Higher body mass index (BMI) has been associated with adverse remodeling of the left ventricle, but predominantly through observational studies, which are susceptible to potential confounding. We therefore used Mendelian randomization (MR) to assess whether associations between higher BMI and a range of left ventricular structural abnormalities are suggestive of a causal link, to provide a basis for preventive measures against the onset of clinical heart failure (HF).

The data that support the findings of this study are available from the corresponding author upon reasonable request. Our genetic instrument included 82 independent single-nucleotide polymorphisms (SNPs) associated with BMI in a prior external genetic analysis (out of 97 SNPs total), after excluding 15 likely pleotropic SNPs associated independently with smoking status or alcohol consumption (P < 0.05).

For subclinical left ventricular (LV) remodeling, we leveraged cardiac magnetic resonance imaging data from the UK Biobank (UKBB) in 33,151 individuals, excluding those with prevalent HF, cardiomyopathy, or coronary artery disease. We assessed LV ejection fraction, LV mass, LV end-diastolic volume (LVEDV), LV end-systolic volume (LVESV), and LV mass-to-volume ratio (calculated as LV mass/LVEDV, a surrogate for concentric LV hypertrophy). For clinical LV remodeling, we evaluated 450,481 individuals in the UKBB, focusing on HF, nonischemic dilated cardiomyopathy, and hypertrophic cardiomyopathy, as defined previously. Informed consent was obtained from all participants, and analyses were approved by the Mass General Brigham Health Care Institutional Review Board (UKBB application 7089).

We tested genetic associations using 2-sample MR. SNP-specific outcome estimates for our genetic instrument were obtained by linear and logistic regression for subclinical and clinical phenotypes, respectively, adjusting for height (for left ventricular traits), age, sex, and the top 10 principal components of genetic ancestry. We defined statistical significance using a Bonferroni-corrected threshold of P < 0.01 (0.05/5 left ventricular traits) for subclinical LV remodeling, and a threshold of P < 0.017 (0.05/3 diseases) for clinical LV remodeling. We excluded participants failing central quality control performed by UKBB, and one individual from each related pair (KING coefficient >0.0884, resulting in exclusion of 36,069 and 2,889 individuals from the full UKBB and imaging sample, respectively).

Within the imaging sample, the mean age was 54.8 years (SD, 7.4 years), mean BMI was 26.5 kg/m² (SD, 4.2 kg/m²), and 15,722 (47%) participants were men. Left ventricular measurements were largely within normal reference ranges. A 1-SD increase in the BMI genetic score was associated with a 0.50-kg/m² increase in BMI (95% CI, 0.48–0.51; P < 1E-200), with a corresponding F statistic of 5078 (F statistic >10 denoting a strong genetic instrument).

In inverse variance–weighted 2-sample MR analyses, a 1-SD increase in genetically predicted BMI was associated with a 6.09-mL increase in LVEDV, 2.78-mL increase in LVESV, 11.3-g increase in LV mass,

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and 0.05-g/mL increase in LV mass-to-volume ratio (all \(P<0.001\), Figure [A]). Associations persisted with weighted median 2-sample MR (all \(P<0.001\)). MR-Egger analyses detected potential residual pleiotropy in associations with LV mass, LVEDV, and LVESV (intercept \(P<0.037\), but associations remained significant after MR-Egger correction (MR-Egger \(P<0.001\). Mendelian randomization-Pleiotropy Residual Sum and Outlier (MR-PRESSO) analyses did not identify outliers or horizontal pleiotropy. Consistent with prior observational analyses, genetically predicted BMI was not significantly associated with LV ejection fraction (inverse variance–weighted \(P=0.191\)).

Genetically predicted BMI associated with an increased risk of HF (inverse variance–weighted odds ratio [OR], 1.70 [95% CI, 1.41–2.04]; \(P<0.001\); Figure [B]). Similar associations with increased risk of dilated cardiomyopathy (OR, 2.01 [95% CI, 1.07–3.76]; \(P<0.029\)) and hypertrophic cardiomyopathy (OR, 2.17 [95% CI, 0.96–4.93]; \(P=0.062\)) were suggestive but did not reach statistical significance. Observations were supported by weighted median analyses, without evidence of pleiotropy (Egger intercepts \(P>0.514\)) or instrument outliers. Subclinical and clinical associations largely persisted without adjustment for height, in both men and women, after adjustment for hypertension, after adjustment for diabetes, and after subsetting to a population of European genetic ancestry; notably, however, effect estimates of genetically predicted BMI with subclinical and clinical HF were generally larger in men than women.

Our findings have important clinical implications. First, the association of genetic BMI with subclinical left ventricular traits and clinical disease strongly suggests a causal link between greater BMI and pathologic LV remodeling, and provides support for weight management for the primary prevention of HF, particularly among patients at elevated risk and/or with preclinical structural abnormalities (stage A/B HF). Second, significant associations with subclinical LVEDV/LVESV and LV mass-to-volume ratio, and consistent trends with clinical dilated cardiomyopathy and hypertrophic cardiomyopathy corroborate recent epidemiological findings, and indicate that higher BMI may be a causal risk factor for both eccentric and concentric left ventricular hypertrophy.

Study limitations include potential residual pleiotropy, a majority European genetic ancestry population, and the potential for a shared genetic basis between BMI and LV phenotypes, rather than a causal relationship. Furthermore, the effects of obesity and increased body size are difficult to disentangle. Finally, use of cross-sectional imaging data may limit temporal inferences around remodeling.

In conclusion, greater genetically predicted BMI was associated with subclinical and clinical cardiomyopathy, suggesting a causal link between greater BMI and pathologic LV remodeling, and supporting early weight management efforts for the primordial prevention of HF.

**Figure 1.** Genetic associations of body mass index (BMI) with (A) subclinical and (B) clinical left ventricular phenotypes. Associations were calculated using inverse variance–weighted 2-sample Mendelian randomization analyses. Beta effect estimates in (A) are normalized to per-standard deviation changes in left ventricular traits. DCM indicates dilated cardiomyopathy; HCM, hypertrophic cardiomyopathy; HF, heart failure; LVEDV, left ventricular end-diastolic volume; LVEF, left ventricular ejection fraction; LVESV, left ventricular end-systolic volume; LVM, left ventricular mass; LVMVR, left ventricular mass-to-volume ratio; N, number; and OR, odds ratio.

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**Affiliations**

Cardiovascular Disease Initiative, Broad Institute of MIT and Harvard, Cambridge, MA (K.J.B., J.P.P., S.K., P.N., S.A.L., P.T.E., K.G.A.); Cardiovascular Research Center (K.J.B., J.P.P., S.K., P.N., S.A.L., P.T.E., K.G.A.); and Center for Genomic Medicine (K.J.B., K.G.A.), Massachusetts General Hospital, Boston, MA; and Cardiovascular Institute and Division of Cardiology, Department of Medicine, Beth Israel Deaconess Medical Center, Boston, MA (J.E.H.).

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