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Twenty-Five–Year Change in Cardiac Structure and Function and Midlife Cognition

The CARDIA Study

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Abstract

Background and Objective

The goal of this work was to determine whether midlife cardiac structure and function and their 25-year change from early to middle adulthood are associated with lower midlife cognition.

Methods

We studied 2,653 participants from the Coronary Artery Risk Development in Young Adults (CARDIA) study (57% women, 46% Black). Echocardiograms were obtained at year 5, 25, and 30 visits (participant mean age 30, 50, and 55 years) to assess left ventricular (LV) mass (LVM), LV systolic function with LV ejection fraction (LVEF), and LV diastolic function with left atrial volume (LAV) and early peak mitral velocity (E)/early peak mitral annular velocity (e') ratio. LVM and LAV were indexed to body surface area (LVMi and LAVi). At year 30, 5 cognitive domains were measured: global cognition, processing speed, executive function, delayed verbal memory, and verbal fluency. We investigated the association between midlife (year 30) and 25-year change in cardiac structure and function on midlife cognition using linear regressions.

Results

Over 25 years, LVMi and LAVi increased with mean change (SD) per year of 0.27 (0.28) g/m^2 and 0.42 (0.15) mL/m^2, while LVEF decreased by 0.11% (0.02%). After adjustment for demographics and education, 25-year increase (≥1 SD) in LVMi was associated with lower cognition on most tests ($p \leq 0.02$); 25-year increase in LAVi was associated with lower global cognition ($p = 0.04$), but 25-year decrease in LVEF was not associated with cognition. Further adjustment for cardiovascular risk factors led to similar results. In addition, unlike year 30 E/e' ratio and LVEF, higher year 30 LVMi and LAVi were significantly associated with worse cognition on most cognitive tests.

Discussion

Midlife cardiac structure and its change from early to middle adulthood are associated with lower midlife cognition even after accounting for confounders. Unlike systolic function, midlife LV diastolic function and its 25-year change were also linked to cognition. Our results provide information linking early to midlife cardiac structure and function to cognition.

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Go to Neurology.org/N for full disclosures. Funding information and disclosures deemed relevant by the authors, if any, are provided at the end of the article.

Glossary

AFib = atrial fibrillation; **AV** = arterial-ventricular; **BP** = blood pressure; **CARDIA** = Coronary Artery Risk Development in Young Adults; **CHD** = coronary heart disease; **CHF** = congestive heart failure; **DSST** = Digit Symbol Substitution Test; **LAV** = left atrial volume; **LAVi** = LAV indexed to body surface area; **LV** = left ventricular; **LVEF** = LV ejection fraction; **LVM** = LV mass; **LVMi** = LVM indexed to body surface area; **MESA** = Multi-Ethnic Study of Atherosclerosis; **MoCA** = Montreal Cognitive Assessment; **RAVLT** = Rey Auditory Verbal Learning Test.

Cardiovascular risk factors have been associated with greater risk of cognitive impairment.[1] Much less is known about the association between cardiac structure and function, often a marker of cumulative cardiac health, and cognitive function, particularly at middle age. Echocardiography, a widely available and noninvasive imaging method, provides quantitative measures of cardiac structure and function, with several parameters such as left ventricular (LV) mass (LVM), LV ejection fraction (LVEF), left atrial volume (LAV), and early peak mitral velocity (E)/early peak mitral annular velocity (e') ratio.

An association between subclinical abnormalities in cardiac structure,[2-4] systolic function,[5,6] diastolic function,[7,8] and lower cognition has been suggested previously, especially in older adults; however, the results are conflicting.[7,9-12] Inconsistencies may be explained by selection of study populations with end-stage heart disease and possibly confounding by cardiovascular risk factors. Moreover, it is unclear whether subclinical abnormalities in cardiac structure and function as early as young adulthood affect brain health. These abnormalities are common and largely underdiagnosed; therefore, the question of whether altered cardiac structure and function could be a risk factor for cognitive impairment has major public health implications and could reveal another important heart-brain connection.

The Coronary Artery Risk Development in Young Adults (CARDIA) study,[13] a community-based prospective cohort study, provides a unique opportunity to explore these relationships over the early adult lifespan. Thus, the aim of our study is to determine whether (1) 25-year change from early to middle adulthood and (2) midlife cardiac structure and function are associated with lower midlife cognition.

Methods

Study Population

The CARDIA study is a multicenter, population-based, longitudinal cohort study with the aim of assessing the development and trajectories of cardiovascular risk factors and disease starting as early as in young adulthood. 5,115 healthy Black and White men and women 18 to 30 years of age were recruited from March 1, 1985, to June 30, 1986, from 4 cities in the United States (Birmingham, AL; Chicago, IL; Minneapolis, MN; and Oakland, CA). After inclusion, participants were followed up at years 2, 5, 7, 10, and every 5 years thereafter until the year 30 examination (71% participation). The study design and methods have been described previously.[13] After exclusion of individuals who did not attend year 5 clinical examination (n = 764), who had missing values or poor image quality for echocardiographic assessments (see below) at years 5, 25, and 30 (n = 1,209), and who did not have at least 1 cognitive test at year 30 (n = 489), our analytic cohort included 2,653 CARDIA participants. Participants who were excluded from the analytic cohort were younger, had a lower education level, and were more likely to be Black, male, and smokers and to have hypertension, diabetes, and obesity ($p < 0.001$).

Standard Protocol Approvals, Registrations, and Patient Consents

Data collection and follow-up protocols were approved by the institutional review boards of each field center. All participants gave and signed an informed consent. This study was conducted in compliance with the principles of the Declaration of Helsinki.

Data Availability

The data underlying this article will be shared on reasonable request.

Echocardiographic Assessment

All participants underwent 2-dimensional guided M-mode echocardiography at years 5, 25, and 30. Standardized protocols were used across all field centers. Sonographers had centralized training, and both intrasonographer reliability and intersonographer reliability were assessed throughout the examinations.[14] At year 5, echocardiographic assessment was made with an ACUSON cardiac ultrasound system (Siemens, Erlangen, Germany) with images read at the University of California, Irvine reading center.[15] At years 25 and 30, an ARTIDA cardiac ultrasound scanner (Toshiba Medical Systems, Otawara, Japan) was used, with images read at the Johns Hopkins University reading center.[16] Image quality was defined as poor, fair, good, or excellent.[14] We studied 4 echocardiographic parameters: cardiac structure with LVM and LAV, LV systolic function with LVEF, LV diastolic function with LAV, and E/e' ratio. LVM was derived from M-mode measurements with the Devereux formula.[17] LVEF and LAV were measured from the 2-dimensional echocardiographic apical 4-chamber view according to the American Society of Echocardiography guidelines.[17] LVM and LAV were indexed to body surface area (LVMi and LAVi). At year 30, peak velocities from the early phase of the mitral inflow (E) were

measured with pulsed Doppler echocardiography recordings of transmitral flow. Early peak diastolic mitral annular velocity (e') was measured at the septal and lateral mitral annulus with tissue Doppler imaging[18] and calculated from the average of the septal and lateral mitral annulus. E/e' ratio, which was available only at year 30, was used to assess LV filling pressure.[19]

Cognitive Assessment

Cognitive function was assessed at year 30 by trained CARDIA technicians using 6 standardized tests: (1) the Montreal Cognitive Assessment (MoCA) assessing global cognition (attention, executive function, memory, language, visuospatial skills, calculation and orientation), with higher scores indicating better performance[20]; (2) the Digit Symbol Substitution Test (DSST) measuring processing speed, with higher scores for digits correctly substituted indicating better performance[21]; (3) the Stroop Test, assessing executive function (participants are asked to name the color a word indicates instead of the color of the ink of the word), with lower scores indicating better performance[22]; (4) the Rey Auditory Verbal Learning Test (RAVLT) evaluating verbal learning and memory (participants are required to recall after 10 minutes as many words as possible from a list previously heard), with higher scores indicating better performance[23]; and (5) the letter and (6) category fluency tests assessing verbal production, semantic memory, phonemic fluency, and language each over 1 minute, with higher score (combining both) indicating better performance.[24] We computed standardized z scores for each cognitive test by dividing the score by the within-CARDIA SD and subtracting the mean. A composite cognitive z score across all domains was also created.[25] The 5 cognitive z scores were weighted equally.

Covariates

Age, sex, race, and education (number of years) were collected at baseline. A total score of physical activity was computed that was based on both self-reported frequency and intensity of 13 activities during the past year.[26] Current alcohol use (converted to milliliters per day) was self-reported, as well as smoking (current smoker vs current nonsmoker). Depression was defined as a score ≥16 on the Center for Epidemiologic Studies Depression Scale.[27] *APOE* ε4 was measured in year 7 blood samples.[28] Hypertension was defined at baseline as systolic blood pressure (BP) ≥140 mm Hg, diastolic BP ≥90 mm Hg, or current use of antihypertensive medication. We also expanded this measure by computing both hypertension presence at each examination (ever present vs never) and cumulative duration of hypertension over 25 years (number of years from baseline at years 5 through 30).[29] Diabetes was defined at baseline as fasting plasma glucose ≥126 mg/dL, insulin or oral hypoglycemic agent use, glucose tolerance test ≥200 mg/dL, or glycated hemoglobin ≥6.5%.[19] Obesity was defined at baseline as body mass index ≥30 kg/m^2. Cardiovascular comorbid conditions (congestive heart failure [CHF], coronary heart disease [CHD], atrial fibrillation [AFib], and TIA/stroke) were based on adjudicated endpoints.[30]

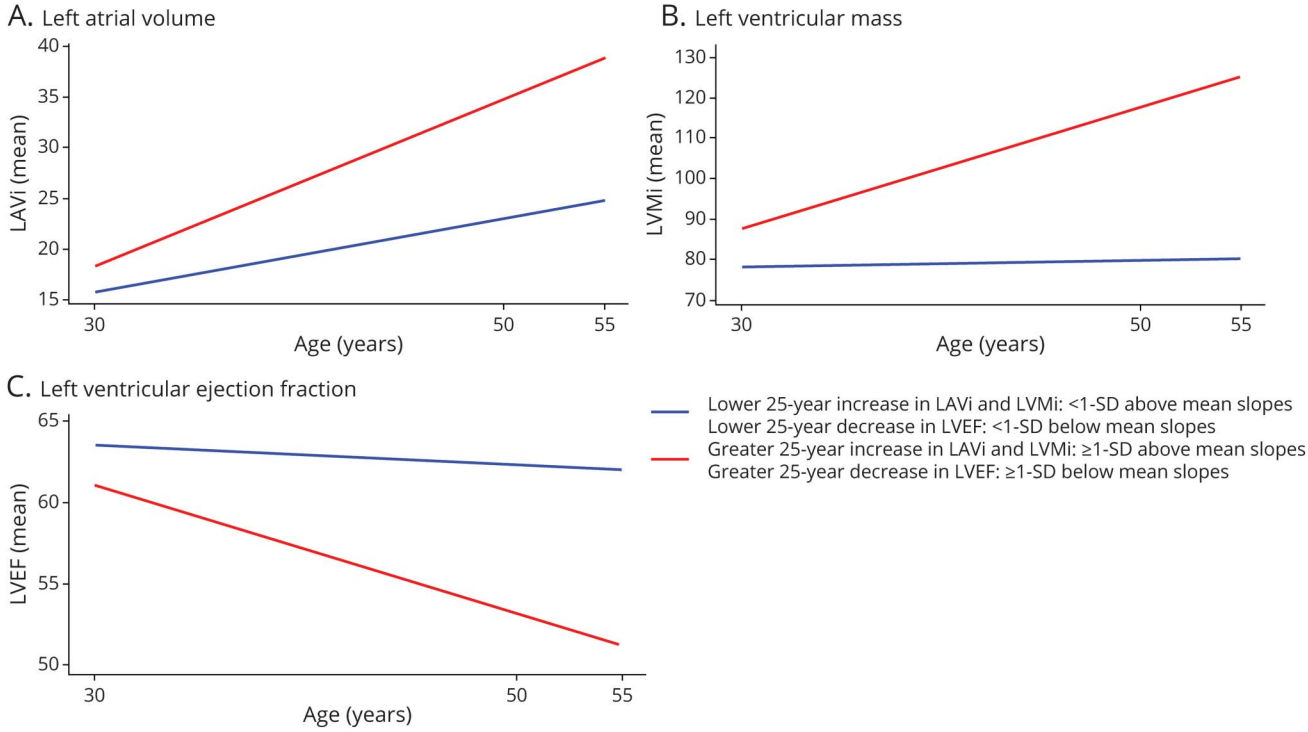
Statistical Analysis

Baseline characteristics of the participants are displayed as mean ± SD for continuous variables and numbers (proportions) for categorical variables, and comparisons between groups were conducted with the Student, Fisher exact, and χ^2 tests as appropriate. We determined echocardiographic groups by 25-year change in 3 parameters: LVMi, LAVi, or LVEF. We estimated 25-year change (years 5, 25, and 30) by the participant-specific slopes for each echocardiographic parameter using linear mixed models with random intercepts and slopes. We then categorized participants into groups by change in their predicted slopes: greater 25-year increase (≥1 SD above the mean slope) in LVMi and LAVi and greater 25-year decrease (≥1-SD below the mean slope) in LVEF. Figure 1 shows 25-year change in echocardiographic parameters (slope for each parameter) according to echocardiographic group. Higher midlife year 30 LVMi, LAVi, and E/e' ratio (≥1 SD above the mean) and lower year 30 LVEF (≥1 SD below the mean) were also analyzed. We then used linear regression models to investigate the association of (1) 25-year change and (2) midlife (year 30) cardiac structure and function on midlife (year 30) cognition. Results were presented as mean (SE) cognitive scores. Multivariable models were adjusted progressively for demographics and education (model 1) and hypertension, diabetes, smoking, and obesity (model 2). Additional model adjustment for CHF, CHD, AFib, and TIA/stroke was then conducted. Interactions with sex and race were checked. A heat map of Pearson correlation coefficient matrix was used for graphical representation of the association between midlife (year 30) cardiac structure and function and midlife cognition. We also conducted sensitivity analyses by (1) taking into account the entire range of the distribution of cardiac structure and function as linear variables and (2) expanding our full model by accounting for both hypertension presence and cumulative duration of hypertension over 25 years.[29] All statistical tests were 2 sided and were performed at the 0.05 level of significance with SAS software, version 9.4 (SAS Institute Inc, Cary, NC).

Results

In our analytic cohort of 2,653 CARDIA participants, mean baseline age was 30.1 (3.5) years, 1,523 (57.4%) were female, and 1,213 (45.7%) were Black. Over 25 years, LVMi and LAVi increased with mean change (SD) per year of 0.27 (0.28) g/m^2 and 0.42 (0.15) mL/m^2, while LVEF decreased with mean change (SD) per year of 0.11% (0.02%) (Table 1). Participants with greater 25-year increase in LVMi (n = 325, 12.6%) were more likely to be male (62.5% vs 39.6%), Black (61.9% vs 43.5%), and less educated and to smoke and drink alcohol (all $p \leq 0.05$). They had significantly more hypertension (61.2% vs 34.0%), diabetes (17.0% vs 11.9%), obesity (58.0% vs 42.3%), CHF, AFib, and TIA/stroke (all $p \leq 0.05$). A similar pattern was found in patients with greater 25-year decrease in LVEF (n = 154, 13.0%). Participants with greater 25-year increase in LAVi (n = 198, 13.3%) were significantly

Figure 1 Twenty-Five–Year Change in Echocardiographic Parameters (Slopes) According to Echocardiographic Group



Echocardiographic groups were determined by change in slope according to 3 echocardiographic parameters from years 5 through 30: left atrial volume (LAVi), left ventricular mass (LVMi), and left ventricular ejection fraction (LVEF), resulting in classifying participants by greater or lower increase (≥1/<1 SD above the mean slope) in LAVi (A) and LVMi (B) and greater or lower decrease (≥1/<1 SD below the mean slope) in LVEF over 25 years (C). Estimated slopes per year, mean (SD) by group: LAVi: ≥1-SD change 0.70 (0.13), <1-SD change 0.38 (0.10), $p < 0.001$; LVMi: ≥1-SD change 0.79 (0.28), <1-SD change 0.18 (0.19), $p < 0.001$; and LVEF: ≥1-SD change −0.14 (0.02), <1-SD change −0.10 (0.01), $p < 0.001$.

more likely to be Black and to have CHF and AFib (all $p < 0.001$) (Table 2).

The 25-Year Change in Cardiac Structure and Function

In unadjusted models (Figure 2 and eTable 1, links.lww.com/WNL/B726), greater 25-year increase in LVMi was associated with lower cognition on all cognitive tests (all $p \leq 0.001$). Greater 25-year increase in LAVi was significantly associated with lower cognition on MoCA, DSST, RAVLT, and verbal fluency (all $p \leq 0.01$). A similar pattern was found with greater 25-year decrease in LVEF on all cognitive tests (all $p \leq 0.01$) except Stroop. Greater 25-year change in all echocardiographic parameters was also associated with lower performance in composite cognitive function (all $p \leq 0.01$). After adjustment for demographics and education (model 1), greater 25-year increase in LVMi was associated with significantly lower cognition on MoCA, DSST, Stroop, and RAVLT (all $p \leq 0.02$). Further adjustment for hypertension, diabetes, smoking, and obesity (model 2) had consistent findings (Table 3). Greater 25-year increase in LAVi was associated only with lower MoCA after adjustment ($p = 0.01$ in model 2). The 25-year decrease in LVEF was no longer associated with cognition in the adjusted models. Additional adjustment for CHF, CHD, AFib, and TIA/stroke did not notably change the results. No interactions were found between 25-year change in echocardiographic

Table 1 Change in Echocardiographic Parameters Over 25 Years From Early to Middle Adulthood

Echocardiographic parameters	Year 5 (mean age 30 y)	Year 25 (mean age 50 y)	Year 30 (mean age 55 y)	Estimated slopes per year, mean (SD)
LVMi (n = 2,581), g/m^2	80.5 (18.9)	85.1 (21.8)	86.0 (22.5)	0.27 (0.28)
LAVi (n = 1,492), mL/m^2	16.0 (4.2)	25.1 (7.2)	26.0 (7.5)	0.42 (0.15)
LVEF (n = 1,188), %	63.3 (11.2)	61.3 (7.2)	59.7 (5.9)	−0.11 (0.02)

Abbreviations: LAVi = left atrial volume; LVEF = left ventricular ejection fraction; LVMi = left ventricular mass.
Twenty-five–year increase in LVMi and LAVi; 25-year decrease in LVEF.

Table 2 Study Population Characteristics According to Echocardiographic Parameters (25-Year Change)

	LVMi (n = 2,581)		LAVi (n = 1,492)		LVEF (n = 1,188)	
Study population characteristics	**Reference (n = 2,256, 87.4%)**	**≥1-SD change[a] (n = 325, 12.6%)**	**Reference (n = 1,294, 86.7%)**	**≥1-SD change[a] (n = 198, 13.3%)**	**Reference (n = 1,034, 87.0%)**	**≥1-SD change[b] (n = 154, 13.0%)**
Baseline age, y	30.1 (3.6)	29.8 (3.6)	29.9 (3.7)	30.2 (3.5)	30.0 (3.6)	29.2 (3.2)[d]
Female, n (%)	1,362 (60.4)	122 (37.5)[c]	719 (55.6)	107 (54.0)	559 (54.1)	48 (31.2)[c]
Black, n (%)	981 (43.5)	201 (61.9)[c]	578 (44.7)	120 (60.6)[c]	480 (46.4)	97 (63.0)[c]
Education, y	14.8 (2.4)	14.0 (2.4)[c]	14.7 (2.5)	14.4 (2.5)	14.7 (2.5)	14.2 (2.5)[d]
Physical activity, units/d	321.1 (263.9)	321.5 (300.8)	332.2 (271.2)	347.0 (300.5)	345.7 (282.9)	360.6 (304.4)
Current smoker, n (%)	266 (11.9)	65 (20.3)[c]	190 (14.8)	25 (13.0)	154 (15.1)	34 (22.7)[e]
Alcohol use, mL/d	10.8 (17.7)	15.5 (26.3)[e]	11.6 (19.1)	11.9 (17.0)	11.7 (18.7)	12.3 (17.1)
Depression, n (%)	365 (16.5)	63 (19.5)	210 (16.6)	30 (15.3)	174 (17.1)	15 (10.1)[e]
***APOE* ε4 allele, n (%)**	621 (30.4)	89 (29.8)	342 (29.0)	55 (30.7)	293 (31.1)	33 (23.9)
Hypertension, n (%)	772 (34.2)	199 (61.2)[c]	460 (35.6)	84 (42.4)	361 (34.9)	71 (46.1)[d]
Diabetes, n (%)	265 (11.9)	55 (17.0)[d]	138 (10.8)	18 (9.2)	94 (9.1)	22 (14.5)[e]
Obesity, n (%)	952 (42.3)	188 (58.0)[c]	513 (39.7)	87 (44.2)	398 (38.6)	68 (44.4)
Congestive heart failure, n (%)	9 (0.4)	12 (3.7)[c]	6 (0.5)	7 (3.5)[c]	2 (0.2)	7 (4.6)[c]
Coronary heart disease, n (%)	39 (1.7)	7 (2.2)	21 (1.6)	3 (1.5)	13 (1.3)	6 (3.9)[e]
Atrial fibrillation, n (%)	16 (0.7)	6 (1.9)[e]	5 (0.4)	8 (4.0) [c]	6 (0.6)	4 (2.6)[e]
TIA/stroke, n (%)	25 (1.1)	12 (3.7)[c]	16 (1.2)	3 (1.5)	11 (1.1)	2 (1.3)

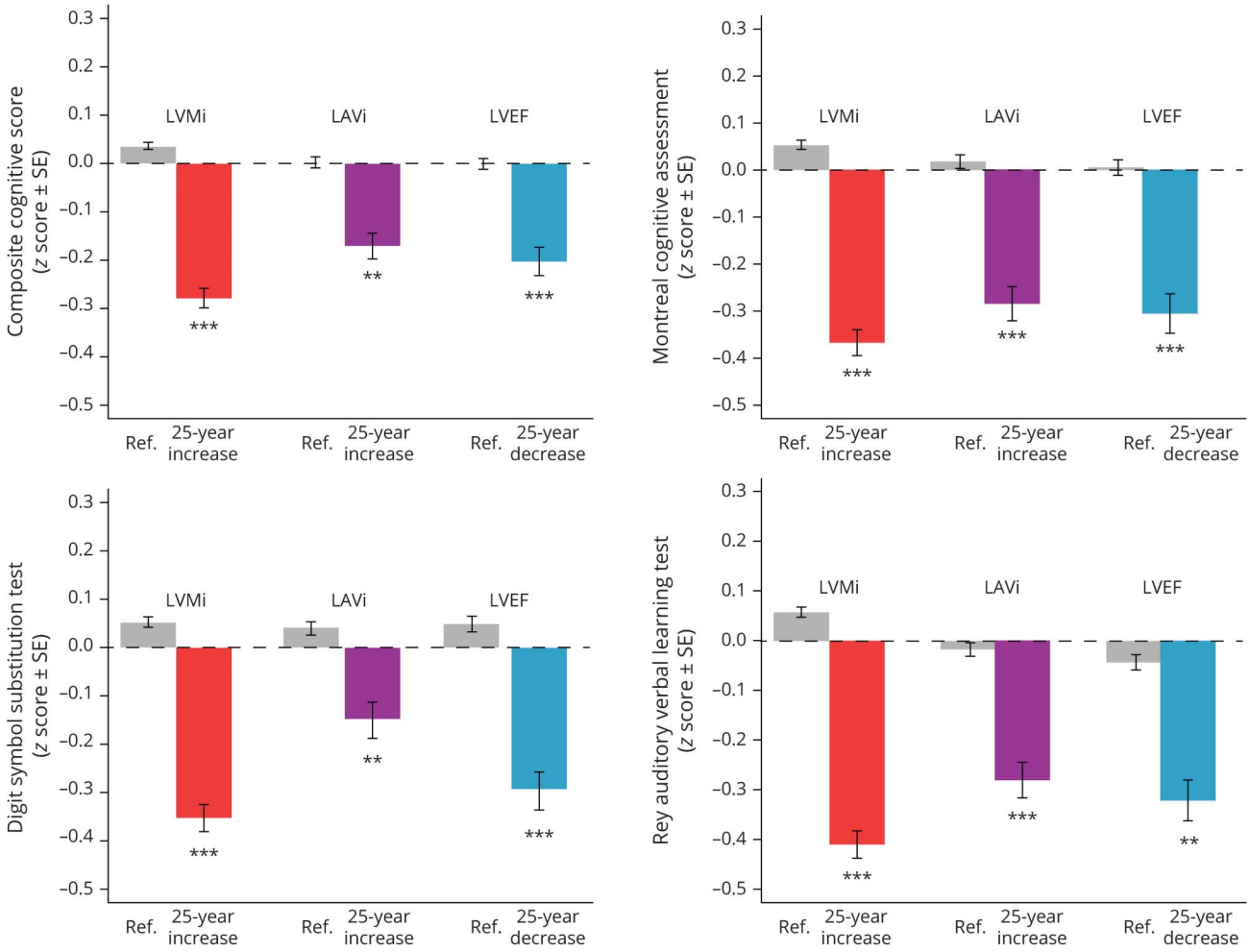
Abbreviations: LAVi = left atrial volume; LVEF = left ventricular ejection fraction; LVMi = left ventricular mass.
Data on physical activity, smoking, alcohol use, depression, hypertension, diabetes, obesity, congestive heart failure, coronary heart disease, atrial fibrillation, TIA/stroke are from the last echocardiographic visit. Values are mean (SD) when appropriate.
[a] Greater 25-year increase (≥1 SD above the mean slopes) in LVMi and LAVi.
[b] Greater 25-year decrease (≥1 SD below the mean slopes) in LVEF.
[c] $p \leq 0.001$.
[d] $p \leq 0.01$.
[e] $p \leq 0.05$.

parameters and sex or race on cognition ($p > 0.1$ for all). A sensitivity analysis in which we expanded our full model by accounting for both hypertension presence and cumulative duration of hypertension over 25 years reported similar results. Greater 25-year increase in LVMi was associated with lower cognition on RAVLT (−0.26 [0.05] vs −0.13 [0.03], $p = 0.01$), MoCA (−0.18 [0.05] vs −0.07 [0.03], $p = 0.03$), and reversed Stroop (−0.19 [0.06] vs −0.08 [0.03], $p = 0.05$). Greater 25-year increase in LAVi was associated with lower cognition on MoCA (−0.22 [0.07] vs −0.08 [0.04], $p = 0.02$). Consistent with previous models, LVEF was not associated with cognition. Sensitivity analyses taking into account the entire range of the distribution of cardiac structure and function as linear variables showed consistent findings in both magnitude and direction (eTable 2, links.lww.com/WNL/B726). Last, when the 3 echocardiographic parameters were examined concurrently, LVMi contributed the most to the change in cognition (model 2: composite cognitive score: greater 25-year increase in LVMi −0.04 [0.01], $p = 0.03$; greater 25-year increase in LAVi −0.01 [0.01], $p = 0.48$; and greater 25-year decrease in LVEF −0.02 [0.01], $p = 0.21$).

Midlife Cardiac Structure and Function

Pearson correlation coefficients (range −0.16 to 0.04) between year 30 cardiac structure and function and midlife cognition are presented in Figure 3. Greater year 30 LVMi was associated with lower performances on all cognitive tests (MoCA score 22.7 [0.2] vs 24.0 [0.1], DSST score 62.3 [0.9] vs 69.1 [0.4], Stroop score 24.9 [0.6] vs 22.4 [0.2], RAVLT score 7.3 [0.2] vs 8.7 [0.1], verbal fluency score 59.5 [0.9] vs 62.7 [0.4]) in unadjusted models ($p \leq 0.001$). The results remained statistically significant after adjustment for demographics and education on MoCA, DSST, and RAVLT scores (all $p \leq 0.05$). Greater year 30 LAVi was significantly associated with lower cognition on all cognitive tests (MoCA score 23.0 [0.2] vs 23.9 [0.1], DSST score 65.4 [0.8] vs 68.3 [0.3], Stroop score 24.1 [0.6] vs 22.5 [0.2], RAVLT score 7.8 [0.2] vs 8.6 [0.1], verbal fluency score 60.1 [0.8] vs 62.6 [0.3]) in unadjusted models ($p \leq 0.01$) and with lower cognition on MoCA and RAVLT after adjustment for demographics and education (all $p \leq 0.01$). Further adjustment for hypertension, diabetes, smoking, and obesity (model 2) did not notably change the results. Last, higher year 30 E/e' ratio and lower

Figure 2 Twenty-Five–Year Change in Cardiac Structure and Function and Midlife Cognition



Unadjusted models. The 25-year increase (≥1 SD above the mean slopes) in left ventricular mass (LVMi) and left atrial volume (LAVi) vs reference (below the mean slopes or <1 SD above the mean slopes). The 25-year decrease (≥1 SD below the mean slopes) in left ventricular ejection fraction (LVEF) vs reference (above the mean slopes or <1 SD below the mean slopes). $^{**}p \leq 0.01$; $^{***}p \leq 0.001$.

year 30 LVEF were associated with lower cognition on most cognitive tests in unadjusted models ($p \leq 0.05$). The results were no longer significant after adjustment.

Discussion

In this large biracial cohort of relatively young adults, midlife cardiac structure and diastolic function and their change from early to middle adulthood were associated with lower cognitive function. These results were independent of demographics, education, smoking, diabetes, hypertension, obesity, and other cardiovascular/cerebrovascular disease. Our findings are of critical importance in the context of identifying potential early markers of increased risk for later-life cognitive decline. They also suggest that the importance of abnormalities in cardiac structure and function and the physiopathology of the heart-brain axis is not limited to patients with advanced heart disease.

Our results are supported by several prior studies in mostly older adults. Altered cardiac structure was associated with worse cognition in the Multi-Ethnic Study of Atherosclerosis (MESA)[3] and in the Framingham Offspring Study[31]; however, the association became nonsignificant after adjustment for BP and cardiovascular risk factors.[31] Consistent with our findings, other studies have shown an association between cardiac dysfunction and lower cognition,[8] especially in patients with heart disease.[32]

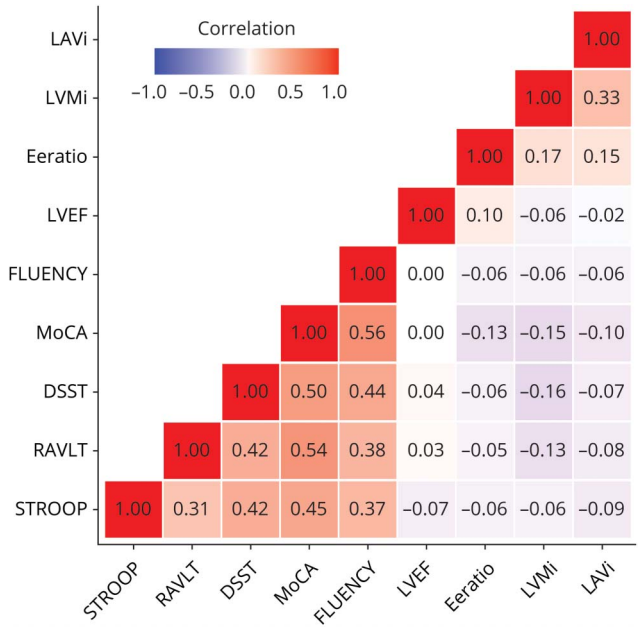
Several hypotheses have been proposed to explain the association between subclinical abnormalities in cardiac structure and function and cognition. Left ventricular hypertrophy reflects chronic exposure to multiple cardiovascular risk factors, including sustained hypertension,[4] that in turn could affect brain function, further highlighting the importance of screening cognition in patients with hypertension.[33] While we adjusted for BP level and results were largely independent, LV structure may be a better cumulative measure of elevated BP. Left

Table 3 Adjusted[a] Association Between 25-Year Change in Cardiac Structure and Function and Midlife Cognitive Function According to Echocardiographic Group

	LVMi group (25-y increase vs reference)					LAVi group (25-y increase vs reference)					LVEF group (25-y decrease vs reference)			
Echocardiographic group by cognitive test	**Mean**	**SE**	**95% CI**	***p* Value**	**Echocardiographic group by cognitive test**	**Mean**	**SE**	**95% CI**	***p* Value**	**Echocardiographic group by cognitive test**	**Mean**	**SE**	**95% CI**	***p* Value**
DSST				0.25	DSST				0.67	DSST				0.31
Reference	−0.18	0.03	(−0.250, −0.124)		Reference	−0.18	0.04	(−0.268, −0.109)		Reference	−0.13	0.04	(−0.220, −0.041)	
≥1-SD change[b]	−0.25	0.05	(−0.359, −0.149)		≥1-SD change[b]	−0.21	0.07	(−0.353, −0.078)		≥1-SD change[c]	−0.20	0.07	(−0.356, −0.055)	
RAVLT				0.01	RAVLT				0.11	RAVLT				0.84
Reference	−0.15	0.03	(−0.216, −0.087)		Reference	−0.20	0.04	(−0.288, −0.124)		Reference	−0.22	0.04	(−0.311, −0.121)	
≥1-SD change[b]	−0.29	0.05	(−0.404, −0.190)		v≥1-SD change[b]	−0.31	0.07	(−0.456, −0.170)		≥1-SD change[c]	−0.20	0.08	(−0.360, −0.041)	
Reversed Stroop				0.03	Reversed Stroop				0.21	Reversed Stroop				0.19
Reference	−0.10	0.03	(−0.174, −0.037)		Reference	−0.18	0.04	(−0.272, −0.098)		Reference	−0.25	0.05	(−0.350, −0.152)	
≥1-SD change[b]	−0.23	0.05	(−0.345, −0.115)		≥1-SD change[b]	−0.09	0.07	(−0.248, 0.054)		≥1-SD change[c]	−0.14	0.08	(−0.312, 0.023)	
MoCA				0.01	MoCA				0.01	MoCA				0.17
Reference	−0.10	0.03	(−0.170, −0.047)		Reference	−0.12	0.04	(−0.204, −0.043)		Reference	−0.11	0.04	(−0.201, −0.018)	
≥1-SD change[b]	−0.24	0.05	(−0.344, −0.141)		≥1-SD change[b]	−0.28	0.07	(−0.426, −0.148)		≥1-SD change[c]	−0.21	0.07	(−0.364, −0.057)	
Verbal fluency				0.87	Verbal fluency				0.65	Verbal fluency				0.52
Reference	−0.06	0.03	(−0.136, 0.001)		Reference	−0.09	0.04	(−0.183, −0.002)		Reference	−0.04	0.05	(−0.148, 0.057)	
≥1-SD change[b]	−0.05	0.05	(−0.172, 0.055)		≥1-SD change[b]	−0.12	0.08	(−0.281, 0.032)		≥1-SD change[c]	−0.10	0.08	(−0.270, 0.073)	
Composite score				0.09	Composite score				0.61	Composite score				0.94
Reference	−0.12	0.02	(−0.166, −0.080)		Reference	−0.15	0.02	(−0.208, −0.098)		Reference	−0.12	0.03	(−0.178, −0.153)	
≥1-SD change[b]	−0.18	0.03	(−0.255, −0.112)		≥1-SD change[b]	−0.17	0.04	(−0.271, −0.081)		≥1-SD change[c]	−0.11	0.05	(−0.216, −0.008)	

Abbreviations: CI = confidence interval; DSST = Digit Symbol Substitution Test; LAVi = left atrial volume; LVEF = left ventricular ejection fraction; LVMi = left ventricular mass; MoCA = Montreal Cognitive Assessment; RAVLT = Rey Auditory Verbal Learning Test; SE = standard error.
For reversed Stroop, lower scores indicate lower cognition.
[a] The *p* values are from linear regression models adjusted for age, race, sex, years of education, hypertension, diabetes, current smoking, and obesity.
[b] Greater 25-year increase (≥1 SD above the mean slopes) in LVMi and LAVi.
[c] Greater 25-year decrease (≥1 SD below the mean slopes) in LVEF.

Figure 3 Heat Map of Midlife (Year 30) Cardiac Structure and Function and Midlife Cognition



Relationship between year 30 cardiac structure and function and midlife cognition was evaluated with Pearson correlation coefficients (reported as Pearson *r*). All measures of cardiac structure and function and cognitive tests are in their original continuous distributions. DSST = Digit Symbol Substitution Test (processing speed); E/e' = early peak mitral velocity/early peak mitral annular velocity ratio; LAVi = left atrial volume; LVEF: left ventricular ejection fraction; LVMi = left ventricular mass; MoCA = Montreal Cognitive Assessment (global cognitive function); RAVLT: Rey Auditory Verbal Learning Test (delayed verbal memory); Stroop (executive function; the reversed Stroop [lower scores indicate lower cognition] test was used in the heat map to allow interpretation of lower cognition on all cognitive tests).

ventricular hypertrophy is associated with both systolic and diastolic LV dysfunction,[34] resulting in systemic hypoperfusion, which could predispose to cerebral ischemia. Consistent with this, LV structure has been found to be associated with cerebral white matter lesions,[35] lacunes,[36] and hippocampal atrophy,[2] which in turn have been associated with cognitive decline[37] and dementia.[38] Greater arterial stiffness, known to increase LV afterload[39] and to be a typical feature of vascular aging associated with both cerebral small vessel disease[40] and cognitive impairment,[41-43] might represent another likely mechanism linking cardiac structure with cognitive function. The pathophysiologic and clinical implications of arterial stiffness should be considered together with LV function. Several possible pathways exist whereby aortic stiffness may contribute to the pathologic changes in the LV, which can be the substrate of diastolic dysfunction.[44] This interplay between cardiac function and arterial system, which is known as arterial-ventricular (AV) coupling, is an expression of global cardiovascular efficiency. Previous findings reported progressive AV uncoupling with aging among healthy individuals free of clinical cardiovascular disease and associations with LV remodeling.[45] Given the associations among arterial stiffness, diastolic dysfunction, and AV uncoupling, it is not surprising that higher LAV was also associated with poorer cognition. Recent findings from CARDIA showed that higher LAV in early adulthood was associated with midlife impairment of white matter integrity.[7] LAV strongly correlates with atrial dysfunction,[46] and white matter lesions may be the result of microembolism or reduced brain perfusion. LAV is also a barometer of LV filling pressure and diastolic dysfunction in subjects without AFib or significant valvular disease.[47] In addition, higher LAV reflects long-term exposure to vascular risk factors, particularly hypertension,[46] and is a predictor of common cardiovascular outcomes such as stroke, CHD, and CHF, which in turn could lead to cognitive impairment.[48] Other possible mechanisms linking LAV to cognition include an adaptive response to endothelial dysfunction[47] and increased levels of atrial natriuretic peptide.[49]

Our study has some limitations that are worth noting. Echocardiograms were performed 25 years apart using slightly different procedures and equipment, which may affect the comparability of the echocardiographic parameters. However, rigorous training and quality control procedures were followed, and the CARDIA echocardiography examinations showed good reproducibility profile.[14] Cognitive scores were standardized on the basis of performances within the CARDIA Study but not according to age, sex, and education-standardized external validated measures. Finally, although LVEF is a common standard of clinical care, it is load dependent, is influenced by heart rate, and may not accurately reflect cardiac contractility as long as AV coupling is maintained or in the presence of hypertrophy.[50] LVEF may be less sensitive than other cardiac measures such as global longitudinal strain at detecting early changes to LV systolic function,[50] and speckle tracking echocardiography was not available earlier in CARDIA. This lack of sensitivity could possibly explain the absence of association between LVEF and midlife cognition in our younger and relatively healthy population. This is consistent with previous findings showing that compromised global longitudinal strain but not LVEF was associated with lower cognitive performances.[50]

Nevertheless, our study has several notable strengths. We were able to investigate the association of long-term change in cardiac structure and function over the early adult lifespan and midlife cognition. Given that our participants were young and relatively healthy at study inception, the absolute numbers of cardiovascular events over the follow-up period were low. Thus, the association between abnormalities in cardiac structure and function and midlife cognition is unlikely to be driven by clinical-level dysfunction. Finally, our findings showing that midlife subclinical abnormalities in cardiac structure and function are associated with lower cognition are also important from a clinical standpoint. A single echocardiographic assessment may help identify subjects at higher risk of cognitive impairment. Another strength is the large sample size with its biracial nature because Black participants are often underrepresented in heart-brain studies. The cohort was well characterized, allowing us to control for important potential confounders. We extensively assessed cardiac structure and systolic and diastolic function using several repeated

high-quality echocardiographic measurements obtained and read under stringent standardized conditions by investigators blinded to the participants' cognitive status. Last, midlife cognition was evaluated with a battery of neuropsychological tests assessing different cognitive domains. Our findings reported consistent results, including lower cognition in processing speed and executive function, domains typically affected in vascular cognitive impairment.

Overall, our findings suggest that even before the occurrence of overt cardiovascular disease, subclinical abnormalities in midlife cardiac structure and diastolic function, but also as early as in young adulthood, could be risk markers for lower midlife cognition. Echocardiography, a widely available and noninvasive imaging modality, may be integrated into a risk assessment for cognitive impairment. Future research should determine whether interventions to improve cardiac structure and diastolic function could also benefit brain health and investigate the role of arterial stiffness and cerebral small vessel disease in the relationship between cardiac structure and function, and cognition.

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Disclosure

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Stephen Sidney, MD, MPH	Kaiser Permanente Northern California, Division of Research, Oakland	Drafting/revision of the manuscript for content, including medical writing for content; analysis or interpretation of data
Joao A.C. Lima, MD	Johns Hopkins University School of Medicine, Baltimore, MD	Drafting/revision of the manuscript for content, including medical writing for content; analysis or interpretation of data
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