Published in final edited form as:

J Neurol Sci. 2007 June 15; 257(1-2): 194–201. doi:10.1016/j.jns.2007.01.030.

Relation between vascular risk factors and neuropsychological test performance among elderly persons with Alzheimer's disease

Christiane Reitz^a, Bindu Patel^a, Ming-Xix Tang^{a,f}, Jennifer Manly^{a,b,d}, Richard Mayeux^{a,b,c,d}, and Jose A. Luchsinger^{a,d,e,*}

^aThe Gertrude H. Sergievsky Center, Columbia University College of Physicians and Surgeons, New York, NY, USA

^bThe Department of Neurology, Columbia University College of Physicians and Surgeons, New York, NY, USA

^cThe Department of Psychiatry, Columbia University College of Physicians and Surgeons, New York, NY, USA

^dThe Taub Institute for Research on Alzheimer's Disease and the Aging Brain, Columbia University College of Physicians and Surgeons, New York, NY, USA

^eThe Department of Medicine, Columbia University College of Physicians and Surgeons, New York, NY, USA

^fThe Department of Biostatistics in the Mailman School of Public Health Columbia University College of Physicians and Surgeons, New York, NY, USA

Abstract

Background—Vascular risk factors increase the risk of Alzheimer's disease (AD). The mechanisms for these associations are unclear, and may be due to misdiagnosis of a vascular dementia syndrome as AD.

Objective—To examine differences in neuropsychological profile among persons diagnosed clinically with AD with and without vascular risk factors or stroke.

Methods—Community based cohort study. Individual and composite scores of neuropsychological tests at the time of clinical diagnosis of incident AD were compared among 243 persons with and without vascular risk factors or stroke.

Results—Among subjects with incident AD, diabetes was associated with lower performance in Delayed Recall of the Selective Reminding Test (SRT), while persons diagnosed with hypertension scored lower in consistent long term recall (CLTR) of the SRT and current smokers scored lower in Category Fluency. None of the risk factors was associated with differences in composite scores in memory, abstract/visuospatial or language domain, nor was the number of risk factors per person. Persons with stroke had a higher delayed recall score at the time of AD diagnosis.

Conclusion—The presence of vascular risk factors among persons with clinically diagnosed AD was associated with subtle differences in neuropsychological profile at the time of diagnosis. This study needs to be replicated in samples with brain imaging, a comprehensive executive abilities battery, and pathological diagnosis of AD.

Keywords

Vascular risk factors; Stroke; Neuropsychological test performance

1. Introduction

Alzheimer's disease (AD) is among the most common diseases in aging societies, and its prevalence is expected to quadruple by the year 2047. [1] Vascular risk factors and stroke, which are highly prevalent in ageing societies, are clearly associated to a higher risk of vascular dementia (VaD), [2,3] but are also associated with a higher risk of AD. [4,5] We previously reported associations of stroke, [6] hyperinsulinemia, [7] diabetes, [8] current smoking, [9] and hypertension, [10] to a higher risk of cognitive impairment or AD. We sought to explore how the presence of vascular risk factors modifies the neuropsychological profile of clinically diagnosed AD.

The objective of this study was to explore the neuropsychological differences among persons with incident clinically diagnosed AD with and without vascular risk factors and stroke at the time of diagnosis.

2. Methods

2.1. Subjects and setting

Participants were part of a longitudinal study of Medicare recipients 65 years or older residing in northern Manhattan (Washington Heights, Hamilton Heights, Inwood) that has been described elsewhere. [11] Each participant underwent an in-person interview of general health and function at the time of the study entry followed by a standard assessment, including medical history, physical and neurological examination as well as a neuropsychological battery. [12] Baseline data were collected from 1992 through 1994. Follow-up data were collected during evaluations at sequential intervals of approximately 18 months, performed from 1994 to 1996, 1996 to 1997, and 1997 to 1999. In this elderly population, some participants did not complete follow up at all intervals due to refusal to participate further, relocation or death. About one half of participants were evaluated at the third follow-up visit. Data collected at each follow-up interval included medical, neurological, and neuropsychological evaluations. [12,13]

The sample for this study was the 243 persons who developed incident clinically defined AD during follow-up, and who did not have dementia at study baseline and when vascular risk factors were ascertained.

2.2. Neuropsychological assessment

All participants underwent a standardized neuropsychological test battery in either English or Spanish. [12] Orientation was evaluated using parts of the modified Mini-Mental State Examination. [14] Language was assessed using the Boston Naming Test, [15] the Controlled Word Association Test, [16] category naming, and the Complex Ideational Material and Phrase Repetition subtests from the Boston Diagnostic Aphasia Evaluation. [15] Abstract Reasoning was evaluated using WAIS-R Similarities subtest, [17] and the non-verbal Identities and Oddities subtest of the Mattis Dementia Rating Scale. [18] Visuospatial ability was examined using the Rosen Drawing Test, [19] and a matching version of the Benton Visual Retention Test. [20] Memory was evaluated using the multiple choice version of the Benton Visual Retention Test [20] and the seven subtests of the Selective Reminding Test [21]: total recall, long-term recall, long-term storage, consistent long-term retrieval (CLTR), words recalled on last trial, delayed recall, and delayed recognition. This neuropsychological test battery has

established norms for the same community. [22] The scores of neuropsychological tests used in this study were those obtained from the first visit the person was diagnosed with dementia and who did not have dementia in previous visits.

A factor analysis was performed using data with the 15 neuropsychological measures using a principal component analysis with varimax rotation and Kaiser normalization. [23] This analysis resulted in three factors: 1) a memory factor, in which the seven subtests of the Selective Reminding Test were the main contributors; 2) an abstract/visuospatial factor, where visuospatial and tests of reasoning were the main contributors; and 3) a language factor, in which language measures from the Boston Naming Test [15], Controlled Oral Word Association Test, [16] and the WAIS-R Similarities [17] were the main contributors. Each factor score was normally distributed. Each test within a factor was standardized to a scale of 100 and a final composite score was obtained from the mean of the main tests contributing to each factor.

2.3. Definition of dementia, possible and probable AD

Results from the neurological, psychiatric and neuropsychological examinations were reviewed in a consensus conference comprised of physicians, neurologists, neuropsychologists and psychiatrists. Based on this review all participants were assigned to one of three categories: normal cognitive function, cognitive impairment without dementia, or dementia. Cognitive impairment without dementia was defined as the presence of abnormal neuropsychological tests for age, gender, and education group without significant cognitive impairment, and a Clinical Dementia Rating (reference) (CDR) of 0.5. Dementia was defined as the presence of abnormalities in several cognitive domains in neuropsychiatric testing accompanied by significant functional impairment (CDR ≥ 1). 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 or 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 or dementia associated with stroke as AD. [24] To address this possible misclassification, we conducted analyses among all persons with incident AD (*possible* or *probable* AD), and additional analyses only among persons with *probable* AD. The diagnosis of dementia and its subtypes was based only on clinical criteria and was not based on pathological or neuroimaging information, which was not available.

2.4. Stroke

Stroke was defined according to the WHO criteria. [25] The presence of stroke was ascertained from an interview with participants and their informants. Persons with stroke were confirmed through their medical records, 85% of which included results of brain imaging. The remaining were confirmed by direct examination. This definition of stroke is related to a higher risk of AD in this cohort [6], and thus is included in our analyses.

2.5. Vascular risk factors

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. 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% using medical records as the gold standard. We previously reported that only diabetes,

hypertension, heart disease, and current smoking have at least marginal associations with a higher risk of AD, [26] while other risk factors, such as homocysteine [27] and dyslipidemia [28,29] are not related to AD risk in this cohort. Thus, the only risk factors that we include in our analyses are diabetes, hypertension, heart disease, and current smoking, in addition to stroke.

2.6. APOE genotyping

APOE genotypes were determined as described by Hixson and Vernier [30] with slight modification. [31] We classified persons as homozygous or heterozygous for the APOE ϵ 4 allele or not having any ϵ 4 allele.

3. Statistical methods

Demographics and other potentially relevant factors were compared among individuals with incident clinically defined AD with and without vascular risk factors and with and without stroke. We only included vascular risk factors which have been observed to be associated with clinically defined AD in our previous studies in the same population [26]: diabetes mellitus, heart disease, hypertension, and current smoking. We used χ^2 tests for categorical data and analysis of variance for continuous variables. ANCOVA was used to compare the means of each individual test among persons with incident *possible and probable* AD with and without each risk factor adjusted for age, gender, ethnic group, and years of education. ANCOVA was then repeated comparing the adjusted means of the composite scores in memory, abstract/visuospatial and language domains among persons with clinically defined incident AD (*possible or probable*) with and without each risk factor. In a third model, adjusted means of individual and composite tests were compared among persons with clinically defined incident AD with and without various clusters of risk factors. To address possible misclassification of vascular dementia or dementia associated with stroke as AD, all analyses were repeated among subjects with clinically defined *probable* AD only. We also conducted secondary analyses relating vascular risk factors to slope of decline in the memory, abstract/visuospatial, and language scores. These analyses were restricted to individuals with clinically diagnosed AD with at least 3 neuropsychological examinations including that at the time of dementia diagnosis. First, the slope of change in scores was calculated per individual using linear regression. Then the individual scores were used as the dependent variable in linear regression with vascular risk factors as the independent variable adjusting for age, gender, ethnic group, and APOE- ϵ 4, and baseline score. SPSS V10 was used for all analyses.

4. Results

There were 1,138 individuals without dementia at baseline with 6292 person-years of follow-up (mean = 5.5; SD = 3.2) and 270 persons developed incident dementia; 243 persons were clinically diagnosed with incident probable or possible AD (90.0% of all incident dementia), 12 (4.4%) with dementia associated with stroke and 15 (5.6%) with other types of dementia (e.g. Parkinson's disease, Lewy body disease). The sample for this study only included persons with clinically defined AD. For subsequent analyses we reclassified the subtypes of dementia by considering *probable* cases only as having AD, and the frequencies of dementia subtypes changed as follows: 175 subjects developed AD (62.1% of all dementia), 72 (26.7%) cases had dementia associated with stroke or mixed (vascular and AD) dementia, and 23 (8.2%) had other types of dementia.

Among persons with incident clinically defined *possible and probable* AD, the mean age was 82.8 ± 6.0 , and 70.0% of the sample were women, 54.7% were Hispanic, 8.2% were White, and 35.8% were Black (Table 1). The mean of years of education was 7.1 ± 4.6 , and 30.4% were homozygous or heterozygous for the APOE- ϵ 4 allele. Prior to the development of

dementia, 33.7% of the subjects reported having diabetes, 83.1% hypertension, 21.0% heart disease, 12.4% had a history of stroke and 14.8% were current smokers. Women reported diabetes, hypertension, heart disease and stroke more often than men, and persons with less years of education were more likely to report hypertension, heart disease, and current smoking compared to persons with more years of education (Table 2).

In analyses relating each putative risk factor with scores in individual neuropsychological tests among persons with clinically defined *possible and probable* AD, persons with diabetes mellitus had significantly lower scores in the Delayed Free Recall Subtest of the Selective Reminding Test (1.1 vs. 1.7; $p = 0.006$) (Table 3), while persons diagnosed with hypertension scored lower in Category Fluency (8.7 vs. 10.0, $p = 0.015$). Current smokers showed lower scores on CLTR Raw (2.1 vs. 3.8, $p = 0.017$), while subjects with a history of stroke or incident stroke performed better in the Delayed Free Recall (2.1 vs. 1.4, $p = 0.029$ and 1.9 vs. 1.4, $p = 0.01$) and WAIS-R Similarities Raw subtests (7.3 vs. 4.9, $p = 0.025$ and 6.5 vs. 4.6, $p = 0.048$) than persons without stroke. When we related each individual risk factor with composite scores in memory, abstract/visuospatial and language domains, none of the risk factors was associated with lower performance in any of the three cognitive domains (Table 4). In subsequent analyses among subjects with *probable* AD only, these results remained unchanged.

We previously reported that the risk of clinically diagnosed AD increases with the number of vascular risk factors (diabetes + hypertension + heart disease + current smoking). [26] We constructed a variable counting the number of risk factors: diabetes, hypertension, heart disease, stroke and current smoking; 5.8% of the individuals with *possible or probable* AD had no risk factors, 30.9% had one risk factor, 44.9% had two risk factors, 15.2% had three risk factors, and 3.3% had four risk factors. We compared the adjusted means from neuropsychological tests among subjects with *possible or probable* AD with one, two, three, and four vascular risk factors, and there was no association between the number of risk factors and any of the three cognitive domains (Table 5). The results remained unchanged among subjects with *probable* AD only.

We conducted secondary analyses relating the vascular risks factors to decline in cognitive scores (memory, abstract visuospatial, language) in 204 persons with clinically diagnosed AD who had at least 3 neuropsychological examinations (Table 6). We found no relation between any of the risk factors and the slopes of the cognitive scores. These results were not different for probable and possible AD.

5. Comment

We found subtle differences in neuropsychological profile at the time of clinical diagnosis of AD among persons with and without vascular risk factors. Diabetes was associated with lower performance in Delayed Recall of the SRT among subjects with *possible or probable* AD. Persons with hypertension scored lower in category fluency and current smokers scored lower in the CLTR subtest of the SRT. Subjects with stroke performed better in the Delayed Recall and WAIS-R Similarities. None of the risk factors was associated with differences in composite scores in memory, abstract/visuospatial or language domain, and increasing number of risk factors was not related to performance in any cognitive domain. The results were the same when comparisons were made only among persons with probable AD. In addition, we found no relation between the risk factors and rate of cognitive decline up to the clinical diagnosis of AD.

The role of vascular risk factors in vascular dementia seems clear. Vascular dementia is related to cerebral small and large vessel disease, [32] which in turn may be caused by diabetes, hypertension, heart disease and smoking. [33] The role of vascular risk factors in AD remains

unclear. [5] The main putative mechanism in the pathogenesis of AD is the deposition of amyloid beta (A β) in the brain, [34] and it is thought that putative risk factors for AD may act through this pathway. [35,36] However, it is also possible that the relation between vascular risk factors and AD is not causal, but may be explained by coexistence of common disorders in the elderly, or by misclassification of cases of vascular dementia as AD. [24] Vascular risk factors are known to be related to cerebrovascular disease, which in turn has been shown to be associated with AD [6,37] but the mechanisms relating cerebrovascular disease to AD remain to be elucidated. Among the vascular risk factors, diabetes seems to have the strongest biologic plausibility for a direct role in AD, [5,7,26] given its relation not only to cerebrovascular disease, but also to other mechanisms that may impair amyloid beta clearance in the brain such as hyperinsulinemia affecting insulin degrading enzyme. [38-40] The clinical definition of AD has a sensitivity of over 90% but a specificity of approximately 50% using pathological diagnosis as the gold standard, [41] which can result in misclassification of other types of dementia, including vascular dementia, as AD. In addition, some researchers have criticized the emphasis on the clinical diagnosis of AD at the expense of the diagnosis of other types of dementia [42] that may include those related to vascular risk factors and stroke. Thus, we sought to explore whether there was evidence of misclassification of dementia by comparing the neuropsychological profiles of persons with and without vascular risk factors.

Diabetes was associated with lower delayed recall scores at the time of diagnosis of AD, but no other differences in neuropsychological profile. Diabetes has the potential to affect amyloid beta directly and through multiple mechanisms, [5] including cerebrovascular disease, [6] inflammation, [43] and glycosylated end products. [44,45] Given that diabetes has been shown to be a strong risk factor for AD in our cohort [8] as well as in other studies [46,47], and given that memory performance is the strongest predictor of AD, [48,49] it is not surprising that memory performance is worse in persons with AD who have diabetes. However, we found no association between diabetes and more rapid memory decline preceding AD clinical diagnosis.

Persons with hypertension and current smokers had a lower category fluency mean and lower values in the CLTR of the SRT, respectively, but no other differences in neuropsychological profile. This could be explained by the fact that hypertension and current smoking may affect more frontal/executive cognitive abilities, [3] and our results may be showing the juxtaposition of frontal cognitive impairment with AD.

Persons with stroke had a higher delayed recall compared to persons without stroke, but no other differences in neuropsychological profile. Of all the comparisons we made, this finding is the only one that would suggest that these persons had a dementia other than AD, given that an abnormal (low) delayed recall is the neuropsychological hallmark of AD; [49] this result suggests that while these persons had a dementia syndrome very similar to AD, their dementia may have been due to cognitive impairment related to stroke that had an additive effect on the AD process and precipitated functional impairment and the diagnosis of dementia despite higher delayed recall.

There are several alternative explanations for our findings. One is that the few differences in neuropsychological profile that we found are due to chance in the context of multiple comparisons. It is possible that the differences were explained by confounding: vascular risk factors are related to lower socioeconomic status, [50] which can be related to lower raw cognitive scores [12], but we adjusted for education and ethnic group as socioeconomic markers in our analyses. Another possible explanation is bias caused by misclassification of the vascular risk factors and stroke; these were ascertained by self-report, and if underestimated, would have resulted in underestimation of differences between persons with and without risk factors. In particular, we lacked neuroimaging data to ascertain "subclinical" cerebrovascular disease. [51] Another possibility is that the neuropsychological battery in this study may have been

biased towards the detection of AD, and thus, we may not be able to find differences because neuropsychological domains more likely to be affected by vascular risk factors were not detected. This last point may indicate that this study is tautological; that is, persons with AD with and without vascular risk factors were going to have the same neuropsychological profile because that profile is what this cohort study sought to detect. In this context, the small differences we found could be interpreted as having clinical significance. We cannot elucidate if this differences are due to mixed additive pathology (vascular and AD), or to differences in the underlying pathophysiologic process because we lacked neuroimaging and pathological data.

This study included a comprehensive neuropsychological battery. However, it may be limited in addressing cognitive domains that are associated with vascular disease. For example, we lacked tests of executive function such as the color trails [52,53] and the stroop color and word tests [54] which may have resulted in underestimation of the differences we sought to find.

It is important to point out that our study only examined differences in neuropsychological profile among persons with the clinical diagnosis, or syndrome, of AD. We did not have neuroimaging or brain pathology data. Thus, we cannot make direct inferences about pathology based on our analyses. We can say that from a neuropsychological standpoint, AD in the presence of vascular risk factors is very similar to that in its absence. The small differences we found may reflect different severity of disease, concomitant pathology, or different pathologic processes. This study needs to be replicated in a sample with a comprehensive battery of tests of executive function, neuroimaging, and ideally, brain pathology.

Acknowledgments

This study was supported by grants PO1 AG07232, AG07702, 1K08AG20856-01, RR00645 from the National Institutes of Health (Bethesda, MD), the Charles S. Robertson Memorial Gift for Research in Alzheimer's disease, the Blanchette Hooker Rockefeller Foundation (New York, NY).

References

- [1]. Brookmeyer R, Gray S, Kawas C. Projections of Alzheimer's disease in the United States and the public health impact of delaying disease onset. *Am J Public Health* 1998;88(9):1337–42. [PubMed: 9736873]
- [2]. Barba R, Martinez-Espinosa S, Rodriguez-Garcia E, et al. Poststroke dementia: clinical features and risk factors. *Stroke* 2000;31(7):1494–501. [PubMed: 10884443]
- [3]. DeCarli C. The role of cerebrovascular disease in dementia. *Neurologist* 2003;9(3):123–36. [PubMed: 12808409]
- [4]. Korczyn AD. The underdiagnosis of the vascular contribution to dementia. *J Neurol Sci* 2005;229-230:3–6. [PubMed: 15760612]
- [5]. Luchsinger JA, Mayeux R. Cardiovascular risk factors and Alzheimer's disease. *Curr Atheroscler Rep* 2004;6(4):261–6. [PubMed: 15191699]
- [6]. Honig LS, Tang MX, Albert S, et al. Stroke and the risk of Alzheimer disease. *Arch Neurol* 2003;60(12):1707–12. [PubMed: 14676044]
- [7]. Luchsinger JA, Tang MX, Shea S, et al. Hyperinsulinemia and risk of Alzheimer disease. *Neurology* 2004;63(7):1187–92. [PubMed: 15477536]
- [8]. Luchsinger JA, Tang MX, Stern Y, et al. Diabetes mellitus and risk of Alzheimer's disease and dementia with stroke in a multiethnic cohort. *Am J Epidemiol* 2001;154(7):635–41. [PubMed: 11581097]
- [9]. Merchant C, Tang MX, Albert S, et al. The influence of smoking on the risk of Alzheimer's disease. *Neurology* 1999;52(7):1408–12. [PubMed: 10227626]
- [10]. Posner HB, Tang MX, Luchsinger J, et al. The relationship of hypertension in the elderly to AD, vascular dementia, and cognitive function. *Neurology* 2002;58(8):1175–81. [PubMed: 11971083]

- [11]. Tang MX, Stern Y, Marder K, et al. The APOE-epsilon4 allele and the risk of Alzheimer disease among African Americans, Whites, and Hispanics. *JAMA* 1998;279(10):751–5. [PubMed: 9508150]
- [12]. Stern Y, Andrews H, Pittman J, et al. Diagnosis of dementia in a heterogeneous population. Development of a neuropsychological paradigm-based diagnosis of dementia and quantified correction for the effects of education. *Arch Neurol* 1992;49(5):453. [PubMed: 1580806]
- [13]. Pittman J, Andrews H, Tatemichi T, et al. Diagnosis of dementia in a heterogeneous population. A comparison of paradigm-based diagnosis and physician's diagnosis. *Arch Neurol* 1992;49(5):461. [PubMed: 1580807]
- [14]. Folstein MF, Folstein SE, McHugh PR. Mini-mental state. A practical method for grading the cognitive state of patients for the clinician. *J Psychiatr Res* 1975;12(3):189. [PubMed: 1202204]
- [15]. Goodglass, H.; Kaplan, E. *The Assessment of Aphasia and Related Disorders*. Vol. 2.ed.. Lea and Febiger; Philadelphia, PA: 1983.
- [16]. Benton, A. *FAS Test*. University of Victoria; Victoria, B.C: 1967.
- [17]. Wechsler, D. *Wechsler Adult Intelligence Scale-Revised*. The Psychological Corporation; New York, NY: 1981.
- [18]. Mattis, S. *Mental status examination for organic mental syndrome in the elderly patient*. Grune and Stratton; New York, NY: 1976.
- [19]. Rosen, W. *The Rosen Drawing Test*. Veterans Administration Medical Center; Bronx, NY: 1981.
- [20]. Benton, A. *The Benton Visual Retention Test*. The Psychological Corporation; New York: 1955.
- [21]. Buschke H, Fuld PA. Evaluating storage, retention, and retrieval in disordered memory and learning. *Neurology* 1974;24(11):1019. [PubMed: 4473151]
- [22]. Stricks L, Pittman J, Jacobs DM, et al. Normative data for a brief neuropsychological battery administered to English-and Spanish-speaking community-dwelling elders. *J Int Neuropsychol Soc* 1998;4(4):311. [PubMed: 9656604]
- [23]. Kleinbaum, D.; Klipper, L.; Muller, K. *Applied regression analysis and other multivariable methods*. Vol. 2nd ed.. PWS-Kent; Boston: 1988.
- [24]. Breteler MM. Vascular risk factors for Alzheimer's disease: an epidemiologic perspective. *Neurobiol Aging* 2000;21(2):153–60. [PubMed: 10867200]
- [25]. Hatano S. Experience from a multicentre stroke register: a preliminary report. *Bull World Health Organ* 1976;54(5):541–53. [PubMed: 1088404]
- [26]. Luchsinger JA, Reitz C, Honig LS, et al. Aggregation of Vascular Risk Factors and Risk of Incident Alzheimer's Disease. *Neurology*. in press
- [27]. Luchsinger JA, Tang MX, Shea S, et al. Plasma homocysteine levels and risk of Alzheimer's disease. *Neurology* 2004;62(11):1972–6. [PubMed: 15184599]
- [28]. Reitz C, Luchsinger J, Tang MX, et al. Impact of plasma lipids and time on memory performance in healthy elderly without dementia. *Neurology* 2005;64(8):1378–83. [PubMed: 15851727]
- [29]. Reitz C, Tang MX, Luchsinger J, et al. Relation of plasma lipids to Alzheimer disease and vascular dementia. *Arch Neurol* 2004;61(5):705–14. [PubMed: 15148148]
- [30]. Hixson JE, Vernier DT. Restriction isotyping of human apolipoprotein E by gene amplification and cleavage with HhaI. *J Lipid Res* 1990;31(3):545. [PubMed: 2341813]
- [31]. Mayeux R, Ottman R, Maestre G, et al. Synergistic effects of traumatic head injury and apolipoprotein-epsilon 4 in patients with Alzheimer's disease. *Neurology* 1995;45(3 Pt 1):555. [PubMed: 7898715]
- [32]. Jellinger KA. Understanding the pathology of vascular cognitive impairment. *J Neurol Sci* 2005;229-230:57–63. [PubMed: 15760620]
- [33]. Mast H, Thompson JL, Lee SH, et al. Hypertension and diabetes mellitus as determinants of multiple lacunar infarcts. *Stroke* 1995;26(1):30–3. [PubMed: 7839393]
- [34]. Selkoe DJ. The origins of Alzheimer disease: a is for amyloid. *JAMA* 2000;283(12):1615–7. [PubMed: 10735401]
- [35]. Petrovitch H, White LR, Izmirlian G, et al. Midlife blood pressure and neuritic plaques, neurofibrillary tangles, and brain weight at death: the HAAS. Honolulu—Asia aging Study. *Neurobiol Aging* 2000;21(1):57–62. [PubMed: 10794849]

- [36]. Sparks DL, Martin TA, Gross DR, et al. Link between heart disease, cholesterol, and Alzheimer's disease: a review. *Microsc Res Tech* 2000;50(4):287–90. [PubMed: 10936882]
- [37]. Vermeer SE, Prins ND, den Heijer T, et al. Silent brain infarcts and the risk of dementia and cognitive decline. *N Engl J Med* 2003;348(13):1215–22. [PubMed: 12660385]
- [38]. Farris W, Mansourian S, Chang Y, et al. Insulin-degrading enzyme regulates the levels of insulin, amyloid beta-protein, and the beta-amyloid precursor protein intracellular domain in vivo. *Proc Natl Acad Sci U S A* 2003;100(7):4162–7. [PubMed: 12634421]
- [39]. Farris W, Mansourian S, Leissring MA, et al. Partial loss-of-function mutations in insulin-degrading enzyme that induce diabetes also impair degradation of amyloid beta-protein. *Am J Pathol* 2004;164(4):1425–34. [PubMed: 15039230]
- [40]. Qiu WQ, Walsh DM, Ye Z, et al. Insulin-degrading enzyme regulates extracellular levels of amyloid beta-protein by degradation. *J Biol Chem* 1998;273(49):32730–8. [PubMed: 9830016]
- [41]. Mayeux R, Saunders AM, Shea S, et al. Utility of the apolipoprotein E genotype in the diagnosis of Alzheimer's disease. Alzheimer's Disease Centers Consortium on Apolipoprotein E and Alzheimer's Disease. *N Engl J Med* 1998;338(8):506–11. [PubMed: 9468467]
- [42]. Royall D. The “Alzheimerization” of dementia research. *J Am Geriatr Soc* 2003;51(2):277–8. [PubMed: 12558730]
- [43]. Yaffe K, Kanaya A, Lindquist K, et al. The metabolic syndrome, inflammation, and risk of cognitive decline. *JAMA* 2004;292(18):2237–42. [PubMed: 15536110]
- [44]. Deane R, Du YS, Subramanian RK, et al. RAGE mediates amyloid-beta peptide transport across the blood-brain barrier and accumulation in brain. *Nat Med* 2003;9(7):907–13. [PubMed: 12808450]
- [45]. Yan SD, Chen X, Fu J, et al. RAGE and amyloid-beta peptide neurotoxicity in Alzheimer's disease. *Nature* 1996;382(6593):685–91. [PubMed: 8751438]
- [46]. Ott A, Stolk RP, van Harskamp F, et al. Diabetes mellitus and the risk of dementia: the Rotterdam study. *Neurology* 1999;53(9):1937–42. [PubMed: 10599761]
- [47]. Peila R, Rodriguez BL, White LR, et al. Fasting insulin and incident dementia in an elderly population of Japanese-American men. *Neurology* 2004;63(2):228–33. [PubMed: 15277613]
- [48]. Ritchie K, Lovestone S. The dementias. *Lancet* 2002;360(9347):1759–66. [PubMed: 12480441]
- [49]. Small SA, Stern Y, Tang MX, et al. Selective decline in memory function among healthy elderly. *Neurology* 1999;52(7):1392–6. [PubMed: 10227623]
- [50]. Luchsinger, JA. Diabetes. In: Aguirre-Molina, M.; Molina, CW.; Zambrana, RE., editors. *Health issues in the Latino community*. Jossey-Bass; San Francisco: 2001. p. 277-300.
- [51]. Royall, DR. Seminars in cerebrovascular diseases and stroke. Vol. vol. 4. 2005. Silent stroke: an oxymoron meaning dementia; p. 97-101.
- [52]. Demakis GJ. Frontal lobe damage and tests of executive processing: a meta-analysis of the category test, stroop test, and trail-making test. *J Clin Exp Neuropsychol* 2004;26(3):441–50. [PubMed: 15512932]
- [53]. Dugbartey AT, Townes BD, Mahurin RK. Equivalence of the Color Trails Test and Trail Making Test in nonnative English-speakers. *Arch Clin Neuropsychol* 2000;15(5):425–31. [PubMed: 14590218]
- [54]. Golden, CJ. *The Stroop Color and Word Test: a manual for clinical and experimental uses*. Stoelting; Chicago, III: 1987.
- [55]. Census of Population and Housing. Summary Tape File1, Technical Documentation (computer program). Bureau of Census; Washington DC: 1991. STF 1A database

Table 1Demographic characteristics of study population (*possible and probable AD*)

Characteristic	Possible and probable AD (n=243)
Sex	
Men	73 (30%)
Women	170 (70%)
Age at enrollment, mean (SD)	
Men	82.5 (6.0)
Women	83.2 (6.3)
Education in years, mean (SD)	7.1 (4.6)
Ethnic group ^a	
White	20 (8.2)
African-American	87 (35.8)
Hispanic	133 (54.7)
Other	3 (1.2)
APOE genotype 4/4	10 (4.1)
APOE genotype 4/-	64 (26.3)
APOE genotype -/-	148 (60.9)
Diabetes	82 (33.7)
Hypertension	202 (83.1)
Heart disease	51 (21.0)
Current smoker	36 (14.8)
Stroke	30 (12.4)

Values are expressed as number (percentage) unless otherwise indicated. Some percentages are based on an incomplete sample due to small amounts of missing data.

^aClassified by self-report using the format of the 1990 US census [55].

Table 2
Comparison of demographics between *possible and probable* AD participants with and without risk factors

Demographics	Diabetes		Hypertension		Heart disease		Stroke		Current smoker	
	No	Yes	No	Yes	No	Yes	No	Yes	No	Yes
	N=161	N=82	N=41	N=202	N=192	N=51	N=213	N=30	N=207	N=36
Age, mean (SD)	83.1 (6.0)	82.7 (6.4)	83.2 (6.7)	82.9 (6.1)	83.0 (6.2)	82.8 (6.0)	83.1 (6.3)	82.3 (5.2)	83.4 (6.2)	80.5 (5.1)
Sex										
Men	53 (32.9)	20 (24.4)	16 (39.0)	57 (28.2)	59 (30.7)	14 (27.5)	65 (30.5)	8 (26.7)	55 (26.6)	18 (50.0)
Women	108 (67.1)	62 (75.6)	25 (61.0)	145 (71.8)	133 (69.3)	37 (72.5)	148 (69.5)	22 (73.3)	152 (73.4)	18 (50.0)
Education in years, mean (SD)	7.1 (4.5)	7.1 (4.7)	7.7 (5.4)	7.0 (4.4)	7.2 (4.6)	6.8 (4.4)	6.9 (4.4)	8.9 (5.1)	7.2 (4.6)	6.6 (4.4)
Ethnic group ^a										
White	13 (8.1)	7 (8.5)	4 (9.8)	16 (7.9)	15 (7.8)	5 (9.8)	14 (6.6)	6 (20.0)	17 (8.2)	3 (8.3)
African-American	59 (36.6)	28 (34.1)	16 (39.0)	71 (35.1)	67 (34.9)	20 (39.2)	75 (35.2)	12 (40.0)	72 (34.8)	15 (41.7)
Hispanic	88 (54.7)	45 (54.9)	20 (48.8)	113 (55.9)	108 (56.3)	25 (49.0)	121 (56.8)	12 (40.0)	116 (56.0)	17 (47.2)
Other	1 (0.6)	2 (2.4)	1 (2.4)	2 (1.0)	2 (1.0)	1 (2.0)	3 (1.4)	-	2 (1.0)	1 (2.8)
APOE allele										
2/4, 3/4, 4/4	51 (34.5)	23 (31.1)	11 (30.6)	63 (33.9)	57 (32.4)	17 (37.0)	66 (33.5)	8 (32.0)	62 (33.0)	12 (35.3)
2/2, 2/3	24 (16.2)	4 (5.4)	4 (11.1)	24 (12.9)	23 (13.1)	5 (10.9)	25 (12.7)	3 (12.0)	23 (12.2)	5 (14.7)
3/3	73 (49.3)	47 (63.5)	21 (58.3)	99 (53.2)	96 (54.5)	24 (52.2)	106 (53.8)	14 (56.0)	103 (54.8)	17 (50.0)

All models adjusted for age, gender, education, ethnicity and APOEε4 allele. Values are expressed as number (percentage) unless otherwise indicated. Some percentages are based on an incomplete sample due to small amounts of missing data.

^a Classified by self-report using the format of the 1990 US census [55].

Table 3

Comparison of adjusted means (SD) from *individual* neuropsychological tests among subjects with *possible and probable* AD with and without each risk factor

Neuropsychological tests	Diabetes		Hypertension		Heart disease		Stroke		Current smoker	
	No	Yes	No	Yes	No	Yes	No	Yes	No	Yes
SRT LTS raw	10.4 (0.5)	10.2 (0.8)	9.4 (1.1)	10.5 (0.5)	10.2 (0.5)	10.8 (1.0)	10.3 (0.5)	10.7 (1.4)	10.4 (0.5)	10.0 (1.2)
SRT total recall	21.3 (0.5)	20.0 (0.7)	20.3 (1.0)	20.9 (0.5)	21.0 (0.5)	20.2 (0.9)	20.7 (0.4)	22.1 (1.3)	21.2 (0.5)	19.0 (1.1)
SRT CLTR raw	3.7 (0.3)	3.1 (0.4)	3.1 (0.6)	3.6 (0.3)	3.7 (0.3)	3.0 (0.5)	3.5 (0.3)	3.5 (0.8)	3.8 (0.3)	2.1 (0.6) ^a
SRT delayed free recall	1.7 (0.1)	1.1 (0.2) ^a	1.4 (0.2)	1.6 (0.1)	1.6 (0.1)	1.4 (0.2)	1.4 (0.1)	2.1 (0.3) ^a	1.6 (0.1)	1.3 (0.3)
SRT delayed recognition	7.6 (0.2)	7.5 (0.3)	7.6 (0.4)	7.5 (0.2)	7.6 (0.2)	7.5 (0.4)	7.5 (0.2)	8.2 (0.5)	7.4 (0.2)	8.1 (0.4)
Benton recognition	4.3 (0.2)	4.6 (0.3)	4.3 (0.3)	4.4 (0.2)	4.3 (0.2)	4.3 (0.3)	4.4 (0.1)	4.0 (0.5)	4.3 (0.1)	4.7 (0.4)
WAIS-R similarities raw	5.3 (0.4)	4.6 (0.6)	4.1 (0.9)	5.3 (0.4)	4.9 (0.4)	5.7 (0.8)	4.9 (0.4)	7.3 (1.2) ^a	5.0 (0.4)	5.7 (1.0)
Benton matching	6.6 (0.2)	6.6 (0.3)	6.4 (0.5)	6.6 (0.2)	6.5 (0.2)	6.8 (0.4)	6.6 (0.2)	6.1 (0.6)	6.6 (0.2)	6.6 (0.5)
CFL mean (Letter fluency)	5.6 (0.3)	5.7 (0.4)	5.9 (0.5)	5.6 (0.2)	5.7 (0.2)	5.3 (0.5)	5.7 (0.2)	5.2 (0.7)	5.6 (0.2)	6.2 (0.6)
Category fluency mean	8.8 (0.2)	9.3 (0.4)	10.0 (0.5)	8.7 (0.2) ^a	8.9 (0.2)	9.1 (0.4)	8.9 (0.2)	9.1 (0.7)	8.8 (0.2)	9.7 (0.6)
Identities/similarities total	12.8 (0.2)	13.2 (0.3)	12.3 (0.4)	13.0 (0.2)	13.0 (0.2)	12.4 (0.4)	12.8 (0.2)	13.3 (0.6)	12.8 (0.2)	13.6 (0.5)
BDAE repetition	7.1 (1.0)	7.2 (0.1)	7.0 (0.2)	7.1 (0.1)	7.1 (0.1)	7.3 (0.2)	7.1 (0.1)	7.1 (0.2)	7.0 (0.1)	7.4 (0.2)
BDAE comprehension	3.9 (0.1)	4.2 (0.2)	3.9 (0.2)	4.0 (0.1)	4.0 (0.1)	4.2 (0.2)	4.0 (0.1)	4.1 (0.3)	4.0 (0.1)	4.2 (0.3)

All models adjusted for age, gender, education, ethnicity and APOEε4 allele.

^aSignificant at a 0.05 level.

Table 4
Comparison of adjusted means (SD) from *composite* scores neuropsychological tests among subjects with *possible and probable* AD with and without each risk factor

	Diabetes		Hypertension		Heart disease		Stroke		Incident stroke		Current smoker	
	No	Yes	No	Yes	No	Yes	No	Yes	No	Yes	No	Yes
Memory performance	25.9 (0.6)	24.1 (0.8)	24.6 (1.2)	25.5 (0.5)	25.5 (0.5)	24.8 (1.0)	25.0 (0.5)	27.9 (1.4)	24.9 (0.6)	26.6 (0.9)	25.4 (0.5)	24.9 (1.2)
Abstract/visuospatial performance	40.9 (0.8)	41.6 (1.2)	40.2 (1.6)	41.3 (0.7)	41.0 (0.7)	41.4 (1.4)	41.1 (0.7)	41.3 (2.1)	40.9 (0.7)	41.9 (1.3)	40.9 (0.7)	43.5 (1.8)
Language performance	77.1 (1.2)	79.4 (1.8)	76.7 (2.5)	78.0 (1.1)	77.0 (1.1)	80.7 (2.2)	77.7 (1.1)	78.9 (2.9)	78.4 (1.2)	76.2 (2.0)	77.1 (1.1)	81.8 (2.7)

All models adjusted for age, gender, education, ethnicity and APOEε4 allele.

Table 5

Comparison of adjusted means (SD) from *composite* scores of neuropsychological tests among subjects with *possible* and *probable* AD and with 0 to 5 risk factors

# of risk factors	Memory performance	Abstract/visuospatial performance	Language performance
0	24.3 (1.9)	40.3 (2.4)	70.4 (4.1)
1	26.4 (0.9)	40.0 (1.2)	78.0 (1.8)
2	24.6 (0.7)	41.1 (0.9)	77.8 (1.5)
3	25.9 (1.2)	44.0 (1.8)	79.8 (2.5)
4	25.0 (2.7)	42.2 (4.6)	82.1 (5.7)
<i>p</i> -value	0.555	0.467	0.350

All models adjusted for age, gender, education, ethnicity and APOEε4 allele.

Table 6
Coefficients and standard deviations from linear regression relating vascular risk factors and stroke to slopes of change in memory, abstract/visuospatial, and language performance, adjusted for age, gender, education, ethnicity, and APOE-ε4 allele

Slope of change	Diabetes	Hypertension	Heart disease	stroke	Incident stroke	Current smoking
Memory	0.1±0.9	1.6±1.2	-0.4±1.25	-0.1±0.9	-0.1±0.6	-0.5±0.7
Abstract /visuospatial	-0.1±0.4	0.5±0.6	-0.7±0.6	-0.4±0.4	-0.1±0.3	-0.6±0.3
Language	0.0±0.3	0.5±0.4	-0.5±0.4	0.0±0.3	0.0±0.2	-0.3±0.2

None of the coefficients were statistically significant.