such as diabetes, HTN, coronary heart disease (CHD) or other known causes.[15] A recent study from Australia assessed obese and non-obese cardiac sudden death subjects aged 18–50 years.[17] Only 10% of those with BMI >50 kg/m^2 had coronary disease, while two-thirds had left ventricular hypertrophy.

The association between obesity and NICM has become a significant topic of discussion. However, the studies on people with MHO have raised doubts about its relevance. Some studies propose that the relationship between obesity and NICM may be influenced by confounding factors.[8,18] Furthermore, most clinical studies have primarily focused on the connection between obesity and HF, as well as ischaemic heart disease.[19–22] There is a lack of research specifically examining non-ischaemic aspects. The effect of different obesity phenotypes on cardiac MRI indices is also unknown.

Traditional observational studies on obesity are susceptible to confounding factors and reverse causation bias. To overcome these limitations, we used Mendelian randomisation. This is a powerful statistical method used in epidemiology to assess causal relationships between exposure and outcome. By utilising genetic variants as instrumental variables, Mendelian randomisation helps to mitigate confounding and reverse causation, which are common challenges in observational studies.[23] The principle behind Mendelian randomisation stems from Mendelian genetics, which states that genetic variants are randomly inherited at conception and remain constant throughout an individual's life. This random inheritance mirrors the randomised controlled trials (RCTs) in many ways because it effectively eliminates bias from the confounding factors that often plague traditional observational analyses. For example, if a specific genetic variant is associated with a modifiable exposure, such as BMI, researchers can infer causal relationships between BMI and health outcomes, such as CVD, without the influence of confounders such as socioeconomic status or lifestyle choices.

Mendelian randomisation can not only overcome the limitations of observational studies by mimicking an RCT, but it also provides evidence beyond clinical studies to establish the causal association. In addition, obesity is significantly influenced by genetic factors, making it suitable for prediction using genetic variation. Confounding factors can be effectively addressed through methods such as multivariable Mendelian randomisation (MVMR). This Mendelian randomisation study independently investigated the causal relationship between genetically predicted obesity and NICM, while also exploring potential mediating factors. Furthermore, the study evaluated the causal relationship between different obesity traits and various cardiovascular MRI indicators. This provided us with the opportunity to identify the obesity trait most strongly associated with obesity-related cardiomyopathy, as well as the cardiac MRI indicators that most closely reflect this condition.

Methods

Study Design

Figure 1 presents a flow diagram delineating the study design and the foundational assumptions of Mendelian randomisation applied in this analysis.[24] Our two-sample Mendelian randomisation approach, using genome-wide association study (GWAS) data, sought to investigate potential causal links between obesity and NICM. The study was performed in accordance with the principles of the declaration of Helsinki, and each dataset used in this study had already undergone the necessary ethics review. Due to the use of anonymised and de-identified public data, no additional ethics review was required. The Mendelian randomisation framework in this study was anchored on three critical principles: the instrumental variables must exhibit a strong association with obesity; the instrumental variables should be free from confounding variables; and the influence of instrumental variables on NICM should occur exclusively via the obesity pathway, as shown in *Figure 1*.[24] The analytic process adhered to the STROBE-MR guidelines.[25]

Genetic Instrument Selection

In this study, single nucleotide polymorphisms (SNPs) associated with obesity, potential confounders, potential mediators, and outcomes were extracted from the GWASs listed in *Supplementary Table 1*. For Mendelian randomisation analysis, we selected SNPs that showed a strong association with the exposure variables, meeting the genome-wide significance threshold ($p<5 \times 10^{-8}$). A relaxed threshold ($p<5 \times 10^{-6}$) was set for obesity class 3, given that few SNPs met the original threshold ($p<5 \times 10^{-8}$). To ensure the independence of these SNPs, instrumental variables were clumped in a 10 Mbp window, applying a stringent linkage disequilibrium threshold (R^2=0.01). Mendelian randomisation–Steiger analysis was used to assess the direction of the potential causal association between the extracted SNPs related to the risk factors and outcomes.[26] Given that missing SNPs had a negligible effect on the results, we used only the available SNPs for all traits as instrumental variables and did not replace any missing SNPs with proxies in the outcome data. The strength of these SNPs as instrumental variables was assessed using the F-statistic (β^2/SE^2).[27] We established an F-statistic threshold of F >10 as indicative of a strong instrument, ensuring the avoidance of biases associated with weak instrumental variables.[27]

Data Sources for Exposures, Mediators and Outcomes

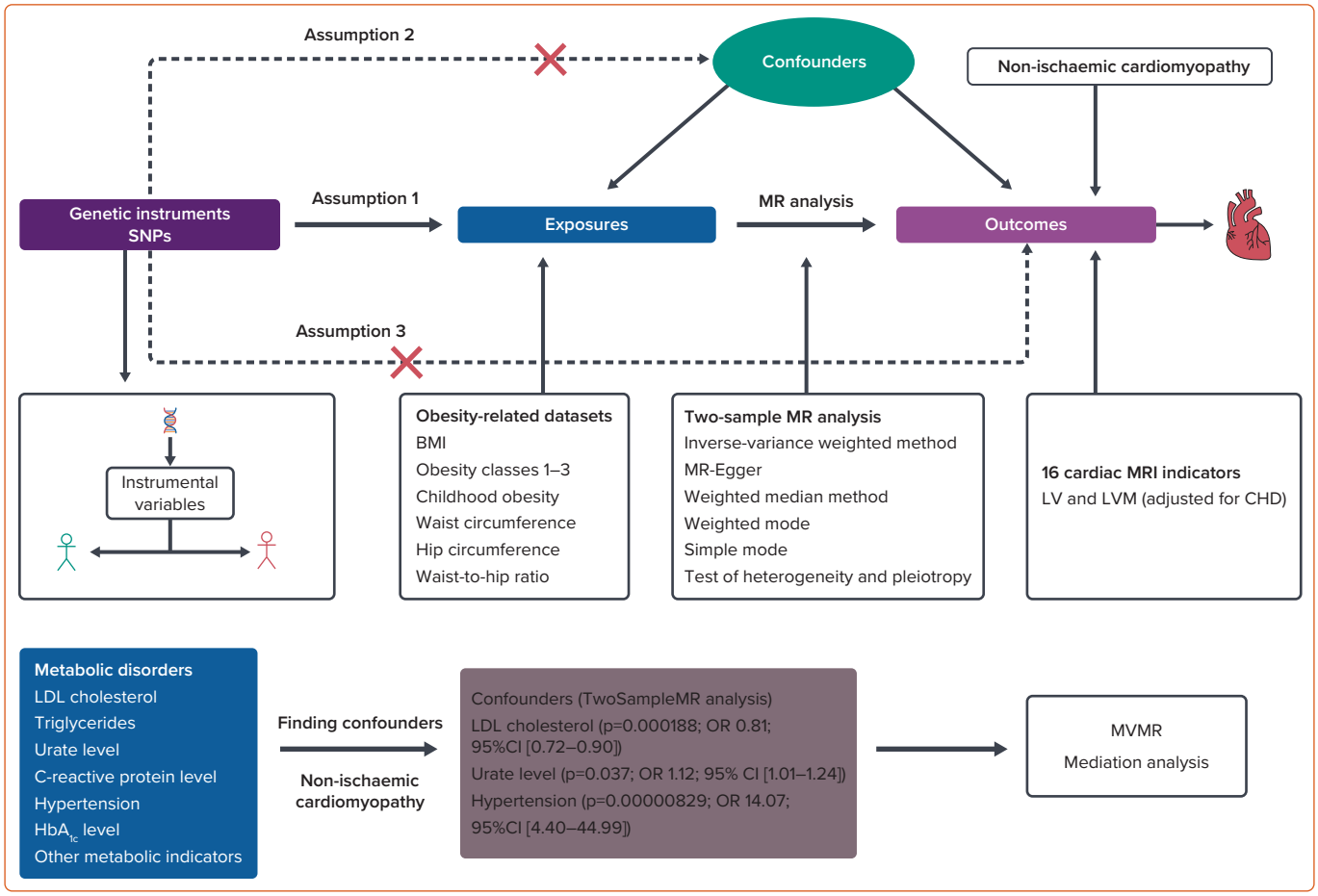
Exposures

The GWAS data in this study primarily originate from the MRC-IEU online database (https://gwas.mrcieu.ac.uk/), CVDKP (https://cvd.hugeamp.org/) and the FinnGen consortium (https://www.finngen.fi/fi) (*Supplementary Table 1*). And to enhance the understanding of obesity as an exposure factor in the context of NICM, our study used genetic variables from diverse obesity-related GWAS datasets. These included BMI, obesity classification (classes 1–3), childhood obesity, waist circumference (WC), hip circumference (HC) and waist-to-hip ratio (WHR). Detailed information on GWAS summary-level data for each trait is listed in *Supplementary Table 1*.

Mediators

When selecting potential mediators, we considered the following. First, based on the collective scientific understanding, the mediators are likely to be involved in the pathway from metabolic disorders to CVDs. Second, these mediators are targets for feasible clinical interventions. Lastly, the GWAS data for these mediators should be available for individuals from sources other than the Finnish database to ensure minimal or no sample overlap with the GWASs of the exposures and outcomes. Currently, the prevailing view is that obesity exerts its pathological effects primarily through metabolic dysregulation, and, as evidenced by observational and

Figure 1: Study Design



LV = maximum left ventricular volume; LVM = left ventricular mass; MR = Mendelian randomisation; MVMR = multivariable Mendelian randomisation; SNP = single-nucleotide polymorphism.

Mendelian randomisation studies, we have identified nine key metabolic-related candidate mediators: type 2 diabetes (T2D), LDL cholesterol, triglycerides, urate level, C-reactive protein (CRP) level, fasting insulin, glycated haemoglobin, homeostasis model assessment of insulin resistance (HOMA-IR) and HTN, as detailed in *Supplementary Table 1*.[28–31]

The three-step Mendelian randomisation analysis provide evidence of a mediating role for a variable in the exposure–outcome effect. The three steps require that the exposure–outcome, exposure–mediator, and mediator–outcome relationships are individually meaningful in the two-sample Mendelian randomisation (TwoSampleMR). The indirect effects of each mediator were estimated using both the MVMR and the two-step Mendelian randomisation method. In the MVMR method, mediation effect (indirect effect) = total effect (exposure to outcome) minus direct effect (exposure to outcome, adjusting for mediator). In the two-step Mendelian randomisation method, mediation effect (indirect effect) = total effect (exposure to mediator) × total effect (mediator to outcomes). We evaluated the proportion of the mediation effect by calculating the ratio of the mediation effect to the total effect. We used the error propagation method to calculate the confidence interval for the mediation effect in MVMR, and the delta method was used to calculate the confidence interval for the mediation effect in the two-step Mendelian randomisation method.[24]

Outcomes

The NICM database was assembled via the collaborative efforts of the FinnGen consortium, and consists of 187,152 individuals of European descent (11,400 cases and 175,752 controls) with a comprehensive dataset of 16,380,358 SNPs.[32] NICM specifically focuses on patients with HF, excluding cases not attributed to ischaemic cardiomyopathy. To further elucidate the relationship between various obesity phenotypes and myocardial structure, genetic association estimates for most cardiac MRI parameters were derived from publicly accessible GWAS summary data from the CVD knowledge portal.[33,34] Some parameters (diastolic strain rate) were derived from the GWAS Catalog. These data are from UK Biobank.[35]

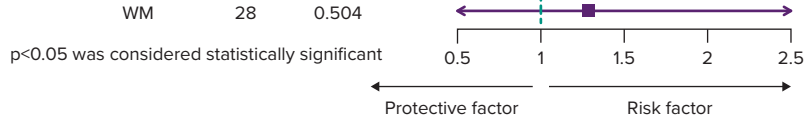
The MRI outcomes under consideration were as follows: ascending aorta (AA) diameter, descending aorta (DA) diameter, pulmonary artery (PA) diameter, maximum indexed left atrial (LA) volume, left ventricular (LV) longitudinal peak diastolic strain rate (LPDSR), LV radial peak diastolic strain rate (RPDSR), maximum LV volume (from 40,000 people),[33] LV end-diastolic volume (LVEDV, from 36,000 people),[34] LV end-systolic volume (LVESV), LV stroke volume (LVSV), LV ejection fraction (LVEF), LV mass (LVM), maximum right atrial (RA) area, right ventricular ejection fraction (RVEF), right ventricular end-diastolic volume (RVEDV), and right ventricular stroke volume (RVSV). LV and LVEDV both represent the maximum LV volume, the only difference being their sample sizes. These parameters collectively assess myocardial health, cardiomyopathy and myocardial remodelling (*Supplementary Table 1*).[36,37]

Statistical Analysis

Causal effects were estimated using the random-effect inverse-variance weighted (IVW) method.[38] Given the IVW method's reliance on the validity of all instrumental variables for an unbiased estimate, we used four

Figure 2: Genetically Predicted Obesity-related Traits: Association with Risk of Non-ischaemic Cardiomyopathy

Exposure	Method	SNPs	p-value	OR [95% CI]	p for H	p for pleio
BMI	IVW	362	2.06×10^{-37}	1.87 [1.70–2.06]	0.43	0.47
	WM	362	0.00000122	2.01 [1.52–2.65]		
Obesity class 1	IVW	14	1.67×10^{-13}	1.35 [1.25–1.46]	0.3	0.78
	WM	14	0.000988	1.30 [1.15–1.48]		
Obesity class 2	IVW	11	0.0000859	1.17 [1.09–1.25]	0.14	0.78
	WM	11	0.00315	1.20 [1.09–1.31]		
Obesity class 3	IVW	10	0.000279	1.09 [1.04–1.14]	0.14	0.73
	WM	10	0.0184	1.12 [1.04–1.22]		
Childhood obesity	IVW	5	0.00392	1.16 [1.05–1.28]	0.7	0.74
	WM	5	0.143	1.16 [0.99–1.37]		
Waist circumference	IVW	459	3.76×10^{-27}	1.83 [1.64–2.04]	0.05	0.12
	WM	459	0.00000757	2.42 [1.65–3.55]		
Hip circumference	IVW	354	0.0564	1.76 [1.57–1.96]	0.0000197	0.77
	WM	354	0.155	2.14 [1.58–2.90]		
Waist-to-hip ratio	IVW	28	0.159	1.49 [1.09–2.03]	0.02	0.56
	WM	28	0.504	1.29 [0.48–3.45]		



In the IVW method, all eight obesity phenotypes demonstrated causal relationships with non-ischaemic cardiomyopathy. Additionally, all results showed no evidence of pleiotropy. H = heterogeneity; IVW = inverse-variance weighted; pleio = pleiotropy; SNP = single-nucleotide polymorphism; WM = weighted mode.

alternative Mendelian randomisation methods, namely the weighted median method, the weighted mode method, the simple mode, and Mendelian randomisation–Egger (MR-Egger), to assess result robustness. Evaluation of potential horizontal pleiotropy involved MR-Egger intercept and Mendelian randomisation pleiotropy residual sum and outlier (MR-PRESSO) global tests. The MR-PRESSO outlier test identified potential outliers, and if an outlier SNP was detected ($p<0.05$), causal effects were re-estimated after removing outliers.[39] Leave-one-out analysis examined the influence of individual outlier variants on effect estimates, identifying high influence points. This comprehensive approach aimed to enhance the reliability of our causal inference. SNPs meeting our univariable Mendelian randomisation (UVMR) selection criteria in each GWAS were used to construct instruments. For significant causal associations identified in the UVMR analysis, the MVMR-IVW method was used. This aimed to mitigate potential confounding factors, including LDL cholesterol, HTN and urate, enhancing the precision of our causal inference. During multiple testing of the Mendelian randomisation analysis with MRI indicators, the p-values were corrected for false discovery rate (FDR). Causal estimates were derived using the TwoSampleMR package, with outlier detection facilitated by the MR-PRESSO package.[40] The MVMR analysis utilised the MVMR and MendelianRandomization packages.[41] The Mendelian randomisation estimates for NICM are reported as odds ratio (OR) with corresponding 95% CI. The Mendelian randomisation estimates for cardiac MRI indicators are reported as beta with corresponding 95% CI. Statistical calculations were conducted using R software version 4.2.2 (https://www.r-project.org/).

Results

UVMR and MVMR for NICM and MRI-based Cardiac Indicators

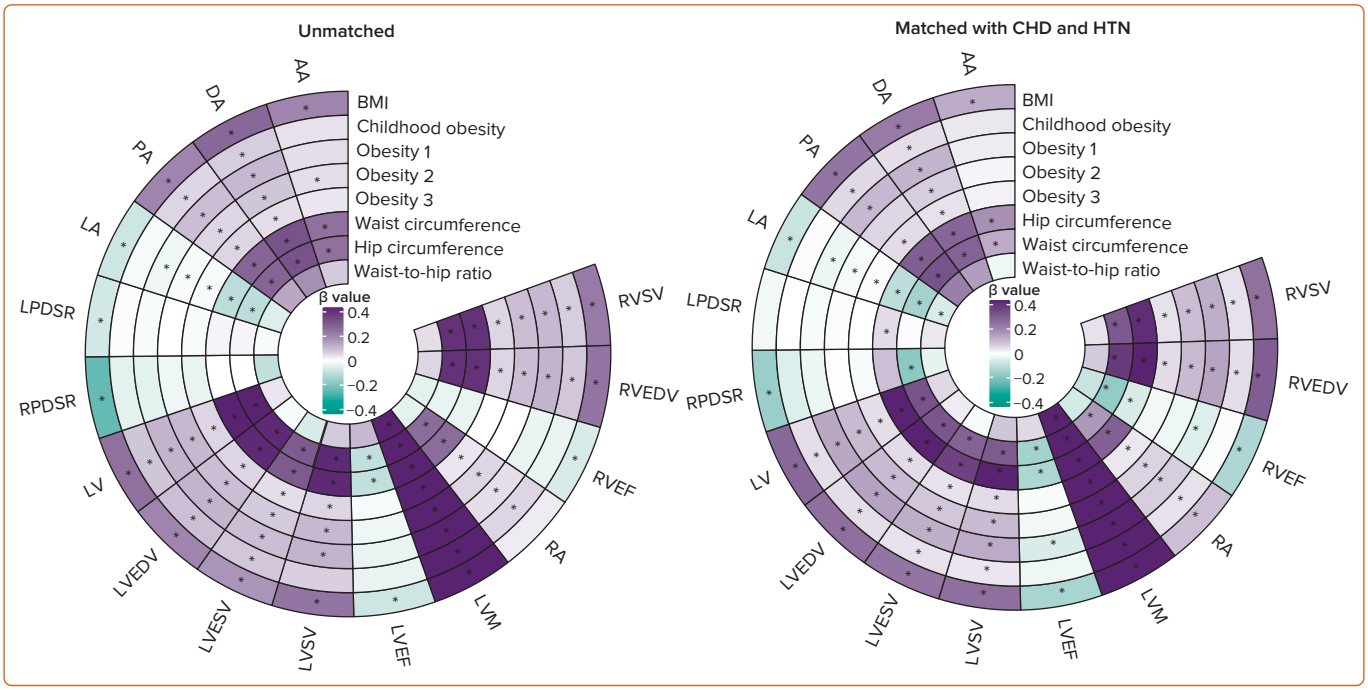
Associations between Eight Obesity Traits and NICM

Figure 2 shows the results of the UVMR analysis, indicating a causal effect of genetically determined BMI on NICM (IVW: OR 1.87; 95% CI [1.7–2.06]; $p<0.001$, per log odds of BMI). This causal effect remained consistent across the four additional Mendelian randomisation methods tested (MR-Egger, weighted median, simple mode, and weighted mode; *Supplementary Figure 1*). The other seven traits of obesity, that is, obesity classes 1–3, childhood obesity, WC, HC and WHR, were significantly associated with an increase in the risk of NICM by the IVW method. Furthermore, we conducted heterogeneity and pleiotropy analyses on the results of the TwoSampleMR analysis. In the analysis of obesity phenotype and NICM, there were no significant pleiotropic effects. Apart from WC and WHR, the remaining analyses did not show heterogeneity. Using the UVMR method, we explored the confounding factors of NICM, including genetically predicted T2D, triglycerides, CRP level, fasting insulin, glycated haemoglobin and HOMA-IR. UVMR analysis identified causal links between HTN, urate level and LDL cholesterol with NICM (LDL cholesterol: OR 0.81; 95% CI [0.72–0.90]; p=0.000188; urate level: OR 1.12; 95% CI [1.01–1.24]; p=0.0371; HTN: OR 14.07; 95% CI [4.40–44.99]; p=0.00000829). However, no increased risk of NICM was found for the other indicators (*Supplementary Figure 2*). Furthermore, MVMR analysis demonstrated that the causal relationship between BMI and NICM remained stable even after adjusting for three confounding factors, namely LDL cholesterol, urate level and HTN (all OR>1, $p<0.05$; *Supplementary Figure 2*).

Effect of Eight Obesity Traits on 16 CMR Indicators

To further explore the influence of obesity on heart structure and function, we conducted Mendelian randomisation between eight obesity traits and 16 cardiac MRI indicators. Noteworthy causal relationships emerged between obesity traits and most cardiac MRI parameters (*Figure 3 and Supplementary Figures 3–10*). All eight obesity traits were identified as significant risk factors for increased internal diameter of the PA, AA and DA (β>0). Except for WHR, the other seven phenotypes were significantly associated with increases in both PA and DA diameters (p-FDR≤0.05). Moreover, BMI, obesity grade 2, HC

Figure 3: Genetically Predicted Obesity-related Traits: Association with 16 Cardiac MRI Indicators



In the IVW method, all phenotypes showed a causal relationship with myocardial structural changes. AA = ascending aorta maximum diameter; DA = descending aorta maximum diameter; HTN = hypertension; IVW = inverse-variance weighted; LA = maximum left atrium volume/body surface area; LPDSR = left ventricular longitudinal peak diastolic strain rate; LV = maximum left ventricular volume; LVEDV = left ventricular end-diastolic volume; LVEF = left ventricular ejection fraction; LVESV = left ventricular end-systolic volume; LVM = left ventricular mass; LVSV = left ventricular stroke volume; PA = pulmonary artery maximum diameter; RA = right atrium maximum diameter; RPDSR = left ventricular radial peak diastolic strain rate; RVEDV = right ventricular end-diastolic volume; RVEF = right ventricular ejection fraction; RVSV = right ventricular stroke volume. LVEDV data samples, with a sample size of 36,000, are sourced from the UKB. These data, along with other left ventricular indicators, were obtained from the same research literature. On the other hand, the LV dataset originates from an updated set of UKB samples, comprising 40,000 individuals.

and WC were all significantly associated with an increase in AA diameter (p-FDR≤0.05). After matching for HTN and CHD, the statistical significance of the correlation between obesity class 2 and AA diameter disappeared (p>0.05), while the results remained consistent for the remaining variables. Although the beta values for the correlation between WHR and AA, DA and PA were greater than 1, they did not reach statistical significance either before or after matching. Except for WHR, all other obesity phenotypes led to an increase in LV, LVEDV, LVESV, LVSV, RVEDV and RVSV (β>0). Of these other obesity phenotypes (i.e. excluding WHR), childhood obesity showed no significant association with LVSV, but the remaining six obesity phenotypes had statistically significant correlations with these MRI indices (p-FDR<0.05). However, after matching for HTN and CHD, a statistically significant causal relationship between childhood obesity and increased LVSV was observed. Except for WHR, all other obesity phenotypes exhibited a trend of increased RA area and decreased LA volume. Furthermore, except for the lack of significance between childhood obesity and LA volume, all others reached statistical significance. Before and after matching, all eight obesity phenotypes were significantly associated with an increase in LVM. An increase in BMI was correlated with decreased LPDSR, RPDSR, LVEF and RVEF (p-FDR<0.05). We used two additional MRI datasets (LV internal dimension in diastole [LVIDd] and LVM) to validate the impact of obesity on cardiac remodelling. Except for the correlation between childhood obesity and LVM, all other obesity traits showed a significant increase in LVIDd and LVM, as detailed in *Figure 4*. The results indicate that obesity may have a causal relationship with changes in heart structure and function, and this relationship is independent of CHD. *Supplementary Material Figures 11–34* show the results of data analysis, and include scatter plots for the pleiotropy analysis, forest plots of the leave-one-out method and single SNP, as well as funnel plots.

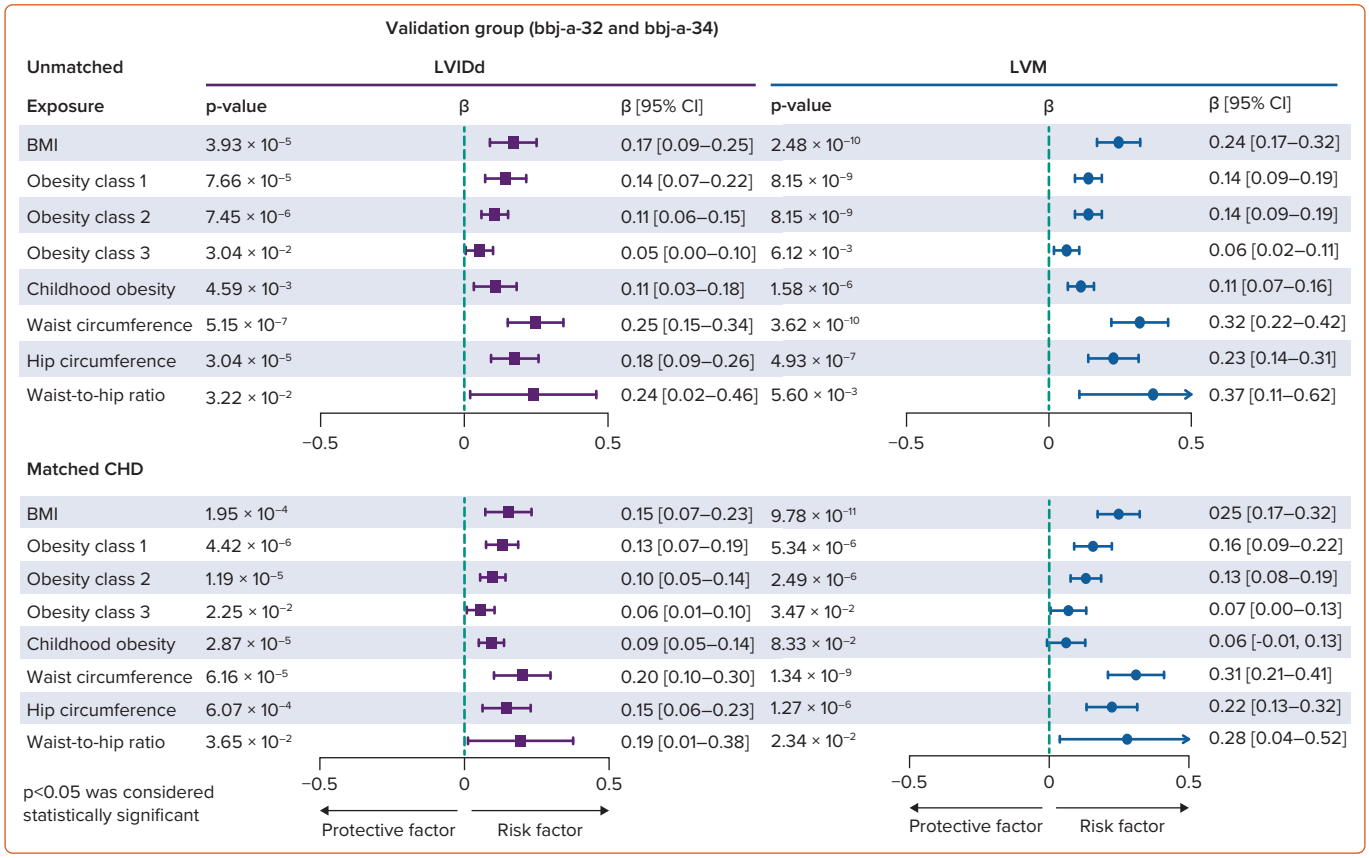
Mediation Analysis

As mentioned earlier, we conducted two-sample Mendelian randomisation by analysing potential mediators (metabolic abnormal parameters). We found that urate, LDL cholesterol and HTN are associated with NICM. We further performed MVMR on these factors to identify indicators that can still increase the risk of NICM after multifactor matching. Remarkably, HTN emerged as a significant risk factor for NICM in UVMR (OR 14.07; 95% CI [4.40–44.50]) and MVMR (OR 4.54, 95%CL: 1.40–14.77) (*Supplementary Figure 2*). In MVMR analysis, potential causal links with urate level attenuated and became non-significant (p>0.05; *Supplementary Figure 2*). Next, we undertook three-step Mendelian randomisation analyses to test the mediating effect of HTN. In the three-step Mendelian randomisation analysis, we confirmed causal relationships between BMI and NICM, as well as causal relationships between BMI and HTN, and HTN and NICM (*Figure 5*). In the MVMR method, the mediation effect of HTN was estimated to be an OR of 1.21 (95% CI [1.04–1.42]), which accounted for 31% of the total effect. Meanwhile, in the two-step method, the mediation effect of HTN was estimated to be an OR of 1.20 (95% CI [1.11–1.30]), accounting for 28% of the total effect.

Discussion

The relationships between obesity and CVDs, such as HF and ischaemic heart disease, have been a persistent topic in clinical research. However, the impact of obesity on NICM remains unclear. The introduction of the concept of MHO has been accompanied by conflicting observations in the current literature. In this study, we used Mendelian randomisation methods to minimise confounding factors and explore the effects of obesity on NICM, as well as its impact on vascular and cardiac structure and function. Our study provides genetic evidence for a causal relationship between obesity and NICM.

Figure 4: Genetically Predicted Association of Eight Obesity-related Traits: Association with Risk of LVIDd and LVM



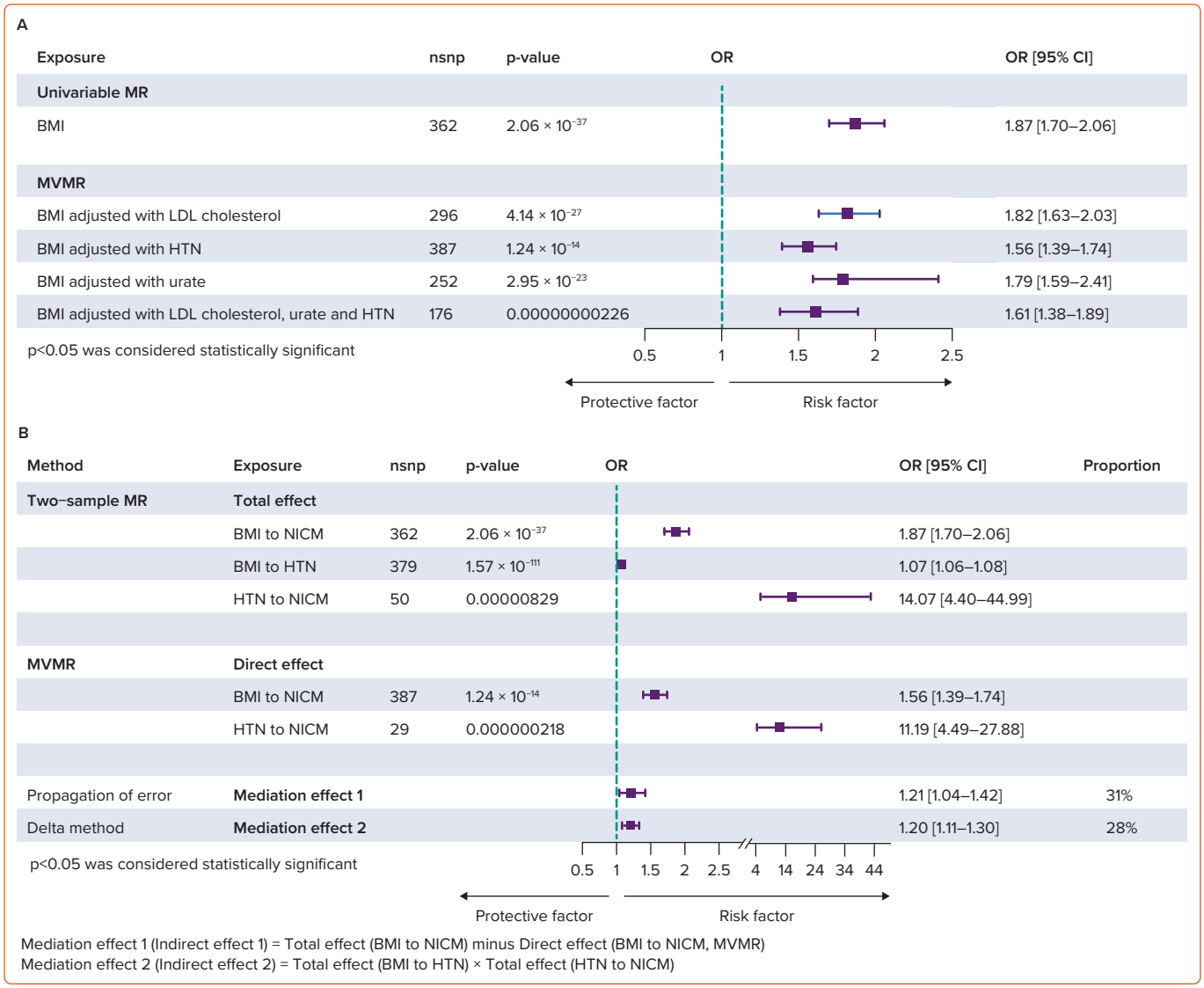
We used another cardiac MRI dataset (left ventricular internal dimension in diastole [LVIDd] and left ventricular mass [LVM]) to validate the causal associations between the eight obesity phenotypes and non-ischaemic cardiomyopathy. Except for class 3 obesity and childhood obesity, the other six obesity phenotypes, regardless of whether they were matched for CHD, had causal associations with LVIDd and LVM. bbj-a-32, bbj-a-34 = Biobank Japan data code.

For a long time, obesity has been recognised as a key risk factor for various CVDs.[42] In a cohort study encompassing 13,730 subjects, elevated BMI was found to have the strongest correlation with HF among the various subtypes of CVD, conferring a risk ratio of 3.74 in the context of severe obesity.[43] BMI has a notably strong correlation with the onset of HF, especially HF with preserved ejection fraction (HFpEF). However, a recent cohort study involving 2,339 participants, along with a cross-sectional study that included 2,316 participants, discovered that metabolically unhealthy phenotypes had a higher risk for CVDs, while the risk was not elevated in individuals with MHO compared with healthy normal-weight individuals.[8,44] Nevertheless, it is important to note that endpoints, such as HF, often take a longer period to develop, thereby making it difficult to observe positive results in a short follow-up period. In our study, using both UVMR and MVMR, a stable causal association between obesity and NICM was identified, independent of metabolic factors. In Mendelian randomisation studies, the utilisation of genetic variants as instrumental variables ensures randomisation at birth, eliminating the need for extended follow-up periods common in clinical research. This distinctive approach effectively mitigates biases arising from confounding factors, thus facilitating more reliable causal inferences in epidemiological investigations.

In addition, the study suggests a causal relationship between obesity and arterial diameter, heart structure and function. Overall, obesity leads to increased artery diameter, LVEDV, RVEDV and stroke volume. Moreover, obesity is causally linked to reductions in LVEF and RVEF. When matching for CHD and HTN, most of the results remained consistent. This may suggest that obesity often leads to a hyperdynamic state, gradually resulting in decreased cardiac function. Some studies indicate that bariatric surgery can improve cardiac function and metabolic syndrome in patients with obesity.[45–47] Compared with other obesity phenotypes, BMI is the only indicator causally associated with both arterial and cardiac MRI structure, as well as left and right ventricular systolic function and left ventricular diastolic function. This suggests that BMI may be the best obesity trait for predicting the impact of obesity on the myocardium. Of the MRI indicators, LVM is the most influenced by the eight obesity phenotypes. LVM could become an indicator for early prediction of obesity-related cardiomyopathy or for assessing the extent of myocardial involvement. Although childhood obesity similarly increases LVM and ventricular diameter, it is not significantly associated with LVEF or RVEF. WHR appears to be correlated only with fewer changes in cardiac structure.

However, although our findings suggest that obesity independently increases the risk of NICM, they do not exclude the possibility of metabolic disorders acting as mediators in this process. Our study screened for nine potential metabolic mediators: T2D, LDL cholesterol, triglycerides, urate level, CRP level, HbA_{1c}, fasting insulin, HOMA-IR and HTN. HTN serves as a significant mediator in the BMI–NICM relationship. This aligns with the well-documented association between obesity and HTN, in which obesity influences elevated blood pressure through various pathways.[48] These pathways encompass an increase in insulin resistance, activation of the renin–angiotensin–aldosterone system and sympathetic nervous system, endothelial dysfunction, and enhanced sodium retention.[48] In our study,

Figure 5: Multivariable Mendelian Randomisation and Mediation Analysis for BMI and Non-ischaemic Cardiomyopathy



A: Multivariable Mendelian randomisation. After conducting a Two Sample Mendelian Randomization study on multiple metabolic-related indicators, we found that LDL cholesterol, hypertension (HTN) and urate have causal associations with non-ischaemic cardiomyopathy (NICM). However, matching for these factors individually or collectively did not affect the causal relationship between BMI and NICM. B: Mediation analysis. Using the propagation of error and the delta method, we evaluated the mediating influence of HTN on the association between BMI and NICM, finding mediating effects of 31% and 28%, respectively. MR = Mendelian randomisation; MVMR = multivariable Mendelian randomisation; nsnp = the number of SNPs.

consistent with prior research, we identified a significant causal effect of BMI on HTN risk without any heterogeneity or pleiotropy. Furthermore, HTN plays a pivotal role in driving myocardial structural changes, remodelling, and decreased myocardial compliance, all of which are closely linked to HFpEF.[49] Consistently, our study confirms a genetic causal link between HTN and NICM. These findings suggest that HTN management can partially mitigate the occurrence of NICM in individuals with obesity, while also highlighting the role of obesity and HTN management in NICM. Furthermore, it warrants further investigation as to whether obesity intervention for patients with HF or cardiac remodelling can slow the progression of NICM. Notably, the weight-loss drug semaglutide has shown promise in reducing the incidence of composite endpoints, including cardiovascular death, non-fatal MI, and non-fatal stroke, among obese individuals without diabetes who have CVD. However, the study population primarily consisted of patients with pre-existing CVD related to atherosclerosis.[50] Despite this, rigorous studies specifically targeting obese individuals without atherosclerotic disease are still lacking. Therefore, the impact of weight loss on NICM in obese populations remains an area for further exploration. Additionally, cardiac MRI metrics may serve as more sensitive predictors for assessing improvements in prognosis.

Strengths and Limitations

This Mendelian randomisation study elucidates the potential causal relationship between obesity and NICM, as well as between obesity and heart structure and function, from a genetic perspective. The study has two significant strengths. First, it confirms, through Mendelian randomisation analysis, that obesity, independent of other metabolic factors, is causally associated with NICM. Using mediation Mendelian randomisation analysis, it further dissects the role of HTN in the development of NICM induced by obesity, thus laying a solid foundation for the development of preventive and therapeutic strategies. Second, the study expands its analytical scope by incorporating eight obesity-related traits from diverse dimensions to systematically outline the factors

associated with obesity exposure. Moving beyond solely considering NICM as an outcome, it integrates assessments of 16 cardiac MRI indicators, providing a more comprehensive evaluation of the relationship between obesity and NICM. MVMR analysis was performed to adjust for CHD, to ensure the robustness of the findings and eliminate the potential influence of ischaemic pathways on myocardial structure. These findings were further validated through additional MRI datasets.

This investigation acknowledges three limitations. First, due to the low number of SNPs extracted in obesity class 3, a lower p-value threshold was chosen for SNP screening. However, the F-values for SNPs in this analysis were all greater than 10. In addition, the robustness of the results can be ensured, given the inclusion of various obesity phenotypes. Second, there is a significant overlap between the obesity dataset and MRI dataset. We used the online tool available at https://sb452.shinyapps.io/overlap to estimate the potential for type I errors. After evaluation, even if the samples completely overlapped, the type I error rate was still maintained at 0.05 in all analyses. We also verified the stability of the results by using additional MRI datasets from different sources. Third, obesity is influenced by both genetic factors and environmental exposure. Genetic prediction of obesity can partially explain obesity in the real world. The relationship between obesity and NICM in the real world may be more complex. Caution should be exercised with this conclusion when referring to obesity caused by specific environmental factors, for example, pharmacological obesity, excessive eating habits, endocrine disease, lack of exercise, and so on. However, regardless of whether obesity is caused by genetics or environmental factors, the pathological physiological changes they cause are similar. This conclusion also holds some value for these populations.

Finally, this study used "maximum LA volume/body surface area" to represent LA size. Given the significant correlation between body surface area and BMI, the conclusions regarding the correlation between LA and BMI in this study need to be interpreted with caution.

Conclusion

The present study offers initial genetic evidence supporting the causal role of obesity in elevating the risk of NICM, using both UVMR and MVMR methodologies. Furthermore, this study has demonstrated the mediating influence of HTN in the link between obesity and NICM. The identification of HTN's mediating role highlights the need to integrate obesity and HTN management into a comprehensive strategy for reducing NICM risk. These findings hold considerable implications for the prevention and management of NICM, especially considering the widespread prevalence of obesity globally. Of the obesity phenotypes, BMI is the only phenotype associated with reduced systolic and diastolic function. LVM is the most sensitive cardiac MRI indicator affected by obesity phenotypes. ❑

Clinical Perspective

- Obesity leads to cardiac structural changes and contributes to non-ischaemic cardiomyopathy (NICM) development, with hypertension (HTN) acting as a mediator in the link between increased BMI and NICM progression.
- Clinicians are encouraged to perform cardiac MRI in obese patients to identify early myocardial structural changes, particularly the increase in left ventricular mass.
- Rigorous HTN management is needed in obese populations to mitigate the risk of NICM.
- This study provides evidence that a comprehensive obesity management approach is crucial for preventing NICM.
- Obesity intervention studies are needed for heart failure patients with obesity.

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