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VASCULAR RISK FACTORS AND COGNITIVE DECLINE IN A POPULATION SAMPLE

Mary Ganguli[1,2,4], **Bo Fu**[1], **Beth E. Snitz**[2], **Frederick W. Unverzagt**[6], **David A. Loewenstein**[7], **Tiffany F. Hughes**[1], and **Chung-Chou H. Chang**[3,5]

[1]University of Pittsburgh School of Medicine, Department of Psychiatry

[2]University of Pittsburgh School of Medicine, Department of Neurology

[3]University of Pittsburgh School of Medicine, Department of Medicine

[4]University of Pittsburgh Graduate School of Public Health, Department of Epidemiology

[5]University of Pittsburgh Graduate School of Public Health, Department of Biostatistics

[6]Indiana University, School of Medicine Department of Psychiatry

[7]University of Miami, Miller School of Medicine, Center on Aging and Department of Psychiatry and Behavioral Sciences

Abstract

We examined several vascular factors in relation to rates of decline in five cognitive domains in a population-based cohort. In an age-stratified random sample (N=1982) aged 65+ years, we assessed at baseline the cognitive domains of attention, executive function, memory, language, and visuospatial function, and also vascular, inflammatory, and metabolic indices. Random effects models generated slopes of cognitive decline over the next four years; linear models identified vascular factors associated with these slopes, adjusting for demographics, baseline cognition, and potential interactions. Several vascular risk factors (history of stroke, diabetes, central obesity, C-Reactive Protein), although associated with lower baseline cognitive performance, did not predict rate of subsequent decline. *APOE*4* genotype was associated with accelerated decline in language, memory, and executive functions. Homocysteine elevation was associated with faster decline in executive function. Hypertension (history or systolic blood pressure >140 mm) was associated with slower decline in memory. Baseline alcohol consumption was associated with slower decline in attention, language, and memory. Different indices of vascular risk are associated with low performance and with rates of decline in different cognitive domains. Cardiovascular mechanisms explain at least some of the variance in cognitive decline. Selective survival may also play a role.

INTRODUCTION

There is growing recognition of the role of vascular factors in the development of cognitive deficits. Cognitive decline is associated not only with cortical strokes but also with widespread small ischemic lesions involving subcortical white matter, often co-existing with degenerative pathologies.[1,2] Traditional risk factors for stroke, such as hypertension, diabetes, and hypercholesterolemia, increase risk not only of vascular cognitive impairment but also of Alzheimer disease dementia.[3,4] Since many vascular risk factors are potentially

Address correspondence to: Dr. Ganguli, Western Psychiatric Institute and Clinic, 3811 O'Hara Street, Pittsburgh, PA 15213, USA. GanguliM@upmc.edu; Telephone 1-412-647-6516; FAX 1-412-647-6555.

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modifiable, prevention approaches focused on these factors could influence not only dementia risk but also the trajectories of cognitive decline in aging.[5] Categorically defined outcomes such as incidence of dementia or mild cognitive impairment (MCI), or of progression from MCI to dementia, are clinically intuitive and readily conceptualized, but they require the setting of arbitrary thresholds between cognitive states. These thresholds can mask or distort additional information that could be gained by examining the entire spectrum or distribution of cognitive decline. In a population-based cohort of older adults, we examined the relationship of a panel of vascular factors to concurrent cognitive performance as well as cognitive decline over the subsequent four years.

METHODS

Study site and population

Our study cohort named the Monongahela-Youghiogheny Healthy Aging Team (MYHAT) is an age-stratified random population sample drawn from the publicly available voter registration lists for a small-town region of southwestern Pennsylvania (USA).[6]

Community outreach, recruitment, and assessment protocols were approved by the University of Pittsburgh IRB for protection of human subjects. All participants provided written informed consent.

Recruitment criteria were (a) age 65 years or older, (b) living within the selected towns, (c) not already in long-term care institutions. Individuals were ineligible if they (d) were too ill to participate, (e) had severe vision or hearing impairments, (f) were decisionally incapacitated. We recruited 2036 individuals over a two-year period. Since the project was designed to study mild cognitive impairment (MCI), we screened out those who exhibited substantial impairment by scoring <21/30 on an age-education-corrected Mini-Mental State Examination.[7,8] The remaining 1982 individuals had demographic characteristics that were largely representative of older adults in the population of the targeted communities.[6] These individuals underwent a detailed assessment including but not limited to the elements below.

Assessments

At baseline and at each annual data collection cycle, we assessed cognitive functioning using a comprehensive test battery tapping the cognitive domains of attention/processing speed, executive function, memory, language, and visuospatial functions (online/supplemental Table 1).[9] To create a composite score for each domain, we first transformed each test score into a standardized score by centering to its mean value and divided by its standard deviation, and then calculated the arithmetic mean of all standardized scores within that domain.

Potential baseline vascular risk factors

We defined each vascular/metabolic/inflammatory variable using data from history and/or examination and/or assay result, alone or in combination (Table 1).[10]

History—We asked participants about health history using a standardized questionnaire and language for each item, i.e. “Has a health care professional ever told you that you had ____ (stroke, TIA, heart attack/myocardial infarction, congestive heart failure, irregular heart rhythm, diabetes mellitus, high blood pressure/hypertension, high cholesterol?)” We asked whether they had ever undergone heart pacemaker insertion, heart catheterization, or coronary bypass surgery, and about current and past smoking and alcohol consumption. Self-reported health history is typical of population surveys; we lacked access to medical record information to confirm self-report, and neuroimaging data to identify silent infarcts.

Examination—Relevant components of the physical examination protocol in all participants included assessment of apical rhythm to detect arrhythmia, measurement of systolic and diastolic blood pressure in mm Hg, and measurement of waist and hip circumference in inches. We calculated waist:hip ratio (WHR), a measure of central (abdominal) adiposityshown to reflect cardiovascular mortality risk.[11]

Laboratory tests—We requested all participants, with specific informed consent, to provide nonfasting blood samples for measurement of cholesterol, for *APOE*4* genotyping, and for banking for unspecified future tests related to aging and health. We assayed total cholesterol (TC) and HDL (HDL) cholesterol, calculating LDL cholesterol as (TC – HDL).

To examine vascular risk in finer-grained detail, we conducted an exploratory study of six vascular/metabolic/inflammatory markers: ApoA1 (the lipoprotein for HDL cholesterol); ApoB (the lipoprotein for LDL cholesterol); [12] Cystatin-C (a measure of glomerular function that is unaffected by race, gender, muscle mass, or diet, and in older adults primarily reflects atherosclerotic burden);[13] HbA1c (glycosylated hemoglobin, which measures glycemic control over the preceding 3 months);[14] homocysteine (an amino acid associated with atherosclerosis when elevated);[15] and C-Reactive Protein (CRP, an inflammatory marker also associated with atherosclerosis).[16] These assays were performed at baseline in banked serum specimens drawn from a randomly selected subgroup of 559 participants with and without MCI.

Assays were performed in the Chemistry and Nutrition Laboratory of the University of Pittsburgh Graduate School of Public Health, Department of Epidemiology, using an Olympus AU4 Chemistry Analyzer (Olympus America, Melville, NY). Reagents for ApoA1, ApoB, CRP, Cystatin C were obtained from Beckman Coulter (Brea, CA), for HbA1c from Pointe Scientific (Canton, OH), Homocysteine from Sekisui (Exton, PA). In-house reagents were used for the assays of total cholesterol[17] and HDL cholesterol. [18]

Tracking and Attrition

We contacted participants by telephone every 3 months to ascertain their status and update key information between annual visits. Over 5 assessment cycles (baseline and 4 years of followup), a total of 862 (43.49%) participants were lost to followup, of whom 302 (15.24%) died, 118 (5.95%) became too ill to participate, while the rest relocated out of the study area or indicated they no longer wished to participate. Note all participants were included in the analyses regardless of whether or not they contributed followup data.

Statistical Analysis

For all vascular factors (Table 1), we calculated frequencies and percentages for categorical variables, and means and standard deviations for continuous variables. We used Pearson correlations to evaluate intercorrelations at baseline among the five cognitive domain composite scores. We examined baseline relationships between each of the vascular factors and the five cognitive domain composites using univariable linear regressions, adjusting for demographics (age, gender, and education [less than, equal to, and greater than high school education]) (Table 2).

We then used a two-stage modeling approach to explore the effect of each vascular factor on subsequent change in each cognitive domain composite. In the first stage, we fit a random effects model for each cognitive domain, to estimate the rate (slope) of change for each participant; this estimated rate served as the outcome variable for the next stage. In the second stage, we used linear regression to evaluate the effect of each vascular factor on the rate of change in each cognitive domain composite scores. We adjusted each model for

demographics, for the corresponding baseline cognitive composite score, and also for interactions between the baseline score and the given vascular factor, to account for the possibility that the effect of a vascular factor on rate of decline in a given domain might depend on the baseline level of function in that domain. (Table 3).

We examined the overall fit of these models to our data using R^2 to calculate per cent of variance explained. These analyses represent separate individual models testing the relationships of each 21 vascular factors to 5 cognitive domains, with appropriate adjustments for covariates, i.e., they were not *post-hoc* tests of a simultaneous/unified omnibus test. Nevertheless, to reduce familywise alpha error, we adopted a conservative significance level of α=0.01.

The modeling approach employed here allows the use of data from all participants who contributed baseline data, regardless of whether they also contributed followup data, i.e. no participants were excluded. However, this approach effectively treats data missing due to attrition as missing at random, and attrition is most likely not random. Therefore, we fit separate linear regression models adjusted for age, sex, and education to examine (a) the associations of baseline cognitive domain scores with years of subsequent followup and (b) the associations of slope of decline in each domain with years of followup. We also fit interval-censored survival models, [19] adjusted for demographics, to evaluate (c) the associations of baseline vascular measures with subsequent attrition. The parametric form of the baseline hazards for each of these models was assumed from a Weibull distribution.

In post-hoc analyses, for the vascular factors which showed significant cross-sectional associations with baseline cognition but not with subsequent decline, we re-fit the longitudinal models substituting the binary education variable (less than high school versus high school or greater) with (i) years of education as a continuous variable, (ii) literacy/ reading ability as assessed by the Wide Range Achievement Test (WRAT-3), and (iii) Full Scale IQ (FSIQ) as estimated by the Wecshler Test of Adult Reading (WTAR).

All statistical analyses were performed using SAS v9.2.[20]

RESULTS

All 1982 study participants underwent the detailed assessment at baseline. Blood specimens were obtained from 1778 individuals for *APOE* genotyping, 1036 for serum cholesterol assay; and 559 of the serum specimens were also used in the exploratory study of the six selected vascular, metabolic, and inflammatory indices. The total available sample for each variable and those with positive results for that variable are shown in Table 1.

At baseline, the 1982 individuals had mean (SD) age 77.65 (7.44) years, median educational level of high school graduate (13.8% less than high school, 45.1% high school, and 41.1% more than high school); 61.05% were women, and 94.8% were of European descent.

As expected, all baseline cognitive domain composites were intercorrelated, with pairwise correlation coefficients ranging from 0.37 to 0.67 (*P <0.0001*).

In the cross-sectional models (Table 2), with adjustment for demographics (age, sex, and educational level), baseline test performance in all 5 cognitive domains (attention, executive, language, memory, and visuospatial functions) were associated with several concurrently measured vascular factors. Lower *attention* scores were associated with history of stroke, history of diabetes and high waist:hip ratio (WHR). Lower *executive function* scores were associated with stroke, elevated diastolic pressure, C-Reactive Protein (CRP), and WHR. Lower *language* scores were associated with stroke, and elevated diastolic pressure. Lower

memory scores were associated with stroke, and *APOE*4* carrier status, while higher score was associated with elevated cholesterol. Lower *visuospatial function* was associated with stroke For *all cognitive domains*, except visuospatial function, higher baseline scores were associated with current (baseline) alcohol consumption.

In the models of rate of change (Table 3), adjusted for demographics, baseline composite scores, and interactions between baseline scores and vascular factors, we found slope of decline in all domains was strongly associated with baseline score. These associations were positive for executive, language, and memory functions (i.e., higher baseline score associated with less rapid decline) and negative for attention and visuospatial functions (higher baseline score associated with more rapid decline). No vascular factors increased the rate of decline in either attention or visuospatial function; slower decline in attention was associated with current alcohol consumption. For *executive function*, more rapid decline was associated with homocysteine elevation and *APOE*4* genotype. For *language*, faster decline was associated with *APOE*4* and slower decline with elevated diastolic BP. For *memory*, faster decline was associated with *APOE*4*, and slower decline with systolic BP and current alcohol consumption.

For both sets of models, Tables 2 and 3 also show additional associations with *p* values between 0.01 and 0.05 which did not meet our *a priori* threshold for statistical significance.

For both cross-sectional (Table 2) and longitudinal rate-of-change (Table 3) analyses, the models explained 20% – 26% of the variance for memory, executive, and visuospatial domains, but only 8%–12% of the variance in language and attention domains.

In separate models, we found increased risk of attrition among those who at baseline had stroke, heart disease, cardiac arrhythmia, heart failure, higher systolic BP (treated as a continuous variable), hypercholesterolemia, current smoking, elevated total cholesterol, HDL cholesterol/ApoA1 (hazard ratios ranged from 1.006 to 1.841, with significance levels ranging from p=<0.001 to p = 0.049). A reduced risk of attrition was associated with LDL/ ApoB elevation, and ApoB: ApoA1 ratio (hazard ratios ranged from 0.390 to 0.393, with significance levels ranging from p=0.041 to p = 0.043). As expected, baseline cognitive composite scores were associated with likelihood of subsequent attrition; in all cognitive domains, the lowest baseline scores were seen in those who had no further followup, while the highest scores were seen in those who completed 5 waves of followup. The greatest decline in executive, language, and memory domains was also seen in those who dropped out the earliest (parameter estimates ranged from −0.036 to −0.009, with significance levels ranging from p=<0.001 to p = 0.037); these relationships were not statistically significant in the attention and visuospatial domains.

In the post-hoc analyses substituting years of education, WTAR, and WRAT scores for the binary education variable, the results did not change.

DISCUSSION

It is increasingly recognized that many vascular risk factors are associated with cognitive impairment and dementia.[1.3] Stroke,[10] diabetes,[10, 21] heart disease,[22] adiposity,[10,23] hypertension,[24] have also been found to be risk factors for incident MCI. However, the same factors may not necessarily predict decline across the spectrum of cognitive aging. In this population-based cohort with up to four years of followup after baseline assessment, our primary objective was to identify baseline vascular indices that predicted the rate of subsequent decline in five cognitive domains. To understand these indices in context, we first examined their cross-sectional associations with baseline cognitive functions to

determine whether the same factors associated with worse performance in concurrently measured cognition would also predict subsequent decline. Recognizing that rate of decline may vary according the starting point (slope as a function of intercept) due to ceiling or floor effects, we adjusted the models not only for baseline scores but also for potential interactions with baseline scores. We also examined vascular factors associated with attrition to help explain the observed effects of the same factors on cognitive performance versus cognitive decline.

In the cross-sectional models, we found history of stroke associated with poorer performance in all cognitive domains; history of diabetes associated with lower executive functioning, language, and memory performance; abdominal obesity with lower attention, executive, and language scores; and C-Reactive protein, an inflammatory measure, with worse executive function. However, none of these variables were associated with subsequent decline in any domains over the subsequent four years. This result suggests that the preceding vascular factors may reflect morbid vascular processes that produce static impairments but not necessarily progressive impairments such as would be expected with degenerative processes. Other studies have shown that post-stroke cognitive impairment may remain static or improve[25,26] unless another stroke occurs, although carotid stenosis and the resulting hemodynamic impairments are associated with cognitive decline.[27] Adiposity in late life has even shown an apparent protective effect against cognitive decline;[28] a trajectory of slowed BMI increase from midlife to late-life was associated with incident dementia;[29] a meta-analysis suggested that underweight as well as overweight/obesity in midlife increased dementia risk.[30] We did not have midlife data with which to evaluate these possibilities. In our study, presence of the *APOE*4* gene was associated with worse performance only in memory, as might be expected if memory impairment reflects underlying Alzheimer disease pathology; but yet showed faster decline in executive, memory, and language functions. This finding is also consistent with expectations for AD but could possibly also reflect a progressive cerebrovascular process.

In contrast to the risk effects, there was consistency in the apparent protective effects. Current alcohol consumption was protective in all cognitive domains except visuospatial function in the cross-sectional analysis, and also protective against decline in attention, language, and memory. A potential interpretation is the salutary cardiovascular effects of light to moderate alcohol consumption.[31] However, current alcohol consumption could also reflect the absence of diseases and medications with which alcohol is contraindicated. Elevated total cholesterol/self-reported hypercholesterolemia was significantly associated with better performance in memory, and in the same direction for memory and attention decline although below our significance threshold. These associations would seem paradoxical except in light of literature showing that risk of late-life dementia is associated with higher cholesterol in midlife[32] but lower cholesterol in late life.[33] This so-called J-shaped relationship has been attributed to weight and lipids declining as part of a progressive aging or dementing process; a more recent report indicated that a declining cholesterol level from midlife through late life was the best indicator of AD risk.[34] The additional possibility of a potential survivor effect due to selective attrition (i.e. premature mortality of individuals with hypercholesterolemia) is discussed below.

We found complex relationships with blood pressure. Elevated diastolic pressure was associated with worse baseline performance in executive and language functions, but protective against decline in language. Systolic BP/history of hypertension had no observable association with baseline cognitive performance, but was protective against decline in memory. As with cholesterol, a similar J-shaped relationship has been described for blood pressure elevation in midlife versus late life in relation to risk of late-life dementia. A long-term study found that those who had an initial steep increase in and later a sharp

decline in midlife blood pressure had increased risk of late-life dementia.[35] Declining BP may reflect an aging vasculature, and hypotension can lead to cerebral hypoperfusion and hypoxia which has been associated with white matter disease.[36] Both hypertension and hypotension affect brain perfusion, reduce cerebrovascular reserve and worsen cognitive outcomes;[37] high BP, decreasing over time, is associated with increased white matter lesions.[38] However, again, a survivor effect must be considered.

To understand survivor effects more completely we would need information on those in the population who did not live long to be enrolled in our study of individuals aged 65+, as would be possible in cohorts that began followup in early or middle adulthood. Within our study, we were able at least to characterize those who were assessed at study entry and later dropped out. As expected, individuals who dropped out earlier had inferior baseline cognitive performance compared to those who remained in the study, even after adjustment for demographics. Also, certain vascular factors were associated with subsequent attrition, thus helping explain some of the associations among these vascular factors, baseline cognitive performance, and subsequent cognitive decline. For example, stroke was cross-sectionally associated with all baseline scores but not with decline, possibly because stroke is also associated with attrition (a case of competing risks). E.g. if a participant died after a stroke, we would be unable to observe whether he would have suffered cognitive decline had he survived. However, diabetes, WHR, and CRP, which were similarly associated with baseline cognitive performance but not with subsequent decline, were not associated with attrition. Here, a possible interpretation is that these conditions can lead to a certain degree of cognitive impairment which may remain static and not progressive. Cholesterol elevation showed apparent “protective” effects both on baseline cognition and against subsequent decline, despite also being associated with attrition. This finding may partly represent survivor bias because those participants with high cholesterol who die or otherwise leave the study would leave behind the healthier survivors who also have better cognition. In contrast, current alcohol use which was associated both with better cognitive and lesser cognitive decline, was not associated either positively or negatively with attrition. Thus, moderate alcohol use may represent a true protective factor rather than a healthy survivor bias.

Although neuropsychological tests are designed and selected to tap specific cognitive functions, they rarely isolate single domains; for example, impaired attention will compromise test performance in all domains, and severely impaired language could interfere with comprehension of test instructions in all domains. It was therefore not unexpected that the cognitive domain composites were all strongly inter-correlated. Therefore we have discussed our results broadly rather than over-interpreting the observed associations of individual vascular factors with individual cognitive domains.

These results extend our previous work on risk and protective factors for incidence of mild cognitive impairment (MCI) in the same cohort.[10] Those analyses found that, after adjustment for attrition, diabetes and abdominal adiposity increased risk of neuropsychologically defined MCI, while *APOE*4* genotype and heart failure increased risk of attrition. Adiposity, stroke, heart failure, and diabetes were risk factors for Non-Amnestic MCI, while HDL cholesterol was protective. The contrast between factors increasing risk of incident MCI in those cognitively normal at baseline, and factors increasing risk of cognitive decline in the entire sample, may be attributed in part to differences in the size and composition of the base sample and also the modeling approach. However, a key distinction is that the former examines the risk of individuals crossing a particular threshold from one category (cognitively normal) to another (mild cognitive impairment), while the latter examines the rate of decline over the entire spectrum of functioning. Note that baseline alcohol use appeared protective against all incidence of all subtypes of MCI, similar to what we report here in relation to cognitive decline.

Potential limitations of our approach include the strong possibility that true associations are being masked by survival, but attrition is inevitable in longitudinal studies of aging populations and we have interpreted our results in this light. Despite our overall large sample size, we had limited power for the vascular variables measured purely by serum assays (Table 1) and several potential associations did not reach the more conservative threshold we established for statistical significance. Lacking medical record and neuroimaging data, for several risk factor variables we relied on participants' self-report of having been thus diagnosed by health care providers, as is typical in population research. Further, the total cholesterol levels may be inflated by having been assayed in nonfasting samples collected as part of the assessments conducted in participants' homes. We assessed the vascular condition in our participants at baseline, and have no information on their duration preceding study entry, or on their midlife health status. Reflecting the elderly population of our Southwestern Pennsylvania study area, our cohort was predominantly of European descent; external validity of our findings will have to be determined by replication in other, more ethnically diverse populations. These limitations are balanced by several advantages of our study. In our large population-based cohort, we undertook careful assessment, including fairly detailed neuropsychological testing, on up to five occasions a year apart. We modeled slope (rate) of decline rather than simply amount of decline, adjusting the models for baseline scores as well interactions to account for floor/ceiling effects. We also investigated the potential effects of attrition on the outcomes of interest. Desirable future directions include continued followup re-assessment of the cohort over a longer period to further explicate the trajectories of cognitive decline; expansion of the chemistry assays to the entire cohort; and analyses of change over time in the risk/protective factors themselves in relation to cognitive change.

Our broad conclusion is that vascular factors explain a substantial proportion of the variance in cognitive decline observed in aging. These findings should spur renewed efforts to understand the underlying mechanisms which are likely to be complex and nuanced. For example, adiposity may represent varied mechanisms related to the location and types of adipose tissue and its endocrine effects;[39] weight maintenance alone may be insufficient to modify these effects. Several cardiovascular factors may have the effect of "relentless brain hypoperfusion" that might precipitate abnormal protein synthesis and neurodegeneration.[36] Aggressive blood-pressure-lowering strategies may therefore be ineffective or even counter-productive in the aging brain. Further, cognition is not a unitary function; when different vascular factors may differentially affect different domains, as we have shown here, they may reflecting diverse cognitive systems and disease processes. [40] Discrepant results between studies with different outcomes (incidence of dementia and MCI, progression of MCI to dementia, global cognitive decline, domain-specific cognitive decline), and between studies beginning in mid-life versus later life, provide opportunities for improved understanding the underlying mechanisms. Here, it is worth recognizing that the most informative studies to date have been those conducted in Scandinavian countries which support decades-long followup prospective studies beginning in mid-life. [29,35,] Although the ultimate goal is to identify potential intervention targets to reduce the rate of cognitive decline, it would be unwise to skip over the intermediate step of understanding the mechanisms underlying signals from observational studies.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1

Definitions and distributions of vascular indices in the MYHAT cohort at baseline

Vascular/Metabolic/Inflammatory Variable	Total N	Frequency (%) for Categorical Variables *OR* *Mean (SD) for Continuous Variables
Stroke (by history)	1978	98 (4.95)
Coronary heart disease (by history of heart attack, cardiac catheterization, coronary bypass surgery)	1976	590 (29.86)
Cardiac arrhythmia (by exam, apical rhythm with >=3 irregular beats)	1971	264 (13.40)
Abdominal obesity (Waist: Hip Ratio, WHR) *	1863	0.09 (0.59)*
Heart failure (by history)	1977	188 (9.51)
Cholesterol elevation (history of high cholesterol and/or total cholesterol >=200 by assay)	1978	1363 (68.91)
HDL cholesterol >=50 **or ApoA1**>=120 (by assay)	1036	642(61.97)
LDL cholesterol >=130 **or ApoB**>=100 (by assay)	1036	650 (62.74)
ApoB: ApoA1 ratio (by assay) *	559	0.71 (0.26) *
Diabetes mellitus (by history)	1979	432 (21.83)
Diabetes (history) **and/or HbA1c** >=6 by assay)	1979	647 (83.48)
Hypertension (by history and/or exam: Systol BP>=140 mm)	1981	1821 (92.11)
Diastolic BP >=80 (exam)	1967	638 (32.44)
Homocysteine>=10 (by assay)	559	363 (64.94)
CystatinC>=1 (by assay)	559	283 (50.63)
C-Reactive Protein (CRP)>=10 (by assay)	559	37 (6.62)
APOE*4 carrier status (by genotyping)	1778	372 (20.92)
Previous drinking (history of alcohol consumption)	1982	399 (20.13)
Current drinking (history of alcohol consumption)	1982	1298 (65.49)
Previous smoking (history of tobacco use)	1982	902 (45.51)
Current smoking (history of tobacco use)	1982	111 (5.60)

Table 2

Associations of baselines cognitive composite scores with vascular factors (cross-sectional, adjusted for demographics.)

	Attention/Speed		Executive Function		Language		Memory		Visuospatial Function	
Vascular Variable (see Table 1)	**Estimate**	***P value***	**Estimate**	***P value***	**Estimate**	***P value***	**Estimate**	***P value***	**Estimate**	**P value**
Stroke	**−0.30**	***<.001***	**−0.34**	***<.001***	**−0.41**	***<.001***	**−0.33**	***<.001***	**−0.46**	***<.001***
Coronary heart disease	0.04	*0.26*	0.02	*0.62*	0.06	*0.09*	0.04	*0.26*	−0.04	*0.40*
Cardiac arrhythmia	−0.002	*0.962*	-−0.08	*0.07*	−0.10	*0.03*	0.01	*0.79*	−0.05	*0.47*
Waist: Hip Ratio (WHR)	**−0.88**	***<.001***	**−0.57**	***<0.01***	**−0.55**	***0.01***	−0.11	*0.63*	−0.02	*0.95*
Heart failure	−0.06	*0.32*	−0.09	*0.09*	0.02	*0.75*	0.08	*0.14*	−0.09	*0.26*
Cholesterol elevation	0.08	***0.031***	0.05	*0.14*	0.05	*0.16*	**0.11**	*<0.005*	0.05	*0.32*
HDL cholesterol >=50 or ApoA1>=120	0.05	*0.29*	0.10	***0.02***	0.04	*0.39*	−0.03	*0.46*	0.09	*0.16*
LDL cholesterol >=130 or ApoB>=100	0.01	*0.91*	0.02	*0.68*	−0.003	*0.95*	−0.06	*0.16*	−0.07	*0.29*
ApoB: ApoA1 ratio	0.18	*0.13*	−0.07	*0.48*	−0.07	*0.49*	−0.11	*0.30*	−0.02	*0.92*
Diabetes mellitus	**−0.14**	***<.001***	**−0.13**	*<0.005*	−0.06	*0.13*	0.01	*0.77*	−0.06	*0.25*
Diabetes and/or HbA1c >=6	−0.06	*0.09*	−0.07	*0.04*	0.001	*0.97*	0.02	*0.55*	0.02	*0.75*
Hypertension and/or Systolic BP>=140	−0.002	*0.98*	0.04	*0.54*	−0.03	*0.62*	0.06	*0.27*	−0.09	*0.28*
Diastolic BP >=80	0.06	*0.11*	**−0.09**	***<0.01***	−0.10	*<0.01*	−0.02	*0.61*	−0.03	*0.47*
Homocysteine>=10	−0.02	*0.73*	−0.03	*0.57*	−0.05	*0.44*	−0.03	*0.61*	−0.07	*0.45*
CystatinC>=1	−0.09	*0.18*	−0.04	*0.46*	−0.06	*0.35*	−0.13	*0.03*	0.01	*0.91*
C-Reactive Protein>=10	−0.14	*0.26*	**−0.28**	***<0.01***	−0.09	*0.45*	−0.11	*0.31*	**−0.38**	***0.02***
APOE*4 carrier status	0.03	*0.52*	<.0001	*1.00*	0.03	*0.41*	**−0.12**	***<0.01***	−0.09	*0.12*
Previous drinking	0.07	*0.20*	−0.05	*0.39*	0.02	*0.73*	−0.04	*0.47*	0.01	*0.93*
Current drinking	0.14	*<0.005*	0.12	*<0.01*	0.19	<.001	0.13	*<0.01*	0.16	*0.02*
Previous smoking	−0.01	*0.74*	0.02	*0.60*	0.02	*0.46*	0.01	*0.85*	−0.06	*0.16*
Current smoking	−0.06	*0.42*	−0.01	*0.87*	0.07	*0.32*	−0.03	*0.72*	−0.11	*0.24*

Table 3

Associations between baseline vascular factors and slope of cognitive composite decline over time, adjusted for demographics and interactions.

	Change in Attention/Speed		Change in Executive Function		Change in Language		Change in Memory		Change in Visuospatial Function	
Vascular variable (see Table 1)	**Estimate**	***P_value***	**Estimate**	***P_value***	**Estimate**	***P_value***	**Estimate**	***P_value***	**Estimate**	***P_value***
Stroke	−0.01	*0.16*	−0.01	*0.19*	−0.002	*0.81*	0.01	*0.32*	0.004	*0.67*
Coronary heart disease	<.0001	*0.89*	−0.004	*0.14*	0.003	*0.53*	0.01	*0.12*	0.002	*0.60*
Cardiac arrhythmia	0.004	*0.06*	−0.002	*0.70*	0.01	***0.05***	0.001	*0.82*	−0.003	*0.54*
Waist: Hip Ratio (WHR)	−0.01	*0.22*	0.01	*0.69*	0.01	*0.65*	0.01	*0.73*	0.01	*0.62*
Heart Failure	<.0001	*1.00*	−0.01	*0.15*	−0.002	*0.81*	−0.01	*0.36*	−0.01	*0.25*
Cholesterol elevation	0.004	*0.03*	0.003	*0.25*	0.01	*0.05*	0.003	*0.47*	0.003	*0.35*
HDL cholesterol >=50 or ApoA1>=120	−0.001	*0.69*	−0.01	*0.09*	<.0001	*0.95*	−0.01	*0.29*	−0.01	*0.11*
LDL cholesterol >=130 or ApoB>=100	0.002	*0.53*	0.01	*0.06*	0.01	*0.28*	0.003	*0.60*	0.001	*0.79*
ApoB: ApoA1 ratio	0.004	*0.61*	0.003	*0.73*	−0.01	*0.64*	0.01	*0.55*	0.002	*0.86*
Diabetes mellitus	−0.001	*0.77*	−0.003	*0.32*	−0.01	*0.31*	0.001	*0.82*	−0.002	*0.65*
Diabetes and/or HbA1c >=6	0.001	*0.47*	<.0001	*0.94*	−0.002	*0.66*	0.01	*0.08*	−0.004	*0.22*
Hypertension and/or Systolic BP>=140	0.004	*0.15*	0.01	*0.31*	0.02	***0.02***	0.02	***<0.01***	0.01	*0.08*
Diastolic BP >=90	0.002	*0.26*	0.01	*0.06*	0.01	***<0.01***	0.01	*0.10*	0.002	*0.51*
Homocysteine>=10	−0.01	*0.14*	−0.02	***<0.01***	−0.01	*0.24*	0.001	*0.85*	−0.01	*0.41*
CystatinC>=1	−0.01	***0.02***	−0.001	*0.79*	<.0001	*0.98*	0.01	*0.26*	−0.01	*0.19*
C-Reactive Protein>=10	−0.01	*0.32*	−0.001	*0.90*	0.01	*0.53*	0.004	*0.78*	0.004	*0.80*
*APOE*4* carrier status	−0.002	*0.29*	−0.01	***<0.01***	−0.03	***<.001***	−0.02	***<.001***	−0.01	***0.03***
Previous drinking	0.01	***0.04***	0.002	*0.69*	0.01	*0.33*	0.01	*0.10*	0.003	*0.63*
Current drinking	0.01	***<.001***	0.01	*0.16*	0.02	*0.01*	0.02	*<0.005*	0.01	*0.17*
Previous smoking	0.003	*0.07*	−0.01	*0.10*	−0.004	*0.40*	0.001	*0.84*	−0.003	*0.32*
Current smoking	0.001	*0.71*	−0.01	*0.07*	−0.02	***0.02***	−0.02	*0.06*	−0.004	*0.57*

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