ORIGINAL RESEARCH

Transitions in Metabolic Risk and Long-Term Cardiovascular Health: Coronary Artery Risk Development in Young Adults (CARDIA) Study

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***Background*—**Despite evidence suggesting that early metabolic dysfunction impacts cardiovascular disease risk, current guidelines focus on risk assessments later in life, missing early transitions in metabolic risk that may represent opportunities for averting the development of cardiovascular disease.

***Methods and Results*—**In 4420 young adults in the Coronary Artery Risk Development in Young Adults (CARDIA) study, we defined a "metabolic" risk score based on components of the Third Report of the Adult Treatment Panel's definition of metabolic syndrome. Using latent class trajectory analysis adjusted for sex, race, and time-dependent body mass index, we identified 6 distinct metabolic trajectories over time, specified by initial and final risk: low-stable, low-worsening, high-stable, intermediate-worsening, intermediate-stable, and high-worsening. Overall, individuals gained weight over time in CARDIA with statistically but not clinically different body mass index trend over time. Dysglycemia and dyslipidemia over time were highest in initially high or worsening trajectory groups. Divergence in metabolic trajectories occurred in early adulthood (before age 40), with 2 of 3 individuals experiencing an increase in metabolic risk over time. Membership in a higher-risk trajectory (defined as initially high or worsening over time) was associated with greater prevalence and extent of coronary artery calcification, left ventricular mass, and decreased left ventricular strain at year 25. Importantly, despite similar rise in body mass index across trajectories over 25 years, coronary artery calcification and left ventricular structure and function more closely tracked risk factor trajectories.

***Conclusions*—**Transitions in metabolic risk occur early in life. Obesity-related metabolic dysfunction is related to subclinical cardiovascular phenotypes independent of evolution in body mass index, including coronary artery calcification and myocardial hypertrophy and dysfunction. **(*J Am Heart Assoc*. 2016;5:e003934 doi: 10.1161/JAHA.116.003934)**

Key Words: epidemiology • metabolic syndrome • obesity • risk factor

Metabolic syndrome is a well-established risk factor for cardiovascular disease (CVD), including coronary artery disease and heart failure.[1] Alterations in metabolic risk linked to CVD may develop over decades before clinical CVD.[2–5] Prior work in large, community-based populations have defined a role for early, cumulative changes in blood pressure(BP)[6] and

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Accompanying Table S1 and Figure S1 are available at http://jaha.ahajournals.org/content/5/10/e003934/DC1/embed/inline-supplementary-material-1.pdf

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obesity[7] in forecasting risk of subclinical CVD in midlife and beyond. This "life-course" perspective on cardiometabolic risk—and resulting recommendations to maintain an ideal body weight, diet, physical activity, and lipid profile—is critical to decrease incident CVD.[8] Although obesity has frequently been cited as a central pathogenic factor for CVD risk, emerging literature suggests that cardiometabolic risk may evolve independently from body mass index (BMI).[9,10] Therefore, defining how cardiometabolic risk evolves during early adulthood—and how these changes are related to CVD risk independent of cumulative exposure to obesity—is critical to differentiate healthy young adult populations from at-risk ones, ultimately to allow for personalized CVD prevention.

We investigated individuals from the Coronary Artery Risk Development in Young Adults (CARDIA) study to define transitions in cardiometabolic risk over 25 years independent of obesity. Furthermore, we sought to compare markers of subclinical CVD—including left ventricular (LV) mass (LVM), function, and coronary artery calcium—at 25 years after baseline visit among different groups of participants that follow distinct patterns of transition in metabolic risk. We hypothesized that individuals who experienced worsening cardiometabolic risk during young adulthood would exhibit a poorer subclinical CVD profile at midlife, defined by increased myocardial mass, decreased myocardial function, and coronary artery calcification (CAC).

Methods

Study Population

The CARDIA trial is a longitudinal cohort designed to study determinants of CVD among 5115 young adults (aged 18–30) initially recruited in 1985–1986. Participants were recruited from 4 sites across the United States, including Birmingham, AL; Chicago, IL; Minneapolis, MN; and Oakland, CA. Recruitment balanced enrollment at each site by sex, age (18–24 years vs 25–30 years), race, and education. Serial follow-up of participants at years 2, 5, 7, 10, 15, 20, and 25 (2010–2011) after enrollment has been performed, with 72% retention of surviving participants at year 20 and 25. All participants provided written informed consent, with annual institutional review board approval. Clinical assessments were performed at each CARDIA visit as described.[11–15] From an initial cohort of 5115 individuals, we excluded individuals with self-reported congenital heart disease, congestive heart failure, cardiomyopathy, myocarditis, rheumatic heart disease, valvular heart disease (all assessed at baseline study visit), prior myocardial infarction reported at baseline or final study visit, bariatric surgery by final study visit, or withdrawn consent for study participation, leaving 4941 CARDIA participants (97% of the study cohort) for analysis.

Metabolic Risk Score for Transitions

To reflect current metrics for metabolic risk assessment in the clinic,[16] we defined a "metabolic risk score" by assigning +1 point for each of the following 5 high-risk features, based on the Third Report of the Adult Treatment Panel (ATP III) definition of metabolic syndrome[17]: (1) triglyceride concentration ≥150 mg/dL; (2) high-density lipoprotein concentration ≤40 mg/dL (in men) or ≤50 mg/dL (in women); (3) waist circumference ≥102 cm (in mend) or ≥89 cm (in women); (4) systolic BP ≥135 mm Hg (mean of two different readings), self-reported history of hypertension, or current or former use of BP medication; and (5) self-reported diabetes or fasting glucose concentration ≥100 mg/dL. Self-reported diabetes only was used for the fifth criteria in examinations at year 2 and year 5, as glucose was not measured on these visits. The range for the metabolic risk score was therefore 0 to 5 points. We did not include BMI in the metabolic risk score, as we sought to measure metabolic risk development independent of obesity status. (Cumulative BMI adjustment was performed in logistic models; see Statistical Analysis below.) The presence of each risk factor used to construct the score over all CARDIA examinations is shown in Table S1.

Cardiovascular Imaging

We examined the CAC score at the most contemporary CARDIA examination (year 25, 2010–2011), using a standard multidetector computed tomography scanner platform as described.[18] CAC score was handled as "non-zero" and as a continuous variable (with log-transformation) for positive CAC scores. Speckle tracking echocardiography and M-mode echocardiography were performed using an Artida cardiac ultrasound scanner (Toshiba Medical Systems, Otawara, Japan) using standardized protocols across all centers at year 25, with offline imaging interpretation (Digisonics, Inc, Houston, TX).[19] LVM was derived from the Devereux formula[20] and indexed to height. Speckle tracking echocardiography images for myocardial strain measurements were analyzed for LV midwall layer, using 2D Wall Motion Tracking software (Toshiba Medical Systems), from 3 cardiac cycles for each view, recorded for offline analyses. Strain was calculated as the change in segment length relative to its end-diastolic length, and the peak systolic value from the 4-chamber images was recorded as the longitudinal strain.

Statistical Analysis

Baseline clinical and demographic characteristics were compared via analysis of variance or nonparametric (Kruskal-Wallis) techniques, as appropriate. From the initial 4941 CARDIA participants, we excluded participants without a measurable metabolic risk score at baseline, fewer than 3

assessments of the metabolic risk score over 8 total CARDIA examinations, or missing BMI, sex, or race assessment at baseline study visit, leaving 4420 CARDIA participants (89% of the initial study cohort) for trajectory analysis.

To specify transitions in metabolic risk over time, we used latent class models to identify groups of CARDIA participants that share a common trajectory of metabolic risk over time.[21] Trajectories in metabolic risk score (using a censored normal model using PROC TRAJ in SAS) were specified as a function of participant age, with baseline adjustment by sex and race (using the RISK option), and time-dependent adjustment for BMI (using the TCOV option). We determined the optimal number of underlying trajectories (starting from 8 total trajectories modeled with second-order terms) by a composite criteria consisting of: (1) confirming visually distinct trajectories; (2) ensuring >5% membership in any single trajectory group; and (3) observing improvement in the Bayesian information criterion. The average posterior probability of group membership was 0.76 (range 0.72–0.82). Metabolic score at year 25 was calculated in 3262 participants (74% of the initial 4420 analytic cohort; compared to a 72% overall retention rate in the overall CARDIA study).

We estimated the relationship between group membership and subclinical CVD using logistic regression models, with group membership entered as an independent variable. "Subclinical CVD" was defined by (1) the presence of CAC (modeled as CAC >0) at year 25 or a significant extent of CAC at year 25 (>100); (2) height-adjusted LVM at year 25; and (3) LV longitudinal strain at year 25. Each model was adjusted for baseline age, race, sex, education, lifetime pack-years of smoking (at year 25), and total intentional (heavy) physical activity (at year 25). Given our central goal to separate obesity from metabolic risk, in addition to using BMI as a time-dependent covariate in defining metabolic groups, we further adjusted for a "cumulative BMI exposure" (in BMI-years), defined as the sum of each product between BMI at a given CARDIA examination and the time between that examination and the following examination. To calculate cumulative BMI exposure, we required participants to have BMI measurements at year 0 and year 25 and a minimum of 2 BMI measurements at interim examinations. We calculated multivariable-adjusted least squares means for LVM and LV strain across all trajectory groups. Because a large number of participants were missing data on the 3 subclinical CVD outcomes, we performed a sensitivity analysis using inverse probability of treatment weighting using the propensity score, as described in our previous work.[22] The propensity score for inclusion in the analysis of the subclinical CVD outcome was based on a logistic regression model containing age, race, sex, systolic BP, education, heavy physical activity, cigarette smoking, total cholesterol, high-density lipoprotein (HDL) cholesterol, triglycerides, BMI, diabetes status, BP medications at baseline, fasting glucose, serum creatinine, alcohol intake, and weighted life-events score as baseline predictors. The inverse propensity probability of inclusion in the analysis was used to perform a weighted regression analysis of the outcomes, without significant change in results. Finally, we evaluated multiplicative interaction terms for sex and race.

Given that latent group modeling assigns individuals to groups in a probabilistic fashion, we generated 50 separate replicates (based on the distribution of posterior probability of group membership). We subsequently estimated logistic regression models for each outcome in every replicate, yielding a composite result across the different imputed group assignment data sets. SAS version 9.3 (SAS Institute, Cary, NC) was used for all analyses, and a two-tailed $P<0.05$ was considered statistically significant.

Results

The 6 metabolic trajectories obtained through latent class trajectory modeling in this analysis to identify metabolic transitions are shown in Figure 1. The baseline clinical and demographic characteristics and outcomes of the 4420 CARDIA participants stratified by metabolic trajectory are displayed in Table 1. Six distinct metabolic trajectories were labeled by the metabolic score at baseline study visit and year 25 study visit: group 1 (low-stable; 17%), group 2 (low-worsening; 21%), group 3 (intermediate-stable; 17%), group 4 (intermediate-worsening; 14%), group 5 (high-stable; 23%), and group 6 (high-worsening; 7%). On average, the overall CARDIA sample in this analysis (N=4420) was evenly divided

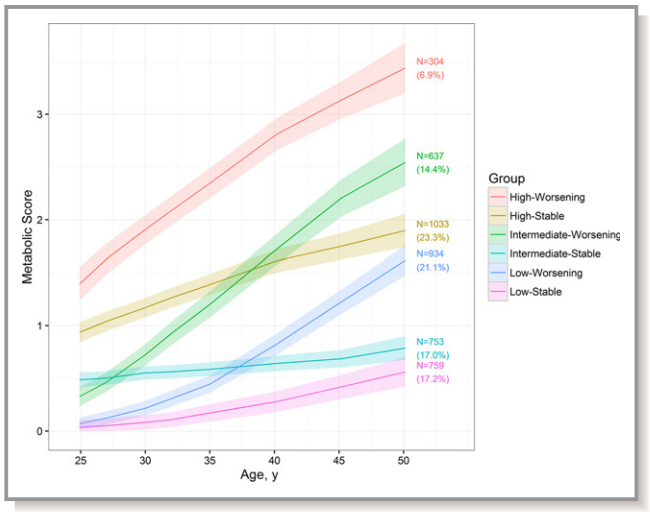

Figure 1. Metabolic trajectories over time in the Coronary Artery Risk Development in Young Adults (CARDIA) trial. Each trajectory is represented by a different color, with shaded bands representing 95% CIs.

Table 1. Characteristics of 4420 CARDIA Participants by Metabolic Trajectory Group

Covariate	Study Population (N=4420)	Metabolic Trajectory Groups						*P* Value
		Group 1 (Low-Stable) (n=759)	Group 2 (Low-Worsening) (n=934)	Group 3 (Int-Stable) (n=753)	Group 4 (Int-Worsening) (n=637)	Group 5 (High-Stable) (n=1033)	Group 6 (High-Worsening) (n=304)	
Baseline demographics								
Age, mean (SD), y	24.9 (3.6)	25.2 (3.6)	25.0 (3.6)	24.7 (3.6)	25.0 (3.7)	24.7 (3.7)	25.2 (3.4)	0.01
Male sex, No. (%)	2020 (45.7)	284 (37.4)	612 (65.5)	204 (27.1)	418 (65.6)	306 (29.6)	196 (64.5)	<0.0001
Black race, No. (%)	2210 (50.0)	371 (48.9)	487 (52.1)	387 (51.4)	332 (52.1)	538 (52.1)	95 (31.3)	<0.0001
Educational attainment at Y0, mean (SD), y	13.9 (2.3)	14.3 (2.3)	14.1 (2.3)	13.9 (2.2)	13.6 (2.2)	13.6 (2.2)	13.6 (2.3)	<0.0001
Current smoker, No. (%) (n=4392)	1289 (29.4)	148 (19.6)	235 (25.4)	200 (26.7)	240 (37.9)	357 (34.7)	109 (36.3)	<0.0001
Physical activity (moderate and vigorous), median at baseline (IQR), exercise units								
Y0 (n=4419)	365 (198–577)	380 (209–620)	426 (246–645)	328 (185–545)	396 (208–620)	305 (156–500)	347 (192–559)	<0.0001
Y25 (n=3251)	279 (134–493)	328 (168–556)	312 (146–522)	266 (120–494)	272 (144–482)	231 (108–410)	247 (112–456)	<0.0001
Alcohol consumption, median (IQR), mL/d (n=4403)	4.8 (0.0–14.6)	4.8 (0–14.3)	7.6 (0–19.8)	2.4 (0–10.6)	7.2 (0–17.7)	2.4 (0–12.1)	4.8 (0–14.5)	<0.0001
Medication use ever, No. (%)								
Antihypertensive	1077 (24.4)	49 (6.5)	234 (25.1)	102 (13.6)	227 (35.6)	307 (29.7)	158 (52.0)	<0.0001
Lipid-lowering	614 (13.9)	41 (5.4)	119 (12.7)	71 (9.4)	140 (22.0)	145 (14.0)	98 (32.2)	<0.0001
Cardiometabolic risk factors								
Mean BMI (SD), kg/m^2								
Baseline (Y0)	24.4 (4.9)	23.5 (3.9)	24.1 (3.7)	25.4 (6.8)	24.0 (4.0)	24.7 (5.2)	24.5 (4.4)	<0.0001
Follow-up (Y25) (n=3274)	30.1 (7.2)	28.6 (6.3)	29.7 (5.4)	31.3 (10.3)	29.0 (5.1)	31.1 (7.5)	30.4 (5.3)	<0.0001
Waist circumference, mean (SD)								
Baseline (Y0)	77.6 (11.2)	73.9 (9.2)	78.0 (9.1)	77.5 (13.8)	78.9 (10.4)	77.7 (11.8)	82.0 (11.4)	<0.0001
Follow-up (Y25) (n=3271)	94.3 (15.9)	88.2 (14.1)	95.5 (13.3)	92.6 (19.6)	96.4 (13.3)	96.1 (16.9)	101.1 (13.1)	<0.0001
Glucose, mean (SD), mg/dL								
Baseline (Y0) (n=4278)	82.3 (13.3)	79.7 (6.9)	82.2 (7.6)	81.2 (9.9)	83.8 (11.6)	82.6 (16.4)	87.9 (27.9)	<0.0001
Follow-up (Y25) (n=3146)	99.3 (27.5)	91.0 (16.0)	101.6 (26.2)	92.0 (15.3)	109.8 (38.6)	97.3 (22.4)	119.1 (46.3)	<0.0001
Diabetes, No. %								
Baseline (Y0)	25 (0.6)	0 (0)	1 (0.1)	5 (0.7)	4 (0.6)	5 (0.5)	10 (3.3)	<0.0001
Follow-up (Y25) (n=3272)	456 (13.9)	20 (3.5)	88 (12.4)	43 (7.5)	114 (24.2)	113 (15.1)	78 (38.6)	<0.0001
Triglycerides, mean (SD), mg/dL								
Baseline (Y0)	72.6 (47.5)	54.7 (21.4)	63.2 (26.4)	66.6 (40.0)	78.7 (49.9)	78.5 (46.1)	128.4 (93.1)	<0.0001
Follow-up (Y25) (n=3147)	113.8 (86.1)	76.0 (30.5)	111.2 (71.3)	84.7 (33.8)	151.7 (106.6)	112.8 (58.7)	229.5 (185.0)	<0.0001

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Table 1. Continued

Covariate	Study Population (N=4420)	Metabolic Trajectory Groups						*P* Value
		Group 1 (Low-Stable) (n=759)	Group 2 (Low-Worsening) (n=934)	Group 3 (Int-Stable) (n=753)	Group 4 (Int-Worsening) (n=637)	Group 5 (High-Stable) (n=1033)	Group 6 (High-Worsening) (n=304)	
HDL mean (SD)								
Baseline (Y0) (n=4322)	53.2 (13.1)	62.6 (11.8)	57.2 (11.2)	53.7 (12.1)	51.1 (11.9)	47.1 (11.4)	40.5 (9.2)	<0.0001
Follow-up (Y25) (n=3269)	57.8 (17.8)	70.2 (17.5)	58.6 (17.1)	63.1 (14.6)	51.4 (19.0)	52.4 (14.0)	40.5 (8.6)	<0.0001
Systolic blood pressure, mean (SD), mm Hg								
Baseline (Y0)	110.4 (10.9)	106.8 (9.6)	111.5 (9.5)	108.6 (10.8)	112.7 (10.2)	110.0 (11.5)	117.0 (12.9)	<0.0001
Follow-up (Y25) (n=3276)	118.7 (15.3)	112.9 (12.7)	120.2 (14.7)	116.2 (15.1)	123.4 (16.6)	118.7 (15.4)	125.3 (15.2)	<0.0001
Diastolic blood pressure, mean (SD), mm Hg								
Baseline (Y0)	68.6 (9.6)	66.4 (8.3)	69.2 (8.8)	67.5 (8.7)	69.1 (10.1)	68.4 (10.2)	73.9 (11.3)	<0.0001
Follow-up (Y25) (n=3275)	74.0 (10.9)	70.0 (9.8)	75.0 (10.7)	72.4 (11.0)	76.7 (11.1)	74.4 (10.5)	78.0 (10.9)	<0.0001
Psychosocial risk factors								
No. of life events at Y0, mean (SD) (n=4418)	8.3 (4.6)	7.9 (4.4)	8.3 (4.8)	8.3 (4.8)	8.5 (4.6)	8.3 (4.5)	8.3 (4.9)	0.31
Weighted life events score at Y0, mean (SD) (n=4418)	2363 (1397)	2281 (1316)	2377 (1463)	2361 (1460)	2437 (1398)	2350 (1331)	2415 (1450)	0.42
Cook-Medley Hostility Score at Y0, mean (SD) (n=4261)	19.4 (8.6)	18.0 (8.1)	20.0 (8.5)	19.1 (8.9)	20.8 (8.5)	19.3 (8.7)	19.5 (8.5)	<0.0001
Markers of subclinical cardiovascular disease								
CAC score at Y25, median (IQR) (n=2997)	0 (0–3.9)	0 (0–0)	0 (0–4.7)	0 (0–0)	0 (0–18.7)	0 (0–3.1)	1.6 (0–60.7)	<0.0001
Presence of any CAC at Y25, No. % (n=2997)	834 (27.8)	86 (17.0)	188 (29.1)	105 (19.7)	169 (39.1)	190 (27.5)	96 (50.8)	<0.0001
LV mass index, mean (SD), $g/m^{2.7}$								
Y5 (n=3868)	35.1 (9.2)	34.0 (9.1)	35.8 (8.7)	35.2 (9.8)	34.5 (8.2)	35.1 (9.2)	36.2 (10.7)	0.0008
Y25 (n=2932)	39.7 (11.6)	36.6 (9.4)	40.2 (10.4)	39.8 (13.6)	40.1 (11.5)	40.3 (11.8)	43.6 (13.4)	<0.0001
LV longitudinal strain at Y25, mean (SD), % (n=2849)	−15.1 (2.4)	−15.7 (2.3)	−14.9 (2.3)	−15.4 (2.4)	−14.6 (2.3)	−15.1 (2.4)	−14.1 (2.4)	<0.0001

Educational attainment is defined as years of education attained by initial Coronary Artery Risk Development in Young Adults (CARDIA) study examination. Psychosocial stress scores (eg, life events, hostility scores) are as described in prior work in CARDIA.[15] BMI indicates body mass index; CAC, coronary artery calcification; HDL, high-density lipoprotein; Int, intermediate; IQR, interquartile range; LV, left ventricular; MI, myocardial infarction; Y, year.

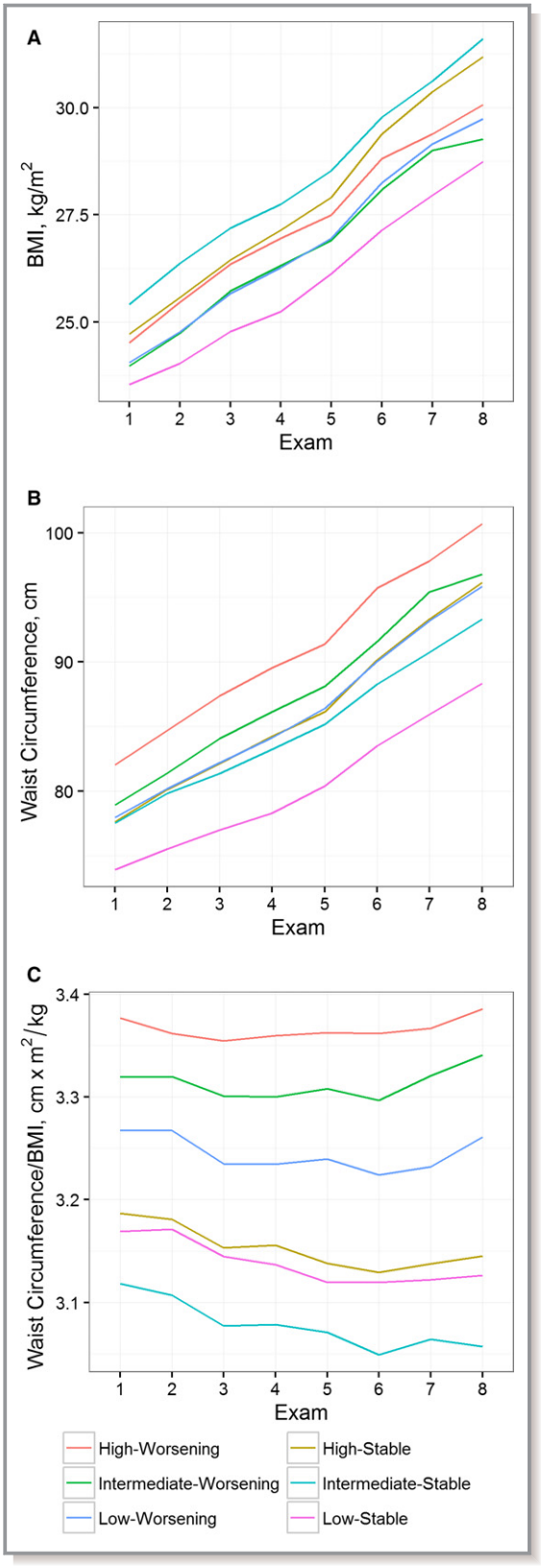

Figure 2. Trends in body mass index (BMI) (A), waist circumference (WC) (B), and ratio of WC/BMI (C) over time in the Coronary Artery Risk Development in Young Adults (CARDIA) trial, stratified by trajectory group computed using linear mixed-effects models with discrete time points for each CARDIA exam and exam×trajectory group interaction terms. Over time, all groups had similar increases in BMI and WC. While worsening groups had stable WC/BMI ratios ($P \geq 0.29$ for exam 1 vs exam 8), the stable groups all had declining WC/BMI ratios ($P \leq 0.0005$ for exam 1 vs exam 8), suggesting greater proportionate increases in abdominal adiposity in the metabolically worsening groups.

by sex (54% female), with a normal BMI (24.4±4.9 kg/m^2), normal fasting glucose (82.3±13.3 mg/dL), and minimal prevalent metabolic dysfunction (only 0.6% prevalent diabetes). We observed very slight, clinically insignificant heterogeneity in BMI and waist circumference across trajectory groups at baseline. There was clinically and statistically significant heterogeneity in baseline proatherogenic dyslipidemia (triglycerides and HDL).

On average, participants who attended the final year 25 CARDIA examination were heavier than those attending the initial study visit (initial BMI 24.4±4.9 kg/m^2 to final BMI 30.1±7.2 kg/m^2), with greater central obesity (by waist circumference), dysglycemia, and a more proatherogenic lipid profile. Of 4420 participants at baseline, 1516 (34%) were overweight or obese (by BMI ≥25 kg/m^2). Of the 3274 CARDIA participants in our analytic sample at year 25, 2435 (74%) were overweight or obese. While individuals on average gained weight over time (with statistically significant differences in weight gain across trajectories, $P<0.0001$), among those participants with BMI assessed at year 0 and year 25 in our analytic cohort, there was an increase in BMI and central obesity, with a similar pattern across all trajectories (Figure 2A and 2B). In addition, we considered waist circumference to BMI ratio (a marker of preferential visceral fat stores; Figure 2C). We found that individuals with worsening metabolic trajectories have a stable ratio over time, while individuals with stable trajectories have a declining ratio, suggesting that less excess weight gained over time is visceral in these individuals. Of note, waist circumference also appeared to have a similar association with baseline metabolic score in lean and overweight/obese individuals (Figure S1).

Despite similar trends in weight gain over time in CARDIA across metabolic trajectories, there was significant heterogeneity in fasting glucose, triglyceride, and HDL levels. Specifically, initially low or intermediate and stable trajectories of metabolic risk (group 1 and 3) had only modest worsening in these metabolic parameters over 25 years, while CARDIA participants in the most adverse trajectories (eg, group 6: high-worsening) had the poorest metabolic indices at year 25 (Table 1).

Logistic models for presence of coronary calcium and extent of CAC, and linear models for LVM and strain are

Table 2. Multivariable Models for CAC and LV Mass and Strain

	Presence of CAC at Y25 (n=2941)		CAC Score at Y25 >100 (n=2941)		Height-Indexed LV Mass at Y25 (n=2882)		LV Strain at Y25 (n=2796)	
Covariate	Odds Ratio	*P* Value	Odds Ratio	*P* Value	β	*P* Value	β	*P* Value
Age, Y25 (per year)	1.15 (1.12–1.18)	<0.0001	1.24 (1.19–1.30)	<0.0001	0.12	0.02	0.03	0.007
Sex								
Female	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref
Male	3.34 (2.74–4.06)	<0.0001	3.48 (2.53–4.78)	<0.0001	1.89	<0.0001	0.75	<0.0001
Race								
White	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref
Black	0.80 (0.65–0.97)	0.03	0.97 (0.72–1.31)	0.86	2.05	<0.0001	0.89	<0.0001
Smoking (per pack-year)	1.03 (1.02–1.04)	<0.0001	1.02 (1.01–1.04)	<0.0001	0.06	0.002	0.004	0.36
Physical activity, Y25 (heavy intensity, per 1 SD)	1.13 (1.04–1.24)	0.007	1.09 (0.95–1.25)	0.23	0.36	0.07	−0.042	0.35
Education, Y25, (per year)	0.97 (0.93–1.00)	0.07	0.93 (0.88–0.98)	0.01	−0.30	0.0001	−0.01	0.48
Cumulative BMI (per 1 SD in BMI, years)	1.41 (1.28–1.55)	<0.0001	1.43 (1.24–1.64)	<0.0001	5.47	<0.0001	0.37	<0.0001
Metabolic trajectory groups								
Group 1: low-stable	1.00 (Ref)	—	Ref	—	Ref	—	Ref	—
Group 2: low-worsening	1.50 (1.10–2.04)	0.01	1.67 (0.99–2.83)	0.057	1.85	0.002	0.51	0.0002
Group 3: intermediate-stable	1.24 (0.89–1.77)	0.20	1.69 (0.94–3.04)	0.08	1.28	0.04	0.25	0.08
Group 4: intermediate-worsening	2.47 (1.78–3.42)	<0.0001	2.57 (1.50–4.39)	0.0006	1.67	0.01	0.80	<0.0001
Group 5: high-stable	1.95 (1.43–2.67)	<0.0001	1.80 (1.05–3.10)	0.03	1.56	0.009	0.58	<0.0001
Group 6: high-worsening	3.61 (2.41–5.41)	<0.0001	3.66 (2.00–6.69)	<0.0001	4.34	<0.0001	1.36	<0.0001

P values for groups are for comparisons with referent (ref; group 1, low-stable). BMI indicates body mass index; CAC, coronary artery calcification; LV, left ventricular; Y25, year 25.

shown in Table 2. After accounting for age, sex, race, education, smoking, physical activity, and obesity exposure (defined in Methods), all groups (except group 3: intermediate-stable) had a higher risk of subclinical coronary artery disease, as reflected by prevalent CAC and CAC score greater than 100 at year 25, compared with the low-stable group. Similarly, after accounting for cumulative BMI and other risk factors, compared with the low-stable population (group 1), all other trajectory groups were associated with significantly greater height-indexed LVM, and all but group 3 were associated with poorer longitudinal strain (Table 2). These results were robust in sensitivity analyses using 50-fold replication over posterior group probabilities and to inverse probability weighting. Relationships between trajectory groups and CAC were similar excluding individuals with prior revascularization. In a sensitivity analysis, we considered the form of the trajectory (stable versus worsening) as an outcome to address whether baseline characteristics would identify metabolic progression over time; baseline characteristics had only a moderate discrimination for worsening versus stable trajectories (C statistic 0.72; 95% CI, 0.70–0.74). In addition, worsening trajectories were associated with greater subclinical CVD.

In examining the sex- and race-based heterogeneity in metabolic risk and CVD, we first observed that men were much more likely to be in metabolically worsening trajectories compared with women. We identified a significant race interaction for LVM ($P<0.0001$) and LV strain ($P=0.01$), and a significant sex interaction for presence of CAC ($P=0.001$). Figure 3 shows the patterns of group differences by race for LVM (Figure 3A) and LV strain (Figure 3B) and by sex for CAC (Figure 3C). We found that the black patients consistently had higher LVM and worse LV strain than white patients in each group (Figure 3). Furthermore, the worsening metabolic trajectory had a greater impact on blacks than whites, most notably in the high-worsening group (group 6). We also found that while women generally had lower rates of coronary calcification at year 25 than men, this difference was attenuated in worse metabolic trajectories (Figure 3C).

Discussion

In a large cohort of young adults followed over 25 years, we defined specific trajectories of metabolic risk associated with prognostic markers of subclinical CVD, including myocardial mass, function, and CAC in midlife. Importantly, metabolic risk

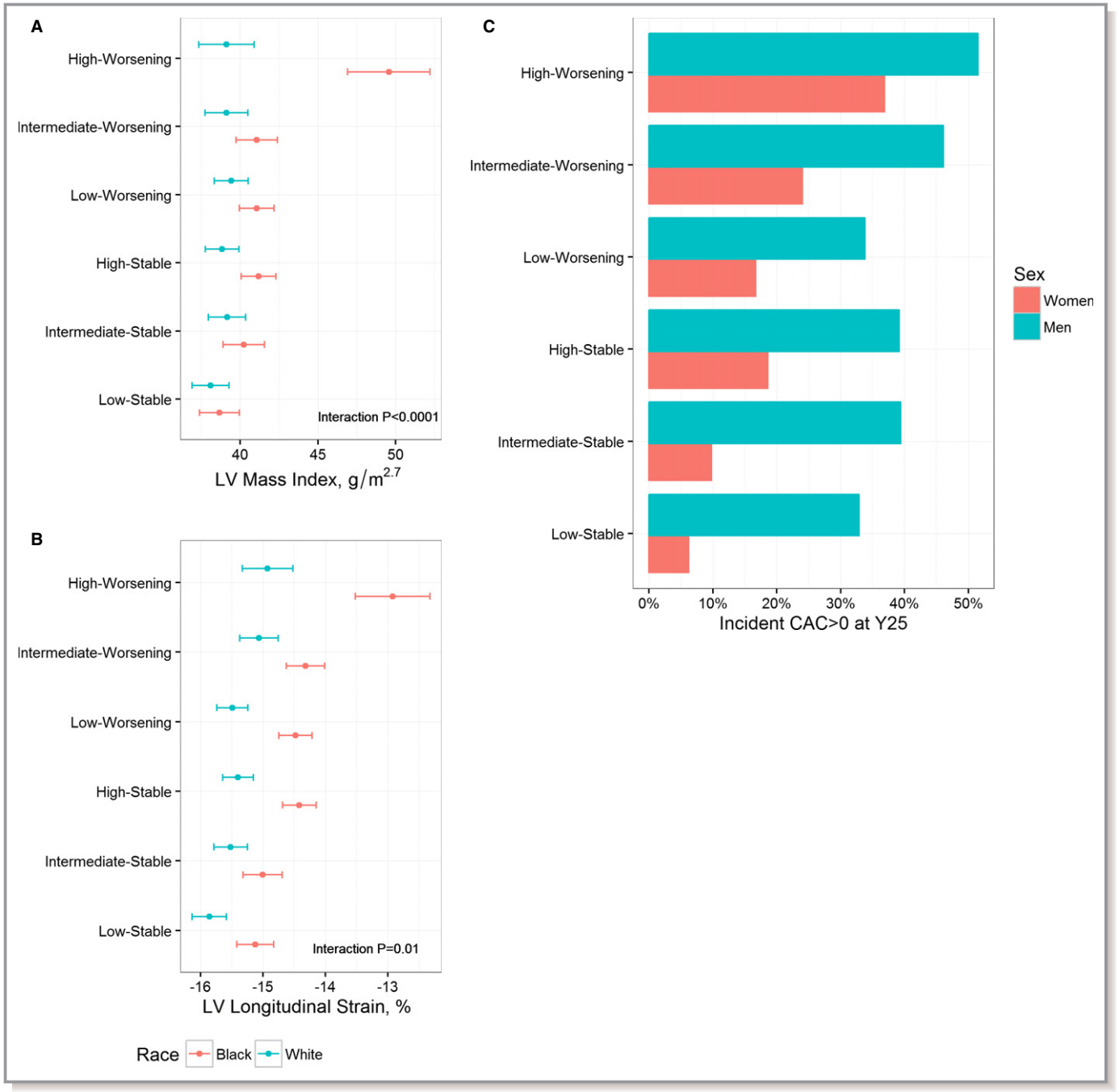

Figure 3. Effect modification by race and sex. Left ventricular (LV) mass index (A) and longitudinal strain (B) across metabolic trajectories by race. The points represent the adjusted least squares means with 95% CIs. C, Rate of coronary artery calcification (CAC) score >0 by metabolic trajectory and sex. Differences by sex are significant (P<0.0001) in each group except high-worsening (P=0.06), with evidence of effect modification of metabolic trajectory by sex (interaction P=0.001).

diverged early, at age 20 to 30 years, before most young adults would be eligible for modern lipid prevention guidelines.[23] We demonstrated that the evolution of metabolic risk during early adulthood may occur independently of changes in BMI. Despite an overall rise in BMI by year 25 in CARDIA (to overweight or obese on average), parameters of cardiometabolic risk (eg, dysglycemia, diabetes risk, dyslipidemia, waist circumference) had distinct patterns of change over time in each trajectory. Moreover, we could not in general identify a trajectory to which a given individual belonged based on baseline BMI or cardiometabolic characteristics, given their similarity at baseline. While we did observe that adverse trajectories (defined by initially high or worsening metabolic risk trajectories) were associated with

worse cardiovascular structure and function at late follow-up, lower-risk, stable trajectories (groups 1 and 3) had a similar risk of coronary calcification and subclinical LV dysfunction. The critical finding of our work is that these associations were observed in the face of a similar pattern of increase in BMI across trajectories, suggesting that BMI may not fully explain metabolic deterioration in young adulthood through midlife. Collectively, despite a "healthy" profile in young adulthood (including normal BMI on average), adverse trajectories in cardiometabolic risk may evolve early in adulthood (before age 40) and are associated with subclinical CVD by midlife.

Metabolic syndrome, defined by abdominal obesity, proatherogenic dyslipidemia, hypertension, and insulin resistance, is a risk factor for incident CVD.[17] Most clinical prevention has focused on BMI as a central arbiter of cardiometabolic risk, with screening beginning in childhood to mitigate chronic consequences of obesity.[24] Indeed, trajectories of obesity in childhood are strongly associated with CVD and diabetes in adulthood.[25] Nevertheless, the US Preventive Services Task Force guidelines do not recommend any additional screening for dysglycemia or dyslipidemia prior to middle age (35 years for men, 45 years for women) in individuals not at "significant risk" for CVD or diabetes (defined as obesity, hypertension, smoking, diabetes, or personal or family history).[26] While prior work in CARDIA has defined the importance of cumulative exposure to obesity[7,27] on cardiovascular structure, the divergence between metabolic risk and obesity (eg, "metabolically healthy obese" and "metabolically unwell lean" subtypes) is increasingly recognized. Previous work by our group[28] and others[29–33] has indicated that differences in metabolic susceptibility defined by visceral adiposity or inflammation may refine obesity-related cardiometabolic risk. In addition, studies involving cardiac magnetic resonance suggest that even tissue-level myocardial phenotypes may be affected in adolescent obesity, in proportion to systemic inflammation and dysglycemia.[34] These findings suggest that early detection of and focus on obesity-associated metabolic risk may provide a more nuanced conception of cardiometabolic disease early in adulthood that may directly impact heart disease and may help to understand heterogeneity in clinical risk in individuals across the spectrum of obesity.[29]

In this context, using well-defined, clinically accessible risk factors, we found that individuals who were at low metabolic risk at baseline had already diverged in terms of metabolic risk in early adulthood (eg, between age 20–40 years), before standard prevention guidelines urge routine screening (eg, for dyslipidemia). Importantly, there were no clinically important differences in these groups in terms of baseline BMI, lipid panel, fasting glucose, or other important cardiometabolic indices to facilitate their distinction. In addition, despite a similar pattern of weight gain across all metabolic risk trajectories over time in CARDIA, we observed distinct associations between metabolic trajectories and subclinical CVD. Importantly, we observed significant race- and sex-based heterogeneity in the relationship between adverse metabolic risk over 25 years and subclinical CVD: African Americans exhibited a higher LVM and poorer systolic function compared with Caucasians, potentially explaining well-described race-related differences in heart failure risk.[35] Moreover, the well-described protection from CVD in premenopausal women (compared with men) was attenuated with worsening metabolic trajectory. Along with general cardiometabolic prevention, these results suggest that focused efforts in select populations to limit the evolution of cardiometabolic risk from young adulthood may curb later CVD and its associated cost and morbidity.

A critical step in the formulation of metabolic trajectories in this work is the metabolic score used to specify risk. We decided to use ATP III–defined metabolic syndrome components to comprise our risk score because of their clinical accessibility and previous association with cardiometabolic disease.[16] While more granular, longitudinal and direct measures of physical activity (by accelerometry), cardiorespiratory fitness (eg, exercise duration), visceral fat,[30] and dietary patterns would likely contribute to defining trajectories, we did not have access to longitudinal accelerometry, fitness, adiposity, or dietary data in every examination within CARDIA. In addition, our score purposefully excluded BMI; instead, we specified a time-dependent BMI adjustment in trajectory modeling to account for longitudinal changes in BMI over time. Ultimately, these results suggest that metabolic deterioration occurs early in adulthood in parallel with (but not necessarily explained completely by) a rise in BMI over time.

The identification of early divergence in metabolic risk independent of BMI prompts several additional questions. First, early clinical differentiation of the different metabolic trajectories would allow the identification of individuals at higher risk at an earlier stage of cardiometabolic disease for prompt prevention. Certainly, those individuals who enter young adulthood at high metabolic risk tended to remain at high metabolic risk or worsen over time, warranting aggressive, guideline-mandated surveillance and prevention. Previous seminal work has demonstrated that changes in waist circumference over time track changes in cardiometabolic risk.[36,37] While clinical factors in our study only modestly discriminated risk of worsening metabolic trajectory over time, CARDIA was an observational (not an interventional) study. As such, directed clinical interventions based on known markers (eg, triglycerides, low fitness or activity levels, poor dietary quality, or increasing waistline[36,37]) may offer preventive benefits. Whether more sensitive markers of early metabolic dysfunction (eg, adipokines and metabolite profiles) central to insulin resistance and cardiometabolic risk would

further call attention to patients at high risk remains an area of active investigation. Moreover, it is critical to note that these results do not negate the importance of BMI in standard risk prediction. Obesity is a well-established marker of increased CVD risk,[1] although these results suggest that it does not fully explain CVD risk. Ultimately, these results suggest that a "life-course" approach to risk assessment that begins early and integrates BMI, known risk factors (eg, waist circumference), and metabolic risk will be critical in halting CVD progression.

Study Limitations

The limitations of this study must be viewed in the context of its design. While the use of self-report to exclude participants with CVD may introduce bias, the overall reduction in study population was modest (5114 to 4941). With patient dropout over time, 3262 participants (74% of the initial 4420 analytic cohort) had quantified metabolic scores at year 25. However, we adjusted for known CVD risk factors (smoking, self-reported physical activity) in our final models to reduce the impact of biases related to systematic differences in characteristics of retained patients.[6] Furthermore, while not all participants had metabolic scores assessed at every CARDIA study visit, the median number of metabolic score assessments was 7 (interquartile range 6–8 of 8 total CARDIA visits, similar across trajectory groups (between 7 and 8 visits across all groups) and suggested that any systematic patterns in missing data are unlikely to impact trajectory assignments. Given the absence of a priori weighting schemes, we weighted each metabolic component equally, ascribing an equivalent degree of cardiometabolic risk to each component. Finally, serial dietary and physical activity assessments were not available at every examination in CARDIA and represent a potential area of future study.

Conclusions

Transitions in metabolic risk occur in early adulthood, are not completely explained by increases in BMI over time, and are associated with CAC and myocardial hypertrophy and dysfunction. Targeting therapeutic interventions focused on weight, body composition, and physical activity maintenance early in life along with regular cardiometabolic surveillance are critical to reduce heart disease.

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Drs Murthy and Shah had full access to the data in this study and take responsibility for the integrity of the data and the accuracy of the data analysis. Drs Shah, Murthy, Abbasi, and Lima are responsible for the conception and study design. Drs Murthy, Siddique, Abbasi, Colangelo, and Shah conducted statistical analysis. Drs Murthy and Shah supervised the analysis. Drs Lima, Carr, and Lewis and Mr Terry were responsible for acquisition of data. Drs Murthy, Abbasi, Reis, Venkatesh, Jerosch-Herold, de Ferranti, Das, Freedman, Carnethon, Lewis, Lima, and Shah were responsible for drafting of the manuscript. All authors were responsible for critical revision of the manuscript. This manuscript has been reviewed by CARDIA for scientific content.

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SUPPLEMENTAL MATERIAL

Table S1. Presence of risk factors used to construct the metabolic risk score over CARDIA examinations. "N present" refers to number of observations that have a measured covariate, and "%" reflects proportion out of 4420 individuals in initial analytic cohort.

Covariate	**Year 0**		**Year 2**		**Year 5**		**Year 7**	
	N Present	%	N Present	%	N Present	%	N Present	%
Body mass index	4420	100	4176	94.5	4086	92.4	3773	85.4
Insulin resistance (diabetes, fasting glucose)	4420	100	4171	94.4	4100	92.8	3862	87.4
Blood pressure	4420	100	4201	95	4104	92.9	3862	87.4
Waist circumference	4420	100	4173	94.4	4070	92.1	3759	85
High-density lipoprotein	4420	100	4094	92.6	4018	90.9	3799	86
Triglyceride	4420	100	4095	92.6	4018	90.9	3799	86
Total Metabolic Risk Score	4420	100	4045	91.5	3984	90.1	3710	83.9
	Year 10		**Year 15**		**Year 20**		**Year 25**	
	N Present	%	N Present	%	N Present	% Present	N Present	% Present
Body mass index	3680	83.3	3439	77.8	3334	75.4	3274	74.1
Insulin resistance (diabetes, fasting glucose)	3731	84.4	3476	78.6	3349	75.8	3279	74.2
Blood pressure	3732	84.4	3478	78.7	3349	75.8	3280	74.2
Waist circumference	3673	83.1	3454	78.1	3338	75.5	3271	74
High-density lipoprotein	3672	83.1	3428	77.6	3318	75.1	3269	74
Triglyceride	3672	83.1	3428	77.6	3318	75.1	3269	74
Total Metabolic Risk Score	3623	82	3408	77.1	3309	74.9	3262	73.8

Figure S1. Baseline metabolic score across waist circumference and categories of weight.