ORIGINAL CONTRIBUTION

Contribution of Vascular Risk Factors to the Progression in Alzheimer Disease

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Background: Vascular factors including medical history (heart disease, stroke, diabetes, and hypertension), smoking, and prediagnosis blood lipid measurements (cholesterol: total, high-density lipoprotein, low-density lipoprotein [LDL-C], and triglyceride concentrations) may be predictors for progression of Alzheimer disease (AD).

Objective: To determine whether prediagnosis vascular risk factors are associated with progression of AD.

Design: Inception cohort followed up longitudinally for a mean of 3.5 (up to 10.2) years.

Setting: Washington Heights/Inwood Columbia Aging Project, New York, New York.

Patients: One hundred fifty-six patients with incident AD (mean age at diagnosis, 83 years).

Main Outcome Measure: Change in a composite score of cognitive ability from diagnosis onward.

Results: In generalized estimating equation models (adjusted for age, race/ethnicity, and years of education), higher cholesterol (total cholesterol and LDL-C) concentrations and history of diabetes were associated with faster cognitive decline. Each 10-U increase in cholesterol and LDL-C was associated with a 0.10-SD decrease in cognitive score per year of follow-up ($P < .001$ for total cholesterol; $P = .001$ for LDL-C). High-density lipoprotein cholesterol and triglyceride concentrations were not associated with rate of decline. A history of diabetes was associated with an additional 0.05-SD decrease in cognitive score per year ($P = .05$). History of heart disease and stroke were associated with cognitive decline only in carriers of the apolipoprotein E ε4 (*APOE-ε4*) gene. In a final generalized estimating equation model that included high-density lipoprotein cholesterol and LDL-C concentrations and history of diabetes, only higher LDL-C was independently associated with faster cognitive decline.

Conclusion: Higher prediagnosis total cholesterol and LDL-C concentrations and history of diabetes were associated with faster cognitive decline in patients with incident AD, which provides further evidence for the role of vascular risk factors in the course of AD.

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FEW TREATMENT OPTIONS ARE available to improve the prognosis in patients with Alzheimer disease (AD). Controlling vascular conditions may be one way of delaying the disease course. Vascular risk factors and vascular disease are associated with higher risk of vascular dementia[1,2] and AD.[3,4] Members of our group previously reported associations between stroke,[5] hyperinsulinemia,[6] diabetes mellitus,[7] current smoking,[8] and hypertension[9] and higher risk of AD. We found that high total cholesterol and low-density lipoprotein cholesterol (LDL-C) concentrations are related to increased risk of vascular dementia[10,11] but not AD.

While vascular risk factors have been studied as predictors of AD,[4,12] few studies have assessed their influence on disease progression.[13,14] We examined the interplay between vascular factors and course of AD in participants from the Washington Heights/Inwood Columbia Aging Project, a multiethnic, community-based, prospective study of aging in northern Manhattan (New York, New York).

METHODS

PARTICIPANTS

Participants in the Washington Heights/Inwood Columbia Aging Project are from 2 population-based cohorts of Medicare enrollees. Recruitment for the first cohort began in January 1992. The study area comprised 41 census tracts in Manhattan between 155th Street and 181st Street. Lists of Medicare recipients in the
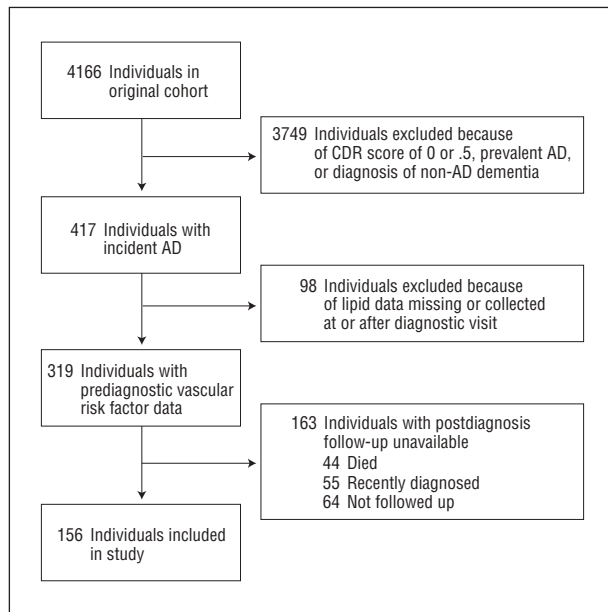
Figure. Flowchart of analysis sample selection. AD indicates Alzheimer disease; CDR, Clinical Dementia Rating Scale.

study area were obtained from the Health Care Financing Administration. Potential participants were selected by systematic random sampling into 1 of 6 strata on the basis of race/ethnicity (Hispanic, non-Hispanic black, and non-Hispanic white) and age (65-74 or >75 years). At baseline, 2125 subjects were interviewed. A cohort of 2183 additional participants was formed in November 1999 using similar methods with several exceptions: new lists of beneficiaries were obtained but those drawn into the 1992 cohort were excluded, subjects who reported receiving a diagnosis of dementia in the course of arranging for the initial evaluation were excluded, and the study area was extended to encompass Manhattan north of 145th Street.

The sample for this analysis was restricted to individuals with lipid assessments before diagnosis of dementia. During follow-up, 417 individuals developed AD. Of these, prediagnosis vascular risk factor data were available for 319, 156 of whom also had postdiagnosis follow-up data (**Figure**). Of the individuals with incident AD with vascular risk factors, 44 (14%) died, 55 (17%) received the diagnosis in the most recent interview wave and, therefore, had no postdiagnosis data available, and 64 (20%) were not followed up because of refusal or study dropout. Excluded patients with AD were similar to the analysis sample insofar as age, sex, race/ethnicity; cognitive status at diagnosis; *APOE*-ε4 status; total cholesterol, high-density lipoprotein cholesterol (HDL-C), and LDL concentrations; and presence of hypertension, stroke, and heart disease. However, excluded participants had achieved higher educational levels (8.1 vs 6.6 years; *P*=.002), had a higher prevalence of diabetes (29% vs 18% of the analysis; *P*=.02), and had lower triglyceride concentrations (mean, 154.9 vs 173.2 mg/dL; *P*=.04) (to convert to millimoles per liter, multiply by 1.8).

The study was approved by the Columbia University Institutional Review Board. Written informed consent was obtained from all subjects.

ASSESSMENT OF INCIDENT AD

Alzheimer disease was diagnosed using physician-administered physical and neurologic examinations along with a standardized neuropsychologic battery of tests.[15] All assessments were administered at baseline and at follow-up visits,

which occurred at approximately 18-month intervals. Evaluations were conducted in English or Spanish according to participant preference. All available information including medical records and imaging studies was considered in the evaluations.

Consensus diagnosis of dementia was made at conferences attended by neurologists and neuropsychologists using the neuropsychologic battery of tests and evidence of social or occupational functional deficits per *Diagnostic and Statistical Manual of Mental Disorders* (Third Edition Revised) criteria. Diagnosis of probable or possible AD was based on the National Institute of Neurological and Communicative Disorders and Stroke/Alzheimer Disease and Related Disorders Association criteria.[16]

OUTCOME MEASURES

Five cognitive domains were assessed including (1) Memory: total and delayed recall of the Selective Reminding Test[17] and the Recognition Subtest of the multiple-choice Benton Visual Retention Test[18]; (2) Abstract Reasoning: Wechsler Adult Intelligence Scale–Revised Similarities Subtest[19]; Identities and Oddities Subtest of the Dementia Rating Scale[20]; (3) Visual-Spatial: 5 items from the Rosen Drawing Test[21]; the matching component of the multiple-choice Benton Visual Retention Test[18]; (4) Language: 15-item Boston Naming Test[22] and the 8 high-probability items from the Repetition Subtest and the first 6 items of the Comprehension Subtest of the Boston Diagnostic Aphasia Examination[22]; and (5) Executive-Speed: mean scores for phonemic fluency assessed by the Controlled Oral Word Association Test and category fluency (Animals, Food, and Clothing) mean scores.[23]

The 12 test scores were transformed into *z* scores. Means and standard deviations were calculated from baseline scores for subjects without dementia matched for age, race/ethnicity, and years of education. The *z* scores were averaged within cognitive domains, which were subsequently averaged to produce the composite cognitive score.[24] The outcome measure was the rate of change in the composite score from diagnosis onward.

PREDICTOR VARIABLES

Baseline age, sex, race/ethnicity, and years of education were collected by interview. Stroke was defined by World Health Organization criteria.[25] Diabetes and hypertension were defined based on self-report or documented treatment of either disorder at any time up to diagnosis of AD. Heart disease was defined as a history of myocardial infarction, congestive heart failure, or angina pectoris at any time up to diagnosis of AD.

Fasting plasma total cholesterol and triglyceride concentrations were measured at a mean (SD) of 3.3 (2.2) years before diagnosis using standard enzymatic techniques. High-density lipoprotein cholesterol concentrations were determined after precipitation of apolipoprotein B–containing lipoproteins with phosphotungstic acid. Low-density lipoprotein cholesterol concentrations were recalculated using the Friedewald formula.[26] Because HDL-C and triglyceride values were not normally distributed, log-transformed versions of these variables were used. Apolipoprotein E (*APOE*) genotype, determined using established methods,[27] was available for 132 of the 156 participants (85%) and was classified on the basis of presence of at least 1 *APOE*-ε4 allele.

STATISTICAL ANALYSIS

Generalized estimating equations[28] were used to examine the relation of vascular factors to rates of cognitive change. By treating each subject's repeated measures as a cluster, generalized

estimating equations account for the correlation of repeated measures in the same individual. Two models were developed.

Model 1

Separate models were developed to assess the association of each vascular variable (heart disease, stroke, diabetes, hypertension, smoking, and prediagnosis lipid concentrations) with postdiagnosis cognitive decline. Taking diabetes as an example, the dependent variable was the composite cognitive score, and predictor variables were diabetes, time (years), and a diabetes-time interaction. Age at AD incidence, sex, race/ethnicity, years of education (years), and study cohort were simultaneously introduced into models. A significant diabetes effect would suggest a diabetes-associated difference in cognition at diagnosis. A significant time effect would suggest change in cognitive scores over time regardless of diabetes status. A significant interaction term would suggest differential rates of postdiagnosis cognitive change associated with diabetes. The interval between lipid measurement and AD incidence was included as a covariate in the lipid models.

Model 2

To determine whether any vascular factor was independently associated with cognitive decline, we constructed a post hoc model that simultaneously included all variables associated with cognitive decline after age- or multivariable-adjustment (cholesterol concentrations and diabetes) (model 1), their interactions with time, and demographic factors. Diabetes and LDL-C and HDL-C concentrations but not total cholesterol concentration were included in this model.

Supplementary Analyses

We repeated our analyses within *APOE*-ε4 strata in the subsample with genotyping data (n=132). We also examined whether use of lipid-lowering agents (LLAs) was associated with cognitive decline and whether cholesterol concentrations predicted rate of decline similarly in LLA users vs nonusers.

RESULTS

Characteristics of the overall sample are given in **Table 1**. At diagnosis, most participants (93%) had a clinical dementia rating of 1.0 (mild).[29] The mean (SD) follow-up time between diagnosis and last follow-up was 3.5 (2.2) years (range, 1.0-10.3 years), with 1.6 (0.9) postdiagnostic assessments (range, 2-5).

PREDICTOR VARIABLES AND BASELINE CHARACTERISTICS

There were no sex-related differences in predictor variables except for higher total cholesterol concentrations in women (201.16 vs 184.53 mg/dL; *P*=.01). At diagnosis, non-Hispanic whites were, on average, 2.6 years older than blacks (*P*=.26) and 3.4 years older than Hispanics (*P*=.03). Prevalent disease variables (heart disease, stroke, diabetes, and hypertension) did not vary by race/ethnicity. Blacks had higher mean HDL-C concentrations (55.3 mg/dL) compared with whites (43.8 mg/dL; *P*=.004) and Hispanics (43.2 mg/dL; *P*<.001) and lower mean triglyceride concentrations (139.5 mg/dL) com-

Table 1. Characteristics of Patients With Incident Alzheimer Disease

Variable	All Patients (N=156)
Age at diagnosis, mean (SD), y	83.0 (6.4)
Male sex, No. (%)	45 (28.8)
Years of education, mean (SD), y	6.6 (4.5)
Baseline cognitive score, mean (SD)	−1.14 (0.56)
Race/ethnicity, No. (%)	
Non-Hispanic white	14 (9.0)
Non-Hispanic black	46 (29.5)
Hispanic	94 (60.3)
Other	2 (1.3)
Cholesterol concentration, mean (SD), mg/dL	
Total	196.4 (36.9)
Low-density lipoprotein	114.5 (34.6)
High-density lipoprotein	47.2 (14.3)
Triglyceride concentration, mean (SD), mg/dL	173.2 (70.9)
Comorbidity, No. (%)	
Diabetes	25 (16.0)
Hypertension	113 (72.4)
Heart disease	28 (17.9)
Stroke	24 (15.4)
Presence of at least 1 *APOE*-ε4 allele, No. (%)	43 (27.6)
Postdiagnosis follow-up, mean (SD), y	3.5 (2.2)

Abbreviation: *APOE*-ε4, apolipoprotein E ε4.
SI conversion factors: To convert all cholesterol to millimoles per liter, multiply by 0.0259; triglyceride to millimoles per liter, multiply by 0.0113.

pared with whites (207.1 mg/dL; *P*=.001) and Hispanics (186.1 mg/dL; *P*<.001). There were no differences by race/ethnicity for sex, total cholesterol or LDL-C concentrations, or *APOE*-ε4 status (data not shown).

COGNITIVE DECLINE OVER TIME

A generalized estimating equation model indicated an overall decline in composite cognitive score of 0.08 SD per year (β=−.08, *P*<.001). A quadratic term for time, added to the model to test whether cognitive change was nonlinear, was nonsignificant.

VASCULAR FACTORS AND COGNITIVE DECLINE

Results of model 1 for each predictor are given in **Table 2**. Higher total cholesterol and LDL-C concentrations were associated with faster cognitive decline. Each 10-mg/dL–U increase in total cholesterol or LDL-C concentration was associated with an additional 0.10-SD decline in cognitive score per year (*P*<.001 for total cholesterol and *P*=.003 for LDL-C) (to convert all types of cholesterol to millimoles per liter, multiply by 0.0259). Neither HDL-C nor triglyceride concentration was associated with cognitive decline. Of the medical history variables, only diabetes was associated with faster decline (β=−.05, *P*=.045).

MODEL 2

In a post hoc model that simultaneously included HDL-C and LDL-C concentrations and diabetes and their interactions with time, only LDL-C was independently associated with faster cognitive decline (**Table 3**).

Table 2. Separate GEE Models Measuring Decline in Cognitive Function Associated With Vascular Risk Factors[a]

| Predictor | Outcome: Composite Cognitive z Score | | | |
| | Age-Adjusted | | Multivariable-Adjusted | |
	β	P Value	β	P Value
Total cholesterol	.000	.95	−.001	.31
Time × total cholesterol, y	**−.001**	**.04**	**−.001**	**.03**
HDL-C, log-transformed	**.35**	**.02**	.22	.15
Time × HDL-C, y	**−.02**	**.61**	−.06	.20
LDL-C, log-transformed	.001	.70	−.001	.31
Time × LDL-C, y	**−.001**	**.04**	**−.001**	**.045**
Triglyceride concentration, log-transformed	−.17	.15	−.15	.22
Time × triglyceride concentration, y	−.01	.66	−.006	.85
Diabetes	−.11	.37	−.08	.46
Time × diabetes, y	**−.05**	**.03**	**−.05**	**.045**
Hypertension	−.21	.16	−.21	.14
Time × hypertension, y	.01	.77	.000	.99
History of stroke	−.03	.88	−.05	.77
Time × stroke, y	−.045	.29	−.04	.31
History of heart disease	.049	.69	.02	.91
Time × heart disease, y	−.07	.07	−.06	.16
Ever smoked, baseline	−.11	.28	−.04	.68
Time × ever smoked, y	.03	.36	.03	.33

Abbreviations: GEE, generalized estimating equation; HDL-C and LDL-C, high-density and low-density lipoprotein cholesterol, respectively.
[a] All models also included the following covariates, entered simultaneously: time, age at incidence, sex, race/ethnicity, years of education (years), and study cohort. Models for lipid variables additionally controlled for and time between the lipid draw and dementia incidence. Significant (P < .05) coefficients are indicated in bold type.

SUPPLEMENTARY ANALYSES

In participants with genotype data, the presence of at least 1 *APOE-ε4* allele was associated with faster cognitive decline (model 1) (multivariable-adjusted β for interaction with time: β = −.08, P = .05). The *APOE-ε4*–stratified models revealed that in *APOE-ε4* noncarriers (n = 89), higher prediagnosis total cholesterol, LDL-C, and HDL-C concentrations were associated with faster cognitive decline (multivariable-adjusted β for interactions with time: total cholesterol, β = −.001, P < .001; LDL-C, β = −.001, P = .02; and HDL-C, β = −.13, P = .01). Triglyceride concentrations and medical history were not associated with cognitive decline (data not shown). Among *APOE-ε4* carriers (n = 41), higher total cholesterol (β = −.002, P = .03) and LDL-C (β = −.002, P = .03) concentrations and stroke (β = −.18, P = .02) and heart disease (β = −.19, P = .001) were associated with faster decline. No associations were seen with the remaining vascular variables (data not shown).

The use of LLAs was not associated with rate of cognitive decline. Models of the association of cholesterol concentration with cognitive decline were repeatedly stratified by use of LLAs, and results were similar (data not shown).

Table 3. Post Hoc GEE Model Including Vascular Risk Factors Significantly Associated With Cognition in Individual Models[a]

Variable	β (95% CI)	P Value
Intercept	−1.25 (−3.05 to 0.55)	.17
Time, diagnosis onward, y	.30 (−0.03 to 0.64)	.08
Cohort, 1999 vs 1992	.008 (−0.10 to 0.11)	.89
Age at diagnosis, per additional year	−.01 (−.02 to 0.002)	.11
Female sex	.07 (−0.17 to 0.31)	.55
Race/ethnicity		
Non-Hispanic black	−.22 (−0.67 to 0.23)	.34
Hispanic	−.292 (−0.733 to 0.150)	.20
Years of education, per additional year	.04 (0.02 to 0.06)	<.001
Time between lipid draw and AD incidence, y	.003 (−0.05 to 0.06)	.90
Cholesterol concentration		
LDL-C	.000 (−0.003 to 0.002)	.67
Time × LDL-C	**−.001 (−0.002 to 0.000)**	**.001**
HDL-C, log-transformed	.25 (−0.06 to 0.56)	.11
Time × HDL-C	−.06 (−0.14 to 0.02)	.16
Diabetes history	−.08 (−.30 to 0.13)	.45
Time × diabetes history, y	−.046 (−0.11 to 0.01)	.14

Abbreviations: AD, Alzheimer disease; CI, confidence interval; GEE, generalized estimating equation; HDL-C and LDL-C, high-density and low-density lipoprotein cholesterol, respectively.
[a] Significant factors associated with differential change in cognition over time are indicated in bold type.

COMMENT

There has been intense interest in identifying modifiable AD risk factors such as cardiovascular risk factors, with the goal of preventing or at least delaying disease onset.[4] However, little attention has been given to the influence of these factors on disease progression. Cerebrovascular lesions, common in patients with AD, may accelerate the clinical manifestation of AD.[30] Vascular risk factors may increase oxidative stress or activate a neuroinflammatory response, triggering amyloid production. Thus, it has been suggested that AD and cerebrovascular disease may work synergistically to cause cognitive decline.[31]

Consistent with previous research,[32] we found that higher total cholesterol and LDL-C concentrations were associated with faster cognitive decline in patients with AD. An earlier study of the Washington Heights/Inwood Columbia Aging Project cohort found that higher total cholesterol concentration was associated with lower risk of incident AD.[10] The prodromal stage of AD is associated with decreased plasma cholesterol concentrations, possibly owing to dietary insufficiency and weight loss. By limiting the present study to incident cases, we may have eliminated bias or confounding in cholesterol concentrations associated with frailty and preclinical AD. This may explain the difference with our findings for incident AD.

Lipid-lowering agents have previously been associated with slower cognitive decline in patients with AD.[33] Nevertheless, consistent with others,[13] we found no association between LLAs and cognitive decline.

Of the medical history variables, only diabetes was associated with faster cognitive decline. Diabetes may in-

fluence AD progression via an inflammatory mechanism or by contributing to amyloid plaque and neurofibrillary tangle formation.[34] Heart disease, stroke, hypertension, and smoking history were not associated with disease progression in the overall sample.

The *APOE*-ɛ4 genotype may contribute to both vascular disease and AD neuropathologic features, with effects of vascular risk factors more pronounced among *APOE*-ɛ4 carriers.[35] A previous study of this cohort found faster cognitive decline in participants with mild AD who were *APOE*-ɛ4 carriers.[36] In our *APOE*-ɛ4–stratified models, higher total cholesterol and LDL-C concentrations predicted faster decline in both groups, whereas history of heart disease or stroke predicted faster decline in *APOE*-ɛ4 carriers only.

Few studies have examined the simultaneous effects of multiple vascular risk factors on AD progression. A study of prevalent AD found that stroke but not other vascular factors was associated with faster decline on the Mini-Mental State Examination.[13] A study of incident cases found faster decline on the Clinical Dementia Rating Scale and the Mini-Mental State Examination in those with a history of atrial fibrillation, systolic hypertension, and angina at baseline, and diabetes was associated with slower decline.[14] Our findings may differ from those of these studies for several reasons: (1) we measured cognitive change using a comprehensive battery of cognitive tests, which is potentially more sensitive than the Mini-Mental State Examination; (2) one of the previous studies[13] included some participants with relatively advanced AD; and (3) both of the previous studies were limited to whites, who, on average, were more highly educated than our multiethnic sample. In our post hoc model, only higher LDL-C concentration emerged as an independent predictor. The negative finding for diabetes as an independent predictor may be to the result of reduced power in the post hoc analysis because the β value associated with diabetes-related cognitive change was similar to the diabetes-specific model.

This study has limitations. Because disease history (heart disease, stroke, and diabetes) was self-reported, the prevalence of these conditions in our sample was likely underestimated. Further, 44 of the participants with incident AD were not included in this analysis because they died before the next follow-up assessment. Cause of death was unavailable; however, it is likely that many of these deaths were due to vascular disease. If so, the effect size we found may be an underestimate. We had only 1 lipid assessment, potentially resulting in measurement error. Although lipid concentrations were measured before diagnosis, some participants may have had prodromal AD. We attempted to account for this by adjusting for the interval between lipid measurement and diagnosis; results were unchanged. Similarly, AD-associated reductions in blood pressure may have masked an association between hypertension and disease progression that might have been noted had blood pressure been measured at midlife. In future longitudinal studies, it would be better to measure these factors earlier in life. Our AD diagnoses were not neuropathologically confirmed, and imaging was not consistently used as part of the diagnostic process. Previous studies using magnetic resonance imaging and neuropathologic data sug-

gest that, especially in the oldest old, mixed dementia (AD plus vascular dementia) is the most common cause of dementia.[37] Therefore, it is likely that some of our patients with AD actually had mixed dementia. In addition, there is always the possibility that our findings could be due to chance.

Despite these limitations, clinical diagnosis was based on uniform application of widely accepted criteria and, unlike cognitive screening instruments used in some studies, our cognitive assessment comprised a comprehensive battery of tests evaluating a range of cognitive domains. Our use of a population-based sample limited to individuals with incident AD reduced biases associated with convenience samples (disease registries and hospital- or clinic-based samples), which may not accurately reflect the course of the disease in the general population.

In conclusion, we found that higher prediagnosis total cholesterol and LDL-C concentrations and prevalent diabetes were associated with accelerated postdiagnostic cognitive decline. History of heart disease or stroke was predictive of faster decline in *APOE*-ɛ4 carriers only. Prevention or treatment of these conditions can potentially slow the course of AD.

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