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ORIGINAL RESEARCH

Longitudinal Associations of Fitness and Obesity in Young Adulthood With Right Ventricular Function and Pulmonary Artery Systolic Pressure in Middle Age: The CARDIA Study

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BACKGROUND: Low cardiorespiratory fitness (CRF) and obesity are risk factors for heart failure but their associations with right ventricular (RV) systolic function and pulmonary artery systolic pressure (PASP) are not well understood.

METHODS AND RESULTS: Participants in the CARDIA (Coronary Artery Risk Development in Young Adults) study who underwent maximal treadmill testing at baseline and had a follow-up echocardiographic examination at year 25 were included. A subset of participants had repeat CRF and body mass index (BMI) assessment at year 20. The associations of baseline and changes in CRF and BMI on follow-up (baseline to year 20) with RV systolic function parameters (tricuspid annular plane systolic excursion, RV Doppler systolic velocity of the lateral tricuspid annulus), and PASP were assessed using multivariable-adjusted linear regression models. The study included 3433 participants. In adjusted analysis, higher baseline BMI but not CRF was significantly associated with higher PASP. Among RV systolic function parameters, higher baseline CRF and BMI were significantly associated with higher tricuspid annular plane systolic excursion and RV systolic velocity of the lateral tricuspid annulus. In the subgroup of participants with follow-up assessment of CRF or BMI at year 20, less decline in CRF was associated with higher RV systolic velocity of the lateral tricuspid annulus and lower PASP, while greater increase in BMI was significantly associated with higher PASP in middle age.

CONCLUSIONS: Higher CRF in young adulthood and less decline in CRF over time are each significantly associated with better RV systolic function. Higher baseline BMI and greater age-related increases in BMI are each significantly associated with higher PASP in middle age. These findings provide insights into possible mechanisms through which low fitness and obesity may contribute toward risk of heart failure.

Key Words: fitness ■ body mass index ■ right ventricular function ■ pulmonary artery systolic pressure

Low cardiorespiratory fitness (CRF) and high body mass index (BMI) are well-established risk factors for cardiovascular disease, particularly heart failure (HF).[1–6] While low CRF and high BMI are each significantly associated with risk of HF,[7–9] several studies have found evidence suggesting that high CRF attenuates the elevated cardiovascular disease risk seen with high BMI.[10–12] The mechanisms through which CRF and BMI influence the risk of HF remain uncertain and could be explained by either

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CLINICAL PERSPECTIVE

What Is New?

- Among young adults enrolled in the CARDIA (Coronary Artery Risk Development in Young Adults) study, less decline in cardiorespiratory fitness over time was associated with better right ventricular systolic function and lower pulmonary artery systolic pressure in middle age.
- Increase in body mass index with aging was associated with higher pulmonary artery systolic pressure in middle age.

What Are the Clinical Implications?

- Cardiorespiratory fitness and body mass index may represent important modifiable lifestyle factors associated with high-risk intermediate cardiac phenotypes.

Nonstandard Abbreviations and Acronyms

CARDIA	Coronary Artery Risk Development in Young Adults
CRF	cardiorespiratory fitness
MESA	Multi-Ethnic Study of Atherosclerosis–Right Ventricle Study
PASP	pulmonary artery systolic pressure
RVS'	right ventricular systolic velocity of the lateral tricuspid annulus
TAPSE	tricuspid annular plane systolic excursion

the impact of these risk factors on established HF risk factors, such as diabetes mellitus and hypertension, or the direct impact of CRF and BMI on cardiac structure and function.

Recent studies have demonstrated that lower CRF levels and higher BMI are each significantly associated with abnormal left ventricular (LV) remodeling patterns and subclinical systolic and diastolic dysfunction, intermediate phenotypes associated with higher risk of developing HF.[13–19] Subclinical abnormalities in right ventricular (RV) structure and function as well as elevated levels of pulmonary artery systolic pressure (PASP) are also associated with higher risk of HF and adverse events.[20–23] However, to our knowledge, the association of both CRF and BMI in young adulthood and midlife measurements of RV systolic function and PASP have not been previously reported. This knowledge could provide insights into the mechanisms through which each of these interrelated risk factors might be associated with HF risk across the lifespan. Identification of modifiable lifestyle factors in young adulthood that are associated with key intermediate cardiac phenotypes in midlife may inform future HF prevention strategies. This is particularly relevant as implementation of intensive lifestyle interventions in early to middle age but not older age have been associated with favorable changes in cardiac structure and function.[24,25] Therefore, in the present study, we sought to characterize the associations of baseline and longitudinal changes in CRF assessed by maximal exercise treadmill test duration and BMI measured in young adulthood and midlife with measures of RV systolic function and PASP in middle age using data from the CARDIA (Coronary Artery Risk Development in Young Adults) study. We hypothesized that lower CRF and higher BMI in young adulthood and worsening of these risk factors over time will be associated with greater abnormalities in RV systolic function and PASP in middle age.

METHODS

The data and materials from the present analysis will not be made available for the purpose of reproducing the study results.

Study Population

The CARDIA study is a multicenter longitudinal cohort study that enrolled 5115 young adults, initially aged 18 to 30 years, from 4 participating centers (Birmingham, Alabama; Chicago, Illinois; Minneapolis, Minnesota; and Oakland, California) in 1985–1986. The details about recruitment procedures and design of the CARDIA study have been previously reported.[26,27] The recruitment strategy was designed to achieve a balance at each of the 4 sites by age, sex, race/ethnicity, and education. Study participants had serial follow-up at 2, 5, 7, 10, 15, 20, and 25 years after the baseline visit (year 0), with retention of greater than two thirds of the surviving cohort at year 25. Informed consent was obtained from all participants before study entry. Institutional review board approval was obtained at each participating center for the study.

Of the 5115 participants who were enrolled in the study, 5048 participants underwent maximal treadmill testing with estimation of CRF at baseline (year 0). Among those participants, 3433 had a detailed echocardiographic examination at year 25 and were included in the present study. Among participants included in the present study, 2544 underwent repeat maximal treadmill testing with estimation of CRF at year 20 follow-up. Participants with repeat CRF measurements were included in analyses examining the association between change in CRF and measures

of RV systolic function and PASP. Participants who underwent repeat BMI measurements at year 20 follow-up were included in similar analyses. The details of inclusion and exclusion criteria for baseline and follow-up CRF testing have been previously reported.[28,29]

Clinical, Anthropometric, and Pulmonary Function Measurements

Standardized protocols were used for collection of relevant clinical, anthropometric, and laboratory data at baseline and follow-up visits as previously reported.[26,27] Demographic characteristics were self-reported. BMI was determined by calculating weight in kilograms divided by height in meters squared. Presence of diabetes mellitus was determined based on fasting glucose levels (≥126 mg/dL) or use of medication for diabetes mellitus. Using a standard protocol and spirometry equipment, forced vital capacity (FVC) and forced expiratory volume in 1 second was measured as previously reported.[30] The highest values for FVC and forced expiratory volume in 1 second from 5 satisfactory maneuvers were used for pulmonary function estimation.

Exercise Treadmill Test

CRF was assessed at baseline (year 0) with a graded, symptom-limited maximal treadmill test using a modified Balke protocol as previously described (Data S1).[28] In brief, there were up to 9 two-minute stages of gradually escalating difficulty, and participants were encouraged to exert maximal effort. Heart rate, blood pressure, and perceived exertion level were assessed at regular intervals during the test. For the present study, we used the maximal treadmill test duration (in seconds) as a measure to estimate CRF. This is consistent with prior analyses from the CARDIA study evaluating the association of measures of CRF (defined as maximal treadmill test duration) with clinical and echocardiographic outcomes.[13,31,32] Prior studies have demonstrated that maximal treadmill test duration was highly correlated with the gold standard for CRF assessment, maximum oxygen consumption, and was significantly associated with all-cause mortality in a seminal study by Blair et al.[33–35] A subset of study participants underwent repeat CRF testing at year 7 and year 20 follow-up. Year 20, but not year 7, CRF test data were used in CRF change analyses owing to significant protocol violation by a large proportion of participants who underwent exercise treadmill testing at the year 7 visit.[36] CRF was also assessed according to estimated metabolic equivalents as previously described.[28] Metabolic equivalents were estimated based on the stage and time completed during the exercise treadmill test (Data S1).

Echocardiographic Assessment

The protocol used for detailed echocardiographic examination at year 25 was consistent with the American Society of Echocardiography guidelines as previously described.[13,37,38] Trained sonographers performed Doppler and M-mode echocardiography using an Artida ultrasound system (Toshiba) across all participating centers. Standard offline image analysis was used to optimize measurements using digitally recorded images.

RV Systolic Function and PASP Assessment

Primary outcomes of interest in our analysis were echocardiographic measures of RV systolic function and PASP. RV systolic function parameters included tricuspid annular plane systolic excursion (TAPSE) and RV systolic velocity of the lateral tricuspid annulus (RVS'). TAPSE measures the longitudinal distance of systolic excursion of the tricuspid annulus between end-diastole and peak systole using M-mode echocardiography. RVS' measures the systolic velocity of the lateral tricuspid annulus using pulsed wave tissue Doppler imaging. As per the American Society of Echocardiography guidelines, TAPSE ≥1.7 cm and RVS' ≥9.5 cm/s suggests normal RV systolic function.[39] Adequate TAPSE and RVS' assessment was available in the majority of study participants who underwent year 25 echocardiographic assessment (3184 [92.7%] and 3273 [95.3%], respectively). PASP was calculated using the tricuspid regurgitation jet velocity, modified Bernoulli equation, and right atrial pressure [PASP=4(V)^2+estimated right atrial pressure, where V=peak velocity of the tricuspid regurgitation regurgitant jet in m/s]. As previously reported, the right atrial pressure was assumed to be 10 mm Hg in all participants.[40] A measurable tricuspid regurgitation jet is required to estimate PASP; therefore, only participants with a measurable tricuspid regurgitation jet sufficient to calculate PASP were included in analyses related to this outcome. According to the American Society of Echocardiography guidelines, PASP ≤36 mm Hg is considered normal.[41]

Statistical Analysis

Study participants were stratified into age-, race-, and sex-specific tertiles of baseline CRF and BMI. Demographic, clinical, and echocardiographic characteristics were compared across these tertiles using the Cochran-Armitage trend test for categorical variables and Jonckheere-Terpstra trend test for continuous variables. Prevalence of abnormal RV systolic function, defined based on the American Society of Echocardiography guideline recommendations

(TAPSE <1.7 cm or RVS' <9.5 cm), and elevated PASP (>36 mm Hg) were compared across CRF and BMI tertiles using Cochran-Armitage trend test. The unadjusted associations of CRF and BMI with certain RV function parameters and PASP were nonlinear and, thus, categorical measures of CRF and BMI were used for adjusted analyses. Multivariable-adjusted linear regression analysis was performed to evaluate the associations of baseline CRF and BMI categories with measures of RV systolic function and PASP measured at year 25. Separate models were constructed for each RV function parameter and PASP and included the following covariates: model 1 consisted of education status, echocardiogram quality score, and cardiovascular risk factors (smoking status, systolic blood pressure, diabetes mellitus status, lung function parameters [forced expiratory volume in 1 second and FVC]), and baseline BMI and CRF categories; and model 2 consisted of covariates from model 1 plus LV end-diastolic volume (LVEDV) and LV ejection fraction. Among participants with available data on CRF and BMI on follow-up (year 20), the association of age-, race-, and sex-specific tertiles of percent change in CRF/BMI with RV function parameters and PASP was also assessed using multivariable-adjusted linear regression models with adjustment for covariates included in model 2. Since the baseline and change categories for CRF and BMI were age-, sex-, and race-specific, these covariates were not adjusted for in the multivariable regression models. To identify significant predictors of RV systolic function parameters and PASP, separate linear regression models were constructed for each outcome of interest with inclusion of the covariates in model 2 except BMI and CRF categories were substituted for age, sex, race/ethnicity, and continuous measures of BMI and CRF. Two-sided *P* values <0.05 were considered statistically significant. All statistical analyses were performed using SAS version 9.4 (SAS Institute Inc.).

RESULTS

Baseline characteristics of the study participants according to age-, sex-, and race-adjusted tertiles of CRF are shown in Table 1. BMI, systolic blood pressure, and prevalence of diabetes mellitus and smoking decreased across increasing tertiles of baseline CRF. Among echocardiographic characterstics, individuals with higher baseline CRF had lower E/e', smaller LVEDV, modestly higher LV stroke volume index, and higher measures of RV systolic function parameters (TAPSE and RVS'). The baseline characteristics of study participants stratified by age-, sex-, and race-adjusted tertiles of BMI are shown in Table S1. Participants with higher BMI had higher systolic BP, lower CRF, larger LVEDV, and higher LV mass index, E/e', and PASP. PASP measures were available in a subset of the study participants (1293 [37.7%]). There were no meaningful differences in the burden of baseline cardiovascular risk factors, BMI, and CRF levels, and echocardiographic parameters among participants with versus those without available PASP measurements (Table S2).

Baseline CRF and BMI Categories and Prevalence of Abnormal RV Systolic Function and PASP

The prevalence of abnormal RV systolic function (RVS' or TAPSE) and PASP across age-, sex-, and race-adjusted tertiles of CRF and BMI are shown in the Figure. The prevalence of abnormal RV systolic function (defined by TAPSE <1.7 cm or RVS' <9.5 cm/s) decreased across increasing CRF categories (9.6% in CRF tertile 1 versus 7.9% in CRF tertile 2 versus 6.6% in CRF tertile 3, *P*=0.01). Similarly, the prevalence of abnormally elevated PASP (defined by PASP >36 mm Hg) was also lower across increasing CRF categories (24.2% in CRF tertile 1 versus 16.7% in CRF tertile 2 versus 15.4% in CRF tertile 3, *P*<0.01).

There were no significant differences in the prevalence of abnormal RV systolic function across tertiles of baseline BMI. In contrast, the prevalence of abnormally elevated PASP was higher across increasing BMI categories (14.1% in BMI tertile 1 versus 18.6% in BMI tertile 2 versus 23.5% in BMI tertile 3, *P*<0.01).

Associations of Baseline CRF and BMI With RV Systolic Function and PASP

In adjusted analysis, a significant association was observed between higher baseline CRF and higher TAPSE and RVS' after adjustment for baseline demographics, cardiovasacular risk factors, and BMI, suggesting better RV function (Table 2). This association was not attenuated with further adjustment for LV structure and function parameters. Similarly, higher baseline BMI was also significantly associated with higher measures of RV function parameters, both TAPSE and RVS', in the most adjusted model.

For PASP, baseline CRF was not significantly associated with measures of PASP after adjustment for baseline characterstics, cardiovascular risk factors, and BMI (Table 2). In contrast, higher BMI was significantly associated with higher PASP after adjusting for baseline CRF and other clinical factors. This association remained significant after additional adjustment for LV parameters, including LVEDV and LV ejection fraction.

Table 1. Baseline Characteristics Stratified by Cardiorespiratory Fitness

	Tertile 1 (n=1124)	Tertile 2 (n=1174)	Tertile 3 (n=1135)	*P* Value
Maximal treadmill test duration, s	452 (360–560)	600 (480–720)	720 (603–840)	<0.01
Age, y	26 (22–28)	25 (22–28)	26 (22–28)	0.70
Women, n (%)	643 (57.2)	665 (56.6)	638 (56.2)	0.63
Black, n (%)	528 (47.0)	544 (46.3)	529 (46.6)	0.86
BMI, kg/m^2	25.8 (22.6–30.4)	23.4 (21.2–25.8)	22.3 (20.6–24.0)	<0.01
Systolic BP, mm Hg	111 (103–119)	109 (103–117)	108 (101–116)	<0.01
Diastolic BP, mm Hg	69 (63, 76)	68 (62–74)	68 (62–74)	<0.01
Diabetes mellitus, n (%)	16 (1.4)	6 (0.5)	1 (0.1)	<0.01
Current smoker, n (%)	384 (34.2)	307 (26.2)	238 (21.0)	<0.01
Education level less than or equal to high school, n (%)	798 (71.1)	747 (63.9)	621 (54.9)	<0.01
METs	10.1 (8.3–12.0)	12.0 (10.1–13.8)	13.8 (13.8–15.7)	<0.01
FEV1 maximum, L	3.4 (2.9–4.0)	3.5 (3.0–4.1)	3.6 (3.1–4.2)	<0.01
FVC maximum, L	4.1 (3.4–4.9)	4.2 (3.6–5.1)	4.3 (3.7–5.2)	<0.01
Indexed LV mass, g/m^2	84.2 (71.0–101.6)	82.8 (71.2–97.0)	83.3 (70.1–98.2)	0.10
Relative wall thickness	0.34 (0.30–0.40)	0.34 (0.30–0.39)	0.34 (0.29–0.39)	0.049
LVEDV, mL	128.7 (109.0–153.1)	126.0 (107.8–146.6)	122.5 (103.7–144.9)	<0.01
LVEF, %	69.4 (63.7–74.2)	69.9 (64.0, 74.7)	70.3 (64.7–74.8)	<0.01
SVI, mL/BSA	42.7 (37.0–50.1)	43.8 (38.0–50.4)	44.3 (38.1–51.7)	<0.01
E/e' septal	9.0 (7.4–11.0)	8.5 (7.0–10.3)	8.4 (6.8–10.1)	<0.01
E/e' lateral	7.0 (5.8–8.6)	6.5 (5.4–8.0)	6.5 (5.4–7.9)	<0.01
TAPSE, cm	2.5 (2.2–2.9)	2.5 (2.2–2.8)	2.6 (2.3, 2.9)	0.02
RVS', m/s	13.0 (11.6–14.7)	13.1 (11.7–14.9)	13.4 (12.1–15.0)	<0.01
PASP, mm Hg	31.4 (28.2–35.9)	30.3 (27.0–34.0)	30.5 (27.2–34.1)	0.01

Data are presented as median (interquartile range) or number (percentage). Comparison across groups performed using Cochran-Armitage trend test and Jonckheere-Terpstra trend test for categorical and continuous variables, respectively.

Abbreviations: BMI indicates body mass index; BP, blood pressure; FEV1, forced expiratory volume in 1 second; FVC, forced vital capacity; LVEDV, left ventricular end-diastolic volume; LVEF, left ventricular ejection fraction; METs, metabolic equivalents; PASP, pulmonary artery systolic pressure; RVS', right ventricular Doppler systolic velocity of the lateral tricuspid annulus; SVI, stroke volume indexed to body surface area; and TAPSE, tricuspid annular plane systolic excursion.

Associations of Percent Change in CRF and BMI With RV Systolic Function and PASP

Among the subgroup of participants with repeat measures of CRF available at year 20 follow-up, CRF declined in the majority of participants. The median percent fitness change among the large (tertile 1), moderate (tertile 2), and mild (tertile 3) CRF decline groups was –46.8%, –29.1%, and –11.4%, respectively. The adjusted associations between change in CRF with RV systolic function parameters are shown in Table 3. In adjusted analysis, less decline in CRF with aging was significantly associated with

higher RVS' in middle age, suggesting better RV systolic function. However, CRF change on longitudinal follow-up was not significantly associated with measures of TAPSE in middle age. For measures of PASP there was a significant inverse association between longitudinal changes in CRF and PASP in middle age such that less decline in CRF with aging was associated with lower PASP.

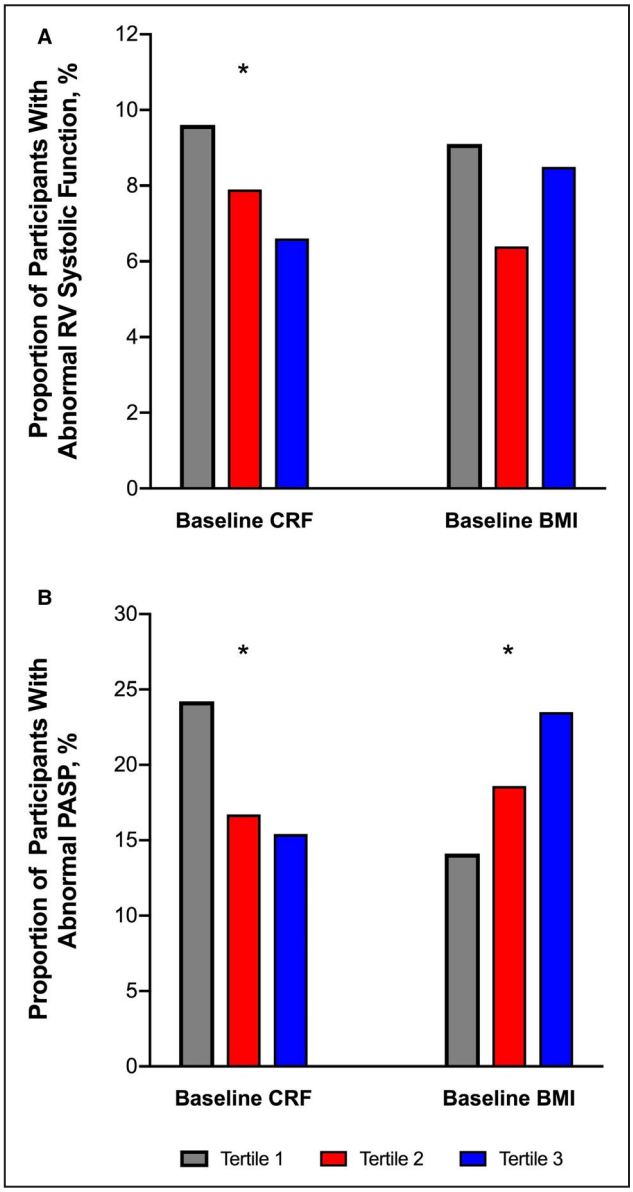

Figure. Prevalence of abnormal right ventricular (RV) systolic function (panel A) and elevated pulmonary artery systolic pressure (PASP; panel B) as defined by the American Society of Echocardiography cutoffs across age-, sex-, and race-specific tertiles of baseline cardiorespiratory fitness (CRF) and body mass index (BMI).
Median (interquartile range) maximal treadmill test duration (seconds) for each age-, sex-, and race-specific tertile of CRF was the following: tertile 1=452 (360 to 560), tertile 2=600 (480 to 720), and tertile 3=720 (603 to 840). Median (interquartile range) BMI (kg/m^2) for each age-, sex-, and race-specific tertile of BMI was the following: tertile 1=20.4 (19.4 to 21.5), tertile 2=23.5 (22.3 to 24.5), and tertile 3=28.1 (25.9 to 31.4). Abnormal RV function: RV Doppler systolic velocity of the lateral tricuspid annulus <9.5 cm/s or tricuspid annular plane systolic excursion <1.7 cm. Abnormal PASP: >36 mm Hg. *P<0.05 using Cochran-Armitage trend test.

Over 20-year follow-up, most participants gained weight. The mild (tertile 1), moderate (tertile 2), and large (tertile 3) BMI increase groups had a median percent BMI change across tertiles of +4.4%, +18.2%, and +36.6%, respectively. In multivariable-adjusted analysis, a nonlinear relationship was observed between change in BMI and RVS' such that a moderate increase in BMI on longitudinal follow-up (tertile 2 versus tertile 1) was associated with lower RVS' in middle age (Table 3). Change in BMI on longitudinal follow-up was not significantly associated with TAPSE in middle age. For PASP, a large increase in BMI on follow-up was significantly associated with higher PASP in middle age after adjusting for baseline CRF and cardiovascular risk factors.

Other Clinical Characteristics Associated With RV Systolic Function and PASP

Additional predictors of RV systolic function and PASP were identified using multivariable-adjusted linear regression. Female sex was significantly associated with better RV systolic function (TAPSE and RVS') in the adjusted analysis (Table 4). In contrast, the association of FVC with RV systolic function parameters was inconsistent such that higher FVC was significantly associated with higher RVS' but not TAPSE. Association of LV parameters with RV systolic function was inconsistent such that higher LVEDV and LV ejection fraction were each significantly associated with higher TAPSE but not RVS'. Among cardiovascular risk factors, age and systolic blood pressure were each associated with PASP but not RV systolic function parameters in the adjusted model. Black (versus White) race was significantly associated with higher RVS' and PASP.

DISCUSSION

In the present study, we observed several important findings. First, higher CRF in young adulthood was associated with higher measures of both RV systolic function parameters, TAPSE and RVS', suggesting better RV systolic function in middle age. In contrast, CRF in young adulthood was not associated with PASP in middle age after adjusting for cardiovascular risk factors. Second, less decline in CRF with aging was associated with higher RVS' and lower PASP in middle age. Third, higher BMI in young adulthood was associated with higher RV systolic function parameters as well as higher PASP in middle age. Finally, increase in BMI with aging

Table 2. Association of Baseline (Year 0) CRF and BMI With RV Systolic Function Parameters (RVS' and TAPSE) and PASP at Year 25

	RVS'				TAPSE				PASP			
	Model 1		Model 2		Model 1		Model 2		Model 1		Model 2	
	Standard ß (95% CI)	*P* Value	Standard ß (95% CI)	*P* Value	Standard ß (95% CI)	*P* Value	Standard ß (95% CI)	*P* Value	Standard ß (95% CI)	*P* Value	Standard ß (95% CI)	*P* Value
CRF												
Baseline CRF categories (referent group: tertile 1)												
CRF tertile 2	0.25 (0.03 to 0.48)	0.03	0.28 (0.05 to 0.52)	0.02	0.01 (–0.04 to 0.06)	0.66	0.01 (–0.04 to 0.06)	0.71	–0.42 (–1.30 to 0.45)	0.34	–0.46 (–1.36 to 0.43)	0.31
CRF tertile 3	0.41 (0.16 to 0.65)	<0.01	0.41 (0.16 to 0.66)	<0.01	0.07 (0.02 to 0.12)	0.01	0.07 (0.01 to 0.12)	0.01	0.27 (–0.63 to 1.17)	0.56	0.10 (–0.82 to 1.02)	0.83
BMI												
Baseline BMI categories (referent group: tertile 1)												
BMI tertile 2	0.04 (–0.18 to 0.26)	0.71	0.08 (–0.15 to 0.30)	0.50	0.05 (0.003 to 0.09)	0.04	0.03 (–0.01 to 0.08)	0.13	0.64 (–0.15 to 1.44)	0.11	0.57 (–0.25 to 1.39)	0.17
BMI tertile 3	0.23 (–0.01 to 0.47)	0.07	0.33 (0.07 to 0.58)	0.01	0.12 (0.07 to 0.17)	<0.01	0.09 (0.04 to 0.14)	<0.01	1.68 (0.78 to 2.58)	<0.01	1.44 (0.50 to 2.38)	<0.01

Separate models were constructed for each right ventricular (RV) parameter and pulmonary artery systolic pressure (PASP) outcome with inclusion of the following covariates: model 1: education, echocardiogram quality score, smoking status, systolic blood pressure, diabetes mellitus status, forced expiratory volume in 1 second, forced vital capacity, baseline body mass index (BMI), and baseline cardiorespiratory fitness (CRF) categories (both included in the same model, each reported as primary exposure variable); and model 2: model 1 covariates plus left ventricular end-diastolic volume and left ventricular ejection fraction.

RVS' indicates right ventricular Doppler systolic velocity of the lateral tricuspid annulus; and TAPSE, tricuspid annular plane systolic excursion.

Table 3. Association of Longitudinal Changes (Year 0 to Year 20) in CRF and BMI With RV Systolic Function Parameters (RVS' and TAPSE) and PASP at Year 25

	RVS'		TAPSE		PASP	
	Standard ß Estimate (95% CI)	*P* Value	Standard ß Estimate (95% CI)	*P* Value	Standard ß Estimate (95% CI)	*P* Value
CRF						
Change in CRF from year 0 to year 20 (referent group: CRF change tertile 1)						
CRF change tertile 2	0.12 (–0.15 to 0.38)	0.39	0.04 (–0.01 to 0.09)	0.13	–1.19 (–2.18 to –0.20)	0.02
CRF change tertile 3	0.31 (0.04 to 0.59)	0.03	0.05 (–0.01 to 0.10)	0.10	–1.00 (–2.01 to 0.01)	0.05
BMI						
Change in BMI from year 0 to year 20 (referent group: BMI change tertile 1)						
BMI change tertile 2	–0.38 (–0.62 to –0.14)	<0.01	–0.02 (–0.07 to 0.02)	0.35	–0.24 (–1.11 to 0.63)	0.58
BMI change tertile 3	–0.20 (–0.45 to 0.05)	0.12	–0.02 (–0.07 to 0.03)	0.54	0.98 (0.07 to 1.90)	0.03

Separate models were constructed for each right ventricular (RV) parameter and pulmonary artery systolic pressure (PASP) outcome with inclusion of the following covariates: model: education, echocardiogram quality score, smoking status, systolic blood pressure, diabetes mellitus status, forced expiratory volume in 1 second, forced vital capacity, left ventricular end-diastolic volume, left ventricular ejection fraction, baseline body mass index (BMI) and baseline cardiorespiratory fitness (CRF) categories (both included in the same model), either change in CRF or change in BMI categories (in separate models as primary exposure variable).

RVS' indicates right ventricular Doppler systolic velocity of the lateral tricuspid annulus; and TAPSE, tricuspid annular plane systolic excursion.

was significantly associated with higher PASP in middle age after adjusting for other baseline risk factors. Taken together, these study findings highlight the contributions of CRF and BMI in young adulthood on measures of RV systolic function and PASP in middle age.

Low CRF and high BMI are important risk factors for HF.[7,42–44] Recent studies have demonstrated that lower physical activity and higher BMI are each significantly associated with risk of HF, particularly HF with preserved ejection fraction.[45,46] However, the mechanisms through which CRF and BMI modify risk of HF are not known. Prior studies have demonstrated that lower CRF and higher BMI are associated with greater burden of abnormal LV remodeling and LV systolic and diastolic dysfunction.[13–17] However, the contribution of these risk factors toward RV systolic function and PASP is not well understood. This is an important knowledge gap as certain echocardiographic measures of RV structure and function and PASP have been identified as important predictors of HF development, morbidity, and mortality.[20–23] A recent cross-sectional study demonstrated a significant association between self-reported physical activity and RV stroke volume.[47] We observed that higher baseline CRF in young adulthood and lesser decline in CRF over follow-up are each associated with better RV systolic function in middle age. These findings suggest that the higher CRF-related lower risk of HF may in part be related to better RV systolic function.

In contrast with CRF, we noted an inconsistent pattern of association between BMI and RV systolic function parameters. In our study cohort, BMI assessed in young adulthood was mostly below the obese threshold and was significantly associated with higher TAPSE and RVS' on follow-up. However, longitudinal increases in BMI with aging were not consistently associated with measures of RV systolic function. Prior studies have evaluated the cross-sectional association between BMI and RV function in healthy cohorts with inconsistent findings. While, Chahal et al[48] demonstrated that obesity was associated with lower RV systolic function in the MESA (Multi-Ethnic Study of Atherosclerosis)–Right Ventricle study, other studies have failed to demonstrate this association.[49,50] Given the well-established relationship between obesity and risk of HF and the inconsistent pattern of association between BMI and RV systolic function parameters observed by us and others, it seems plausible that BMI-associated HF risk may not be related to its impact on RV systolic function. Future studies investigating alternative measures of RV systolic and diastolic function, such as RV strain, will further our understanding of the association between BMI and RV function and may help us understand the mechanisms underlying BMI-associated HF risk.

We observed that higher BMI in young adulthood and an increase in BMI over follow-up were associated with higher PASP in middle age. Prior studies have demonstrated a direct association between BMI and PASP.[23,40,51] However, these studies were mostly cross-sectional and did not adjust for CRF while evaluating the association between BMI and PASP.

Table 4. Other Clinical Characteristics Associated With RV Systolic Function Parameters (RVS' and TAPSE) and PASP at Year 25

Clinical Characteristic	Standard ß Estimate (95% CI)	*P* Value
RVS'		
Sex (male vsfemale [reference])	−0.12 (−0.19 to −0.06)	<0.01
Race (Black vs White [reference])	0.08 (0.04 to 0.13)	<0.01
Maximum FVC (per 1 SD higher)	0.19 (0.07 to 0.31)	<0.01
TAPSE		
Sex (male vs female [reference])	−0.20 (−0.26, −0.14)	<0.01
LVEDV (per 1 SD higher)	0.12 (0.07 to 0.16)	<0.01
LVEF (per 1 SD higher)	0.08 (0.04 to 0.12)	<0.01
PASP		
Age (per 1 SD higher)	0.10 (0.03 to 0.16)	<0.01
Race (Black vs White [reference])	0.08 (0.01 to 0.16)	0.02
Education (some college vs less than or equal to high school [reference])	0.08 (0.01 to 0.16)	0.03
Systolic BP (per 1 SD higher)	0.17 (0.11 to 0.24)	<0.01

Standard ß estimate for the association of baseline characteristic with each echocardiographic parameter represents the number of SDs the outcome will change per 1-SD increase in the exposure variable keeping other covariates fixed. Separate models were constructed for each right ventricular (RV) parameter and pulmonary artery systolic pressure (PASP) outcome with inclusion of the following covariates: age, sex, race/ethnicity, education status, smoking, systolic blood pressure (BP), diabetes mellitus status, echocardiogram quality score, forced expiratory volume in 1 second, forced vital capacity (FVC), left ventricular end-diastolic volume (LVEDV), left ventricular ejection fraction (LVEF), and continuous measures of body mass index (BMI) and cardiorespiratory fitness (CRF).

RVS' indicates right ventricular Doppler systolic velocity of the lateral tricuspid annulus; and TAPSE, tricuspid annular plane systolic excursion.

Furthermore, we observed that a greater increase in BMI and decline in CRF with aging was associated with higher PASP on follow-up. Given the previously reported association between PASP and risk of HF,[21] it is plausible that obesity and CRF decline–associated HF risk is at least partially influenced by higher PASP. Taken together, greater efforts are needed to prevent development and progression of obesity in young and middle age to reduce the burden of HF in older age.[52] Furthermore, improvement in CRF through promotion of greater physical activity in early and middle ages may also lower the risk of HF through its favorable effects on different aspects of cardiac structure and function.[13,53] Future studies are needed to evaluate whether intensive lifestyle interventions focused on weight loss and improvement in CRF may improve key intermediate cardiac phenotypes and lower the risk of HF.[52,53]

CRF and obesity have many cardiovascular effects, and multiple mechanisms likely underlie their associations with RV systolic function and PASP. High CRF may be associated with better RV systolic function indirectly through lower burden of cardiovascular risk factors. Additionally, individuals who exercise have increased cardiac capillary density and antioxidative and mitochondrial function, which may contribute to RV systolic function.[54,55] The adverse association between BMI and PASP is likely related to both flow characteristics and vascular remodeling. For example, obese individuals had higher baseline RV systolic function in the present study and are known to have higher cardiac output, and this increased flow, without a concomitant decrease in pulmonary vascular resistance, can lead to elevations in PASP.[51,56] Additionally, obesity often coexists with obstructive sleep apnea, which may lead to hypoxic vasoconstriction and increased PASP.[57] Finally, adipose tissue releases adipokines, including leptin and adiponectin, which may be involved with pulmonary vascular remodeling and lead to elevated PASP.[58,59] Specific body composition measures, such as fat mass and lean mass, may have differential contributions to cardiac remodeling patterns and risk of HF.[60]

Measures of RV structure and function such as presence of RV hypertrophy, RV systolic dysfunction, and increased PASP are associated with higher risk of HF.[20–22] The mechanisms underlying these associations are not well understood and could be related to several factors. First, RV dysfunction and elevated PASP may directly lead to clinical symptoms of HF such as lower extremity swelling, pulmonary edema, and dyspnea.[61] Second, abnormalities in LV structure and function that underlie the transition from at-risk (stage A) to clinical HF (stage C) may also contribute to abnormalities in right-sided heart function. LV systolic or diastolic dysfunction leads to elevated LV end-diastolic pressure, which may cause pulmonary venous hypertension and resultant high PASP and RV systolic dysfunction. Therefore, RV function and PASP may integrate the downstream consequences of LV dysfunction. Finally, risk factors for HF can adversely affect both RV and LV function such that subclinical abnormalities in RV function may precede and contribute to the development of HF. Consistent with this notion, we observed that low CRF and high BMI can adversely affect RV systolic function and PASP, after adjusting for LV function and other cardiovascular risk factors, which could contribute to downstream risk of HF. Taken together with our study findings, low CRF- and high BMI-associated risk of HF may be related to RV systolic function and PASP. Future

studies in cohorts with available CRF and BMI data, well phenotyped RV parameters on follow-up and subsequent HF events, are needed to better understand how abnormalities in RV function may contribute to low CRF- and obesity-associated risk of HF.

The primary strengths of our study include the large sample size, availability of objective measures of primary exposure variables of interest (CRF and BMI) at baseline and at year 20 follow-up, and detailed echocardiographic assessment of RV systolic function and PASP at year 25 follow-up. Several limitations of our analysis are also noteworthy. First, we cannot rule out the possibility of residual confounding in the observed associations owing to the observational study design. Second, we do not have measures of RV structure and function at the time of the baseline examination and, thus, we cannot rule out the possibility of reverse causation. However, owing to the young age and relative health of this cohort at baseline, the likelihood that differences in CRF are related to abnormalities in RV systolic function and PASP at baseline is low. Third, while RV systolic function assessment was available in the majority of participants (>90% for both TAPSE and RVS'), PASP assessment on follow-up was available in only one third of the CARDIA study population, raising the possibility of potential selection bias. However, the baseline characterstics of participants with versus those without available PASP measurement, including measures of BMI and CRF levels, were not meaningfully different, arguing against a significant selection bias in our analysis. Fourth, the observed associations were not adjusted for multiple testing, which may increase the likelihood of a type I error and, thus, our study findings are hypothesis generating and need further validation in other prospective cohorts. Finally, owing to the young age of the study population and few HF events, we cannot evaluate how abnormalities in RV function may contribute to low CRF and obesity-associated risk of HF. However, given the importance of BMI and CRF in this relatively young and healthy study population, these risk factors may have important prognostic implications in a cohort of older individuals with multiple comorbidities and this requires further study.

CONCLUSIONS

Our findings suggest that higher CRF and less decline in CRF with aging may favorably influence RV function in middle age. Similarly, lower BMI in young adulthood and less increase in BMI with aging is associated with lower PASP in middle age. Future studies are needed to determine how RV systolic function and PASP may modify high BMI– and low CRF–related risk of downstream clinical events such as HF and associated long-term prognosis.

ARTICLE INFORMATION

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This article has been reviewed by CARDIA for scientific content. The corresponding author had full access to all of the data in the study and had final responsibility for the decision to submit for publication. All authors have read and agree to the article as written. The views expressed in this article are those of the authors and do not necessarily represent the views of the National Heart, Lung, and Blood Institute; the National Institutes of Health; or the US Department of Health and Human Services.

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Disclosures

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Supplementary Material

Data S1
Table S1–S2

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SUPPLEMENTAL MATERIAL

Data S1.

Supplemental Methods

During the graded exercise treadmill test protocol, each subsequent stage became increasingly difficult (28). Stage 1 speed was 3 miles per hour (mph) at a grade of 2%. During stages 2 through 6, the speed was 3.4 mph while grade started at 6% and increased by 4% each stage. At a constant speed of 4.2 mph, stage 7 grade was 22% and stage 8 grade was 25%. The speed was 5.6 mph and grade was 25% during the final stage. During the initial six stages, participants were typically able to walk. This exercise protocol facilitated test performance for participants not familiar with jogging. Participants achieved 4.1, 6.4, 8.3, 10.1, 12.0, 13.8, 15.7, 17.1, and 19.0 METs with completion of stages 1, 2, 3, 4, 5, 6, 7, 8, and 9, respectively. For participants who did not finish the test protocol at the end of the two-minute stage, METs were calculated by linear interpolation. For example, a participant who exercised for 12 minutes and 12 seconds completed stage 6 (13.8 METs) and 10% (12/120) of stage 7 which would lead to an estimated total of 14 METs (13.8 METs + [(12/120) x (15.7-13.8)]).

Table S1. Baseline characteristics stratified by body mass index.

	Tertile 1 (n = 1,116)	Tertile 2 (n = 1,172)	Tertile 3 (n = 1,137)	P value
BMI, kg/m^2	20.4 (19.4, 21.5)	23.5 (22.3, 24.5)	28.1 (25.9, 31.4)	<0.01
Age, years	26 (22, 28)	26 (22, 28)	26 (22, 28)	0.92
Females, n (%)	633 (56.7)	665 (56.7)	642 (56.5)	0.90
Black, n (%)	521 (46.7)	545 (46.5)	532 (46.8)	0.96
Systolic BP, mm Hg	107 (101, 115)	109 (102, 116)	112 (105, 120)	<0.01
Diastolic BP, mm Hg	68 (62, 74)	68 (62, 73)	70 (64, 76)	<0.01
Diabetes, n (%)	6 (0.5)	5 (0.4)	11 (1.0)	0.20
Current smoker, n (%)	325 (29.1)	302 (25.8)	300 (26.4)	0.15
Education level less than or equal to high school, n (%)	680 (61.2)	717 (61.3)	764 (67.3)	<0.01
METs	13.8 (12.0, 15.7)	12.0 (10.1, 13.8)	12.0 (10.1, 13.8)	<0.01
FEV1 maximum, L	3.4 (3.0, 4.1)	3.5 (3.0, 4.1)	3.5 (2.9, 4.2)	0.52
FVC maximum, L	4.1 (3.5, 4.9)	4.2 (3.6, 5.1)	4.2 (3.5, 5.1)	0.04
Maximal treadmill test duration, seconds	630 (502, 765)	600 (480, 720)	511 (404, 660)	<0.01
Indexed LV mass, g/m^2	80.1 (68.6, 94.0)	83.4 (71.2, 98.4)	86.9 (73.8, 103.7)	<0.01
Relative wall thickness	0.33 (0.29, 0.39)	0.34 (0.30, 0.39)	0.34 (0.30, 0.40)	0.01
LVEDV, mL	116.0 (99.6, 137.0)	126.0 (108.0, 146.0)	136.0 (115.6, 159.8)	<0.01
LVEF, %	70.2 (64.3, 74.8)	70.1 (64.6, 74.6)	69.3 (63.7, 74.4)	0.04
SVI, mL/BSA	43.2 (37.1, 51.0)	43.9 (38.3, 50.8)	43.7 (37.9, 50.8)	0.58
E/e' septal	8.3 (6.8, 10.1)	8.5 (7.1, 10.4)	9.0 (7.4, 11.1)	<0.01
E/e' lateral	6.5 (5.3, 7.8)	6.6 (5.5, 8.0)	6.9 (5.8, 8.6)	<0.01
TAPSE, cm	2.5 (2.2, 2.8)	2.5 (2.3, 2.8)	2.6 (2.3, 2.9)	<0.01
RVS', m/s	13.1 (11.7, 14.7)	13.2 (11.9, 14.9)	13.2 (11.7, 15.0)	0.31
PASP, mm Hg	30.2 (27.0, 33.7)	30.6 (27.0, 34.8)	31.4 (28.4, 35.5)	<0.01

Data presented as median (interquartile range) or n (%). Comparison across groups performed using Cochran-Armitage trend test and Jonckheere-Terpstra trend test for categorical and continuous variables, respectively.BMI = body mass index; BP = blood pressure; FEV1 = forced expiratory volume in 1 second; FVC = forced vital capacity; LVEDV = left ventricular end-diastolic volume; LVEF = left ventricular ejection fraction; METs = metabolic equivalents; PASP: pulmonary artery systolic pressure;

RVS’ = right ventricular Doppler systolic velocity of the lateral tricuspid annulus; SVI = stroke volume indexed to body surface area; TAPSE = tricuspid annular plane systolic excursion.

Table S2. Baseline characteristics of participants who had an echocardiogram performed stratified by PASP availability at year 25.

	No PASP available (n = 2,140)	PASP available (n = 1,293)
Age, years	25 (22, 28)	26 (22, 28)
Females, n (%)	1,150 (53.7)	796 (61.6)
Black, n (%)	967 (45.2)	634 (49.0)
BMI, kg/m^2	23.7 (21.4, 26.7)	23.0 (20.9, 25.9)
Systolic BP, mm Hg	110 (103, 118)	108 (101, 116)
Diastolic BP, mm Hg	69 (63, 75)	68 (62, 74)
Diabetes, n (%)	14 (0.7)	9 (0.7)
Current smoker, n (%)	585 (27.3)	344 (26.6)
Education level less than or equal to high school, n (%)	1,342 (62.9)	824 (63.9)
FEV1 maximum, L	3.4 (2.9, 4.0)	3.5 (3.0, 4.2)
FVC maximum, L	4.1 (3.5, 4.9)	4.3 (3.6, 5.1)
Maximal treadmill test duration, seconds	600 (460, 720)	597 (479, 720)
Indexed LV mass, g/m^2	83.5 (71.5, 97.7)	82.8 (69.8, 99.6)
Relative wall thickness	0.34 (0.29, 0.39)	0.34 (0.30, 0.39)
LVEDV, mL	127.0 (108.0, 148.3)	123.0 (104.0, 146.0)
LVEF, %	69.8 (64.2, 74.3)	70.0 (64.6, 75.1)
SVI, mL/BSA	43.8 (38.0, 50.4)	43.5 (37.1, 51.4)
E/e' septal	8.5 (7.0, 10.4)	8.7 (7.1, 10.5)
E/e' lateral	6.6 (5.5, 8.1)	6.8 (5.7, 8.2)
TAPSE, cm	2.5 (2.3, 2.9)	2.5 (2.2, 2.9)
RVS', m/s	13.2 (11.7, 14.8)	13.2 (11.8, 14.9)

Data presented as median (interquartile range) or n (%). BMI = body mass index; BP = blood pressure; FEV1 = forced expiratory volume in 1 second; FVC = forced vital capacity; LVEDV = left ventricular end-diastolic volume; LVEF = left ventricular ejection fraction; PASP: pulmonary artery systolic pressure; RVS' = right ventricular Doppler systolic velocity of the lateral tricuspid annulus; SVI = stroke volume indexed to body surface area; TAPSE = tricuspid annular plane systolic excursion.