CE 1.5 HOURS
Continuing Education
ORIGINAL RESEARCH

Midlife Hypertension and Hypercholesterolemia in Relation to Cognitive Function Later in Life in Black Women

Trends suggest associations that warrant further investigation.

The prevalence of many forms of vascular disease, including cerebrovascular disease and hypertension, has been found to be higher in the black population than in the white population.[1] In studies among predominantly white older adults, vascular risk factors such as hypertension, hypercholesterolemia, atrial fibrillation, and diabetes have been found to be significant contributors to cognitive decline and dementia.[2] The presence of such risk factors at midlife may have a particularly strong influence on cognitive outcomes later in life,[3,4] given that midlife can be a time during which cognitive pathology begins developing.[5] But associations between vascular risk factors and cognitive function have been understudied in black older adults.

Prior research investigating associations between hypertension and cognitive function has yielded mixed results with regard to black subjects.[6-11] Few studies have performed these investigations in well-characterized cohorts that involved longitudinal assessments of health, lifestyle, and cognition from midlife through later life. And very few studies have investigated associations between hypercholesterolemia and cognitive function with regard to black subjects. Treatment and prevention strategies for hypertension and hypercholesterolemia are well known and relatively straightforward. But more research is needed for us to understand how these conditions, especially when present at midlife, may contribute to cognitive function in later life among blacks.

Study purpose and theoretical framework. Using data from participants in the Nurses' Health Study (NHS; www.nurseshealthstudy.org) and the Women's Health Study (WHS; http://whs.bwh.harvard.edu), we sought to explore associations between two vascular risk factors—midlife hypertension and midlife hypercholesterolemia—and cognitive function later in life among black women. The participants were health professionals with knowledge of and access to health care, which limits some of the potential confounding likely in studies of more general populations.

In conceptualizing this study, we used the theoretical framework known as the Neuman Systems Model. In this model, each patient is considered to have five dimensions (physiological, psychological, sociocultural, developmental, and spiritual), and to exist as a system that can be affected by internal stressors, external stressors, and interactions between them.[12] Vascular health is an aspect of a patient's physiological dimension. As such it can be adversely influenced by both internal stressors (such as a genetic predisposition to vascular disease and chronic psychological stress) and external stressors (such as poor dietary habits and inadequate physical activity); the interaction of such stressors over time can produce vascular disease.

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ABSTRACT

Purpose: This study sought to evaluate midlife hypertension and hypercholesterolemia in relation to cognitive function later in life among black women.

Methods: Participants were drawn from the Nurses' Health Study and the Women's Health Study databases. In these studies, health professionals reported health information by questionnaire at baseline and at regular follow-up intervals, including diagnoses of hypertension, hypercholesterolemia, or both; and they completed telephone-based cognitive assessments later in life. Multivariable-adjusted linear regression models were used to estimate mean differences in global cognition and executive function scores, comparing women with and without a history of hypertension at midlife and women with and without a history of hypercholesterolemia at midlife.

Results: Data for 363 black female health professionals were analyzed. Those with a history of hypertension or hypercholesterolemia at midlife did not have lower global cognition and executive function scores later in life compared with those without such a history, although there were trends in this direction.

Conclusion: In the study sample, a history of hypertension or hypercholesterolemia at midlife was not related to worse cognitive function in later life. But there was a suggestive pattern of trends that warrants further exploration in larger studies.

Keywords: cognition, diverse populations, epidemiology, hypercholesterolemia, hypertension, minority populations, vascular disease

We hypothesized that hypertension and hypercholesterolemia may be internal stressors that contribute to cognitive aging. Furthermore, we hypothesized that black race may affect these internal stressors and may also exacerbate their effects on such aging. There is strong evidence that, compared with whites, black people are more likely to have uncontrolled hypertension[13]; and that blacks and others who experience perceived discrimination are more likely to develop hypertension and other illnesses.[14, 15] These connections suggest that black race might interact with hypertension through various physiological, psychological, sociocultural, developmental, and spiritual pathways to accelerate cognitive aging.

METHODS

Study population. Data from black women participating in two ongoing cohorts, the NHS and the WHS, were used in these analyses. The NHS began in 1976 as a prospective study investigating the long-term effects of various factors on the development of chronic disease. Its cohort comprised 121,700 female RNs ages 30 to 55 years who completed a mailed questionnaire on health and lifestyle.[16] Follow-up questionnaires have been sent every two years, and participation rates have been at least 90% for most two-year cycles. The WHS, which ran from 1991 through 2004, was a double-blind, placebo-controlled trial exploring the effectiveness of vitamin E supplements and aspirin in the primary prevention of cardiovascular disease and cancer in initially healthy women.[17, 18] Its cohort comprised 39,876 female health professionals ages 45 years and older who were randomized to four treatment groups using a 2 × 2 factorial design. Follow-up continued via annual questionnaires, with an overall participation rate of greater than 90%.

Associations between vascular risk factors and cognitive function have been understudied in black older adults.

From 1995 through 2000, substudies of cognitive function were conducted among the oldest participants in the NHS (those ages 70 years and older). In 1998, a substudy of cognitive function was conducted among the oldest participants in the WHS (those ages 65 years and older). In 2013 and 2014, the NHS substudy was expanded to include additional black participants who had been too young to take part in the original substudy. The institutional review board of Brigham and Women's Hospital approved these substudies.

Study sample and definitions. Black women were included in our analyses if their exposure history (a history of hypertension and hypercholesterolemia) could be determined at the time of the analytic baseline—which was 1990 for NHS participants and at time of enrollment between 1992 and 1995

for WHS participants—and if they had participated in an initial cognitive assessment either from 1995 through 2000 or from 2013 through 2014. The analytic baseline time varied because we originally included only NHS participants in our analyses; WHS participants were added later to increase the information (power). The final analytic sample consisted of 363 women meeting these criteria.

We defined *midlife* in terms of participants' age at the time of the analytic baseline, which varied by cohort. Participants who reported a diagnosis of hypertension or use of blood pressure–lowering medication as of 1990 (for the NHS participants) or at time of enrollment between 1992 and 1995 (for the WHS participants) were considered to have a history of hypertension at midlife. A similar criterion was applied with regard to hypercholesterolemia and cholesterol-lowering drug use to identify participants with a history of hypercholesterolemia at midlife.

In a secondary analysis of a subset of NHS participants, we used a stricter definition of midlife hypertension and hypercholesterolemia (diagnosis by age 55) in evaluating the effect of earlier diagnosis of these conditions. Such data were unavailable for WHS participants.

Data collection. *Cognitive function.* In the NHS, from 1995 through 2000, women ages 70 years and older who had no history of stroke were invited to participate in a substudy of cognitive function. The first several years were largely devoted to pilot interviews; the majority of participants were assessed beginning in 2000. Of the eligible participants, 93% (19,415 women, including 247 black women) completed an initial cognitive interview. In 2013 and 2014, the same cognitive interview was administered to 82 additional black participants as noted above; these later interviews were added specifically for the purpose of the present analyses. In the WHS, active participants ages 65 years and older were selected for cognitive testing in 1998. Of these, 89% (6,377 women, including 41 black women) participated in the initial cognitive interview.

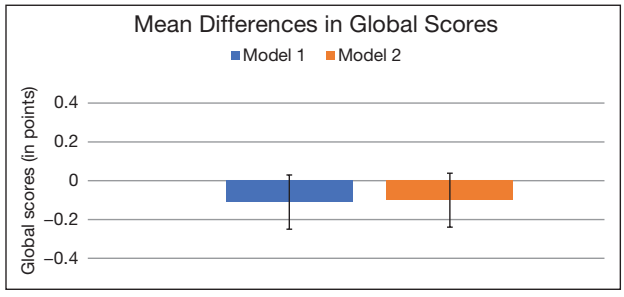
A telephone-based interview was used to assess cognitive function. Although the NHS and WHS interviews varied somewhat, each included five common tests: the Telephone Interview for Cognitive Status (TICS), which correlates highly with the Mini-Mental State Exam[19]; immediate and delayed recall testing using the East Boston Memory Test, which assesses verbal memory[20]; delayed recall of the TICS 10-word list to assess verbal memory; and a category

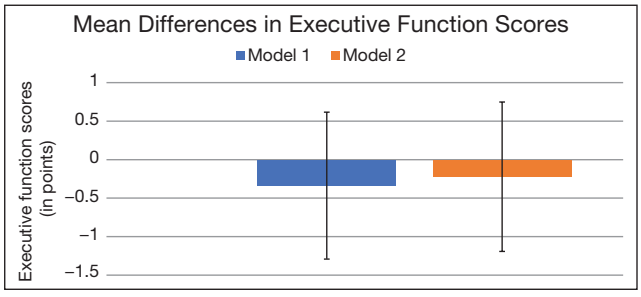
Table 1. Participant Characteristics Across Categories of Midlife Hypertension and Hypercholesterolemia in the NHS and WHS (N = 363)

Characteristics	No Hypertension	Hypertension	No Hypercholesterolemia	Hypercholesterolemia
Total sample, n (%)	152 (42)	211 (58)	201 (55)	161 (44)
Mean age, years	62.1	64.3	62.7	64.1
Education, n (%)				
RN, non-bachelor's degree	71 (47)	118 (56)	108 (54)	81 (50)
RN, bachelor's degree	41 (27)	40 (19)	43 (21)	38 (24)
RN, post-bachelor's degree	40 (26)	53 (25)	50 (25)	42 (26)
Ever smokers, n (%)	81 (53)	101 (48)	103 (51)	78 (48)
Alcohol abstainers, n (%)	73 (55)	89 (51)	85 (49)	77 (57)
Overweight, n (%)	94 (62)	150 (73)	138 (70)	106 (67)
Low level of physical activity, n (%)	67 (47)	95 (52)	84 (47)	78 (54)
History of myocardial infarction, n (%)	0 (0)	4 (2)	1 (0.5)	3 (2)
Condition-specific drug treatment, n (%)	N/A	111 (53)	N/A	8 (5)

NHS = Nurses' Health Study; WHS = Women's Health Study.
Note: n's reflect number of respondents answering a given question; "missing" responses were also included in calculating percentages. Because of rounding, percentages may not sum to 100%.

Figure 1. Mean Differences in Global Scores (n = 348) and Executive Function Scores (n = 362) Between NHS and WHS Participants with and Without Midlife Hypertension





	Model 1					Model 2				
	Point estimate	Lower bound	Upper bound	Negative error	Positive error	Point estimate	Lower bound	Upper bound	Negative error	Positive error
Global scores	−0.11	−0.25	0.03	0.14	0.14	−0.1	−0.24	0.04	0.14	0.14
Executive function scores	−0.34	−1.29	0.62	0.95	0.96	−0.22	−1.19	0.75	0.97	0.97

NHS = Nurses' Health Study; WHS = Women's Health Study.
The reference group is women without midlife hypertension; by definition, the mean difference for this group is 0. The mean difference of the group with midlife hypertension is not significantly different from that of the reference group because the error bar (representing the confidence interval) crosses 0. Model 1 is adjusted for age at cognitive interview, education, and cohort. Model 2 is adjusted for age at cognitive interview, education, smoking, alcohol intake, physical activity, body mass index, and cohort.

fluency test that involved asking participants to name as many animals as they could in one minute.[21] In a validation study, conducted among a similar sample of 61 women, this telephone-based cognitive battery performed well compared with in-person neuropsychological interviews.[22]

Two primary cognitive outcomes were selected a priori: a global composite score (averaging all tests) as well as a category fluency score, which represents (in part) executive function. Executive function is a cognitive domain that is particularly affected by vascular disease.[23] Because the five cognitive tests are each scaled differently, *z* scores were used to create the global composite measure. (A *z* score refers to how many standard deviations a data point is from the mean.) Specifically, we calculated the difference between each participant's individual score on a given test measure and the overall mean score for our population, divided by the population standard deviation, and then averaged together *z* scores for all six cognitive tests.[24]

Vascular factors. In both the NHS and the WHS, baseline and follow-up questionnaires asked participants to report diagnoses of hypertension or hypercholesterolemia and whether they were taking medications for these conditions. In a validation study, conducted among a subsample of NHS participants, self-reports of hypertension and hypercholesterolemia were found to be highly accurate compared with medical record review and in-person measurements.[25]

Possible confounding factors. In both the NHS and the WHS, baseline and follow-up questionnaires asked participants to self-report about a variety of demographic, health, and lifestyle factors. Studies evaluating several possible confounding factors, conducted in subsamples of NHS and WHS cohorts, have validated the accuracy of self-report compared with gold-standard assessments; such factors include alcohol intake,[26] physical activity,[27] and body mass index (BMI).[28]

Statistical analyses. Multivariable-adjusted linear regression models were used to estimate mean differences in global cognition scores and executive function scores comparing women with a history of hypertension with those without and women with a history of hypercholesterolemia with those without. In additional analyses, treatment status for each condition was also considered. Possible confounding factors with known or suspected associations with vascular status or cognitive function were specified a priori, as such factors have the potential to induce bias in observed associations. Initial models were adjusted for age and education as possible confounding factors. Additional models were further adjusted for the following possible confounders: smoking status (ever versus never), usual alcohol intake (any versus none), usual physical activity (high versus low, based on metabolic equivalent of task [MET]–hours per week), and BMI (25 kg/m^2 or greater versus less than 25 kg/m^2). (The NHS and WHS use slightly different definitions for

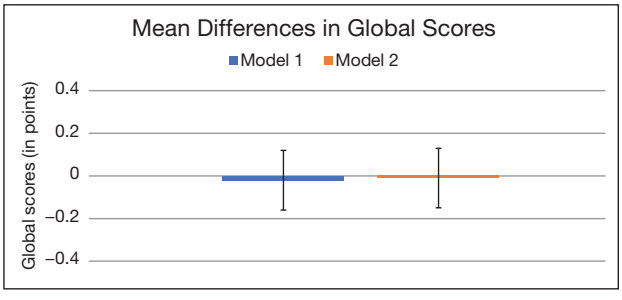
high and low levels of physical activity. In the NHS, a high level of physical activity was defined as 7.8 MET-hours per week or greater; a low level was defined as less than 7.8 MET-hours per week. In the WHS, a high level of physical activity was defined as exercising anywhere from less than once per week to more than four times per week; a low level was defined as rarely or never exercising.) For these possible confounders, we used data collected in 1990 (for NHS participants) or at time of enrollment between 1992 and 1995 (for WHS participants) to correspond with the time frame used to define hypertension and hypercholesterolemia at midlife. The models were also adjusted for sample—which of the three cognitive substudy groups participants belonged to—and "missing" indicators were used to handle missing data. Models adjusting for depression status at the time of the cognitive interview (to reduce variation in the outcome measures) yielded similar results to those without such adjustment; thus, this variable was not included in the final models. All statistical analyses were conducted using SAS statistical software, version 9.4 (SAS Institute, Inc., Cary, NC).

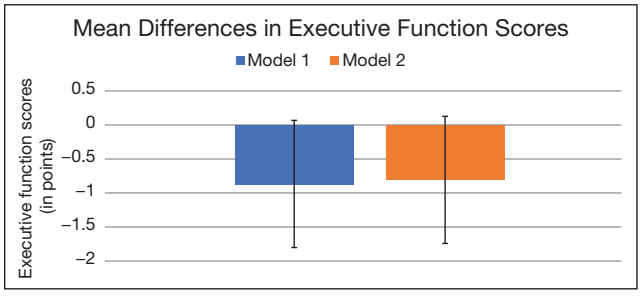
RESULTS

Table 1 depicts characteristics reported at analytic baseline for participants with and without a history of hypertension at midlife and for those with and without a history of hypercholesterolemia at midlife. For all participants, the mean age was 63.4 years (range, 46 to 80 years). Women with a history of hypertension were slightly older, more likely to have a non-bachelor's RN degree, and more likely to be overweight (BMI of 25 kg/m^2 or greater) compared with those without such history. Women with a history of hypercholesterolemia were slightly older, more likely to abstain from drinking alcohol, and slightly more likely to report a low level of physical activity compared with those without such history. About half of the women with hypertension reported taking at least one antihypertensive medication. Only 5% of women with hypercholesterolemia reported taking at least one cholesterol-lowering drug.

Figure 1 depicts associations between hypertension status at midlife and cognitive function later in life. In models adjusted for age and education, women with a history of hypertension appeared to have lower cognitive function (indicated by a *negative* mean difference in global and executive function scores) than those without a history of hypertension. For global cognition scores (n = 348), the mean difference was –0.11 standard units, (95% confidence interval [CI], –0.25 to 0.03). (In other words, the mean difference between the two populations is estimated to be –0.11 and we are 95% confident that the true value lies between –0.25 and 0.03.) For executive function scores (n = 362), the mean difference was –0.34 (95% CI, –1.29 to 0.62). However, these results weren't statistically significant. Results were similar after additional adjustments for smoking status, alcohol intake, level of physical activity, and BMI: women with a history of hypertension appeared to have lower cognitive

Figure 2. Mean Differences in Global Scores (n = 347) and Executive Function Scores (n = 361) Between NHS and WHS Participants with and Without Midlife Hypercholesterolemia

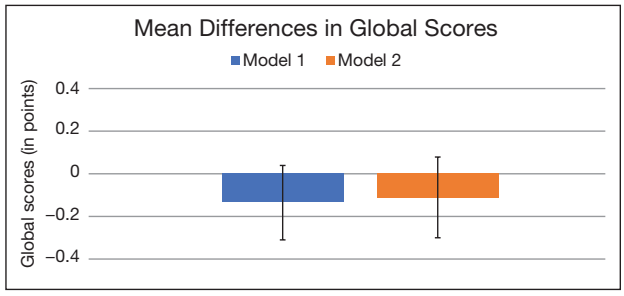


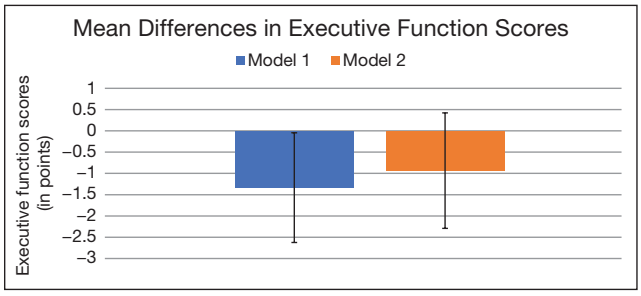


	Model 1					Model 2				
	Point estimate	Lower bound	Upper bound	Negative error	Positive error	Point estimate	Lower bound	Upper bound	Negative error	Positive error
Global scores	–0.02	–0.16	0.12	0.14	0.14	–0.01	–0.15	0.13	0.14	0.14
Executive function scores	–0.87	–1.8	0.07	0.93	0.94	–0.8	–1.74	0.13	0.94	0.93

NHS = Nurses' Health Study; WHS = Women's Health Study.
The reference group is women without midlife hypercholesterolemia; by definition, the mean difference for this group is 0. The mean difference of the group with midlife hypercholesterolemia is not significantly different from that of the reference group because the error bar (representing the confidence interval) crosses 0. Model 1 is adjusted for age at cognitive interview, education, and cohort. Model 2 is adjusted for age at cognitive interview, education, smoking, alcohol intake, physical activity, body mass index, and cohort.

Figure 3. Mean Differences in Global Scores (n = 207) and Executive Function Scores (n = 217) Between NHS Participants with and Without Midlife Hypertension





	Model 1					Model 2				
	Point estimate	Lower bound	Upper bound	Negative error	Positive error	Point estimate	Lower bound	Upper bound	Negative error	Positive error
Global scores	−0.13	−0.31	0.04	0.18	0.17	−0.11	−0.3	0.08	0.19	0.19
Executive function scores	−1.33	−2.62	−0.04	1.29	1.29	−0.93	−2.29	0.43	1.36	1.36

NHS = Nurses' Health Study.
The reference group is women without midlife hypertension; by definition, the mean difference for this group is 0. The mean difference of the group with midlife hypertension is not significantly different from that of the reference group because the error bar (representing the confidence interval) crosses 0. Model 1 is adjusted for age at cognitive interview, education, and cohort. Model 2 is adjusted for age at cognitive interview, education, smoking, alcohol intake, physical activity, body mass index, and cohort.

function compared with those without such history. For global scores, the mean difference was –0.10 (95% CI, –0.24 to 0.04); for executive function scores, the mean difference was –0.22 (95% CI, –1.19 to 0.75). Results were also mostly similar when we evaluated hypertension according to treatment status in relation to global scores.

models adjusted for age and education, the mean difference was –0.87 (95% CI, –1.80 to 0.07). In models adjusted for multiple additional confounders, the mean difference was –0.80 (95% CI, –1.74 to 0.13). But these results didn't reach statistical significance. Results were similar when considered by treatment status; only 2% of women with hypercholesterolemia

In this sample of black women, having a history of midlife hypertension or hypercholesterolemia was not associated with lower cognitive function later in life. But there were trends in this direction.

Figure 2 depicts associations between hypercholesterolemia status at midlife and cognitive function later in life. In both models controlling for age and education and models adjusting for additional potential confounders (smoking status, alcohol intake, level of physical activity, and BMI), the results indicated that women with a history of hypercholesterolemia had similar global cognitive function, but somewhat poorer executive function, compared with those without hypercholesterolemia. Regarding executive function (n = 361), in

by midlife reported taking cholesterol-lowering drug treatment.

In secondary analyses, which used the stricter definition for "midlife" (hypertension or hypercholesterolemia before age 55 years), results were largely similar to those obtained in our main analyses (see Figures 3 and 4).

DISCUSSION

In this sample of black women, having a history of midlife hypertension or hypercholesterolemia was

not associated with lower cognitive function later in life. But there were trends in this direction. It's possible that the lack of significant associations is attributable to the modest sample size and resulting low statistical power. If a larger study were to show similar findings at levels that reached statistical significance, this would provide a rationale for improving midlife treatment and prevention of hypertension and hypercholesterolemia in black people, in order to reduce the adverse cognitive impact of these conditions later in life.

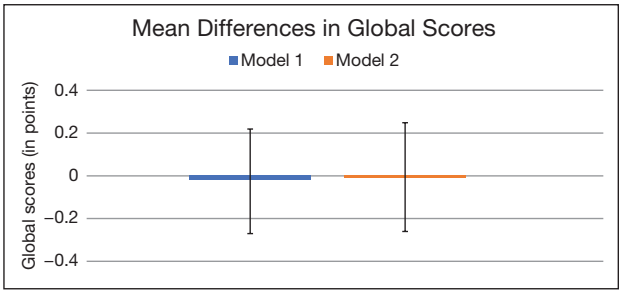
involved a battery of neuropsychological tests. After adjusting for demographic, lifestyle, and health factors in multivariable models, the researchers found that higher systolic and diastolic blood pressures were each correlated with lower cognitive function scores. Although the age range was wide, the mean age was 43 years, supporting the notion that midlife hypertension might be predictive of cognitive function in this population. The Atherosclerosis Risk in Communities study included 3,229 African Americans ages 48 to 67 years.[7] Blood pressure was determined based

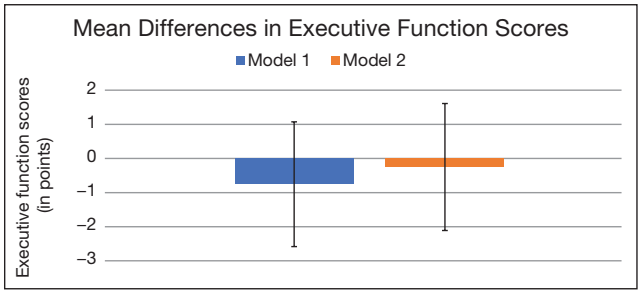
Nurses and other health professionals should prioritize prevention and treatment strategies related to vascular risk factors for blacks throughout adulthood.

Only a few previous studies have assessed the role of midlife vascular factors in this regard among blacks. The Maine-Syracuse Longitudinal Study included 147 non-Hispanic African Americans ages 18 to 76 years.[9] Participants had their blood pressure measured 18 times—six times while standing, six times while sitting, and six times while lying down; readings were then averaged to provide the most accurate measurement. Cognitive evaluation

on an average of two measurements; hypertension was defined as having a systolic blood pressure of 140 mmHg or greater, diastolic blood pressure of 90 mmHg or greater, or use of antihypertensive drugs. Cognitive testing was performed at the same visit, and then repeated multiple times over 20 years of follow-up.[7] After adjusting for multiple potential confounders, the researchers found that hypertension at midlife was associated with a steeper cognitive decline than

Figure 4. Mean Differences in Global Scores (n = 202) and Executive Function Scores (n = 212) Between NHS Participants with and Without Midlife Hypercholesterolemia





	Model 1					Model 2				
	Point estimate	Lower bound	Upper bound	Negative error	Positive error	Point estimate	Lower bound	Upper bound	Negative error	Positive error
Global scores	−0.02	−0.27	0.22	0.25	0.24	−0.01	−0.26	0.25	0.25	0.26
Executive function scores	−0.75	−2.58	1.08	1.83	1.83	−0.24	−2.11	1.62	1.87	1.86

NHS = Nurses' Health Study.

The reference group is women without midlife hypercholesterolemia; by definition, the mean difference for this group is 0. The mean difference of the group with midlife hypercholesterolemia is not significantly different from that of the reference group because the error bar (representing the confidence interval) crosses 0. Model 1 is adjusted for age at cognitive interview, education, and cohort. Model 2 is adjusted for age at cognitive interview, education, smoking, alcohol intake, physical activity, body mass index, and cohort.

normal blood pressure. Lastly, in a small sample of 121 African Americans ages 21 to 73 years (mean, 44 years), higher triglyceride levels in middle age were associated with lower cognitive scores, after controlling for age, sex, and education.[11] This is the only study we found that examined triglyceride levels in relation to cognitive function in black people. Our study findings add to this existing evidence, which demonstrates a general pattern of associations between midlife hypertension and hypercholesterolemia and poor cognitive status later in life among blacks.

Together, these findings further suggest that nurses and other health professionals prioritize prevention and treatment strategies related to vascular risk factors for blacks throughout adulthood. As Neuman's model attests, it's appropriate to consider primary, secondary, and tertiary interventions to protect and restore vascular health in black patients to reduce their risk of accelerated cognitive aging.[12,29] According to this model, primary interventions aimed at preventing or reducing stressors should include comprehensive patient education regarding the importance of a heart-healthy diet, regular physical activity, smoking cessation, and weight reduction.[12,29] Secondary interventions should encompass regular blood pressure monitoring by patients (as appropriate) and blood pressure and cholesterol screening by clinicians, as well as tight control of these factors and treatment according to evolving evidence-based guidelines in order to promote healthy aging overall.[12,29] Such efforts can strengthen the patient's "lines of resistance" (so named in Neuman's model) after health has been compromised by a diagnosis of hypertension or hypercholesterolemia. Lastly, tertiary interventions should include comprehensive patient education on diet, lifestyle, and medication changes to orient patients to their new circumstances following overt vascular events (such as heart attack or stroke).[12,29] Such efforts can empower patients to take positive steps that can potentially preserve cognitive function later in life.

Strengths of this study include the use of well-defined cohorts with midlife assessment of vascular factors and later-life assessment of cognitive function, which allowed us to evaluate possible associations during a biologically relevant time frame. The cohorts were also relatively homogeneous with respect to their educational background and their knowledge of and access to health care, which limited the potential for confounding by these factors. Moreover, the availability of data on multiple midlife health and lifestyle factors—which were adjusted for in the statistical models—further reduced the potential for confounding bias in the observed associations.

Limitations. First, the sample size of 363 participants was modest, reducing the study's power to detect significant associations between vascular factors and cognitive function. Although we observed a relatively consistent pattern of associations between having a history of midlife hypertension or hypercholesterolemia and worsening cognition later in life in the study sample, these associations did not reach statistical significance. Second, participants self-reported such history, which might have led to some misclassifications. (That said, an early validation study of NHS participants found that they reported their health status well.[25]) Other limitations included the lack of information on the severity and degree of control of hypertension and hypercholesterolemia, and varying definitions of midlife that meant participants' exposure history was captured at somewhat different ages. Lastly, the study sample was limited to black women; thus, the findings may not be generalizable to black men.

CONCLUSION

The study findings do not indicate that midlife hypertension and hypercholesterolemia are associated with lower cognitive function later in life among black women. But we observed trends in this direction, and these associations might have reached statistical significance in a larger sample. Further investigation among black women—and black men—is essential. Given the observed trends, in order to minimize the risk of cognitive decline later in life, nurses and other health professionals should renew their efforts to prevent and manage vascular conditions in the black population. ▼

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