American Journal of Preventive Cardiology 20 (2024) 100889

Contents lists available at ScienceDirect

American Journal of Preventive Cardiology

journal homepage: www.journals.elsevier.com/american-journal-of-preventive-cardiology

Short Report

Latent class analysis of cardiac structure and function and association with premature cardiovascular disease: The Coronary Artery Risk Development in Young Adults (CARDIA) study

Michael C. Wang [a], Toluwalase Awoyemi [b], Norrina B. Allen [c], Ravi Shah [d], Matthew Nayor [e], Yuan Luo [c], Joao A.C. Lima [f], Donald M. Lloyd-Jones [c,g], Sadiya S. Khan [c,g,*]

[a] Department of Medicine, Perelman School of Medicine at the University of Pennsylvania, Philadelphia, PA, United States
[b] Department of Medicine, Northwestern University, Feinberg School of Medicine, Chicago, IL, United States
[c] Department of Preventive Medicine, Northwestern University Feinberg School of Medicine, Chicago, IL, United States
[d] Division of Cardiology, Vanderbilt University Medical Center, Nashville, TN, United States
[e] Division of Cardiology, Boston University School of Medicine, Boston, MA, United States
[f] Division of Cardiology, Johns Hopkins University School of Medicine, Baltimore, MD, United States
[g] Division of Cardiology, Northwestern University Feinberg School of Medicine, Chicago, IL, United States

ARTICLE INFO

Keywords:
Echocardiogram
Latent class analysis
Phenogroup
Cardiovascular disease

ABSTRACT

Objective: To generate data-driven phenogroups of cardiac structure and function based on echocardiographic measures assessed in asymptomatic middle-aged adults free of CVD, and examine associations between these newly defined phenogroups and incident premature cardiovascular disease (CVD).

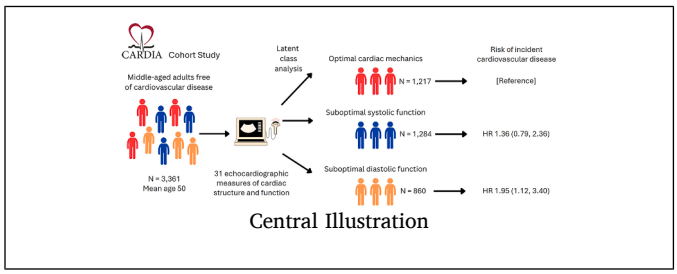
Methods: Data were analyzed from participants in the Coronary Artery Risk Development in Young Adults (CARDIA) cohort study free of CVD who underwent an echocardiogram at the Year 25 (2010-2011) in-person examination. Continuous echocardiographic measures of left heart structure, left ventricular systolic function (including strain) and diastolic function, right ventricular systolic function, and hemodynamic measures were included in latent class analysis to generate novel phenogroups. Associations between data-driven phenogroups and risk of premature CVD (coronary artery disease, stroke, or heart failure) were estimated using Cox proportional hazards regression adjusted for traditional CVD risk factors.

Results: Among 3361 participants, mean (standard deviation) age was 50.1 (3.6) years, 57% were female, and 46% were non-Hispanic Black. Three overall phenogroups were identified and labeled as: (1) optimal cardiac mechanics (36.2%); (2) suboptimal systolic function (38.2%); and (3) suboptimal diastolic function (25.6%). Over a median 8.9 years of follow-up, 121 premature CVD events occurred. Risk of CVD was higher in the suboptimal diastolic function group (unadjusted hazard ratio [HR] 4.08 [95% CI: 2.48, 6.71] and adjusted HR 1.95 [1.12, 3.40]) compared with the optimal group. The suboptimal systolic function group had a higher unadjusted risk of CVD (1.86 [1.10, 3.15]), which was attenuated after adjustment for CVD risk factors (1.36 [0.79, 2.36]).

Conclusions and relevance: Unbiased, data-driven clustering of echocardiographic measures in middle-aged adults identified distinct patterns of cardiac remodeling that were associated with risk of premature CVD. Premature CVD risk was highest with the pattern of suboptimal diastolic function. This suggests potential utility of a composite echocardiography-based index for prioritizing prevention strategies earlier in the life course.

* Corresponding author at: Division of Cardiology, Department of Medicine and Preventive Medicine, Northwestern University Feinberg School of Medicine, 680 N. Lake Shore Drive Ste, 1400, Chicago, IL 60611, United States.
E-mail address: s-khan-1@northwestern.edu (S.S. Khan).

https://doi.org/10.1016/j.ajpc.2024.100889
Received 19 June 2024; Received in revised form 24 October 2024; Accepted 5 November 2024
Available online 15 November 2024



Central Illustration

1. Introduction

Alterations in cardiac structure and function are well described with aging [1], and asymptomatic changes in certain echocardiographic measures, such as left ventricular size, left atrial size, and global longitudinal strain, are associated with higher risk of incident cardiovascular disease (CVD) [2–5]. However, a comprehensive echocardiogram may report more than forty measures that may provide diverse perspectives on remodeling and risk, but the interpretability and clinical relevance of an integrated profile of echocardiographic measures is unknown.

Statistical analytic methods, such as model-based latent class analysis (LCA) [6], can discover underlying patterns in complex data and are well-suited to identify distinct clusters or novel phenogroups, such as from a large number of echocardiographic parameters. These methods have previously been used to integrate clinical and imaging data to characterize phenogroups among symptomatic patients with HF with preserved ejection fraction [7], but phenogroups for risk based on subclinical changes in cardiac structure and function and their clinical implications are less well characterized.

Therefore, we applied LCA to generate distinct phenogroups based on echocardiographic measures assessed in asymptomatic middle-aged adults and examined whether the resulting novel phenogroups were associated with incident premature CVD.

2. Methods

2.1. Data source

We used data from participants in the Coronary Artery Risk Development in Young Adults (CARDIA) study, a cohort study of cardiovascular health and disease [8]. In brief, CARDIA enrolled 5,115 self-identified Black and White adults aged 18-30 years from Birmingham, AL; Chicago, IL; Minneapolis, MN; and Oakland, CA in 1985-1986. Participants underwent detailed in-person examinations approximately every 2-5 years, including an echocardiogram at the Year 25 examination (2010-2011). The CARDIA study was approved by Institutional Review Boards (IRBs) at each study site, and all participants gave written informed consent at each examination. This secondary analysis of de-identified CARDIA data was covered under the Northwestern University IRB approval of CARDIA.

2.2. Study population

We included CARDIA participants without CVD who underwent an echocardiogram at the Year 25 (2010-2011) visit. The final analytic sample contained 3361 participants **(eFig. 1)**. All baseline data were collected at Year 25.

2.3. Exposures

Continuous echocardiographic measures (**eTable 1** and Fig. 1) were eligible for inclusion in the analysis and included variables representing left heart structure, left ventricular systolic function (including strain)

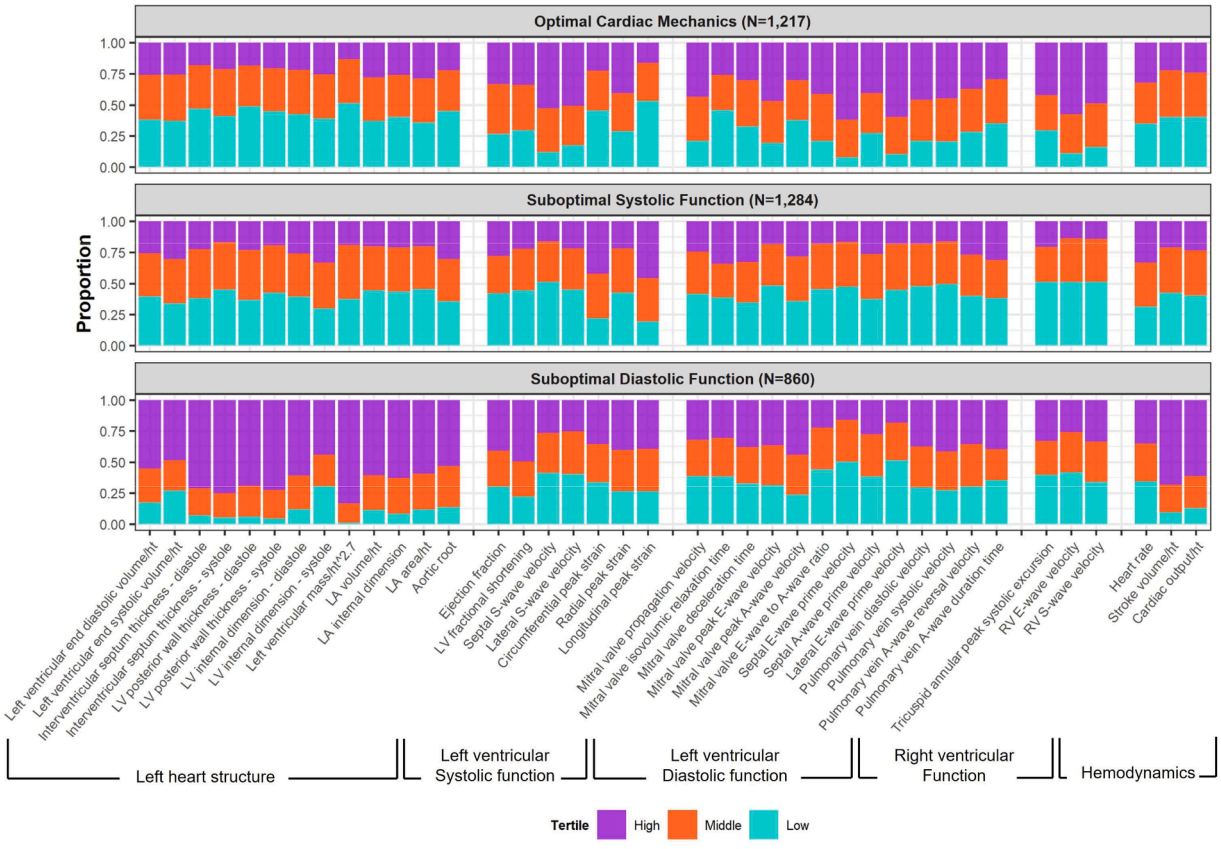


Fig. 1. Latent classes of cardiac structure and function among CARDIA participants.

and diastolic function, right ventricular systolic function, and hemodynamic measures [9].

2.4. Outcomes

The primary outcome was incident CVD (fatal or nonfatal coronary heart disease, stroke, or heart failure) occurring after exam Y25 through May 2021. Coronary heart disease events comprised acute coronary syndrome events (as opposed to purely radiographic or subclinical atherosclerosis). Stroke events included both ischemic and hemorrhagic strokes. Heart failure events comprised acute decompensated heart failure events regardless of left ventricular ejection fraction. Events were ascertained through annual telephone interviews with participants and National Death Index queries for vital status and adjudicated by the CARDIA endpoints committee using medical record review [10]. Since all events occurred at <65 years, we considered them premature. Prior studies have observed associations with echocardiographic measures across all CVD subtypes, supporting use of a composite CVD outcome [3–5]. Secondary outcomes included subtypes of CVD.

2.5. Covariates

Covariates used for adjustment comprised demographics (age, sex), social determinants of health (self-reported race, education), and clinical characteristics (body mass index, smoking, systolic blood pressure, hypertension medication, fasting glucose, diabetes medication, total cholesterol, high-density lipoprotein cholesterol, and cholesterol medication) [8]. Covariates were selected for clinical relevance based on known associations with CVD and included all variables used in the Pooled Cohort Equations [11] in addition to cholesterol treatment.

2.6. Statistical analysis

Echocardiographic measures (**eTable 1** and Fig. 1) were indexed to participant height if appropriate, as in previous CARDIA analyses [1, 12], and standardized to mean 0 and standard deviation 1. Right ventricular systolic pressure was excluded given the high degree of missingness (62%); for the remaining measures, missingness ranged from 1% to 12%. Missing data were imputed with the vector-based SVDImpute algorithm in R, and measures were filtered to remove variables with collinearity (defined as pairwise correlations >0.6), consistent with a prior study [7]. Of 40 original echocardiogram measures, 31 were included in the analysis.

We then applied LCA to the 31 standardized, continuous measures to identify distinct phenogroups of cardiac structure and function. The final number of groups was selected based on successful model convergence and minimization of the Bayesian Information Criterion (BIC) (**eTable 2**), resulting in three groups for the final model. We conducted sensitivity analyses leaving out a single measure from each echocardiographic domain to assure high concordance of class allocation (**eTable 3**). We summarized baseline characteristics of CARDIA participants in each phenogroup. We then examined the association between phenogroups and risk of incident CVD with Cox propotional hazards regression adjusted for demographic and traditional CVD risk factors. For reference, associations between known meaningful echocardiographic measures (longitudinal peak strain and septal E/e' ratio) and incident CVD were also computed. Analyses were conducted using Stata Version 15.1 (College Station, TX) and R Version 4.0. A two-sided p-value <0.05 was considered statistically significant.

3. Results

3.1. Cardiac structure and function phenogroups

The three data-driven phenogroups of cardiac structure and function were designated as "optimal cardiac mechanics," "suboptimal systolic function", and "suboptimal diastolic function," and echocardiographic measures stratified by phenogroup were plotted as tertiles of the overall analytic sample (Fig. 1). The "suboptimal systolic function" group had generally lower measures of both left and right ventricular systolic and diastolic function. The "suboptimal diastolic function" group had lower measures of left ventricular diastolic function, as well as the highest left heart volume and mass. Measures of left ventricular systolic function were similar in the "suboptimal diastolic function" and "optimal cardiac mechanics" groups.

3.2. Baseline characteristics by phenogroup

Of 3,361 participants, mean age was 50.1 (3.6) years in the overall sample and similar when stratified by phenogroup (Table 1). The "optimal cardiac mechanics" group had the highest proportion of women (66.8%) and the lowest proportion of self-reported Black race (37.4%). The "suboptimal diastolic function" group had the highest proportion of participants with unfavorable cardiovascular health metrics, including higher body mass index, and greater prevalence of smoking and medication for hypertension, diabetes, and cholesterol.

3.3. Association between phenogroups and premature CVD

Over a median 8.9 years of follow-up, 121 premature CVD events occurred, including 21 (1.7%) in the "optimal cardiac mechanics" group, 41 (3.2%) in the "suboptimal systolic function" group, and 59 (6.9%) in the "suboptimal diastolic function" group. Compared with the "optimal cardiac mechanics" group, the unadjusted hazard ratios (95% CI) for incident CVD were 1.86 (1.10, 3.15) in the "suboptimal systolic function" group and 4.08 (2.48, 6.71) in the "suboptimal diastolic function" group. These associations were partially attenuated after adjustment for demographic and traditional CVD risk factors (Table 2). When CVD subtypes were considered as individual outcomes, associations were stronger for stroke and heart failure than coronary heart disease, although confidence intervals were wide (**eTable 4**). Of selected individual measures of systolic (longitudinal peak strain) and diastolic (septal E/e' ratio) function, only the highest tertile of septal E/e' ratio was associated with incident CVD after adjustment (**eTable 5**).

4. Discussion

In a cohort of middle-aged Black and White adults without CVD, LCA of echocardiographic data revealed three distinct phenogroups of

Table 1
Baseline characteristics of CARDIA participants by phenogroup.

Characteristic	Optimal Cardiac Mechanics (N=1,217)	Suboptimal Systolic Function (N=1,284)	Suboptimal Diastolic Function (N=860)
Age, mean (SD)	49.8 (3.6)	50.3 (3.7)	50.3 (3.6)
Female, N (%)	813 (66.8%)	748 (58.3%)	356 (41.4%)
Black, N (%)	455 (37.4%)	609 (47.4%)	489 (56.9%)
Any College, N (%)	1005 (82.8%)	984 (76.9%)	626 (73.2%)
Current Smoking, N (%)	168 (14.0%)	208 (16.5%)	171 (20.2%)
Antihypertensive, N (%)	201 (16.6%)	318 (24.9%)	335 (39.2%)
Fasting glucose (mg/dL), mean (SD)	94.8 (22.7)	99.4 (27.8)	104.4 (30.6)
Diabetes medication, N (%)	36 (3.0%)	95 (7.4%)	96 (11.2%)
Cholesterol medication, N (%)	118 (9.8%)	194 (15.2%)	166 (19.4%)
BMI, mean (SD)	28.1 (6.4)	29.3 (6.5)	34.2 (7.6)
Systolic BP, mean (SD)	114.3 (13.1)	118.0 (14.8)	125.3 (16.8)

BMI: body mass index; BP: blood pressure

Table 2
Association between phenogroup and incident premature cardiovascular disease.

Class	CVD Events, N (%)	Unadjusted HR (95% CI)	Adjusted HR[1] (95% CI)
Optimal Cardiac Mechanics (N=1,217, 36.2%)	21 (1.7)	[Reference]	[Reference]
Suboptimal Systolic Function (N=1,284, 38.2%)	41 (3.2)	1.86 (1.10, 3.15)	1.36 (0.79, 2.36)
Suboptimal Diastolic Function (N=860, 25.6%)	59 (6.9)	4.08 (2.48, 6.71)	1.95 (1.12, 3.40)

[1] Adjusted for age, sex, race, education, BMI, smoking, systolic BP, antihypertensive medication, fasting glucose, diabetes medication, total cholesterol, HDL cholesterol, and cholesterol medication

CVD: cardiovascular disease; HR: hazard ratio

cardiac structure and function: "optimal cardiac mechanics" (the reference group), "suboptimal systolic sunction" (with lower average measures of both systolic and diastolic function), and "suboptimal diastolic function" (with larger hearts and lower average measures of diastolic function). The suboptimal diastolic function group was in turn associated with development of premature CVD, particularly heart failure and stroke events, after adjustment for traditional CVD risk factors.

Whereas prior literature has linked individual echocardiographic indices (e.g., left atrial size) or physiologic patterns (e.g., left ventricular remodeling) to CVD [3,13], our analysis extends prior findings by integrating echocardiographic measures across multiple domains to generate unbiased, data-driven clusters of cardiac structure and function. The phenogroups demonstrated clinical utility through association with incident premature CVD, which included both atherosclerotic CVD and heart failure events, likely through endothelial dysfunction, increased vascular tone, and inflammatory pathways [14]. This suggests potential contributions of many echocardiographic indices for prognostic relevance that are not currently in widespread clinical use. Although *a priori* knowledge was not used to specify phenogroups in this study, further studies may identify meaningful subgroupings of the broad phenogroups in this study, such as through stratifying by left ventricular ejection fraction.

The features of the "suboptimal diastolic function" group identified by our analysis are consistent with that observed in echocardiograms from patients with heart failure with preserved ejection fraction (HFpEF). Both are associated with a high burden of cardiometabolic dysfunction, including prevalent obesity, hypertension, diabetes, and dyslipidemia [15]. In addition, both are characterized by abnormalities in diastolic function with preserved systolic function compared with a reference group of individuals with optimal cardiac mechanics [16]. Patients with HFpEF have also been demonstrated to have an elevated risk of atherosclerotic CVD and stroke, in addition to risk for hospitalization due to decompensated HF [17]. In contrast with prior literature on HFpEF, we focused on individuals free of CVD at the time the echocardiogram was performed to develop subclinical clusters in midlife that may represent a precursor to overt, symptomatic CVD later in life.

The association of suboptimal diastolic function with incident CVD was stronger that than of suboptimal systolic function in this study even though subclinical systolic dysfunction has been known to have a strong association with incident CVD in other studies [18]. This may in part reflect that the "suboptimal systolic function" group includes individuals who would not be considered to have overt systolic dysfunction as defined in other studies, and that the "suboptimal diastolic function" group had a greater degree of left ventricular remodeling which is known to be strongly associated with CVD [2,5]. These results, if validated, may help inform patterns of subclinical echocardiographic changes that represent elevated risk for incident CVD and may be amenable to increased intensity of primary prevention measures.

This study has several limitations. First, given few CVD events occurred, there was limited statistical power to detect differences. Second, results may not be generalizable to other racial and ethnic groups given CARDIA enrolled only Black and White adults. Third, the associations identified in this study do not imply causality between the echocardiographic phenogroups and subsequent CVD. Fourth, although normal ranges of echocardiographic parameters are not currently indexed to sex, lack of stratification by sex may have obscured potential reclassification by sex differences that have been identified in prior studies [19]. Fifth, LCA assigns classes by the probability of being in a class based on a participant's phenotypic profile and does not guarantee the external validity of the class; further studies in other cohorts are needed to strengthen the validity of the phenogroups identified in this study.

In conclusion, unbiased, data-driven clustering of echocardiographic measures in middle-aged adults identified distinct patterns of cardiac remodeling that were associated with risk of premature CVD. Premature CVD risk was highest with the pattern of suboptimal diastolic function. This suggests potential utility of a composite echocardiography-based index for prioritizing prevention strategies earlier in the life course.

For each of three phenogroups identified, measures listed on the horizontal axis were grouped into tertiles based on each participant's value relative to the overall sample. Shaded bars represent the proportion of individuals in the designated phenogroup with echocardiographic values within each tertile.

Funding

Supported by grants from the NHLBI (HL159250) to SSK.

The Coronary Artery Risk Development in Young Adults Study (CARDIA) is conducted and supported by the National Heart, Lung, and Blood Institute (NHLBI) in collaboration with the University of Alabama at Birmingham (75N92023D00002 & 75N92023D00005), Northwestern University (75N92023D00004), University of Minnesota (75N92023D00006), and Kaiser Foundation Research Institute (75N92023D00003). This manuscript has been reviewed by CARDIA for scientific content.

CRediT authorship contribution statement

Michael C. Wang: Formal analysis, Writing – original draft. **Toluwalase Awoyemi:** Writing – review & editing. **Norrina B. Allen:** Writing – review & editing. **Ravi Shah:** Writing – review & editing. **Matthew Nayor:** Writing – review & editing. **Yuan Luo:** Writing – review & editing. **Joao A.C. Lima:** Writing – review & editing. **Donald M. Lloyd-Jones:** Writing – review & editing, Resources. **Sadiya S. Khan:** Writing – original draft, Supervision, Funding acquisition, Data curation, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgments

NHLBI had input into the overall design and conduct of the CARDIA study. The funding sponsors did not contribute to analysis or interpretation of the data or preparation, review, or approval of the manuscript. The authors take responsibility for decision to submit the manuscript for publication. Dr. Khan had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.ajpc.2024.100889.

References

[1] Perak AM, Khan SS, Colangelo LA, et al. Age-related development of cardiac remodeling and dysfunction in young black and white adults: the coronary artery risk development in young adults study. J Am Soc Echocardiogr 2021;34(4):388–400. https://doi.org/10.1016/j.echo.2020.11.002.

[2] Vasan RS, Larson MG, Benjamin EJ, Evans JC, Levy D. Left ventricular dilatation and the risk of congestive heart failure in people without myocardial infarction. N Engl J Med 1997;336(19):1350–5. https://doi.org/10.1056/nejm199705083361903. May 8.

[3] Kizer JR, Bella JN, Palmieri V, et al. Left atrial diameter as an independent predictor of first clinical cardiovascular events in middle-aged and elderly adults: the Strong Heart Study (SHS). Am Heart J 2006;151(2):412–8. https://doi.org/10.1016/j.ahj.2005.04.031. Feb.

[4] Kuznetsova T, Cauwenberghs N, Knez J, et al. Additive prognostic value of left ventricular systolic dysfunction in a population-based cohort. Circ Cardiovasc Imaging 2016;9(7). https://doi.org/10.1161/circimaging.116.004661. Jul.

[5] Lauer MS, Evans JC, Levy D. Prognostic implications of subclinical left ventricular dilatation and systolic dysfunction in men free of overt cardiovascular disease (the Framingham Heart Study). Am J Cardiol 1992;70(13):1180–4. https://doi.org/10.1016/0002-9149(92)90052-z. Nov 1.

[6] Mori M, Krumholz HM, Allore HG. Using latent class analysis to identify hidden clinical phenotypes. JAMA 2020;324(7):700–1. https://doi.org/10.1001/jama.2020.2278.

[7] Shah SJ, Katz DH, Selvaraj S, et al. Phenomapping for novel classification of heart failure with preserved ejection fraction. Circulation 2015;131(3):269–79. https://doi.org/10.1161/CIRCULATIONAHA.114.010637.

[8] Friedman GD, Cutter GR, Donahue RP, et al. CARDIA: study design, recruitment, and some characteristics of the examined subjects. J Clin Epidemiol 1988;41(11):1105–16. https://doi.org/10.1016/0895-4356(88)90080-7.

[9] CARDIA Study. CARDIA study year 25 exam protocol. Accessed July 14, 2022, https://www.cardia.dopm.uab.edu/images/more/CARDIA_Y25_Exam_Protocol_v2012-03-01.pdf.

[10] CARDIA Endpoint events manual of operations. November 6, 2023. https://www.cardia.dopm.uab.edu/images/more/recent/CARDIA_Endpoint_Events_MOO_v03_20_2015.pdf.

[11] Goff D.C., Lloyd-Jones D.M., Bennett G., et al. 2013 ACC/AHA guideline on the assessment of cardiovascular risk. *A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines*. 2014;63(25 Part B):2935-2959. doi:10.1016/j.jacc.2013.11.005.

[12] Desai CS, Ning H, Liu K, et al. Cardiovascular health in young adulthood and association with left ventricular structure and function later in life: the coronary artery risk development in young adults study. J Am Soc Echocardiogr 2015;28(12):1452–61. https://doi.org/10.1016/j.echo.2015.07.026. 2015/12/01.

[13] Cheng S, Fernandes VR, Bluemke DA, McClelland RL, Kronmal RA, Lima JA. Age-related left ventricular remodeling and associated risk for cardiovascular outcomes: the multi-ethnic study of atherosclerosis. Circ Cardiovasc Imaging 2009;2(3):191–8. https://doi.org/10.1161/circimaging.108.819938. May.

[14] Alexander Y, Osto E, Schmidt-Trucksäss A, et al. Endothelial function in cardiovascular medicine: a consensus paper of the European society of cardiology working groups on atherosclerosis and vascular biology, aorta and peripheral vascular diseases, coronary pathophysiology and microcirculation, and thrombosis. Cardiovasc Res 2021;117(1):29–42. https://doi.org/10.1093/cvr/cvaa085. Jan 1.

[15] Redfield MM, Borlaug BA. Heart failure with preserved ejection fraction: a review. JAMA 2023;329(10):827–38. https://doi.org/10.1001/jama.2023.2020. Mar 14.

[16] Mohammed SF, Borlaug BA, Roger VL, et al. Comorbidity and ventricular and vascular structure and function in heart failure with preserved ejection fraction: a community-based study. Circ Heart Fail 2012;5(6):710–9. https://doi.org/10.1161/circheartfailure.112.968594. Nov.

[17] Grigorian-Shamagian L, Otero Raviña F, Abu Assi E, et al. Why and when do patients with heart failure and normal left ventricular ejection fraction die? Analysis of >600 deaths in a community long-term study. Am Heart J 2008;156(6):1184–90. https://doi.org/10.1016/j.ahj.2008.07.011. Dec.

[18] Goldberg LR, Jessup M. Stage B heart failure: management of asymptomatic left ventricular systolic dysfunction. Circulation 2006;113(24):2851–60. https://doi.org/10.1161/circulationaha.105.600437. Jun 20.

[19] Gerdts E, Okin PM, de Simone G, et al. Gender differences in left ventricular structure and function during antihypertensive treatment: the losartan intervention for endpoint reduction in hypertension study. Hypertension 2008;51(4):1109–14. https://doi.org/10.1161/hypertensionaha.107.107474. Apr.