Published in final edited form as:

Am J Cardiol. 2014 January 15; 113(2): 377–383. doi:10.1016/j.amjcard.2013.08.052.

Relation of Left Ventricular Mass at Age 23 to 35 years to Global Left Ventricular Systolic Function 20 Years Later (From the Coronary Artery Risk Development in Young Adults Study)

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Abstract

Left ventricular (LV) mass and LV ejection fraction (EF) are major independent predictors of future cardiovascular disease. The association of LV mass with future LVEF in younger populations has not been studied. We investigated the relation of LV mass index (LVMI) at age 23 to 35 years to LV function after 20 years of follow-up in the Coronary Artery Risk Development in Young Adults (CARDIA) Study. CARDIA is a longitudinal study that enrolled young adults in 1985–1986. We included participants with echocardiographic examinations at both years-5 and -25. LVMI and LVEF were assessed using M-mode echocardiography at year-5 and using both M-mode and 2-dimensional images at year-25. Statistical analytic models assessed the correlation between LVMI and LV functional parameters both cross-sectionally and longitudinally. A total of 2,339 participants were included. The mean LVEF at year-25 was 62%. Although there was no cross-sectional correlation between LVMI and LVEF at year-5, there was a small, but statistically significant negative correlation between LVMI at year-5 and LVEF 20 years later ($r = -0.10$, $p < 0.0001$); this inverse association persisted for LVMI in the multivariable model. High LVMI was an independent predictor of systolic dysfunction (LVEF < 50%) 20 years later (odds ratio 1.46, $p = 0.0018$). In conclusion, we have shown that LVMI in young adulthood in association with chronic risk exposure impacts systolic function in middle age; the antecedents of heart failure may occur at younger ages than previously thought.

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Conflict of Interest Statements

All authors have nothing to disclose.

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Keywords

left ventricular mass; left ventricular ejection fraction; echocardiography; left ventricular remodeling

Left ventricular (LV) mass and LV ejection fraction (EF) are major independent predictors of future cardiovascular disease.^{1–3} Quantitation of LV function and geometry provides significant information for the evaluation and management of patients with heart disease.^{4,5} In cross-sectional studies, LV mass is associated with decreased regional systolic function.⁶ Furthermore, in an elderly population, increased LV mass has shown predictive ability for depressed LVEF over a 5-year follow-up period.⁷ The Coronary Artery Risk Development in Young Adults (CARDIA) study prospectively assessed a young adult bi-racial cohort and reported depressed LVEF as a strong predictor of incident heart failure in black participants over a 10-year follow-up period.² However, the association of LV mass with future LVEF in younger populations has not been studied. Using the CARDIA cohort, we investigate the role of greater myocardial mass in young adults as a predictor of LV dysfunction over a 20-year follow-up period, evaluating the association between LV mass at the age of 23–35 years with LVEF 20 years later. We also explored the relations of LV mass with LV volumes. We hypothesized that LV mass and ejection capability are not necessarily strongly correlated early in life (when both mass is generally normal and ejection power is at its peak), but that small echocardiographic differences in LV mass early in life predict development of reduced ejection performance as early as mid adulthood.

Methods

CARDIA is an NIH-sponsored multi-center study designed to investigate the development of coronary disease in young adults. Initially, 5,115 black and white men and women 18 to 30 years of age at the time of enrollment (1985 to 1986) were recruited and examined at four CARDIA Field Centers in: Birmingham, Alabama; Chicago, Illinois; Minneapolis, Minnesota; and Oakland, California. Echocardiography was performed in the cohort in the follow-up years-5 and -25 examinations. The overall design and objectives of the CARDIA study have been presented elsewhere.⁸ Of the 4,352 participants attending the year-5 examination (year-5), 4,243 participants underwent echocardiography. Of the 3,498 participants attending the year-25 examination (year-25), 3,474 underwent echocardiography. For this study, we evaluated 3,145 participants with echocardiography assessment at CARDIA examinations for year-5 (baseline, from 1990 to 1991) and year-25 (2010 to 2011). Exclusions were: pregnancy at either exam (n=38), year-5 LVEF < 50% (n=88), and absence of specific echocardiography variables or other risk factors (n = 680). The remaining 2,339 patients were included in our analytic cohort.

CARDIA participants at year-5 underwent 2-dimensional (D)-guided M-mode echocardiography to assess LV mass as previously described.⁹ substitute my new paper for this reference LV functional parameters (LV end-diastolic volume [LVEDV], LV end-systolic volume [LVESV], and LVEF) at the year-5 CARDIA were assessed by M-mode echocardiography in a para-sternal acoustic window, using the Teicholz technique.¹⁰ CARDIA participants at the year-25 underwent 2D-guided M-mode echocardiography at para-sternal window and 2D four-chamber apical views following American Society of Echocardiography recommendations.¹¹ All studies were recorded on digital format using an Artida cardiac ultrasound scanner (Toshiba Medical Systems) and read at the Johns Hopkins University Echocardiography Reading Center in Baltimore, MD. Measurements were made by experienced analysts from digitized images using a standard software off-line image analysis system (Digisonics, Inc.). LV mass index (LVMI) was acquired after dividing LV

mass by the body surface area (BSA) at the year-5 and year-25.¹⁰ LVEF was assessed using the formula: $LVEF = [(LVEDV - LVESV) / LVEDV] \times 100$. At year-5, LVEDV and LVESV were assessed using M-mode technique (Teicholz Method). At year-25, LVEDV and LVESV were measured from apical 2D four-chamber images. LVEF at year-25 between M-mode and 2D was a positive correlation ($r = 0.41$, $p < 0.0001$) and mean difference was 8.2% which M-mode was greater than 2D ($p < 0.0001$). For the endpoint of LV volumes, LVEDV and LVESV were indexed to BSA (LVEDVI and LVESVI).

Standardized protocols were used to measure height, weight, cholesterol, heart rate, blood pressure, smoking, educational level, and physical activity at the baseline (year-5).¹² Sex and race were self-reported by the study participants. We used the average of a second and third of three blood pressure measurements after five minutes rest; blood pressure was measured by random-zero sphygmomanometry at year-5, and by an Omron device at year-25. Weight (in kilograms) and height (in meters) were in light clothing and body mass index (BMI) was calculated (weight [kg]/meters²). Cigarette smoking was determined by self-report at each examination. Physical activity (in exercise units) was determined by a questionnaire.¹³ Diabetes mellitus was determined by fasting glucose ≥ 126 mg/dl or use of medication for diabetes. We used fasting glucose level at year-0 examination as a year-5 variable because glucose was not measured at year-5. Total cholesterol, triglycerides, and high density lipoprotein (HDL) cholesterol were determined using an enzymatic assay; low density lipoprotein (LDL) cholesterol was calculated with the use of the Friedewald equation.¹⁴ Educational level was categorized into two groups: ≤ 12 years or equivalent and > 12 years. History of heart disease at year-25 was determined by a questionnaire.

Descriptive statistics for the participants were summarized by using means and standard deviations (SD) for continuous variables. Categorical variables are presented as numbers and percentages. Chi-square tests and *F*-tests compared the difference in prevalence of various risk factors among the subgroups. Univariate linear regression analysis was conducted to assess the association of LVEF at the year-5 and year-25. The correlation between LV mass and LV functional parameters (LVEDV, LVESV, and LVEF) was assessed on a cross-sectional basis at the years-5 and -25 to evaluate whether a longitudinal association between LV mass and LV functional parameters could be explained by baseline cross-sectional relationship between the two parameters. A longitudinal analysis explored the relation between year-5 LV mass and year-25 LV functional parameters. We created three multivariate linear regression analysis models to evaluate the association of year-5 LVMI with year-25 LVEF. In Model 1, we adjusted for the following year-5 variables: age, sex, and race. Model 2 was adjusted for Model 1 + educational level, systolic blood pressure (SBP), heart rate, BMI, diabetes status, use of anti-hypertensive medications, smoking status (current smoker or former/non-smoker), total physical activity score, HDL-cholesterol, and LDL-cholesterol. Model 3 was adjusted for Model 2 variables, plus year-5 LVEF.

For a categorical approach, systolic dysfunction at year-25 was defined as LVEF $< 50\%$.^{15,16} We explored relations between LVMI at year-5 (per SD increase) and clinically relevant systolic dysfunction at year-25 using univariate and multivariate logistic regression analysis, reporting odds ratios (OR) and 95% Confidence intervals (95% CI). In multivariate logistic regression models, LVMI was adjusted for the same variables used in the multivariate linear regression analysis models. In additional analyses, the association between year-5 LVMI and year-25 LVEDVI or LVESVI was explored as LVEF is computed using measurements of LVEDV and LVESV. In Model 1, we adjusted for the year-5 covariates: age, sex, race, educational level, SBP, heart rate, BMI, diabetes status, use of anti-hypertensive medications, smoking status (current smoker or former/non-smoker), physical activity score, HDL-cholesterol, and LDL-cholesterol. Model 2 was adjusted for Model 1, plus year-5 LVEDVI or LVESVI, according to the dependent variable

under investigation. A two-sided probability value of < 0.05 was considered to indicate statistical significance. All statistical analyses were performed using JMP (version 10.0 for Windows, SAS Institute Inc., Cary, NC, USA) and STATA (version 11.0, Stata Corp., College Station, Texas, USA).

Results

Demographic and risk factor data for the 2,339 CARDIA participants at baseline and echocardiographic parameters at the years-5 and -25 are presented in Table 1. The study population was 43.0% male and 44.8% black with a mean age of 30.1. LVMI increased over the 20-year follow-up, while LV volumes and LVEF decreased in the same period. There were significant differences in all echocardiographic parameters between year-5 and year-25 ($p < 0.0001$). LVMI of the whole population was in the normal range. LVMI for those who developed LV systolic dysfunction was greater than for those who did not develop LV systolic dysfunction (88.7 g/m^2 vs. 78.3 g/m^2 , $p < 0.0001$). LVMI among young adults who developed LV systolic dysfunction was similar to the upper quartile of LVMI distribution in the full cohort at year-5. The cross-sectional correlations between LV mass and LVEF were close to zero at year-5 ($r = -0.02$, $p = 0.91$) and at year-25 ($r = -0.002$, $p = 0.32$). When LV mass was indexed by BSA, a modest, but significant correlation was found with LVEF at year-25 ($r = 0.07$; $p = 0.0005$); but no relation was found at year-5. In a longitudinal univariate analysis, LV mass and LVMI measured at baseline were significantly associated with LVEF 20 years later (in both cases, $r = -0.1$; $p < 0.0001$). This significant relation remained after adjustment for anthropometrics, risk factors, and LVEF at the year-5 (Table 2). There were 71 (3.0%) participants with LVEF $< 50\%$ at year-25; of these, 83.1% did not self-report any history of heart disease. In a univariate analysis, each 1 SD increase in LVMI at baseline predicted LVEF $< 50\%$ after 20 years with an OR of 1.59 (95% CI 1.30 to 1.94; $p < 0.0001$). This association was consistent (OR 1.46; 95% CI 1.15 to 1.83; $p = 0.0018$) after adjustment for anthropometrics, risk factors, and LVEF at the year-5. There were negative correlations between LVEDVI and LVEF at both year-5 and -25 cross-sectionally (year-5: $r = -0.08$; $p < 0.0001$; year-25: $r = -0.26$; $p < 0.0001$) and between LVEDVI at baseline and LVEF at year-25 ($r = -0.13$; $p < 0.0001$). LVMI at baseline had a direct positive correlation with both LVEDVI ($r = 0.27$; $p < 0.0001$) and LVESVI ($r = 0.24$; $p < 0.0001$) at year-25. This association remained after adjustment for other risk factors and baseline echocardiographic parameters (Table 3).

Discussion

This study assessed the relationship between LVMI and LV function over a 20-year follow-up period in a large, bi-racial cohort of young, generally healthy adults. Though LVMI and LVEF were not related at baseline, higher LVMI was a strong predictor of lower LVEF after 20 years. High LVMI was also related to high LV volumes 20 years later. Our results suggest that LVMI in young adulthood is an early marker of future impaired cardiac performance. When comparing those with LV systolic dysfunction and normal systolic function at year-25, there were significant difference for gender, race, BMI, blood pressure, and LV structure and function at year-5 suggesting chronic risk exposure and cardiac remodeling interact in producing future systolic dysfunction.

In cross-sectional analyses, LV mass and LVEF were not related at either year-5 or -25; there was a modest positive relationship when LV mass was indexed to BSA at year-25. Previous cross-sectional studies have shown an inverse relationship between LV mass and systolic function in middle-to-old-age populations.^{6,17} Compared to the Strong Heart Study, there were fewer CARDIA participants with LVEF $< 50\%$ at years-5 and -25. Furthermore,

LVMI was lower in our study than the Strong Heart Study¹⁷, probably reflecting the younger, healthier profile of the CARDIA cohort.

Low LVEF is a major independent predictor of future heart failure.² A previous study reported that asymptomatic systolic dysfunction may be at least twice as common as symptomatic heart failure.¹⁸ Redfield et al. reported that systolic dysfunction is frequently present in individuals without clinically recognized heart failure.¹⁵ Similarly, Wang et al. reported that asymptomatic left ventricular systolic dysfunction predicts a 2- to 4-fold higher risk of heart failure and death compared to normal systolic function.³ In the SOLVD trial, low LVEF had a higher cumulative rate of all-cause mortality than high LVEF for 12 months; low LVEF with high LV mass had the highest mortality rate.¹⁹

In cohort studies from populations older than the CARDIA cohort, LV mass contributed to incidence of heart failure.^{2,20–22} In the MESA Study, Cheng et al. reported that cardiac remodeling over middle to late adult life is characterized by a distinct pattern, of increased LV mass/volume ratio and decreasing LV volumes by MRI.²³ This pattern was confirmed by analysis of echocardiographic measures in the Framingham Study with increasing LV wall thickness and decreasing LV dimensions with advancing age.²⁴ Similarly, the MESA study reported that LVEDV as well as LV mass were predictors of incident heart failure.²⁵ LVESV has also been documented as a predictor of CVD.⁴ The Cardiovascular Health Study investigators found that, in an elderly population, increased baseline LV mass is an independent risk factor for the development of depressed LVEF five years later.⁷ Our data suggest increased LV mass as a young adult may initiate the process at an earlier age than previously reported.

Our study findings indicate exposure to cardiovascular risk factors at young age leads to early cardiac remodeling and LV systolic dysfunction. Advancing age and gender may also have an effect on myocardial remodeling and deformations.^{24,26,27} These mechanisms may have an effect on the decreased LVEF.^{24,26} Elevated resting heart rate is also associated with LV systolic dysfunction and is a prognostic indicator in cardiovascular mortality and morbidity.²⁸ Heart rate is a major determinant of cardiac energy metabolism supporting a possible explanation for the prognostic role of heart rate.²⁸ Additionally, genetic factors may also be implicated in the cardiac remodeling pathway, starting early in life. The Framingham study suggested the association between sarcomere protein gene mutation among individuals with unexplained increased LV wall thickness.²⁹ Our findings convey the need for a reliable assessment of clinically relevant cardiac remodeling in early life. Thus, our findings suggest that maintenance of cardiovascular risk factors in early life is clinically very important to prevent LV systolic dysfunction and possibly heart failure later in life.

Limitations include the use of different echocardiographic equipment and sonographers at the year-5 and -25; this may affect comparability of LV mass calculations as in the latter examination, harmonic imaging was used. We used different techniques to compute LVEF in years-5 and -25.³⁰ We also did not include an assessment of incident heart failure in our study due to the low numbers affected; future studies should address the role of LVMI in predicting incident heart failure among young adults.

Acknowledgments

Funding Sources

This study was supported by the CARDIA contract (clinics N01-HC-48047 – N01-HC-48050, Coordinating Center N01-HC-95095, Year-5 Echocardiographic Reading Center N01-HC-45134, and Year-25 Echocardiographic Reading Center NIH NHLBI-HC-09-08). This manuscript has been reviewed by CARDIA for scientific content. A full list of participating investigators and institutions can be found at <http://www.cardia.dopm.uab.edu/>, as well as access to publications and information concerning collaboration and data sharing of CARDIA resources.

The authors thank the other investigators, the staff, and the participants of the CARDIA study for their valuable contributions. This study was supported by the CARDIA contract (clinics N01-HC-48047 – N01-HC-48050, Coordinating Center N01-HC-95095, Year-5 Echocardiographic Reading Center N01-HC-45134, and Year-25 Echocardiographic Reading Center NIH NHLBI-HC-09-08).

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Table 1

Participants' characteristics at the year-5 examination

Variable	Systolic dysfunction at year-25 (n = 71)	Normal systolic function at year-25 (n = 2,268)	p - value
Age (years)	30.2 ± 3.9	30.1 ± 3.6	0.8183
Male	45 (63.4%)	960 (42.3%)	0.0004
Black	42 (59.2%)	1,005 (44.3%)	0.0133
Educational level 12 years	24 (33.8%)	575 (25.4%)	0.1082
Body mass index (kg/m ²)	28.1 ± 6.2	25.3 ± 5.2	< 0.0001
Body surface area (m ²)	1.96 ± 0.22	1.84 ± 0.21	< 0.0001
Heart rate (bpm)	68.4 ± 9.2	67.4 ± 9.7	0.3715
Systolic blood pressure (mmHg)	111.1 ± 10.1	106.6 ± 10.8	0.0005
Diastolic blood pressure (mmHg)	71.6 ± 9.4	68.3 ± 9.5	0.0044
Hypertension	4 (5.6%)	78 (3.4%)	0.3221
Diabetes mellitus	0 (0%)	38 (1.7%)	0.2715
Current smoker	22 (31.0%)	557 (24.6%)	0.2166
Using anti-hypertensive medications	1 (1.4%)	31 (1.4%)	0.9763
Physical Activity score (EU)	401 ± 331	383 ± 294	0.6087
Total cholesterol (mg/dl)	187.2 ± 34.2	177.2 ± 33.3	0.0171
High-density lipoprotein cholesterol (mg/dl)	50.2 ± 13.8	54.1 ± 13.6	0.0239
Low-density lipoprotein cholesterol (mg/dl)	117.2 ± 33.1	108.0 ± 31.5	0.0223
Triglycerides (mg/dl)	96.5 ± 77.2	73.4 ± 46.7	0.0143
Echocardiography variable			
Left ventricular mass (g)	year-5 173.9 ± 49.3	145.1 ± 41.9	< 0.0001
Left ventricular massindex (g/m ²)	year-25 206.2 ± 78.1	165.0 ± 48.6	< 0.0001
	year-5 88.7 ± 22.3	78.3 ± 18.2	< 0.0001
	year-25 99.5 ± 33.6	84.0 ± 20.2	< 0.0001
	year-5 69.0 ± 11.8	63.4 ± 11.3	< 0.0001
Left ventricular end-diastolic volume index (ml/m ²)	year-25 66.4 ± 15.7	56.0 ± 11.6	< 0.0001
	year-5 26.6 ± 6.6	22.0 ± 6.2	< 0.0001
Left ventricular end-systolic volume index (ml/m ²)	year-25 36.6 ± 10.5	21.4 ± 6.2	< 0.0001
	year-5 61.5 ± 6.4	65.4 ± 6.9	< 0.0001

Variable	Systolic dysfunction at year-25 (n = 71)	Normal systolic function at year-25 (n = 2,268)	p - value
Left ventricular ejection fraction (%)	year-25 45.2 ± 5.4	62.1 ± 6.3	< 0.0001

Values are mean ± SD unless otherwise indicated.
Bpm = beats per minutes; EU = exercise unit.

Table 2

Association between left ventricular mass index at the year-5 examination to left ventricular ejection fraction at the year-25 examination (n = 2,339)

Year-5 exam variable	Model 1 (R ² = 0.02) [§]			Model 2 (R ² = 0.02) [§]			Model 3 (R ² = 0.04) [§]		
	β-coefficient (standardized)	95% CI		β-coefficient (standardized)	95% CI		β-coefficient (standardized)	95% CI	
Left ventricular mass index (g/m ²)	-0.03 (-0.07)	(-0.04, -0.01) [‡]		-0.03 (-0.07)	(-0.04, -0.01) [§]		-0.03 (-0.08)	(-0.05, -0.01) [‡]	
Age (years)	0.10 (0.05)	(0.02, 0.18) [*]		0.10 (0.05)	(0.02, 0.18) [*]		0.09 (0.05)	(0.01, 0.16) [*]	
Male	-0.64 (-0.09)	(-0.94, -0.34) [§]		-0.70 (-0.10)	(-1.04, -0.35) [§]		-0.49 (-0.07)	(-0.84, -0.14) [‡]	
Black	0.04 (0.006)	(-0.24, 0.32)		0.11 (0.02)	(-0.20, 0.41)		0.12 (0.02)	(-0.19, 0.42)	
Educational level 12 years				-0.08 (-0.01)	(-0.42, 0.26)		-0.06 (-0.007)	(-0.40, 0.27)	
Systolic blood pressure (mmHg)				-0.01 (-0.01)	(-0.04, 0.02)		-0.02 (-0.03)	(-0.05, 0.01)	
Body mass index (kg/m ²)				-0.02 (-0.01)	(-0.08, 0.04)		-0.02 (-0.02)	(-0.08, 0.04)	
Heart rate (bpm)				-0.04 (-0.05)	(-0.07, -0.01) [*]		-0.04 (-0.05)	(-0.07, -0.01) [*]	
Using hypertensive medications (vs. none)				0.05 (0.002)	(-1.18, 1.28)		-0.19 (-0.007)	(-1.41, 1.03)	
Diabetes mellitus				0.20 (0.008)	(-0.85, 1.24)		0.27 (0.01)	(-0.77, 1.30)	
Current smoking (vs. former/never)				0.12 (0.02)	(-0.21, 0.46)		0.16 (0.02)	(-0.17, 0.50)	
Physical activity score (EU)				-0.002 (-0.01)	(-0.001, 0.001)		-0.0003 (-0.001)	(-0.001, 0.001)	
High-density lipoprotein cholesterol (mg/dl)				-0.01 (-0.02)	(-0.03, 0.01)		-0.01 (-0.02)	(-0.03, 0.01)	
Low-density lipoprotein cholesterol (mg/dl)				-0.002 (-0.008)	(-0.01, 0.01)		-0.001(-0.005)	(-0.01, 0.01)	
M-mode left ventricular ejection fraction (%)							0.16 (0.16)	(0.12, 0.20) [§]	

* p < 0.05,

[‡] p < 0.01,

[‡] p < 0.001,

[§] p < 0.0001

Model 1 adjusts for age, sex, and race at the year-5 examination.

Model 2 adjusts for Model 1, plus educational level, systolic blood pressure, body mass index, heart rate, use of anti-hypertensive medications, diabetes status, current smoking, intensity score, high-density lipoprotein cholesterol -cholesterol, low-density lipoprotein cholesterol at the year-5 examination.

Model 3 adjusts for Model 2, plus left ventricular ejection fraction at the year-5 examination.

Bpm = beats per minutes; EU = exercise unit; CI = confidence interval.

Association between left ventricular mass index at the year-5 examination to left ventricular end-systolic volume index or left ventricular end-systolic volume index at the year-25 examination (n = 2,339)

Table 3

Year-5 exam variable	Left ventricular end-systolic volume index (ml/m ²)					Left ventricular end-systolic volume index (ml/m ²)				
	Model 1 (R ² = 0.15) [§]		Model 2 (R ² = 0.18) [§]		Model 1 (R ² = 0.11) [§]	Model 2 (R ² = 0.16) [§]		Model 1 (R ² = 0.11) [§]	Model 2 (R ² = 0.16) [§]	Model 1 (R ² = 0.11) [§]
	β-coefficient (standardized)	95% CI	β-coefficient (standardized)	95% CI		β-coefficient (standardized)	95% CI			
Left ventricular mass index (g/m ²)	0.10 (0.15)	(0.07, 0.13) [§]	0.03 (0.05)	(0.003, 0.06) [*]	0.05 (0.14)	0.03 (0.08)	(0.04, 0.07) [§]	0.03 (0.08)	(0.01, 0.05) [§]	0.03 (0.08)
Age (years)	−0.04 (−0.01)	(−0.17, 0.08)	−0.03 (−0.009)	(−0.16, 0.09)	−0.07 (−0.03)	−0.05 (−0.03)	(−0.14, 0.01)	−0.05 (−0.03)	(−0.12, 0.02)	−0.05 (−0.03)
Male	2.62 (0.22)	(2.06, 3.18) [§]	2.59 (0.22)	(2.04, 3.14) [§]	1.44 (0.21)	1.21 (0.18)	(1.11, 1.77) [§]	1.21 (0.18)	(0.89, 1.54) [§]	1.21 (0.18)
Black	−0.38 (−0.03)	(−0.88, 0.11)	−0.06 (−0.005)	(−0.55, 0.43)	−0.15 (−0.02)	−0.03 (−0.005)	(−0.44, 0.14)	−0.03 (−0.005)	(−0.32, 0.25)	−0.03 (−0.005)
Educational level 12 years	0.01 (0.0005)	(−0.54, 0.55)	−0.07 (−0.005)	(−0.60, 0.47)	0.09 (0.01)	0.04 (0.005)	(−0.23, 0.41)	0.04 (0.005)	(−0.27, 0.35)	0.04 (0.005)
Systolic blood pressure (mmHg)	0.09 (0.08)	(0.05, 0.14) [‡]	0.10 (0.09)	(0.06, 0.15) [§]	0.04 (0.07)	0.05 (0.09)	(0.02, 0.07) [‡]	0.05 (0.09)	(0.03, 0.08) [§]	0.05 (0.09)
Body mass index (kg/m ²)	−0.06 (−0.03)	(−0.15, 0.04)	−0.03 (−0.01)	(−0.12, 0.07)	−0.002 (−0.002)	0.01 (0.009)	(−0.06, 0.05)	0.01 (0.009)	(−0.04, 0.07)	0.01 (0.009)
Heart rate (bpm)	−0.11 (−0.09)	(−0.16, −0.06) [§]	−0.10 (−0.08)	(−0.14, −0.05) [‡]	−0.02 (−0.02)	−0.01 (−0.02)	(−0.05, 0.01)	−0.01 (−0.02)	(−0.04, 0.02)	−0.01 (−0.02)
Using hypertensive medications (vs. none)	1.53 (0.03)	(−0.45, 3.51)	1.22 (0.02)	(−0.73, 3.16)	0.37 (0.01)	0.53 (0.02)	(−0.79, 1.54)	0.53 (0.02)	(−0.61, 1.66)	0.53 (0.02)
Diabetes mellitus	−1.33 (−0.03)	(−3.01, 0.35)	−1.36 (−0.03)	(−3.01, 0.29)	−0.68 (−0.03)	−0.76 (−0.03)	(−1.69, 0.31)	−0.76 (−0.03)	(−1.72, 0.21)	−0.76 (−0.03)
Current smoking (vs. former/never)	0.22 (0.02)	(−0.32, 0.76)	0.24 (0.02)	(−0.29, 0.78)	0.04 (0.005)	0.01 (0.002)	(−0.28, 0.36)	0.01 (0.002)	(−0.30, 0.33)	0.01 (0.002)
Physical activity score (EU)	0.002 (0.05)	(0.0003, 0.004) [*]	0.002 (0.04)	(0.0002, 0.003) [*]	0.001 (0.005)	0.001 (0.04)	(−2.53e ^{−5} , 0.002)	0.001 (0.04)	(2.32e ^{−5} , 0.002) [*]	0.001 (0.04)
High-density lipoprotein cholesterol (mg/dl)	0.01 (0.007)	(−0.03, 0.04)	0.004 (0.004)	(−0.03, 0.04)	0.01 (0.04)	0.005 (0.01)	(−0.01, 0.03)	0.005 (0.01)	(−0.02, 0.03)	0.005 (0.01)
Low-density lipoprotein cholesterol (mg/dl)	−0.01 (−0.01)	(−0.02, 0.01)	−0.02 (−0.005)	(−0.02, 0.01)	−0.001 (−0.002)	0.001 (0.03)	(−0.01, 0.01)	0.001 (0.03)	(−0.01, 0.01)	0.001 (0.03)
Left ventricular end-diastolic volume index (ml/m ²)			0.21 (0.2)	(0.17, 0.26) [§]						
Left ventricular end-systolic volume index (ml/m ²)						0.26 (0.23)			(0.22, 0.30) [§]	0.26 (0.23)

^{*} p < 0.05,
[‡] p < 0.01,
[‡] p < 0.001,
[§] p < 0.0001

Model 1 adjusts for age, sex, race, educational level, systolic blood pressure, body mass index, heart rate, use of anti-hypertensive medications, diabetes status, current smoking, intensity score, high-density lipoprotein cholesterol, and low-density lipoprotein cholesterol at the year-5 examination.

Model 2 adjusts for Model 1, plus left ventricular end-diastolic volume index or left ventricular end-systolic volume index at the year-5 examination.

Bpm = beats per minutes; EU = exercise unit; CI = confidence interval.