Vascular factors predict rate of progression in Alzheimer disease

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ABSTRACT

Background: While there is considerable epidemiologic evidence that cardiovascular risk factors increase risk of incident Alzheimer disease (AD), few studies have examined their effect on progression after an established AD diagnosis.

Objective: To examine the effect of vascular factors, and potential age modification, on rate of progression in a longitudinal study of incident dementia.

Methods: A total of 135 individuals with incident AD, identified in a population-based sample of elderly persons in Cache County, UT, were followed with in-home visits for a mean of 3.0 years (range: 0.8 to 9.5) and 2.1 follow-up visits (range: 1 to 5). The Clinical Dementia Rating (CDR) Scale and Mini-Mental State Examination (MMSE) were administered at each visit. Baseline vascular factors were determined by interview and physical examination. Generalized least-squares random-effects regression was performed with CDR Sum of Boxes (CDR-Sum) or MMSE as the outcome, and vascular index or individual vascular factors as independent variables.

Results: Atrial fibrillation, systolic hypertension, and angina were associated with more rapid decline on both the CDR-Sum and MMSE, while history of coronary artery bypass graft surgery, diabetes, and antihypertensive medications were associated with a slower rate of decline. There was an age interaction such that systolic hypertension, angina, and myocardial infarction were associated with greater decline with increasing baseline age.

Conclusion: Atrial fibrillation, hypertension, and angina were associated with a greater rate of decline and may represent modifiable risk factors for secondary prevention in Alzheimer disease. The attenuated decline for diabetes and coronary artery bypass graft surgery may be due to selective survival. Some of these effects appear to vary with age. ***Neurology*® 2007;69:1850–1858**

GLOSSARY

3MS = revised Modified Mini-Mental State Examination for epidemiologic studies; **AF** = atrial fibrillation; **CABG** = coronary artery bypass graft surgery; **CCHS** = Copenhagen City Heart Study; **CCSMHA** = Cache County Study on Memory, Health, and Aging; **CDR** = Clinical Dementia Rating; **CVD** = cardiovascular disease; **DM** = diabetes mellitus; **DPS** = Dementia Progression Study; **MI** = myocardial infarction; **MMSE** = Mini-Mental State Examination; **SBP** = systolic blood pressure.

Vascular factors and diseases have been shown to alter the biologic processes associated with Alzheimer disease (AD). For example, elevated cholesterol intake increases amyloid-beta deposition in the brains of transgenic mice expressing human amyloid precursor protein.[1] Additionally, vascular factors are risk factors for AD in longitudinal, population-based studies, including hypertension,[2,3] atherosclerosis,[4] atrial fibrillation,[5] diabetes,[6] and stroke.[7] However, some studies have only found these relationships in certain age or APOE ε4 subgroups.[8] Because the effects of risk factors may differ at the various stages of the disease (i.e., stage-specific risk factors), it is not known whether these vascular factors affect progression once the diagnosis of AD is established. Only

Supplemental data at www.neurology.org

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three studies of selected dementia populations have examined vascular factors of AD progression. One study did not find an association between baseline cardiovascular risk factors and progression from a CDR = 1.0 to a CDR = 2.0 over an 18-month follow-up.[9] However, two other studies reported that decreased cardiovascular reactivity[10] and cerebrovascular events[11] predicted cognitive or functional progression in AD. Thus, it is possible that vascular factors may modify the rate of functional and cognitive decline in AD. Because vascular factors are modifiable, this association suggests a path for secondary prevention of the functional progression of AD and warrants examination in a population-based sample with a longer follow-up.

The aim of the current study was to examine whether vascular factors, including a vascular index (VI) and individual factors, modify the rate of decline among patients with AD in the Cache County Dementia Progression Study (DPS). The DPS enrolls incident dementia cases from the ongoing population-based Cache County Study on Memory, Health, and Aging (CCSMHA), and therefore offers distinct advantages for studying the natural history of AD in community-dwelling elderly. In additional analyses, we also examined possible age by vascular interactions in predicting AD progression because epidemiologic studies have suggested the association between vascular factors and risk of AD may be modified with age.[12,13]

METHODS

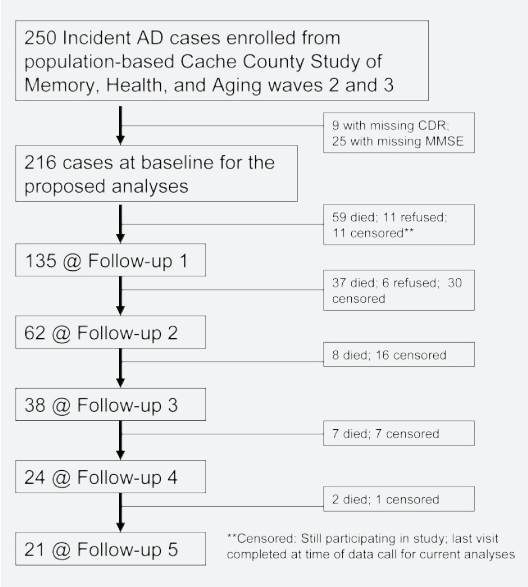
Participant screening. The Dementia Progression Study (DPS) is composed of participants with incident dementia who are enrolled in the Cache County Study on Memory, Health, and Aging (CCSMHA). Selection methods for CCSMHA have been reported in detail elsewhere.[14,15] Briefly, of the 5,677 permanent residents of Cache County, Utah, aged 65 or older on January 1, 1995, 5,092 (90%) enrolled in the study and underwent a multistage screening and assessment. Individuals with prevalent dementia were identified at the initial study wave (1995 to 1996) and those developing incident dementia were identified at two follow-up waves (1998 to 1999 and 2002 to 2003). At each wave, participants were screened for dementia using the revised Modified Mini-Mental State Examination for epidemiologic studies (3MS[16]). Individuals whose 3MS scores (adjusted for education and sensory deficits) fell below 87 out of a possible 100 were studied further using the Dementia Questionnaire.[17] Participants with suspected dementia, or its prodrome, and members of a designated subsample of cognitively normal individuals underwent baseline clinical assessment, including an interview to ascertain medical, cognitive, and demographic history, a brief medical and neurologic examination, and a neuropsychological test battery.

Assessment of dementia and dementia severity. Dementia diagnoses have been reported in detail elsewhere.[14] Briefly, diagnoses were assigned by a panel of experienced clinicians in geropsychiatry, neurology, and neuropsychology after thorough review of all available information including results of the clinical assessment, geropsychiatry examination, and neuroimaging and laboratory studies. Dementia was diagnosed using Diagnostic and Statistical Manual of Mental Disorders, 3rd ed., revised criteria, except that we did not insist on a demonstrable deficit in both short-term and long-term memory. AD was diagnosed following National Institute of Neurological and Communicative Disorders and Stroke–Alzheimer's Disease and Related Disorders Association criteria,[18] with the exception that a diagnosis of probable AD was deferred for neuroimaging results if these were forthcoming. Vascular dementia was diagnosed following National Institute of Neurological Diseases and Stroke and Association International pour la Recherche et l'Enseignement en Neurosciences criteria.[19] Individuals with a dementia diagnosis were followed approximately 18 months after their clinical evaluation to further refine or confirm their diagnoses.

DPS enrollment and follow-up. Participants with a diagnosis of incident dementia (n = 432) over the two waves of follow-up in CCSMHA had the option of continuing in the DPS. Of these, 250 participants (58%) had probable or possible AD without concomitant vascular dementia. DPS participants were followed with in-home assessments, similar to that of the CCSMHA, by an interdisciplinary specialty geropsychiatry team. The baseline assessment for the DPS is considered to be the wave of dementia diagnosis in CCSMHA. A total of 135 (54%) of the 250 participants with AD had at least one additional follow-up and, therefore, comprise our longitudinal sample. A flowchart showing rate of follow-up and reasons for dropout is presented in figure 1. As the DPS is an ongoing study of incident cases of dementia in CCSMHA, participants are continuously being enrolled and will have a varied number of follow-ups depending on when they entered the study. Those still in the study (have not died or refused) and pending another visit are considered to be censored for descriptive purposes. The DPS was approved by the institutional review boards at Johns Hopkins University and Utah State University. All participants and their next of kin signed an informed consent document for each stage of the study.

Outcomes. Outcomes reflecting progression include the Mini-Mental State Examination (MMSE)[20] and the Clinical Dementia Rating Scale (CDR).[21] The MMSE is a global measure of cognition that is widely used in clinical trials assessing potential treatments on AD progression.[22] The CDR uses a seven-point anchored ordinal scale to characterize six domains of cognitive and functional performance: memory, orientation, judgment, community, hobbies, and personal care. The CDR is assessed with a semi-structured interview and has excellent reliability and validity.[23] Scores are re-

Figure 1 Dementia Progression Study (DPS) enrollment and follow-up



ported here both as a composite score (CDR-composite) and sum of boxes (CDR-Sum), which is the sum of ratings in each of six domains, with a range of 0 (no impairment) to 30 (maximum impairment in all domains). The primary outcome was CDR-Sum, which was chosen instead of CDR-composite because of its greater range and demonstrated sensitivity to change in MCI and AD as demonstrated in epidemiologic[24] and functional MRI studies.[25] CDR raters were blind to the diagnosis of vascular risk factors.

Assessment of vascular factors. Information on all vascular-related variables was obtained at the baseline visit (i.e., visit at which dementia was diagnosed) via proxy- and self-report. We examined both the utility of a VI and individual vascular risk factors in predicting AD progression. The VI was adapted from the stroke risk profile developed in the Copenhagen City Heart Study (CCHS).[26] This index is similar to the Framingham Stroke Risk Profile[27] but incorporates more self-reported data and is therefore closer to methods of the present study. Two modifications were made to the CCHS VI: 1) left ventricular hypertrophy was excluded because we did not have information on this condition in the CCSMHA; 2) age was excluded from the VI in order to study its effect as a potential confounder or modifier.

Using the same point system as the CCHS, we included the following variables in a VI: systolic blood pressure (SBP); history of atrial fibrillation (AF), diabetes mellitus (DM), smoking, and cardiovascular disease (CVD) (defined as history of myocardial infarction [MI], angina, or coronary artery bypass surgery [CABG]); and current antihypertensive medication use. SBP was measured at the baseline visit by a nurse while sitting after 5 minutes of rest. Information on AF, DM, smoking, and CVD was obtained via proxy- and self report. Ascertainment of medications in this study has been previously described[28] and relied on visual inspection of all available medication vials at each follow-up. When participants were institutionalized, this information was obtained from nursing home records. We classified participants as current antihypertensive medication users if they were regularly (≥4 times per week) taking a medication from the following drug classes at baseline: angiotensin converting enzyme inhibitors, β-blocking antiadrenergics (β-blockers), calcium ion channel blockers, and diuretics. Each vascular variable was also examined individually in relation to AD progression.

Data analysis. At DPS baseline, nine participants did not have a CDR score and 25 did not have a MMSE, leaving 216 participants with incident AD, 135 (63%) with at least one follow-up, for the present analyses (figure 1). Differences between individuals with or without a CDR or MMSE score were evaluated with t tests and χ^2 tests. The a priori p value was set at $p < 0.05$. Longitudinal analyses were conducted using linear mixed models, with time specified as a random effect, to examine baseline vascular factors as predictors of AD progression. These models are a form of a multilevel analysis in which repeated observations are nested within persons, thus controlling for within-subject variation. We examined baseline vascular factors as predictors of decline using CDR-Sum and MMSE as the primary outcomes. Each model included terms for time (in years since baseline), presence of vascular factors (or VI score), and their interaction. The term for time indicates the average annual rate of progression. The term for the VI or vascular factor indicates the average effect of the vascular variable at baseline. For example, it indicates the average difference in baseline CDR-Sum or MMSE score for a person with hypertension vs without. The interaction term indicates the average effect of the vascular factor on rate of progression per year. In additional analyses, we examined possible interactions between vascular factors (vf) and baseline age by incorporating two additional terms: vf*age and vf*age*time. Age was treated as a continuous variable in all analyses.

Covariates were chosen according to 1) statistical significance in univariate regression analyses, using $p < 0.05$ as cutoff for significance; 2) covariates known to be associated with AD incidence or progression from the literature. As unadjusted and adjusted models did not differ, we have only presented the adjusted models. Model 1 controlled for demographics including baseline age, gender, education, any vs no *APOE* ε4 alleles, dementia duration (years), baseline MMSE or CDR-Sum, and depression (defined as Neuropsychiatric Inventory depression subscale [frequency × severity] >4). Model 2 controlled for variables in model 1 plus all other cardiovascular variables except for models examining the VI because the vascular variables were used to determine the VI. SBP was examined as a continuous variable for the VI, and when examined as a separate variable, as continuous and dichotomous using two cutpoints (≥140 vs <140 and ≥160 vs <160). As we did not find associations between SBP as a continuous variable and when dichotomized at 140 mm Hg in relation to decline on either the MMSE or CDR, we have focused on SBP dichotomized at 160 mm Hg.

To assess the effects of mortality on the relationship between vascular factors and AD progression, we first examined baseline differences, using t tests and χ^2 analyses, between participants who died over the follow-up and those who did not. We then repeated the longitudinal analyses after excluding anyone who died in order to obtain the most conservative relationship between vascular factors and progression. All analyses were conducted using Stata Version 8.2 (StataCorp, College Station, TX).

RESULTS Of the 216 participants with incident

Table 1 Comparison of baseline information at incident Alzheimer disease diagnosis in participants with available CDR and MMSE measures and ≥1 follow-up (n = 135) and participants with no follow-up (n = 81)

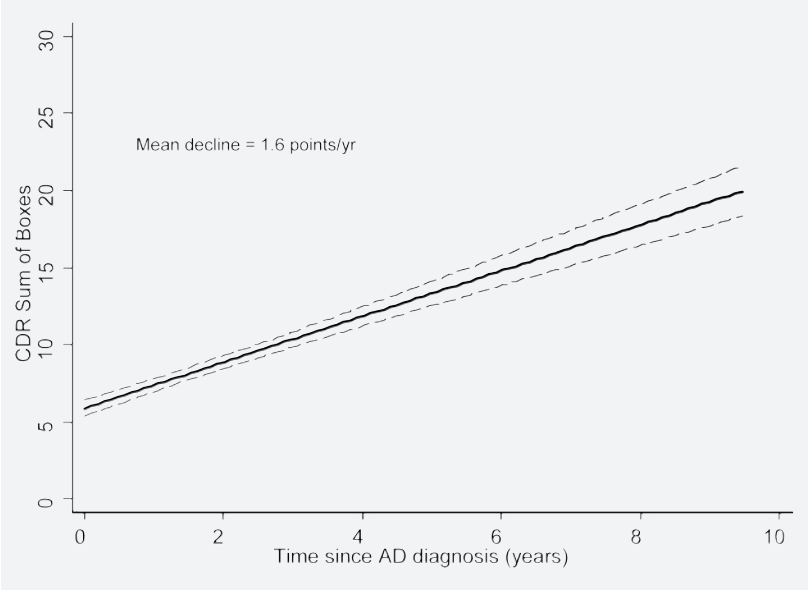
	≥1 Follow-up		No follow-up	
Variable	Total n	Mean (SD) or n (%)	Total n	Mean (SD) or n (%)
Demographics				
Baseline DPS age (t0)	135	84.2 (6.5)	81	87.3 (6.2)*
Female	135	89 (65.9%)	81	60 (74.1%)
White	135	135 (100%)	81	81 (100%)
Education	135	13.2 (2.8)	81	13.4 (2.9)
Married	135	69 (51.1%)	81	41 (50.6%)
Widowed/separated/divorced		63 (46.7%)		40 (49.4%)
Never married		3 (2.22%)		0
Any APOE ε4 allele	135	55 (40.7%)	81	37 (45.7%)
Dementia duration, y	135	2.1 (1.3)	81	1.7 (1.2)†
Functional/cognitive measures				
CDR Total Score	135	1.0 (0.5)	81	1.1 (0.5)
CDR Sum of boxes	135	6.3 (3.2)	81	6.4 (3.3)
MMSE	135	22.3 (4.3)	81	20.4 (4.8)*
GMHR	135	2.8 (0.6)	81	2.9 (0.7)
Cardiovascular				
Vascular index score	135	6.8 (4.9)	78	7.8 (7.3)
Current atrial fibrillation	135	10 (7.4%)	81	9 (11.1%)
Systolic blood pressure (continuous)	135	128.0 (16.9)	80	129.4 (18.9%)
Systolic blood pressure >160	135	10 (7.4%)	80	9 (11.3%)
Current smoking	135	2 (1.5%)	81	0
Ever stroke	135	9 (6.7%)	81	5 (6.2%)
Ever angina	135	14 (10.4%)	81	14 (17.3%)
Ever CABG	135	10 (7.4%)	81	5 (6.2%)
Ever MI	135	22 (16.3%)	81	16 (19.8%)
Ever diabetes	135	25 (18.52%)	81	12 (14.8%)
Any antihypertensive drug	135	49 (36.3%)	81	27 (34.2%)

†$p < 0.05$; *$p < 0.01$.
CDR = Clinical Dementia Rating; MMSE = Mini-Mental State Examination; DPS = Dementia Progression Study; CABG = coronary artery bypass graft surgery; MI = myocardial infarction.

AD and who had baseline CDR and MMSE scores, 135 (62.5%) had at least one additional follow-up. These participants were followed for a mean of 3.0 years (range: 0.8 to 9.5) and 2.1 follow-up visits (range: 1 to 5). Baseline characteristics of these participants are presented in table 1. Overall, the 135 participants assessed longitudinally were predominantly white women with mild dementia severity (mean Global CDR score = 1.0). Of the eight vascular factors (AF, SBP >160, angina, CABG, MI, DM, antihypertensive drug use, and stroke), 51 (37.8%) had no factors at baseline, 45 (33.3%) had one, 25 (18.5%) had two, and 14 (10.4%) had three or more. Compared to those with at least one follow-up visit, participants who did not have a DPS follow-up visit were older (87.3 vs 84.2 years, $p < 0.01$), had a lower MMSE (20.4 vs 22.3, $p < 0.01$), and a shorter dementia duration (1.7 vs 2.1 years, $p < 0.05$) but there were no differences with regards to baseline vascular factors. Mean baseline CDR-Sum was 6.3 (SD = 3.2) and increased an average of 1.6 points/year (95% CI: 1.3 to 1.6) while mean MMSE was 22.3 (AD = 4.3) and decreased an average of 1.9 points/year (95% CI: 1.7 to 2. 1) (figures 2 and 3).

Using linear mixed models to examine vascular factors as predictors of CDR-Sum and MMSE progression, the VI was not associated with either scale at baseline or with rate of decline (tables 2

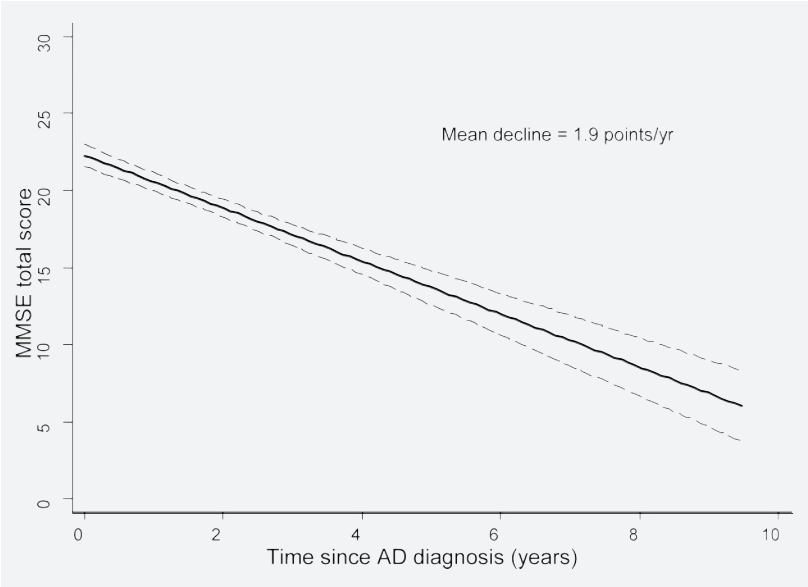
Figure 2 Annual mean decline and 95% CI for Mini-Mental State Examination (MMSE) after diagnosis of Alzheimer disease (AD)



CDR = Clinical Dementia Rating.

and 3). However, several individual vascular factors did predict rate of decline on both measures. In multivariate analyses controlling for demographic and other vascular variables (Model 2), AF and systolic hypertension (SBP >160 mm Hg) were independently associated with faster annual rates of decline on both the CDR-Sum and MMSE compared to participants without these conditions. Further, a history of DM or CABG was associated with slower rates of decline on both measures. Regular use of antihypertensive drugs at baseline was also associated with less decline on the CDR-Sum (table 2).

Figure 3 Annual mean decline and 95% CI for Clinical Dementia Rating (CDR)–Sum after diagnosis of Alzheimer disease (AD)



MMSE = Mini-Mental State Examination.

As vascular factors are associated with mortality, we conducted additional analyses to examine the effect of this type of censoring on our findings. Of the 216 participants initially enrolled in the DPS study, 113 (52.3%) died; 59 prior to the first follow-up (figure 1). Examining the VI and individual vascular factors at baseline, there were no differences ($p > 0.05$) in the prevalence of these factors between those who died and those who did not (data not shown). To further assess the effects of mortality, we repeated the linear mixed models excluding those who had died over the follow-up (tables E-1 and E-2 on the *Neurology*® Web site at www.neurology.org). The results were essentially the same, including the DM and CABG coefficients, except that a history of stroke at baseline was now associated with a faster rate of decline on the MMSE and a history of MI was associated with a slower rate of decline on the CDR-Sum.

Possible age interactions were examined with baseline age as a continuous variable. Using Student *t* tests, there were no differences in mean age ($p > 0.05$) for participants with and without each vascular factor. Using linear mixed models, baseline age was not associated with rate of decline on either the CDR-Sum or MMSE, controlling for sex, education, number of *APOE* ε4 alleles, and dementia duration. There were, however, interactions between vascular factors and age in predicting rate of decline (table 4). SBP ≥ 160, angina, and MI were associated with faster decline in older individuals on both the CDR-Sum and MMSE. An example of this interaction is observed in figure 4 using age 85 as an arbitrary cutoff for interpretability and rate of decline using CDR-Sum. Participants older than 85 with a SBP > 160 (3.01 point increase per year, 95% CI: 1.78, 4.25) had a faster rate of decline than participants younger than 85 with a SBP >160 (1.65; 95% CI: 0.99, 2.31), or older than 85 without hypertension (0.32; 95% CI: −0.02, 0.66). Similar results were found using the MMSE.

DISCUSSION In this population-based study of incident AD cases, we found no association between a VI and rate of progression on either the CDR-Sum or MMSE. A main reason for this null finding was that, upon further examination, some individual vascular factors were associated with an increased rate of decline whereas others were associated with a decreased rate. A recent study

Table 2 Baseline vascular factors as predictors of CDR-Sum decline in Alzheimer disease

	Multivariate model 1		Multivariate model 2	
Variable	coeff (95% CI)	coeff × time (95% CI)	coeff (95% CI)	coeff × time (95% CI)
Vascular index	0.03 (−0.05, 0.10)	0.01 (−0.02, 0.03)		
Atrial fibrillation	−0.01 (−1.52, 1.50)	1.31 (0.74, 1.88)*	−0.08 (−1.61, 1.45)	1.27 (0.70, 1.84)*
SBP (continuous)	0.01 (−0.13, 0.04)	0.01 (−0.004, 0.01)	0.01 (−0.01, 0.04)	0.01 (−0.003, 0.01)
SBP ≥160 vs <160	−0.10 (−1.59, 1.39)	1.80 (1.23, 2.38)*	−0.06 (−1.56, 1.45)	1.78 (1.20, 2.36)*
Angina	−0.56 (−1.86, 0.73)	0.55 (0.08, 1.02)†	−0.72 (−2.16, 0.71)	0.45 (−0.02, 0.92)†
CABG	0.90 (−0.76, 2.58)	−1.52 (−2.30, −0.74)*	0.61 (−1.18, 2.40)	−1.46 (−2.24, −0.69)*
MI	0.37 (−0.79, 1.54)	0.07 (−0.37, 0.50)	0.62 (−0.69, 1.94)	0.11 (−0.32, 0.55)
Diabetes	1.00 (−0.15, 2.16)	−0.88 (−1.26, −0.50)*	0.57 (−0.62, 1.77)	−0.84 (−1.22, −0.47)*
Any antihypertension medication	0.43 (−0.51, 1.36)	−0.54 (−0.96, −0.13)‡	0.45 (−0.47, 1.36)	−0.61 (−1.03, −0.19)‡
Stroke	0.55 (−1.18, 2.28)	−0.11 (−0.67, 0.45)	0.75 (−0.98, 2.47)	−0.04 (−0.59, 0.51)

Model 1: Controlling for age, sex, education, dementia duration, any *APOE* ε4 alleles, depression (Neuropsychiatric Inventory > 4), Mini-Mental State Examination. Model 2: Controlling for model 1 + other vascular variables.
*$p < 0.001$, †$p < 0.05$, ‡$p < 0.01$.
CDR = Clinical Dementia Rating; SBP = systolic blood pressure; CABG = coronary artery bypass graft surgery; MI = myocardial infarction.

reported that a vascular risk score calculated in middle-aged people predicted risk of dementia 20 years later.[29] Our findings suggest that combining vascular factors to create a VI at the time of AD diagnosis does not predict subsequent progression, indicating that the benefits of incorporating a VI may be stage-specific.

Our initial hypothesis, that vascular factors would increase the rate of progression in AD, was supported in that systolic hypertension, AF, and angina were associated with faster rates of decline on the CDR-Sum or MMSE. Systolic hypertension and AF have been reported as risk factors for incident dementia and AD,[2,3,5] and our results suggest that they are also associated with a faster rate of progression after the diagnosis of AD. In addition, AD has been associated with small-vessel atherosclerotic disease and angina is a likely marker for atherosclerosis throughout the body; not surprisingly, angina is associated with faster decline in patients with AD dementia.

We also report that vascular factors including antihypertensive medication use, CABG, and diabetes are associated with less decline on both the

Table 3 Baseline vascular factors as predictors of cognitive (Mini-Mental State Examination) decline in Alzheimer disease

	Multivariate model 1		Multivariate model 2	
Variable	coeff (95% CI)	coeff × time (95% CI)	coeff (95% CI)	coeff × time (95% CI)
Vascular index	0.02 (−0.08, 0.12)	−0.01 (−0.05, 0.02)		
Atrial fibrillation	−0.21 (−2.27, 1.84)	−1.57 (−2.40, −0.73)*	−0.06 (−2.13, 2.02)	−1.56 (−2.39, −0.73)*
SBP (continuous)	0.004 (−0.03, 0.04)	−0.01 (−0.02, 0.003)	0.002 (−0.03, 0.03)	−0.01 (−0.02, 0.003)
SBP ≥160 vs <160	0.29 (−1.75, 2.33)	−2.48 (−3.33, −1.62)*	0.12 (−1.92, 2.17)	−2.38 (−3.23, −1.53)*
Angina	−0.38 (−2.13, 1.37)	−0.35 (−0.99, 0.28)	−0.14 (−2.09, 1.80)	−0.30 (−0.94, 0.33)
CABG	−0.03 (−2.32, 2.27)	1.80 (0.80, 2.80)*	0.82 (−1.67, 3.31)	1.75 (0.76, 2.74)†
MI	−0.57 (−2.16, 1.01)	−0.51 (−1.07, 0.05)	−1.10 (−2.91, 0.71)	−0.55 (−1.11, 0.001)
Diabetes	0.07 (−1.49, 1.64)	1.17 (0.68, 1.65)*	0.25 (−1.39, 1.89)	1.13 (0.65, 1.62)*
Any antihypertension medication	0.12 (−1.13, 1.37)	0.27 (−0.26, 0.80)	0.09 (−1.16, 1.34)	0.32 (−0.21, 0.85)
Stroke	0.40 (−1.96, 2.75)	−0.29 (−1.00, 0.41)	−0.03 (−2.37, 2.32)	−0.34 (−1.04, 0.35)

Model 1: Controlling for age, sex, education, dementia duration, any *APOE* ε4 alleles, depression (Neuropsychiatric Inventory > 4), CDR-Sum of Boxes. Model 2: Controlling for model 1 + other vascular variables.
*$p < 0.001$, †$p < 0.01$.
CDR = Clinical Dementia Rating; SBP = systolic blood pressure; CABG = coronary artery bypass graft surgery; MI = myocardial infarction.

Table 4 Vascular and age interactions in predicting progression (vascular factor × age and vascular factor × age × time)

	CDR*				MMSE†			
Variable	coeff (95% CI)	*p* Value	coeff × time (95% CI)	*p* Value	coeff (95% CI)	*p* Value	coeff × time (95% CI)	*p* Value
Atrial fibrillation	0.07 (−0.19, 0.33)	0.581	−0.03 (−0.13, 0.08)	0.599	0.14 (−0.22, 0.49)	0.452	0.11 (−0.02, 0.25)	0.103
SBP ≥160 vs <160	−0.01 (−0.33, 0.31)	0.947	0.20 (0.01, 0.39)	0.040	0.22 (−0.21, 0.65)	0.317	−0.26 (−0.52, −0.01)	0.045
Angina	−0.18 (−0.37, 0.001)	0.052	0.14 (0.07, 0.22)	<0.001	−0.03 (−0.23, 0.28)	0.847	−0.12 (−0.22, −0.03)	0.013
CABG	−0.07 (−0.38, 0.24)	0.639	0.15 (−0.06, 0.36)	0.166	0.02 (−0.41, 0.44)	0.933	−0.01 (−0.26, 0.04)	0.939
MI	−0.10 (−0.30, 0.09)	0.297	0.18 (0.09, 0.27)	<0.001	0.35 (0.08, 0.61)	0.011	−0.12 (−0.23, 0.002)	0.053
Diabetes	−0.03 (−0.21, 0.16)	0.784	0.02 (−0.05, 0.10)	0.529	0.07 (−0.19, 0.32)	0.609	−0.02 (−0.11, 0.08)	0.717
Any antihypertension medication	−0.13 (−0.27, 0.02)	0.093	0.05 (−0.03, 0.13)	0.207	−0.06 (−0.26, 0.14)	0.537	−0.09 (−0.19, 0.01)	0.087

Positive numbers indicate worse functioning on Clinical Dementia Rating (CDR); negative numbers indicate worse functioning on Mini-Mental State Examination (MMSE).

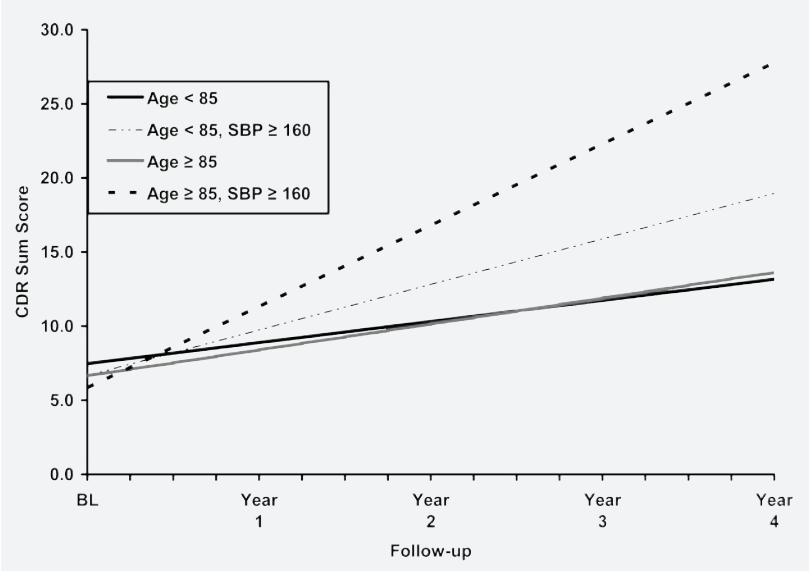
*Controlling for age, sex, education, dementia duration, any *APOE* ε4 alleles, depression (Neuropsychiatric Inventory > 4), MMSE, and other vascular variables.

†Controlling for age, sex, education, dementia duration, any *APOE* ε4 alleles, depression (Neuropsychiatric Inventory > 4), CDR-Sum, and other vascular variables.

SBP = systolic blood pressure; CABG = coronary artery bypass graft surgery; MI = myocardial infarction.

CDR-Sum an MMSE. Antihypertensive medications have been reported to decrease the risk of AD onset in the Cache County Study.[30] Our findings further suggest that these medications may also be important in slowing progression once a person is diagnosed with AD. However, the association between CABG and slower rate of decline is somewhat surprising. CABG has been associated with cognitive impairment and dementia in a previous report from the Cache County Study[31] and others,[32] although not specifically with AD onset. A potential mechanism by which CABG may be associated with slower decline is through improved cardiac output. This could lead to improved cerebral perfusion, which in turn improves outcome in AD by enhancing function of marginally functioning brain regions or by increasing clearance of toxic AD moieties from the brain including amyloid-beta. There may also be an inherent bias such that individuals who undergo CABG might be health seekers who are examined and treated aggressively by their clinicians. As such, they could progress more slowly because of better general health that might not be measurable in demographic terms.

Figure 4 Interaction between age and systolic blood pressure in predicting more rapid decline on Clinical Dementia Rating (CDR)-Sum progression in patients with Alzheimer disease



The slower decline observed with diabetes is counterintuitive because type II diabetes is associated with atherosclerosis and increased risk of AD.[6,33,34] However, other epidemiologic studies[8,35-37] have either reported that diabetes does not increase the risk for AD or find an association only in specific subgroups (specific age groups; *APOE* ε4 negative). One caveat is that the DPS cohort is elderly with a mean age of 85 years, and diabetics in the study may be hearty survivors not representative of the typical course of disease. Another possible explanation is that elderly diabetic patients were taking PPAR-gamma antagonists, such as rosiglitazone, which improved cognition and function in a recent AD clinical trial.[38] Alternatively, it is also possible that individuals who have medical conditions which are diagnosed and treated may be different from those who have the same conditions but go untreated. Finally, it is possible that the effect of diabetes, as well as CABG, on AD depends on the stage of the disease. For example, diabetes may be a risk factor for incident AD, but may not be associated with progression after the onset.

Epidemiologic studies have highlighted the timing of hypertension and hypercholesterolemia

in relation to risk of AD. Both factors, when measured in midlife,[2,3,39,40] have been found to increase the risk of AD but, when measured in late life, either have no effect or are found to decrease the risk of subsequent AD.[12,13] Interestingly, we also found age interactions in predicting progression after the onset of AD. Systolic hypertension, angina, and MI were associated with greater progression on both the CDR and MMSE with increasing age. Clearly these risk factors need to be addressed at younger ages before the onset of cognitive impairment. Future research is needed in this area because determination of age-specific risk factors is important in defining the patient population in which intervention may lead to effective secondary prevention of AD.

There are several strengths to this study. This was a longitudinal population-based study with incident AD cases, thereby attenuating selection bias found in clinical studies of Alzheimer progression. Second, the participants have been well-characterized over many years of observation (from the Cache County Memory Study and the DPS). Third, participants with primary or comorbid vascular dementia were excluded so as to prevent circularity with regards to vascular risk factors and diagnosis of AD. Despite these strengths several limitations warrant consideration. The sample size was small, especially with regard to multiple follow-ups. Thus, we may have not had enough power to detect associations between other vascular factors not found to be associated with progression. The continuation of DPS, including additional enrollees and longer-term follow-up, will provide more data for future evaluations to clarify these results. Additionally, information on vascular factors was primarily based on self- and proxy-report. As underreporting is more likely than over-reporting, these findings are conservative and, therefore, vascular factors could play a larger role in AD progression. Finally, dates of onset for vascular factors were not available. It is possible, for example in diabetes, that older onset cases are less severe and therefore may not be as important in predicting AD progression compared to earlier onset cases.

This study suggests that the use of a vascular index to predict rate of progression in AD is not useful at this stage of the disease. However, the presence of individual vascular factors at the time of AD diagnosis does influence rate of cognitive and functional progression. Specifically, AF, systolic hypertension, and angina were associated with more rapid progression and may suggest strategies for secondary prevention in AD. The findings that CABG and diabetes were associated with less decline are counterintuitive and more research is clearly needed before recommendations can be made. Importantly, we also found that MI, angina, and systolic hypertension had a greater affect on decline in the older vs younger participants. This suggests that these factors may be age-specific and that there is continued need to treat these conditions as early as possible. On average, this population experienced an annual increase of 1.6 points on the CDR-Sum and an annual decrease of 1.9 points on the MMSE. Some vascular factors, such as systolic hypertension, had progression exceeding these levels, thereby doubling the rate in the presence of this factor. As vascular variables are potentially modifiable, these findings suggest means for secondary prevention in AD. Further research and attention to these vascular factors in relation to AD progression is clearly warranted.

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