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Fitness in Young Adulthood and Long-Term Cardiac Structure and Function

The CARDIA Study

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ABSTRACT

OBJECTIVES This study sought to evaluate the association between early-life cardiorespiratory fitness (CRF) and measures of left ventricular (LV) structure and function in midlife.

BACKGROUND Low CRF in midlife is associated with a higher risk of heart failure. However, the unique contributions of early-life CRF toward measures of LV structure and function in middle age are not known.

METHODS CARDIA (Coronary Artery Risk Development in Young Adults) study participants with a baseline maximal treadmill test and an echocardiogram at year 25 were included. Associations among baseline CRF, CRF change, and echocardiographic LV parameters (global longitudinal strain [GLS] and global circumferential strain, E/e′) were assessed using multivariable linear regression.

RESULTS The study included 3,433 participants. After adjustment for baseline demographic and clinical characteristics, lower baseline CRF was significantly associated with higher LV strain (standardized parameter estimate [Std β] $= -0.06$; $p = 0.03$ for GLS) and ratio of early transmitral flow velocity to early peak diastolic mitral annular velocity (E/e′) (Std $\beta = -0.10$; $p = 0.0001$ for lateral E/e′), findings suggesting impaired contractility and elevated diastolic filling pressure in midlife. After additional adjustment for cumulative cardiovascular risk factor burden observed over the follow-up period, the association of CRF with LV strain attenuated substantially ($p = 0.36$), whereas the association with diastolic filling pressure remained significant (Std $\beta = -0.05$; $p = 0.02$ for lateral E/e′). In a subgroup of participants with repeat CRF tests at year 20, greater decline in CRF was significantly associated with increased abnormalities in GLS (Std $\beta = -0.05$; $p = 0.02$) and higher diastolic filling pressure (Std $\beta = -0.06$; $p = 0.006$ for lateral E/e′) in middle age.

CONCLUSIONS CRF in young adulthood and CRF change were associated with measures of LV systolic function and diastolic filling pressure in middle age. Low CRF-associated abnormalities in systolic function were related to the associated higher cardiovascular risk factor burden. In contrast, the inverse association between CRF and LV diastolic filling pressure was independent of cardiovascular risk factor burden. (J Am Coll Cardiol HF 2017;5:347-55)
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ABBREVIATIONS AND ACRONYMS

BMI = body mass index

CRF = cardiorespiratory fitness

ΔCRF = change in cardiorespiratory fitness

CV = cardiovascular

GCS = global circumferential strain

GLS = global peak systolic longitudinal strain

HF = heart failure

HFrEF = heart failure with reduced ejection fraction

HFpEF = heart failure with preserved ejection fraction

LVEDV = left ventricular end-diastolic volume

RWT = relative wall thickness

Std β = standardized parameter estimate

Heart failure (HF) with preserved ejection fraction (HFpEF) is common and represents approximately 50% of admissions for HF in the population (1,2). In contrast to HF with reduced ejection fraction (HFrEF), numerous therapies have failed in large randomized trials to mitigate the unfavorable natural history of HFpEF (3). Because HFpEF has proven to be recalcitrant to therapy once it occurs, the focus must be shifted to prevention. To prevent HFpEF, a more comprehensive understanding of the natural history, pathophysiology, and targets for prevention is required.

Seminal studies have identified distinct intermediate at-risk cardiac phenotypes that are associated with development of HFrEF and HFpEF. Subclinical left ventricular (LV) systolic dysfunction and eccentric LV hypertrophy with increased LV diameter are strong predictors of HFrEF development (4,5). In contrast, subclinical diastolic dysfunction and concentric LV hypertrophy with increased relative wall thickness (RWT) is more strongly associated with increased risk of HFpEF (4–6). Identifying novel, early-life determinants of these intermediate cardiac phenotypes in middle age therefore represents an important step in understanding the natural history of both HFpEF and HFrEF that could have potential implications for novel preventive strategies.

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Studies have established physical inactivity and lower midlife cardiorespiratory fitness (CRF) as independent modifiable risk factors for HF in older age (7–9). However, the influence of early-life CRF on measures of LV structure and function in middle age, independent of other well-established risk factors such as hypertension, obesity, and diabetes, is not well understood. The aim of this study was to determine the association of CRF in young adulthood and age-related CRF change (ΔCRF) with measures of LV structure and function in middle age among participants of the CARDIA (Coronary Artery Risk Development in Young Adults) study. On the basis of previous cross-sectional observations (10,11), we hypothesize that lower CRF in young adulthood will be more strongly associated with abnormalities in LV diastolic than systolic function in middle age.

METHODS

STUDY SAMPLE. The CARDIA study is a multicenter longitudinal cohort study that enrolled 5,115 young adults who were initially 18 to 30 years of age in 1985 to 1986. The details of the recruitment procedures and design of the CARDIA study have been reported previously and are explained in Online Appendix (12). Baseline CRF test data were available in 5,048 participants; 3,433 of these participants had a detailed echocardiographic examination at year 25 and were included in the present study. Of these participants, 2,544 also had repeat CRF test data available from the 20-year follow-up visit and were included in additional analysis examining the association between age-related ΔCRF and echocardiographic outcomes. The details of exclusion and inclusion criteria for baseline and follow-up CRF testing have been previously reported (13,14).

CLINICAL AND ANTHROPOMETRIC MEASUREMENTS. Standardized protocols were used for collection of relevant clinical, anthropometric, and laboratory data at baseline and follow-up visits as previously reported (12). Demographic characteristics and physical activity levels were self-reported. Body mass index (BMI) was determined by calculating weight in kilograms divided by height in meters squared. The presence of diabetes was determined on the basis of fasting glucose levels (≥126 mg/dl) or the use of medication for diabetes mellitus. Physical activity levels were calculated in exercise units on the basis of the intensity, frequency, and consistency of participation.

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EXERCISE TREADMILL TEST. CRF was assessed at baseline and follow-up with a graded, symptom-limited maximal treadmill test using a modified Balke protocol as detailed in Online Appendix. For the present study, we used the maximal treadmill test duration (in seconds) as the measure of CRF.

ECHOCARDIOGRAPHIC ASSESSMENT. The protocol used for detailed echocardiographic examination at year 25 was consistent with the American Society of Echocardiography (ASE) guidelines as described previously and detailed in Online Appendix (15). Left atrial volume, left ventricular end-diastolic volume (LVEDV), and LV end-systolic volume were measured from the apical 4-chamber view. Left ventricular end-diastolic diameter (LVEDD) was measured from the parasternal long-axis view using M-mode. LV mass was calculated using the Devereux formula (16). All these measures were indexed to body surface area. Relative wall thickness (RWT) was calculated as follows: 2 × posterior wall thickness / LVEDD. For diastolic function assessment, the early transmitral flow velocity (E) was measured from pulsed Doppler echocardiographic recordings, and early peak diastolic mitral annular velocity (e′) was measured using tissue Doppler imaging at the septal and lateral mitral annulus. Septal E/e′ and lateral E/e′, measures of LV diastolic filling pressures, were used as surrogate measures of diastolic function.

For systolic function assessment, global peak systolic circumferential and longitudinal strain (GCS and GLS, respectively) measurements were analyzed for the LV midwall from the short-axis and 4-chamber views (at the midventricular level) respectively, using the Advanced Cardiology Package 2D Wall Motion Tracking software version 3.0 (Toshiba Medical Systems, Tochigi, Japan). Global strain values were calculated from the average of segmental peak values for each phase (%). GCS and GLS, which represent LV shortening in the circumferential and longitudinal planes, respectively, normally have a negative value, with less negative values indicating decreased shortening and thus greater impairment in myocardial contractility.

STATISTICAL ANALYSIS. The study participants were stratified into age-, sex-, and race/ethnicity-adjusted tertiles of baseline CRF. Baseline characteristics and echocardiographic measures of cardiac structure and function at year 25 follow-up were compared across the 3 baseline CRF tertiles using the chi-square test for categorical variables and the Kruskal-Wallis test for continuous variables. In the subgroup of participants with repeat CRF measurement in middle age (year 20), ΔCRF was defined as the percentage of change in maximal treadmill time between the 2 examinations ([Year 20 CRF − Year 0 CRF] / Year 0 CRF × 100). Echocardiographic outcomes of interest were measures of systolic function (GLS and GCS), diastolic filling pressure (septal and lateral E/e′), and LV remodeling (LVEDV and RWT) at year 25.

For categorical analyses of significant LV dysfunction, systolic dysfunction was defined as measures of strain that were 2 standard deviations higher than the previously reported normal range (17). Significant diastolic dysfunction was defined as elevated diastolic filling pressures with an average E/e′ >14 (18). The prevalence of significant impairment in LV systolic and diastolic function was compared across the 3 baseline CRF tertiles.

Multivariable adjusted linear regression analysis was performed to evaluate the independent associations of baseline CRF and ΔCRF with measures of LV structure and function. The models were adjusted for clinically relevant covariates on the basis of our previous knowledge from published scientific reports about biological factors that may influence the relationship between CRF and echocardiographic parameters. Four separate models were created for each echocardiographic outcome: model 1 included age, sex, race/ethnicity, education level, participating center, echocardiographic quality score, and baseline CRF level; model 2 included all covariates in model 1 plus prevalent cardiovascular (CV) risk factors at the time of baseline examination including systolic blood pressure, total cholesterol, BMI, smoking status, and diabetes status; model 3 included all covariates in model 1 plus cumulative burden of CV risk factors observed over the 25-year follow-up. This included diabetes status at year 25, smoking status at year 25, and cumulative measures of systolic blood pressure, cholesterol, and BMI. Cumulative measures of the continuous exposures were calculated as the product of the average measure of the covariate during follow-up and the number of follow-up years. To understand the independent contributions of ΔCRF toward measures of LV structure and function, an additional model was created with adjustment for covariates in model 3 and ΔCRF.

Several sensitivity analyses were performed to test the robustness of our study findings. First, multivariable adjusted association between CRF and measures of LV structure and function was also evaluated using peak exercise heart rate as a surrogate measure of exercise capacity. For this analysis, maximum treadmill time was replaced with peak exercise heart rate in the model 3 detailed earlier. Second, we also evaluated the adjusted associations

TABLE 1 Demographic and Clinical Characteristics of the Study Participants Across Age-, Sex-, Ethnicity-Adjusted Baseline CRF Tertiles*

	Low Fit Tertile 1 (n = 1,124)	Moderate Fit Tertile 2 (n = 1,174)	High Fit Tertile 3 (n = 1,135)	p Trend
Age, yrs	25.1 ± 3.6	25.0 ± 3.7	25.1 ± 3.6	0.70
Females, %	57.2	56.6	56.2	0.63
Blacks, %	47.0	46.3	46.6	0.86
BMI, kg/m^2	27.1 ± 6.3	23.8 ± 3.7	22.6 ± 2.8	<0.0001
Systolic BP, mm Hg	111 ± 11	110 ± 10	109 ± 10	<0.0001
Diabetes mellitus, %	1.4	0.5	0.1	0.0001
Current smoking, %	34.2	26.1	21.0	<0.0001
Education level less than high school, %	71.1	63.8	54.9	<0.0001
Physical activity levels (total intensity score)	289.7 ± 247.5	335. 8 ± 277.5	391.6 ± 291.2	<0.0001
Treadmill time, s	443.7 ± 153.0	593.7 ± 127.4	721.7 ± 141.9	<0.0001

Values are mean ± SD or %. *CRF tertiles derived from baseline maximal treadmill time and adjusted for age, sex, and ethnicity.

BMI = body mass index; BP = blood pressure; CRF = cardiorespiratory fitness.

among CRF, ΔCRF, and measures of posterior wall thickness on follow-up to understand the association between CRF and LV wall thickness independent of LVEDD more clearly. Third, consistent with the updated recommendations of the ASE (18), categorical prevalence of diastolic dysfunction across baseline CRF tertiles was also compared using e′-based cutoffs (septal e′ <7 cm/s or lateral e′ <10 cm/s). All statistical analyses were performed using SAS version 9.4 (SAS Institute, Cary, North Carolina).

RESULTS

Baseline characteristics of the study participants across age-, sex-, and ethnicity-adjusted tertiles of CRF are shown in **Table 1**. Higher CRF was associated with lower BMI, higher physical activity levels, and lower prevalence of CV risk factors. Baseline characteristics of study participants with versus without echocardiographic examination on follow-up are compared in Online Table 1. Compared with study participants who had echocardiographic examination on follow-up, those without follow-up echocardiographic examination were more commonly African American, smoker, and had lower CRF levels. Echocardiographic characteristics of study participants measured at year 25 follow-up across CRF tertiles are shown in **Table 2**.

ASSOCIATION BETWEEN BASELINE CRF AND MEASURES OF LV REMODELING. CRF in young adulthood was not associated with LVEDV in the linear regression model adjusted for demographic characteristics (model 1, **Table 3**). However, a significant association between CRF and LVEDV was unmasked with additional adjustment for prevalent CV risk factors at baseline (standardized parameter estimate [Std β]: 0.09 [0.03 to 0.14]; model 2, **Table 3**), as well as cumulative CV risk factor burden observed during the follow-up period (Std β: 0.05 [0.001 to 0.10]; model 3, **Table 3**) such that lower CRF was associated with smaller LV volumes. In contrast, we observed a significant inverse association between baseline CRF and RWT after adjustment for demographic characteristics; this association was attenuated with additional adjustment for baseline and cumulative CV risk factor burden (Std β: −0.02 [−0.08 to 0.03]; model 3, **Table 3**).

ASSOCIATION BETWEEN BASELINE CRF AND MEASURES OF LV SYSTOLIC FUNCTION. In multivariable adjusted linear regression analysis with adjustment for demographic characteristics, we observed an inverse association between CRF levels and measures of GLS and GCS such that lower CRF in young adulthood was associated with less negative measures of GLS and GCS in middle age, thus indicating worse systolic function (model 1, **Table 3**). The magnitude of association between CRF and GLS (Std β: −0.09 [−0.14 to −0.04]) (Online Table 2) was numerically stronger than that observed between CRF and GCS (Std β: −0.05 [−0.10 to −0.004]). However, the association between CRF and measures of GCS was attenuated substantially and was no longer significant after additional adjustment for prevalent CV risk factors (model 2, **Table 3**) at the baseline examination. Similarly, the association between CRF and GLS became insignificant after additional adjustment for the cumulative CV risk factor burden observed over the follow-up period (model 3, **Table 3**, Online Table 2).

ASSOCIATION BETWEEN BASELINE CRF AND MEASURES OF LV DIASTOLIC FILLING PRESSURE. We observed an inverse association between CRF levels and measures of septal and lateral E/e′ after adjustment for demographic characteristics such that lower baseline CRF was associated with higher septal and lateral E/e′, thus indicating higher LV diastolic filling pressure in middle age (septal E/e′ Std β: −0.13 [−0.18 to −0.09]; lateral E/e′ Std β: −0.15 [−0.19 to −0.10]) (model 1, **Table 3**, Online Table 2) This association was attenuated modestly in magnitude and remained significant after additional adjustment for baseline CV risk factors (septal E/e′ Std β: −0.09 [−0.13 to −0.04]; lateral E/e′ Std β: −0.10 [−0.15 to −0.05]) (model 2, **Table 3**, Online Appendix) as well as cumulative CV risk factor burden observed over the

25-year follow-up (septal E/e′ Std β: −0.06 [−0.11 to −0.01]; lateral E/e′ Std β: −0.05 [−0.10 to −0.01]) (model 3, **Table 3**, Online Table 2). No significant statistical interaction was observed between baseline CRF levels and BMI, sex, smoking status, and race/ethnicity for follow-up measures of diastolic filling pressure (p interaction >0.2 for each).

CATEGORICAL ASSOCIATION BETWEEN BASELINE CRF AND PREVALENCE OF LV DYSFUNCTION IN MIDDLE AGE. We did not observe a difference in the prevalence of categorically defined significant impairment in GLS and GCS in middle age across the baseline CRF tertiles (**Figures 1A and 1B**). In contrast, the prevalence of significant LV diastolic dysfunction as defined by average E/e′ >14 was significantly higher in the lowest-CRF group as compared with the high-CRF groups (**Figure 1C**).

ASSOCIATION BETWEEN CRF CHANGE AND CARDIAC STRUCTURE AND FUNCTION. The average decrease in treadmill time of the study population over the 20-year follow-up was 28%, with more than 92% of participants experiencing a decline in CRF. In adjusted analyses, we observed a significant inverse association between ΔCRF and GLS such that greater decline in CRF was associated with less negative GLS, thus indicating worse systolic function (Std β: −0.05 [−0.10 to −0.01]) (**Table 4**). The ΔCRF was not independently associated with GCS in the adjusted analysis (**Table 4**). Among diastolic function parameters, greater decline in CRF was independently associated with higher lateral E/e′, thus indicating higher diastolic filling pressure (Std β: −0.06 [−0.09 to −0.01]) (**Table 4**). A similar association with trend toward statistical significance was also observed between ΔCRF and septal E/e′ (**Table 4**). Among the LV remodeling parameters, greater decline in CRF was independently associated with smaller LV volume and higher RWT in middle age (**Table 4**).

SENSITIVITY ANALYSIS. In multivariable adjusted models using peak exercise heart rate as a measure of exercise capacity, the association between peak exercise heart rate and measures of LV structure and function was not different from that observed between maximum treadmill time and LV parameters (Online Table 3). In multivariable adjusted models evaluating the associations among baseline CRF, ΔCRF, and posterior wall thickness, greater decline in CRF was associated with higher posterior wall thickness measures, a finding suggesting greater adverse remodeling (Online Table 4). Finally, in an analysis comparing the prevalence of significant diastolic dysfunction as identified using ASE-defined e′ cutoffs, higher baseline CRF levels were associated with lower prevalence of diastolic dysfunction (Online Figure 1). This finding was consistent with the trend in prevalence of abnormally elevated E/e′ across CRF categories.

TABLE 2 Echocardiographic Characteristics of Study Participants on Year 25 Follow-Up Across Age-, Sex-, Ethnicity-Adjusted Baseline CRF Tertiles

	Low Fit Tertile 1 (n = 1,124)	Moderate Fit Tertile 2 (n = 1,174)	High Fit Tertile 3 (n = 1,135)	p Value
Indexed left ventricular mass, g/m^2	87.9 ± 24.1	85.2 ± 20.9	85.5 ± 21.8	0.09
Indexed left atrial volume, ml/m^2	24.6 ± 6.9	24.3 ± 7.1	25.5 ± 7.2	0.002
Relative wall thickness	0.36 ± 0.08	0.35 ± 0.07	0.35 ± 0.07	0.02
Global circumferential strain, %	−15.09 ± 2.97	−15.26 ± 2.82	−15.55 ± 2.74	0.0001
Global longitudinal strain, %	−14.78 ± 2.49	−15.03 ± 2.41	−15.39 ± 2.33	<0.0001
Indexed left ventricular end-diastolic volume, ml/m^2	63.6 ± 13.9	64.2 ± 13.7	64.8 ± 14.8	0.16
E/e′ septal	9.45 ± 3.01	8.83 ± 2.64	8.72 ± 2.64	<0.0001
E/e′ lateral	7.54 ± 2.61	6.94 ± 2.28	6.85 ± 2.20	<0.0001

Values are mean ± SD.
CRF = Cardiorespiratory fitness; E/e′ = ratio of early transmitral flow velocity to early peak diastolic mitral annular velocity.

DISCUSSION

We observed several important findings in the present study. First, lower CRF in young adulthood was associated with abnormal LV remodeling and a higher prevalence of subclinical abnormalities in LV systolic and diastolic function in middle age. Second, CRF was more strongly associated with LV diastolic parameters compared with measures of systolic function. Third, the association between low CRF and higher LV diastolic filling pressure was independent of the CV risk factor burden observed at the baseline and follow-up examinations. In contrast, associations of low CRF with abnormalities in LV systolic function were attenuated by adjustment for the higher burden of CV risk factors. Finally, decline in CRF over follow-up was also a significant predictor of subclinical systolic dysfunction and elevated diastolic filling pressure in middle age independent of baseline CRF levels.

CRF IN YOUNG ADULTHOOD AND GLOBAL LV STRUCTURE IN MIDDLE AGE. Previous cross-sectional studies among athletes as well as sedentary individuals have demonstrated that higher levels of exercise and CRF are associated with larger LV volume (10,19). Findings from the present study extend these observations by demonstrating a significant association between higher CRF levels and larger LV volume, independent of CV risk factors in a longitudinal cohort of healthy, young adults.

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TABLE 3 Association* Between Baseline CRF Measured at Year 0 and Echocardiographic Measures of LV Structure and Function at Year 25

Echocardiographic Parameters (Outcome)	Model 1† Std β (95% CI)	Model 1† p Value	Model 2‡ Std β (95% CI)	Model 2‡ p Value	Model 3§ Std β (95% CI)	Model 3§ p Value
GCS, %	−0.05 (−0.10 to −0.004)	0.03	−0.02 (−0.07 to 0.04)	0.56	−0.01 (−0.07 to 0.04)	0.60
GLS, %	−0.09 (−0.14 to −0.04)	0.0002	−0.06 (−0.11 to −0.004)	0.03	−0.02 (−0.07 to 0.03)	0.36
E/e′ septal	−0.13 (−0.18 to −0.09)	<0.0001	−0.09 (−0.13 to −0.04)	0.0005	−0.06 (−0.11 to −0.01)	0.01
E/e′ lateral	−0.15 (−0.19 to −0.10)	<0.0001	−0.10 (−0.15 to −0.05)	0.0001	−0.05 (−0.10 to −0.01)	0.02
Indexed LVEDV, ml/m^2	0.04 (−0.11 to 0.09)	0.13	0.09 (0.03 to 0.14)	0.002	0.05 (0.001 to 0.10)	0.047
RWT	−0.08 (−0.12 to −0.03)	0.002	−0.04 (−0.10 to 0.005)	0.08	−0.02 (−0.08 to 0.03)	0.34

*Std β refers to the standardized parameter estimates for the association between measured CRF and each echocardiographic parameter included in separate linear regression models. †Model 1 included following covariates: age, sex, ethnicity, education level, center, echocardiographic quality score, and baseline CRF level. ‡Model 2 was adjusted for all covariates in model 1 plus prevalent cardiovascular risk factors at the time of baseline examination including systolic blood pressure, total cholesterol, body mass index, smoking status, and diabetes status. §Model 3 was adjusted for covariates in model 1 plus cumulative burden of cardiovascular risk factors observed over the 25-year follow-up.

CI = confidence interval; CRF = cardiorespiratory fitness; E/e′ = ratio of early transmitral flow velocity to early peak diastolic mitral annular velocity; GCS = global circumferential strain; GLS = global longitudinal strain; LV = left ventricular; LVEDV = left ventricular end diastolic volume; RWT = relative wall thickness.

This association may be related to physiological remodeling among highly fit individuals and highlights the need to account for differences in lifestyle factors such as CRF or exercise levels when comparing LV volumes. Consistent with cross-sectional observations from other cohorts (10,11,20), we also observed an inverse association between CRF and RWT that was attenuated with adjustment for CV risk factors, a finding suggesting that higher CRF may be protective against age-related pathological LV remodeling in middle age by reducing the downstream CV risk factor burden.

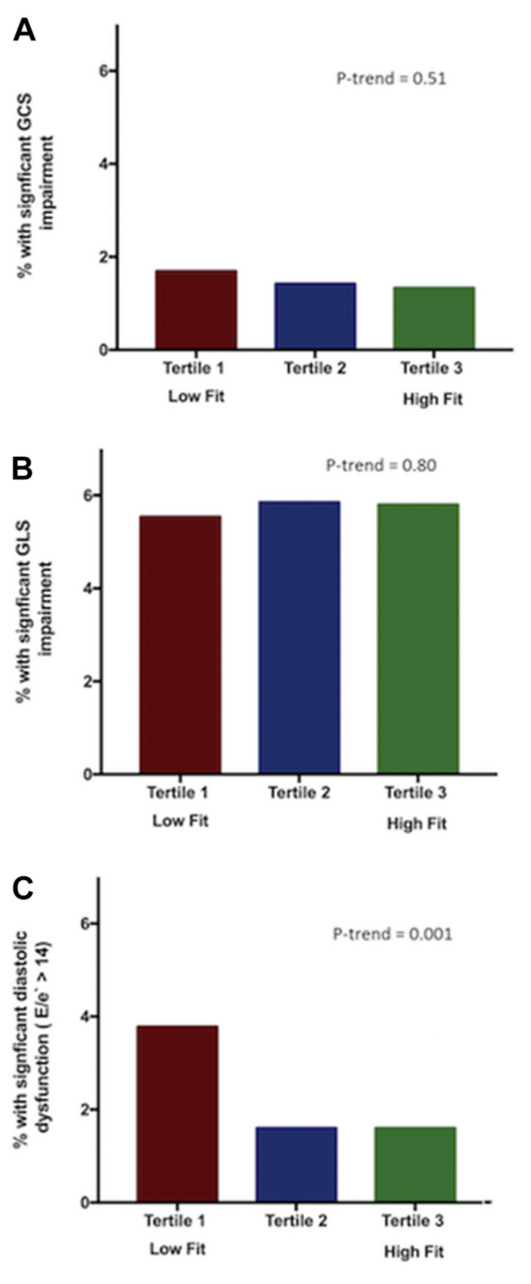
CRF IN YOUNG ADULTHOOD AND LV FUNCTION IN MIDDLE AGE. Low CRF in midlife is strongly associated with an increased risk of HF through mechanisms that are not well understood (7,8). Cross-sectional studies have demonstrated a significant association between low CRF and diastolic dysfunction but not LV ejection fraction (10,19). However, ejection fraction may miss subtle, subclinical abnormalities in systolic function. The present study significantly adds to the available published reports by evaluating the independent contributions of CRF and age-related ΔCRF on sensitive measures of LV contractility and diastolic filling pressure over 25 years of follow-up in a cohort of healthy adults.

Our study findings demonstrate a distinct pattern of association between CRF and LV systolic versus diastolic function. Low CRF-associated abnormalities in LV systolic function were largely mediated by higher risk factor burden, which in turn may be linked to low CRF. In contrast, the association between low CRF and higher diastolic filling pressure was independent of the risk factor burden. It is plausible that low CRF in young adulthood may be related to subclinical LV relaxation impairment at baseline that progresses with aging and eventually evolves into clinical HFpEF. Alternatively, lower CRF and exercise levels may have a direct effect on LV relaxation and play a more direct role in progression of diastolic dysfunction. Finally, the overall low incidence of acute coronary syndrome may also explain the disparate relationship between CRF and systolic versus diastolic function on follow-up (21).

CRF DECLINE AND LV FUNCTION IN MIDDLE AGE. Greater age-related CRF decline is associated with a higher risk of HF in older age (8). In the present study, using 20-year ΔCRF data in a subset of the CARDIA study participants, we illustrate the potential mechanisms through which CRF decline over the long term may predispose to increased HF risk, independent of baseline CRF levels. We observed significantly increased LV diastolic filling pressure and RWT among individuals with greater decline in CRF. Furthermore, CRF decline was also significantly associated with impairment in GLS, which is more sensitive to cardiac remodeling than is GCS (22). Taken together, these findings suggest that CRF decline-associated increased HF risk may be related to greater adverse LV remodeling.

CLINICAL IMPLICATIONS. Our study findings have important clinical implications. Findings from our study suggest that both low CRF in young adulthood and greater CRF decline with aging may identify individuals at higher risk of LV dysfunction in middle age. Low CRF-associated abnormalities in systolic function appear to be mediated by the greater burden of CV risk factors. In contrast, the contributions of low CRF to abnormalities in diastolic function are stronger and independent of the downstream risk

FIGURE 1 Categorical Prevalence of Significant Impairment in Measures of Left Ventricular Function at Year 25 Follow-Up Across Baseline CRF Categories



Global circumferential strain (GCS) **(A),** global longitudinal strain (GLS) **(B),** and elevated diastolic filling pressure (E/e′) **(C)**. CRF = Cardiorespiratory fitness.

TABLE 4 Association* Between Age-Related CRF Change From Baseline to Year 20 Follow-Up and Echocardiographic Measures of Cardiac Structure and Function at Year 25

Echocardiographic Parameter Outcome	Std β (95% CI)	p Value
GCS, %	−0.03 (−0.08 to 0.01)	0.18
GLS, %	−0.05 (−0.10 to −0.009)	0.02
E/e′ septal	−0.04 (−0.08 to 0.001)	0.059
E/e′ lateral	−0.06 (−0.09 to −0.01)	0.006
Indexed LVEDV, ml/m^2	0.11 (0.06 to 0.15)	<0.0001
RWT	−0.06 (−0.10 to −0.01)	0.01

*Std β refers to the standardized parameter estimates for the association between percent CRF change from baseline to follow-up and each echocardiographic parameter included in separate linear regression models. The linear regression model included following covariates: age, sex, ethnicity, education level, participating center, echocardiographic quality score, cardiovascular risk factors observed over the 25-year follow-up, baseline CRF level, and CRF change.

Abbreviations as in Tables 1 and 3.

factor burden. Considering the well-established role of subclinical systolic dysfunction and diastolic dysfunction as precursors for development of HFrEF and HFpEF, respectively (4,6), our study findings provide insight into pathways through which low CRF may increase the risk of the 2 distinct HF subtypes and suggest that the low CRF-associated risk of HF may be stronger for HFpEF compared with HFrEF. This suggestion is supported by findings from the Framingham Heart Study that demonstrated greater risk of HFpEF than HFrEF among participants with low versus high physical activity levels (23). Moreover, in another study, Bhella et al. (24) demonstrated that sedentary middle-aged adults with high levels of exercise throughout adulthood had higher LV compliance than did those with a low dose of lifetime exercise. Future studies with well-adjudicated follow-up HF outcome events are needed to confirm our study findings.

STUDY LIMITATIONS. First, directly measured peak oxygen uptake was not available among study participants as a measure of CRF. However, previous studies demonstrated a very high correlation between treadmill time and peak oxygen consumption ($r = 0.92$) (25). Second, because of the observational nature of our analysis, there is a potential for residual confounding and reverse causation. Moreover, baseline measures of echocardiographic outcomes of interest are not available, and it is plausible that abnormalities in LV function at baseline may lead to low CRF and greater CRF decline with aging. However, the youth and good health of our study population at baseline with previously reported normal LV function in year 5 of the study (26) suggest that the variability in CRF at baseline is less likely to be related to subclinical dysfunction in baseline cardiac function. Third, we do not have data on cardiac biomarkers such as N-terminal pro-B-type natriuretic peptide and cardiac troponin levels that may be useful to identify myocardial injury and/or stress. Fourth, echocardiographic data are available only in approximately 50% of the CARDIA participants. Thus there is a potential for selection bias in the observed associations. Finally, we did not adjust for multiple comparisons in our analysis, and future studies are needed to validate our study findings.

CONCLUSIONS

Lower CRF in young adulthood and greater CRF decline with aging are significantly associated with smaller LV size and higher diastolic filling pressure in middle age, independent of cumulative CV disease risk factor burden. Future studies are needed to determine whether the inverse association between CRF in young adulthood and diastolic dysfunction in older age is causal and modifiable by interventions aimed at improving CRF levels.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: Lower CRF in young adulthood is more strongly associated with abnormalities in LV diastolic function than systolic function in middle age.

TRANSLATIONAL OUTLOOK: Future studies are needed to determine whether lifestyle interventions in early life aimed at improving CRF may improve cardiac function and lower heart failure risk in older age.

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KEY WORDS cardiorespiratory fitness, diastolic dysfunction, left ventricular strain, systolic function

APPENDIX For a supplemental methods section as well as supplemental tables and a figure, please see the online version of this article.