Association Between Northern Manhattan Study Global Vascular Risk Score and Successful Aging

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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, myocardial infarction, 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 a magnetic resonance imaging (MRI) substudy of NOMAS, a population-based prospective cohort study.

PARTICIPANTS: One thousand two hundred ninety individuals in whom a cognitive screen was administered at baseline and at enrollment in the MRI substudy.

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

RESULTS: Data at baseline and follow-up were available for 1,162 participants (mean age 70 ± 9; 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 1-point decrease on the GVRS (odds ratio = 1.38, 95% confidence interval = 1.17–1.61; $P < .001$). An inverse dose-response was observed between quartiles of GVRS and SA-ND. Greater diastolic blood pressure in participants taking antihypertensive medication and a history of claudication ($P = .003$) or peripheral arterial disease ($P < .001$) were inversely associated with SA-ND in the fully adjusted model.

CONCLUSION: Potentially modifiable vascular risk factors were independently associated with SA-ND in a multiethnic community-based sample. Improvements in GVRSs could help promote healthy longevity in the aging population. **J Am Geriatr Soc 61:519–524, 2013.**

Key words: successful aging; cognitive aging; global vascular risk; vascular risk factors

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 involves the avoidance of diseases that affect cognition—including vascular cognitive impairment (VCI), defined as cognitive impairment contributed to by vascular disease.[2] Although 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, whereas 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 in the Cardiovascular Risk Factors, Aging, and Dementia Study who were obese with high systolic blood pressures (SBP) and total cholesterol had six times the risk of dementia of 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

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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 (BP) and quantification of physical activity and alcohol consumption—the Global Vascular Risk Score (GVRS)—were better than the traditional Framingham measures in predicting incident stroke, myocardial infarction (MI), and vascular death.[11] In providing better 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. Because the NOMAS GVRS predicts the overall combined risk of adverse vascular outcomes, it was hypothesized that it would be inversely associated with successful aging with no cognitive decline (SA-ND) in this multiethnic, 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 nonpublished telephone numbers. People were eligible if they had never been diagnosed with a stroke, were aged 39 and older, 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 Mini-Mental State Examination (MMSE) twice, once at baseline and once at the time of enrollment in a magnetic resonance imaging (MRI) substudy. Criteria for inclusion into the substudy were aged 55 and older, no contraindications to MRI, and provision of written informed consent. Participants were enrolled in the substudy an average of 6.1 ± 3.5 years after baseline. Within this sample, participants were classified 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 (MI, coronary artery disease, congestive heart failure, atrial fibrillation, or valvular heart disease). The sample was stroke free according to NOMAS enrollment criteria and remained stroke free at the time of the second MMSE measurement;
2. A creatinine clearance rate of 45 mL/min or greater. Creatinine clearance (CrCl) 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 individuals with chronic kidney disease is a novel part of this 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] More recently, even mild chronic kidney disease was found to be associated with cognitive decline in this cohort.[15] A CrCl of 45 mL/min or greater was chosen based on results from several large cohorts showing that the risks of death, cardiovascular events, and hospitalization rise sharply below a glomerular filtration rate of 45 mL/min per 1.73 m^2, as do the odds of incident cognitive impairment.[16,17]

3. A global score of 95 or greater on the Barthel activities of daily living scale; and
4. A baseline MMSE score greater than education-specific cutoffs (>17 for those with ≤8 years of education and >23 for ≥9 years).

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

Participants were considered to have 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

The NOMAS GVRS has been described previously and was found to be better than the Framingham Risk Score (FRS) in predicting stroke, MI, and vascular death in the NOMAS multiethnic urban sample.[11] In the prior study, a survival model was constructed to predict combined cardiovascular outcomes, which included stroke (ischemic or intracerebral hemorrhage), MI, and vascular death. Age, sex, race, ethnicity, waist circumference, alcohol use, smoking, physical activity, the interaction between sex and physical activity, SBP and diastolic BP (DBP), the interaction between DBP and antihypertensive medication use, peripheral vascular disease, fasting blood sugar, and total cholesterol to high-density lipoprotein cholesterol (HDL-C) ratio contributed significantly to model fit and are included in the GVRS. In the NOMAS cohort, GVRS (calculated at baseline) ranged from 4.4 to 11.6 (mean 8.6 ± 1.0), and each individual's score was calculated from a multivariable regression model.[11] A GVRS of 9.0 indicated a 10-year probability of experiencing a vascular event of 0.20, a

GVRS of 8.2 indicated a 10-year probability of 0.10, and a GVRS of 6.6 indicated a 10-year probability of 0.02. Thirty-five percent of the population had a GVRS of at least 9.0.

Statistical Analysis

Logistic regression was used to examine the relationship between GVRS (using data at enrollment in the MRI substudy) and 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 $P \leq .20$. SAS version 9.2 (SAS Institute, Inc., Cary, NC) was used, and significance was assessed according to a preset two-sided alpha level of .05, with the exception of covariate selection.

RESULTS

Sample Characteristics

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

GVRS and Successful Aging

Examining the GVRS as a continuous measure, an inverse association was found such that there were greater odds of SA-ND with lower (better) GVRS. For each additional 1-point decrease on the GVRS, the odds of SA-ND were 38% greater (odds ratio (OR) = 1.38, 95% confidence interval (CI) = 1.17–1.61; $P < .001$). The association was stronger after adjustment for level of education and socioeconomic status (OR = 1.56, 95% CI = 1.32–1.85; $P < .001$). 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. The odds of SA-ND were 1.5 times as great for the third quartile of

Table 1. Criteria for Successful Aging—No Decline

Criterion	n (%)
Disease and disability	565 (49)
No cancer	1,076 (93)
No chronic obstructive pulmonary disease	1,053 (91)
No cardiac disease	966 (83)
Creatinine clearance rate ≥ 45 mL/min	957 (82)
Barthel activity of daily living score ≥ 95	1,098 (95)
Cognition	1,011 (87)
Baseline MMSE score >17 for ≤8 years of education or >23 for ≥9 years of education	1,112 (96)
≤3-point decline on MMSE score at follow-up	1,037 (89)

MMSE = Mini-Mental State Examination.

Table 2. Sample Characteristics

Characteristic	Overall, N = 1,162	Successful Aging without Cognitive Decline: Yes, n = 430	Successful Aging without Cognitive Decline: No, n = 732	P-Value
GVRS, mean ± SD	8.6 ± 0.9	8.5 ± 0.9	8.8 ± 0.8	<.001
GVRS components				
Age, mean ± SD	70 ± 9	70 ± 8	71 ± 10	.12
Male, n (%)	451 (39)	195 (45)	256 (35)	
Race and ethnicity, n (%)				
Non-Hispanic white	157 (14)	54 (13)	103 (14)	.60
Non-Hispanic black	186 (16)	72 (17)	114 (16)	
Hispanic	796 (70)	299 (69)	497 (68)	
Moderate alcohol drinker, n (%)	476 (41)	186 (43)	290 (40)	.30
Smoker, n (%)				
Current	190 (16)	78 (18)	112 (15)	.24
Former	419 (36)	153 (36)	266 (36)	.69
Never	553 (48)	202 (47)	351 (48)	.62
Moderate or heavy physical activity, n (%)				
Total	112 (10)	46 (11)	66 (9)	.38
Men	52 (4)	23 (5)	29 (4)	.29
Waist circumference, inches	38 ± 5	38 ± 5	38 ± 5	.17
History of leg pain or arterial disease, n (%)	143 (12)	33 (8)	110 (15)	<.001
Systolic blood pressure (mmHg)	136 ± 17	137 ± 17	136 ± 17	.31
Diastolic blood pressure (mmHg)	78 ± 10	78 ± 9	78 ± 10	.24
Diastolic blood pressure (mmHg) among those on antihypertensive medication (N = 472)	80 ± 10	81 ± 9	79 ± 10	.12
Glucose, mg/dL	101 ± 34	101 ± 36	101 ± 33	.89
Total cholesterol to high-density lipoprotein cholesterol ratio	4 ± 2	4 ± 2	4 ± 1	.06
Other covariates				
Education, years	10 ± 5	10 ± 5	9 ± 5	.14
Medicaid or no insurance, n (%)	469 (49)	194 (45)	275 (38)	.03
Years between baseline and follow-up cognitive testing	6 ± 4	7 ± 2	5 ± 4	<.001

All global vascular risk score (GVRS) components from validated vascular risk prediction model are included.[9]
SD = standard deviation.

GVRS, 1.6 times as great for the second quartile, and more than 3 times as great for the lowest quartile as for the fourth quartile (>9.3).

GVRS Components and Successful Aging

Individual components of the GVRS were also examined to determine important factors associated with SA-ND, adjusting for education, health insurance status, and length of follow-up time. Older age, greater DBP in individuals taking antihypertensive medication, and a history of claudication or peripheral arterial disease (PAD) were each independently associated with a lower likelihood of SA-ND (Table 3).

Comparison with FRS

The association between the FRS for coronary heart disease and SA-ND was compared with the association between SA-ND and the GVRS using 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 1.3–12.8) and was significantly lower (better) in those with SA-ND (7.8 ± 3.6 vs 8.4 ± 3.5; $P = .003$). Examining the FRS as a continuous variable, an inverse association was found such that each point decrease on the FRS was associated with 6% greater odds of SA-ND (OR = 1.06, 95% CI = 1.02–1.10; $P < .001$). The odds were marginally lower after adjusting for level of education and socioeconomic status (OR = 1.05, 95% CI = 1.01–1.09; $P = .007$).

DISCUSSION

A low vascular risk factor profile does not guarantee successful aging, but the high mortality and morbidity associated with vascular outcomes suggests it may be an important determinant. For NOMAS participants, the odds of SA-ND were 38% greater for each 1-point decrease on the GVRS, and an inverse dose-response was observed, with greater odds of SA-ND for the lowest quartiles of GVRS. The odds of SA-ND were also greater for lower FRS, but the GVRS was more strongly associated with SA-ND in this cohort, further suggesting that it may be more applicable to a racially and ethnically diverse urban sample.

Although the literature supports an association between the presence of vascular risk factors and lower likelihood of successful aging, this study is one of the first, to the knowledge of the authors, to examine the effect of global vascular risk. Given the importance of avoiding vascular outcomes such as stroke, MI, peripheral vascular disease, and vascular death, global risk scores such as the GVRS add value if they identify those at risk early on. The 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 poorer 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 they quantify risk and translate comorbidities into a useful number that provides a target for intervention. The current study also explored the individual components most associated with SA-ND in this cohort and found that age, a history of claudication or arterial disease, and DBP among individuals with hypertension, were each independently associated with SA-ND. PAD and 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 greater risk of vascular and nonvascular events, and has been related to disability, cognitive impairment, and unsuccessful aging.[27,28] Up to 90% of individuals with

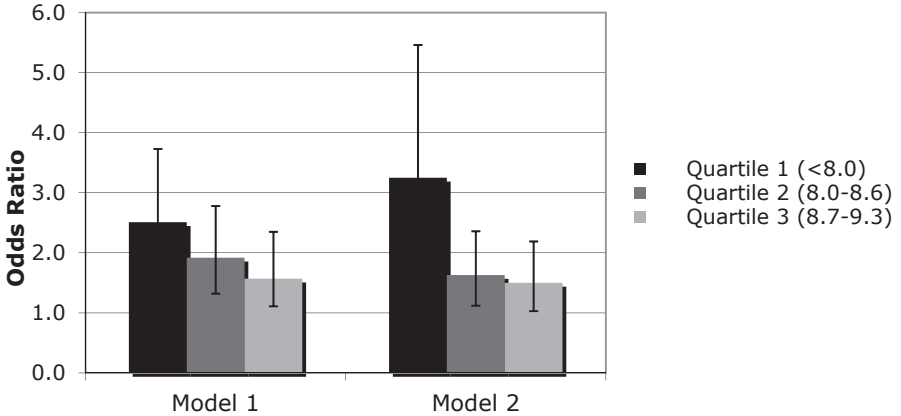

Figure 1. Odds of successful aging without cognitive decline according to quartile of global vascular risk score (GVRS). A dose response was observed for increasing quartiles of GVRS. The odds of successful aging without cognitive decline were 1.50 (95% confidence interval (CI) = 1.03–2.19) times as great for the third quartile of GVRS, 1.63 (95% CI = 1.12–2.36) times as great for the second quartile, and 3.25 (95% CI = 2.13–4.94) times as great for the lowest quartile as for the highest quartile of GVRS ($\geq$9.3). 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 3. Relationship Between Global Vascular Risk Score (GVRS) Components and Odds of Successful Aging—No Decline

Component	Odds Ratio (95% Confidence Interval)	*P*-Value
Age (per year)	0.95 (0.94–0.97)	<.001
Male	1.06 (0.77–1.46)	.74
Race and ethnicity (reference white)		
Hispanic	1.59 (0.94–2.70)	.08
Black	1.26 (0.75–2.13)	.38
Moderate alcohol consumption	1.13 (0.84–1.52)	.44
Smoker (reference never)		
Current	0.99 (0.72–1.37)	.97
Former	1.10 (0.73–1.65)	.65
Moderate or heavy physical activity		
Total	0.90 (0.47–1.75)	.77
In men	1.28 (0.49–3.38)	.61
Waist circumference (per inch)	1.02 (0.99–1.05)	.15
History of leg pain or arterial disease	0.39 (0.25–0.61)	<.001
Systolic blood pressure (per 10 mmHg)	1.05 (0.96–1.16)	.29
Diastolic blood pressure (per 10 mmHg)	1.06 (0.89–1.27)	.52
Interaction between diastolic blood pressure (per 10 mmHg) and antihypertensive medication use	0.94 (0.91–0.98)	.003
Glucose (per 10 mg/dL)	0.99 (0.95–1.03)	.67
Total cholesterol to high-density lipoprotein cholesterol ratio	1.00 (0.91–1.12)	.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.

PAD have angiographically determined coronary artery atherosclerosis, and up to half have evidence of cerebrovascular disease. Comorbid cardiovascular risk factors, including smoking and diabetes mellitus, are more common in these people as well,[29] yet individuals with PAD tend to be undertreated with regard to risk factor modification, though screening for PAD is noninvasive and widely available.[30]

The current study also shows that, in individuals taking antihypertensive medication, each 10-mm Hg increase in DBP was associated with 6% lower odds of SA-ND. Although SBP and DBP have been related to cardiovascular morbidity and mortality, in older adults, cardiovascular risk appears to be directly proportional to SBP and eventual health outcome inversely proportional to DBP,[31] although it was recently reported that DBP and not SBP was associated with greater white matter lesion load. DBP has also been independently associated with cognitive decline, and subclinical cerebral infarction and ischemic white matter damage may mediate this relationship.[32] DBP may reflect peripheral vascular resistance and thus be more specific to small vessel damage than SBP, which is most affected by large vessel stiffness, although a history of hypertension treatment confers cardiovascular risk even after adjustment for BP and other traditional risk factors; however 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 the current study indicate that higher DBP may decrease the likelihood of successful aging in individuals taking antihypertensive drugs (i.e., with established hypertension), but because hypotension also affects brain perfusion and has been shown to worsen vascular and cognitive outcomes, more research is needed to determine the optimal BP levels that should be targeted to achieve successful aging.[34]

This study had several limitations. The NOMAS GVRS has not been validated in other cohorts, although it is a strength that the score is applicable to this urban race/ethnically diverse U.S. population. Only participants in the MRI substudy were included, and therefore the substudy sample was somewhat healthier than the overall cohort because of a survivor effect typical of MRI substudies (i.e., participants had to be well enough to visit the center). The methods would tend to underestimate the effect of vascular risk factors because of this healthy cohort effect, but the 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, a definition of successful aging was created that incorporated physical well-being and cognitive abilities. Only diseases that are major causes of mortality in older adults were considered—cancer, chronic lung disease, heart disease, and stroke. The definition of successful aging was unique in that chronic kidney disease was included as a novel component; not including this in the definition would have increased the number of people in the successful aging category, but this would have biased the findings toward the null by including less-successful agers in the successful aging category. Otherwise, criteria similar to those used in other large studies were chosen, which helps in comparing them. Because 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 that 50 million have hypertension, and the prevalence of cardiovascular disease is expected to rise as other risk factors such as obesity, diabetes mellitus, and dyslipidemia become ever more prevalent.[35–37] The data from the current study suggest that the GVRS provides meaningful information about the risk of SA-ND in a race/ethnically diverse urban U.S. population 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 modify the course of cognitive aging, and further studies are needed to clarify this. The 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 successful aging, may be an effective means of guiding comprehensive public health efforts.

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