RESEARCH ARTICLE

Premature Cardiovascular Disease and Brain Health in Midlife

The CARDIA Study

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Abstract

Background and Objectives

To understand the role of premature (defined as ≤ 60 years) cardiovascular disease (CVD) in brain health earlier in life, we examined the associations of premature CVD with midlife cognition and white matter health.

Methods

We studied a prospective cohort in the Coronary Artery Risk Development in Young Adults study, who were 18–30 years at baseline (1985–1986) and followed up to 30 years when 5 cognitive tests measuring different domains were administered. A subset (656 participants) had brain MRI measures of white matter hyperintensity (WMH) and white matter integrity. A premature CVD event was adjudicated based on medical records of coronary heart disease, stroke/TIA, congestive heart failure, carotid artery disease, and peripheral artery disease. We conducted linear regression to determine the associations of nonfatal premature CVD with cognitive performance (z-standardized), cognitive decline, and MRI measures.

Results

Among 3,146 participants, the mean age (57% women and 48% Black) was 55.1 ± 3.6 years, with 5% (n = 147) having premature CVD. Adjusting for demographics, education, literacy, income, depressive symptoms, physical activity, diet, and *APOE*, premature CVD was associated with lower cognition in 4 of 5 domains: global cognition (−0.22, 95% CI −0.37 to −0.08), verbal memory (−0.28, 95% CI −0.44 to −0.12), processing speed (−0.46, 95% CI −0.62 to −0.31), and executive function (−0.38, 95% CI −0.55 to −0.22). Premature CVD was associated with greater WMH (total, temporal, and parietal lobes) and higher white matter mean diffusivity (total and temporal lobes) after adjustment for covariates. These associations remained significant after adjusting for cardiovascular risk factors (CVRFs) and excluding those with stroke/TIA. Premature CVD was also associated with accelerated cognitive decline over 5 years (adjusted OR 3.07, 95% CI 1.65–5.71).

Discussion

Premature CVD is associated with worse midlife cognition and white matter health, which is not entirely driven by stroke/TIA and even independent of CVRFs. Preventing CVD in early adulthood may delay the onset of cognitive decline and promote brain health over the life course.

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Glossary

APDQS = A Priori Diet Quality Score; **BMI** = body mass index; **CARDIA** = coronary artery risk development in young adults; **CHD** = coronary heart disease; **CHF** = congestive heart failure; **CVD** = cardiovascular disease; **CVRF** = cardiovascular risk factor; **DSST** = Digit Symbol Substitution Test; **DTI** = diffusion tensor imaging; **HDL** = high-density lipoprotein; **ICV** = intracranial volume; **IPW** = inverse probability weighting; **PAD** = peripheral artery disease; **RAVLT** = Rey Auditory Verbal Learning Test; **WMH** = white matter hyperintensity.

Cardiovascular disease (CVD) is the leading cause of death in the United States.[1] In contrast to the declining CVD incidence and mortality among older adults over the last 2 decades, the incidence and mortality among young and middle-aged adults have been steady or increasing.[1,2] Indeed, about half of CVD events among men and one-third among women occur during young and middle adulthood.[3] Midlife is also a critical time when cognitive function in several domains may begin to decline.[4] Understanding the effect of premature (≤60 years) CVD on midlife cognition and brain health could inform risk stratification, as well as the optimal timing and design of more targeted interventions for cognitive aging.

Prior studies have shown that individual CVDs, such as coronary heart disease, stroke and TIA, and heart failure, are associated with an increased risk of cognitive impairment and dementia,[5-7] although mixed results have been reported.[8-10] Most previous work on CVDs and cognition has focused primarily on older adults. The pathophysiologic process of dementia takes place over decades when subtle brain changes are present that may not manifest clinically,[11] and yet few studies have investigated the impact of premature CVD events on cognition and brain health earlier in the life course.

Neuroimaging studies have shown that individuals with a higher risk of CVD or those with subclinical CVD have structural and functional brain alterations, including decreased brain volumes, greater white matter hyperintensity (WMH) burden, and lower white matter integrity.[12-14] This suggests that CVD may contribute to worse brain health and cognition through both vascular and neurodegenerative pathologies.[15-18] Long-standing CVD may lead to increasingly worse cognitive function.[19] However, it is unclear when this process begins and if midlife is an important time for divergent cognitive and brain health trajectories.

As part of the ongoing Coronary Artery Risk Development in Young Adults (CARDIA) Study, we sought to investigate the associations of long-term exposure to premature CVD with cognitive function and brain MRI measures in middle-aged adults. We hypothesized that having a history of nonfatal premature CVD in young and middle adulthood would be associated with worse cognitive function, accelerated cognitive decline, and worse white matter health in midlife.

Methods

Study Population

CARDIA is a multicenter prospective cohort study that enrolled 5,115 Black and White men and women, aged 18–30 years, between 1985 and 1986 (baseline) from population-based samples of 4 US cities (Birmingham, AL; Chicago, IL; Minneapolis, MN; and Oakland, CA) and has completed 8 follow-up examinations every 2–5 years with high retention rates. The participant composition of each site at baseline was approximately balanced by sex, race (White and Black), and education (high school or less and more than high school). Detailed methods of the CARDIA study have been published previously.[20]

For this study, we analyzed the 3,146 participants who completed the year 30 visit with an assessment on at least 1 of 5 cognitive tests. Compared with participants in the analytical cohort, those who were alive but did not participate in the year 30 examination (N = 1,372) or were missing all cognitive tests (N = 212) were younger, more likely to be male, Black, less educated, current smoker, obese, and have dyslipidemia at baseline ($p < 0.05$ for all), but they did not differ on the baseline prevalence of hypertension, diabetes, physical activity, and *APOE ε4*.

Standard Protocol Approvals, Registrations, and Patient Consents

At each visit, participants provided written informed consent, and study protocols were reviewed by institutional review boards from each study site, the CARDIA Coordinating Center at the University of Alabama at Birmingham, and the University of California, San Francisco.

Premature Cardiovascular Disease Events

Premature CVD events, defined as those occurring before or at age 60 years,[21,22] including coronary heart disease [CHD] (myocardial infarction, acute coronary syndrome without evidence of myocardial necrosis, and coronary artery revascularization), stroke and TIA, congestive heart failure (CHF), carotid artery disease, and peripheral artery disease (PAD), were ascertained through scheduled CARDIA examinations and annual contacts. During these assessments, participants or their proxies were asked about interim hospital admissions and outpatient procedures. Medical records of hospitalization and outpatient revascularization procedures were collected by trained research staff and reviewed independently by 2 physicians on the CARDIA Endpoints

Surveillance and Adjudication Subcommittee applying standard outcome definitions to classify each CVD event.[23] If disagreement occurred between the primary reviewers, the case was further reviewed by the full committee.

Cognitive Function Assessment

At year 30, cognition was assessed through a battery of 5 cognitive tests administered by CARDIA technicians who underwent centralized training and certification. The Montreal Cognitive Assessment assesses global cognitive function (range 0–30). The Rey Auditory Verbal Learning Test (RAVLT) assesses verbal learning and memory with the delayed score (range 0–15) for the number of words correctly recalled after 10 minutes.[24] The Digit Symbol Substitution Test (DSST) assesses processing speed, executive function, and working memory (range 0–133).[25] The Stroop Test assesses executive function[26]; we used the inverse of the Stroop Interference score (range −160 to 160) so that higher scores indicate better performance. Verbal fluency was calculated using an average score of the Letter and Category Fluency tests.[27] All scores were z-standardized using the sample mean and SD, and higher scores indicate better cognitive performance. Three cognitive tests (DSST, RAVLT, and Stroop Interference) were also available at year 25. We additionally estimated the 5-year change in the composite cognitive z scores based on the 3 tests and defined accelerated cognitive decline as a race-specific decline ≥1.5 SD from the mean change on the composite cognitive score.[28]

Brain MRI Measures

At year 30, a subset (N = 663) of the CARDIA cohort had brain MRIs.[14] Briefly, brain MRI was acquired on 3-T MR scanners at 3 of the 4 CARDIA field centers (Oakland and Minneapolis: Siemens 3T Tim Trio/VB 15 platform; Birmingham: Philips 3T Achieva/2.6.3.6 platform), and the data were transferred to the MRI reading center at the University of Pennsylvania with image processing, quality control checks, and automated brain tissue volume computations as described previously.[14] For the current study, we analyzed WMH volumes and diffusion tensor imaging (DTI) measures of fractional anisotropy and mean diffusivity. White matter was classified into regions of interest according to the Jakob atlas and further into normal and abnormal tissue.[14] The volume of WMH was estimated from the sagittal 3D fluid-attenuated inversion recovery (FLAIR), T1, and T2 sequences that contain tissue damaged because of ischemia, demyelination or inflammation, and penumbra surrounding brain infarcts. Due to skewness, WMH was modeled as a natural logarithm of WMH plus the smallest observed value. Fractional anisotropy and mean diffusivity are sensitive measures of white-matter integrity. Increases in mean diffusivity and decreases in fractional anisotropy are often observed in the degeneration of microstructural barrier when the integrity of axons and myelin is disrupted.[29] Total intracranial volume (ICV) was estimated from the sagittal 3D T1 sequence as a measure of head size. We examined the WMH and white matter integrity overall and by lobe (frontal, temporal, parietal, and occipital lobes), such that the mean values overall and within specific lobes were averaged across the left and right hemispheres.

Covariates

Demographic characteristics (age, sex, race, and marital status), education, and alcohol use were obtained from self-report and interviewer-administered questionnaires at baseline. We considered time-varying physical activity, depressive symptoms, and diet patterns using the average scores over 30 years of follow-up. Physical activity was assessed by an average of the CARDIA Physical Activity questionnaire (collected at baseline and every follow-up examination) and dichotomized as achieving recommended levels of physical activity (≥300 exercise units).[30] Depressive symptoms were assessed using an average score of the Center for Epidemiologic Studies Depression scale measured every 5 years. We assessed long-term dietary patterns using an average of the CARDIA A Priori Diet Quality Scores (APDQS) collected at baseline and years 7 and 20. The presence of the *APOE ε4* allele was determined using standard techniques.[31] We also considered literacy measured by the Rapid Estimate of Adult Literacy in Medicine–Short Form, household income, and key cardiovascular risk factors (CVRFs) at year 30, including hypertension, dyslipidemia, diabetes, obesity, and current smoking. Hypertension was defined as systolic blood pressure ≥140 mm Hg, diastolic blood pressure ≥90 mm Hg, or taking antihypertensive medication. We defined dyslipidemia as triglycerides ≥150 mg/dL or high-density lipoprotein (HDL) cholesterol <35 mg/dL for men and HDL cholesterol <45 mg/dL for women. Diabetes was defined as fasting glucose level ≥126 mg/dL or taking antidiabetic medication. We calculated the body mass index (BMI) using measured height in meters and weight in kilograms and defined obesity as a BMI ≥30 kg/m^2. Current cigarette smoking was defined as self-reported smoking at least 5 cigarettes per week, almost every week.

Statistical Analysis

Descriptive statistics of participant characteristics were compared between those with and without a premature CVD event using χ^2 and Mann-Whitney *U* tests. Linearity between continuous covariates (age, education, and APDQS) and cognitive function or brain MRI measures was examined, and suitable transformations were explored. Continuous covariates were modeled linearly as generalized additive models with smoothing splines did not provide a better fit. We assessed the associations of premature CVD with cognitive function and brain MRI parameters using linear regression models. We conducted stratified analysis and examined possible effect modification of premature CVD by sex, race, and *APOE ε4* in fully adjusted models. In sensitivity analyses, we estimated the association between premature CVD and cognition by further adjusting for CVRFs or excluding participants with stroke/TIA. To eliminate potential bias due to differential study attrition and conduct the analysis in a sample

representative of all CARDIA participants, we used the inverse probability weighting (IPW) approach to up weight those participants in the analytic cohort who were similar to those excluded (eMethods and eTable 1, links.lww.com/WNL/C607).[32] Results from the complete case analysis were compared with results from the weighted models. Among participants with premature CVD, we also examined the effect of the age at the first event, as well as CVD duration, on cognition at year 30 in linear regression models. To examine the age at the first event, we dichotomized CVD events based on the age at the first event (occurred <50 vs ≥50 years). We examined the duration of CVD by fitting a single linear term for the CVD duration (<5, 5–10, and >10 years since the first event) and tested for a trend. In addition, we examined the association between premature CVD and accelerated cognitive decline over 5 years using logistic regression. Statistical analyses were conducted with SAS 9.4 and R 4.0.2.

Data Availability

Anonymized data are available from the CARDIA Coordinating Center (cardia.dopm.uab.edu/contact-cardia). A description of the National Heart, Lung, and Blood Institute policies governing the data and describing access to the data can be found online (cardia.dopm.uab.edu/study-information/nhlbi-data-repository-data).

Results

Among the 3,146 participants (57% female and 48% Black) examined at year 30 with cognitive assessments, the mean age was 55.1 ± 3.6 years and mean education was 15.2 ± 2.6 years. Over the 30-year follow-up, 147 (4.7%) participants developed one or more premature CVD events, including CHD (n = 71), stroke (n = 55), TIA (n = 13), CHF (n = 37), carotid artery disease (n = 1), and PAD (n = 5). The mean age at the first CVD event was 48.4 ± 6.4 years (eFigure 1, links.lww.com/WNL/C607). Compared with participants without premature CVD, those who had premature CVD events were older and more likely to be male, Black, and less educated; less likely to have adequate literacy (≥9th grade), household income ≥$50,000, and to be married or live with a partner; and more likely to have depressive symptoms, CVRFs (hypertension, dyslipidemia, diabetes, obesity, and current smoking), lower levels of physical activity, and lower diet quality (Table 1).

Cognitive Function and Accelerated Decline in Midlife

The mean follow-up time between the first CVD event and cognitive assessment at year 30 was 7.7 ± 6.1 years. Participants with premature CVD had significantly lower cognitive

Table 1 Characteristics of the 3,146 CARDIA Participants by Premature CVD Status at Year 30, 2015–2016

	Without premature CVD (N = 2,999)	With premature CVD (N = 147)	*p* Value[a]
Age, y, median (IQR)	56 (52–58)	57 (54–59)	0.002
Female, n (%)	1,735 (57.9)	59 (40.1)	<0.001
Black, n (%)	1,404 (46.8)	96 (65.3)	<0.001
Education, y, median (IQR)	16 (13–17)	14 (12–16)	0.96
Literacy ≥9th grade, n (%)	2,381 (80)	93 (65.5)	<0.001
Household income ≥50K, n (%)	2,021 (68.4)	59 (41.5)	<0.001
Married or live with a partner, n (%)	1,778 (60.3)	67 (46.9)	0.001
Depressive symptoms, n (%), 30-y average	425 (14.2)	34 (23.3)	0.002
***APOE ε4*, n (%)**	783 (30)	43 (36.1)	0.16
Physical activity, ≥300 exercise units, n (%), 30-y average	1,614 (53.8)	64 (43.5)	0.015
CVRFs			
Hypertension, n (%)	1,112 (37.1)	117 (79.6)	<0.001
Diabetes, n (%)	425 (14.3)	51 (35.4)	<0.001
Dyslipidemia, n (%)	771 (25.9)	50 (35.5)	0.012
Current smoking, n (%)	402 (13.5)	33 (23.4)	0.001
Obesity, n (%)	1,365 (45.7)	80 (54.8)	0.031
Alcohol, drinks/wk, median (IQR)	3 (0–8)	3 (0–7)	0.96
Diet quality, median (IQR), 30-y average	62.3 (54.5–71)	59.3 (51–67)	<0.001

Abbreviations: CVD = cardiovascular disease; CVRFs = cardiovascular risk factors; IQR = interquartile range
[a] χ^2 test for categorical variable and Mann-Whitney *U* tests for continuous variables.

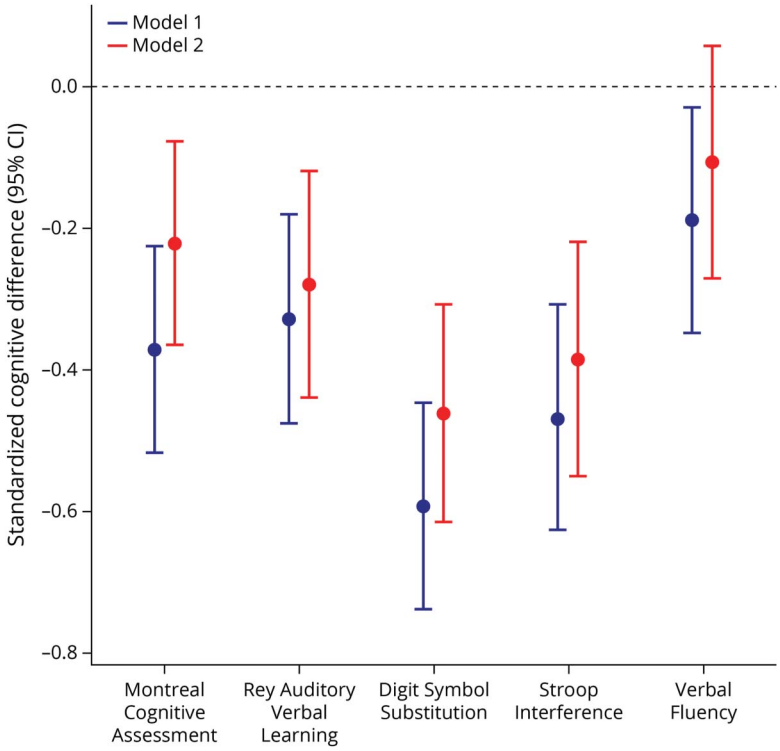
Table 2 Mean Unadjusted Cognitive Function (SD) Among the 3,146 Middle-aged CARDIA Participants at Year 30 by Premature CVD Status

	Without premature CVD (N = 2,999)	With premature CVD (N = 147)	*p* Value[a]
Montreal Cognitive Assessment (N = 3,121)	23.9 (3.8)	21.4 (5.2)	<0.001
Rey Auditory Verbal Learning (N = 3,123)	8.5 (3.4)	6.4 (3.4)	<0.001
Digit Symbol Substitution (N = 3,107)	68.2 (16.5)	52.9 (18.4)	<0.001
Stroop Interference (N = 3,140)	22.6 (11.3)	30.5 (17.7)	<0.001
Verbal Fluency (N = 3,120)	30.9 (8.3)	27.7 (9.9)	<0.001

Abbreviation: CVD = cardiovascular disease.
[a] Mann-Whitney *U* tests.

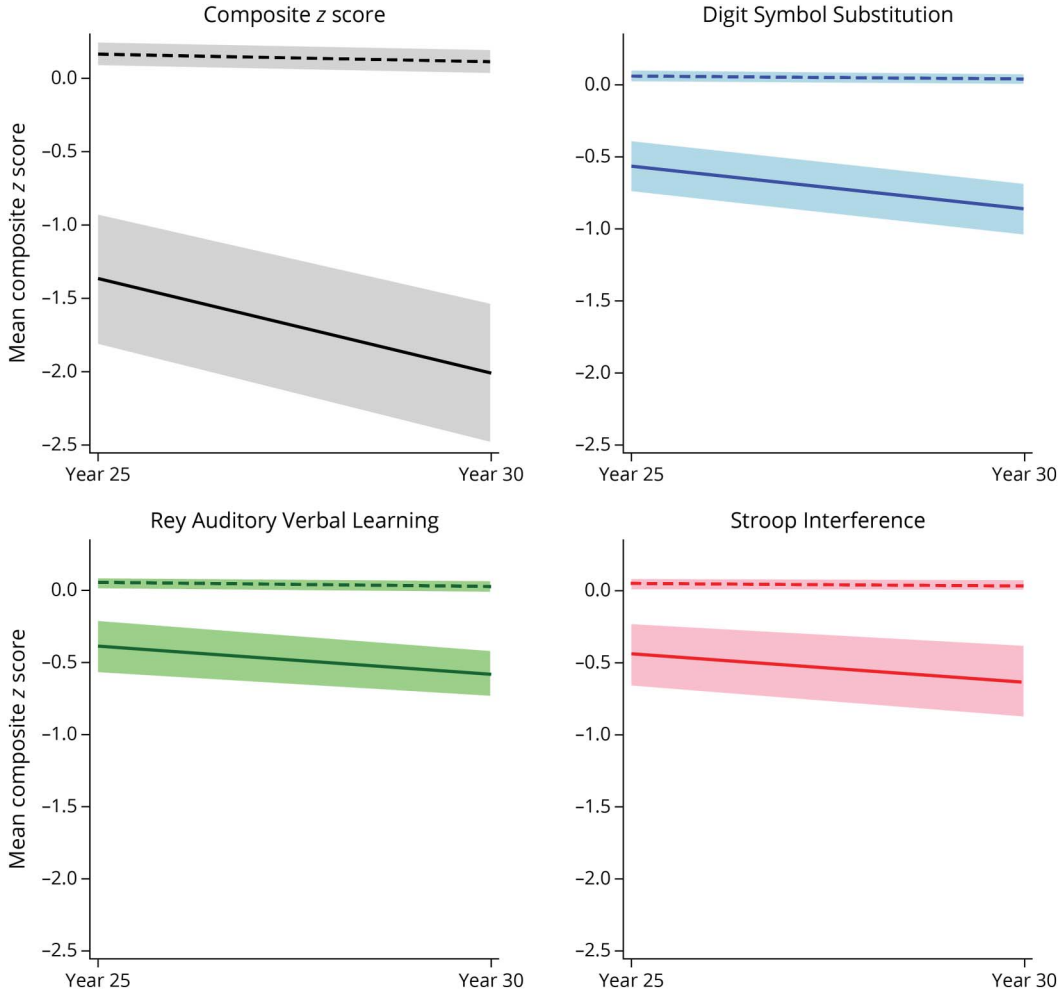
performance compared with those without premature CVD on all tests (Table 2). After adjusting for demographics, education, literacy, household income, depressive symptoms, physical activity, diet, and *APOE*, having premature CVD (vs without premature CVD) remained significantly associated with worse cognitive function on most tests, except for verbal fluency (Figure 1): global cognition (−0.22, 95% CI −0.37 to −0.08), verbal memory (−0.28, 95% CI −0.44 to −0.12), processing speed (−0.46, 95% CI −0.62 to −0.31), and executive function (−0.38, 95% CI −0.55 to −0.22). The magnitude of the associations was slightly attenuated but remained significant after further adjustment for CVRFs (eTable 2, links.lww.com/WNL/C607). Using weights derived from the IPW models to account for differential attrition among participants with and without premature CVD did not change the findings (eTable 3 and eTable 4, links.lww.com/WNL/C607). In sensitivity analyses excluding participants with stroke/TIA, premature CVD remained significantly associated with processing speed (−0.24, 95% CI −0.45 to −0.04) and executive function (−0.22, 95% CI −0.43 to −0.01) even after adjusting for CVRFs (eTable 5, links.lww.com/WNL/C607). There was a significant interaction between premature CVD and sex for verbal fluency (p = 0.019), whereby premature CVD was significantly associated with lower verbal

Figure 1 Multivariable-Adjusted Association of Premature Cardiovascular Disease (CVD) and Cognitive Performance in Midlife From Unweighted Linear Regression Models



Standardized cognitive differences (95% CI) between participants with and without premature CVD for the 5 tests. Model 1 adjusted for demographics (age, sex, race, and marital status); model 2 additionally adjusted for depressive symptoms, physical activity, diet, education, literacy, household income, and *APOE*.

Figure 2 Cognitive Performance From Years 25 to 30 in Middle-aged Participants With and Without Premature Cardiovascular Disease (CVD)



Dashed lines showed the mean cognitive performance from years 25 to 30 of participants without premature CVD; solid lines showed the mean cognitive performance from years 25 to 30 of participants with premature CVD; 95% CIs are shown as the shaded area.

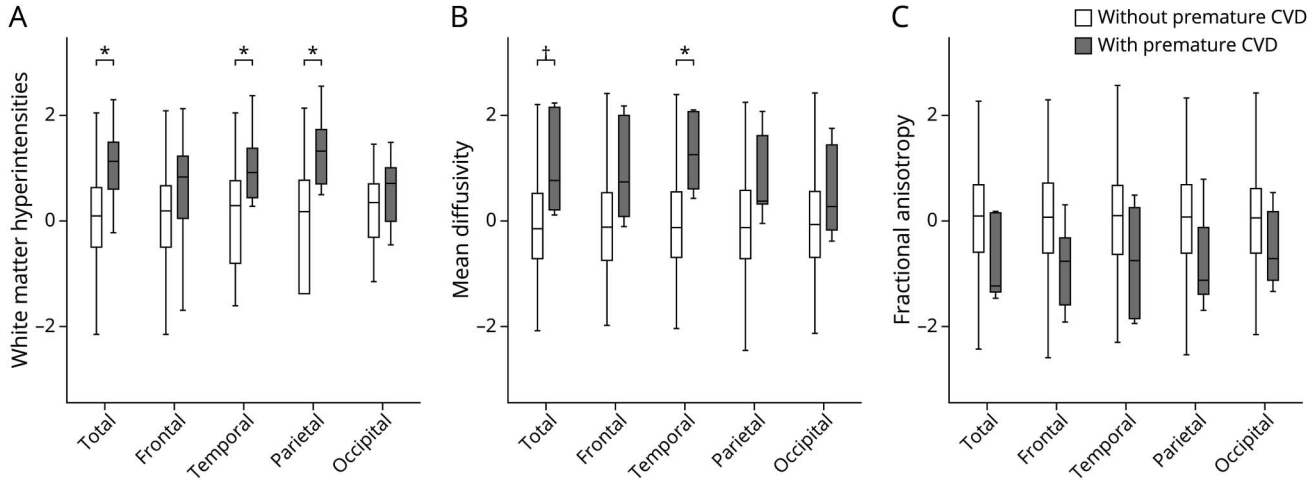
fluency in women (−0.35, 95% CI −0.62 to −0.08) but not in men (0.13, 95% CI −0.10 to 0.37). Premature CVD also has significant interaction with race for executive function (p = 0.029), whereby the associations were stronger in Black (−0.56, 95% CI −0.83 to −0.29) than in White (−0.20, 95% CI −0.41 to 0.02) middle-aged adults. We did not find evidence of an effect modification by *APOE ε4* (all $p > 0.05$). Neither the duration of CVD nor the age at CVD onset was significantly associated with cognition at year 30 (eTables 6 and 7, links.lww.com/WNL/C607).

Among the 2,722 participants with cognitive assessment both at years 25 and 30, 143 (5%) participants met the criteria for accelerated cognitive decline. Thirteen and 5 percent of the participants with and without premature CVD experienced accelerated cognitive decline, respectively. Compared with participants without premature CVD, those with premature CVD had greater cognitive decline over 5 years (Figure 2) in the composite score, as well as in processing speed, executive function, and verbal memory. After adjusting for demographics, education, literacy, income, depressive symptoms, physical activity, diet, and *APOE*, participants with premature CVD had significantly high odds of experiencing accelerated cognitive decline (OR 3.07, 95% CI 1.65–5.71). The association remained significant after additional adjustment for CVRFs (OR 2.66, 95% CI 1.38–5.12). Accounting for differential attrition using IPW weight slightly strengthened the association (OR 2.88, 95% CI 1.56–5.33). The association was in the same direction but nonsignificant after excluding participants who had their first CVD event between years 25 and 30 (OR 1.44, 95% CI 0.53–3.91).

Brain MRI Measures

Among the subset of 663 CARDIA participants who underwent brain MRI examination at year 30, 656 (99%) and 481 (73%) participants had measures on WMH and DTI, respectively. Having premature CVD was significantly associated with white matter alterations, including greater

Figure 3 Brain MRI Measures (Z-Standardized) in Middle-aged Participants With and Without Premature Cardiovascular Disease (CVD)



A, White matter hyperintensities. B, Diffusion tensor imaging (DTI) mean diffusivity. C, DTI fractional anisotropy. *The difference was statistically significant ($p < 0.05$) in a model adjusted for demographics, total ICV, depressive symptoms, physical activity, diet, education, literacy, income, *APOE*, and cardiovascular risk factors. †The difference was statistically significant ($p < 0.05$) in a model adjusted for demographics, total ICV, depressive symptoms, physical activity, diet, education, literacy, income, and *APOE* but was no longer significant with additional adjustment for cardiovascular risk factors.

volumes of WMH (total, temporal, and parietal lobes) and higher mean diffusivity (total and temporal lobes) in unadjusted models and after adjustment for demographics, education, literacy, income, depressive symptoms, physical activity, diet, *APOE*, and ICV. These associations remained statistically significant with further adjustment for CVRFs, except for total mean diffusivity (Figure 3). Using weights from IPW to adjust for differential attrition due to nonparticipation led to little change in these associations. In addition, in multivariable-adjusted models, these brain MRI parameters (total, temporal, and parietal lobe WMH volumes and temporal mean diffusivity) were independently associated with worse cognitive function in several domains, including global cognition, verbal learning and memory, processing speed, and executive function (eTable 8, links.lww.com/WNL/C607).

Discussion

In this biracial cohort of middle-aged adults, we found that having premature CVD was associated with worse cognitive performance on most domains and accelerated cognitive decline over 5 years. The association between premature CVD and cognitive function in some specific domains may differ by sex and race. In addition, having premature CVD was associated with a greater burden of WMH and alterations of white matter integrity overall and in several brain regions. These associations were not entirely driven by stroke/TIA and were independent of shared risk factors for CVD, cognitive function, and brain health, including demographics, education, literacy, income, depressive symptoms, physical activity, diet, and *APOE*, as well as for CVRFs.

Previous studies on the contribution of CVD to cognition have mostly been conducted among the elderly and focused more on cerebrovascular disease as a predictor. Indeed, results from several prospective studies of aging have demonstrated the important role of individual CVD diagnoses, including CHD,[5,33] heart failure,[9,34] and subclinical cardiac dysfunction,[35,36] for late-life cognition. Among young and middle-aged adults, the effect of cerebrovascular disease, including stroke and TIA, on cognitive outcomes is also well known.[37,38] However, very little is known about other premature CVD and midlife cognition.

Our study focused on premature CVD, cognition, and structural and functional brain MRI parameters in middle-aged adults. Our results demonstrated the early divergences of cognitive function and brain health among those with and without CVD in their early adulthood. These differences were seen in almost all cognitive domains, multiple structural and functional brain MRI measures, and were independent of other shared risk factors, including CVRFs. With the emergence of a greater CVD burden among young and middle-aged adults, premature CVD events that occur earlier in life may have an important effect on cognitive aging and brain health trajectories starting in midlife. Our finding on the significant association between premature CVD and verbal fluency in women but not men aligned with recent findings.[39] Furthermore, we showed that brain MRI alterations that have been linked to CVD in the elderly were also seen in middle-aged adults.[7,40] Our findings on the associations of greater WMH and altered white matter integrity with lower executive function and processing speed are consistent with previous studies in smaller or older populations.[41,42] These MRI findings could potentially explain some of the differences in cognitive performance associated with premature CVD that we observed.

There are several possible mechanisms by which CVD contributes to lower cognitive function. Hypoperfusion and fluctuation in cerebral perfusion due to stroke or reduced cardiac output in CVD may lead to altered brain metabolism, changes in microvascular structure and permeability, and vascular remodeling, which can, in turn, promote small vessel disease.[15-17,43] Inflammation and oxidative stress due to CVD and underlying CVRF exposures may lead to the destruction of the blood-brain barrier, neuroinflammation, and β-amyloid deposition.[18,44] Our findings support that premature CVD may contribute to worse midlife cognition and brain health through vascular pathways. These findings may not completely attributable to the direct effect of stroke/TIA. The mechanism of the differential association with verbal fluency by sex is unclear but may be related to hormones and menopause.[39,45] The potential reasons for stronger associations with processing speed and executive function in Black compared with White adults are also unclear but may include differential social and structural factors that contribute to the care and hospitalization of CVD, which invites future studies. The attenuated associations with cognition and brain MRI parameters after adjusting for CVRFs suggest that premature CVD may indirectly contribute to these pathways through association with greater CVRF burden. However, it also indicates that our results are not entirely driven by shared mechanisms of CVRF and clinical CVD. Other mechanisms may be involved, including those related to CVD treatment, hospitalization, diagnostic procedures, or shared genetic risk between CVD and neurodegeneration unrelated to CVRFs.[46]

Although the prevalence of premature CVD was low (<5%), we were able to detect a small to medium association with midlife cognition after adjusting for various confounders. Although the 5-year cognitive change among CARDIA participants was small and may not yet be clinically significant at midlife, it is possible that such change may be the start of an early diverging trajectory that could lead to late-life cognitive impairment. Our findings on sex and race differences in the associations between premature CVD and specific cognitive function domains invite more studies in diverse populations. More research is needed to understand the potential benefit of expanding the current CVD prevention guidelines for intervention and identification to earlier stages of life than midlife when premature CVD may already contribute to pathways leading to dementia risk.[47] However, some studies showed that drug treatment and surgical intervention of CVD might also benefit cognitive function,[48-50] suggesting that the risk of cognitive decline in middle-aged adults with premature CVD may be modifiable with early prevention and intervention. Further studies on the longitudinal effects of premature CVD that take both disease duration and temporality into consideration might be necessary for optimizing the timing of intervention and understanding the effect on cognitive trajectories to minimize the lifetime risk of cognitive decline.

This study is one of the largest to examine the association of premature CVD with cognition and brain health in midlife. CARDIA provides a unique opportunity to accurately capture adjudicated premature CVD events with 30 years of longitudinal follow-up and a high retention rate. We examined neuroimaging parameters to explore potential mechanisms linking premature CVD to cognitive function, which complements our primary findings. To limit the potential for selection bias due to differential mortality and nonparticipation by premature CVD history, we used the IPW statistical approach and observed little difference between the weighted and unweighted results, suggesting that selection bias may not be a big factor. Our study also has some limitations. We do not have baseline cognitive and MRI assessment in CARDIA, which limits causal inferences on the effect of premature CVD, although baseline cognitive impairment and brain alterations were unlikely given participants' young age. Our primary results are supported by an association of premature CVD and 5-year accelerated cognitive decline as well. Although we could not examine the acute effect of premature CVD by comparing the cognitive change trajectory before and after the CVD events due to the lack of more frequent cognitive testing with short intervals, we conceptualized the association as being driven by both acute and chronic mechanisms that occur after premature CVD. With the small number of premature CVD events, we were underpowered to detect a potential differential association by CVD duration and age at onset, although longer-standing CVD may have a greater effect.[19] Future investigations by individual CVD etiologies and comparisons by treatment groups in larger samples are warranted. Confounding may also be a concern. Although we adjusted for several socioeconomic factors, including education, literacy, and household income, unmeasured confounding from other social, structural, and environmental factors may still substantially and nonconservatively bias the association that we observed between premature CVD and cognitive performance at year 30. Our findings may not be generalizable to other racial/ethnic groups as our cohort only included Black and White adults.

In conclusion, premature CVD is associated with worse cognitive performance, accelerated cognitive decline, and white matter health in midlife. Early adulthood is a critical time for CVD prevention and intervention with the emergence of premature CVD. Thus, CVD prevention efforts in young adulthood may delay the onset of cognitive decline and promote brain health over a lifetime.

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Disclosure

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