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# The Coronary Artery Risk Development In Young Adults (CARDIA) Study



## JACC Focus Seminar 8/8

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### ABSTRACT

The CARDIA (Coronary Artery Risk Development in Young Adults) study began in 1985 to 1986 with enrollment of 5,115 Black or White men and women ages 18 to 30 years from 4 US communities. Over 35 years, CARDIA has contributed fundamentally to our understanding of the contemporary epidemiology and life course of cardiovascular health and disease, as well as pulmonary, renal, neurological, and other manifestations of aging. CARDIA has established associations between the neighborhood environment and the evolution of lifestyle behaviors with biological risk factors, sub-clinical disease, and early clinical events. CARDIA has also identified the nature and major determinants of Black-White differences in the development of cardiovascular risk. CARDIA will continue to be a unique resource for understanding determinants, mechanisms, and outcomes of cardiovascular health and disease across the life course, leveraging ongoing pan-omics work from genomics to metabolomics that will define mechanistic pathways involved in cardiometabolic aging. (J Am Coll Cardiol 2021;78:260-77) © 2021 the American College of Cardiology Foundation. Published by Elsevier. All rights reserved.

**T**he CARDIA (Coronary Artery Risk Development in Young Adults) study (1) was begun in 1985 to 1986. The study enrolled 5,115 Black and White men and women 18 to 30 years of age at 4 centers in Birmingham, Alabama, Chicago, Illinois, Minneapolis, Minnesota, and Oakland, California. Originally conceived as a study to understand the contributing factors (behavioral, environmental, and race- and sex-associated) underlying the transition from healthy young adulthood to the development of cardiovascular disease (CVD) risk factors (RFs), CARDIA has now become one of the premier studies of aging, cardiovascular health (CVH), and CVD across

the life course. It has also contributed substantially to our understanding of the effects of the US obesity epidemic (which had its inflection point in 1985) on cardiovascular and overall health. This monograph describes the original goals and most important contributions of CARDIA to date, as well as future research directions.

### ORIGINAL GOALS, STUDY DESIGN, AND FOLLOW-UP

The original aims of CARDIA were as follows: to examine the distribution of CVD RFs in young



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### HIGHLIGHTS

- Cardiovascular health steadily diminishes through young adulthood, and this has implications for long-term risk.
- Racial disparities in cardiovascular risk are related to social determinants of health and discrimination.
- Obesity has major impact on cardiac structure and function and cardiometabolic risk.
- The CARDIA Study continues to define the life course and mechanisms of CVD and aging.

adults; to identify associated lifestyle, psychosocial, and other factors; and to assess longitudinal RF evolution in early adulthood. Recruitment strategies were designed to achieve a representative sample of the underlying US Black and White populations at the time from diverse geographic regions, and involved random-digit dialing or in-person contact with households in selected areas and census tracts in Birmingham, Chicago, and Minneapolis. Participants at the Oakland center were randomly selected from among subscribers of the Kaiser Permanente Medical Care Program living in specific residential areas around Oakland. Within each field center, attempts were made to achieve approximately equal numbers balanced on age (older than/younger than 25 years of age), sex (male/female), self-reported race (Black/White), and education status (high school or less/more than high school). Self-reported Hispanic (or other) ethnicity was not initially gathered but the proportion of Hispanic individuals is low. The final cohort included 5,115 Black or White men and women, whose baseline and follow-up characteristics at each examination are shown in [Table 1](#).

Follow-up in-person examinations have been completed at Years 2 (1987-1988), 5 (1990-1991), 7 (1992-1993), 10 (1995-1996), 15 (2000-2001), 20 (2005-2006), 25 (2010-2011), and 30 (2015-2016). Participation in the follow-up examinations is displayed in [Figure 1](#); >71% of surviving participants attended the Year 30 examination. The Year 35 examination is ongoing. Contact is maintained with participants every 6 months, with annual interim medical history ascertainment. Over the last 5 years, >90% of the surviving cohort members have been directly contacted, and follow-up for vital status is virtually complete.

Beyond standard anthropometric and laboratory measures, and collection of biospecimen samples for storage, phenotypic assessments of attending CARDIA participants have included: physical fitness at Years 0, 7, and 20; diet at Years 0, 7, and 20; pulmonary function at Years 0, 2, 5, 10, 20, and 30; coronary artery calcium (CAC) at Years 10 (subset), 15, 20, and 25; carotid intima-media thickness at Year 20; echocardiography at Years 5, 10 (subset), 25, and 30; cognitive function at Years 25 and 30; brain magnetic resonance in a subset at Years 25 and 30; body composition including dual-energy X-ray absorptiometry at Year 20 and abdominal computed tomography at Year 25; and repeated assessment of genetic, psychosocial, neighborhood, environmental, lifestyle and behavioral factors; prescription, recreational, and illicit drug use; and more. Hundreds of ancillary studies have also been undertaken to collect additional data or leverage existing data. A full list of data elements collected at each examination cycle is available at the CARDIA Web site.

Use of novel phenotyping methods (as they have developed over the course of the study) has allowed observation of the evolution from high early life health status to development of CVD RFs, to manifestations of subclinical and clinical CVD and other chronic diseases of aging. The unique design of CARDIA with regard to its balance on race and sex has also allowed for important potential insights into aging in demographic subgroups, and associated upstream social determinants of health, including structural racism and psychosocial and behavioral factors.

CARDIA has repeatedly measured biomarkers related to oxidative stress, inflammation, endothelial function, and many other pathways over time. Extensive use of the biorepository has enabled an increasing focus on systems biology, with studies of genetic, epigenetic, transcriptomic, proteomic, and metabolomic patterns at multiple time points. As a biracial cohort that follows diverse individuals from young adulthood to middle age, CARDIA is also a critical linchpin in data sharing and harmonization across cohorts to define the life course of CVH and CVD.

### TOP 10 MOST IMPORTANT CONTRIBUTIONS

CARDIA has defined key processes in the progression from healthy young adulthood to middle age across diverse states of health and preclinical and clinical

### ABBREVIATIONS AND ACRONYMS

- BMI** = body mass index
- BP** = blood pressure
- CAC** = coronary artery calcium
- CI** = confidence interval
- CVD** = cardiovascular disease
- CVH** = cardiovascular health
- HR** = hazard ratio
- LV** = left ventricular
- OR** = odds ratio
- RF** = risk factor

**TABLE 1** Characteristics of the CARDIA Cohort at Each Examination Cycle

	Year 0 1985-1986 (n = 5,115)	Year 2 1987-1988 (n = 4,624)	Year 5 1990-1991 (n = 4,352)	Year 7 1992-1993 (n = 4,086)	Year 10 1995-1996 (n = 3,950)	Year 15 2000-2001 (n = 3,672)	Year 20 2005-2006 (n = 3,549)	Year 25 2010-2011 (n = 3,499)	Year 30 2015-2016 (n = 3,358)
Black	2,637 (51.6)	2,285 (49.4)	2,116 (48.7)	1,973 (48.3)	1,922 (48.8)	1,730 (47.1)	1,651 (46.5)	1,640 (46.9)	1,605 (47.8)
Male	2,327 (45.5)	2,089 (45.2)	1,958 (45.0)	1,836 (45.0)	1,754 (44.5)	1,619 (44.1)	1,535 (43.3)	1,517 (43.4)	1,444 (43.0)
Mean age, y	24.8 ± 3.7	26.9 ± 3.6	30.0 ± 3.6	32.0 ± 3.6	35.0 ± 3.7	40.2 ± 3.6	45.2 ± 3.6	50.2 ± 3.6	55.1 ± 3.6
Mean education, y	13.8 ± 2.3	14.1 ± 2.9	14.4 ± 2.4	14.6 ± 2.5	14.7 ± 3.2	14.9 ± 2.5	15.0 ± 2.6	15.1 ± 2.7	15.1 ± 2.6
<High School	510 (10.0)	347 (7.6)	267 (6.2)	233 (5.8)	247 (6.3)	183 (5.0)	150 (4.3)	160 (4.6)	143 (0.04)
High school	1,519 (29.7)	1,209 (26.4)	1,112 (25.6)	947 (23.4)	907 (23.1)	659 (18.0)	702 (19.9)	628 (18.0)	632 (19.0)
>High school	3,080 (60.3)	3,024 (66.0)	2,958 (68.2)	2,871 (70.9)	2,766 (70.6)	2,817 (77.0)	2,676 (75.9)	2,694 (77.4)	2,557 (76.7)
Alcohol, mL/d	12.1 ± 22.0	14.2 ± 24.0	11.2 ± 25.6	11.2 ± 23.4	10.9 ± 22.1	11.0 ± 24.9	10.8 ± 22.2	11.7 ± 23.4	11.2 ± 19.8
AHA ideal diet	615 (12.0)			565 (14.3)			325 (10.3)		
AHA intermediate diet	2,817 (55.1)			2,330 (59.1)			2,135 (68.0)		
AHA poor diet	1,676 (32.8)			1,046 (26.5)			682 (21.7)		
Mean physical activity intensity score, units	420.1 ± 300.8	382.1 ± 288.8	379.3 ± 292.5	338.1 ± 274.0	330.7 ± 274.8	347.2 ± 283.6	335.9 ± 274.1	337.8 ± 275.6	321.3 ± 271.5
Body mass index, kg/m <sup>2</sup>	24.5 ± 5.0	25.2 ± 5.4	26.1 ± 5.9	26.8 ± 6.1	27.5 ± 6.5	28.8 ± 6.8	29.4 ± 7.0	30.2 ± 7.2	30.5 ± 7.2
Mean systolic blood pressure, mm Hg	110.4 ± 11.0	107.9 ± 10.8	107.8 ± 11.6	108.7 ± 12.4	110.0 ± 12.8	113.2 ± 14.9	115.7 ± 14.7	119.7 ± 16.2	120.8 ± 16.7
Mean diastolic blood pressure, mm Hg	68.6 ± 9.6	67.4 ± 9.7	69.2 ± 10.2	69.3 ± 10.3	72.4 ± 10.2	74.5 ± 11.6	72.2 ± 11.2	74.9 ± 11.3	74.1 ± 11.1
Mean fasting glucose, mg/dL	82.6 ± 16.3			90.1 ± 19.4	88.2 ± 20.4	86.7 ± 21.0	98.0 ± 26.5	99.5 ± 28.6	102.6 ± 31.8
Current smoker	1,544 (30.4)	1,358 (29.6)	1,241 (28.6)	1,096 (27.0)	1,002 (25.6)	807 (22.0)	683 (19.4)	589 (17.1)	463 (14.0)
Lipid-lowering treatment			11 (0.3)	10 (0.2)	19 (0.5)	87 (2.4)	313 (8.8)	544 (15.6)	671 (20.0)
Blood pressure-lowering treatment	115 (2.2)	123 (2.7)	69 (1.6)	80 (2.0)	135 (3.4)	292 (8.0)	619 (17.5)	942 (27.1)	1,114 (33.2)
Mean total cholesterol, mg/dL	176.8 ± 33.5	177.0 ± 34.1	178.1 ± 34.4	177.0 ± 34.3	178.0 ± 34.6	184.7 ± 35.8	185.7 ± 35.0	192.3 ± 36.9	191.3 ± 38.1
Mean HDL-cholesterol, mg/dL	53.2 ± 13.2	53.1 ± 13.7	53.3 ± 14.2	52.1 ± 14.2	50.3 ± 14.0	50.7 ± 14.6	54.2 ± 16.7	58.0 ± 18.0	59.8 ± 18.9
Mean LDL-cholesterol, mg/dL	109.1 ± 31.2	112.5 ± 33.4	108.5 ± 32.1	107.6 ± 31.6	109.2 ± 32.1	113.0 ± 32.3	110.0 ± 32.1	111.9 ± 32.8	110.3 ± 33.2
Mean triglycerides, mg/dL	72.9 ± 48.5	78.9 ± 53.4	80.8 ± 72.3	86.4 ± 75.7	92.1 ± 74.7	105.5 ± 92.8	109.4 ± 79.7	114.2 ± 87.2	107.9 ± 97.8
Diabetes	32 (0.6)	33 (0.7)	37 (0.9)	70 (1.8)	101 (2.7)	159 (4.4)	272 (7.8)	381 (11.0)	492 (14.9)
Mean AHA cardiovascular health CVH score, of 14 points	10.2 ± 1.9			9.9 ± 2.1			9.1 ± 2.2		
Mean AHA cardiovascular health CVH score excluding diet, of 12 points	9.42 ± 1.7	9.45 ± 1.7	9.3 ± 1.7	9.1 ± 1.9	9.0 ± 1.9	8.6 ± 2.0	8.2 ± 2.1	7.7 ± 2.2	7.6 ± 2.2

Values are n (%) or mean ± SD.

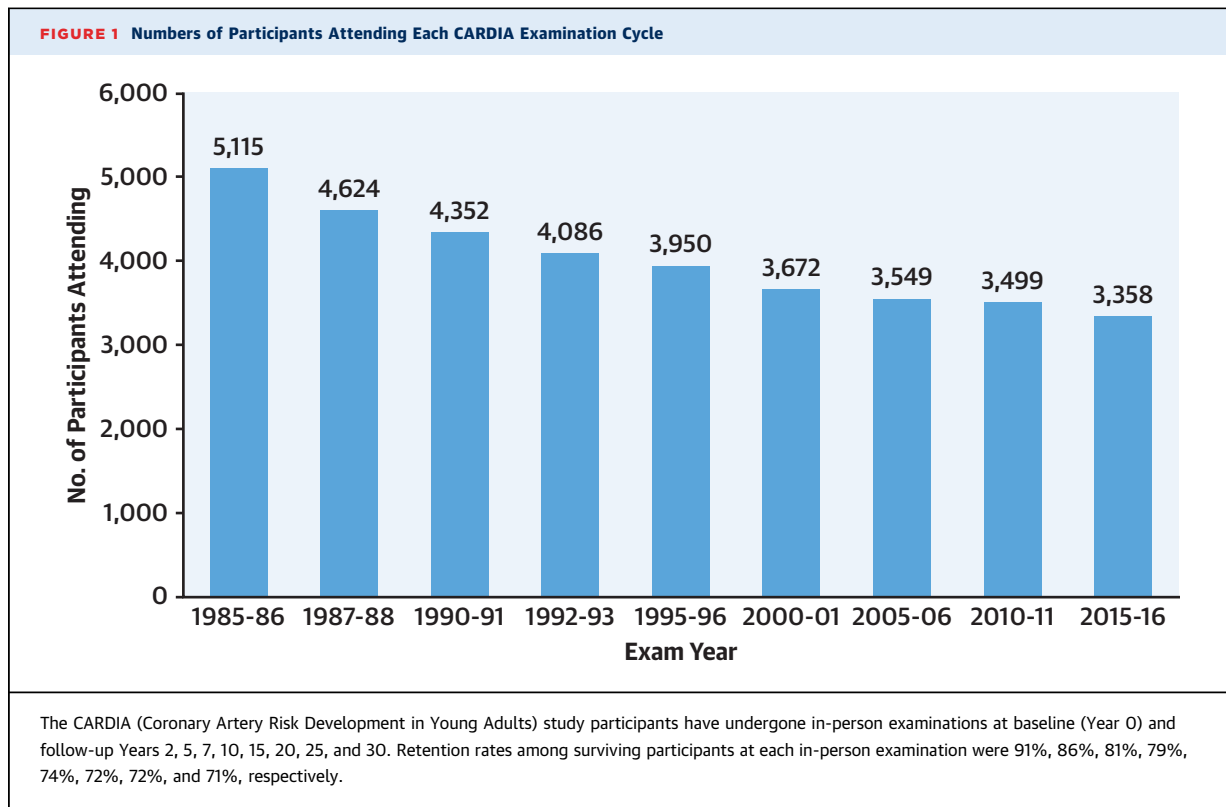
AHA = American Heart Association; CVH = cardiovascular health; HDL = high-density lipoprotein; LDL = low-density lipoprotein.

disease (Central Illustration). As the cohort has entered middle age, the number of clinical events has started to increase. Through 35 years of follow-up, CARDIA participants have experienced 545 total deaths (106.5 deaths per 1,000 participants since 1985), of which 17.3% were due to CVD, 20.9% to cancer, 18.6% to homicide, suicide, or trauma, and 10.9% to HIV/AIDS. In addition, there have been 478 participants with adjudicated definite and probable incident CVD events, including 107 incident myocardial infarctions, 108 strokes, and 86 heart failure events. There are notable differences in incidence of

death and CVD events across race/sex subgroups (Figure 2).

The following sections summarize the top 10 most important contributions to date from the CARDIA study, as judged by consensus of long-standing study leadership.

**TRANSITION FROM HEALTHY YOUNG ADULTHOOD TO DEVELOPMENT OF CVD RISK FACTORS.** CARDIA's age range, long-term follow-up, and serial deep phenotyping make it uniquely suited to answer important questions regarding the natural history of CVD RF development before the onset of extensive



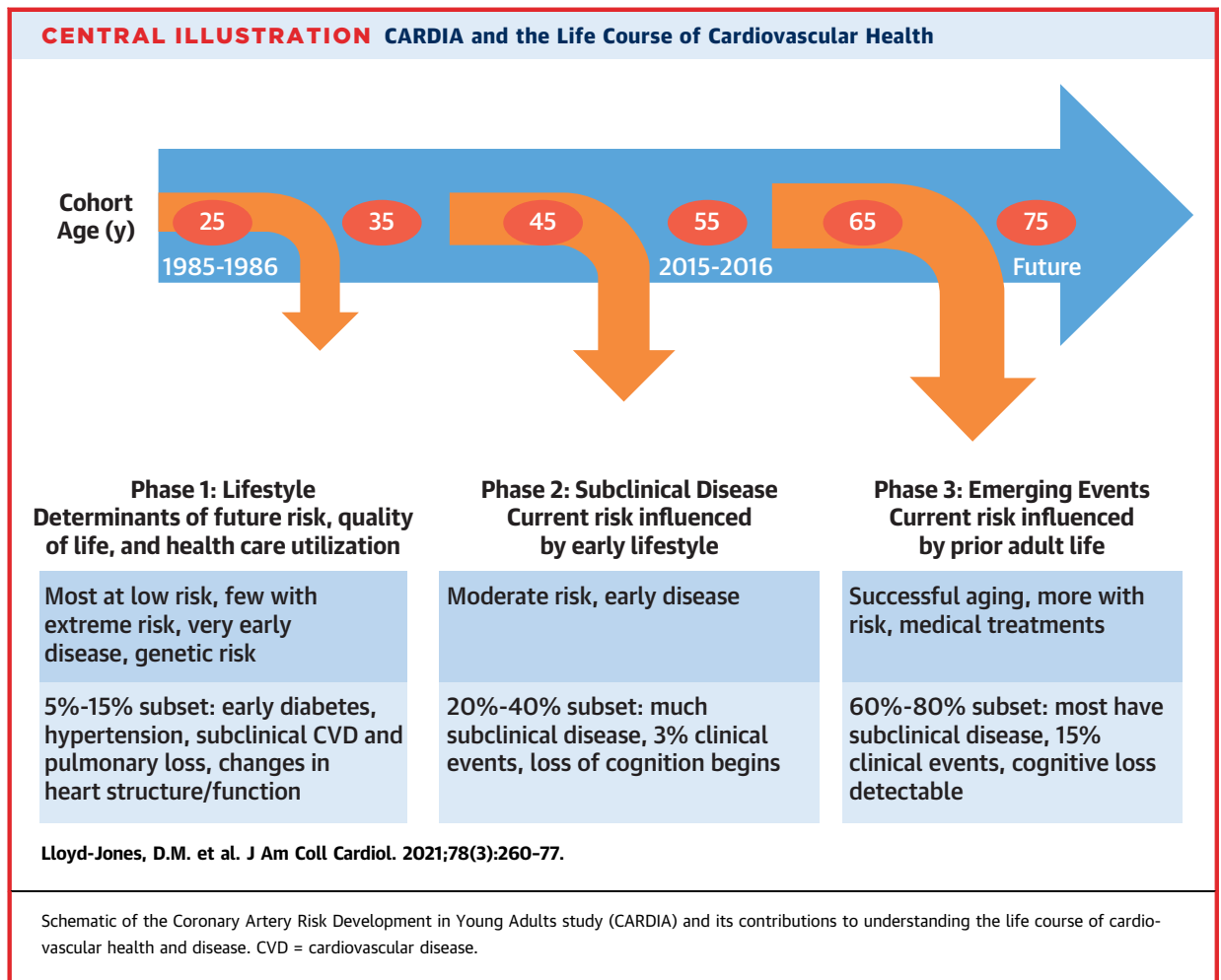
comorbidities or use of drug therapies. CARDIA investigators have been at the forefront of developing and applying novel techniques to exploit the longitudinal, repeated measures data structure. These pioneering studies have provided critical insights on disentangling aging from secular trends (2), analyses of RF trajectories and cumulative exposures (3), elucidation of critical exposure periods and “points of no return” (4), analyses of highly correlated data, and missing data patterns.

**Blood pressure.** Blood pressure (BP) has been known to be a major RF for the development of atherosclerosis for decades. However, most prospective analyses have examined a single baseline BP measurement and its association with subsequent outcomes. In a novel analysis of BP exposure patterns over the life course, Allen et al. (3) examined repeated measures from CARDIA participants collected from Years 0 to 25. Latent mixture modeling was used to identify groups of participants with distinct BP trajectories, describing both the levels and shape of change in BP over time. There were 5 distinct trajectories of BP (Figure 3), which were described by their baseline levels and the shape of change over time as: “low-stable” (representing 21.8% of participants), “moderate-stable” (42.3%), “moderate-increasing”

(12.2%), “elevated-stable” (19.0%), and “elevated-increasing” (4.8%) (3).

Groups with elevated BP levels at baseline and those with increasing trajectories over time had greater odds of having a CAC score of 100 AU or greater at Year 25 (Figure 3). Of note, associations with CAC were not altered after adjustment for baseline and Year 25 BP levels, or by cumulative BP exposure, indicating a unique contribution of the trajectory of BP rise over time (3). BP trajectory data that may be increasingly available through electronic health records may thus assist in more accurate identification of individuals at risk for atherosclerosis.

**Cholesterol concentrations.** In addition to trajectory analysis, RF exposure can also be described by considering the cumulative exposure and the slope of exposure over time, or by examining early age cumulative versus later age cumulative exposure, to understand whether there may be critical age periods of exposure. Domanski et al. (5) recently used novel analytic methods to understand early exposure patterns to low-density lipoprotein cholesterol, and their ultimate associations with CVD events. Using repeated measures, each participant’s cumulative exposure before age 40 years was quantified in

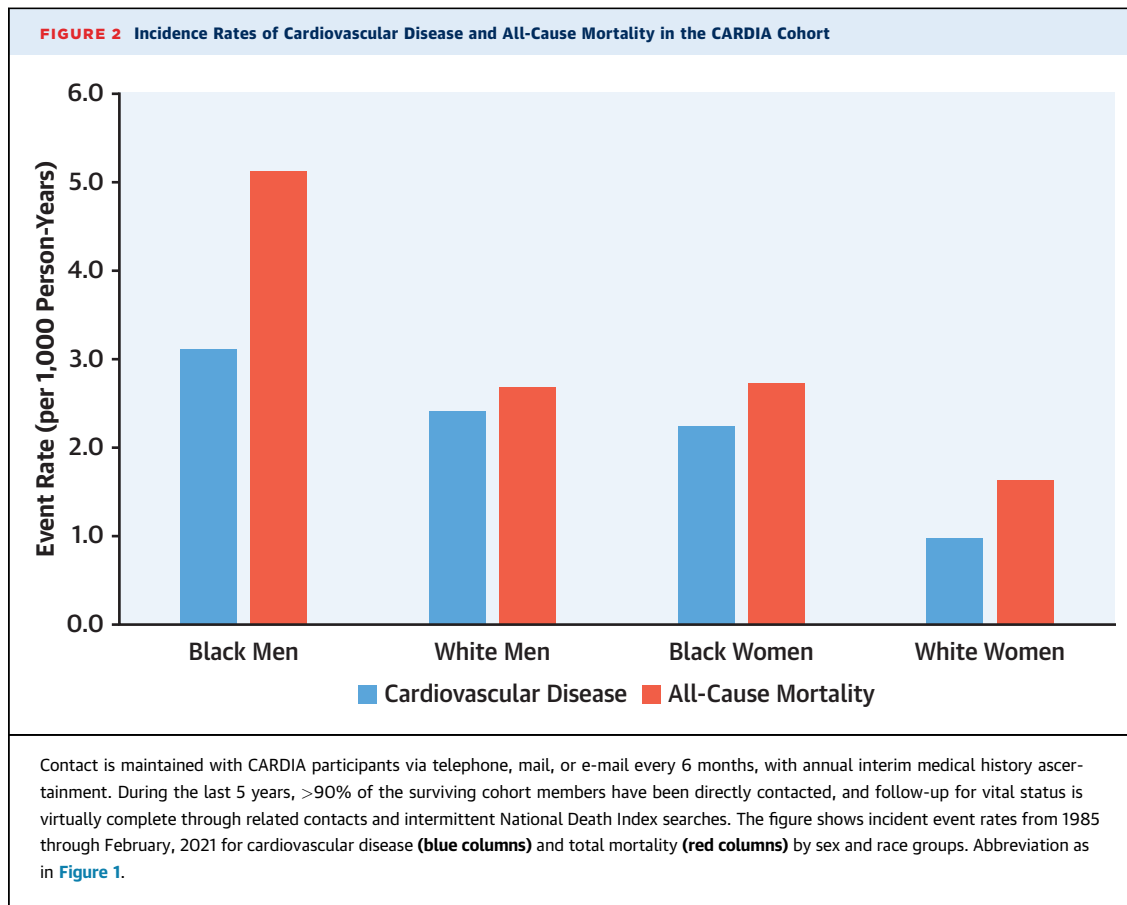


mg/dL  $\times$  y; in addition, the slope of change from baseline to age 40, as well as the cumulative exposure from ages 18 to 30 versus 30 to 40 years, was quantified (5).

Low-density lipoprotein cholesterol exposure before age 40 years was associated with occurrence of CVD events after age 40 years. Both cumulative exposure before age 40 years (hazard ratio [HR]: 1.05 per 100 mg/dL  $\times$  y cumulative exposure;  $P < 0.001$ ) and the slope of exposure (HR: 0.80 per 1 mg/dL/y change;  $P = 0.045$ ) were significantly associated with CVD risk after age 40. The inverse association for the slope indicates that higher earlier exposure was associated with greater risk than was later exposure. Exclusion of participants taking lipid-lowering medications did not alter these findings, and they were confirmed with models showing that cumulative low-density lipoprotein cholesterol exposure from age 18 to 30 was significantly associated with CVD risk after age 40, whereas cumulative exposure from age 30 to

40 was not, when both variables were in the model. These findings indicate that both cumulative exposure and exposure that happens earlier in young adulthood are more important contributors to mid-life CVD events than later concentrations, with potential implications for early life primordial prevention strategies (5).

**Loss of CVH.** In 2010, the American Heart Association defined a novel construct of CVH that relies on levels of 7 health behaviors and health factors: diet, physical activity, smoking status, body weight, BP, blood cholesterol, and blood glucose concentrations. Each of the component metrics is classified as ideal (optimal levels), intermediate (treated and controlled, or untreated/elevated), or poor (uncontrolled) using clinical thresholds. A composite CVH score (range: 0 to 14 points) can be created for an individual by assigning 2 points for each ideal metric, 1 point for each intermediate metric, and 0 points for each poor metric.

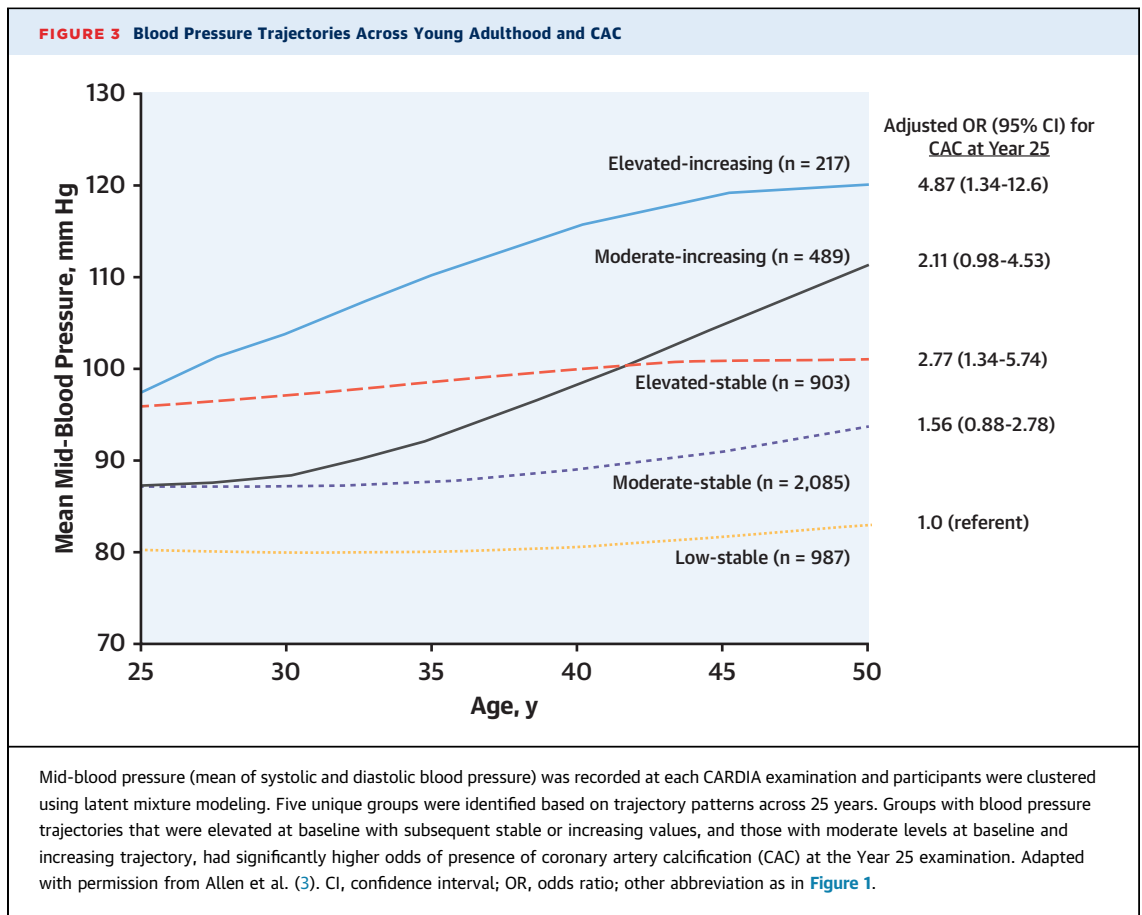


CARDIA has produced key data on the evolution of CVH through young adulthood, and antecedent health behaviors that are associated with maintenance of higher CVH. Among CARDIA participants who attended the Year 0, 7, and 20 examinations, Liu et al. (6) examined pursuit of 5 healthy lifestyle indicators (lean body mass index [BMI], low or no alcohol intake, healthy diet score, higher levels of physical activity, and nonsmoking). For participants who followed 0 or 1, 2, 3, 4, or all 5 healthy lifestyle factors at baseline, the age-, sex-, and race-adjusted prevalences of the ideal CVH profile at Year 25 were 3.0%, 14.6%, 29.5%, 39.2%, and 60.7%, respectively ( $P_{\text{trend}} < 0.001$ ). Similar associations were observed for each race/sex group. Whereas longer duration of healthy lifestyles was associated with the highest prevalence of ideal mid-life CVH, those whose healthy lifestyle factors improved over time were more likely to maintain ideal CVH than those whose lifestyles did not, indicating that healthy change was an important predictor of mid-life ideal CVH, and the earlier that change occurred, the better (6).

#### Women's reproductive health and RF changes.

CARDIA has contributed substantially to our understanding of the associations between women's reproductive health and CVD RFs with measurement of RF levels before and after pregnancy, a unique design feature. For example, among overweight women, 26.7% with 1 or more CVD RFs developed gestational diabetes mellitus versus 7.4% with none (7). Impaired fasting glucose and low levels of high-density lipoprotein cholesterol before pregnancy were particularly strong RFs. CARDIA investigators have also shown significant associations between longer duration of postpartum lactation and lower incidence of diabetes or metabolic syndrome (8,9), as well as lower burden of subclinical atherosclerosis (10).

CARDIA affords the opportunity to study landmark life events (eg, menopause, which may occur at diverse ages) and subsequent changes in RFs. Appiah et al. (11) examined changes in CVD RF levels before and after menopause (Figure 4). They observed significantly steeper increases in low-density lipoprotein cholesterol after menopause in women with



natural menopause compared with surgical menopause with hysterectomy only or with bilateral oophorectomy. Women with natural menopause also had a steeper slope of high-density lipoprotein cholesterol increase compared with the other 2 groups before menopause, and all 3 groups had similar rates of increase after menopause (11).

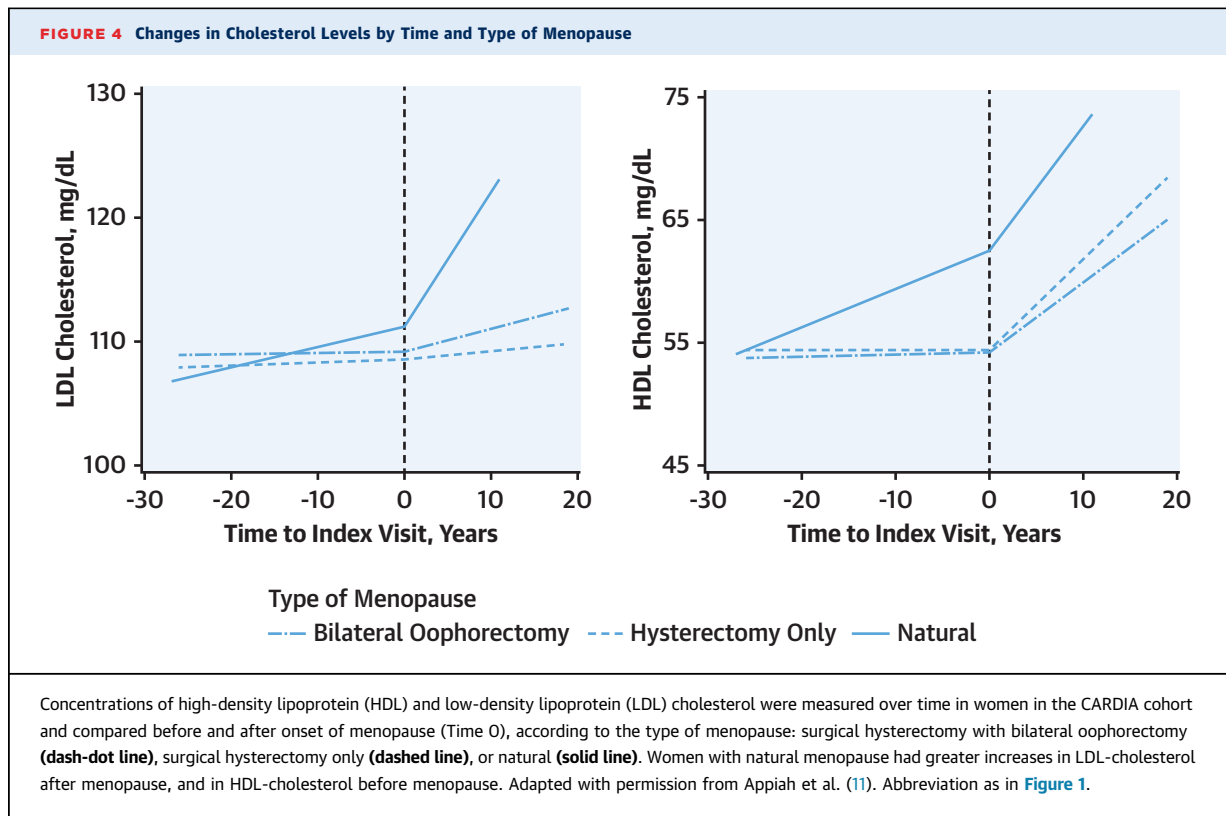
**TRANSITIONS FROM CVD RFS TO SUBCLINICAL CVD AND CLINICAL EVENTS. Development of CAC and progression to clinical CVD events.** CARDIA was one of the first population-based cohort studies to implement CAC measurement systematically, and CARDIA data have been instrumental in shaping clinical practice prevention guideline recommendations. CAC measurement was performed in the vast majority of participants attending the Year 15, 20, and 25 examinations, spanning the age range of 32 to 56 years, including large numbers of repeat measurements within individual participants.

At Year 15 (mean age: 40 years), 10% of CARDIA participants had any CAC, with a greater prevalence among men than women (15.0% vs 5.1%) and among White than Black men (17.6% vs 11.3%). CAC prevalence was also higher for those aged 40 to 45 years

than 33 to 39 years (13.3% vs 5.5%). RF levels measured at Year 0 (mean age: 25 years) discriminated CAC presence equally as well as average RF levels measured over examination Years 0, 2, 5, 7, 10, and 15, and better than concurrent levels at Year 15. Multivariable-adjusted odds ratios (ORs) of having CAC by ages 33 to 45 years were 1.5 (95% confidence interval [CI]: 1.3-1.7) per 10 cigarettes, 1.5 (95% CI: 1.3-1.8) per 30 mg/dL low-density lipoprotein cholesterol, 1.3 (95% CI: 1.1-1.5) per 10 mm Hg systolic BP, and 1.2 (95% CI: 1.1-1.4) per 15 mg/dL glucose at baseline (12).

The 5-year incidence of CAC was 11.9% between Years 15 and 20 (mean ages: 40 and 45 years) and 14.4% between Years 20 and 25 (45 and 50 years). As expected, incidence of CAC was highly associated with prior RF levels (13).

After 12.5 years of follow-up, those with any CAC at Year 15 had a multivariable-adjusted HR of 5.0 (95% CI: 2.8-8.7) for coronary heart disease events and 3.0 (95% CI: 1.9-4.7) for CVD events, even after adjustment for demographics and RFs. Within CAC score strata of 1 to 19, 20-99, and  $\geq 100$  AU, the HRs for coronary events were 2.6 (95% CI: 1.0-5.7), 5.8



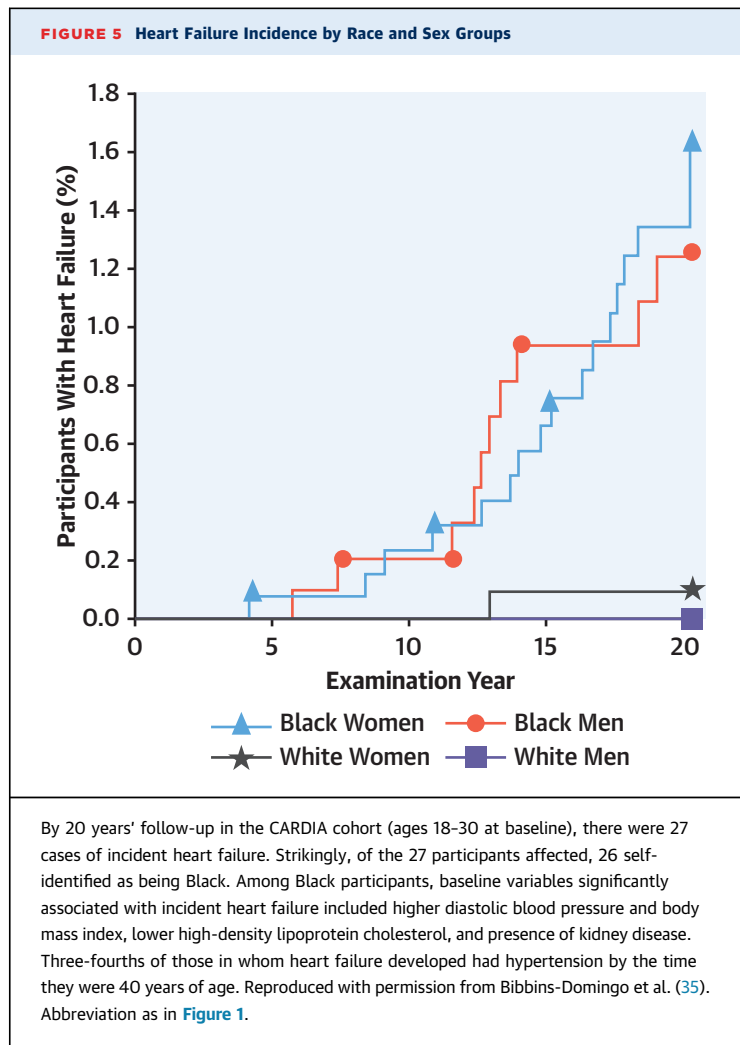
(95% CI: 2.6-12.1), and 9.8 (95% CI: 4.5-20.5), respectively. Addition of CAC score information added significant value to the Framingham risk score, particularly when 10-year predicted coronary risk was 5% to 11% (13).

**Progression from early adult RFs to left ventricular structural and functional abnormalities and clinical events.** CARDIA participants have undergone echocardiographic examinations at Years 5, 25, and 30, with recent examinations including tissue Doppler, speckle tracking, strain measurements, and 3-dimensional imaging. Consequently, CARDIA is one of the few studies that has been able to document reference ranges and normative findings (14-17) and changes throughout young adulthood, as well as prevalence of abnormal findings and their antecedent RFs, in a nonreferral setting.

Numerous investigations have documented antecedent RFs and risk markers for development of adverse left ventricular (LV) structure and function. Among those factors found to be associated with echocardiographic outcomes in CARDIA are as follows: self-identified race (18); obesity/adiposity (19-21), duration of obesity and patterns of obesity, and weight gain over time; insulin resistance and glycemia patterns as well as diabetes and duration of

diabetes (22,23); nonalcoholic fatty liver disease (24); baseline and cumulative BP exposures (25), as well as long-term visit-to-visit BP variability (26); renal function (27); menopause (28); alcohol intake (29); and level of composite CVH (30,31).

Using echocardiographic data from Years 5, 25, and 30, CARDIA investigators recently defined normative age-related changes (32,33). With increasing age, LV relative wall thickness, LV mass index, and indexed left atrial diameter all increased significantly and monotonically over time, whereas the ratio of mitral early to late diastolic velocities decreased substantially and monotonically. LV ejection fraction tended to increase until the mid-40s, followed by a decrease. The prevalence of any Stage B heart failure abnormality (asymptomatic abnormal LV geometry such as concentric remodeling, concentric hypertrophy, and eccentric hypertrophy; LV ejection fraction <50%; and/or presence of diastolic dysfunction) increased from a mean of 10.5% (95% CI: 9.4%-11.8%) at age 25 years to 45.0% (95% CI: 42.0%-48.1%) at age 60. Black participants had far higher prevalences than White participants of all adverse LV outcomes. The most significant predictors of incident Stage B abnormalities with aging were cumulative RF values from Year 5 to Year 30, rather than baseline or change values. In



turn, both Year 5 echo parameters and the cumulative RF levels also were significantly associated with incident clinical heart failure (32,33).

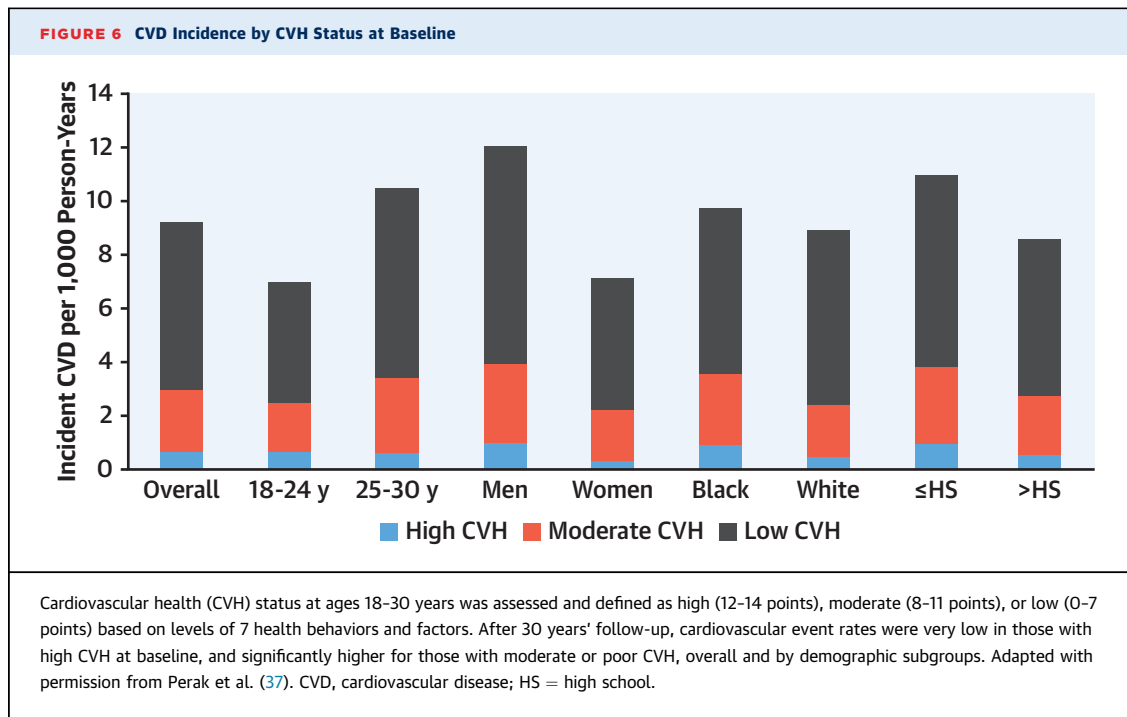
Using data from the Year 5 examination (mean age: 23 to 35 years), severe diastolic dysfunction was present in 1.1% and abnormal relaxation in 9.3% of CARDIA participants. After multivariable adjustment, those with severe diastolic dysfunction and abnormal relaxation had greater risk of a composite outcome of death, myocardial infarction, heart failure, or stroke, with HRs of 4.3 (95% CI: 2.0-9.3) and 1.6 (95% CI: 1.1-2.5), respectively, over 20 years (34).

**INCIDENCE AND PREDICTORS OF PREMATURE CARDIOVASCULAR EVENTS. Premature heart failure and stroke events.** Whereas overall event incidence has been relatively low to date because of the young cohort age at inception, nonetheless CARDIA has provided key data on the incidence of premature CVD events. In one seminal analysis of CARDIA

participants up to the age of 50 years, Bibbins-Domingo et al. (35) observed that incident heart failure developed in 27 participants with mean age at onset of  $39 \pm 6$  years. Strikingly, 26 of the 27 participants with early-onset heart failure self-identified as being Black (Figure 5). Cumulative incidence rates of heart failure before the age of 50 years were 1.1% (95% CI: 0.6%-1.7%) in Black women, 0.9% (95% CI: 0.5%-1.4%) in Black men, 0.08% (95% CI: 0.0%-0.5%) in White women, and 0% (95% CI: 0%-0.4%) in White men ( $P = 0.001$  for Black vs White participants). Among Black participants, baseline variables that were significantly associated with incident heart failure included higher diastolic BP, higher BMI, lower high-density lipoprotein cholesterol, and presence of kidney disease. Three-fourths of those in whom heart failure developed had hypertension by the time they were 40 years of age, compared with a hypertension prevalence of 12% among those who did not develop heart failure. Depressed LV systolic function measured at CARDIA Year 5 was also independently associated with incident heart failure. Thus, hypertension, obesity, and systolic dysfunction that are present before 35 years of age, particularly in Black American individuals, appear to be especially important antecedents that may be targets for the prevention of clinical heart failure (35).

Gerber et al. (36) also noted marked disparities in premature stroke events between Black and White participants during 30 years' follow-up. Stroke incidence was 4 times higher in Black (120 per 100,000 person-years; 95% CI: 95-149 per 100,000 person-years) versus White (29 per 100,000 person-years; 95% CI: 18-46 per 100,000 person-years) participants. BP was a key driver of stroke risk, even within levels below the threshold for diagnosing hypertension. These findings further highlight the importance of primordial prevention strategies to reduce population BP levels, particularly in young Black adults (36).

**Premature CVD events.** In a recent analysis, Perak et al. (37) examined the incidence of all premature CVD events (including CVD death and incident nonfatal myocardial infarction, coronary revascularization, stroke, and heart failure) before approximately age 60 years among CARDIA participants. They examined the association of CVH status measured at ages 18 to 30 years with incident events and estimated population attributable fractions for CVD events. Year 0 CVH was high in 28.8%, moderate in 65.0%, and low in 6.3%. There were modest differences in the prevalence of high CVH status across subgroups by age and sex, and notable differences by self-reported race (20.7% in Black participants



compared with 37.0% in White participants) and maximal educational attainment (13.6% among participants with less than or equal to high school completion compared with 32.6% among participants with more than high school education). The adjusted HR for high (vs low) CVH was 0.14 (95% CI: 0.09-0.22) for CVD events (Figure 6). The population attributable fractions for combined moderate or low (vs high) CVH were 0.63 (95% CI: 0.47-0.74) for CVD, 0.81 (95% CI: 0.55-0.92) for CVD mortality, and 0.42 (95% CI: 0.26-0.54) for all-cause mortality. Among individuals with high CVH, rates of premature events were very low in all sociodemographic subgroups. Thus, maintenance of high CVH into late adolescence or early adulthood is associated with markedly lower risk for premature onset CVD, and these data suggest that maintenance of high CVH into young adulthood could prevent as much as 60% to 80% of premature CVD events and mortality (37).

**HEALTH DISPARITIES ASSOCIATED WITH SELF-IDENTIFIED RACE AND DISCRIMINATION.** The CARDIA cohort was designed explicitly to understand differences in CVD RF development in young adulthood by self-identified race and sex, and has matured to the point of observing major disparities in premature CVD events (Figures 5 and 6), particularly heart failure and stroke. Early CARDIA results documented disparities in RF levels, similar to those seen in national data, among young Black or White men and

women, but CARDIA also provided critical insights into the reasons for those differences. For example, Greenlund et al. (38) documented significant differences in prevalence of RFs (BP, obesity) and health behaviors (such as smoking) across race and sex groups overall, with Black participants having more unfavorable levels at the baseline examination. However, they also noted striking differences in prevalence of RFs and health behaviors within individual race/sex strata (eg, smoking prevalence in Black women) depending on geography and education status. Race differences in smoking rates were particularly apparent among those with less than or up to a high school education. Wagenknecht et al. (39) provided further insight, noting that after adjustment for age and education, race and sex differences in prevalence of smoking were no longer evident. Smoking prevalence was lower with greater educational attainment, from 54% among participants with less than a high school education to 12% among those with graduate degrees ( $P < 0.001$ ). These data were early indications of the strong underlying influence of social determinants of health on apparent racial differences in cardiovascular risk (38,39).

CARDIA has assessed participants' self-reported lived experiences with racial/ethnic discrimination using a validated instrument at Years 7, 15, 25, and 30. As early as Year 7, associations of discriminatory experiences with RF levels were noted to be significant.

For example, at Year 7, 48% of Black women and 57% of Black men reported experiencing 3 or more episodes of racial discrimination in life situations, compared with 5% and 4% of White men and women, respectively. Observed Black-White differences in BP were substantially reduced by taking into account reported experiences of racial discrimination and responses to unfair treatment. These early data highlighted the complex nature of lived experiences in association with physiological CVD RFs (40,41).

Subsequent analyses have examined self-reported discrimination and its associations with Black-White differences in birth outcomes (42), weight change (43), and self-rated physical and mental health (44,45), among other outcomes. In one study using data from Year 7 and 15, an increase in self-reported experiences of racial/ethnic discrimination over time was significantly associated with an increase in waist circumference and BMI among Black women (43). In another study, discrimination was statistically significantly associated with worse physical and mental health in both men and women, even after adjustment for age, education, income, and skin color (44).

**Weathering and psychosocial stress.** A number of recent CARDIA publications have examined “weathering,” or the difference between chronological age and composite measures of biological aging in Black and White participants (46,47). In one study using 7 age-related biomarkers (including lipid levels, glucose, C-reactive protein, BMI, pulmonary function, and mean arterial pressure) to gauge accelerated biological versus chronological aging, Black participants on average had a biological age that was  $2.6 \pm 11.8$  years older than their chronological age, whereas the average biological age among White participants was  $3.5 \pm 10.0$  years younger than their chronological age. In other words, Black individuals weathered a mean of 6.1 years faster than White individuals. Belonging to more social groups was associated with less weathering in Black but not White participants, and lower socioeconomic position and more depressive symptoms were associated with more weathering among Black than White individuals (47). In a follow-up analysis examining outcomes, a 1-year greater difference in weathering (ie, 1 year greater difference in biological minus chronological age) was associated with greater odds of developing CVD (OR: 1.04 per year; 95% CI: 1.02-1.06), stroke (OR: 1.12; 95% CI: 1.07-1.17), and all-cause mortality (OR: 1.05; 95% CI: 1.02-1.08). There were no significant overall racial differences in associations, but given the greater burden of weathering in Black participants, the implication is that these measures of accelerated

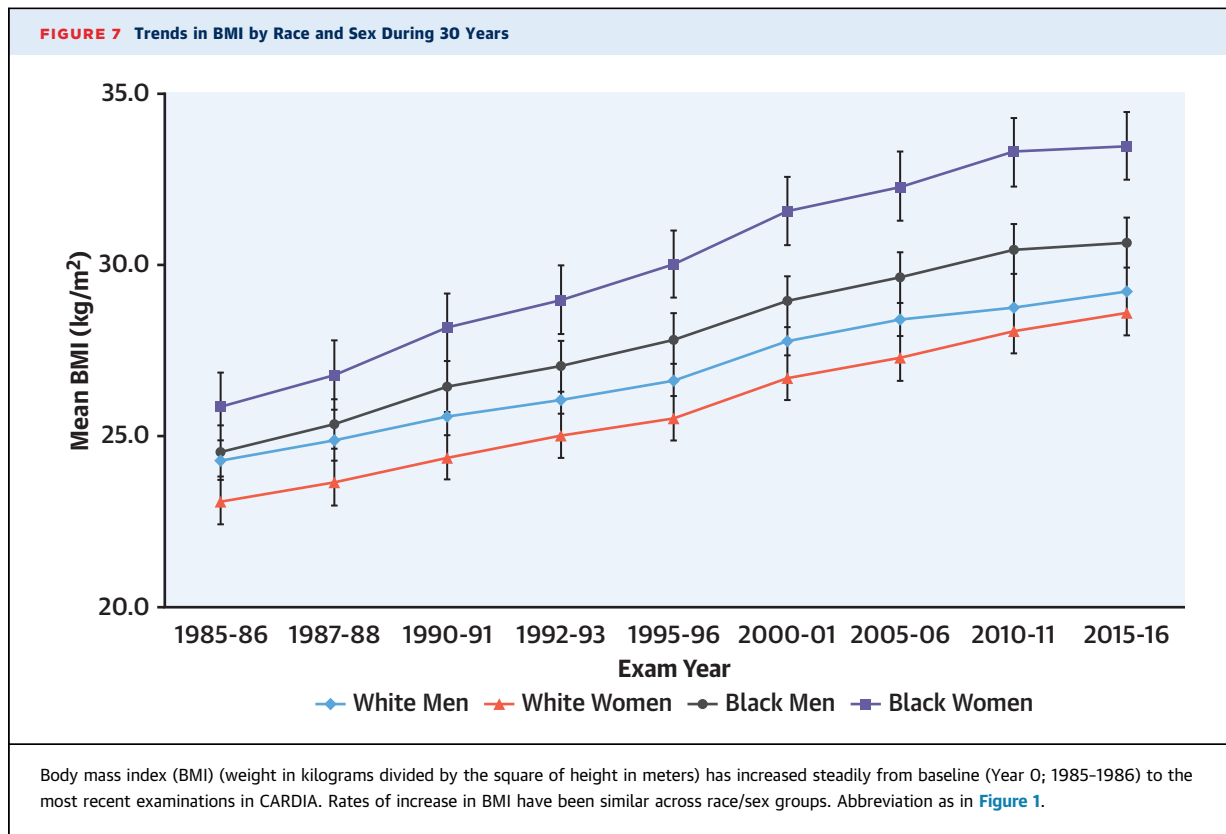
aging may indicate an important marker of risk for Black individuals (46).

Other measures, such as leukocyte telomere length and epigenetic age acceleration, also provide evidence of accelerated biological aging in Black compared with White individuals. For example, burden of racial discrimination reported at Year 15 was associated with more rapid shortening of telomere length over the ensuing 10 years, adding to evidence that racial discrimination contributes to accelerated physiological weathering and health declines among Black Americans through its impact on biological systems (48).

**SOCIAL DETERMINANTS OF HEALTH AS MEDIATORS OF RACIAL DISPARITIES.** CARDIA has measured numerous metrics of social determinants and socioeconomic position multiple times through young adulthood. Early reports identified racial disparities in RF levels and health disparities; however, associations of more adverse RFs with Black race were typically attenuated to nonsignificance with simple adjustment for socioeconomic factors (49).

Socioeconomic position, even at young ages, has been associated with adverse health outcomes. Matthews et al. (50) used data from CARDIA Year 20, at which 19% of participants had CAC, in association with reported early life socioeconomic position. They found that lower paternal education in Black participants and lower maternal occupational status in all participants were associated with higher risk of having CAC, independent of adult socioeconomic position. Lower average adult education, occupation, and income were also associated with higher risk of having CAC, with associations seen primarily in Black individuals (50). Elfassy et al. (51) examined income volatility in young adulthood and associations with subsequent CVD events. Income status was assessed at examinations from 1990 to 2005, and CVD events were assessed from 2005 to 2015. Black participants were far more likely than White ones to experience income volatility and income decreases from mean ages 30 to 45 years. After adjustment for demographic, behavioral, and other CVD RFs, higher income volatility (HR: 2.07; 95% CI: 1.10-3.90) and more income decreases (HR: 2.54 for  $\geq 2$  vs 0 income decreases; 95% CI: 1.24-5.19) were associated with risk for CVD (51).

Education has been associated consistently with health outcomes, and the differences in education attainment between Black and White participants may account for some disparities in health outcomes. For example, to date, cancer and cardiovascular diseases have been the most common causes of death in this younger cohort, but homicide and AIDS, which



disproportionately affected Black participants, were associated with the most years of potential life lost. In multivariable models, each higher level of education achieved (from high school or less to some college to college degree or more) was associated with 1.37 fewer years of potential life lost (95% CI: -2.37 to -0.37), whereas race was no longer independently associated (52).

Both White and Black participants in CARDIA have had worsening of health behaviors and RF levels through young adulthood, although deterioration for Black participants has been more significant (53). Whitaker et al. (54) examined whether socioeconomic, psychosocial, and neighborhood environmental factors may mediate racial differences in CVH behaviors (as represented by smoking, physical activity, and diet patterns). They found that Black participants had significantly lower CVH behavior scores than White participants consistently across 30 years of follow-up. Individual socioeconomic factors mediated 49% to 70% of the association between race and health behavior score, psychosocial factors 20% to 30%, and neighborhood factors 22% to 41% ( $P < 0.01$  for all). Thus, racial disparities in health behavior scores appeared to be mediated predominantly by large race-related differences in socioeconomic

factors, highlighting the profound impact of factors that are mostly not under an individual's control (54).

The availability of geocoding has allowed for additional insights into social determinants of health and the potential influence of neighborhood racial segregation patterns on CVD risk and outcomes. For example, Kershaw et al. (55) found that 81.6% of CARDIA participants were living in a high-segregation, 12.2% in a medium-segregation, and 6.2% in a low-segregation neighborhood. Systolic BP increased by a mean of 0.16 mm Hg (95% CI: 0.06-0.26 mm Hg) with each 1-SD increase in segregation score after adjusting for interactions of time with age, sex, and field center. Among those who lived in high-segregation neighborhoods at baseline, reductions in exposure to segregation were associated with reductions in systolic BP (55). Similarly, data from the first 25 years of CARDIA follow-up indicated that Black women living in highly segregated neighborhoods were 30% more likely to become obese between examination periods compared with women living in neighborhoods with low levels of segregation (56).

**OBESITY INCIDENCE AS A FUNCTION OF YOUNG ADULT BEHAVIORS.** Given the CARDIA study's

inception in 1985, the year in which US obesity prevalence started to climb, investigators have been uniquely positioned to assess the upstream determinants and correlates of weight gain in the CARDIA cohort.

**Weight gain in all race/sex groups.** From Year 0 to Year 30 (mean ages: 25 to 55 years), there have been significant mean weight gains in the cohort overall and in all 4 race/sex groups in CARDIA (Figure 7). There were larger gains noted early in CARDIA, with some flattening of increases in weight in later years, but overall consistent patterns across groups. The slope for time-related weight gain was consistent for those with normal weight, overweight, and obesity at baseline in young adulthood. Thus, among groups defined by baseline BMI in young adulthood, BMI tended to track and to increase consistently across all groups (57).

**Dietary quality, fast food availability, and weight change.** CARDIA has administered a detailed dietary history at examination Years 0, 7, and 20 (and is doing so again at Year 35). The diet history method obtains much more in-depth information than a food frequency questionnaire, obtaining all food items eaten in the past 28 days, named by the participant, by brand name where possible, in response to >100 open-ended questions, such as “Do you eat meat?” with in-depth follow-up of answers. Diet quality was assessed as a function of the proportion of plant-based whole foods. Diet quality was associated differentially with weight gain in Black and White participants. Among White participants, high versus low diet quality was associated with less mean 20-year weight gain (+11.2 kg in high vs +13.9 kg in low-quality diet groups), whereas among Black participants high diet quality was associated with greater weight gain (+19.4 kg vs +17.8 kg) (58). Another analysis assessed change in plant-centered diet quality. In multivariable analysis, each 1-SD increment in plant-based diet quality over 20 years was associated with lower gains in BMI ( $-0.39 \pm 0.14$  kg/m<sup>2</sup>;  $P = 0.004$ ), waist circumference ( $-0.90 \pm 0.27$  cm;  $P < 0.001$ ), and weight ( $-1.14 \pm 0.33$  kg;  $P < 0.001$ ) during the same period, as well as with lower risk for subsequent diabetes (59).

Geocoding of the CARDIA participants' addresses at diverse examination cycles has also allowed assessment of neighborhood food availability. In general, higher numbers of neighborhood fast food restaurants and lower numbers of sit-down restaurants have been associated with higher consumption of an obesogenic fast food-type diet and greater BMI gains (60). Also, there were inverse associations noted between fast food price and overall

consumption, as well as with BMI, with stronger inverse associations in more (vs less) deprived neighborhoods (61), indicating that fast food availability and cheaper pricing in economically vulnerable neighborhoods appear to be strong correlates of greater obesity prevalence in participants living in those neighborhoods.

In CARDIA participants, frequency of fast-food dining was lowest for White women (1.3 times per week) compared with other race/sex groups (about twice weekly). Compared with the average 15-year weight gain in participants with infrequent (less than once a week) fast-food restaurant use at baseline and follow-up, those with frequent (more than twice weekly) visits to fast-food restaurants at baseline and follow-up gained an extra 4.5 kg of bodyweight and had a 2-fold greater increase in insulin resistance (62).

**Physical and sedentary activity.** CARDIA has collected self-reported physical activity at all examinations, as well as intermittent measures of sedentary activities (eg, television viewing), and objective measures of physical activity and sedentary behavior via accelerometry and cardiorespiratory fitness based on graded treadmill tests. Using self-reported activity level during 20 years, Hankinson et al. (63) noted that CARDIA participants at all levels of physical activity gained weight. However, maintaining high levels of activity was associated with smaller gains in BMI and waist circumference compared with low activity levels. Men and women maintaining high activity (compared with those maintaining the lowest activity) gained 2.6 and 6.1 fewer kg, and 3.1 and 3.8 fewer cm in waist circumference, respectively (63).

With regard to sedentary activity, television viewing was directly associated with size of abdominal fat depots on computed tomography imaging. For each 1-SD increment in television viewing (1.5 h/d), visceral, subcutaneous, and intramuscular adipose tissue depots were greater by 3.5, 3.4, and 3.9 cm, respectively. In the same study, for each 1-SD increment in physical activity, visceral, subcutaneous, and intramuscular adipose tissue were lower by 7.6, 6.7, and 8.1 cm, respectively (64). In further analyses, statistical replacement of sedentary time with light-intensity physical activity or moderate-to-vigorous intensity physical activity was associated with improved indices of adiposity and cardiometabolic health 10 years later (65).

**METABOLIC HEALTH THROUGH YOUNG ADULTHOOD: METABOLIC SYNDROME, DIABETES, AND NONALCOHOLIC FATTY LIVER DISEASE.** Influence of weight gain on RF levels and development of metabolic syndrome. Through 15 years of follow-

up, 16.3% of CARDIA participants maintained a stable BMI, 73.9% had an increasing BMI, and 9.8% had a fluctuating BMI. Participants with stable BMI had essentially unchanged levels of cardiometabolic RFs, regardless of baseline BMI, whereas those with increasing BMI had progressively worsening levels. For example, among men with a baseline normal BMI, those who also had stable BMI during follow-up had a mean increase of only 15 mg/dL in fasting triglycerides over 15 years, compared with 65 mg/dL ( $P < 0.001$ ) in those whose BMI increased over time. Incidence of metabolic syndrome at Year 15 was lower in the stable BMI group (2.2%) compared with the increased BMI group (18.8%;  $P < 0.001$ ). These data suggest that adverse progression of cardiometabolic RFs with advancing age may not be inevitable. Young adults who maintained stable BMI over time had minimal progression of RFs and lower incidence of metabolic syndrome regardless of baseline BMI, indicating the importance of weight stabilization as a clinical and public health strategy (66,67).

**Weight and incident diabetes.** Obesity and weight gain are significant RFs for incident diabetes. Reis et al. (68) examined years of exposure to abdominal obesity (defined as waist circumference  $>102$  cm in men and  $>88$  cm in women) during 25 years. HRs for 0, 1-5, 6-10, 11-15, 16-20, and  $>20$  years of abdominal obesity were 1.00 (referent), 2.06 (95% CI: 1.43-2.98), 3.45 (95% CI: 2.28-5.22), 3.43 (95% CI: 2.28-5.22), 2.80 (95% CI: 1.73-4.54), and 2.91 (95% CI: 1.60-5.29), respectively ( $P < 0.001$ ) (68).

**LONGITUDINAL PULMONARY FUNCTION AND LUNG AND CARDIOVASCULAR OUTCOMES.** Pulmonary function testing with spirometry has been obtained at Years 0, 2, 5, 10, 20, and 30. Evidence for airflow obstruction was present in 6.9% and 7.8% of participants at Years 0 and 20, respectively. Lung function decreased in all groups with age, but the effect of cigarette smoking on lung function decrease was most evident in young adults with pre-existing airflow obstruction. The forced expiratory volume in 1 second/forced vital capacity ratio at Year 0 was highly predictive of airflow obstruction 20 years later (69).

Trajectories of change in lung function in CARDIA participants during 30 years were associated with emphysema identified on computed tomography imaging. There were 5 distinct trajectories describing peak and change in forced expiratory volume, denoted as "Preserved Ideal," "Preserved Good," "Preserved Impaired," "Worsening," and "Persistently

Poor." Ever smokers comprised part of all 5 trajectory groups. The prevalence of emphysema at mean ages of 40, 45, and 50 years was 1.7%, 2.5%, and 7.1%, respectively. Baseline poor and worsening lung health trajectories were associated with 5-fold higher odds of future emphysema independent of chronic tobacco smoke exposure. Thus, lower peak and accelerated decrease in lung function were found to be significant RFs for future emphysema independent of smoking status (70).

Following the observation in CARDIA that decrease in forced vital capacity from average age at peak (29 years) to 35 years of age predicted incident hypertension between average ages 35 and 45 years (71), Cuttica et al. (72) examined 20-year changes in lung function and observed significant associations with left-sided heart structure and function. Specifically, decrease in forced vital capacity from peak was associated with larger LV mass and greater cardiac output. Decrease in airflow was associated with smaller left atrial internal dimension and lower cardiac output. Finally, decrease in forced vital capacity was associated with diastolic dysfunction. They concluded that decrease in airflow is associated with underfilling of the left-sided heart and low cardiac output, whereas decrease in forced vital capacity with preserved airflow is associated with LV hypertrophy and diastolic dysfunction. These cardiopulmonary interactions appeared to evolve concurrently from early adulthood forward, but the precise mechanisms remain obscure (72).

Pulmonary function at baseline (mean age: 25 years) was also found to be independently associated with CVD events during 29 years' follow-up. Baseline forced expiratory volume in 1 second (HR: 1.18 per 10-unit lower; 95% CI: 1.06-1.3) and forced vital capacity (HR: 1.19 per 10-unit lower; 95% CI: 1.06-1.33) were both associated with incident CVD events independent of traditional RFs, including BMI. These associations were observed for outcomes of heart failure and cerebrovascular events but not coronary events. These findings add to a growing body of evidence that peak lung function in young adulthood has important implications for future respiratory and overall health (73).

**COGNITIVE FUNCTION AND BRAIN HEALTH IN MID-LIFE.** Cognitive function was first measured at Year 25 (mean age: 50 years), and was repeated at Year 30. State-of-the-art brain magnetic resonance imaging was obtained in a subset of participants at Year 25 and repeated in the same participants at Year 30.

**TABLE 2 Summary of Key Findings From the CARDIA Study, 1985-2021**

<p>Transition from healthy young adulthood to development of CVD risk factors</p> <ul style="list-style-type: none"> <li>• There are diverse trajectories of CVD RF changes by race and sex through young adulthood</li> <li>• Early RF exposures are important determinants of risk, and patterns of RF change add information in predicting future CVD risk</li> </ul>	<p>Obesity incidence as a function of young adult behaviors</p> <ul style="list-style-type: none"> <li>• During the American obesity epidemic, CARDIA participants have experienced similar degrees of BMI gain regardless of race, sex, and baseline BMI</li> <li>• Diet quality and patterns of physical and sedentary activity are significantly associated with weight gain</li> </ul>
<p>Transitions from CVD RFs to subclinical CVD and clinical events</p> <ul style="list-style-type: none"> <li>• CVD RFs are major determinants of CAC in younger adults, and CAC measured at ages 32-46 y is strongly associated with premature coronary events in adults</li> <li>• Longitudinal changes in LV structure and function through young adulthood are evident in Black and White men and women, and are associated with cumulative risk factor exposures</li> </ul>	<p>Metabolic health through young adulthood: metabolic syndrome, diabetes, and NAFLD</p> <ul style="list-style-type: none"> <li>• RF changes and incidence of metabolic syndrome through young adulthood are associated with amount of weight gain over time, rather than baseline weight</li> <li>• Duration of higher BMI exposure and especially central adiposity are important predictors of DM and NAFLD</li> </ul>
<p>Incidence and predictors of premature cardiovascular events</p> <ul style="list-style-type: none"> <li>• Black young adults are at substantially higher risk for premature incidence of heart failure and stroke, largely related to higher BP levels, even within normative ranges</li> <li>• Poor CVH status in late adolescence is a significant predictor of premature ASCVD events, and high CVH is associated with very low risk</li> </ul>	<p>Longitudinal pulmonary function and lung and cardiovascular outcomes</p> <ul style="list-style-type: none"> <li>• Peak lung function in early adulthood is an important metric of future lung and CVH; lung function decreases throughout adulthood in all groups, more rapidly in cigarette smokers</li> <li>• Pulmonary function over time is associated with downstream LV structure and function, as well as with heart failure and stroke incidence</li> </ul>
<p>Health disparities associated with self-identified race and discrimination</p> <ul style="list-style-type: none"> <li>• Major disparities exist by self-identified race in health behaviors and RFs, even in young adulthood, leading to evidence of more rapid biological aging in Black participants</li> <li>• Disparities in RFs and behaviors are significantly associated with lived and internalized experiences of discrimination</li> </ul>	<p>Cognitive function and brain health in mid-life</p> <ul style="list-style-type: none"> <li>• Diet and CVH status in young adulthood, as well as cumulative RF exposures through young adulthood, are associated with mid-life cognitive function</li> <li>• CVD RF levels through young adulthood are associated with measurable differences in brain volume, white matter lesions, and cerebral blood flow in mid-life</li> </ul>
<p>Social determinants of health as mediators of racial disparities</p> <ul style="list-style-type: none"> <li>• Social determinants of health (socioeconomic position, education, and individual- and neighborhood-level assets) largely account for disparities in CVD RFs between Black and White participants</li> <li>• Neighborhood segregation is associated with worse RF levels, and moving to lower segregated neighborhoods is associated with improvement</li> </ul>	<p>Effects of chronic marijuana exposure on health</p> <ul style="list-style-type: none"> <li>• Cumulative lifetime marijuana use is associated with other unhealthy behaviors but not with physiological RFs</li> <li>• Cumulative lifetime marijuana use is associated with cognitive function in mid-life</li> </ul>

ASCVD = atherosclerotic cardiovascular disease; BMI = body mass index; BP = blood pressure; CAC = coronary artery calcium; CARDIA = Coronary Artery Risk Development in Young Adults; CVD = cardiovascular disease; DM = diabetes mellitus; LV = left ventricular; NAFLD = nonalcoholic fatty liver disease; RF = risk factor; other abbreviation as in Table 1.

Higher quality dietary patterns at Year 0 and 20 were associated with better cognitive function at Year 25 among apparently healthy middle-aged participants (74). Specifically, greater adherence to Mediterranean or more plant-based dietary patterns during young adulthood were associated with better midlife cognitive performance (75). Likewise, greater cardiorespiratory fitness at baseline (Year 0) and maintenance of fitness from Year 0 to 20 were also associated with higher performance on diverse domains of cognitive function at Year 25 (76).

Cumulative CVD RF exposures have also proven to be significantly associated with mid-life cognitive function. Higher cumulative systolic and diastolic BP and fasting blood glucose across 25 years were significantly associated with worse cognition on all domains of testing. Fewer significant associations were observed for cholesterol exposure (77). Similarly, a greater number of ideal CVH metrics in young adulthood and middle age were independently associated with better cognitive function in midlife. Participants who had  $\geq 5$  ideal metrics at a greater number of examinations during the 25-year period exhibited better performance on each cognitive test in middle age (78). Between Years 25

and 30 (mean ages: 50 and 55, respectively), 5% of participants had accelerated cognitive decline. Midlife smoking, hypertension, and diabetes mellitus were associated with greater likelihood of accelerated decline in both Black and White participants (79).

In parallel with cognitive function testing, longitudinal CVD RFs have been associated with structural and functional findings on brain imaging. Current smoking, hypertension, and higher BMI were significantly associated with lower gray matter cerebral blood flow; current smoking, hypertension, and diabetes with lower total brain volume; higher BMI and hypertension with more abnormal white matter lesions; and hypertension with white matter fractional anisotropy. These findings suggest that worsening mid-life CVD RFs should be considered for early intervention and as markers of future risk for cerebrovascular disease and dementia (80).

**EFFECTS OF CHRONIC MARIJUANA EXPOSURE ON HEALTH.** CARDIA has ascertained drug and alcohol use patterns at all examinations through young adulthood, allowing assessment of cumulative lifetime exposure. More than 84% of CARDIA participants have reported a history of marijuana use at any

point in time, although <12% persisted with use in middle age (81).

In an analysis after Year 15, although marijuana use was not independently associated with presence of any of the traditional CVD RFs, it was associated with other unhealthy behaviors, such as high energy intake, smoking, and other nonprescription drug use. With regard to CVD events, compared with no marijuana use, cumulative lifetime and recent marijuana use showed no association with incident CVD overall or in any subgroups (82). However, when analyzing cognitive function at Year 25, current daily use of marijuana was associated with worse verbal memory and processing speed, and cumulative lifetime exposure was associated with worse performance in all domains of cognitive function. After excluding current users and adjusting for potential confounders, cumulative lifetime exposure to marijuana remained significantly associated with worse verbal memory, corresponding to participants remembering 1 word fewer from a list of 15 words for every 5 years of use (81).

### FUTURE RESEARCH DIRECTIONS

Future CARDIA research directions will incorporate data from the ongoing Year 35 examination in 2020 to 2022 and leverage the expanding resource of multi-omics data across young adulthood. For example, whole-genome sequencing and genome-wide DNA methylation data (from 4 examinations from Years 15 to 30) are available in approximately 4,000 CARDIA participants. Initial studies indicate the potential power and limitations of polygenic risk scores (83,84), and of epigenetic age acceleration (85,86), for young adult cardiometabolic phenotypes. In addition, RNA has been collected and stored at 2 examinations. Proteomic and metabolomic analyses are ongoing and are delineating the correlates and predictive utility of these platforms for cardiometabolic and other health outcomes. At Year 35, data collection will include first-time assessments of physical functioning (eg, chair stand, grip strength), hearing and vestibular dysfunction, and dedicated lung and abdominal imaging, as well as repeat measures of RFs, sleep and accelerometry, cognitive function and brain imaging, and dietary quality, among other measures.

As the CARDIA cohort ages toward retirement and later life, it will continue to be a unique resource for understanding the determinants, mechanisms, and outcomes of CVH and CVD across the life course from young adulthood on. Future examination cycles will

continue to provide opportunities for insight into the processes of aging.

### CONCLUSIONS

In summary, CARDIA has become one of the premier US population-based cohort studies, and has contributed fundamentally to our understanding of the life course of CVH and CVD, as well as pulmonary, renal, neurological, and other manifestations of aging (Central Illustration, Table 2). Due to its inception in early adulthood, CARDIA has defined the contemporary epidemiology of CVH/CVD in the first half of adult life in a cohort that has experienced the obesity and diabetes epidemics. CARDIA has established associations between the neighborhood environment and the life course evolution of lifestyle behaviors with biological RFs, subclinical disease, and early clinical CVD events from early adulthood on. CARDIA has also identified the nature and major determinants of Black-White differences in the loss of CVH and development of CVD risk, studying the progression of subclinical disease to clinical events during early to middle adulthood. Leveraging ongoing pan-omics work from genomic to metabolomics and the microbiome will allow CARDIA investigators to make unique insights into the systems biology of cardiometabolic aging. CARDIA investigators are eager to collaborate with new, and particularly early-stage, investigators, and can be contacted through the CARDIA Web site.

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## REFERENCES

- Friedman GD, Cutter GR, Donahue RP, et al. CARDIA: study design, recruitment, and some characteristics of the examined subjects. *J Clin Epidemiol* 1988;41:1105-16.
- Jacobs DR Jr., Hannan PJ, Wallace D, Liu K, Williams OD, Lewis CE. Interpreting age, period and cohort effects in plasma lipids and serum insulin using repeated measures regression analysis: the CARDIA Study. *Stat Med* 1999;18:655-79.
- Allen NB, Siddique J, Wilkins JT, et al. Blood pressure trajectories in early adulthood and subclinical atherosclerosis in middle age. *JAMA* 2014;311:490-7.
- Liu K, Colangelo LA, Daviglius ML, et al. Can antihypertensive treatment restore the risk of cardiovascular disease to ideal levels? *J Am Heart Assoc* 2015;4:e002275.
- Domanski MJ, Tian X, Wu CO, et al. Time course of LDL cholesterol exposure and cardiovascular disease event risk. *J Am Coll Cardiol* 2020;76:1507-16.
- Liu K, Daviglius ML, Loria CM, et al. Healthy lifestyle through young adulthood and the presence of low cardiovascular disease risk profile in middle age. *Circulation* 2012;125:996-1004.
- Gunderson EP, Quesenberry CP Jr., Jacobs DR Jr., Feng J, Lewis CE, Sidney S. Longitudinal study of prepregnancy cardiometabolic risk factors and subsequent risk of gestational diabetes mellitus. *Am J Epidemiol* 2010;172:1131-43.
- Gunderson EP, Jacobs DR Jr., Chiang V, et al. Duration of lactation and incidence of the metabolic syndrome in women of reproductive age according to gestational diabetes mellitus status. *Diabetes* 2010;59:495-504.
- Gunderson EP, Lewis CE, Lin Y, et al. Lactation duration and progression to diabetes in women across the childbearing years. *JAMA Intern Med* 2018;178:328-37.
- Gunderson EP, Quesenberry CP Jr., Ning X, et al. Lactation duration and midlife atherosclerosis. *Obstet Gynecol* 2015;126:381-90.
- Appiah D, Schreiner PJ, Bower JK, Sternfeld B, Lewis CE, Wellons MF. Is surgical menopause associated with future levels of cardiovascular risk factor independent of antecedent levels? *Am J Epidemiol* 2015;182:991-9.
- Loria CM, Liu K, Lewis CE, et al. Early adult risk factor levels and subsequent coronary artery calcification. *J Am Coll Cardiol* 2007;49:2013-20.
- Carr JJ, Jacobs DR Jr., Terry JG, et al. Association of coronary artery calcium in adults aged 32 to 46 years with incident coronary heart disease and death. *JAMA Cardiol* 2017;2:391-9.
- Moreira HT, Nwabuo CC, Armstrong AC, et al. Reference ranges and regional patterns of left ventricular strain and strain rate using two-dimensional speckle-tracking echocardiography in a healthy middle-aged black and white population. *J Am Soc Echocardiogr* 2017;30:647-58.e2.
- Ogunyankin KO, Liu K, Lloyd-Jones DM, Colangelo LA, Gardin JM. Reference values of right ventricular end-diastolic area defined by ethnicity and gender in a young adult population. *Echocardiography* 2011;28:142-9.
- Rasmussen-Torvik LJ, Colangelo LA, Lima JAC, et al. Prevalence and predictors of diastolic dysfunction according to different classification criteria. *Am J Epidemiol* 2017;185:1221-7.
- Teixido-Tura G, Almeida AL, Choi EY, et al. Determinants of aortic root dilatation and reference values among young adults over a 20-year period. *Hypertension* 2015;66:23-9.
- Kishi S, Reis JP, Venkatesh BA, et al. Race-ethnic and sex differences in left ventricular structure and function. *J Am Heart Assoc* 2015;4:e001264.
- Khan SS, Shah SJ, Colangelo LA, et al. Association of patterns of change in adiposity with diastolic function and systolic myocardial mechanics from early adulthood to middle age. *J Am Soc Echocardiogr* 2018;31:1261-9.e8.
- Kishi S, Armstrong AC, Gidding SS, et al. Association of obesity in early adulthood and middle age with incipient left ventricular dysfunction and structural remodeling. *J Am Coll Cardiol HF* 2014;2:500-8.
- Reis JP, Allen N, Gibbs BB, et al. Association of the degree of adiposity and duration of obesity with measures of cardiac structure and function. *Obesity (Silver Spring)* 2014;22:2434-40.
- Kishi S, Gidding SS, Reis JP, et al. Association of insulin resistance and glycemic metabolic abnormalities with lv structure and function in middle age. *J Am Coll Cardiol Img* 2017;10:105-14.
- Reis JP, Allen NB, Bancks MP, et al. Duration of diabetes and prediabetes during adulthood and subclinical atherosclerosis and cardiac dysfunction in middle age. *Diabetes Care* 2018;41:731-8.
- VanWagner LB, Wilcox JE, Colangelo LA, et al. Association of nonalcoholic fatty liver disease with subclinical myocardial remodeling and dysfunction. *Hepatology* 2015;62:773-83.
- Kishi S, Teixido-Tura G, Ning H, et al. Cumulative blood pressure in early adulthood and cardiac dysfunction in middle age. *J Am Coll Cardiol* 2015;65:2679-87.
- Nwabuo CC, Yano Y, Moreira HT, et al. Association between visit-to-visit blood pressure variability in early adulthood and myocardial structure and function in later life. *JAMA Cardiol* 2020;5:795-801.
- Bansal N, Lin F, Vittinghoff E, et al. Estimated GFR and subsequent higher left ventricular mass in young and middle-aged adults with normal kidney function. *Am J Kidney Dis* 2016;67:227-34.
- Appiah D, Schreiner PJ, Nwabuo CC, Wellons MF, Lewis CE, Lima JA. The association of surgical versus natural menopause with future left ventricular structure and function. *Menopause* 2017;24:1269-76.
- Rodrigues P, Santos-Ribeiro S, Teodoro T, et al. Association between alcohol intake and cardiac remodeling. *J Am Coll Cardiol* 2018;72:1452-62.
- Desai CS, Ning H, Liu K, et al. Cardiovascular health in young adulthood and association with left ventricular structure and function later in life. *J Am Soc Echocardiogr* 2015;28:1452-61.
- Gidding SS, Carnethon MR, Daniels S, et al. Low cardiovascular risk is associated with favorable left ventricular mass, left ventricular relative wall thickness, and left atrial size. *J Am Soc Echocardiogr* 2010;23:816-22.
- Gidding SS, Lloyd-Jones D, Lima J, et al. Prevalence of American Heart Association heart failure stages in black and white young and middle-aged adults. *Circ Heart Fail* 2019;12:e005730.
- Perak AM, Khan SS, Colangelo LA, et al. Age-related development of cardiac remodeling and dysfunction in young black and white adults. *J Am Soc Echocardiogr* 2021;34:388-400.
- Desai CS, Colangelo LA, Liu K, et al. Prevalence, prospective risk markers, and prognosis associated with the presence of left ventricular diastolic dysfunction in young adults. *Am J Epidemiol* 2013;177:20-32.
- Bibbins-Domingo K, Pletcher MJ, Lin F, et al. Racial differences in incident heart failure among young adults. *N Engl J Med* 2009;360:1179-90.
- Gerber Y, Rana JS, Jacobs DR Jr., et al. Blood pressure levels in young adulthood and midlife stroke incidence in a diverse cohort. *Hypertension* 2021;77:1683-93.
- Perak AM, Ning H, Khan SS, et al. Associations of late adolescent or young adult cardiovascular health with premature cardiovascular disease and mortality. *J Am Coll Cardiol* 2020;76:2695-707.
- Greenlund KJ, Kiefe CI, Gidding SS, et al. Differences in cardiovascular disease risk factors in black and white young adults. *Ann Epidemiol* 1998;8:22-30.
- Wagenknecht LE, Cutter GR, Haley NJ, et al. Racial differences in serum cotinine levels among smokers. *Am J Public Health* 1990;80:1053-6.
- Krieger N, Sidney S. Racial discrimination and blood pressure. *Am J Public Health* 1996;86:1370-8.
- Krieger N, Smith K, Naishadham D, Hartman C, Barbeau EM. Experiences of discrimination: validity and reliability of a self-report measure for population health research on racism and health. *Soc Sci Med* 2005;61:1576-96.
- Mustillo S, Krieger N, Gunderson EP, Sidney S, McCreath H, Kiefe CI. Self-reported experiences of racial discrimination and black-white differences in preterm and low-birthweight deliveries. *Am J Public Health* 2004;94:2125-31.
- Cunningham TJ, Berkman LF, Kawachi I, et al. Changes in waist circumference and body mass index in the US CARDIA cohort. *J Biosci* 2013;45:267-78.
- Borrell LN, Kiefe CI, Williams DR, Diez-Roux AV, Gordon-Larsen P. Self-reported health, perceived racial discrimination, and skin color in African Americans in the CARDIA study. *Soc Sci Med* 2006;63:1415-27.

45. Hudson DL, Puterman E, Bibbins-Domingo K, Matthews KA, Adler NE. Race, life course socioeconomic position, racial discrimination, depressive symptoms and self-rated health. *Soc Sci Med* 2013;97:7-14.
46. Forrester SN, Zmora R, Schreiner PJ, et al. Racial differences in the association of accelerated aging with future cardiovascular events and all-cause mortality. *Ethn Health* 2020 Nov 21 [E-pub ahead of print].
47. Forrester SN, Zmora R, Schreiner PJ, et al. Accelerated aging: a marker for social factors resulting in cardiovascular events? *SSM Popul Health* 2021;13:100733.
48. Chae DH, Wang Y, Martz CD, et al. Racial discrimination and telomere shortening among African Americans. *Health Psychol* 2020;39:209-19.
49. Kiefe CI, Williams OD, Lewis CE, Allison JJ, Sekar P, Wagenknecht LE. Ten-year changes in smoking among young adults. *Am J Public Health* 2001;91:213-8.
50. Matthews KA, Schwartz JE, Cohen S. Indices of socioeconomic position across the life course as predictors of coronary calcification in black and white men and women. *Soc Sci Med* 2011;73:768-74.
51. Elfassy T, Swift SL, Glymour MM, et al. Associations of income volatility with incident cardiovascular disease and all-cause mortality in a US cohort. *Circulation* 2019;139:850-9.
52. Roy B, Kiefe CI, Jacobs DR, et al. Education, race/ethnicity, and causes of premature mortality among middle-aged adults in 4 US urban communities. *Am J Public Health* 2020;110:530-6.
53. Booth JN 3rd., Allen NB, Calhoun D, et al. Racial differences in maintaining optimal health behaviors into middle age. *Am J Prev Med* 2019;56:368-75.
54. Whitaker KM, Jacobs DR Jr., Kershaw KN, et al. Racial disparities in cardiovascular health behaviors. *Am J Prev Med* 2018;55:63-71.
55. Kershaw KN, Robinson WR, Gordon-Larsen P, et al. Association of changes in neighborhood-level racial residential segregation with changes in blood pressure among black adults. *JAMA Intern Med* 2017;177:996-1002.
56. Pool LR, Carnethon MR, Goff DC Jr., Gordon-Larsen P, Robinson WR, Kershaw KN. Longitudinal associations of neighborhood-level racial residential segregation with obesity among blacks. *Epidemiology* 2018;29:207-14.
57. Dutton GR, Kim Y, Jacobs DR Jr., et al. 25-year weight gain in a racially balanced sample of U.S. adults. *Obesity (Silver Spring)* 2016;24:1962-8.
58. Zamora D, Gordon-Larsen P, Jacobs DR Jr., Popkin BM. Diet quality and weight gain among black and white young adults. *Am J Clin Nutr* 2010;92:784-93.
59. Choi Y, Larson N, Gallaher DD, et al. A shift toward a plant-centered diet from young to middle adulthood and subsequent risk of type 2 diabetes and weight gain. *Diabetes Care* 2020;43:2796-803.
60. Richardson AS, Meyer KA, Howard AG, et al. Multiple pathways from the neighborhood food environment to increased body mass index through dietary behaviors. *Health Place* 2015;36:74-87.
61. Rummo PE, Meyer KA, Green Howard A, Shikany JM, Guilkey DK, Gordon-Larsen P. Fast food price, diet behavior, and cardiometabolic health. *Health Place* 2015;35:128-35.
62. Pereira MA, Kartashov AI, Ebbeling CB, et al. Fast-food habits, weight gain, and insulin resistance. *Lancet* 2005;365:36-42.
63. Hankinson AL, Daviglius ML, Bouchard C, et al. Maintaining a high physical activity level over 20 years and weight gain. *JAMA* 2010;304:2603-10.
64. Whitaker KM, Pereira MA, Jacobs DR Jr., Sidney S, Odegaard AO. Sedentary behavior, physical activity, and abdominal adipose tissue deposition. *Med Sci Sports Exerc* 2017;49:450-8.
65. Whitaker KM, Pettee Gabriel K, Buman MP, et al. Associations of accelerometer-measured sedentary time and physical activity with prospectively assessed cardiometabolic risk factors. *J Am Heart Assoc* 2019;8:e010212.
66. Lloyd-Jones DM, Liu K, Colangelo LA, et al. Consistently stable or decreased body mass index in young adulthood and longitudinal changes in metabolic syndrome components. *Circulation* 2007;115:1004-11.
67. Truesdale KP, Stevens J, Lewis CE, Schreiner PJ, Loria CM, Cai J. Changes in risk factors for cardiovascular disease by baseline weight status in young adults who maintain or gain weight over 15 years. *Int J Obes (Lond)* 2006;30:1397-407.
68. Reis JP, Hankinson AL, Loria CM, et al. Duration of abdominal obesity beginning in young adulthood and incident diabetes through middle age. *Diabetes Care* 2013;36:1241-7.
69. Kalhan R, Arynchyn A, Colangelo LA, Dransfield MT, Gerald LB, Smith LJ. Lung function in young adults predicts airflow obstruction 20 years later. *Am J Med* 2010;123:468.e1-7.
70. Washko GR, Colangelo LA, Estepar RSJ, et al. Adult life-course trajectories of lung function and the development of emphysema. *Am J Med* 2020;133:222-30.e11.
71. Jacobs DR Jr., Yatsuya H, Hearst MO, et al. Rate of decline of forced vital capacity predicts future arterial hypertension. *Hypertension* 2012;59:219-25.
72. Cuttica MJ, Colangelo LA, Shah SJ, et al. Loss of lung health from young adulthood and cardiac phenotypes in middle age. *Am J Respir Crit Care Med* 2015;192:76-85.
73. Cuttica MJ, Colangelo LA, Dransfield MT, et al. Lung function in young adults and risk of cardiovascular events over 29 years. *J Am Heart Assoc* 2018;7:e010672.
74. Zhu N, Jacobs DR, Meyer KA, et al. Cognitive function in a middle aged cohort is related to higher quality dietary pattern 5 and 25 years earlier. *J Nutr Health Aging* 2015;19:33-8.
75. McEvoy CT, Hoang T, Sidney S, et al. Dietary patterns during adulthood and cognitive performance in midlife. *Neurology* 2019;92:e1589-99.
76. Zhu N, Jacobs DR Jr., Schreiner PJ, et al. Cardiorespiratory fitness and cognitive function in middle age. *Neurology* 2014;82:1339-46.
77. Yaffe K, Vittinghoff E, Fletcher MJ, et al. Early adult to midlife cardiovascular risk factors and cognitive function. *Circulation* 2014;129:1560-7.
78. Reis JP, Loria CM, Launer LJ, et al. Cardiovascular health through young adulthood and cognitive functioning in midlife. *Ann Neurol* 2013;73:170-9.
79. Yaffe K, Bahorik AL, Hoang TD, et al. Cardiovascular risk factors and accelerated cognitive decline in midlife. *Neurology* 2020;95:e839-46.
80. Launer LJ, Lewis CE, Schreiner PJ, et al. Vascular factors and multiple measures of early brain health. *PLoS One* 2015;10:e0122138.
81. Auer R, Vittinghoff E, Yaffe K, et al. Association between lifetime marijuana use and cognitive function in middle age. *JAMA Intern Med* 2016;176:352-61.
82. Reis JP, Auer R, Bancks MP, et al. Cumulative lifetime marijuana use and incident cardiovascular disease in middle age. *Am J Public Health* 2017;107:601-6.
83. Murthy VL, Xia R, Baldrige AS, et al. Polygenic risk, fitness, and obesity. *JAMA Cardiol* 2020;5:40-8.
84. Natarajan P, Young R, Stitzel NO, et al. Polygenic risk score identifies subgroup with higher burden of atherosclerosis and greater relative benefit from statin therapy in the primary prevention setting. *Circulation* 2017;135:2091-101.
85. Kim K, Joyce B, Zheng Y, et al. DNA methylation GrimAge and incident diabetes. *Diabetes* 2021 Apr 5 [E-pub ahead of print].
86. Nannini DR, Joyce BT, Zheng Y, et al. Epigenetic age acceleration and metabolic syndrome. *Clin Epigenetics* 2019;11:160.

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