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Research Article

Impact of Cardiovascular Risk Factors in Adolescence, Young Adulthood, and Midlife on Late-Life Cognition: Study of Healthy Aging in African Americans

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Abstract

Background: Midlife cardiovascular risk factors (CVRFs) increase risk of dementia. Black Americans experience an elevated prevalence of CVRFs and dementia. However, little is known of how CVRFs prior to midlife affect late-life cognition. We examined CVRFs in adolescence, young adulthood, and midlife with late-life cognition in the Study of Healthy Aging in African Americans (STAR).

Method: STAR assesses cognitive aging among 764 Black Americans aged ≥50 (mean age = 69; *SD* = 9; range = 53–95). Participants' body mass index, blood pressure, glucose, and total cholesterol were collected during Multiphasic Health Checkups (MHC; 1964–1985). At STAR baseline (2018–2019), executive function, verbal episodic memory, and semantic memory were measured using the Spanish and English Neuropsychological Assessment Scales. Linear regression models examined associations between CVRFs and cognition adjusting for demographics and years since MHC.

Results: At MHC, 36% of participants had 1 CVRF and 26% had ≥2. Twenty-two percent of participants were adolescents (age 12–20), 62% young adults (age 21–34), and 16% midlife adults (age 35–56). Overweight/obesity was not associated with cognition. Hypertension was associated with worse executive function (β [95% CI]: −0.14 [−0.28, −0.0003]) and verbal episodic memory (β [95% CI]: −0.22 [−0.37, −0.07]) compared to normotension. Diabetes was associated with worse executive function (β [95% CI]: −0.43 [−0.83, −0.03]). Having ≥2 CVRFs (vs 0) was associated with worse executive function (β [95% CI]: −0.19 [−0.34, −0.03]) and verbal episodic memory (β [95% CI]: −0.25 [−0.41, −0.08]). Adolescents with hypertension had lower late-life executive function compared to normotensive adolescents (β [95% CI]: −0.39 [−0.67, −0.11]). Young adulthood hypertension (β [95% CI]: −0.29 [−0.49, −0.09]) and midlife hyperlipidemia (β [95% CI]: −0.386 [−0.70, −0.02]) were associated with lower verbal episodic memory.

Conclusions: Among Black Americans, life-course CVRFs were associated with poorer executive function and verbal episodic memory emphasizing the importance of cardiovascular health on the aging brain.

Keywords: Black Americans, Cardiovascular disease, Cognitive aging, Dementia, Life course

Black Americans experience a disproportionate burden of cardiovascular risk factors (CVRFs) including overweight/obesity, hypertension, diabetes, and hyperlipidemia (1,2). The National Health and Nutrition Examination Survey (NHANES) estimated age-adjusted prevalence of 48% for obesity, 42% for hypertension, 20% for diabetes, and 10% for high total cholesterol

among Black Americans aged 20 and older (2). However, due to the long and ongoing history of racism against Black Americans, they are also more likely to experience discrimination and low socioeconomic status across the life course (3). These psychosocial factors are associated with inflammatory biomarkers that, over time, have deleterious effects on health in a process called weathering (4). Weathering is associated with overweight/obesity, hypertension, hyperlipidemia, and diabetes (4) and may make Black Americans more vulnerable to the chronic conditions associated with CVRFs.

CVRFs have been linked to a number of poor health outcomes including cardiovascular disease (CVD), stroke, and CVD mortality (5–10) and are increasingly recognized as risk factors for poor brain health including lower cognitive function, cognitive decline, and dementia (11–17). Several studies have noted that Black Americans have worse late-life cognitive function and higher risk of cognitive impairment compared to other racial/ethnic groups (18–20). However, it remains unclear whether high rates of cognitive impairment in this population are driven by the disproportionate burden of CVRFs. The majority of studies linking cardiovascular and brain health have been conducted in predominantly White, middle-aged cohorts (21). Additionally, little is known about the impact of life-course timing of risk factors on cognition, particularly when risk factors develop prior to midlife (22–24). The disparate burden of CVRFs and dementia in Black Americans needs further examination from a life-course perspective.

Using data from the Study of Healthy Aging in African Americans (STAR), our aim was to characterize the relationship between CVRFs measured in adolescence, young adulthood, and midlife with late-life cognition. We hypothesized that prevalence of CVRFs would be highest in midlife, followed by young adulthood and adolescence. Further, we hypothesized that CVRFs during adolescence, young adulthood, and midlife would be associated with worse late-life cognition and that having multiple CVRFs would have a cumulative, negative effect on cognitive function.

Method

STAR includes community-dwelling older Black adults living in the San Francisco Bay area of California, primarily the cities of Oakland and Richmond. The objective of STAR is to evaluate how life-course vascular and sociocultural factors influence the trajectory of cognitive aging and burden of cognitive impairment among Black Americans. Individuals eligible for study participation were long-term members of an integrated health care delivery system, Kaiser Permanente Northern California (KPNC). Participants had to identify as Black American, be aged 50 years or older by January 1, 2018, and have previously participated in Kaiser Permanente Multiphasic Health Checkup (MHC) exams between 1964 and 1985. In order to recruit approximately equal proportions of participants aged 50–64 and 65 and older, stratified random sampling by age and educational attainment was used (age range: 53–95 years). Individuals were excluded from participation if they had an electronic medical record diagnosis of dementia or other neurodegenerative diseases (eg, frontotemporal dementia, Lewy body disease, Parkinson's disease with dementia) or health conditions that would hinder participation in study interviews (eg, hospice activity in the last year, history of end-stage renal disease or dialysis in the last year, history of severe chronic obstructive pulmonary disease in the last 6 months, or congestive heart failure hospitalizations in the last 6 months). This study was conducted with IRB approval (#1121043-6), and all participants provided written, informed consent.

MHC exams were conducted as part of routine care at KPNC and administered in 5 waves from 1964 to 1973, 1973 to 1977, 1977 to 1985, 1985 to 1992, and 1992 to 1996. Participants could attend multiple MHCs; however, only data from each participant's first MHC were available for this analysis. As such, all first visits fell during the first 3 MHC waves (1964–1985). Data collection at MHC included blood and urine samples, physical measures (such as weight and height), and questionnaires about lifestyle, health behaviors, and health history. These data were used to ascertain CVRFs. Participants were put into MHC age groups based on their first MHC exam age: adolescents (age 12–20), young adults (age 21–34), and midlife adults (age 35–56). Risk factors of hypertension (defined as a systolic blood pressure ≥140 mm Hg, diastolic blood pressure ≥90 mm Hg, self-report of high blood pressure diagnosis, or self-report of antihypertensive medication use), overweight/obesity (defined as a body mass index of ≥25 kg/m^2), hyperlipidemia (defined as a fasting serum total cholesterol ≥200 mg/dL), and diabetes (defined as a fasting serum glucose ≥126 mg/dL or a nonfasting serum glucose of ≥ 200, self-report of a diabetes diagnosis, or self-report of insulin medication use) were measured by clinical staff using standard methods and dichotomized (yes/no). We could not differentiate between cases of type 1 and type 2 diabetes, and it is likely we captured cases of both. We also created a categorical risk factor variable based on the number of risk factors each participant had at their first MHC with categories of 0 risk factors, 1 risk factor, or 2+ risk factors.

Cognitive function was measured using the Spanish and English Neuropsychological Assessment Scales (SENAS). The SENAS is a battery of cognitive tests that was developed using item response theory (IRT) methodology and has been extensively validated for measuring and comparing cognitive change across diverse racial/ethnic groups and English and Spanish language administrations (25–32). It has been used as the primary cognitive outcome in many studies examining how late-life cognitive decline in diverse older adults is associated with life-course risk and protective factors (33,34), change in clinical status (27), neuroimaging (35–37), and cognitive reserve (38–42). SENAS administration procedures, development, and psychometric characteristics are described in detail elsewhere (26,29). All STAR participants completed the SENAS in English. An executive function composite score was calculated from IRT-based component measures of category fluency, phonemic (letter) fluency, and working memory (digit-span backward, visual-span backward, list sorting). Verbal episodic memory composite scores were derived using an IRT-based multitrial word-list learning test, and a semantic memory composite score was calculated from IRT-based verbal (object-naming) and nonverbal (picture association) tests. These scores do not have floor or ceiling affects and are normally distributed (26). Cognitive test scores for each domain were *z*-standardized using the mean and standard deviation from the full baseline sample.

Covariates included age at STAR interview (from participants' medical records), years since first MHC exam (estimated by subtracting age at MHC from age at STAR interview), gender (male/female), educational attainment, and parental education. At STAR Wave 1, participants were asked about their gender with the following response options: male, female, other (with space to write in gender identity), or refused. For participants with missing gender data, gender was ascertained from the medical record and likely based on sex. Education was self-reported at Wave 1 as the last or highest level of school completed for credit and then dichotomized

as some college or less education or college graduate or more education for analyses. Parental education was ascertained by asking participants for the highest educational level of their mother, father, or the person that raised them. Responses were dichotomized as less than high school or high school graduate or more. If educational attainment of 2 parents/guardians was provided, parental education was determined by the highest level of education reported between the 2. These covariates were chosen as possible confounders on the relationship between CVRFs and cognition.

Statistical Analysis

Of 764 participants enrolled in STAR, 9 were excluded from the analyses due to missing age at MHC (n = 4), any of the 3 cognitive domain scores (n = 5), or data on all 4 CVRFs (n = 0) for a final analytic sample of 755 participants. We provided means and prevalence of baseline characteristics and CVRFs stratified by MHC age group. We used linear regression to assess the associations of overweight/obesity, hypertension, hyperlipidemia, and diabetes with late-life cognitive domain z-scores. Each risk factor was tested separately and participants without the risk factor of interest were used as the reference. Linear regression was also used to assess the relationship between number of risk factors with domain-specific late-life cognition using those with no CVRF as the reference. Models were run in 3 stages, all of which adjusted for age at STAR Wave 1 interview, years since first MHC, gender, education, and parental education. We first ran overall models, followed by overall models testing for a CVRF × Age group interaction, and models stratified by MHC age group. We explored stratified results regardless of whether interaction terms were significant, because small sample sizes limited our ability to detect statistically significant interactions, but we wanted to examine exploratory trends. The association between diabetes and cognition stratified by age group was not assessed due to the small number of cases. Analyses were conducted using SAS 9.4 (SAS Institute Inc., Cary, NC).

Results

At MHC, 22% (n = 166) of participants were adolescents (age 12–20; mean age = 18, SD = 2), 62% (n = 468) of participants were young adults (age 21–34; mean age = 27, SD = 4), and 16% (n = 121) of participants were midlife adults (age 35–56; mean age = 39, SD = 4). Overall, the mean age of participants at MHC was 27 (SD = 7) years, and the mean age at STAR was 69 (SD = 9) years. An average of 42 (SD = 5) years elapsed between CVRF measurement at MHC and cognitive assessment at STAR. Participants who were categorized as midlife adults at MHC were more likely to be male (37%), more likely to have not graduated college (72%), and more likely to have 2 or more CVRFs at MHC (48%) compared to younger age groups (Table 1; Figure 1). Participants who were adolescents at MHC were the less likely to be male (25%), less likely to have not graduated college (63%), and the least likely to have 2 or more CVRFs at MHC (14%) compared to older age groups. Young adults at MHC fell between adults and adolescents in the proportion that were male (33%), did not graduate college (64%), and had 2 or more CVRFs (24%).

Overall, the prevalence of CVRFs increased with advancing age (Figure 1). Approximately 50% of adolescents at MHC had no CVRFs versus 39% of young adults and 21% of midlife adults, and

Table 1. STAR Participant Baseline Characteristics Stratified by Age Group at Multiphasic Health Checkups

	Overall	Adolescence (age 12–20)	Young Adulthood (age 21–34)	Midlife Adulthood (age 35–56)
Variables	n = 755	n = 166	n = 468	n = 121
MHC[a] (1964–1985)				
Age at MHC, y	26.8 ± 7.3	18.2 ± 1.5	26.6 ± 3.8	39.3 ± 4.1
Overweight/obese[b], % (n)	33.2 (251)	22.9 (38)	32.5 (152)	50.4 (61)
Hypertension[c], % (n)	20.7 (156)	19.6 (32)	19.2 (90)	28.1 (34)
Hyperlipidemia[d], % (n)	36.5 (269)	21.8 (36)	36.4 (165)	56.7 (68)
Diabetes[e], % (n)	2.1 (16)	1.2 (2)	1.5 (7)	5.8 (7)
STAR baseline (2018–2019)				
Age at STAR, y	68.7± 8.8	60.9 ± 4.2	68.5 ± 7.3	80.2 ± 6.0
Time between MHC and STAR, y	41.9 ± 5.4	42.7 ± 4.7	41.9 ± 5.5	41.0 ± 5.7
Male gender, % (n)	31.7 (239)	25.3 (42)	32.5 (152)	37.2 (45)
Participant education				
College graduate, % (n)	34.6 (260)	37.0 (61)	35.6 (166)	27.5 (33)
Some college or vocational/ trade school, % (n)	34.6 (260)	37.0 (61)	35.6 (166)	27.5 (33)
High school graduate or less, % (n)	34.6 (260)	37.0 (61)	35.6 (166)	27.5 (33)
Parental education				
High school graduate or less, % (n)	40.0 (304)	31.0 (52)	43.1 (202)	41.0 (50)

Notes: MHC = Multiphasic Health Checkups; STAR = Study of Healthy Aging in African Americans.

[a]MHC conducted as part of routine care between 1964 and 1985.

[b]Overweight defined as body mass index (BMI) of ≥25 kg/m^2 and <30 kg/m^2 and obese = BMI ≥ 30 kg/m^2.

[c]Hypertension defined as systolic blood pressure ≥130 mm Hg, diastolic blood pressure ≥80 mm Hg, self-report of high blood pressure diagnosis, or self-report of antihypertensive medication use.

[d]Hyperlipidemia defined as serum total cholesterol ≥200 mg/dL.

[e]Diabetes defined as defined as a fasting serum glucose ≥120 mg/dL or a nonfasting serum glucose of ≥200 mg/dL, self-report of diabetes diagnosis, or self-report of insulin medication use.

these differences were statistically significant (χ^2 $p < .0001$). In contrast, only 14% of adolescents had 2 or more CVRFs compared to 24% of young adults and 48% of midlife adults. Similar age trends were seen in individual risk factors. Among adolescents, 23% were overweight or obese versus 33% of young adults and 50% of midlife adults (χ^2 $p < .0001$). Twenty-two percent of adolescents had hyperlipidemia compared to 36% of young adults and 57% of midlife adults (χ^2 $p < .0001$). For hypertension, prevalence was similar for adolescents (20%) and young adults (19%), but higher in midlife adults (28%) (χ^2 $p = .07$). Prevalence of diabetes was low in this sample at 2% overall and was not assessed by MHC age group.

Executive Function

In overall models, hypertension (overall β [95% CI]: −0.14 [−0.28, −0.00003]) and diabetes (overall β [95% CI]: −0.43 [−0.83, −0.03]) were associated with significantly lower executive function *z*-scores (Figure 2) compared to those without hypertension or diabetes. We found no statistically significant associations between overweight/obesity or hyperlipidemia with late-life executive function. Compared to having no CVRF, having 2 or more risk factors was associated with significantly worse executive function (overall β [95% CI]: −0.19 [−0.34, −0.03]), while having 1 risk factor did not significantly differ (overall β [95% CI]: −0.06 [−0.19, 0.08]). There were no statistically significant CVRFs by age group interactions, suggesting hypertension and diabetes are detrimental to late-life executive function across age groups. Nevertheless, we examined MHC age group-stratified results and found a significant association between adolescent hypertension (β [95% CI]: −0.39 [−0.67, −0.11]) and worse late-life executive function compared to normotensive adolescents.

Verbal Episodic Memory

In overall analyses, hypertension was associated with significantly lower late-life verbal episodic memory (overall β [95% CI]: −0.22 [−0.37, −0.07]) compared to those without hypertension (Figure 3). We found no statistically significant associations between overweight/obesity, hyperlipidemia, or diabetes with late-life verbal episodic memory. Compared to those with no CVRFs, having 2 or more risk factors was associated with significantly worse verbal episodic memory (overall β [95% CI]: −0.25 [−0.41, −0.08]) and having 1 risk factor was not significantly associated (overall β [95% CI]: −0.05 [−0.19, 0.10]). There were no statistically significant CVRFs by age group interactions. In MHC age group-stratified analyses, we found significant associations between young adulthood hypertension and worse verbal episodic memory (β [95% CI]: −0.29 [−0.49, −0.09]) compared to young adults without hypertension. We also found that midlife hyperlipidemia was associated with significantly worse verbal episodic memory (β [95% CI]: −0.36 [−0.70, −0.02]) compared to midlife adults without hyperlipidemia.

Semantic Memory

We found no statistically significant associations between individual CVRF or number of CVRF with late-life semantic memory (Figure 4). There was no statistically significant risk factor by age group interactions nor significant associations in MHC age group-stratified analyses.

Additional CVRF Models

We assessed overweight/obesity, hypertension, and hyperlipidemia in the same regression models testing associations with executive function, verbal episodic memory, and semantic memory. When adjusted for in the same regression models, effect estimates for overweight/

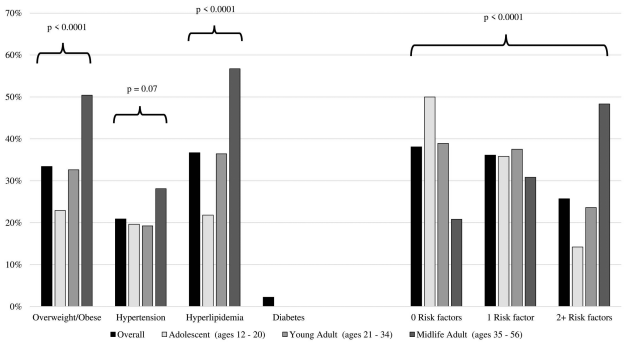

Figure 1. Prevalence of cardiovascular risk factors stratified by Multiphasic Health Checkup age group.

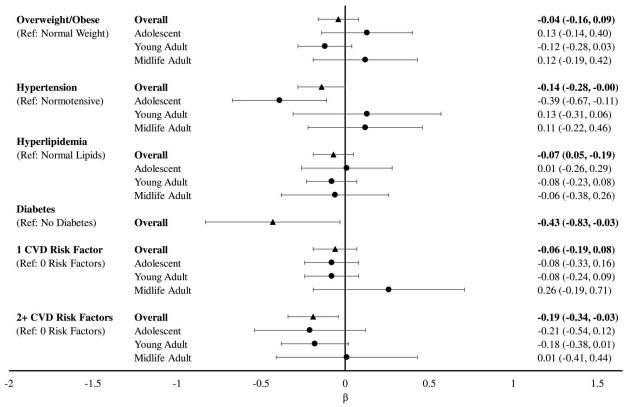

Figure 2. Linear regression models[a] of the association between cardiovascular risk factors and executive function overall and stratified by Multiphasic Health Checkup age group[b]. [a]Models adjusted for age at STAR interview, years since Multiphasic Health Checkup, gender, and education. [b]Adolescent: age 12–20; young adult: age 21–34; midlife adult: age 35–56. STAR = Study of Healthy Aging in African Americans.

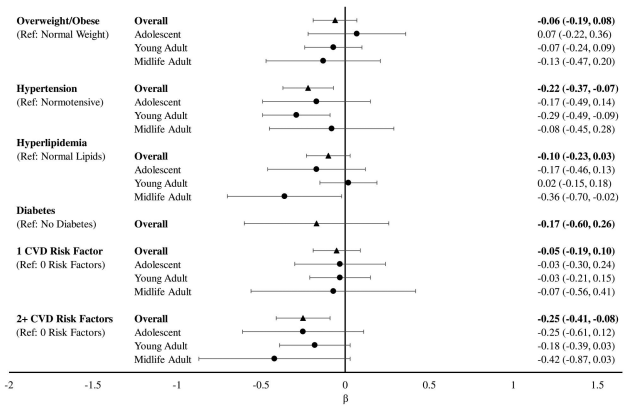

Figure 3. Linear regression models[a] of the association between cardiovascular risk factors and verbal episodic memory overall and stratified by Multiphasic Health Checkup age group[b]. [a]Models adjusted for age at STAR interview, years since Multiphasic Health Checkup, gender, and education. [b]Adolescent: age 12–20; young adult: age 21–34; midlife adult: age 35–56. STAR = Study of Healthy Aging in African Americans.

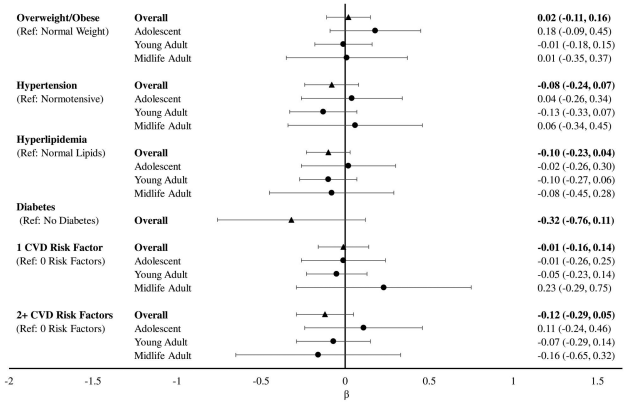

Figure 4. Linear regression models[a] of the association between cardiovascular risk factors and semantic memory overall and stratified by Multiphasic Health Checkup age group[b]. [a]Models adjusted for age at STAR interview, years since Multiphasic Health Checkup, gender, and education. [b]Adolescent: age 12–20; young adult: age 21–34; midlife adult: age 35–56. STAR = Study of Healthy Aging in African Americans.

obesity, hypertension, and hyperlipidemia with each of the 3 cognitive domains were similar to the results described when testing these risk factors individually (Supplementary Table 1). Diabetes was not included due to small numbers.

Discussion

Our study evaluated cognitive aging among community-dwelling Black Americans with exposure data as early as adolescence and cognitive assessments in late life. Consistent with prior literature, prevalence of CVRFs increased with advancing age (43). Almost half of participants who were midlife adults (age 35–56) during their MHC exam had 2 or more CVRFs, while only 24% of young adults (age 21–34) and 14% of adolescents (age 12–20) had multiple CVRFs. Compared to a nationally representative sample of Americans aged 20–49 from the NHANES (1971–1975), prevalence of CVRFs was 0.04%–12.8% lower among STAR participants aged 12–56 (1964–1985) (44). However, age and temporal trends limit comparison of data on life-course CVRFs. There is a dearth of information on CVRFs in Black adults before middle age (10) as well as cognitive aging and dementia among Black Americans (45), which is why studies like STAR are so important.

Midlife overweight/obesity, hypertension, and hypercholesteremia, as well as mid- and late-life diabetes have been identified as risk factors for cognitive decline and dementia (15,22,23,46–49). A limitation of these studies is that they primarily focused on individuals aged 40 and older and did not assess risk factors developed earlier in the life course (22,23,50–52). Given the long preclinical and prodromal periods of cognitive impairment and dementia, public health interventions on CVRFs may be needed decades prior to the onset of symptoms (53–56). Timing of risk factors in relation to timing of cognitive impairment and dementia is severely understudied, particularly in diverse populations where CRVF burden is disproportionately higher. Neuropathological studies have found that among Black Americans, there is a disproportionate burden of cerebrovascular disease compared to other racial/ethnic groups, which makes understanding the contributions of CVRFs to late-life cognition particularly important for older Black adults (57,58).

In age-stratified models, we found that midlife (age 35–56) hyperlipidemia was associated with worse verbal episodic memory, a finding consistent with the literature (22). Hypertension present in adolescence (age 12–20) was associated with significantly worse executive function in late life, and hypertension in young adulthood (age 21–34) was associated with significantly worse verbal episodic memory. Previous research has identified young adulthood hypertension as a risk factor for dementia (59). Deficits in episodic memory and executive function are hallmark features of dementia, while semantic memory is often only partially impacted, particularly in Alzheimer's disease (60,61). While midlife appears to be a sensitive period for CVRFs (22,23,62,63), particularly hypertension (64–66), our analysis suggests that this sensitive period may start as early as adolescence (age 12–20) or young adulthood (age 21–34). Screening for CVRFs and treatment through medication and lifestyle interventions throughout the life course is not only important for maintaining cardiovascular health, but also the maintenance of late-life brain health in Black Americans (67). This group is more likely to experience chronic stress and weathering that may contribute to the development of CVRFs at earlier ages (68,69) and, may, in part, be driving racial/ethnic disparities in late-life cognitive outcomes (70).

Our study has several strengths including a large number of Black participants with diverse ethnic and educational backgrounds (18% high school or less, 47% some college, vocational, or trade school, and 35% college graduate or more education). The wide range of ages at which individuals first participated in an MHC exam enables us to examine possible sensitive periods between CVRFs, as early as adolescence, with late-life cognition. MHC exams are a source of prospectively collected clinical and self-reported measures of CVRFs. Another strength is the assessment of cognitive function using the SENAS, a comprehensive and sensitive assessment tool that has been validated across diverse racial/ethnic groups. Over 40 years elapsed between assessment of CVRFs at MHC and measurement of cognition in STAR ensuring that risk factors were captured well before the onset of any age-related changes or disease.

Despite these strengths, there were several limitations including limited power to assess statistically significant differences in the association between CVRFs and cognition across MHC age groups. Due to the distribution of participant ages at MHC, the young adults were overrepresented while adolescents and midlife adults were underrepresented, limiting power to test for MHC age group interactions. However, we did see evidence of heterogeneity across age groups that warrants further investigation. We were also limited to measurement of CVRFs at one time point and thus compared individuals at different ages at CVRF measurement versus following the same person over time. Similarly, cognition was only available at one time point, which did not allow us to assess cognitive decline or impairment. Finally, we were unable to adjust for social determinants of health beyond participant education and parental education. We used education as a proxy for socioeconomic status; however, there are many other determinants that may influence the effect of CVRFs on cognition. As we continue to collect data, future research in this cohort will assess CVRFs at multiple time points in the life course, characterize life-course patterns of risk factors, and evaluate cognitive decline.

Black Americans are at high risk of developing common CVRFs including overweight/obesity, hyperlipidemia, hypertension, and diabetes (1,2,5,9,10). Prevalence of these risk factors over the life course

increases with advancing age and can have a negative impact on late-life cognitive function even when developed in adolescence or young adulthood. Public health initiatives to reduce the burden of CVRFs among Black Americans need to include individuals from adolescence through midlife. These modifiable risk factors provide an opportunity for risk reduction through targeted treatment and management in a population at excess risk due to experiences of racism and its impact on the body through weathering. Treatment and management of CVRFs will not only help in reducing risk of CVD but may also prevent detrimental effects of CVRFs on late-life brain health.

Supplementary Material

Supplementary data are available at *The Journals of Gerontology, Series A: Biological Sciences and Medical Sciences* online.

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Conflict of Interest

None declared.

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