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Vascular health across young adulthood and midlife cerebral autoregulation, gait, and cognition

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Abstract

Introduction: To test the association of vascular health (VH) across young adulthood with midlife dynamic cerebral autoregulation (dCA), gait, and cognition; and to test whether dCA is a modifying factor.

Methods: We studied 196 participants from the Coronary Artery Risk Development in Young Adults cohort who were followed over 30 years. VH was assessed at each visit according to American Heart Association recommendations. At year 30, dCA was measured using transcranial Doppler ultrasound and several gait and cognitive domains were assessed.

Results: Worse VH from baseline through year 7, but not at year 30, was associated with less efficient dCA (all $P < .05$). Worse VH at all visits was associated with slower gait speed, and at year 7 with worse executive and global cognition (all $P < .05$). The association of baseline VH and midlife gait, but not cognition, was moderated by dCA (interaction $P < .05$).

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CONFLICTS OF INTEREST

The authors have no conflicts of interest to declare.

SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Conclusions: VH as early as young adulthood may influence midlife brain health, and dCA may modify this relationship.

Keywords

cerebral autoregulation; cognitive function; gait; midlife; vascular risk factors

1 | INTRODUCTION

Vascular health plays a critical role in preservation of brain health across the lifespan.^{1,2} In fact, vascular risk factors, including hypertension, diabetes, obesity, and smoking have all been established as major contributors to late-life cognitive impairment and dementia.² Moreover, hypertension and obesity also have been linked to functional disability, increased risk of falls, and slower gait speed among older adults.^{3–5} In line with these observations, recent recommendations from the American Heart Association (AHA)/American Stroke Association (ASA) have identified the ideal levels of seven modifiable vascular risk factors that are essential for preservation of brain health across the lifespan: nonsmoking status, physical activity at goal levels, body mass index (BMI) < 25 kg/m², healthy diet consistent with current guidelines, untreated blood pressure < 120/80 mmHg, untreated total cholesterol < 200 mg/dL, and fasting glucose < 100 mg/dL.¹ Importantly, recent data suggest that interventions focused on these modifiable risk factors may ideally need to be started in young adulthood, possibly even during childhood, to be impactful.^{1,6,7} Nevertheless, little is known about the association of vascular risk exposure across young adulthood with midlife mobility and cognition. Because midlife mobility and cognitive function likely contribute to and precede dementia among older adults,⁸ it is important to identify these early and potentially modifiable markers of future, later-in-life health status.

While the underlying mechanisms linking vascular risk exposure with cognitive and mobility impairment remain unclear, impaired cerebral autoregulation is often implicated as the leading mechanism.^{9,10} In this context, decades of cumulative and chronic vascular dysfunction possibly beginning in young adulthood may hamper cerebral autoregulation through endothelial damage, impaired vascular tone, and injured vascular structure.^{2,11} This may, in turn, predispose the brain to perfusion pressure disturbances;^{1,9} accumulation of neuronal injury; and ultimately, cognitive and mobility impairment.^{12–14} Indeed, hypertension and diabetes have both been associated with impaired cerebral autoregulation among older adults.^{15–17} While these observations suggest that vascular dysfunction may contribute to mobility and cognitive impairment through impaired cerebral autoregulation, the link between vascular risk exposure across young adulthood and midlife cerebral autoregulation is not yet fully clear. Furthermore, there is a knowledge gap around the interaction between vascular risk exposure, cerebral autoregulation, mobility, and cognitive function in midlife.

We assessed the association of vascular risk exposure across a period of about 30 years, spanning young adulthood to midlife, with cerebral autoregulation, gait, and cognition in midlife. We leveraged available data from the Coronary Artery Risk Development in Young Adults (CARDIA) cohort with detailed longitudinal assessment of vascular risk

factors. We hypothesized that better vascular health during early adulthood would be associated with better cerebral autoregulation, gait, and cognition in midlife and, further, that cerebral autoregulation would modify the association of vascular risk exposure with gait and cognition.

2 | METHODS

2.1 | Study population

Study participants were included from the CARDIA cohort, a community-based biracial (Black/White) cohort of men and women aged 18 to 30 years. The CARDIA study began in 1985–1986 to examine the development of cardiovascular disease and associated risk factors in four U.S. sites (Birmingham, Alabama [n = 1178 at baseline]; Chicago, Illinois [n = 1109 at baseline]; Minneapolis, Minnesota [n = 1402 at baseline] and Oakland, California [n = 1426 at baseline]) over 30 years through eight follow-up examinations (year 2, 5, 7, 10, 15, 20, 25, and 30 examinations).^{18,19} Over the follow-up period, contact has been maintained with > 90% of the surviving cohort, with a retention rate of 72% up to year 25 exam (74.5%, 74.4%, 69.4%, and 70.6% for Birmingham, Chicago, Minneapolis, and Oakland, respectively).²⁰ Details of survival rate, lost to follow-up, and retention strategies have been described elsewhere.²⁰ At year 30 examination, all participants from the Chicago site (n = 745) were invited to participate in the Cerebral Small Vessels in Motor and Cognitive Decline substudy with the aim of investigating early markers of cerebrovascular damage during midlife. Out of those who responded, a total of 202 participants were eligible for assessment of transcranial Doppler (TCD) ultrasound (had acoustic window), and detailed gait and cognitive measures. Out of these 202 participants, 196 had complete vascular health assessment at baseline (year 0) and were included in analyses for this study. Specifically, participants for the current study were those who attended year 0 (baseline), 7, 10, 15, 20, 25, and 30 examinations. We excluded year 2 and year 5 examinations in our analyses because fasting glucose was not measured at those timepoints. Figure S1 in supporting information shows a timetable of available data used in this study. Characteristics of participants included in this study (n = 196) were not different compared to Chicago center participants (n = 543), except that those included were slightly younger and more frequently males (Table S1 in supporting information). All participants provided written informed consent and the study protocol was approved by the institutional review board.

2.2 | Vascular health assessment

Standardized protocols were used to assess vascular risk factors at each visit.²¹ Details about measurement of each vascular risk factor are provided in supporting information (supplemental text). We calculated a vascular health score according to the metrics recommended by AHA/ASA.^{12, 22} Because diet was not assessed at all timepoints in CARDIA, we used a modified version of AHA/ASA recommendations to assess six vascular risk factors: smoking, BMI, blood pressure, total cholesterol, fasting glucose, and physical activity. A vascular health score was calculated for each visit by assigning each risk factor 2 points for ideal health, 1 point for intermediate health, and 0 points for poor health, then summing the scores of all components to yield a total vascular health score ranging from 0 (poor vascular health) to 12 (ideal vascular health).^{1,22} Table S2 in supporting information

shows the cutpoints for assigning poor, intermediate, and ideal levels based on AHA/ASA definitions, with only slight modifications made for physical activity according to a previous CARDIA study.¹³ We also calculated a cumulative vascular health score across all follow-up visits as the sum of [average of vascular health score between consecutive visits $\times$ years between the visits]. Finally, we calculated a cumulative ideal vascular health score for each vascular health item as the sum of having ideal health score during follow-up ranging between 0 to 7 with 0 indicating never having ideal score and 7 indicating having ideal score in all exam visits.

2.3 | Assessment of dynamic cerebral autoregulation by TCD ultrasound

TCD ultrasound was used to assess dynamic cerebral autoregulation (dCA) at year 30 examination by measuring spontaneous beat-to-beat oscillations in mean blood flow velocity (MFV) of the major cerebral arteries in response to spontaneous mean arterial pressure (MAP) oscillations. This approach allows for the assessment of dCA by analyzing the relationship between beat-to-beat spontaneous oscillations of MFV and MAP using transfer function analyses.^{23,24} Hence, dCA was defined as transfer function gain and phase shift angles of the two oscillating signals according to the Cerebral Autoregulation Research Network recommendations.²⁵ In the cerebral circulation, gain quantifies the damping effect of CA on the magnitude of blood pressure oscillations. A low gain value indicates effective CA whereas a high gain is interpreted as ineffective dCA.^{10,26} The phase shift represents the temporal difference between transmissions of oscillation from MAP to MFV. Phase shift approaches zero as the oscillations of MFV and MAP become synchronous. Thus, a low phase value indicates impaired dCA, while a high phase value indicates effective dCA.^{10,26} Figure 1 illustrates the phase and gain values of dCA. Further details about TCD procedure, data processing, and quantification of phase and gain values are provided in supporting information (supplemental text).

2.4 | Cognitive function and gait assessments

Cognitive function was assessed at year 30 examination using a battery of neuropsychological tests. These cognitive tests were Hopkin's Verbal Learning Test-Revised (HVLT-R); Digit Span Test (DST); Digit Symbol Substitution Test (DSST); Trail Making Test A and B; Stroop test; and the National Institute of Health (NIH)-Flanker Inhibitory test, -List Sorting Working Memory test (NIH-LSWM), and -Picture Sequence Memory test (NIH-PSM). By averaging the z-scores of the cognitive tests, we constructed three composite cognitive domains of executive, memory, and global cognitive function as previously described.⁷ The executive domain was the composite score of NIH-Flanker Inhibitory test, NIH-LSWM test, Trail Making test B, DSST test, and Stroop test. The memory domain was the composite score of NIH-PSM test and HVLT-R test. The global cognitive domain was the composite score of all the cognitive tests.

Gait was assessed during a 40-foot walk on a 20 $\times$ 2 foot Zeno mat (Protokinetics Zeno Walkway) as previously described.⁷ Participants were asked to walk at their normal pace starting 4 feet before the mat. The walking trial consisted of two passes over the mat. The turns were completed off the mat and were not included in analysis. Step velocity (gait speed in cm/sec) was measured automatically using ProtoKinetics Movement Analysis software as

distance over time. The measurements were averaged over the entire walking trial for the right and left feet.

2.5 | Statistical analysis

Separate multivariable linear regression models were used to assess the association of vascular health score at each visit with dCA, cognition, and gait. The primary exposures were vascular health scores at each visit. The primary outcome variables were transfer function measures of dCA (phase and gain), composite cognitive domains, and gait speed at year 30. Normality of residuals was checked by visual inspection of histograms and normal probability plots. All analyses were adjusted for age, sex, and race. Furthermore, analyses involving cognition as the primary outcome were additionally adjusted for education at year 30, and analyses involving gait as the primary outcome were additionally adjusted for height. Similarly, we assessed the association of cumulative vascular health score during follow-up and individual ideal vascular health items during follow-up with the outcomes (dCA, gait, and cognition) using multivariable linear regression models. To account for multiple comparisons, the false discovery rate (FDR) approach by Benjamini and Hochberg²⁷ was applied.

To test whether dCA moderated the association of vascular health with gait or cognition, participants were stratified at the median of dCA and tested for interactions. Furthermore, given the known disproportionate burden of vascular risk factors among Blacks and Whites,²⁸ we stratified the participants by race (Blacks vs Whites) and tested for interaction using linear regression models. Finally, to account for interindividual differences in follow-up visit attendance, we calculated the time interval between each visit and baseline (year 0) using the exact attendance date. This term was then added to the linear regression models as a covariate, which did not materially change the results. Statistical significance was defined by a P -value $< .05$. All statistical analyses were conducted using SPSS (version 25.0) or RStudio software (version 3.5.1).

3 | RESULTS

The mean age of the participants at baseline was 24 ± 4 years old, a total of 90 (45%) participants were female, and 92 (46%) were Black (Table 1). Vascular health score at baseline ranged from 5 to 12 points, and 20% of the participants had ideal vascular health (12 points), while vascular health at year 30 ranged between 3 and 12 points, and 2% of the participants had ideal vascular health (Figure 2). Overall, the prevalence of meeting ideal health for all vascular health components declined during follow-up ($P < .001$), except for smoking, which marginally increased (from 61% at baseline to 65% at year 30; Figure 2). Detailed vascular health scores (poor, intermediate, and ideal) for each vascular health item are illustrated in Figure S2 in supporting information.

A lower vascular health score at year 0, 7, and 25, but not at year 30, was associated with less efficient dCA (lower phase; Table 2, all $P < .05$). We observed a trend showing that the effect estimates for the association between vascular health and phase decreased from baseline through year 30 examinations (Table 2, β per 1 score decrease in vascular health score at baseline = -3.12 degrees of phase vs -1.28 degrees of phase at year 30).

Vascular health score was not associated with transfer function gain at any examination visit (Table 1). Furthermore, lower cumulative vascular health across all follow-up visits was also associated with less efficient dCA as measured by phase ($P = .010$), but not with gain (Table 2). After FDR correction for multiple comparisons, a lower vascular health at year 0, 7, and lower cumulative vascular health during follow-up, remained associated with lower dCA phase (Table 2).

Lower vascular health score at all visits was associated with slower step velocity (Table 3, all $P < .05$), with decreasing estimates from baseline through year 30 examinations (Table 3, β per 1 score decrease in total vascular health score at baseline = -2.80 cm/sec of step velocity vs -1.88 cm/sec of step velocity at year 30). The association between vascular health score from year 0 through year 25 and step velocity remained significant even after a FDR correction for multiple comparisons (Table 3). Lower vascular health score at year 7, but not at subsequent visits, was associated with lower performance in the executive and global cognitive domains (Table 3, all $P < .05$). This association was not significant after FDR correction for multiple comparisons. Furthermore, lower cumulative vascular health across all follow-up visits was associated with slower step velocity (Table 3, $P < .001$) even after FDR correction for multiple comparisons, but not cognition.

Figure S3 in supporting information shows the association of cumulative ideal vascular health items during follow-up with dCA, gait, and cognition at year 30 examination. Ideal fasting glucose during follow-up was associated with more efficient dCA ($P = .035$) and faster step velocity ($P = .009$). Ideal blood pressure during follow-up was associated with faster step velocity ($P < .001$), and better global and executive cognitive measures ($P = .012$ and $.029$, respectively). Ideal BMI during follow-up was associated with faster step velocity ($P = .001$), and ideal physical activity during follow-up was associated with better global cognitive performance ($P = .031$).

To test for effect modification by dCA, participants were stratified at the median of phase into two groups (low phase group ranged -39 to 44 degrees, and high phase group ranged 44 to 102 degrees). The association between baseline vascular health and step velocity was strongest in those with lower phase (Figure 3, P for interaction = $.002$). However, the association between baseline vascular health and cognitive function did not vary across the two phase groups (Figure 3, all P for interactions $> .05$). There was no significant interaction between phase and vascular health score at other visits, or with cumulative vascular health score in relation to gait or cognition (all P for interactions $> .05$). Finally, there was no significant interaction between race and vascular health score at year 0 or year 30 in relation to dCA, gait, or cognition, although the effect estimates were marginally higher for Black participants (all P for interaction $> .05$; Table S3 in supporting information).

4 | DISCUSSION

The findings of this study suggest that poor vascular health at early adulthood, but not in midlife, is associated with less efficient cerebral autoregulation, and worse gait and cognitive function in midlife. Furthermore, we found that poor vascular health at early adulthood is

associated with worse midlife gait in those with less efficient cerebral autoregulation, while the association of vascular health with cognition is not affected by cerebral autoregulation.

Vascular risk factors and cerebral autoregulation have been linked in older adults but this relationship has not been studied across young adulthood and midlife. Our work addresses this knowledge gap and shows that similar to observations related to cognitive function, the greater burden of vascular risk exposure in younger adulthood has the strongest link to the efficiency of dCA at midlife, while midlife vascular health does not seem to be associated with midlife dCA. Several mechanisms may underlie the observed link between vascular health and dCA. Vascular risk factors may injure vascular structure and function, hence hampering cerebrovascular autoregulation, endothelial function, and neurovascular coupling.^{1,2,10,29} For example, hypertension enhances cerebral vascular damage and leads to subacute ischemic injury that manifests as cerebral small vessel disease on magnetic resonance imaging (MRI).³⁰ Smoking has also been associated with changes in brain perfusion and volume loss, leading to compromised circulation in the brain.³¹ Additionally, a greater number of ideal vascular measures were associated with higher cerebral vessel density and caliber, higher cerebral blood flow, and fewer white matter hyperintensities (WMH) on MRI.³² Given these observations, it is plausible that vascular risk factors may result in neurovascular dysfunction and suboptimal brain health through impaired cerebral autoregulation.^{1,2} In line with this premise, our findings suggest that disturbances in cerebral autoregulation may reflect the level of vascular dysfunction resulting from life-long exposure of cerebral vessels to vascular risk factors. It should be noted that the association between vascular health and cerebral autoregulation at year 25 was somewhat unexpected, because the point estimates (β) were higher than those observed at years 10 through 20. However, this association did not remain significant after correction for multiple comparisons, suggesting a possible false positive finding. As such, future studies are needed to determine whether the association of vascular health and dCA over the life course is linear, or whether there are inflection points with different trajectories. Finally, given that autonomic failure may associate with impaired dCA,³³ future studies should assess whether autonomic dysfunction plays a role in the relationship between vascular health and dCA in midlife.

Our findings on the relationship among vascular risk, cognition, and gait support previous data in middle age and older adults. These studies showed that vascular risk factors in midlife, rather than late-life, were associated with cognitive impairment in later life.^{34–39} High blood pressure, diabetes, and low physical activity also have been associated with slow gait speed, increased risk of falls, and disability in older adult.^{3,5,40,41} While the link between vascular risk exposure, and cognitive and gait impairment have been shown in old age, limited information exists among younger individuals. A previous study in the CARDIA cohort, for example, demonstrated that better cardiovascular health in young adulthood was associated with better cognitive function in midlife over a 25-year follow-up period.⁶ Our findings extend the previous work from CARDIA by using a longer duration of follow-up (30 years), a more extensive set of neuropsychological tests to assess different cognitive domains, and assessing the association of vascular risk at different timepoints from young adulthood to midlife with midlife cognition and gait to detect the window of vulnerability at which vascular risk exposure may be most deleterious to brain health.

Importantly, the current study shows a strong link between combined exposure to several vascular risk factors during young adulthood and gait in midlife, whereas only year 7 vascular health was associated with cognitive function, which was no longer significant after correction for multiple comparisons. Furthermore, vascular health remained associated with gait throughout the follow-up period, while vascular health was associated with dCA only at younger adulthood. These findings suggest that there may be different mechanisms by which vascular health impacts gait across life course and this needs to be addressed in future studies. Furthermore, our results may suggest gait as a potential more sensitive marker of vascular damage during midlife. Taken together, our findings highlight the idea that primordial prevention of vascular risk exposure may be more effective than secondary prevention for adverse brain outcomes.⁴² Currently, the presence of ideal cardiovascular health in the United States is extremely low at approximately 5%,²² hence, it is important to recognize the implications of ideal cardiovascular health in middle age because these individuals have greater longevity, longer morbidity-free survival, greater health-related quality of life in older age, and substantially lower health-care costs later in life.²² Future studies are, therefore, needed to determine the cerebrovascular effects of early preventive strategies on vascular risk factors among young individuals. Given the growing body of evidence that vascular disturbances are implicated in the pathology of dementia including in Alzheimer's disease (AD),¹¹ future work should address whether modification of vascular risk factors during early adulthood could prevent the development of dementia and AD in older age.

When analyzing the effect of individual vascular risk factors, we observed that only higher fasting glucose during follow-up was associated with less efficient dCA at midlife. This is consistent with previous findings in which it has been shown that cerebral autoregulation is impaired among diabetic patients.⁴³ Alternatively, our results may also indicate that the overall burden of several vascular risk factors is more deleterious to cerebrovascular hemodynamics, compared to a single vascular risk factor. Moreover, we observed that higher blood pressure during follow-up was strongly associated with worse gait and cognitive function during midlife. These findings are consistent with our recent work, showing that higher cumulative exposure to blood pressure beginning in young adulthood associates with worse gait and cognitive function in midlife.⁷ Given the failure of current large randomized clinical trial of SPRINT-MIND to reduce dementia incidence after intensive blood pressure treatment in individuals aged 68 ± 9 years old,⁴⁴ future work should determine whether sustained interventions through earlier stages of life are more effective compared to interventions among older adults.

Emerging findings suggest that dysfunction in cerebrovascular hemodynamics may be a key link that connects vascular risk exposure with dementia and cognitive impairment.^{1,2,11} In support of this premise, evidence from animal and human studies indicates that vascular risk factors dampen vasoactive capability (dilation, constriction) of cerebral vessels, functional hyperemia, and cerebrovascular autoregulation.¹¹ The findings from the present study support a moderating effect of cerebral autoregulation on the link between young adulthood vascular risk exposure, and gait. Somewhat surprisingly, however, the link between young adulthood vascular risk and cognition was not moderated by cerebral autoregulation. Consistent with these observations, previous studies showed that gait abnormalities may

precede cognitive decline, and that gait may be an earlier marker of brain injury than cognition.⁸ For example, Buracchio et al. showed that slowing of gait speed was accelerated up to 12 years prior to development of mild cognitive impairment in 204 participants from the Oregon Brain Aging Study.⁴⁵ Slowing of gait preceded cognitive decline in all domains in 1478 participants from the Mayo Clinic Study of Aging.⁴⁶ Given that cognitive function is relatively preserved in the middle-aged CARDIA participants, gait may be a useful clinical biomarker of early cerebrovascular alterations in a subclinical state. It should also be noted that early structural and morphometric changes of the brain, such as WMH, may provide another mechanistic explanation for the link between vascular risk factors and gait. Consistent with this premise, we have recently shown that WMH moderate the link between young-to-midlife cumulative exposure to higher blood pressure and gait in midlife, but not cognition.⁷ Moreover, we have also shown that morphometric changes in basal ganglia and thalamus, rather than volume changes, may represent earlier manifestation of blood pressure exposure on the brain that impact gait in midlife.⁴⁷ Future studies, therefore, should further explore the effect of overall vascular health on WMH or brain morphometric changes in the context of gait and cognition.

The strengths of this study include the long follow-up consisting of standardized measurements of vascular risk factors in a community-based, biracial cohort of young individuals. We also consider the limitations of this study. Cerebral autoregulation, extended cognitive, and gait measures were only assessed at year 30 and we were not able to address changes in cerebral autoregulation or gait and cognition over time. Given the relatively small sample size of our study, future prospective and larger scale studies are needed to better elucidate the mechanisms underlying the link between vascular risk factors and brain health across the lifespan. Furthermore, our vascular health metrics did not include diet, which may also be associated with the outcomes measured in this study. Last, it should be noted that given the observational nature of this study causality cannot be inferred.

5 | CONCLUSION

In summary, the present study shows that higher vascular risk exposure during young adulthood is associated with less efficient cerebral autoregulation, gait, and cognition in midlife. Furthermore, cerebral autoregulation moderated the association between early-life vascular risk exposure and gait, but not cognition. Taken together, these results emphasize the importance of early life vascular risk exposure on brain health and highlight the need for primordial prevention of risk factors during early adulthood. The assessment of vascular and brain health throughout the life course is essential for the prevention of age-related disability and cognitive impairment in our aging population.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Research in context

1. **Systematic review:** The authors reviewed the literature using traditional (e.g., PubMed) sources. While the link between vascular risk exposure and brain health is less studied during young adulthood, numerous publications have assessed this association among older adults. These relevant citations are appropriately cited.
2. **Interpretations:** Our findings show that higher exposure to vascular risk factors in young adulthood, but not in midlife, is associated with worse brain health as assessed by cerebral autoregulation, gait, and cognition. Furthermore, we show that alterations in cerebral autoregulation may be a key link connecting vascular risk exposure and brain health in midlife.
3. **Future directions:** Future work should assess whether primordial prevention of vascular diseases impact brain health in later life. Assessment of vascular and brain health throughout the life course is essential for preventing age-related disability and cognitive impairment in our aging population.

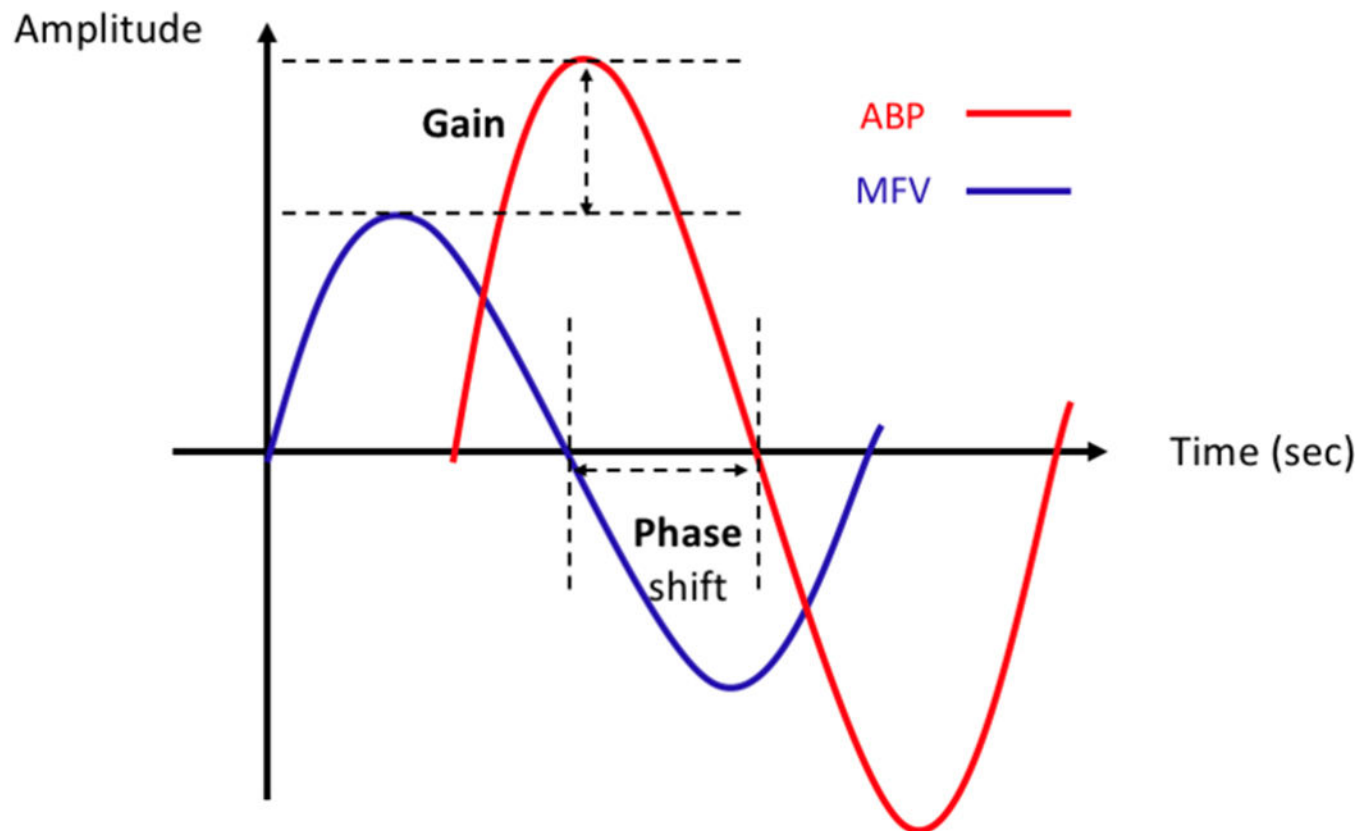


FIGURE 1.

Transfer function measures of dynamic cerebral autoregulation derived from transcranial Doppler ultrasound. Cerebral autoregulation refers to the ability of cerebral vessels to maintain relatively constant blood flow to the brain despite fluctuations in arterial blood pressure. This relationship between beat-to-beat fluctuations in arterial blood pressure and mean flow velocity in the cerebral vessels is quantified using transfer function analyses to derive gain and phase values. Gain (amplitude) quantifies the damping effect of cerebral autoregulation on the magnitude of blood pressure oscillations. The phase shift represents the temporal difference between transmissions of oscillation from mean arterial pressure to mean flow velocity. ABP, arterial blood pressure; MFV, mean flow velocity

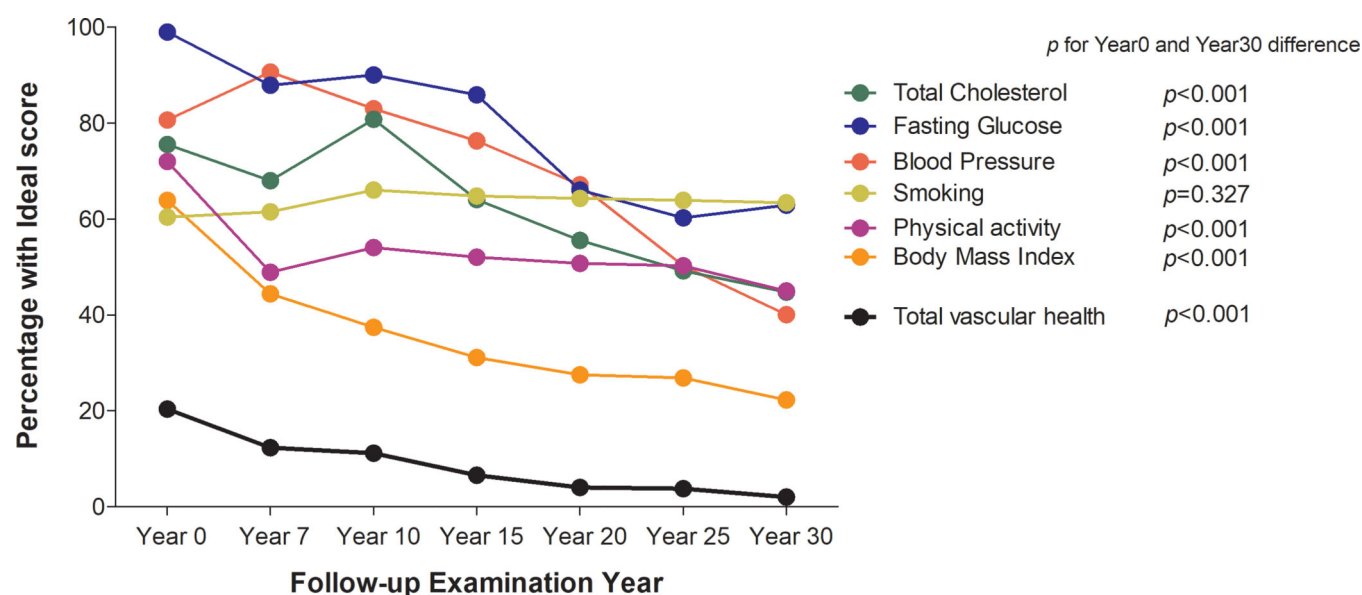


FIGURE 2.

Frequency of ideal vascular health components from young adulthood to midlife. The figure shows the percentage of participants with ideal (2 points) vascular health components from baseline up to year 30 examination. Number of participants with ideal score for blood pressure, total cholesterol, fasting glucose, body mass index, smoking, and physical activity were $n = 158, 149, 194, 124, 120,$ and 142 , respectively, for year 0; $n = 159, 120, 141, 76, 110,$ and 86 , respectively, for year 7; $n = 145, 143, 150, 66, 116,$ and 96 , respectively, for year 10; $n = 143, 121, 152, 59, 121,$ and 99 , respectively, for year 15; $n = 124, 103, 116, 51, 115,$ and 94 , respectively, for year 20; $n = 97, 95, 110, 51, 121,$ and 95 , respectively for year 25; and $n = 79, 88, 119, 44, 126,$ and 88 , respectively, for year 30

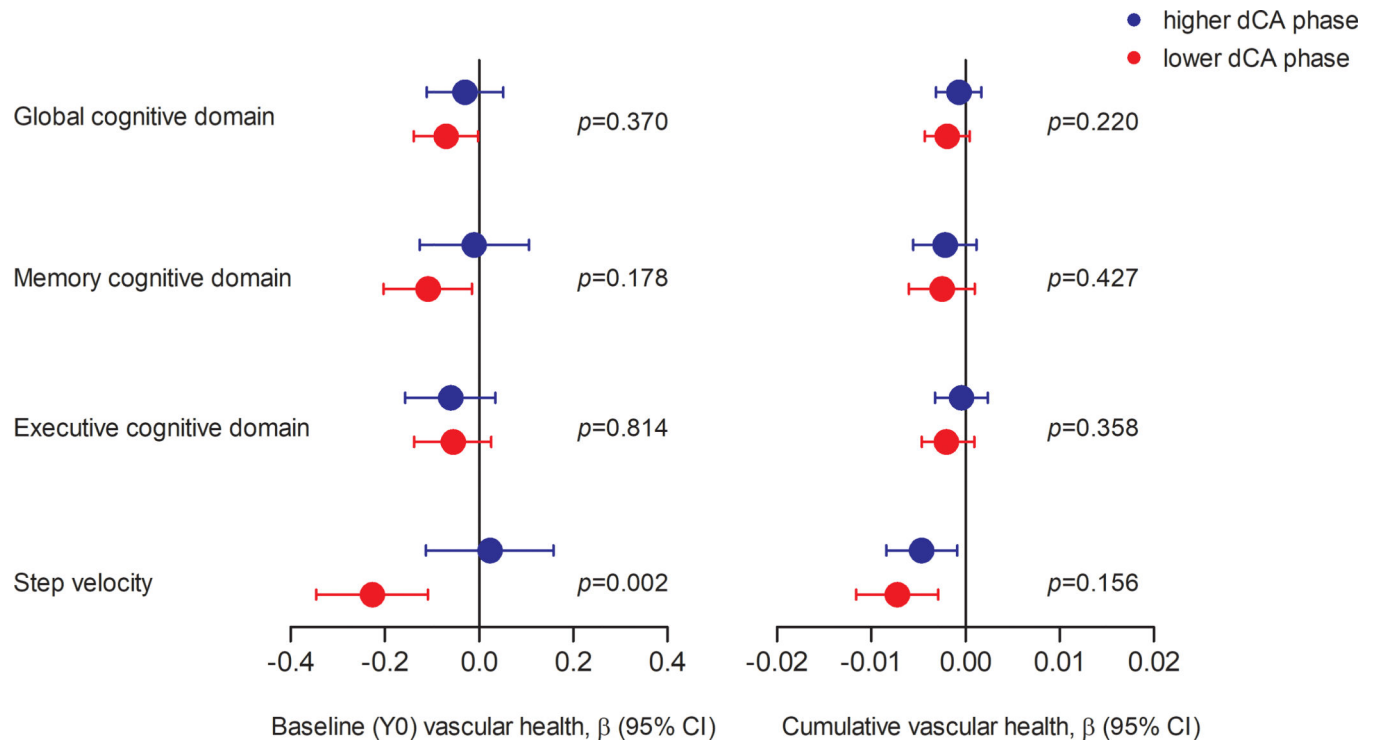


FIGURE 3.

Association of vascular health during young adulthood with midlife gait and cognition, stratified for those with lower and higher dCA phase. The β represents unstandardized regression coefficients per 1 score decrease in vascular health. Step velocity values were transformed to z-scores. All analyses were adjusted for age, sex, race, and height (for analyses using gait as outcome) or education (for analyses using cognition as outcome). P -values show p for interaction. dCA phase was divided into lower and higher groups at the median of dCA phase. dCA, dynamic cerebral autoregulation

Characteristics of study participants

TABLE 1

	Year 0 examination (n = 196)	Year 30 examination (n = 191)	P-value
Demographics			
Age, years	24 ± 4	54 ± 4	<.001
Female, %	45	45	-
Black, %	45	45	-
Education, years	14 ± 3	15 ± 3	<.001
Cardiovascular risk factors			
Body mass index, kg/m ²	24 ± 4	30 ± 7	<.001
Smoking status, %			
Current	28	14	<.001
Former	11	21	.002
Total cholesterol, mg/dL	177 ± 32	192 ± 37	<.001
SBP, mmHg	108 ± 10	120 ± 15	<.001
DBP, mmHg	66 ± 10	73 ± 11	<.001
Fasting glucose, mg/dL	81 ± 8	102 ± 28	<.001
Physical activity, exercise units, median (IQR)	468 (266-729)	264 (126-475)	<.001
Diabetes medication use, %	0	9	<.001
Cholesterol-lowering medication use, %	0	19	<.001
Antihypertensive medication use, %	1	27	<.001
Total vascular health score, range	5-12	3-12	<.001
Measures of cerebrovascular function			
dCA Phase by TCD, degree ^a	-	41 ± 24	-
dCA Gain by TCD, cm/s/mmHG ^a	-	0.70 ± 0.3	-
Gait step velocity, cm/sec ^a	-	121 ± 21	-
Executive cognitive domain	-	-0.02 ± 0.7	-
Memory cognitive domain	-	0.01 ± 0.8	-
Global cognitive domain	-	-0.002 ± 0.6	-

Notes: Data are expressed as mean ± SD or %, unless otherwise stated.

^aThree subjects had missing TCD measurement, and another three subjects had missing step velocity measurement.

P-values were calculated using paired *t*-test or Wilcoxon signed ranked test (depending on the distribution of data) for continuous variables; and using McNemar test for categorical variables.
Abbreviations: DBP: diastolic blood pressure; dCA: dynamic cerebral autoregulation; IQR: interquartile range; SBP: systolic blood pressure; SD: standard deviation; TCD: transcranial Doppler.

TABLE 2
Association between vascular health from young adulthood to midlife with midlife dynamic cerebral autoregulation

<i>B (95% CI) per 1 score decrease in vascular health</i>				
Vascular health	dCA phase, degree	P-value	dCA gain, cm/s/mmHg	P-value
Y ₀ examination	-3.12 (-5.51, -0.74)	.011 *	0.012 (-0.02, 0.04)	.403
Y ₇ examination	-3.69 (-5.99, -1.39)	.002 *	-0.001 (-0.03, 0.03)	.948
Y ₁₀ examination	-1.31 (-3.32, 0.70)	.201	-0.005 (-0.03, 0.02)	.736
Y ₁₅ examination	-1.46 (-3.60, 0.68)	.180	0.016 (-0.01, 0.04)	.195
Y ₂₀ examination	-1.54 (-3.44, 0.35)	.110	0.010 (-0.01, 0.03)	.386
Y ₂₅ examination	-2.39 (-4.31, -0.48)	.015	0.023 (-0.001, 0.05)	.050
Y ₃₀ examination	-1.28 (-3.16, 0.59)	.179	-0.005 (-0.03, 0.02)	.686
CumVH score	-0.11 (-0.03, -0.19)	.010 *	0.0001 (0.001, -0.001)	.489

Notes: Data shows unstandardized regression coefficient (95% CI) for the relation between vascular health score at each visit and dCA phase or gain at year 30. All analyses were adjusted for age, sex, and race.

* indicates a *P*-value < .05 after adjustment for multiple comparison using the false discovery rate approach.

Abbreviations: CI, confidence interval; cumVH score: cumulative vascular health score; dCA: dynamic cerebral autoregulation; Y₀, Y₇, ..., Y₃₀ examination: year 0, year 7, ..., year 30 examination.

TABLE 3
Association of vascular health from young adulthood to midlife with midlife gait and cognition

<i>B (95% CI) per 1 score decrease in vascular health</i>				
Vascular health	Gait step velocity (cm/sec)	Executive cognitive domain	Memory cognitive domain	Global cognitive domain
Y ₀ examination	-2.80 (-4.68, -0.92)*,§	-0.06 (-0.12, 0.002)	-0.05 (-0.12, 0.02)	-0.05 (-0.10, 0.004)
Y ₇ examination	-3.27 (-5.05, -1.49)*,§	-0.06 (-0.12, -0.01)*	-0.05 (-0.13, 0.02)	-0.05 (-0.10, -0.005)*
Y ₁₀ examination	-2.90 (-4.66, -1.15)*,§	-0.02 (-0.07, 0.04)	-0.03 (-0.10, 0.04)	-0.02 (-0.07, 0.03)
Y ₁₅ examination	-2.41 (-4.17, -0.65)*,§	-0.04 (-0.09, 0.01)	-0.06 (-0.12, 0.01)	-0.04 (-0.08, 0.007)
Y ₂₀ examination	-2.44 (-4.06, -0.83)*,§	-0.02 (-0.07, 0.04)	-0.03 (-0.09, 0.03)	-0.02 (-0.07, 0.02)
Y ₂₅ examination	-2.71 (-4.21, -1.22)*,§	-0.01 (-0.06, 0.04)	-0.04 (-0.10, 0.01)	-0.02 (-0.06, 0.02)
Y ₃₀ examination	-1.88 (-3.35, -0.41)*	-0.009 (-0.06, 0.04)	-0.03 (-0.09, 0.02)	-0.02 (-0.06, 0.02)
CumVH score	-0.14 (-0.20, -0.07)*,§	-0.002 (-0.002, 0.001)	-0.002 (-0.005, 0.00002)	-0.002 (-0.003, 0.0003)

Notes: Data show unstandardized regression coefficient (95% CI) for the relation of vascular health score at each visit with gait and cognition at year 30. All analyses were adjusted for age, sex, race, and education (where cognition was the primary outcome) or height (where gait was the primary outcome).

* Indicates a *P*-value < .05.

§ Indicates a *P*-value < .05 after adjustment for multiple comparison using the false discovery rate approach.

Abbreviations: CI, confidence interval; cumVH score: cumulative vascular health score.; Y₀, Y₇, ..., Y₃₀ examination: year 0, year 7, ..., year 30 examination.