

# Stroke and the Risk of Alzheimer Disease

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**Background:** Alzheimer disease (AD) and stroke are common in elderly individuals, but the relation between these 2 disorders remains uncertain.

**Objective:** To investigate the association between a clinical history of stroke and subsequent risk of AD.

**Design:** A cohort of 1766 Medicare recipients without dementia participated in a longitudinal follow-up study from 1992 through 1999 in upper Manhattan, New York, NY. History of stroke and presence of cardiovascular risk factors were ascertained at the onset of the study. Incidence rates for AD among those with and without stroke were calculated; proportional hazards ratios were computed using age at onset of the disease as the time-to-event variable.

**Results:** The annual incidence for AD was 5.2% among individuals with stroke vs 4% for those without stroke. The hazards ratio for AD among those with a history of

stroke was 1.6 (95% confidence interval, 1.0-2.4) compared with those without stroke. Of the vascular risk factors, hypertension, diabetes, and heart disease, only diabetes related to risk of AD in the absence of stroke. Stroke remained weakly associated with AD in the absence of these factors, but risk significantly increased with the additional factors of hypertension (relative risk, 2.3; 95% confidence interval, 1.4-3.6), diabetes (relative risk, 4.6; 95% confidence interval, 2.2-9.5), or heart disease (relative risk, 2.0; 95% confidence interval, 1.2-3.2).

**Conclusions:** Stroke is associated with AD among elderly individuals. The relation is strongest in the presence of known vascular risk factors. The observed association between stroke and AD might relate to an underlying systemic vascular disease process, or alternatively, to the additive effects of stroke and AD pathologic features, leading to an earlier age at onset of disease.

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**T**HE ROLE of stroke in the pathogenesis of Alzheimer disease (AD) remains unclear.<sup>1-8</sup> Cerebrovascular disease and its antecedents have been proposed as precursors to AD<sup>1,2</sup> but may simply be coincident processes causing additive damage to the aging brain.<sup>8,9</sup> Among persons with AD confirmed post mortem, those with stroke were found to have more severe dementia.<sup>10</sup> Shared susceptibility to AD and stroke might account for the frequent association. Apolipoprotein E (APOE) is related to AD and to mortality from heart disease, but there is no established interaction between these 2 factors and AD.<sup>3,11,12</sup> Furthermore, there is no convincing evidence of a role for the APOE  $\epsilon 4$  allele in cerebrovascular disease.<sup>13-19</sup> Previously, we investigated the association of diabetes and hypertension with AD in a prospective cohort of Medicare recipients living in the Washington Heights and Inwood commu-

nities of upper Manhattan, New York, NY.<sup>20,21</sup> In this article, we have used data from this cohort to broaden the investigation of the relationship between stroke, other cardiovascular risk factors, and AD.

## METHODS

### PARTICIPANTS AND SETTING

The Washington Heights–Inwood Columbia Aging Project represents a cohort of individuals older than 65 years from a stratified (by age and ethnic group) random sample of several census tracts in upper Manhattan.<sup>22-25</sup> This project was approved by the institutional review board of Columbia Presbyterian Medical Center, New York. Written informed consent was obtained for all participants. Names were drawn from the US Health Care Financing Administration (Medicare) eligibility files in 1992. Participants did not significantly differ from nonparticipants with respect to age or ethnic group. Because nonparticipants did not

- 1 Have you ever had a stroke of the brain, ministroke, CVA (cerebrovascular accident), or TIA (transient ischemic attack)?
- 1a Did a doctor tell you that you had a stroke of the brain, ministroke, CVA (cerebrovascular accident) or TIA (transient ischemic attack)?
- 1b Did you have a stroke of the brain, ministroke, CVA (cerebrovascular accident), or TIA (transient ischemic attack) within the past year?
- 2 Have you ever had a sudden paralysis (weakness) or numbness (loss of sensation) on one side of the body but not the other?
- 3 Have you ever suddenly lost the use of speech (not being able to talk at all) or suddenly had slurred speech (not being able to say words clearly)?
- 4 Have you ever had sudden loss of consciousness with severe headache, nausea, or vomiting?
- 5a Did the stroke or stroke symptoms last more than 24 hours?
- 5b Have the stroke symptoms continued without ever going away?

**Figure 1.** Survey questions regarding stroke. Stroke was defined as an affirmative answer to one of these questions.

consent to participate or contribute data, we do not have information regarding the occurrence of stroke or dementia in this group. The overall rate of participation was 62%, and the total number of recruited individuals was 2126. Participants ranged in age from 65 to 105 years; the mean (SD) age at baseline was 77 (7) years. Baseline data were collected from 1992 through 1994. Follow-up data were collected during evaluations at sequential intervals of 18 months, performed from 1994 to 1996, 1996 to 1997, and 1997 to 1999. In this elderly population, some participants did not complete the follow-up at all intervals because of relocation, death, or refusal to participate further. About one half of participants were still living and were evaluated at the third follow-up visit. There was no differential dropout rate among individuals with a history of stroke (at baseline or subsequently), including those with and without dementia.

Of the 2126 individuals, 327 participants (15.4%) had dementia at the time of baseline assessment and, thus, were excluded from this study analyzing incident dementia. The resultant population of 1799 individuals included 760 (42%) Hispanic individuals, 610 (34%) non-Hispanic African American individuals, and 418 (23%) non-Hispanic white individuals; 11 individuals were excluded from analysis because they did not belong to any of these ethnic categories. An additional 22 remaining individuals (1%) were excluded because they were missing essential stroke information data. Thus, the analysis was based on 1766 individuals without dementia (83% of total participants) from the 3 ethnic groups, who were followed for 6 to 8 years.

#### DATA COLLECTION

At baseline, each participant received a health questionnaire and a medical evaluation. Neuropsychological testing consisted of a standardized battery<sup>5</sup> that included orientation from the Mini-Mental State Examination,<sup>26</sup> the Selective Reminding Test,<sup>27</sup> the Benton Visual Retention Test,<sup>28</sup> the Boston Naming Test,<sup>29</sup> the Controlled Oral Word Association Tests for categories and letters,<sup>30</sup> the Complex Ideation and Phrase Repetition subtests of the Boston Diagnostic Aphasia Examination,<sup>29</sup> the Abstract Reasoning and Similarities subtests from the Wechsler Adult Intelligence Scale,<sup>31</sup> the Identities and Oddities subtests from the Dementia Rating Scale,<sup>32</sup> and the Rosen Drawing Test.<sup>33</sup> Individuals deemed to have possible cognitive deficits, either by the physician or through neuropsychological testing, were additionally evaluated by a neurological specialist.

Examination data from each individual were discussed at a consensus conference staffed by neuropsychologists and neurologists after each follow-up examination. Incident dementia was diagnosed using research criteria<sup>34</sup> and National Institutes of Neurological and Communication Disorders and Stroke–Alzheimer's Disease and Related Disorders Association<sup>35</sup> criteria

for probable and possible AD. In these criteria, stroke does not preclude the diagnosis of AD unless cerebrovascular disease was considered the primary cause of the dementia.

The presence of stroke was ascertained from an interview with participants and their informants (generally a family member). Positive response(s) to any 1 of the 8 questions shown in **Figure 1** was considered as suggestive of a history of stroke. Persons with stroke were confirmed through their medical records, 85% of which included results of brain imaging.<sup>36</sup> The remainder were confirmed by direct examination. Dementia consistent with the clinical diagnosis of AD combined with stroke was classified as possible AD.<sup>35</sup>

#### ETHNIC GROUP

At baseline, ethnic group was documented by self-report using the format of the 1990 US census.<sup>37</sup> Individuals were asked to indicate their ethnic group and additionally whether they were of Hispanic origin.

#### HYPERTENSION, DIABETES, AND HEART DISEASE

At baseline, all participants were asked whether they had a history of hypertension or diabetes at any time during their life. If affirmed, they were asked whether they were undergoing treatment and the specific type of treatment. Heart disease was defined as a history of myocardial infarction, congestive heart failure, or angina. This was similar to the strategy used in our previous studies.<sup>20,21</sup>

#### APOE GENOTYPE

Genotypes were obtained by amplification of genomic DNA by means of a polymerase chain reaction with products subjected to *CfoI* restriction analysis using *APOE* primers and conditions similar to those described by Hixson and Vernier<sup>38</sup> and modified by Maestre et al.<sup>39</sup>

#### DATA ANALYSIS

The primary outcome variable was AD, but data were also separately analyzed for the broader outcome of dementia. Continuous variables were compared using analysis of variance, and categorical variables were compared using  $\chi^2$  tests. Cox proportional hazards regression models were used to examine the effects of a history of stroke at the initial interview on the development of AD. The time-to-event variable was the age at onset of AD. Data from individuals who did not develop AD or who died or were lost to follow-up prior to developing AD were censored at the time of their last evaluation. In subsequent models, data obtained at baseline were used as covariates including age, education, and a history of hypertension, diabetes, or heart disease. Survival curves were generated to show the comparison in the frequency of AD by age among individuals with and without a history of stroke. Data analysis was performed using SPSS software version 11.0 (SPSS Inc, Chicago, Ill).

### RESULTS

Among the 1766 individuals without dementia at baseline in our analysis, stroke, as defined by World Health Organization criteria,<sup>40</sup> occurred in 331 individuals (18.5%). Among these 331 individuals, 188 (10.5%) had a history of stroke at baseline, whereas an additional 143 (8%) developed stroke during the follow-up and before the onset of dementia. These latter 143 individuals were evenly divided among first ( $n=64$ ; 3.6%), second ( $n=31$ ;

**Table 1. Baseline Characteristics of Individuals With and Without Prevalent Stroke\***

	Stroke Absent		Stroke Present		P Value
	Mean (SD)	Sample Size	Mean (SD)	Sample Size	
Men†	31.9	1578	30.3	188	.68
African American†	34.3	1578	33.5	188	.66
Hispanic†	42.5	1578	40.4	188	.66
Age at baseline, y	75.8 (6.4)	1578	74.5 (5.7)	188	.01
Education, y	8.6 (4.6)	1578	8.9 (4.5)	188	.35
Body mass index, kg/m <sup>2</sup>	27.4 (5.7)	1102	27.2 (5.3)	129	.80
APOE $\epsilon$ 4 allele†	27.9	1043	31.4	124	.40
Hypertension†	57.4	1578	70.7	188	.001
Type 2 diabetes mellitus†	12.6	1577	20.7	188	.003
Heart disease†	30.4	1578	52.1	188	.001
Total cholesterol, mg/dL	201 (41)	1073	208 (39)	128	.06
HDL cholesterol, mg/dL	46 (16)	1073	48 (14)	128	.73
LDL cholesterol, mg/dL	121 (35)	1072	128 (34)	128	.04
Triglycerides, mg/dL	72 (42)	1072	72 (42)	128	.84
SRT total recall‡	36.4 (9.5)	702	36.5 (9.8)	150	.32
SRT delayed recall‡	5.0 (2.4)	702	5.1 (2.6)	148	.52
Orientation§	9.3 (1.0)	702	9.3 (1.0)	150	.75
Short Blessed test‡	5.3 (4.8)	715	5.3 (5.1)	144	.97

Abbreviations: HDL, high-density lipoprotein; LDL, low-density lipoprotein; SRT, selective reminding test.

SI conversion factors: To convert total, HDL, and LDL cholesterol from milligrams per deciliter to millimoles per liter, multiply by 0.0259; to convert triglycerides from milligrams per deciliter to millimoles per liter, multiply by 0.0113.

\*Mean values and SDs were compared by analysis of variance and  $\chi^2$  tests.

†Values are expressed as a percentage of individuals with 1 or more APOE  $\epsilon$ 4 alleles.

‡Values are expressed on a scale where higher numbers represent better scores for SRT and orientation with maxima for total recalls, 72; delayed recalls, 12; and orientation, 10; and lower numbers represent a better score for the Short Blessed test on a scale of 0 to 28.

1.7%), and third (n=48; 2.7%) follow-up periods and were included only when the stroke occurred prior to the onset of AD. With the exception of heart disease in African American individuals, the frequency of diabetes, heart disease, and hypertension was significantly higher in African American individuals and Caribbean Hispanic individuals than in white individuals (diabetes: 18.8% and 22.1% vs 10.3%, respectively; heart disease: 24.9% and 33.3% vs 29.2%, respectively; hypertension: 73.3% and 71.4% vs 55.5%, respectively;  $P < .001$ ).

Dementia occurred in 212 participants (10% of the total number). Specific diagnosis of AD was made in 181 of these 212 individuals (85% of patients with dementia; 8.5% of total participants). Other forms of dementia were diagnosed in 31 individuals (15% of patients with dementia; 1.5% of total participants), including 7 (0.3% of total participants) with stroke-related dementia. The proportion of individuals with dementia due to AD in this study was similar to that in other studies.<sup>41,42</sup>

#### COMPARISON OF INDIVIDUALS WITH AND WITHOUT STROKE AT BASELINE

Comparison of participants with and without a history of stroke at baseline revealed no differences by sex or ethnic group or by the number of years of education, body mass index, or APOE genotype. The age at baseline was slightly younger among those with a history of stroke (**Table 1**). Persons with stroke were more likely to have a history of hypertension, type 2 diabetes mellitus, or heart disease, and they had slightly higher total cholesterol and

**Table 2. Relative Risk of Alzheimer Disease Related to Stroke\***

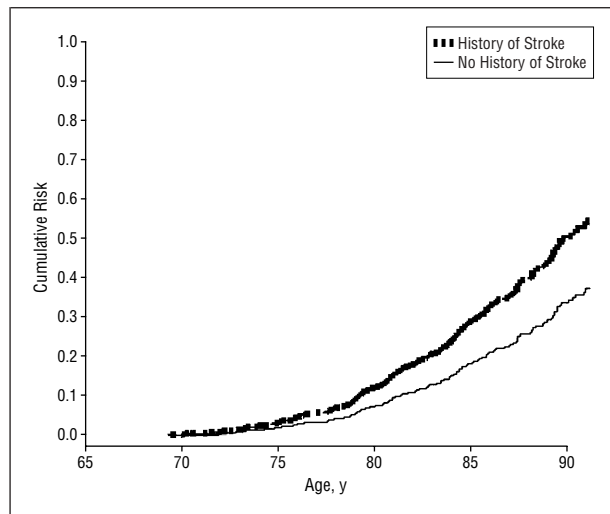
Model	Relative Risk	95% Confidence Interval	P Value
Unadjusted	1.57	1.02-2.42	.04
Plus sex	1.58	1.03-2.43	.04
Plus ethnic group	1.78	1.16-2.75	.01
Plus education	1.73	1.12-2.67	.01
Plus sex, ethnic group, and education	1.84	1.19-2.85	.01
Plus sex, ethnic group, education, smoking, diabetes, heart disease, and hypertension	1.83	1.14-2.95	.01

\*The Cox proportional hazards regression model, with age at onset of Alzheimer disease as the time variable, was used to determine the relative risk of stroke at baseline for subsequent incidence of Alzheimer disease. Adjustments are as listed.

low-density lipoprotein cholesterol levels (**Table 2**). The 2 groups showed similar cognitive performance at baseline (Table 2).

#### COMPARISON OF RISK OF AD IN PERSONS WITH AND WITHOUT STROKE

The incidence rate for AD among individuals with stroke was 5.2% per person-year, while that for individuals without stroke was 4% per person-year. The incidence rate ratio was 1.3 (95% confidence interval, 0.9-2.0). The unadjusted hazards ratio for AD associated with a history of stroke was 1.6 (95% confidence interval, 1.02-2.4) (Table 2). Persons with stroke



**Figure 2.** Cumulative risk of Alzheimer disease by age. Individuals with stroke ( $n=188$ ) showed increased frequency of Alzheimer disease at each age compared with those individuals without a history of stroke ( $n=1578$ ).

showed an earlier onset of AD compared with those without stroke (eg, the first quartile of individuals with stroke developed AD at age 85.3 years, compared with age 88.7 years for those without stroke) (**Figure 2**). Models with covariates, hypertension, diabetes, and heart disease still resulted in a significant effect of stroke on the risk of AD (Table 2).

To further investigate the risk of stroke on incidence of AD, we examined the influence of cardiovascular risk factors, stratifying the analyses by each factor: hypertension, type 2 diabetes mellitus, and heart disease. Stroke in the absence of these factors remained weakly associated with AD but did not achieve statistical significance (**Table 3**). These analyses also revealed that the association between stroke and AD was highest in those groups with at least 1 vascular risk factor and stroke. Of the risk factors, only diabetes in the absence of stroke showed an association with AD (Table 4). Remarkably, any combination of these 3 risk factors with stroke led to a significantly increased risk of AD. Finally, we completed an analysis of stroke using a model that included hypertension, diabetes, and heart disease as both independent risk factors and interaction terms (data not shown). We again found stroke and diabetes to be associated with an increased risk of AD.<sup>21</sup> The interaction between hypertension and heart disease also independently significantly increased risk.<sup>20</sup> Logistic regression was performed using age, sex, education, stroke, hypertension, diabetes, and heart disease to examine the relative importance of contributions to dementia. We found the expected age and education effects, but of all 4 vascular variables (stroke, hypertension, diabetes, and heart disease), only stroke by itself was statistically significantly related to dementia (data not shown).

We also performed the identical set of statistical analyses reported earlier, using data from all 212 persons with dementia as an outcome variable rather than using only the 188 persons with AD; the risks for outcome of dementia were unchanged.

These results demonstrate an association between a history of stroke and AD. Compared with persons with no history of stroke, there was an increased risk of AD in persons with a history of stroke. The risk was highest for those with stroke who also had established vascular risk factors, such as high blood pressure, type 2 diabetes mellitus, or heart disease. Moreover, a history of stroke was associated with an earlier age at onset of dementia. Although the frequency of cardiovascular risk factors differed by ethnic group, the relationship of AD risk with stroke remained the same.

Stroke may represent an independent injury that simply worsens the symptoms of incipient AD, leading to earlier diagnosis. Such an explanation, in its simplest form, would be one of independent additive effects. The presence of cerebrovascular injury, even if it does not cause measurable deficits itself, might cause increased cognitive dysfunction in the presence of a concomitant degenerative process. In cases in which dementia relates solely to vascular injury, the presence of cognitive deficits may relate not only to the strategic placement of the stroke but also to the volume of damaged brain tissue. By extension, if a certain amount of brain tissue was injured by stroke, this might lessen the burden of AD pathologic changes required to produce symptoms of dementia. An alternative but related explanation is an independent synergistic effects model. In such a scenario, there might be a nonlinear relationship between amount of brain injury, by whatever source, and the occurrence of AD. For example, preexisting brain damage by stroke might additionally increase the likelihood of AD by increasing the extent of injury from the molecular and cellular cascade of AD. That stroke is a greater risk for AD in the presence of other cardiovascular factors might indicate either the presence of a greater degree of stroke damage in patients with such risk factors or a modulating adverse effect of these systemic conditions.

It is possible that AD might increase the likelihood of stroke. The presence of neuropathologic changes in AD could predispose some individuals to stroke, perhaps owing to amyloid angiopathy, brain parenchymal changes, or the secondary consequences of the presymptomatic disease (eg, dietary or activity changes). While such a relationship cannot be excluded by the data in this study, it is somewhat unlikely given that in the principal analysis of this cohort, the history of stroke preceded the development of dementia. Further arguing against this model, the neuropsychological test measurements at baseline showed no differences between participants with and without stroke.

Finally, the pathologic characteristics of AD might be accelerated by cerebrovascular diathesis or disease. For example, atherosclerotic lesions or hypertensive or diabetic vessel changes in the cerebrovascular bed might alter endothelial permeability of the blood-brain barrier, allowing greater exposure of parenchyma to systemically circulating molecules, including oxidants, cytokines, or  $\beta$ -amyloid. There might be effects on the degree of brain parenchymal oxidative stress, microglial invasion and activation, or the extent of parenchymal cy-

**Table 3. Relative Risk of Alzheimer Disease Related to Stroke and Other Risk Factors\***

	No. of Individuals	No. of Individuals	Alzheimer Disease			
			Stroke at Baseline	Stroke Before Dementia Diagnosis	Stroke Before or at Dementia Diagnosis	Stroke Ever
<b>HTN</b>						
Neither HTN nor stroke	673	72	1.00	1.00	1.00	1.00
HTN only	905	86	1.04 (0.76-1.43)	1.03 (0.75-1.43)	1.03 (0.73-1.44)	1.09 (0.77-1.54)
Stroke only	55	5	0.95 (0.38-2.35)	1.40 (0.67-2.92)	2.11 (1.20-3.71)	1.86 (1.11-3.13)
Both HTN and stroke	133	18	1.97 (1.18-3.29)	2.28 (1.42-3.64)	3.00 (1.95-4.64)	2.14 (1.40-3.27)
<b>DM</b>						
Neither DM nor stroke	1379	132	1.00	1.00	1.00	1.00
DM only	198	26	1.59 (1.04-2.42)	1.55 (1.00-2.41)	1.41 (0.88-2.27)	1.38 (0.84-2.28)
Stroke only	149	17	1.39 (0.85-2.28)	1.73 (1.11-2.67)	2.27 (1.55-3.31)	1.71 (1.19-2.45)
Both DM and stroke	39	6	4.24 (1.85-9.74)	4.59 (2.23-9.46)	6.48 (3.53-11.9)	4.12 (2.35-7.23)
<b>HD</b>						
Neither HD nor stroke	1098	104	1.00	1.00	1.00	1.00
HD only	480	54	1.03 (0.74-1.42)	1.03 (0.74-1.44)	1.00 (0.70-1.42)	1.05 (0.73-1.51)
Stroke only	90	9	1.39 (0.71-2.76)	1.95 (1.11-3.43)	2.62 (1.65-4.15)	2.19 (1.41-3.40)
Both HD and stroke	98	14	1.73 (1.01-2.98)	1.95 (1.18-3.23)	2.59 (1.65-4.07)	1.81 (1.18-2.77)

Abbreviations: DM, diabetes mellitus; HD, heart disease; HTN, hypertension.

\*Values expressed as risk ratios with 95% confidence intervals unless indicated otherwise. "Stroke Ever" refers to stroke occurring at any time in study, before or after diagnosis of Alzheimer disease dementia.

tokine or neuroinflammatory activity. Such factors might result in greater  $\beta$ -amyloid-related AD burden, either through increased  $\beta$ -amyloid production or accumulation or decreased ability to clear  $\beta$ -amyloid. Alternatively, these factors could result in greater neuronal injury because of an increased degree of neurofibrillary tangle formation, oxidative stress, or apoptosis for a given load of cerebral amyloid. While some investigators have found no relationship between overall cardiovascular disease factors and  $\beta$ -amyloid brain burden,<sup>43</sup> there are few data on the molecular changes surrounding stroke lesions in elderly patients. Our data do lend support to the possibility that there might be some systemic disease predisposition to AD. A variety of other data, including data from the Framingham,<sup>44</sup> Honolulu-Asia,<sup>8</sup> and Rotterdam<sup>45</sup> epidemiological studies, have variably supported the viewpoint that a systemic cerebrovascular disease diathesis might increase the risk of AD.<sup>1,2,8,44,46,47</sup> Recent demonstrations of an elevated homocysteine level as a risk factor for AD<sup>45</sup> suggest 1 possible biological effector molecule. The fact that our analyses show that the presence of stroke affects the risk of developing AD, more so in the presence of other cardiovascular disease risk factors such as hypertension, diabetes, or heart disease, could be explained by a systemic disease process rather than the effect of a single or multiple strokes.

This study has limitations. It is possible that despite the neurological and neuropsychological data suggesting AD, the primary neuropathologic abnormalities in some of the individuals with stroke might actually be those of vascular dementia, not AD. Only a careful post-mortem study could determine if that was the case. Autopsy data to date from this population<sup>48</sup> do suggest more cerebrovascular injuries than might otherwise be expected. We were also unable to determine the extent of silent cerebral infarcts in this population.

We found that a history of stroke was associated with the subsequent development of AD, primarily in the pres-

ence of other risk factors related to both cardiovascular and cerebrovascular disease. Whether stroke is directly involved in the pathogenesis of AD or acts indirectly as a contributor to the manifestations of AD needs to be established. Nonetheless, prevention of stroke and treatment of stroke antecedents may have important implications for AD risk and deserve further investigation.

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## Correction

**Error in Table References.** In the Original Contribution by Honig et al titled "Stroke and the Risk of Alzheimer Disease," published in the December issue of the ARCHIVES (2003;60:1707-1712), an error occurred in the table references. On page 1710, there is a reference to Table 4. This should have referred to Table 3. The journal regrets the error.