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Aggregation of Vascular Risk Factors and Risk of Incident Alzheimer's Disease

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Abstract

Background—The prevalence of Alzheimer disease (AD) is increasing in the elderly and vascular risk factors may increase its risk. We explored the association of the aggregation of vascular risk factors to AD.

Methods—we followed 1,138 individuals without dementia at baseline (mean age = 76.2 years) for a mean of 5.5 years. The presence of vascular risk factors was related to incident *possible and probable* AD.

Results—Four risk factors, diabetes, hypertension, heart disease, and current smoking, were associated with a higher risk of AD ($p < 0.10$) when analyzed individually. The risk of AD increased with the number of risk factors (diabetes + hypertension + heart disease + current smoking). The adjusted HR of *probable* AD for the presence of 3 or more risk factors was 3.4 (95% CI: 1.8,6.3; p for trend < 0.0001) compared to no risk factors. Diabetes and current smoking were the strongest risk factors in isolation or in clusters, but hypertension and heart disease were also related to a higher risk of AD when clustered with diabetes, smoking, or each other.

Conclusions—The risk of AD increased with the number of vascular risk factors. Diabetes and current smoking were the strongest risk factors, but clusters including hypertension and heart disease also increased the risk of AD. These associations are unlikely to be explained by misclassification of the outcome given strong associations when only probable AD is considered.

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The prevalence of Alzheimer disease (AD) is projected to quadruple by the year 2047(1). Vascular risk factors may increase the risk of AD (2), and are highly prevalent in the elderly. The prevalence of diabetes and glucose intolerance in the elderly was over 40 percent in NHANES III (3). Persons in midlife have a 90 percent lifetime risk of developing hypertension (4). Hyperlipidemia increases the risk of cardiovascular disease and it increases in adult life (5). More importantly, these risk factors are all modifiable, representing an opportunity for the prevention of AD.

Diabetes (6–8), hyperlipidemia (9), hypertension (10), heart disease (11), smoking (12,13), homocysteine (14), and obesity (15) are associated with a higher risk of AD. Explanations for these associations include the coincidence of common disorders in the elderly, vascular and cerebrovascular disease precipitating AD, an additive or synergistic (AD + vascular) pathogenesis of dementia, or misclassification of vascular dementia as AD (16). The mechanisms linking vascular risk factors to AD remain unclear.

Epidemiologic studies examine risk factors individually while adjusting for other risk factors. Hypertension, hyperlipidemia, and diabetes coexist (17) and participate in mutual causal pathways. Thus, inclusion of all risk factors in one statistical model may result in overadjustment (18) and underestimation of associations. Furthermore, the aggregation of risk factors may have a greater impact on the development of AD than each risk factor individually.

We previously reported associations of diabetes (19,20), and current smoking(12,21) to a higher risk of AD, and a lack of an association of hypertension (22), hyperlipidemia (23,24), hyperhomocysteinemia (25) to AD in a prospective cohort of Medicare recipients living in northern Manhattan (20,22,26). In the present study, we explored the association of the aggregation of vascular risk factors to risk of AD.

METHODS

Participants were enrolled in a longitudinal cohort study by a random sampling of Medicare recipients 65 years or older residing in northern Manhattan (Washington Heights, Hamilton Heights, Inwood)(27). Participants underwent in-person interviews of general health and function, medical history, physical and neurological examination as well as a neuropsychological battery (28). Baseline data were collected from 1992 through 1994. Follow-up data were collected at intervals of approximately 18 months. This study includes data collected up to 2003. Of the 2,126 subjects who accepted to participate in the study, 340 individuals were excluded due to dementia at baseline, and 648 individuals were excluded due to loss to follow-up, leaving a final sample for analyses of 1,138. Persons excluded due to prevalent dementia were older at baseline compared to the final sample, had a higher proportion of Hispanics, a lower proportion of Whites, a higher proportion of heart disease, and a lower proportion of ever smokers (Table 1). Persons lost to follow-up were older, had a lower proportion of Hispanics, a lower proportion of diabetes and hypertension, and a higher proportion of current and ever smokers.

Informed consent was obtained from all participants at the time of study enrollment and at each follow-up. The Columbia University Institutional Review Board approved this project.

Diabetes mellitus and hypertension were defined by self-report at baseline and at each follow-up interval or by the use of disease specific medications. Blood pressure measurements were also considered in the definition of hypertension. Hypertension was defined as a systolic blood pressure over 140 mmHg or a diastolic blood pressure over 90 mmHg(29). Blood pressure levels did not increase the predictive value of the self-report of hypertension, and we report results only for the definition by self-report. Heart disease was defined as a history of atrial fibrillation and other arrhythmias, myocardial infarction, congestive heart failure or angina

pectoris. Smoking was also ascertained by self report, and was classified as current smoking or ever smoking. These diagnoses have shown a sensitivity and specificity of over 90 percent using medical records as the gold standard. Fasting plasma total cholesterol and triglyceride levels were determined at initial assessment using standard enzymatic techniques. High-density lipoprotein (HDL) cholesterol levels were determined after precipitation of apolipoprotein B containing lipoproteins with phosphotungstic acid (30). Low-density lipoprotein (LDL) cholesterol was recalculated using the formula of Friedewald et al (31). BMI was calculated by the formula $BMI = \text{weight (Kg)}/\text{height (m)}^2$

APOE genotypes were determined as described by Hixson and Vernier (32) with slight modification (33). We classified persons by the presence (homozygous or heterozygous) or absence of the APOE $\epsilon 4$ allele; 126 subjects in the final sample had missing data on APOE genotype. APOE- $\epsilon 4$ was included as a covariate because it increases the risk of AD(34) and it may modify the association between vascular risk factors and AD(35).

Stroke was defined according to the WHO criteria (36). The diagnosis was based on questioning of the participant or relatives, supplemented by a neurological examination or review of medical records. Results of brain imaging were available on 85 percent of subjects with vascular dementia. Ethnic group was based on self-report using the format of the 1990 census (37). Individuals were also asked if they were of Hispanic origin. Participants were then assigned to one of three groups: African American, Hispanic, or White (non-Hispanic). We examined education both as a continuous variable (years of education completed), and as a categorical variable (≤ 6 years of education, 7–12 years, 13–16 years, and > 16 years). We included ethnic group and education as covariates because Hispanics and African-Americans, and subjects with lower years of education have a higher prevalence of vascular risk factors (38), and also a higher risk of AD (39).

The diagnosis of dementia was established based on all available information gathered from the initial and follow-up assessments. Dementia was determined by consensus at a conference of physicians, neurologists, neuropsychologists and psychiatrists. The diagnosis of dementia was based on standard research criteria (40) and required evidence of cognitive decline, including memory impairment, on the neuropsychological test battery as well as evidence of impairment in social or occupational function (clinical dementia rating > 0.5) (41). The diagnosis of AD was based on the National Institute of Neurological and Cognitive Disorders and Stroke/Alzheimer's Disease and Related Disorders Association Criteria (42). A diagnosis of *probable* AD was made when the dementia could not be explained by any other disorder. A diagnosis of *possible* AD was made when the most likely cause of dementia was AD, but there were other disorders that could contribute to the dementia such as stroke and Parkinson disease (PD). A diagnosis of dementia associated with stroke was made when the dementia started within 3 months of the stroke.

The association between vascular risk factors and AD could be explained by misclassification of vascular dementia as AD (16). To address this possible misclassification, we conducted analyses with *possible* or *probable* AD as the outcome, and then only with *probable* AD as the outcome. In both analyses subjects with types of dementia other than the outcome were censored at the time of dementia diagnosis.

Statistical Methods

First, we examined the association of risk factors with AD in models adjusting for age, gender, education, ethnic group and APOE- $\epsilon 4$. We sought to identify those risk factors that had even marginal associations with incident AD without adjusting for other vascular risk factors. The variables that attained a 0.1 significance level or less were used in the final analyses. Each variable was given a value of 1 if present, and a value of 0 if absent. Each risk factor was treated

as a time dependent covariate specified by the follow-up date when the diagnosis was made. Vascular risk factors included diabetes mellitus, heart disease, hypertension, smoking, LDL and BMI; homocysteine levels, which we previously reported have no association to a higher risk of AD in our cohort(25), were not available for the whole sample and were not included in the analyses. LDL and BMI were analyzed as continuous variables, and categorized by the median and by quartiles. We estimated the association of a composite score of vascular risk factors on the development of AD by summing the retained variables and relating the resulting scores to the risk of incident AD. Demographic, clinical characteristics and the proportion of subjects with incident AD were compared between the vascular risk factor scores. Continuous variables were compared by analysis of variance, and categorical variables were compared by χ^2 test. If the global p values were significant, we compared each risk factor score group to subjects without risk factors. Cox proportional hazards regression models (43) were used to estimate the association between vascular risk factors and the risk of incident AD. We present two models for the multivariate analyses: one adjusted including gender as a covariate, and the other including years of education, the APOE- ϵ 4 allele, and stratified by ethnic group and education category. We also conducted secondary analyses adjusting for the presence of stroke. The time-to-event variable was the age at onset of dementia (44). Individuals who did not develop the outcome of interest, or who died or were lost to follow-up were censored at the time of their last evaluation. If individuals had dementias other than the one used as the outcome in the analyses, they were censored at the time of dementia diagnosis. SAS for windows version 9 (SAS Institute, Inc., Cary, North Carolina) was used for all analyses.

RESULTS

There were 1,138 individuals without dementia at baseline with 6,292 person-years of follow-up (mean = 5.5; SD = 3.2). 270 developed dementia, 246 (91.1 percent of all dementia) were diagnosed as having incident *probable* or *possible* AD, nine (3.3 percent) had dementia associated with stroke, and 15 (5.6 percent) had other types of dementia (e.g. PD, Lewy body disease). We reclassified the subtypes of dementia by considering *probable* cases only as having AD, and the frequencies of dementia subtypes changed in the following manner: 176 subjects developed AD (65.2 percent of all dementia), 72 (26.7 percent) cases had dementia associated with stroke or mixed (vascular and AD) dementia, and 22 (8.1 percent) had other types of dementia. The mean age of the sample was 76.2 ± 5.9 years, 69.8 percent were women, 33.1 percent were African-American, 44.4 percent were Hispanic, and 22.5 percent were White. The median of years of education was 8, and 28.6 percent were homozygous or heterozygous for the APOE- ϵ 4 allele. During the follow-up period 20.3 percent reported having diabetes, 60.7 percent hypertension, 28.9 percent heart disease, 34.7 percent past smoking and 10.2 percent current smoking. At baseline, the mean LDL was 121.9 mg/dl and the mean BMI was 27.4 kg/m².

In analyses examining each putative cardiovascular risk factor adjusting for age, gender, education, and APOE- ϵ 4, only diabetes, hypertension, heart disease, and current smoking were related to a higher risk of *probable* or *possible* AD and met the criteria for consideration in the analyses ($p < 0.10$). The hazard ratios (HR) and 95 % CI of the risk of *possible* or *probable* AD were 2.4 (95 % CI: 1.8, 3.2) for diabetes, 1.3 (95% CI: 0.9, 2.1) for heart disease, 1.4 (95% CI: 1.1, 1.8) for hypertension, and 2.0 (95% CI:1.3,3.2) for current smoking. If all four were included in the same model, only diabetes (HR =2.0; 95% CI:1.4, 2.9) and current smoking (HR = 1.9; 95% CI: 1.4, 2.9) remained significant and the associations for heart disease (HR = 1.1; 95% CI: 0.8, 1.5) and hypertension (HR = 1.1; 95% CI: 0.9, 1.5) were appreciably attenuated. The results were similar when *probable* AD was used as the outcome. Bivariate comparisons of characteristics between subjects with and without risk factors can be seen in Table 2.

We constructed a variable counting the number of the four risk factors that met our criteria: 26.6 percent individuals had no risk factors, 37.8 percent had one risk factor, 25.3 percent had two risk factors, 9.4 percent had three risk factors, and 0.9 percent had all risk factors. Hypertension was the most common risk factor in persons with one (71.0%), two (93.4%), and three risk factors (99.1%). The prevalence of diabetes increased from 10.9% in persons with one risk factor to 33.7% in persons with two risk factors, and 81.5% in person with three risk factors. The prevalence of heart disease increased from 10.9% in persons with one risk factor to 59.0% in persons with two risk factors, and 95.4% in persons with three risk factors. The prevalence of current smoking increased from 9.5% in persons with one risk factor to 13.9% in persons with two risk factors, and 24.1% in persons with three risk factors.

In multivariate analyses relating the number of risk factors to *probable* or *possible* AD we found that the risk of AD increased with increasing number of risk factors. The number of persons with all four risk factors was small (n=9), and persons with 3 or 4 risk factors were grouped together (table 3); the hazard ratio of possible and probable AD for this group was 3.4 (95% CI: 2.1,5.7; *p* for trend <0.0001). This hazard ratio was similar when only *probable* AD was used as the outcome (HR=3.4; 95% CI: 1.8, 6.3; *p* for trend <0.0001) (Table 3). We conducted additional analyses excluding 204 persons with less than 2 years of time to onset of dementia or censoring and found that the HR of AD for persons with 3 or more risk factors was 3.4 (95% CI :1.7, 6.8; *p* for trend < 0.0001). When 468 persons with less than 4 years of time to onset of dementia or censoring were excluded from the analyses the HR of AD for persons with 3 or more risk factors was 2.6 (95% CI: 1.0, 6.8; *p* for trend = 0.006).

We also classified subjects by specific clusters of risk factors (Table 4). We found that the risk of *possible or probable* AD was appreciably and significantly increased compared to subjects without risk factors for subjects with isolated diabetes (HR = 3.8; 95% CI:1.8, 8.2), isolated smoking (HR =2.2; 95% CI: 1.0,4.9), diabetes and hypertension (HR = 3.3; 95% CI:1.9, 5.9), diabetes and heart disease (HR =3.7; 95% CI:1.2,11.1), hypertension and heart disease (HR = 2.3; 95% CI:1.4,3.7), and hypertension and smoking (HR = 2.7; 95% CI:1.2,6.1). Most persons with 3 or 4 risk factors had a combination of diabetes, hypertension, and heart disease (82 out of 117) and we present them as one cluster as in the results above. The interpretation of the hazard ratio for diabetes and heart disease was limited due to the small number of subjects in that cluster. When only *probable* AD was considered as the outcome, the associations with the vascular risk factor clusters remained strong, with the exception of the cluster of diabetes and heart disease (Table 4). We repeated all the analyses including stroke in the models and the results were unchanged.

Our main hypothesis was that the aggregation of vascular risk factors increased the risk of AD. However, we conducted secondary analyses exploring effect modification of one risk factor by another (e.g. diabetes by hypertension, heart disease or smoking, and the only significant interaction term was for diabetes and hypertension (coefficient = -0.80; *p* = 0.03), indicating that the risk of AD in persons with diabetes was lower in the presence of hypertension and vice versa.

The association between the number of risk factors and probable AD was not modified by the presence of the APOE-ε4 allele (*p* for interaction = 0.58) or by gender (*p* for interaction =0.08).

DISCUSSION

In longitudinal analyses of 1,138 subjects (6,292 person-years of follow-up) we found that the risk of AD increased with the number of vascular risk factors, diabetes, hypertension, heart disease, and current smoking. We also found that different combinations of risk factors were associated with a high risk of AD. Diabetes and smoking were the strongest risk factors.

The role of vascular risk factors in vascular dementia seems clear. Vascular dementia is related to stroke (46,47) and may be caused by small and large vessel disease (48,49) associated with diabetes, heart disease and hypertension (50–54). The role of vascular risk factors in AD is controversial (2). The main putative mechanism in the pathogenesis of AD is the deposition of amyloid beta (A β) in the brain (55), and it is thought that putative risk factors for AD act directly through this pathway (56,57). The association between vascular risk factors to AD may not be causal, and could be explained by the incidental coexistence of common disorders in the elderly, or by misclassification of cases of vascular or mixed dementia as AD (16). Vascular risk factors are known to be related to stroke, and stroke has been shown to be associated with AD (26,58), but the mechanisms relating cerebrovascular disease to AD remain to be elucidated. Our results show strong associations between the number of vascular risk factors and AD and support an important role for vascular disease in its pathogenesis.

Hypertension may cause AD through cerebrovascular disease. Hypertension is a risk factor for subcortical white matter lesions (WMLs) found commonly in AD (59–61). Hypertension is related to increased vascular permeability with protein extravasation (62), a common finding in brain parenchyma in AD (63,64). Blood pressure was increased 10–15 years before the onset of both AD and vascular dementia in one study (65), but it was found to be lower in old individuals with dementia (66). Others have found no association between hypertension and cognitive impairment (67,68), and there is conflicting data on the effect of antihypertensive treatment on cognition (69,70). Isolated hypertension did not have a strong association with AD in our data, but hypertension clustered with diabetes, heart disease, or smoking did show a higher risk of AD. It is possible that hypertension increases the risk of AD in the presence of other risk factors.

Heart disease can lead to cognitive impairment through cerebral hypoperfusion or embolism (71) and is also known to be linked with the APOE- ϵ 4 allele, a known risk factor for AD (72,73). The Rotterdam study (74) observed an 1.8-fold increased risk of AD in patients with atrial fibrillation. There is a higher frequency of cerebral beta-amyloid-containing senile plaques among individuals with coronary artery disease compared to age-matched controls without heart disease (56). Heart disease alone did not significantly increase the risk of AD, but subjects with heart disease clustered with diabetes or hypertension had a higher risk of AD.

Diabetes may affect cognition and increase the risk of dementia via oxidative stress, protein glycosylation, and ischemia (75). Type 2 diabetes is associated with hyperinsulinemia (17), and peripheral insulin is transported to the CNS across the blood brain barrier (76–79). Insulin receptors have been found in the hippocampus (80), the part of the brain first affected by AD (81), indicating the potential for peripheral insulin to cause direct injury in AD. Insulin degrading enzyme in the brain is a regulator of extracellular amyloid beta levels (82,83) inhibited by insulin (83,84). Insulin also has a role in the regulation of phosphorylation of Tau protein, the main component of neurofibrillary tangles (80). Peripheral insulin infusion in humans increases the levels of amyloid beta in CSF (85), further suggesting an important role of hyperinsulinemia in AD pathogenesis. These observations are supported by several epidemiologic studies linking hyperinsulinemia (19,86), and diabetes (6–8,20) to an increased risk of AD. Diabetes was strongly related to a higher risk of AD in isolation, or when clustered with other vascular risk factors. The wealth of epidemiologic and mechanistic data relating diabetes and AD make it a strong putative risk factor for AD and our results strongly support this notion. Smoking is an important cardiovascular and cerebrovascular risk factor (87) and could increase the risk of AD through cerebrovascular disease. There have been conflicting data about the association between smoking and AD (88), but prospective studies have found an increased risk of AD in smokers. A study from the Netherlands found an association between smoking and a higher risk of AD (89) among persons without the APOE- ϵ 4 allele. A study from Northern Manhattan found a higher risk of AD among current smokers with the APOE-

ε4 allele, and no increased risk among smokers who had quit (21). Current smoking in the absence of other risk factors was strongly related to a higher risk of AD in our data. Furthermore, the presence of current smoking in clusters with other risk factors appreciably increased the risk of AD as compared with smoking alone or other risk factors in isolation, providing compelling support for a role of smoking in increasing the risk of AD.

Vascular risk factors are seldom found in isolation and often coexist (90). The usual statistical approach of examining each risk factor individually while adjusting for others may result in the elimination of any real association because of wrong assumptions of confounding (18). The fact that different risk factors potentially affect the AD process through different direct and indirect pathways as described above raises the possibility that these risk factors act in additive or synergistic manners. We cannot directly address this with our data, but current knowledge on mechanisms related to AD suggests that the associations between different clusters of risk factors and AD that we demonstrate may be explained by the combination of different mechanistic pathways.

There are several potential explanations for our findings. One is that vascular risk factors are associated with a higher risk of vascular dementia and not AD, and that our results are explained by misclassification (16). The definition of AD has a sensitivity of over 90 percent but a specificity of approximately 50 percent using pathological diagnosis as the gold standard (91), which can result in misclassification of other types of dementia, including vascular dementia, as AD. We addressed this issue by examining only *probable* AD as the outcome, and the association with clusters of risk factors remained strong, suggesting that misclassification is an unlikely explanation for our findings. Another potential explanation is confounding. Lower educational attainment and minority status (African American or Hispanic) are related to a higher risk of dementia (39) and to a higher prevalence of diabetes, hypertension, and heart disease (20,38). We addressed this by stratifying our analyses by ethnic group and education and it did not change our results appreciably. It is also possible that subjects who developed AD were more likely to acquire vascular risk factors due to age or to processes related to preclinical AD. We addressed this possibility by doing analyses excluding subjects with shorter follow-ups, and the results were essentially unchanged. Another potential explanation is chance. This seems unlikely given the strength of our findings and the high level of significance. One important consideration in our data is that the vascular risk factors in our final analyses were ascertained by self-report and we lacked sub-clinical measures of disease, such as echocardiography data. This is likely to underestimate the real prevalence of disease (38,92), as is the case with diabetes. The prevalence of self reported diabetes in our sample is comparable to previous reports for the same age groups and ethnic composition (92). However, the prevalence of diabetes in the general population is higher than what is diagnosed (92), and self reported diabetes underestimates the true prevalence. We lacked data on the precise duration and severity of the vascular risk factors and there may be considerable measurement error in their estimation; thus, our results may be biased towards the null, and assuming no confounding, other sources of bias, or chance findings, the strong results of our study are likely an underestimation of the true associations between vascular risk factors and AD. Another important consideration is that the cohort in this study is comprised of subjects 65 years and older, with a high prevalence of vascular risk factors, and the results should be interpreted in this context; in fact, persons in the final sample seemed to have a worse vascular risk factor profile than those who were lost to follow-up, with the exception of current smoking. The relationship between vascular risk factors in middle age and AD in later life is likely to be different than what we report due to biases related to survival, and to changes in the measurement of risk factors with aging(2). Our findings support an important role of modifiable vascular risk factors in the development of AD in the elderly.

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Comparison of characteristics between individuals excluded due to prevalent dementia, lost to follow-up, and the final sample in the study using the latter as the reference.

Table 1

	Baseline dementia (n=340)	Lost to follow-up (n = 648)	Final sample (n =1138)
Age [mean in years(SD)]	81.8 (7.6)***	76.8 (6.8)*	76.2(5.9)
Female (%)	73.5***	66.2	69.8
Education (years)	6.4 (4.4)***	8.5 (4.6)	8.6 (4.6)
Black (%)	34.8	36.8	33.1
Hispanic (%)	52.8	38.2	44.4
White (%)	12.4***	25.0	22.5
APOE-ε4 (%)	35.8	20.7	28.6
Diabetes (%)	18.9	12.7**	20.3
Hypertension (%)	49.2	44.6***	60.7
Heart disease (%)	27.1	23.2	28.9
Current smoking (%)	7.1	14.6*	10.2
Past smoking (%)	20.1***	37.5	34.7

* = $p < 0.05$

** = $p < 0.01$

*** = $p < 0.001$

Table 2

Comparisons of clinical characteristics between individuals with and without diabetes, hypertension, heart disease, and current smoking.

	DIABETES		HYPERTENSION		HEART DISEASE		CURRENT SMOKING	
	Absent N=908	Present N=230	Absent N=447	Present N=691	Absent N=809	Present N=329	Absent N=1,022	Present N=116
Age (years)	76.2±6.0	75.3±5.6*	76.3±6.8	75.8±6.0	75.8±5.8	76.4±6.3	76.2±6.1	74.7±4.8**
Female gender (%)	71.5	70.9	72.7	70.5	72.3	69.0	71.2	72.4
Education (years)	8.2±4.6	8.1±4.8	8.3±4.6	8.1±4.6	8.2±4.6	8.1±4.6	8.2±4.6	8.1±4.9
African American (%)	29.5	29.1	26.9	28.5	28.8	25.5	27.6	30.2
Hispanic (%)	39.2	51.3	49.4	47.3	47.5	49.9	47.6	53.5
White (%)	23.1	9.1***	23.7	24.2	23.7	24.6	24.9	16.4
BMI (kg/m ²)	27.1±5.0	27.1±5.6	27.0±5.1	27.1±5.2	27.1±5.3	27.0±4.7	26.7±5.2	26.1±4.2
Diabetes (%)	-	-	11.6	25.8***	15.6	31.6***	20.7	15.5
LDL (mg/dl)	121.6±34.1	113.3±39.3**	120.3±35.0	119.8±35.5	120.5±35.1	118.6±35.5	120.6±34.9	114.6±37.9
Hypertension (%)	56.5	77.4***	-	-	52.7	80.6***	61.1	57.8
Heart disease (%)	24.8	45.2***	14.3	38.4***	-	-	28.9	29.3
Current smoker (%)	10.8	7.8	10.9	9.7	10.1	10.3	-	-
APOE-ε4 (%)	29.5	26.9	27.9	29.7	28.5	30.1	28.7	31.5
Possible AD (%)	19.4	30.4***	17.5	24.3**	17.9	30.7***	20.7	29.3*
Probable AD (%)	14.3	20.0*	12.3	17.5*	13.1	21.3	14.6	23.3*

* = $p < 0.05$

** = $p < 0.01$

*** = $p < 0.001$

AD= Alzheimer's disease

Table 3

Hazard ratios and 95% confidence intervals relating number of vascular risk factors to incident Alzheimer's disease (AD). Model 1 is adjusted for age and gender. Model 2 is adjusted for age, gender, education, APOE-ε4 allele, and ethnicity. Analyses for model 2 are on a sample of 1,012 subjects (126 subjects had missing APOE genotyping). In analyses with probable AD as the outcome, cases of possible AD were censored at the time of onset of dementia.

Number of risk factors	At risk	Probable and possible Alzheimer's disease (n=246)		Probable Alzheimer's disease (n=176)		
		Cases	Model 1	Model 2	Model 1	Model 2
No risk factors	303	41 (13.5)	1.0	1.0	1.0	1.0
1 risk factor	430	78 (18.1)	1.6 (1.1,2.4)	1.7 (1.1, 2.6)	1.6 (1.0,2.6)	1.8 (1.1,3.0)
2 risk factors	288	89 (30.9)	2.6 (1.7,3.8)	2.5 (1.6,3.9)	2.7 (1.7,4.2)	2.8 (1.7,4.7)
3 or 4 risk factors	117	38 (32.5)	3.8 (2.4,5.9)	3.4 (2.1,5.7)	3.5 (2.0,6.1)	3.4 (1.8,6.5)
p for trend			< 0.0001	< 0.0001	< 0.0001	< 0.0001

Table 4

Hazard ratios and 95% confidence intervals relating specific individual clusters of diabetes (DM), hypertension (HTN), heart (HEART) disease and current smoking (SMOKE) to Alzheimer's disease. The reference group is individuals without risk factors. Model 1 is adjusted for age and gender, and model 2 is adjusted for age, gender, ethnic group, education, and APOE-ε4 allele. Analyses for model 2 are on a sample 1,012 subjects (126 subjects had missing APOE genotyping).

Risk profile	At risk	Probable and possible Alzheimer's disease (n=246)		Probable Alzheimer's disease (n=176)		
		Cases (%)	Model 1	Model 2	Model 1	Model 2
No risk factors	303	41 (13.5)	1.0	1.0	1.0	1.0
DM only	36	11 (30.6)	3.6 (1.8,7.1)	3.8 (1.8, 8.2)	3.8 (1.7,8.5)	4.8 (1.9,11.6)
HTN only	306	48 (15.7)	1.4 (0.9,2.1)	1.5 (0.9,2.4)	1.4 (0.8,2.3)	1.5 (0.9,2.6)
HEART only	47	10 (21.3)	1.7 (0.8, 3.3)	1.0 (0.4,2.6)	1.6 (0.7,3.7)	1.2 (0.4,3.5)
SMOKE only	41	9 (21.9)	2.2 (1.1,4.7)	2.2 (1.0,4.9)	2.9 (1.3,6.3)	2.7 (1.2,6.3)
DM + HTN	82	26 (31.7)	3.3 (1.9,5.4)	3.3 (1.9,5.9)	3.5 (1.9,6.3)	3.3 (1.7,6.4)
DM + HEART	12	5 (41.7)	3.5 (1.4,9.0)	3.7 (1.2,11.1)	0.9 (0.1,7.2)	0.6 (0.1,5.7)
DM + SMOKE	3	1 (33.3)	13.7 (1.8,101.7)	7.4 (0.5,108.9)	18.5 (2.4,140.6)	22.2 (0.8, 592.9)
HTN + HEART	154	48 (31.2)	2.3 (1.5,3.5)	2.3 (1.4,3.7)	2.5 (1.5,4.1)	2.7 (1.5,4.7)
HTN + SMOKE	33	8 (24.2)	2.2 (1.0, 4.7)	2.7 (1.2,6.1)	2.7 (1.2,6.2)	2.9 (1.2,7.3)
HEART + SMOKE	4	1 (25.0)	3.1 (0.4,22.5)	5.9 (0.7, 46.9)	0 (0,-)	0 (0,-)
3 or 4 risk factors	117	38 (32.5)	3.8 (2.4,5.9)	3.4 (2.1,5.7)	3.5 (2.0,6.1)	3.4 (1.8,6.3)