ORIGINAL RESEARCH

Inappropriate Left Ventricular Mass and Cardiovascular Disease Events and Mortality in Blacks: The Jackson Heart Study

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Background—Left ventricular hypertrophy (LVH) is associated with an increased risk for cardiovascular disease (CVD) events and all-cause mortality. Many individuals without LVH have a left ventricular mass that exceeds the level predicted by their sex, body size, and cardiac workload, a condition called inappropriate left ventricular mass (iLVM). We investigated the association of iLVM with CVD events and all-cause mortality among blacks.

Methods and Results—We analyzed data from the Jackson Heart Study, a community-based cohort of blacks. The current analysis included 4424 participants without CVD and with an echocardiogram at baseline. Among this cohort, the prevalence of iLVM was 13.8%. There were 262 CVD events and 419 deaths over a median follow-up of 9.7 years (maximum, 12 years). Compared with participants without iLVM, participants with iLVM had a higher rate of CVD events and all-cause mortality. After multivariable adjustment, including for the presence of LVH, iLVM was associated with an increased risk of CVD events (hazard ratio, 1.87; 95% CI, 1.33–2.62). The multivariable-adjusted hazard ratio for all-cause mortality was 1.29 (95% CI, 0.98–1.70). Among participants without and with LVH, the multivariable-adjusted hazard ratios of iLVM for CVD events were 2.53 (95% CI, 1.68–3.81) and 1.21 (95% CI, 0.74–2.00), respectively ($P_{interaction}$=0.029); and for all-cause mortality, the hazard ratios were 1.24 (95% CI, 0.81–1.89) and 1.26 (95% CI, 0.86–1.85), respectively ($P_{interaction}$=0.664).

Conclusions—iLVM is associated with an increased risk for CVD events among blacks without LVH. **(*J Am Heart Assoc*. 2019;8: e011897. DOI: 10.1161/JAHA.118.011897.)**

Key Words: black • cardiovascular disease • inappropriate left ventricular mass • left ventricular hypertrophy • mortality

Alterations in left ventricular mass (LVM) can be affected by an individual's sex, body size, and cardiac workload.[1–3] There is considerable interindividual variability in the extent to which LVM is affected by increased cardiac workload. Left ventricular hypertrophy (LVH), defined as LVM above a prespecified population-derived threshold, is considered a pathological response to increased blood pressure (BP) and cardiac workload and is associated with an increased risk for cardiovascular disease (CVD) events and mortality.[4–6] However, LVH, defined using population-derived thresholds, does not correctly identify pathological increases in LVM for all individuals, especially when body composition is altered or in different racial/ethnic groups.[7] Furthermore, an increase in LVM above a prespecified threshold is not always pathological as there are certain normal physiological states (ie, pregnancy or athlete's heart) where an increase in LVM represents an "appropriate" and compensatory response to increased cardiac workload and is not associated with increased cardiovascular risk.[1–3] Therefore, approaches to distinguish between compensatory increases in LVM and pathological changes may provide additional information on CVD risk.

An approach that may better characterize the response to increased cardiac workload than consideration of LVM above a certain prespecified threshold is the observed/predicted LVM ratio.[8,9] The term "inappropriate" LVM (iLVM) refers to an elevated observed/predicted LVM ratio and is used to characterize the presence of LVM that exceeds a predicted value that is based on an individual's sex, body size, and cardiac workload.[9] There are few published data on the prevalence of, and factors associated with, iLVM or its prognostic significance among blacks, a group who is at high

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Accompanying Data S1, Tables S1 through S5 are available at https://www.ahajournals.org/doi/suppl/10.1161/JAHA.118.011897

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Clinical Perspective

What Is New?

- This is the first study to examine the association of inappropriate left ventricular mass with cardiovascular disease events and mortality among a cohort of blacks.
- The prevalence of inappropriate left ventricular mass among blacks is 13.8%.
- In adjusted analyses, inappropriate left ventricular mass was associated with an increased risk of cardiovascular disease events but not mortality.

What Are the Clinical Implications?

- By accounting for multiple characteristics, including cardiac workload, sex, and body size, inappropriate left ventricular mass may provide an individualized approach to identify blacks at increased cardiovascular risk.

risk for CVD events and mortality compared with other racial/ethnic groups in the United States.[10,11] We determined the association of iLVM with CVD events and, secondarily, all-cause mortality among participants in the JHS (Jackson Heart Study), a community-based cohort study composed exclusively of blacks.

Methods

Study Population

The data that support the findings of this study are available from the corresponding author on reasonable request. The JHS is a community-based prospective cohort study designed to evaluate CVD risk among blacks.[12] The JHS enrolled 5306 noninstitutionalized blacks, aged ≥21 years, from the ARIC (Atherosclerosis Risk in Communities) study site in Jackson, MS, a representative sample of urban and rural Jackson metropolitan tricounty (Hinds, Madison, and Rankin Counties) residents, volunteers, randomly contacted individuals, and secondary family members of participants.[13]

Participants were excluded from the current analysis if they had incomplete echocardiographic data (n=276) or missing data (ie, age, sex, height, and weight) required to calculate observed and predicted LVM (n=11). Because the predicted LVM equation was developed among adults aged <85 years,[9] participants aged >85 years (n=14) were excluded. Participants with a history of myocardial infarction or stroke (n=427) at baseline were excluded. As described below, consistent with prior studies,[14,15] participants with an observed/predicted LVM ratio below the fifth percentile (n=151) were considered to have "low" LVM and were excluded from the current study. Finally, participants with an observed/predicted LVM ratio >400% (n=3) were excluded for physiologic implausibility, leaving a final sample size of 4424 participants for all analyses.

The JHS protocol and all data collection procedures were approved by the Institutional Review Boards of University of Mississippi Medical Center, Jackson State University, and Tougaloo College. All study participants provided written informed consent. The current analysis was approved by the Institutional Review Board at Columbia University and University of Alabama at Birmingham.

Study Procedures

At the baseline study visit in 2000 to 2004, participants completed interviewer and self-administered questionnaires and an examination that included blood and urine collection and 2-dimensional echocardiography. Detailed descriptions of data collection, methods, and processing have been described previously[13] and are available in Data S1. During the baseline in-home interview, trained staff administered questionnaires to collect self-reported information on demographics, health behaviors (eg, alcohol consumption, current smoking, and physical activity), and previously diagnosed comorbid conditions. Antihypertensive medication use was defined by self-report. A standardized protocol was followed to measure BP.[16,17] Prevalent hypertension was defined as a systolic BP (SBP) ≥140 mm Hg, a diastolic BP (DBP) ≥90 mm Hg, or antihypertensive medication use. Estimated glomerular filtration rate (eGFR) was calculated using the Chronic Kidney Disease Epidemiology Collaboration equation.[18] Reduced eGFR was defined as levels <60 mL/min per 1.73 m^2.[18]

Echocardiography

Certified technicians performed 2-dimensional transthoracic echocardiograms (Sonos-4500; Philips Medical Systems) using standardized protocols.[19] Clinical interpretations and analytical measurements of the echocardiograms were performed by experienced cardiologists (DA, MA) on networked image workstations (Vericis; Camtronics Medical Systems).[19] Left ventricular dimensions, including left ventricular internal diameter in diastole (LVIDd; millimeters), left ventricular internal diameter in systole (LVIDs; millimeters), interventricular septal thickness in diastole (IVSd; millimeters), and posterior wall thickness in diastole (PWTd; millimeters), were assessed according to 2015 American Society of Echocardiography and European Association of Cardiovascular Imaging recommendations and used to calculate LVM, LVM index (LVMI), and LVH.[20]

Relative wall thickness (RWT) was calculated using the American Society of Echocardiography formula: RWT=(2×PWTd)/LVIDd.[21] Normal RWT was defined as RWT ≤0.42, and increased RWT was defined as RWT >0.42.[21] Patterns of left ventricular structure

were defined as follows: normal (normal LVMI and normal RWT); concentric remodeling (normal LVMI and increased RWT); eccentric hypertrophy (LVH and normal RWT); and concentric hypertrophy (LVH and increased RWT).[21,22] Fractional shortening was defined as follows: [(LVIDd–LVIDs)/(LVIDd)]×100%. Left ventricular ejection fraction was derived semiquantitatively (to nearest 5%).[23]

LVM was calculated using the 2015 American Society of Echocardiography/European Association of Cardiovascular Imaging formula: $0.8\times\{1.04\times[(IVSd+LVIDd+PWTD)^3-(LVIDd)^3]\}+0.6$.[20] LVMI was calculated as LVM indexed to height$^{2.7}$, and LVH was defined as LVMI ≥45 g/m$^{2.7}$ in women and ≥49 g/m$^{2.7}$ in men.[21,24] As previously described, stroke work was calculated as follows: (SBP×stroke volume)×0.0144.[25] Stroke volume was defined as left ventricular end-diastolic volume minus left ventricular end-systolic volume, determined using the Teichholz formula: Volume=[7.0/(2.4+D)]×D^3, where D=LVIDd and LVIDs, respectively.[25] Predicted LVM was calculated for each participant as follows: 55.37+[(6.64×height$^{2.7}$)+(0.64×stroke work)]–(18.07×sex), where sex=1 for men and 2 for women.[9] The observed/predicted LVM ratio was calculated as 100×(observed LVM/predicted LVM). This ratio was first estimated in a healthy reference population of JHS participants at the baseline visit. The healthy population was defined as JHS participants who were free from hypertension, were free from diabetes mellitus, and had a body mass index <30 kg/m^2 (n=892). This population was then used to identify the 5th and 95th percentiles in the observed/predicted LVM distribution (71.6% and 128.2%, respectively). Participants with an observed/predicted ratio >128.2% were categorized as having iLVM, whereas those with an observed/predicted ratio between 71.6% and 128.2% were categorized as having "appropriate" LVM (aLVM).

Outcomes

The primary outcome was a composite of CVD events (definite or probable nonfatal myocardial infarction, fatal coronary heart disease, or stroke, defined as noncarotid embolic or thrombotic brain infarction, brain hemorrhage, or subarachnoid hemorrhage).[26] All-cause mortality was examined as a secondary outcome. A detailed description of event adjudication and follow-up procedures have been described previously and are available in Data S1.[26] CVD events and all-cause mortality were available through December 31, 2012.

Statistical Analysis

Participant characteristics were calculated for the study population, overall, and for participants with iLVM and aLVM, separately. Characteristics of participants with iLVM and aLVM were also calculated stratified by LVH status. To account for participants with missing data for covariates (n=484; Table S1), multiple imputation was performed using chained equations and 10 data sets.[27]

The cumulative incidence of CVD events was calculated for participants with iLVM and aLVM using the Kaplan-Meier method. CVD incidence rates were calculated for participants with iLVM and aLVM, separately. Using Cox proportional hazards regression, the hazard ratios (HRs) and 95% CIs for CVD events associated with iLVM versus aLVM were calculated in nested models with progressive adjustment. Model 1 included adjustment for age, sex, and body mass index. Model 2 included the variables in model 1 and education, current smoking, alcohol use, physical activity, diabetes mellitus, and reduced eGFR. Model 3 included the variables in model 2 and SBP, DBP, and antihypertensive medication use. Model 4 included the variables in model 3 and LVH. Subgroup analyses were conducted by calculating CVD incidence rates and HRs associated with iLVM versus aLVM among participants with and without LVH, separately. Tests for interaction between iLVM and LVH for CVD events were calculated in models including the full population, main effect terms, and a multiplicative interaction term (ie, iLVM×LVH). Adjusted HRs (95% CIs) for CVD events were calculated for each SD higher observed/predicted LVM ratio for all models in the overall cohort and after stratifying by LVH status. The above analyses were repeated using all-cause mortality as the outcome. $P<0.05$ was considered statistically significant. All data analyses were conducted using SAS, version 9.4 (SAS Institute, Cary, NC), or Stata/IC, version 12.1 (Stata Inc, College Station, TX).

Results

Participant Characteristics

Overall, 13.8% of participants had iLVM and 14.0% had LVH (Table 1). Compared with participants with aLVM, those with iLVM were older, were more likely to be women, to have less than a high school education, to have diabetes mellitus, to have reduced eGFR, and to have prevalent hypertension, and were more likely to be taking antihypertensive medication. Also, participants with iLVM had a higher mean body mass index, a higher pulse pressure, and a lower DBP. Compared with their counterparts who had aLVM, participants with iLVM had a higher LVMI and a higher prevalence of LVH. Participants with iLVM had a higher prevalence of reduced ejection fraction, eccentric hypertrophy, and concentric hypertrophy. Other echocardiographic parameters for participants with aLVM and iLVM are shown in Table S2. iLVM was present in 6.5% of participants without LVH and 58.5% of participants with LVH. Characteristics of participants with aLVM and iLVM by LVH status are shown in Table S3.

Table 1. Characteristics of the JHS Participants With aLVM and iLVM

Characteristics	Overall Sample (n=4424)	aLVM (n=3815)	iLVM (n=609)	*P* Value*
Age, mean (SD), y	54.48 (12.66)	53.91 (12.65)	58.08 (12.10)	<0.001
Women, %	64.94	64.35	68.64	0.040
Body mass index, mean (SD), kg/m^2	31.92 (7.22)	31.48 (7.00)	34.66 (7.97)	<0.001
Education less than high school, %	17.97	17.08	23.52	<0.001
Current smoking, %	12.05	11.90	12.97	0.451
Physical activity category, %				
Ideal	47.79	46.80	54.02	0.002
Intermediate	32.28	32.63	30.05	
Poor	19.93	20.57	15.93	
Alcohol use, %				
Nondrinker	63.90	62.67	71.59	<0.001
Moderate drinker	32.75	33.66	27.09	
Heavy drinker	3.35	3.67	1.31	
Diabetes mellitus, %	20.57	18.89	31.07	<0.001
eGFR <60 mL/min per m^2, %	7.60	6.55	14.12	<0.001
HDL cholesterol, mean (SD), mg/dL	51.94 (14.56)	52.05 (14.58)	51.25 (14.39)	0.239
Total cholesterol, mean (SD), mg/dL	199.70 (39.79)	199.70 (39.32)	199.90 (42.74)	0.905
SBP, mean (SD), mm Hg	126.62 (16.32)	126.60 (15.96)	127.00 (18.40)	0.574
DBP, mean (SD), mm Hg	75.75 (8.62)	75.92 (8.39)	74.68 (9.89)	0.003
Pulse pressure, mean (SD), mm Hg	50.88 (14.05)	50.64 (13.90)	52.33 (14.84)	0.009
Prevalent hypertension, %	54.34	51.79	70.58	<0.001
No. of antihypertensive medication classes, %				
0	52.12	54.78	35.47	<0.001
1	18.74	18.53	20.03	
2	18.58	17.27	26.77	
3	10.56	9.41	17.73	
Antihypertensive medication use, %	47.42	44.62	65.31	<0.001
LVM, mean (SD), g	149.04 (42.33)	140.00 (32.04)	205.90 (53.37)	<0.001
LVMI, mean (SD), g/m$^{2.7}$	36.37 (10.21)	34.05 (7.61)	50.88 (12.27)	<0.001
LVH, %	13.95	6.71	59.28	<0.001
Ejection fraction, mean (SD), %	61.91 (7.26)	62.16 (6.85)	60.34 (9.25)	<0.001
Ejection fraction ≤40%, %	0.66	0.26	3.15	<0.001
Eccentric hypertrophy, %	8.34	5.58	25.62	<0.001
Concentric hypertrophy, %	5.61	1.13	33.66	<0.001

LVH is defined as LVMI ≥45 g/m$^{2.7}$ in women and ≥49 g/m$^{2.7}$ in men. LVMI is calculated as LVM/height$^{2.7}$. Relative wall thickness (RWT) was calculated using the American Society of Echocardiography formula: RWT=2×(posterior wall thickness in diastole/left ventricular internal dimension in diastole). Increased RWT is defined as RWT >0.42. Normal RWT is defined as RWT ≤0.42. Eccentric hypertrophy is defined as follows: LVH and normal RWT. Concentric hypertrophy is defined as follows: LVH and increased RWT. aLVM indicates appropriate LVM; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; HDL, high-density lipoprotein; iLVM, inappropriate LVM; JHS, Jackson Heart Study; LVH, left ventricular hypertrophy; LVM, left ventricular mass; LVMI, LVM index; SBP, systolic blood pressure.
**P* value comparing participants with aLVM and iLVM.

iLVM and Risk of CVD Events

Over a median follow-up of 9.7 years (maximum, 12.3 years), there were 262 CVD events (182 among participants with aLVM and 80 among those with iLVM). The cumulative incidence and incidence rates of CVD events were higher for participants with iLVM versus aLVM (Figure 1 and Table 2). After each level of adjustment, including a model with adjustment for LVH, iLVM

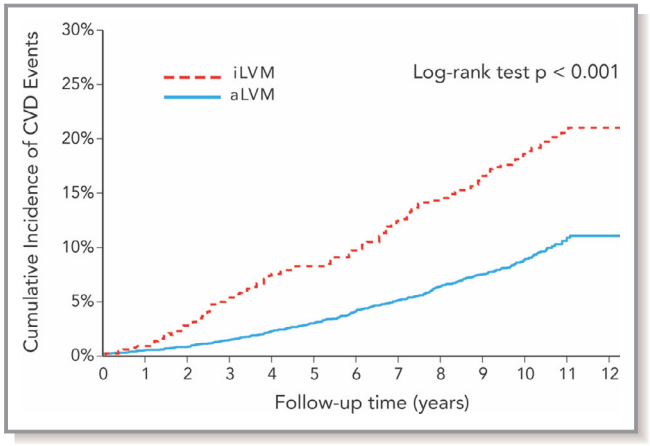

Figure 1. Cumulative incidence of cardiovascular disease (CVD) events associated with appropriate left ventricular mass (aLVM) and inappropriate left ventricular mass (iLVM). Cumulative incidence of CVD events among participants with aLVM (solid line) and iLVM (dashed line) in the overall analytic sample.

was associated with an increased HR for CVD. Among participants with and without LVH, the incidence rates of CVD events were higher for those with iLVM compared with aLVM. Higher observed/predicted LVM ratio, modeled as a continuous variable, was associated with an increased risk of CVD events overall and among participants with and without LVH after multivariable adjustment (Table S4).

iLVM and Risk of All-Cause Mortality

Over a median follow-up of 9.8 years (maximum, 12.3 years), there were 419 deaths (309 and 110 among participants with aLVM and iLVM, respectively). Cumulative mortality was higher among participants with iLVM compared with their counterparts with aLVM (Figure 2 and Table 3). After multivariable adjustment, including for LVH, the HR for all-cause mortality comparing participants with iLVM versus aLVM was 1.29 (95% CI, 0.98–1.70). After multivariable adjustment, higher observed/predicted LVM ratio, modeled as a continuous variable, was associated with an increased risk of all-cause mortality in the overall cohort and among participants with LVH (Table S5).

Discussion

In this community-based cohort of blacks, 13.8% of participants had iLVM. iLVM was associated with an increased risk of CVD events. This association remained statistically significant after multivariable adjustment, including adjustment for LVH. When modeled as a continuous variable, progressively higher observed/predicted LVM ratio was also associated with an increased risk of CVD events. iLVM was not associated with the secondary outcome of all-cause mortality.

Several studies have reported the prevalence of iLVM among whites and Asians. In these studies, the prevalence has ranged from 9% to 46%.[14,28–31] In a study of 626 South African blacks, the prevalence of iLVM was 18.5%.[32] However, there are few population-based studies that have examined the prevalence of iLVM among blacks, a group who is at high risk for CVD events. In the current analysis of 4424 blacks in the JHS, the prevalence of iLVM was 13.8%.

Table 2. Incidence Rates and HRs for CVD Events Associated With iLVM Versus aLVM in the Overall Analytic Sample and Among Participants Without and With LVH

Variable	CVD Events/No. at Risk	Incidence Rate (95% CI)*	HR (95% CI)			
			Model 1	Model 2	Model 3	Model 4
Overall (N=4424)						
aLVM	182/3815	5.34 (4.62–6.18)	1 (Reference)	1 (Reference)	1 (Reference)	1 (Reference)
iLVM	80/609	15.40 (12.37–19.17)	2.53 (1.93–3.31)	2.14 (1.63–2.80)	2.08 (1.59–2.74)	1.87 (1.33–2.62)
Without LVH (N=3807)						
aLVM	155/3559	4.86 (4.16–5.69)	1 (Reference)	1 (Reference)	1 (Reference)	†
iLVM	29/248	13.45 (9.35–19.36)	2.72 (1.82–4.06)	2.31 (1.54–3.46)	2.53 (1.68–3.81)	†
With LVH (N=617)						
aLVM	27/256	12.36 (8.48–18.02)	1 (Reference)	1 (Reference)	1 (Reference)	†
iLVM	51/361	16.77 (12.75–22.07)	1.29 (0.81–2.08)	1.05 (0.65–1.70)	1.21 (0.74–2.00)	†

Model 1: adjusted for age, sex, and body mass index. Model 2: adjusted for the variables in model 1 and diabetes mellitus, estimated glomerular filtration rate <60 mL/min per 1.73 m^2, education level (less than high school), current smoking, physical activity, and alcohol use (none, moderate, or heavy). Model 3: adjusted for the variables in model 2 and systolic blood pressure, diastolic blood pressure, and antihypertensive medication use. Model 4: adjusted for the variables in model 3 and LVH. The test for interaction between LVH and iLVM for CVD events had a $P_{interaction}$=0.029 (on model 4). aLVM indicates appropriate left ventricular mass; CVD, cardiovascular disease; HR, hazard ratio; iLVM, inappropriate left ventricular mass; LVH, left ventricular hypertrophy.

*Incidence rate per 1000 person-years (95% CI).

†Model 4 was not performed as these analyses are stratified by LVH status.

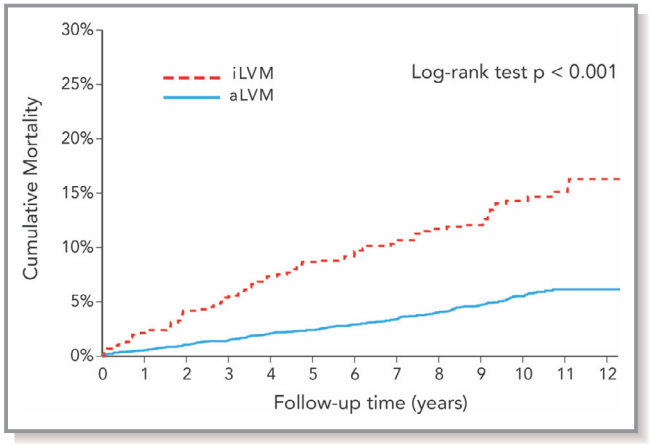

Figure 2. Cumulative all-cause mortality associated with appropriate left ventricular mass (aLVM) and inappropriate left ventricular mass (iLVM). Cumulative all-cause mortality among participants with aLVM (solid line) and iLVM (dashed line) in the overall analytic sample.

Among participants without LVH, 6.5% had iLVM, whereas 58.5% of participants with LVH had iLVM. These data suggest that iLVM is not a subset or category within traditionally defined LVH.[14,15] In addition, although iLVM was not common among participants without LVH, it was associated with increased CVD risk in this group, suggesting it may provide meaningful additional prognostic information beyond traditionally defined LVH. LVH is a known risk factor for CVD events and all-cause mortality, but it has important limitations.[1] In particular, LVH is known to vary substantially between individuals on the basis of their race, sex, and the presence of other concomitant conditions.[1] The observed/predicted LVM ratio may be useful when assessing the appropriateness of LVM accounting for characteristics, including cardiac workload or hemodynamic burden.

Prior studies that have examined the association between iLVM and CVD events have been conducted in clinic-based settings among special populations of adults with prevalent hypertension,[8,14,33,34] chronic kidney disease,[35] or diabetes mellitus.[36] In the current community-based study of blacks, iLVM was associated with >2 times higher risk of CVD events over a median follow-up of 9.7 years. In stratified analyses, the association between iLVM and CVD events was stronger among participants without LVH. These findings may suggest that iLVM may be useful as an additional marker of increased CVD risk, even among individuals without traditionally defined LVH.

Consistent with prior studies,[14,15] an observed/predicted LVM ratio >95th percentile in a healthy JHS population was first calculated, and then used to define individuals as having iLVM. Among this cohort of blacks, the calculated cut point was 128.2%. More important, this value is similar to the cut point that has been calculated among separate, predominantly white cohorts (128%).[14] Therefore, our findings both identify a threshold to define iLVM for a black cohort and also suggest that the same threshold to categorize excess LVM can appropriately be applied to multiple racial groups. The underlying mechanisms for iLVM are not understood. In the current analysis, compared with those with aLVM, individuals

Table 3. Mortality Rates and HRs for All-Cause Mortality Associated With iLVM Versus aLVM in the Overall Analytic Sample and Among Participants Without and With LVH

Variable	Deaths/No. at Risk	Mortality Rate (95% CI)*	HR (95% CI)			
			Model 1	Model 2	Model 3	Model 4
Overall (N=4424)						
aLVM	309/3807	8.92 (7.98–9.97)	1 (Reference)	1 (Reference)	1 (Reference)	1 (Reference)
iLVM	110/617	20.00 (16.59–24.11)	1.82 (1.46–2.28)	1.62 (1.30–2.03)	1.63 (1.30–2.04)	1.29 (0.98–1.70)
Without LVH (N=3807)						
aLVM	263/3559	8.13 (7.21–9.18)	1 (Reference)	1 (Reference)	1 (Reference)	†
iLVM	25/248	11.04 (7.46–16.34)	1.25 (0.82–1.88)	1.08 (0.71–1.64)	1.24 (0.81–1.89)	†
With LVH (N=617)						
aLVM	46/256	19.98 (14.96–26.67)	1 (Reference)	1 (Reference)	1 (Reference)	†
iLVM	85/361	26.26 (21.23–32.48)	1.28 (0.89–1.85)	1.17 (0.80–1.69)	1.26 (0.86–1.85)	†

Model 1: adjusted for age, sex, and body mass index. Model 2: adjusted for the variables in model 1 and diabetes mellitus, estimated glomerular filtration rate <60 mL/min per 1.73 m^2, education level (less than high school), current smoking, physical activity, and alcohol use (none, moderate, or heavy). Model 3: adjusted for the variables in model 2 and systolic blood pressure, diastolic blood pressure, and antihypertensive medication use. Model 4: adjusted for the variables in model 3 and LVH. The test for interaction between LVH and iLVM for all-cause mortality had a $P_{interaction}$=0.664 (on model 4). aLVM indicates appropriate left ventricular mass; HR, hazard ratio; iLVM, inappropriate left ventricular mass; LVH, left ventricular hypertrophy.

*Mortality rate per 1000 person-years (95% CI).

†Model 4 was not performed as these analyses are stratified by LVH status.

with iLVM were older, had a higher body mass index, and had a reduced eGFR, results consistent with prior studies.[8,14,28,30,31,33,37–39] In addition, current smoking was more prevalent among those with iLVM. Although individuals with iLVM took more classes of antihypertensive medication and had a lower DBP, SBP was not higher among this group. Consequently, individuals with iLVM had a higher pulse pressure, primarily caused by a decrease in DBP, as opposed to an increase in SBP. There are baseline differences among participants with iLVM, including a higher prevalence of LVH, reduced ejection fraction, and concentric and eccentric hypertrophy.

It is unclear the extent to which iLVM is driven by changes in BP as iLVM has been associated with higher BP in some,[30,31] but not all, studies.[8,28,30,37–39] There are important hemodynamic and nonhemodynamic stimuli to left ventricular growth.[1,29,40–43] In response to hemodynamic stress is a cascade of cellular and biologic events that can result in the development of compensatory myocardial cell growth, including intracellular gene expression of proto-oncogenes and the transcription of growth mediators, such as growth hormone and insulin-like growth factor 1.[43–45] However, prior studies have demonstrated that hemodynamic stress, such as elevated BP, may explain only a proportion of the variability of LVM.[1] Nonhemodynamic stimuli, such as genetics, sex, and body size, may cause, or significantly modify, the effects of increased load and contribute to left ventricular growth.[42,43] It has been hypothesized that iLVM similarly reflects the interaction of genetic, neurohormonal, and biologic factors other than BP.[1,29,40,41] In understanding the mechanism behind why excess LVM is associated with an increased risk of CVD events, one explanation is that the biologic underpinnings of increases in LVM are also associated with high-risk pathologic changes in body composition and chemistry, such as impaired glucose tolerance or metabolic syndrome.[46,47] Understanding the causes of and how to distinguish compensatory versus pathologic changes in cardiac remodeling remains a clinical challenge and an important area of research.

The current study has several strengths. We used data from the JHS, a community-based cohort composed of blacks. This study represents one of the largest samples of blacks with echocardiographic data, and we were able to derive cut points for defining aLVM and iLVM in a healthy subgroup within the JHS and investigate the impact of iLVM among participants with and without LVH, separately. The current study used a common, validated method for calculating iLVM.[14,28–31] Furthermore, the JHS actively identified CVD events and all-cause mortality among participants, and events were adjudicated following a standardized protocol. However, there are several limitations to the current study. Calculating LVM by echocardiography requires geometric assumptions, including a fixed left ventricular shape of a prolate ellipsoid, which may not be applicable to some pathologic conditions.[20] In addition, many of the components of the iLVM formula are dependent on reliable 2-dimensional echocardiography, which may be subject to interobserver, and day-to-day, variability. This is partially overcome in the JHS cohort by using standardized protocols for obtaining and interpreting echocardiograms. Although echocardiography correlates well with cardiac magnetic resonance imaging, the gold standard and most precise way to assess LVM is cardiac magnetic resonance imaging, which does not require cardiac geometric assumptions.[48,49] Cardiac magnetic resonance imaging was not performed at the JHS baseline study visit and, therefore, cardiac magnetic resonance imaging results could not be used or correlated to echocardiographic findings in our analysis. Furthermore, echocardiograms were only obtained at the baseline study visit, and changes in iLVM status over time could not be evaluated. An additional limitation is that there were only a limited number of CVD events and deaths and the stratified analyses may have been underpowered to detect statistically significant associations. In addition, although iLVM was not a common phenotype among participants without LVH, it was associated with increased CVD risk in this group, suggesting it may provide meaningful additional prognostic information beyond traditional LVH, a finding that should be confirmed in future studies. Finally, consistent with prior studies, we adjusted for potential confounders in our models.[8,14,33] However, it is possible that the associations between iLVM and CVD and all-cause mortality are, in part, related to unidentified confounders that were not adjusted for in our multivariable analysis.

In conclusion, the prevalence of iLVM was high among blacks in the JHS. This phenotype, which is distinct from LVH, was associated with an increased risk of CVD events among participants without LVH. Also, iLVM was associated with an increased risk for all-cause mortality. By accounting for multiple characteristics, including cardiac workload, sex, and body size, iLVM may provide an individualized approach to identify blacks at increased cardiovascular risk.

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Supplemental Material

Data S1.

SUPPLEMENTAL METHODS

Data Collection & Clinical Covariates

Detailed descriptions of data collection, methodology, specimen collection and processing have been previously described.[1, 2] Age, sex, and education level were obtained by self-report using standardized interviewer-administered questionnaires. Current smoking was defined by affirmative responses to the questions “Have you smoked more than 400 cigarettes in your lifetime?” and “Do you now smoke cigarettes?” Antihypertensive medication use in the two weeks prior to the study visit was self-reported. Participants were asked to bring any medications taken within 2 weeks prior to the baseline examination to the clinic visit and were transcribed verbatim. Medication coding was performed by a pharmacist using the Medispan dictionary and classified into categories according to the Therapeutic Classification System. The number of medications were also recorded. Alcohol consumption was categorized None (no drinks per week), Moderate (1-7 drinks per week for women and 1-14 drinks per week for men), or Heavy (≥8 drinks per week for women or ≥14 drinks per week for men). Using a modified Baecke questionnaire, validated in the Jackson Heart Study (JHS) using pedometers and accelerometers, the weekly duration and annual frequency of participation in sports/exercises during the previous year were recorded and summed to calculate the total number of minutes per week spent in moderate or vigorous physical activity.[3, 4] Physical activity was categorized according to American Heart

Association Life's Simple 7 categories: Poor (0 mins of moderate physical activity and 0 minutes of vigorous physical activity), Intermediate (1-149 minutes of moderate physical activity or 1-74 minutes of vigorous physical activity or 1-149 minutes of combined moderate and vigorous physical activity), and Ideal (≥150 minutes of moderate physical activity or ≥75 minutes of vigorous physical activity or ≥150 minutes of combined moderate and vigorous physical activity).[5] Height, weight, and blood pressure were measured and blood samples were collected by trained staff during the study visit. Body mass index was calculated as weight in kilograms divided by height in meters squared. Total and high-density lipoprotein cholesterol were quantified by an oxidase method.[1] Serum glucose was measured using a glucose oxidase method on a Vitros 250 or 950, Ortho-Clinical Diagnostics analyzer.[1] Hemoglobin A1c was measured using a TOSOH high performance liquid chromatography system. Diabetes was defined as a fasting (≥8 hours) serum glucose ≥126 mg/dL or hemoglobin A1c ≥6.5% or self-reported use of insulin or oral hypoglycemic medications within 2 weeks prior to the study visit. Serum creatinine was measured using a multi-point enzymatic spectrophotometric assay on a Vitros 950 Ortho-Clinical Diagnostic analyzer.

Blood pressure was measured according to a standardized protocol. Participants were asked to avoid heavy physical activity, caffeine, eating, smoking and alcohol intake for 12 hours prior to their study visit. Two blood pressure measurements were obtained using an appropriately sized cuff, determined from a measurement of arm circumference, and a random-zero sphygmomanometer (Hawksley and Sons Ltd).[6, 7] Participants were seated in an upright position with their back and arms supported, feet flat on the floor and legs uncrossed for at least five minutes after which trained staff

conducted the two blood pressure measurements, separated by one minute, in the right arm. The average of these two blood pressure measurements was used as the reported blood pressure. As previously described, random-zero blood pressure measurements were calibrated to an oscillometric device using robust regression.[8] Pulse pressure was defined as the difference between average systolic blood pressure and average diastolic blood pressure.

Outcomes

Detailed description of cardiovascular disease (CVD) and all-cause mortality event adjudication have been previously described.[9] JHS participants or their proxies were contacted annually via telephone to assess potential CVD events and vital status. Hospital discharge lists with specific diagnosis criteria were also obtained from the Jackson, Mississippi, tri-county area hospitals. Death certificates were requested from the Mississippi State Department of Health for JHS participants as needed. When a potential CVD-related hospitalization or death was identified, medical records were retrieved and abstracted. Trained clinicians adjudicated events following published guidelines using the information available about the circumstance surrounding each event.[9]

Table S1. Percentage of missing data among Jackson Heart Study participants included in the analytic sample.

Variable	N (%)
Age	0 (0)
Sex	0 (0)
Body mass index	0 (0)
Diabetes	44 (0.99)
eGFR	69 (1.56)
HDL cholesterol	369 (8.34)
Total cholesterol	368 (8.32)
Education	17 (0.38)
Smoking status	0 (0)
Physical activity category	3 (0.07)
Alcohol use	0 (0)
Systolic blood pressure	14 (0.32)
Diastolic blood pressure	14 (0.32)
Antihypertensive medication use	82 (1.85)

eGFR: Estimated glomerular filtration rate
HDL: High-density lipoprotein

Table S2. Echocardiographic parameters of Jackson Heart Study participants with appropriate and inappropriate left ventricular mass.

	Overall Sample (n = 4,424)	aLVM (n = 3,815)	iLVM (n = 609)	p-value*
Stroke work, g-m	137.10 (35.90)	137.70 (35.25)	133.50 (39.53)	0.015
Stroke volume, mL	75.08 (16.42)	75.41 (16.01)	73.02 (18.66)	0.003
Fractional shortening, %	4.93	3.44	17.45	<0.001
Interventricular septum thickness in diastole, cm	0.88 (0.14)	0.86 (0.12)	1.08 (0.16)	<0.001
Posterior wall thickness in diastole, cm	0.84 (0.13)	0.82 (0.11)	1.03 (0.15)	<0.001
RWT	0.36 (0.07)	0.35 (0.06)	0.44 (0.09)	<0.001
Left ventricular end-diastolic diameter, cm	4.84 (0.45)	4.82 (0.42)	4.96 (0.59)	<0.001
Left ventricular end-systolic diameter, cm	2.98 (0.47)	2.94 (0.41)	3.25 (0.69)	<0.001

The numbers in the table are mean ± standard deviation.
aLVM: Appropriate left ventricular mass**;** iLVM: Inappropriate left ventricular mass
Relative wall thickness (RWT) was calculated using the ASE formula; RWT = 2 x posterior wall thickness in diastole/left ventricular internal dimension in diastole. Increased RWT is defined as RWT >0.42. Normal RWT is defined as RWT ≤0.42

Table S3. Characteristics of the Jackson Heart Study participants included in the analytic sample by left ventricular mass (LVM) status for participants without left ventricular hypertrophy (LVH, left) and with LVH (right).

	Without LVH (N=3,807)			With LVH (N=617)		
	aLVM (N= 3,559)	iLVM (N= 248)	p-value*	aLVM (N= 256)	iLVM (N= 361)	p-value*
Age, years	53.41 (12.60)	55.11 (12.39)	0.040	60.77 (11.38)	60.11 (11.47)	0.479
Female, %	62.66	64.11	0.647	87.89	71.75	<0.001
Body mass index, kg/m^2	31.18 (6.84)	33.61 (6.95)	<0.001	35.73 (7.79)	35.37 (8.53)	0.592
Education < high school, %	16.09	19.35	0.178	30.86	26.39	0.225
Current smoking, %	11.97	10.89	0.611	10.94	14.40	0.207
Physical activity category						
Ideal	46.20	50.81	0.241	55.08	56.23	0.950
Intermediate	32.90	32.26		28.91	28.53	
Poor	20.89	16.94		16.02	15.24	
Alcohol use, %						
Non-drinker	61.87	66.53	0.256	73.83	75.07	0.270
Moderate drinker	34.34	31.05		24.22	24.38	

Heavy drinker	3.79	2.42		1.95	0.55	
Diabetes, %	18.36	27.53	<0.001	26.29	33.52	0.057
eGFR <60 ml/min/m^2, %	5.82	9.72	0.013	16.87	17.18	0.919
HDL cholesterol, mg/dL	51.87 (14.49)	48.43 (12.93)	<0.001	54.51 (15.71)	53.21 (15.05)	0.325
Total cholesterol, mg/dL	199.30 (39.10)	197.90 (43.00)	0.627	204.00 (42.18)	201.30 (42.57)	0.458
SBP, mmHg	125.50 (15.17)	119.80 (15.10)	<0.001	141.00 (19.45)	132.00 (18.82)	<0.001
DBP, mmHg	75.81 (8.35)	73.38 (8.71)	<0.001	77.42 (8.70)	75.57 (10.54)	0.018
Pulse Pressure, mmHg	49.72 (13.04)	46.38 (12.37)	<0.001	63.61 (18.53)	56.42 (15.04)	<0.001
Prevalent hypertension, %	49.46	59.84	0.002	84.96	78.20	0.039
Antihypertensive medication use, %	42.81	56.15	<0.001	70.00	71.80	0.633
Number of antihypertensive medication classes						
0	56.53	43.15	<0.001	30.47	30.19	0.330
1	18.07	18.95		25.00	20.78	

2	16.91	24.60		22.27	28.25	
3+	8.49	13.31		22.27	20.78	
LVM, g	136.40 (28.79)	173.10 (32.59)	<0.001	189.30 (34.27)	228.30 (53.27)	<0.001
LVMI, g/m$^{2.7}$	32.80 (5.94)	40.43 (4.23)	<0.001	51.42 (7.06)	58.06 (10.72)	<0.001
Mean ejection fraction, %	62.01 (6.76)	60.22 (7.75)	<0.001	64.32 (7.70)	60.42 (10.16)	<0.001
Ejection fraction ≤ 40%, %	0.23	1.22	0.030	0.78	4.46	0.007
Stroke work, g-m	134.00 (32.02)	109.30 (23.90)	<0.001	188.80 (38.90)	150.10 (39.61)	<0.001
Stroke volume, mL	74.14 (15.08)	63.99 (14.26)	<0.001	93.11 (17.93)	79.22 (18.81)	<0.001
Fractional shortening, %	3.38	18.84	<0.001	4.38	16.39	<0.001
Interventricular septum thickness in diastole, cm	0.85 (0.11)	1.03 (0.14)	<0.001	0.98 (0.12)	1.13 (0.16)	<0.001
Posterior wall thickness in diastole, cm	0.81 (0.11)	0.97 (0.13)	<0.001	0.93 (0.11)	1.07 (0.15)	<0.001
RWT	0.35 (0.06)	0.43 (0.07)	<0.001	0.37 (0.07)	0.44 (0.10)	<0.001

Left ventricular end-diastolic diameter, cm	4.79 (0.40)	4.73 (0.43)	0.024	5.21 (0.45)	5.12 (0.63)	0.046
Left ventricular end-systolic diameter, cm	2.93 (0.41)	3.16 (0.50)	<0.001	3.06 (0.50)	3.31 (0.78)	<0.001
Eccentric Hypertrophy, %	--	--	---	83.20	43.21	<0.001
Concentric Hypertrophy, %	--	--	---	16.80	56.79	<0.001

The numbers in the table are mean ± standard deviation or percentages.
*p-value comparing aLVM and iLVM

Left Ventricular Hypertrophy (LVH) is defined as LVM index (LVMI) ≥45 g/$m^{2.7}$ in females and ≥49 g/$m^{2.7}$ in males
LVMI is calculated as LVM/$height^{2.7}$
Relative wall thickness (RWT) was calculated using the American Society of Echocardiography formula; RWT = 2 x posterior wall thickness in diastole/left ventricular internal dimension in diastole.
Increased RWT is defined as RWT >0.42. Normal RWT is defined as RWT ≤0.42
Eccentric Hypertrophy is defined as: LVH and normal Relative wall thickness
Concentric Hypertrophy is defined as: LVH and increased Relative wall thickness

aLVM: Appropriate left ventricular mass
iLVM: Inappropriate left ventricular mass
eGFR: Estimated glomerular filtration rate
HDL: High-density lipoprotein
SBP: Systolic blood pressure
DBP: Diastolic blood pressure
LVM: Left ventricular mass

Table S4. Hazard ratios for cardiovascular disease events associated with an observed-to-predicted LVM ratio, modeled as a continuous variable, in the overall analytic sample and among participants without and with left ventricular hypertrophy.

	Hazard Ratios (95% CI) per one SD higher observed-to-predicted LVM ratio			
CVD events / n at risk	**Model 1**	**Model 2**	**Model 3**	**Model 4**
		Overall (N=4,424)		
262 / 4424	1.35 (1.25 – 1.45)	1.29 (1.19 – 1.40)	1.31 (1.21 – 1.42)	1.28 (1.16 – 1.43)
		Without LVH (N=3,807)		
184 / 3807	1.64 (1.37 – 1.96)	1.52 (1.28 – 1.82)	1.60 (1.34 – 1.91)	#
		With LVH (N=617)		
78 / 617	1.11 (0.96 – 1.29)	1.05 (0.90 – 1.23)	1.16 (0.99 – 1.37)	#

CVD: Cardiovascular disease
CI: Confidence Interval
LVM: Left ventricular mass
SD: Standard deviation. 1 SD = 0.235 = 23.5%
LVH: Left ventricular hypertrophy
Model 1: Adjusted for age, sex, and body mass index
Model 2: Adjusted for the variables in Model 1 and diabetes, estimated glomerular filtration rate < 60 ml/min/1.73m^2, education level (less than high school), current smoking, physical activity, and alcohol use (none, moderate, heavy)
Model 3: Adjusted for the variables in Model 2 and mean systolic blood pressure, mean diastolic blood pressure, and antihypertensive medication use
Model 4: Adjusted for the variables in Model 3 and left ventricular hypertrophy
Model 4 was not performed as these analyses are stratified by left ventricular hypertrophy status
The test for interaction between LVH and iLVM for CVD events had a $P_{interaction} = 0.004$ (on Model 4)

Table S5. Hazard ratios for all-cause mortality associated with observed-to-predicted LVM ratio, modeled as a continuous variable in the overall analytic sample and among participants without and with left ventricular hypertrophy.

	Hazard Ratios (95% CI) per one SD higher observed-to-predicted LVM ratio			
Deaths / n at risk	**Model 1**	**Model 2**	**Model 3**	**Model 4**
		Overall (N=4,424)		
419 / 4424	1.26 (1.18 – 1.35)	1.21 (1.13 – 1.30)	1.24 (1.15 – 1.33)	1.18 (1.08 – 1.29)
		Without LVH (N=3,807)		
288 / 3807	1.12 (0.95 – 1.31)	1.06 (0.90 – 1.24)	1.14 (0.97 – 1.34)	#
		With LVH (N=617)		
131 / 617	1.17 (1.05 – 1.30)	1.12 (1.00 – 1.25)	1.17 (1.05 – 1.32)	#

CI: Confidence Interval
LVM: Left ventricular mass
SD: Standard deviation. 1 SD = 0.235 = 23.5%
LVH: Left ventricular hypertrophy

Model 1: Adjusted for age, sex, and body mass index
Model 2: Adjusted for the variables in Model 1 and diabetes, estimated glomerular filtration rate < 60 ml/min/1.73m^2, education level (less than high school), current smoking, physical activity, and alcohol use (none, moderate, heavy)
Model 3: Adjusted for the variables in Model 2 and mean systolic blood pressure, mean diastolic blood pressure, and antihypertensive medication use
Model 4: Adjusted for the variables in Model 3 and left ventricular hypertrophy
Model 4 was not performed as these analyses are stratified by left ventricular hypertrophy status

The test for interaction between LVH and iLVM for all-cause mortality had a $P_{interaction}$ =0.534 (on Model 4)

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