

## **Supplementary Materials**

### **Metabolic biomarkers predict subclinical cardiac remodeling in obese individuals**

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**Supplementary Table 2. Indexed cardiac structural parameters (BSA-adjusted)**

<b>Parameter</b>	<b>Class I (<i>n</i> = 47)</b>	<b>Class II (<i>n</i> = 40)</b>	<b>Class III (<i>n</i> = 20)</b>	<b><i>P</i></b>
LVMi (g/m <sup>2</sup> )	49.00 (45.05-54.65)	53.77 (44.91-64.13)	48.85 (44.78-54.19)	0.790
EDVi (mL/m <sup>2</sup> )	68.00 (61.51-77.13)	67.69 (62.33-71.86)	72.20 (68.87-77.13)	0.434
ESVi (mL/m <sup>2</sup> )	23.30 (20.07-28.51)	23.48 (19.25-28.39)	25.94 (23.13-27.57)	0.338
SVi (mL/m <sup>2</sup> )	43.02 (39.30-50.00)	43.88 (38.90-48.81)	47.72 (42.78-51.29)	0.475

Data are expressed as median (interquartile range). *P* values represent comparisons across the three obesity classes. Cardiac MRI-derived structural parameters were normalized to body surface area (BSA).

**Supplementary Table 3. Cardiac structural parameters normalized to height<sup>2.7</sup> across BMI categories**

<b>Parameter</b>	<b>Class I (<i>n</i> = 47)</b>	<b>Class II (<i>n</i> = 40)</b>	<b>Class III (<i>n</i> = 20)</b>	<b><i>P</i></b>
LVM/ht <sup>2.7</sup> (g/m <sup>2.7</sup> )	24.98 (23.67-26.29)	28.30 (26.17-30.43)	31.12 (25.75-36.49)	0.004
EDV/ht <sup>2.7</sup> (mL/m <sup>2.7</sup> )	35.88 (34.06-37.70)	36.75 (34.85-38.66)	42.42 (38.96-45.88)	0.001
ESV/ht <sup>2.7</sup> (mL/m <sup>2.7</sup> )	12.88 (11.90-13.87)	13.23 (12.30-14.15)	16.34 (14.31-18.36)	0.001
SV/ht <sup>2.7</sup> (mL/m <sup>2.7</sup> )	22.96 (21.75-24.21)	23.53 (21.72-25.17)	25.06 (23.54-26.70)	0.054

Data are expressed as median (interquartile range). LVM: Left ventricular mass; EDV: end-diastolic volume; ESV: end-systolic volume; SV: stroke volume; ht<sup>2.7</sup>: height raised to the power of 2.7.

**Supplementary Table 4. Cardiac functional parameters between MetS- and MetS+ groups**

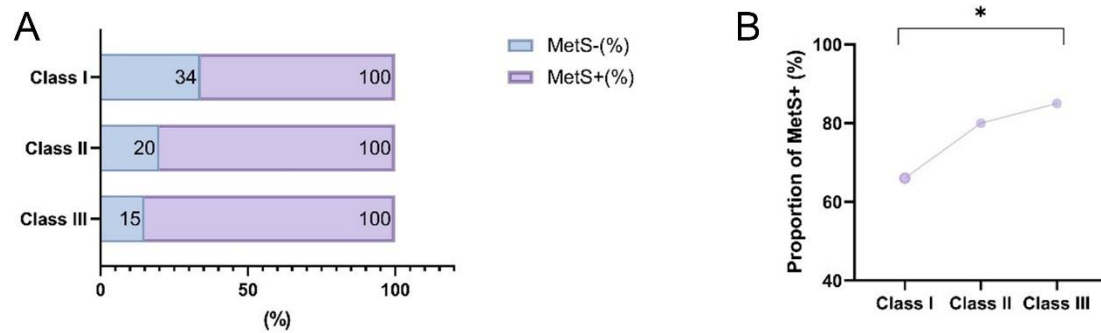
Parameter	MetS- ( <i>n</i> = 28)	MetS+ ( <i>n</i> = 79)	<i>P</i>
LVEF (%)	65.69 (59.84-71.70)	63.02 (57.92-68.14)	0.143
CO (L/min)	7.27 (6.47-9.66)	6.67 (5.44-7.86)	0.017
CI (L/min/m <sup>2</sup> )	3.20 (3.13-3.86)	3.09 (2.66-3.62)	0.013

Data are expressed as median (interquartile range). *P* values represent comparisons between the two groups (Mann-Whitney *U* test). MetS: Metabolic syndrome; LVEF: left ventricular ejection fraction; CO: cardiac output; CI: cardiac index.

**Supplementary Table 5. Comparison of cardiac structural parameters between MetS- and MetS+**

<b>Parameter</b>	<b>MetS- (<i>n</i> = 28)</b>	<b>MetS+ (<i>n</i> = 79)</b>	<b><i>P</i></b>
LVM (g)	99.18 (89.31-122.65)	102.97 (89.58-122.43)	0.662
EDV (mL)	156.06 (131.91-168.73)	144.13 (129.22-164.03)	0.021
ESV (mL)	49.50 (39.45-68.49)	53.29 (42.74-62.51)	0.738
SV (mL)	100.96 (92.10-111.00)	90.91 (79.21- 101.26)	< 0.001
LVMi (g/m <sup>2</sup> )	47.09 (42.50-55.42)	48.75 (44.75-56.28)	0.061
EDVi (mL/m <sup>2</sup> )	71.90 (68.00-81.80)	69.00 (61.99-74.74)	0.003
ESVi (mL/m <sup>2</sup> )	25.47 (19.00-35.79)	24.25 (20.25-28.87)	0.257
SVi (mL/m <sup>2</sup> )	45.55 (44.13-51.52)	42.49 (37.12-49.00)	0.004

Data are expressed as median (interquartile range). *P* values represent comparisons between the MetS- group (*n* = 28) and the MetS+ group (*n* = 79) using the Mann-Whitney *U* test. MetS: Metabolic syndrome; LVM: left ventricular mass; EDV: end-diastolic volume; ESV: end-systolic volume; SV: stroke volume; LVMi: left ventricular mass index; EDVi: end-diastolic volume index; ESVi: end-systolic volume index; SVi: stroke volume index.



**Supplementary Figure 1.** Prevalence and Trend of Metabolic Syndrome Across Obesity Classes. Supplementary Figure 1 illustrates the distribution of metabolic syndrome (MetS) across obesity classes. Panel A displays the percentage of MetS+ individuals within Class I, II, and III groups. Panel B demonstrates a significant stepwise increase in MetS prevalence with rising BMI (66.0% → 85.0%), as confirmed by the Cochran-Armitage trend test ( $Z = 1.836$ ,  $P = 0.044$ ). These findings highlight the strong correlation between obesity severity and increasing metabolic burden.

**Supplementary Table 7. LASSO regression coefficients ( $\lambda_{\min}$ ) for cardiac MRI outcomes**

Endpoint	(Intercept)	INS	FFAs	TG	HDL	GGT	GLU	TC	ALT	WBC
CI	3.092411354	0.003518689	-	-	-	-	-	-	0.001512106	-
CO	6.221259538	0.016010178	-	-	-	-	-	-	0.006182464	-
EDV	147.2415888	-	-	-	-	-	-	-	-	-
EDVi	69.32878505	-	-	-	-	-	-	-	-	-
ESV	53.9317757	-	-	-	-	-	-	-	-	-
ESVi	25.38665415	-	-	-	-	-	-	-	-	-
LVEF	-	-	-	-	-	-	-	-	-	-0.302498874
LVM	83.07807652	0.284238229	0.01629163	6.641708636	-4.363460361	0.184780576	0.164062686	-1.906484684	-	-
LVMi	51.30485981	-	-	-	-	-	-	-	-	-
SV	93.33906542	-	-	-	-	-	-	-	-	-
SVi	43.77271028	-	-	-	-	-	-	-	-	-

Coefficients shown correspond to predictors selected at  $\lambda_{\min}$  by 10-fold cross-validation (glmnet v4.1-8). See Supplementary Methods for the R code used to reproduce these results.

# Load package

library(glmnet)

# Read data (replace with actual path or dataset name)

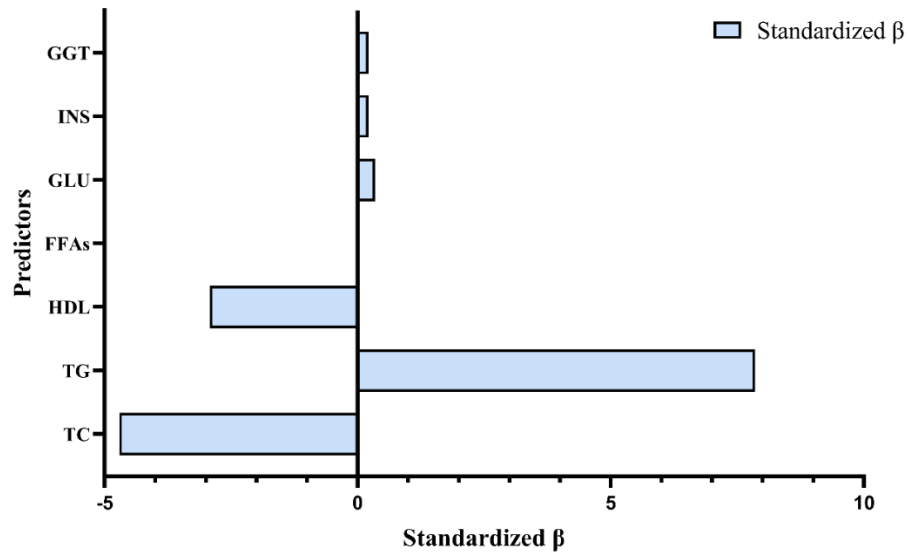
data <- read.csv("Raw\_data\_lasso.csv")

# Define endpoints and predictors

targets <- c("LVEF", "CO", "CI", "EDV", "ESV", "SV", "LVM", "EDVi", "ESVi", "SVi", "LVMi")

```
predictors <- c("GLU","INS","HbA1C","Cpeptide","Home_IR",  
              "TC","TG","HDL","LDL","FFAS","WBC","ALT","AST","GGT")  
# Loop over each endpoint  
for (target in targets) {  
  model_data <- na.omit(data[c(target, predictors)])  
  y <- model_data[[target]]  
  x <- as.matrix(model_data[predictors])  
  # Run 10-fold cross-validated LASSO  
  lasso_model <- cv.glmnet(x, y, alpha=1)  
  # Extract coefficients at lambda.min  
  print(coef(lasso_model, s="lambda.min"))
```





**Supplementary Figure 2.** Standardized Regression Coefficients of Metabolic Variables for Left Ventricular Mass (LVM) in LASSO Regression. The bar chart displays the standardized coefficients of key metabolic predictors identified by LASSO regression. INS, TG, and FFAs were among the primary positive predictors, while HDL showed a negative association with LVM. In the subsequent multivariable linear model, TG remained the most robust independent metabolic predictor of LVM.

**Supplementary Table 9. Logistic regression analysis of metabolic predictors for LVH**

Model	Variable	OR (95%CI)	P value
Univariable	INS	1.053 (1.014-1.094)	0.007
Multivariable	INS	1.046 (1.002-1.092)	0.038
Multivariable	FFAs	1.003 (1.001-1.006)	0.018
Multivariable	GGT	1.018 (0.995-1.042)	0.122
Multivariable	TG	1.160 (0.734-1.835)	0.525
Multivariable	HDL	1.329 (0.109-16.229)	0.824
Multivariable	GLU	0.956 (0.759-1.204)	0.701

Odds ratios (OR), 95% confidence intervals (CI), and P values for univariable and multivariable models assessing associations between metabolic indicators and left ventricular hypertrophy. LVH was defined for logistic regression analyses using sex-specific absolute thresholds (men > 115 g, women > 95 g). INS: Insulin; FFAs: free fatty acids; GGT: gamma-glutamyl transferase; TG: triglycerides; HDL: high-density lipoprotein; GLU: fasting glucose.

**Supplementary Table 10. Hierarchical linear regression with LVM/height<sup>2.7</sup> as a continuous outcome (sensitivity analysis; *N* = 107)**

Model/Predictor	<i>B</i>	95%CI	<i>P</i>
<b>Model 1</b> (age, sex, BMI)			
<b><i>R</i><sup>2</sup> (Adj. <i>R</i><sup>2</sup>)</b>	<b>0.263 (0.241)</b>		
<b>Model 2</b> (+ INS, FFAs, TG, GGT)			
<b>TG</b>	<b>2.045</b>	<b>1.337-2.754</b>	<b>&lt; 0.001</b>
<b>BMI</b>	<b>0.378</b>	<b>0.074-0.682</b>	<b>0.015</b>
Sex (male vs. female*)	-2.890	-5.835-0.055	0.054
FFAs	0.006	0.000-0.013	0.064
INS	0.060	-0.022-0.143	0.150
GGT	-0.002	-0.039-0.036	0.933
Age	0.006	-0.107-0.119	0.918
<b>Total <i>R</i><sup>2</sup> (Adj. <i>R</i><sup>2</sup>)</b>	<b>0.528 (0.495)</b>		
<b><math>\Delta R^2</math> vs. Model 1</b>	<b>0.265</b>		<b>&lt; 0.001</b>

To test robustness, we re-modeled left ventricular mass indexed to height<sup>2.7</sup> (LVM/height<sup>2.7</sup>) as a continuous outcome using hierarchical ordinary least squares regression (*N* = 107). Model 1 included age, sex, and BMI; Model 2 additionally included INS, FFAs, TG, and GGT (all continuous, entered at once). Assumptions were checked by histogram/P-P plot and ZPRED-ZRESID scatterplots; no material deviations from normality or homoscedasticity were observed, and all VIF < 1.7. Values are unstandardized coefficients (*B*) per 1-unit increase in each predictor; Total *R*<sup>2</sup> and  $\Delta R^2$  refer to Model 2 vs. Model 1. Sex coded female = 1, male = 2. CMR-derived LVM with papillary muscles/trabeculations treated as specified in the main Methods.

**Supplementary Table 11. ROC performance metrics for LVH prediction models**

Model type	AUC (95% CI)	<i>P</i> value	Optimal cut-off	Sensitivity (%)	Specificity (%)
INS univariable model	0.632 (0.525- 0.739)	0.015	0.513	74.20	46.70
Combined multivariable model (INS + FFAs)	0.757 (0.667- 0.848)	< 0.001	0.410	88.70	37.80

Discriminative performance of univariable and multivariable logistic regression models for predicting left ventricular hypertrophy (LVH). AUC: Area under the curve; INS: insulin; FFAs: free fatty acids; CI: confidence interval.