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Association of the Northern Manhattan Study Global Vascular Risk Score and Successful Aging

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Abstract

Objectives—To examine the association between successful aging without subsequent cognitive decline (SA-ND) and the Northern Manhattan Study (NOMAS) global vascular risk score (GVRs), which is predictive of stroke, MI, and vascular death.

Design—Prospective cohort study.

Setting—A stroke-free sample of Hispanic, black, and white participants living in the same community enrolled in an MRI substudy of NOMAS, a population-based prospective cohort study.

Participants—A cognitive screen was administered at baseline and at enrollment in the MRI substudy (n=1,290).

Measurements—SA-ND was based on disease, disability, and cognitive function. The GVRs includes age, sex, race-ethnicity, waist circumference, alcohol intake, smoking, physical activity, blood pressure, antihypertensive medication use, fasting blood sugar, lipid levels, and peripheral vascular disease.

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Conflict of Interest

Results—Data at baseline and follow-up were available for 1,162 participants (mean age 70 ± 9 years; 61% women; 13% white, 16% black, 69% Hispanic; mean GVRS 8.6 ± 0.9). Logistic regression, adjusted for education, socioeconomic status, and follow-up time, showed that the odds of SA-ND were 38% greater for each additional one-point decrease on the GVRS (OR=1.38, 95% C.I. 1.17-1.61; $p < 0.0001$). We also observed an inverse dose-response for quartiles of GVRS with SA-ND. Greater diastolic blood pressure among those on antihypertensive medication, and a history of claudication or peripheral arterial disease, were inversely associated with SA-ND in our fully adjusted model ($p < 0.005$).

Conclusion—Potentially modifiable vascular risk factors were independently associated with SA-ND in a multi-ethnic community-based sample. Improvements in global vascular risk scores could help promote healthy longevity in the aging population.

Keywords

Successful Aging; Cognitive Aging; Global Vascular Risk; Vascular Risk Factors

INTRODUCTION

Successful aging is a multidimensional process, involving physical, functional, and psychosocial domains [1], and entails living free of diseases that adversely affect quality of life despite some physical limitations. Successful *cognitive aging* further implies the avoidance of diseases that affect cognition – including vascular cognitive impairment (VCI), defined as cognitive impairment contributed to by vascular disease.[2] While aging is unavoidable, VCI is potentially preventable if means to identify those at risk are available and the risk factors themselves are modifiable.

Heart disease and stroke are the leading causes of death in older adults, and vascular disease is an important contributor to cognitive decline.[3] More than one-quarter of American adults have multiple risk factors for heart disease and stroke, while the percentage of adults with no risk factors, and the proportion that engage in healthy lifestyles, is low.[4] Clustering of cardiovascular risk is associated not only with physical disease and disability, but also with cognitive health. For instance, participants of the Cardiovascular Risk Factors, Aging, and Dementia (CAIDE) study who were obese with high systolic blood pressures and total cholesterol had six times the risk of dementia compared to those with no risk factors.[5] The metabolic syndrome, perhaps the most well known cluster of cardiovascular risk factors, is also a risk factor for accelerated cognitive aging (2).[6-7] A number of cardiovascular risk scores have been developed and include determinants such as age, hypertension, hyperlipidemia, and a history of smoking.[8] More recently, behavioral and anthropometric indices have been used to estimate risk.[9-11] In the Northern Manhattan Study (NOMAS), an urban population that includes whites, blacks, and Hispanics determined to be stroke-free at baseline, continuous measures of obesity, lipids, fasting glucose, and blood pressure, as well as quantification of physical activity and alcohol consumption – the Global Vascular Risk Score (GVRS) – improved upon traditional Framingham measures in predicting incident stroke, MI, or vascular death.[11] In providing improved risk stratification, such models allow for better targeting of preventive therapies.

Central to successful cognitive aging is a protective vascular risk factor profile, yet little is known about the effect of global vascular risk. As the NOMAS GVRS predicts the overall combined risk of adverse vascular outcomes, we hypothesized that it would be inversely associated with having successful aging and no cognitive decline (SA-ND) in this multi-ethnic stroke-free cohort.

METHODS

Study Design

The Northern Manhattan Study—NOMAS is a population-based cohort study that includes 3,298 stroke-free participants identified from random digit dialing using dual-frame sampling to identify published and non-published telephone numbers. People were eligible if they had never been diagnosed with a stroke, were above 39 years of age, and were residents of Northern Manhattan for at least 3 months in a household with a telephone. Those eligible from the telephone sample were recruited for in-person assessments between 1993 and 2001 with an overall response rate of 68%. [11]

Definition of Successful Aging at Baseline—The current study is limited to NOMAS participants who were administered the MMSE twice, once at baseline and once at the time of enrollment in an MRI substudy. Criteria for inclusion into the substudy were as follows: (1) age older than 55 years; (2) no contraindications to MRI; and (3) provided written informed consent. Participants were enrolled in the substudy an average of 6.1 ± 3.5 years after baseline. Within this sample we classified participants at the time of their baseline enrollment in NOMAS (between 1993 and 2001) based on disease, disability, and cognitive function using definitions of successful aging from other large cohort studies. [1, 12]

Successful aging (SA) at baseline was defined as:

1. no history of cancer, chronic obstructive pulmonary disease, or cardiac disease (myocardial infarction, coronary artery disease, congestive heart failure, atrial fibrillation, or valvular heart disease) – the sample was stroke-free by NOMAS enrollment criteria and remained stroke free at the time of the second MMSE measurement;
2. a creatinine clearance rate of ≥ 45 mL/min;

Creatinine clearance rate (CCL) was derived from the Cockcroft-Gault formula [13]:

$$\text{CCL} = (140 - \text{age}) / (\text{serum creatinine in mg/dL}) \times (\text{weight in kg} / 72) \times (0.85 \text{ for women})$$

Excluding those with chronic kidney disease is a novel part of our definition of SA. Chronic kidney disease was found in NOMAS to be a significant risk factor for stroke and combined vascular events, especially in blacks. [14] And, more recently, decreased kidney function was associated with cognitive decline even in those with mild chronic kidney disease in our cohort. [15] We chose a CCL of >45 mL/min based on results from several large cohorts showing that the risks of death, cardiovascular events, and hospitalization rise sharply below a GFR of $45 \text{ mL/min}/1.73\text{m}^2$, as do the odds of incident cognitive impairment. [16-17]

- 3) a global score of ≥ 95 on the Barthel Activities of Daily Living scale; and
- 4) a baseline Mini-Mental State Examination (MMSE) score above education-specific cutoffs (>17 for those with 8 years or less of education or >23 for at least 9 years).

In addition to advancing age, socioeconomic factors, particularly race/ethnicity and level of education, may influence performance on the MMSE independent of other conditions. [18-19] Therefore, to avoid misclassification, the MMSE cutoff for this study was based on level of education as determined by analyses comparing educational attainment, MMSE score, and in depth cognitive assessments in our multi-ethnic cohort (data not shown).

Participants were then considered to have successful aging without cognitive decline (*SA-ND*) if they continued to meet the above disease and disability criteria and declined less than 3 points on the MMSE [20-21] between baseline and follow-up cognitive testing at enrollment in the MRI substudy.

Global Vascular Risk Score (GVRs)—The NOMAS GVRs has been described previously and improved upon the Framingham risk score in predicting stroke, MI, and vascular death in the NOMAS multi-ethnic urban sample.[11] In the prior study, a survival model was constructed to predict combined cardiovascular outcomes, which included stroke (ischemic or intracerebral hemorrhage), myocardial infarction (MI), and vascular death. The following variables contributed significantly to model fit and are included in the GVRs: age, sex, black race, Hispanic ethnicity, waist circumference, moderate alcohol use, current and former smoking, moderate to heavy physical activity, the interaction between sex and moderate to heavy physical activity, systolic and diastolic blood pressures, the interaction between diastolic blood pressure and anti-hypertensive medication use, peripheral vascular disease, fasting blood sugar, and total cholesterol to HDL ratio. In the NOMAS cohort, GVRs (calculated at baseline) ranged from 4.4 to 11.6 (mean 8.6 ± 1.0 standard deviation) and each individual's score was calculated from a multivariable regression model.[11] A GVRs of 9.0 implied a 10-year probability of experiencing a vascular event of 0.20, a GVRs of 8.2 implied a 10-year probability of 0.10, and a GVRs of 6.6 implied a 10-year probability of 0.02. Thirty-five percent of our population had a GVRs of at least 9.0.

Statistical Analysis

We used logistic regression to examine the relationship between GVRs (using data at enrollment in the MRI substudy) and the odds of achieving the *SA-ND* outcome. Generalized linear models were used for regression, adjusting for duration of follow-up time (time between baseline and follow-up cognitive assessment), with other covariates included if associated with *SA-ND* and GVRs at a p-value ≤ 0.20 . We used SAS statistical software (version 9.2, SAS Institute, Cary, NC) and significance was assessed according to a pre-set two-sided alpha level of 0.05, with the exception of covariate selection.

RESULTS

Sample Characteristics

Of the 1,290 individuals in the NOMAS MRI substudy cohort, data to determine *SA-ND* status were available in 1,162 (90%). The prevalence of *SA-ND* in this sample was 37%. The number of persons meeting each of the disease, disability, and cognition criteria in our definition of *SA-ND* is shown in **Table 1**. Characteristics, including components of the GVRs, of the overall sample and by *SA-ND* status are presented in **Table 2**. The average age of participants was 70 ± 9 years, with 51% between ages 70 and 96; 13% were white, 16% black, and 69% Hispanic, and 61% were women. Mean GVRs score was 8.6 ± 0.9 .

Global Vascular Risk Score and Successful Aging

Examining the GVRs as a continuous measure, we found an inverse association such that that there was a greater odds of *SA-ND* with lower (better) GVRs. For each additional one-point decrease on the GVRs, the odds of *SA-ND* were 38% greater (OR=1.38, 95% C.I. 1.17-1.61; $p < 0.0001$). The association was strengthened after adjustment for level of education and socioeconomic status (OR=1.56, 95% C.I. 1.32-1.85; $p < 0.0001$). Results of logistic regression analyses comparing the odds of *SA-ND* across quartiles of GVRs, adjusted for length of follow-up time, are shown in **Figure 1**. Compared to the fourth quartile of GVRs (>9.3), the odds of *SA-ND* were 1.5 times greater for the third quartile of

GVRS, 1.6 times greater for the second quartile, and more than three-fold greater for the lowest quartile of GVRS.

GVRS Components and Successful Aging

We also examined individual components of the GVRS to determine key factors associated with *SA-ND*, adjusting for education, health insurance status, and length of follow-up time. Older age, greater diastolic blood pressure among those on antihypertensive medication, and a history of claudication or peripheral arterial disease were each independently associated with a lower likelihood of *SA-ND* (Table 3).

Comparison with Framingham Risk Score

We also explored the relationship between the Framingham Risk Score for coronary heart disease (FRS) and *SA-ND* to compare the GVRS with an established risk prediction tool [22]. Data were available to calculate the FRS in 1,138 (98%) of the 1,162 participants with *SA-ND* data. The mean FRS score was 8.2 ± 3.6 (range 1.3 to 12.8), and was significantly lower (better) in those who experienced *SA-ND* (7.8 ± 3.6 vs. 8.4 ± 3.5 ; $p=0.003$). Examining the FRS as a continuous variable, we found an inverse association such that each point decrease on the FRS was associated with 6% greater odds of *SA-ND* (OR=1.06, 95% C.I. 1.02-1.10; $p=0.0009$). The odds were marginally decreased after adjusting for level of education and socioeconomic status (OR=1.05, 95% C.I. 1.01-1.09; $p=0.007$).

DISCUSSION

A low vascular risk factor profile does not guarantee successful aging, but the elevated mortality and morbidity associated with vascular outcomes suggests it may be a key determinant. We found that for NOMAS participants the odds of *SA-ND* was 38% greater for each additional one-point decrease on the GVRS, and observed an inverse dose-response with greater odds of *SA-ND* for the lowest quartiles of GVRS. The odds of *SA-ND* was also greater for lower FRS, but the GVRS was more strongly associated with *SA-ND* in our cohort, further suggesting that it may be more applicable to a race/ethnically diverse urban sample.

While the literature supports an association between the presence of vascular risk factors and a lower likelihood of *SA*, this study is one of the first, to our knowledge, to examine the effect of global vascular risk. Given the importance of avoiding vascular outcomes such as stroke, myocardial infarction, peripheral vascular disease, and vascular death, global risk scores such as the GVRS add value if they identify those at risk early on. A greater burden of cardiovascular risk factors increases with age, limiting healthy longevity, and a poor cardiovascular risk profile is strongly associated with cardiovascular events and cardiovascular mortality.[3, 23] Individuals with more cardiovascular risk factors also have lower health-related quality of life, independent of sociodemographic characteristics and other comorbidities, and are at least 40% less likely to be employed, whereas a beneficial cardiovascular risk profile is related to greater productivity and lower Medicare costs in later years.[24-26]

The value of the GVRS and other risk scores is that it quantifies risk and translates comorbidities into a useful number that provides a target for intervention. Here, we also explored the individual components that were most associated with *SA-ND* in our cohort and found that age, a history of claudication or arterial disease, and diastolic blood pressure among hypertensives, were each independently associated with *SA-ND*. Peripheral arterial disease, along with other markers of generalized atherosclerosis such as carotid artery intima and media thickness, angina pectoris, and ankle-arm index, has implications for overall

cardiovascular health, including an increased risk of vascular and non-vascular events, and has been related to disability, cognitive impairment, and unsuccessful aging.[27-28] Up to 90% of PAD patients have angiographically-determined coronary artery atherosclerosis, and up to half have evidence of cerebrovascular disease. Comorbid cardiovascular risk factors including smoking and diabetes are more common in these individuals as well [29]. Yet, patients with PAD tend to be undertreated in regards to risk factor modification, and screening for PAD is non-invasive and widely available [30].

We also found that, among individuals on antihypertensive medication, each 10-mm Hg of diastolic blood pressure was associated with a 6% lower odds of *SA-ND*. While both systolic and diastolic blood pressures have been related to cardiovascular morbidity and mortality, in older adults cardiovascular risk appears to be directly proportional to systolic blood pressure, and eventual health outcome inversely proportional to diastolic blood pressure [31]. However, we have recently reported that diastolic and not systolic pressure was associated with greater white matter lesion load. Diastolic blood pressure has also been independently associated with cognitive decline, and subclinical cerebral infarction and ischemic white matter damage may mediate this relationship [32]. Diastolic blood pressure may reflect peripheral vascular resistance, and thus be more specific to small vessel damage than systolic pressure that is most affected by large vessel stiffness. However, a history of hypertension treatment confers cardiovascular risk even after adjustment for blood pressure and other traditional risk factors, though it is not known whether this is due to an incomplete reversal of hypertension-induced end-organ damage, or a possible deleterious effect of medications.[33] The findings from our study indicate that greater diastolic blood pressure may decrease the likelihood of *SA* in those on antihypertensive drugs (i.e., with established hypertension). However, because hypotension, too, affects brain perfusion and has been shown to worsen vascular and cognitive outcomes, more research is needed to determine the optimal blood pressure levels that should be targeted to achieve *SA*.[34]

We acknowledge several study limitations. The NOMAS GVRs has not been validated in other cohorts, although it is a strength that the score is applicable to this urban multi-ethnic U.S. population. We only included people who were enrolled in the MRI substudy, and therefore the substudy sample was somewhat healthier than the overall cohort due to a survivor effect typical of MRI substudies (i.e., participants had to be well enough to visit our center). We acknowledge that our methods would tend to underestimate the effect of vascular risk factors because of this healthy cohort effect. However, our findings do not depend on loss to follow-up related to the outcome.

Successful cognitive aging is a multidimensional construct for which there is no currently accepted standard definition. For this study, we created a definition of successful aging that incorporates both physical well-being and cognitive abilities. We considered only those diseases that are major causes of mortality among older adults – cancer, chronic lung disease, heart disease, and stroke. Additionally, our definition of *SA* is unique in that we included chronic kidney disease as a novel component - not including this in our definition would have increased the number of people in the *SA* category. However, we believe this would bias our findings toward the null by including less successful agers in the *SA* category. Otherwise, we chose similar criteria to other large studies and this aids in comparing across them. As the manner in which successful cognitive aging is defined and measured affects its prevalence and observed associations, further research is needed to refine the concept of successful cognitive aging. Consideration of biopsychosocial factors including socioeconomic status, social support, quality of life, and depressive symptoms alongside novel indicators of disease and disability such as global vascular risk, may lead to a more robust definition of successful cognitive aging replete with opportunities to modify the aging process. Current estimates suggest that 44 million adults in the United States are

obese and 50 million are hypertensive, and the prevalence of cardiovascular disease is expected to rise as other risk factors, such as obesity, diabetes, and dyslipidemia become ever more prevalent.[35-37] Our data suggest that the GVRs provides meaningful information about the risk of SA-ND in a multi-ethnic urban U.S. sample, and that identification of hypertension and PAD may be of particular importance in estimating risk of unsuccessful cognitive aging. Application of existing treatments for cardiovascular risk reduction, coupled with primary prevention efforts, could potentially modify the course of cognitive aging and further studies are needed to clarify this. Our results stress the importance of considering the range of global vascular risk instead of isolated cardiovascular risk factors, given that even moderate increases in risk are met with substantial decreases in the odds of SA. With early detection of at-risk persons crucial to the success of medical management and behavioral interventions, comprehensive global risk assessment tools such as the GVRs, if found to predict SA, may be an effective means of guiding comprehensive public health efforts.

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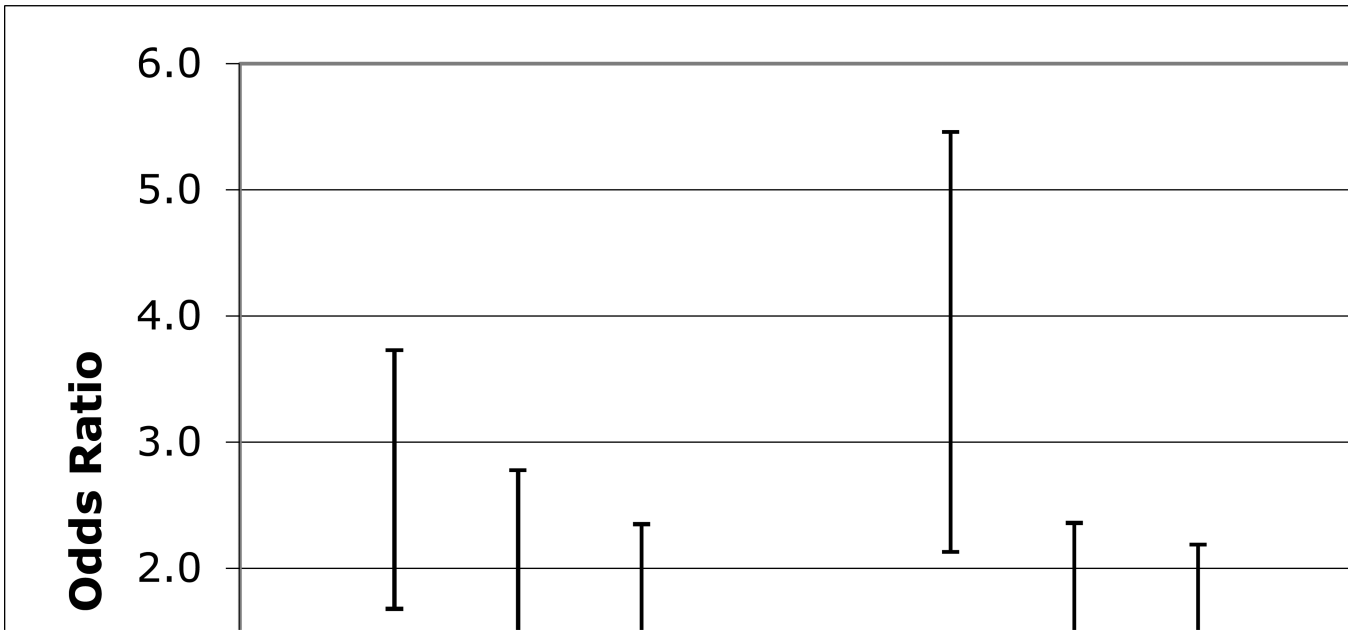


Figure 1.
Odds of Successful Aging – No Decline by Quartile of GVRs
We observed a dose response for increasing quartiles of GVRs. Compared to the highest quartile of GVRs (9.3+), the odds of successful aging without cognitive decline (SA-ND) were 1.50 (95% C.I. 1.03-2.19) times greater for the third quartile of GVRs, 1.63 (1.12-2.36) times greater for the second quartile, and 3.25 (2.13-4.94) times greater for the lowest quartile. Odds ratios in Model 1 are adjusted for length of time between baseline and follow-up cognitive testing only, and in Model 2 for years of education, health insurance status, and follow-up time.

Table 1

Criteria for Successful Aging – No Decline

	% (N)
Disease and Disability	49 (565)
No cancer	93 (1076)
No chronic obstructive pulmonary disease	91 (1053)
No cardiac disease	83 (966)
Creatinine clearance rate \geq 45 mL/min	82 (957)
Barthel ADL score \geq 95	95 (1098)
Cognition	87 (1011)
Baseline MMSE $>$ 17 for \leq 8 years of education or $>$ 23 for $>$ 9 years of education	96 (1112)
3-point decline on MMSE at follow-up	89 (1037)

Table 2

Sample Characteristics^{*}

Global Vascular Risk Score (GVRS) And Its Components [^]	Overall (N=1,162)	SA-ND ^{**}		<i>p</i> -value
		Yes (N=430)	No (N=732)	
GVRS	8.6 ± 0.9	8.5 ± 0.9	8.8 ± 0.8	<0.001
Age (years)	70 ± 9	70 ± 8	71 ± 10	0.12
Sex				<0.001
Male	39 (451)	45 (195)	35 (256)	
Race/ethnicity				0.60
Non-Hispanic white	14 (157)	13 (54)	14 (103)	
Non-Hispanic black	16 (186)	17 (72)	16 (114)	
Hispanic	70 (796)	69 (299)	68 (497)	
Moderate alcohol drinker	41 (476)	43 (186)	40 (290)	0.30
Current smoker	16 (190)	18 (78)	15 (112)	0.24
Former smoker	36 (419)	36 (153)	36 (266)	0.69
Never smoker	48 (553)	47 (202)	48 (351)	0.62
Moderate or heavy physical activity	10 (112)	11 (46)	9 (66)	0.38
Among men	4 (52)	5 (23)	4 (29)	0.29
Waist circumference (inches)	38 ± 5	38 ± 5	38 ± 5	0.17
History of leg pain or arterial disease	12 (143)	8 (33)	15 (110)	<0.001
Systolic blood pressure (mmHg)	136 ± 17	137 ± 17	136 ± 17	0.31
Diastolic blood pressure (mmHg)	78 ± 10	78 ± 9	78 ± 10	0.24
Diastolic blood pressure (mmHg) among those on anti-hypertensive medication (N=472)	80 ± 10	81 ± 9	79 ± 10	0.12
Glucose (mg/dL)	101 ± 34	101 ± 36	101 ± 33	0.89
Total cholesterol to HDL ratio	4 ± 2	4 ± 2	4 ± 1	0.06
Other Covariates				
Education (years)	10 ± 5	10 ± 5	9 ± 5	0.14
Medicaid or no insurance	49 (469)	45 (194)	38 (275)	0.03
Time between baseline and follow-up cognitive testing (years)	6 ± 4	7 ± 2	5 ± 4	<0.001

^{*} % (N) or Mean ± SD

^{**} Successful aging without cognitive decline

[^] All GVRS components from validated vascular risk prediction model are included [9].

Table 3Relationship Between GVRs Components[^] and Odds of Successful Aging – No Decline^{*}

Component	OR (95% C.I.)	p-value
Age (per year)	0.95 (0.94-0.97)	<0.0001
Men	1.06 (0.77-1.46)	0.74
Race-ethnicity		
Hispanic	1.59 (0.94-2.70)	0.08
Black	1.26 (0.75-2.13)	0.38
White	reference	--
Moderate alcohol consumption	1.13 (0.84-1.52)	0.44
Current smoker	0.99 (0.72-1.37)	0.97
Former smoker	1.10 (0.73-1.65)	0.65
Never smoker	reference	--
Moderate or heavy physical activity	0.90 (0.47-1.75)	0.77
Among men	1.28 (0.49-3.38)	0.61
Waist circumference (per inch)	1.02 (0.99-1.05)	0.15
History of leg pain or arterial disease	0.39 (0.25-0.61)	<0.0001
Systolic blood pressure (per 10 mmHg)	1.05 (0.96-1.16)	0.29
Interaction between diastolic blood pressure (per 10 mmHg) and anti-hypertensive medication use	1.06 (0.89-1.27)	0.52
anti-hypertensive medication use	0.94 (0.91-0.98)	0.003
Glucose (per 10 mg/dL)	0.99 (0.95-1.03)	0.67
Total cholesterol to HDL ratio	1.00 (0.91-1.12)	0.86

[^] All GVRs components from validated vascular risk prediction model are included [9].

^{*} Multivariable model further adjusted for education, health insurance status, and time between baseline and follow-up cognitive testing.