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Associations between stroke risk and cognition in normal aging and Alzheimer's disease with and without depression

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Abstract

Background—Stroke risk factors have been increasingly implicated in the development of age-related cognitive decline, the spectrum of vascular cognitive impairment, and, more recently, Alzheimer's disease (AD). In addition, depression and the apolipoprotein (APOE) ε4 allele have been reported to influence the association between stroke risk and cognition. However, few studies have described the relations among stroke risk, cognition, and APOE genotype in AD, and the findings have been equivocal.

Methods—Thirty cognitively normal older adults, 30 AD patients with depression, and 30 AD patients without depression were administered a comprehensive neuropsychological battery measuring several domains including memory, attention, language, visuospatial skills, executive functions, and speed of information processing. The Framingham Stroke Risk Profile (FSRP), a validated scale that was developed to predict 10-year probability of stroke, was used to quantify stroke risk burden.

Results—AD patients with depression demonstrated greater stroke risk burden relative to the cognitively normal group and, across all participants, increased stroke risk was associated with poorer performance on memory and processing speed measures. Moreover, stroke risk accurately predicted AD diagnosis. Notably, there were no significant differences in stroke risk or cognitive performance between the AD participants with depression and those without depression.

Conclusion—Given that many markers of stroke risk are modifiable or treatable, our findings have implications for assessment, prevention, and treatment of cognitive decline.

Keywords

Alzheimer's disease; depression; stroke risk; apolipoprotein E; cognition

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Conflict of interest

None known.

Introduction

Increasing attention has focused on the contributions of cardiovascular risk factors for stroke to the pathogenesis and exacerbation of Alzheimer's disease (AD). Research in this area has shown that stroke risk factors, such as diabetes (Ott *et al.*, 1999) and hypertension (Skoog *et al.*, 1996), are associated with increased risk for developing AD. Stroke risk factors are also associated with an accelerated rate of decline after establishment of an AD diagnosis (Mielke *et al.*, 2007). Although the precise mechanisms linking stroke risk factors and AD are not fully understood, proposed theories suggest that (1) vascular pathology may have an additive effect by increasing the overall burden of pathology (Chui *et al.*, 2006), (2) AD and vascular disease may interact to worsen pathologic effects (Honig *et al.*, 2003), and (3) AD itself may be conceptualized as a vascular disorder with amyloid deposition linked to a breakdown in the blood-brain barrier and alterations in brain perfusion (Kalaria, 1997; for review, see Thal *et al.*, 2008).

Stroke risk factors are also associated with cognitive decline in older adults who are free of dementia and clinical stroke. This relationship has been shown for executive functions (Brady *et al.*, 2001), attention, visuospatial memory (Elias *et al.*, 2004), and verbal episodic memory (Bangen *et al.*, 2007). Although the mechanism underlying the relationship between increased stroke risk and cognitive decline remains unclear, greater stroke risk, in general, is associated with smaller brain volume in older adults without evidence of clinical stroke (Bangen *et al.*, 2007). Moreover, stroke risk factors are associated with the development of white matter lesion pathology that is related to cognitive impairment across the aging spectrum (Delano-Wood *et al.*, 2008a).

In addition to the relationship between the presence of stroke risk factors and cognitive decline, there is some evidence that vascular disease predisposes nondemented older adults to depressive symptoms (the 'vascular depression' hypothesis; Thomas *et al.*, 2004). Depression is associated with neuropsychological impairment and increased risk of developing dementia (Thomas and O'Brien, 2008), and vascular disease may be a mechanism linking depression and AD (Luchsinger *et al.*, 2008). However, the relationship among these variables is complex, and it is possible that vascular disease and depression contribute independently or synergistically to the development of cognitive decline and dementia (Alexopoulos, 2003).

Results from studies examining the associations among stroke risk, cognition, and depressive symptoms have been equivocal. For instance, two studies of adults with major depressive disorder (MDD) reported that greater stroke risk was associated with poorer cognitive performance (Smith *et al.*, 2007; Steffens *et al.*, 2007). In contrast, a longitudinal study by Luchsinger *et al.* (2008) demonstrated greater AD risk with increased depressive symptomatology in older adults who were not demented at baseline. Their results were unchanged after adjustment for vascular risk, indicating that the link between depressive symptoms and AD is likely not explained by a history of stroke risk factors.

Given these equivocal findings, there remains debate whether stroke risk or depression appreciably modify cognition either in mild cognitive impairment (MCI) or dementia. We therefore examined stroke risk and cognitive functioning in AD patients with and without depression, as well as in cognitively normal adults free of clinical stroke, in an effort to further clarify the associations among stroke risk, cognition, and depression. Given that the apolipoprotein E (APOE) $\epsilon 4$ allele is associated with increased risk for developing AD (Corder *et al.*, 1993) and greater stroke risk burden (Ilveskoski *et al.*, 1999), we also assessed the association between APOE genotype and stroke risk. We hypothesized that greater stroke risk would be related to poorer cognitive performance across AD and cognitively normal

participants, and that stroke risk would be highest in AD patients with depression, intermediate in AD patients without depression, and lowest in cognitively normal older adults.

Methods

Participants

Assessment and Diagnosis of Dementia—Sixty individuals with clinically diagnosed probable AD and 30 cognitively normal older adults (NC) were selected for this study from the larger cohort of research volunteers of the Alzheimer's Disease Research Center (ADRC) at the University of California, San Diego (UCSD). The AD participants included 30 consecutively enrolled AD participants with depression who were selected for the present study from the larger cohort based solely on their diagnoses of AD and depression (see below for details). Thirty AD participants characterized as nondepressed and 30 cognitively normal older adults were selected from the larger cohort based on their demographic similarity to the depressed AD group on age, education, and sex distributions as well as study enrollment date. In addition, the two AD groups were matched on overall level of cognitive impairment as measured by the total score on the Mattis dementia rating scale (DRS; Mattis, 1976). Participants were selected without regard to race, ethnicity, socioeconomic status, or APOE genotype. The study was approved by the UCSD institutional review board and written informed consent was obtained from all participants or from caregivers.

The three groups did not significantly differ in terms of age ($F_{(2,87)} = 0.15, p = 0.86, \eta_p^2 = 0.01$), education ($F_{(2,87)} = 2.52, p = 0.09, \eta_p^2 = 0.06$), or women/men ratio ($\chi^2 = 0.09, p = 0.96$). As expected, the groups significantly differed in APOE genotype distribution ($\chi^2 = 24.63, p < 0.001$). The NC group included five $\epsilon 4$ carriers (16.7%) and 25 non- $\epsilon 4$ carriers (83.3%). The nondepressed AD group included 17 $\epsilon 4$ carriers (56.7%) and 13 non- $\epsilon 4$ carriers (43.3%). The depressed AD group included 24 $\epsilon 4$ carriers (80.0%) and six non- $\epsilon 4$ carriers (20.0%; see Table 1).

Participants underwent a clinical evaluation that included neurological, neuropsychological, psychiatric, and medical examinations, as well as laboratory tests and APOE genotyping. Patients received a diagnosis of probable AD by two independent, senior staff neurologists according to the criteria developed by the National Institute of Neurological and Communicative Disorders and Stroke (NINCDS) and the Alzheimer's Disease and Related Disorders Association (McKhann *et al.*, 1984). Individuals were excluded from this study if they had causes of dementia other than AD, a history of severe head injury, substance abuse, or psychiatric disorders (with the exception of depressive disorders). In addition, participants with a history of stroke or transient ischemic attack (TIA) or who had a modified Hachinski score greater than 4 were excluded. Thus, individuals whose dementia may have had a significant vascular component were not included in this study.

Assessment and diagnosis of depression—All participants were evaluated for depression according to the protocol described elsewhere (Delano-Wood *et al.*, 2008b). Briefly, the Diagnostic Interview Schedule (DIS), a DSM-based semi-structured interview for psychiatric diagnoses, was used. The DIS was administered by trained nurse practitioners who were highly experienced in the assessment of older adults with cognitive impairment. In addition, two board certified geriatric psychiatrists supervised the nurse practitioners' evaluations and made the determination regarding the diagnosis of a depressive disorder. Responses to the DIS were obtained from both the patient and an informant/caregiver and any inconsistencies were resolved by medical chart review, clinical assessment, and consensus judgment. Of the 30 AD patients with a current diagnosis of co-occurring depression, 19 were diagnosed with dementia with depression, six were diagnosed with major depressive disorder,

four were diagnosed with adjustment disorder with depressed mood, and one was diagnosed with atypical depression. Based on self or informant reports, 12 of the 30 depressed AD patients had a history of depression prior to their enrollment in the study. None of the 30 nondepressed AD patients had a prior history or current diagnosis of depression.

Neuropsychological assessment

All participants received global cognitive screening (DRS) and the ADRC Core Neuropsychological Battery (for a detailed description of the tests that comprise this battery, see Salmon and Butters, 1992). Neuropsychological tests of interest included measures from six cognitive domains: memory, attention, language, visuospatial functioning, executive functioning, and speed of information processing. The conceptually-based inclusion of each measure within one of the six domains was supported by six separate principal components analyses, each of which yielded a single factor solution (eigenvalues ranged from 1.17 to 3.36). The raw scores for each of the 15 measures listed below were *z*-transformed using the means and standard deviations of the NC group. Then the *z*-scores for the individual tests were averaged to create a summary score for each cognitive domain. The specific measures that comprise each domain were as follows: (1) *Memory* was assessed with the Wechsler Memory Scale—Revised (Wechsler, 1987) Logical Memory Subtest (WMS-R; immediate and delayed free recall) and the California Verbal Learning Test (CVLT; Trials 1–5 total recall and long delay free recall; Delis *et al.*, 1987); (2) *Attention* was measured with the Attention subscale of the DRS and the Digit Span subtest of the Wechsler Adult Intelligence Scale—Revised (WAIS-R; Wechsler, 1981); (3) *Language* was measured with the Boston Naming Test (Kaplan *et al.*, 1983) and the WAIS-R Vocabulary subtest; (4) *Visuospatial skills* were assessed with the Block Design subtest of the Wechsler Intelligence Scale for Children—Revised (WISC-R; Wechsler, 1974) and the Construction sub-scale of the DRS; (5) *Executive functioning* was measured with the Wisconsin Card Sorting Test (WCST-48-card version; number of perseverative errors; Lineweaver *et al.*, 1999), letter fluency (FAS), and Trail Making Test, Part B (Reitan and Wolfson, 1985); (6) *Speed of information processing* was assessed with the Trail Making Test, Part A (Reitan and Wolfson, 1985) and the Digit Symbol subtest of WAIS-R (Wechsler, 1981).

Stroke risk

Using methods previously described by D'Agostino *et al.* (1994) stroke risk was quantified using the Framingham Stroke Risk Profile (FSRP). The FSRP is a validated scale that was developed to predict 10-year probability of stroke. The FSRP provides gender-corrected scores based on the following risk factors which were identified from 36 years of longitudinal data from the Framingham Heart Study: age, systolic blood pressure, diabetes mellitus, cigarette smoking, history of cardiovascular disease, atrial fibrillation, left ventricular hypertrophy as identified by electrocardiogram, and use of antihypertensive medications. Total allocated points ranged from 1 (a 10-year stroke probability of 1% in women and 3% in men) to 30 (a 10-year stroke risk of 84% in women and 88% in men). Given that no electrocardiograms were performed on participants, the presence of left ventricular hypertrophy could not be determined and was, therefore, not included in any statistical analyses. In addition to the variables composing the FSRP score, total cholesterol was also measured.

Statistical analyses—Correlational analyses were conducted to examine the associations among APOE genotype (participants were classified as either $\epsilon 4$ carriers or non- $\epsilon 4$ carriers), stroke risk, and cognition. Analyses of variance (ANOVAs) and χ^2 tests were conducted to examine group differences for variables of interest. In cases where the omnibus F-test demonstrated statistical significance, Tukey's Honestly Significant Differences (HSD) *post hoc* tests were conducted to determine which specific groups differed. Logistic regression was

used to assess the contribution of stroke risk to diagnostic group classification. All analyses were performed using SPSS.

Results

Within-subjects associations of stroke risk, cognition, and APOE status

Correlational analyses revealed that, across the entire sample (i.e., NC subjects and AD patients), greater stroke risk was significantly associated with poorer performance on memory ($r = -0.22, p = 0.02$) and processing speed ($r = -0.22, p = 0.02$) measures (see Figure 1). Stroke risk was not significantly correlated with performance on measures of global cognitive functioning (i.e., DRS total score; $r = -0.15, p = 0.08$), attention ($r = -0.01, p = 0.45$), language ($r = -0.03, p = 0.39$), visuospatial skills ($r = 0.02, p = 0.44$), or executive functioning ($r = -0.04, p = 0.38$). In addition, stroke risk was not associated with the presence of the APOE $\epsilon 4$ allele ($r = 0.05, p = 0.62$). The same correlational analyses were conducted separately for each of the three participant groups as well as for the two AD groups combined. There were no significant correlations between stroke risk, cognition, and the presence of the APOE $\epsilon 4$ allele (all p -values > 0.05).

Group stroke risk and neuropsychological differences

ANOVAs demonstrated that the NC, nondepressed AD, and depressed AD groups significantly differed in stroke risk ($F_{(2,87)} = 3.33, p = 0.04, \eta_p^2 = 0.07$). *Post hoc* pairwise comparisons using Tukey's HSD tests showed that stroke risk was significantly greater in the depressed AD patients than in NC participants ($p = 0.03$). There were no significant differences in stroke risk scores between the NC participants and the nondepressed AD patients ($p = 0.36$), or between depressed and non-depressed AD patients ($p = 0.45$; see Figure 2).

The three participant groups were compared on each of the individual variables composing the FSRP score. χ^2 analyses demonstrated that the groups significantly differed in terms of frequency of cardiovascular disease ($\chi^2 = 7.73, p = 0.02$). Follow-up *post hoc* χ^2 analyses demonstrated that the depressed AD ($\chi^2 = 7.50, p = 0.006$) group had a significantly greater frequency of cardiovascular disease as compared to the NC group; however, there were no significant differences between the nondepressed AD and NC groups or between the two AD groups (p -values > 0.05). In addition, a one-way ANOVA revealed a trend toward significant differences among the NC, nondepressed AD, and depressed AD groups in terms of systolic blood pressure ($F_{(2,87)} = 3.04, p = 0.05, \eta_p^2 = 0.07$). In contrast, there were no significant between-group differences in terms of frequency of anti-hypertensive medication use ($\chi^2 = 2.10, p = 0.35$), diabetes mellitus ($\chi^2 = 0.42, p = 0.81$), cigarette smoking ($\chi^2 = 2.22, p = 0.33$), or history of atrial fibrillation ($\chi^2 = 0.31, p = 0.86$), or in total cholesterol ($F_{(2,87)} = 1.74, p = 0.18, \eta_p^2 = 0.04$). Not surprisingly, given its role in cholesterol transport (e.g., Mahley, 1988), APOE genotype was significantly associated with total cholesterol level such that APOE $\epsilon 4$ carriers had higher cholesterol than non- $\epsilon 4$ carriers ($r = 0.26, p = 0.01$).

The three participant groups differed on DRS total score ($F_{(2,87)} = 51.08, p < 0.001, \eta_p^2 = 0.54$) and on the memory ($F_{(2,87)} = 245.22, p < 0.001, \eta_p^2 = 0.85$), attention ($F_{(2,87)} = 11.10, p < 0.001, \eta_p^2 = 0.20$), language ($F_{(2,87)} = 26.30, p < 0.001, \eta_p^2 = 0.38$), visuospatial function ($F_{(2,87)} = 19.27, p < 0.001, \eta_p^2 = 0.31$), executive function ($F_{(2,87)} = 39.01, p < 0.001, \eta_p^2 = 0.47$), and speed of information processing ($F_{(2,87)} = 38.16, p < 0.001, \eta_p^2 = 0.47$) summary scores. *Post hoc* pairwise comparisons showed that both depressed and nondepressed AD patients performed significantly worse than NC participants on the DRS total score and each of the six cognitive

domain scores (all p -values <0.05). The two AD groups did not differ significantly on any of these cognitive measures (all p -values >0.10).

Diagnostic group classification based on stroke risk and APOE genotype

Binary logistic regression analyses showed that when NC participants and nondepressed AD patients were included in the analyses and stroke risk was the only predictor variable, it did not produce a significant improvement in the model relative to the null model ($\chi^2 = 2.29$, $p = 0.13$, Nagelkerke $R^2 = 0.05$). The model accurately classified 51.7% of the participants as either nondepressed AD or cognitively normal. In a second model, both stroke risk and APOE genotype were added as predictors. This model was a significant improvement over the null model ($\chi^2 = 15.13$, $p = 0.001$, Nagelkerke $R^2 = 0.30$) and accurately classified 75.0% of participants as nondepressed AD or cognitively normal.

A second set of binary logistic regression analyses included NC participants and depressed AD patients. When stroke risk was the only predictor variable, it produced a significant improvement in the model relative to the null model ($\chi^2 = 7.11$, $p = 0.008$, Nagelkerke $R^2 = 0.15$). The model accurately classified 56.7% of the participants as either belonging to the depressed AD or NC group. When both stroke risk and APOE genotype were added as predictors, the model was a significant improvement over the null model ($\chi^2 = 30.21$, $p < 0.001$, Nagelkerke $R^2 = 0.53$) and accurately classified 83.3% of participants as depressed AD or cognitively normal.

Discussion

Our results indicate that AD patients with depression have a greater degree of stroke risk than cognitively normal individuals, even after excluding those with cerebrovascular disease. Stroke risk for AD patients without depression fell between that of depressed AD patients and cognitively normal individuals, but did not differ significantly from either group. Correspondingly, logistic regression analyses showed that stroke risk was more effective at differentiating depressed AD patients than nondepressed AD patients from cognitively normal individuals. These results highlight the complex and subtle nature of the relations among AD, stroke risk, and depression. The group differences in overall stroke risk appeared to be driven by differences in the rate of cardiovascular disease and possibly also in blood pressure.

The finding that stroke risk was not significantly higher in the depressed AD group than in the nondepressed AD group is consistent with other studies reporting that stroke risk alone does not appear to explain the link between depression and AD (Luchsinger *et al.*, 2008). As Luchsinger *et al.* (2008) note, there are several mechanisms other than stroke risk factors that could explain the link between depression and AD, including a psychological reaction to cognitive decline, damage to catecholaminergic circuits during AD development and progression, or degeneration of limbic structures leading to vulnerability to depression.

The present results demonstrated that the frequency of the APOE $\epsilon 4$ allele was significantly different across the three groups. APOE $\epsilon 4$ allele frequencies were 80.0%, 56.7%, and 16.7% for the depressed AD, nondepressed AD, and NC groups, respectively. The observed $\epsilon 4$ allele frequencies are consistent with previously published reports of approximate frequencies of 72% (Delano-Wood *et al.*, 2008b), 50% (Saunders *et al.*, 1993), and 16% (Strittmatter *et al.*, 1993) in these populations, respectively.

Given its role in cholesterol transport and neuronal repair (e.g., Mahley, 1988), it is proposed that the APOE $\epsilon 4$ allele may be related to stroke risk factors which, in turn, may be linked to depressive symptoms. However, stroke risk burden did not differ between depressed and nondepressed AD patients in the present study, suggesting that other APOE $\epsilon 4$ -related

mechanisms may be involved. In a population-based study of older adults, the presence of the APOE $\epsilon 4$ allele was associated with greater risk of severe depression even after adjusting for both cardiovascular conditions and lipid profile (Yen *et al.*, 2007). Their findings suggest that the APOE $\epsilon 4$ allele and stroke risk factors are independent risk factors for the development of depression. In the present study, an association between stroke risk and APOE genotype was not demonstrated.

In conjunction with previous findings indicating that stroke risk is associated with increased rate of decline in individuals with MCI (Reitz *et al.*, 2007) and AD (Mielke *et al.*, 2007), the present findings suggest that assessment of stroke risk may aid in the early detection and monitoring of individuals who are vulnerable to future cognitive decline. It is well known that depression is common in stroke patients and is associated with decreased quality of life and increased mortality, and as noted by Robinson (2005), it is reasonable to expect that depression associated with vascular disease is also associated with a high mortality rate. Fortunately, evidence suggests that treatment with antidepressants reduces mortality in post-stroke depression (Jorge *et al.*, 2003).

A second finding from the present study is that across all participants stroke risk was associated with decrements in memory and speed of information processing. Notably, the pattern of neuropsychological test performance in vascular dementia and AD dementia can be similar (Desmond, 2004). Indeed, the moderately demented AD patients in the present study exhibited deficits in executive functioning, speed of information processing, and attention that were similar to those observed in vascular dementia, but the cognitive domain most strongly associated with vascular risk factors was episodic memory, the cognitive ability that is often first to decline during the course of AD (Salmon and Bondi, 2009).

An important aspect of the present study was the careful characterization of the participant groups and the exclusion of individuals with a history of TIA, clinical stroke, or significant cerebrovascular disease. These measures were taken in an effort to exclude any nondemented older adults with cognitive impairment from participating in the study and to exclude individuals whose dementia may have had a significant vascular component. However, by excluding individuals with greater stroke risk burden, it is possible that the link between stroke risk and cognition was underestimated.

Despite these limitations, our findings highlight the possibility that prevention and treatment of stroke risk factors may lead to the preservation of cognitive functioning or the slowing of cognitive decline (Bowler and Hachinski, 2003). AD and stroke are growing public health concerns due to increasing longevity in the US population, and both have devastating psychological and financial effects. The present findings emphasize the importance of assessing and monitoring stroke risk factors not only in individuals with AD but also in healthy, cognitively normal older adults with no history of stroke or significant cerebrovascular disease.

Key Points

- Alzheimer's disease (AD) patients with depression demonstrate greater stroke risk burden relative to their cognitively normal (NC) counterparts.
- Greater stroke risk is associated with poorer cognitive performance across AD and NC individuals.
- Findings highlight the importance of monitoring and treating both stroke risk factors and depression given that such treatment may result in less risk of cognitive decline and improved quality of life.

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References

- Alexopoulos GS. Vascular disease, depression, and dementia. *J Am Geriatr Soc* 2003;51:1178–1180. [PubMed: 12890087]
- Bangen KJ, Restom K, Liu TT, et al. Agedifferences in cerebral blood flow but not BOLD response during encoding: associations with neuropsychological functioning and stroke risk. *Neurobiol Aging*. 2007;10.1016/j.neurobiolaging.2007.11.012
- Bowler, JV.; Hachinski, V. *Vascular Cognitive Impairment*. Oxford University Press; Oxford: 2003.
- Brady CB, Spiro A, McGlinchy-Berroth R, et al. Stroke risk predicts verbal fluency decline in healthy older men: evidence from the normative aging study. *J Gerontol B Psychol Sci Soc Sci* 2001;56B:P340–P346. [PubMed: 11682587]
- Chui HC, Zarow C, Mack WJ, et al. Cognitive impact of subcortical vascular and Alzheimer's disease pathology. *Ann Neurol* 2006;60:677–687. [PubMed: 17192928]
- Corder EH, Saunders AM, Strittmatter WJ, et al. Gene dose of apolipoprotein E type 4 allele and the risk if Alzheimer's disease in late onset families. *Science* 1993;261:921–923. [PubMed: 8346443]
- D'Agostino RB, Wolf PA, Belanger AJ, et al. Stroke risk profile: adjustment for antihypertensive medication. The Framingham study. *Stroke* 1994;25:40–43. [PubMed: 8266381]
- Delano-Wood L, Abeles N, Sacco JM, et al. Regional white matter pathology in mild cognitive impairment: differential influence of lesion type of neuropsychological functioning. *Stroke* 2008a; 39:794–799. [PubMed: 18258826]
- Delano-Wood L, Houston WS, Emond JA, et al. APOE genotype predicts depression in women with Alzheimer's disease: a retrospective study. *Int J Geriatr Psychiatry* 2008b;23:632–636. [PubMed: 18058831]
- Delis, DC.; Kramer, JH.; Kaplan, E., et al. *The California Verbal Learning Test*. Psychological Corporation; New York: 1987.
- Desmond DW. The neuropsychology of vascular cognitive impairment: is there a specific cognitive deficit? *J Neurol Sci* 2004;226:3–7. [PubMed: 15537510]
- Elias MF, Sullivan LM, D'Agostino RB, et al. Framingham stroke risk profile and lowered cognitive performance. *Stroke* 2004;35:404–409. [PubMed: 14726556]
- Honig LS, Tang MX, Albert S, et al. Stroke and the risk of Alzheimer disease. *Arch Neurol* 2003;60:1707–1712. [PubMed: 14676044]
- Ilveskoski E, Perola M, Lehtimäki T, et al. Age-dependent association of apolipoprotein E genotype with coronary and aortic atherosclerosis in middle-aged men—an autopsy study. *Circulation* 1999;100:608–613. [PubMed: 10441097]
- Jorge RE, Robinson RG, Arndt S, et al. Mortality and poststroke depression: a placebo-controlled trial of antidepressants. *Am J Psychiatry* 2003;160:1823–1829. [PubMed: 14514497]
- Kalaria RN. Cerebrovascular degeneration is related to amyloid- β protein deposition in Alzheimer's disease. *Ann N Y Acad Sci* 1997;826:263–271. [PubMed: 9329698]
- Kaplan, EF.; Goodglass, H.; Weintraub, S. *The Boston Naming Test*. Lea & Febiger; Philadelphia: 1983.
- Lineweaver TT, Bondi MW, Thomas RG, et al. A normative study of Nelson's (1976) modified version of the Wisconsin Card Sorting Test in healthy older adults. *Clin Neuropsychol* 1999;13:328–347. [PubMed: 10726604]
- Luchsinger JA, Honig LS, Tang MX, et al. Depressive symptoms, vascular risk factors, and Alzheimer's disease. *Int J Geriatr Psychiatry* 2008;23:922–928.
- Mahley RW. Apolipoprotein E: cholesterol transport protein with expanding role in cell biology. *Science* 1988;240:622–630. [PubMed: 3283935]

- Mattis, S. Mental status examination for organic mental syndromes in the elderly patient. In: Bellak, L.; Karasu, TE., editors. *Geriatric Psychiatry: A Handbook for Psychiatrists and Primary Care Physicians*. Grune and Stratton; New York: 1976. p. 77-101.
- McKhann G, Drachman D, Folstein M, et al. Clinical diagnosis of Alzheimer's disease: report of the NINCDS-ADRDA work group under the auspices of the Department of Health and Human Services Task Force on Alzheimer's disease. *Neurology* 1984;34:939-944. [PubMed: 6610841]
- Mielke MM, Rosenberg PB, Tschanz J, et al. Vascular factors predict rate of progression in Alzheimer disease. *Neurology* 2007;69:1850-1858. [PubMed: 17984453]
- Ott A, Stolk RP, van Harskamp F, et al. Diabetes mellitus and the risk of dementia: the Rotterdam study. *Neurology* 1999;53:1937-1942. [PubMed: 10599761]
- Reitan, RM.; Wolfson, D. *The Halstead-Reitan Neuropsychological Test Battery*. Neuropsychology Press; Tucson: 1985.
- Reitz C, Tang MX, Manly J, et al. Hypertension and the risk of mild cognitive impairment. *Arch Neurol* 2007;64:1734-1740. [PubMed: 18071036]
- Robinson RG. Vascular depression and poststroke depression: where do we go from here? *Am J Geriatr Psychiatry* 2005;13:85-87. [PubMed: 15703316]
- Salmon DP, Bondi MW. Neuropsychological assessment of dementia. *Annu Rev Psychol* 2009;60:257-282. [PubMed: 18616392]
- Salmon, DP.; Butters, N. Neuropsychological assessment of dementia in the elderly. In: Katzman, R.; Rowe, JW., editors. *Principles of Geriatric Neurology*. F. A. Davis; Philadelphia: 1992. p. 144-163.
- Saunders AM, Strittmatter WJ, Schmechel D, et al. Association of apolipoprotein E allele ϵ 4 with late-onset familial and sporadic Alzheimer's disease. *Neurology* 1993;43:1467-1472. [PubMed: 8350998]
- Skoog I, Lernfelt B, Landahl S, et al. 15-year longitudinal study of blood pressure and dementia. *Lancet* 1996;347:1141-1145. [PubMed: 8609748]
- Smith PJ, Blumenthal JA, Babyak MA, et al. Cerebrovascular risk factors, vascular disease, and neuropsychological outcomes in adults with major depression. *Psychosom Med* 2007;69:578-586. [PubMed: 17634564]
- Steffens DC, Potter GG, McQuoid DR, et al. Longitudinal magnetic resonance imaging vascular changes, apolipoprotein E genotype, and development of dementia in the neurocognitive outcomes of depression in the elderly study. *Am J Geriatr Psychiatry* 2007;15:839-849. [PubMed: 17623814]
- Strittmatter WJ, Saunderson AM, Schmechel D, et al. Apolipoprotein E: high-avidity binding to beta-amyloid and increased frequency of type 4 allele in late-onset familial Alzheimer disease. *Proc Natl Acad Sci USA* 1993;90:1977-1981. [PubMed: 8446617]
- Thal DR, Griffin WS, Braak H. Parenchymal and vascular Abeta-deposition and its effects on the degeneration of neurons and cognition in Alzheimer's disease. *J Cell Mol Med* 2008;12(5B):1848-1862. [PubMed: 18624777]
- Thomas AJ, Kalaria RN, O'Brien JT. Depression and vascular disease: what is the relationship? *J Affect Disord* 2004;79:81-95. [PubMed: 15023483]
- Thomas AJ, O'Brien JT. Depression and cognition in older adults. *Curr Opin Psychiatry* 2008;21:8-13. [PubMed: 18281834]
- Wechsler, D. *Wechsler Intelligence Scale for Children—Revised*. Psychological Corporation; New York: 1974.
- Wechsler, D. *Wechsler Adult Intelligence Scale—Revised Manual*. The Psychological Corporation; San Antonio: 1981.
- Wechsler, D. *Wechsler Memory Scale—Revised*. Psychological Corporation; New York: 1987.
- Yen YC, Rebok GW, Gallo JJ, et al. ApoE4 allele is associated with late-life depression: a population-based study. *Am J Geriatr Psychiatry* 2007;15:858-868. [PubMed: 17911363]

Figure 1. Scatterplots of the correlations between stroke risk and memory and speed of information processing summary scores for all participants. + cognitively normal; □ nondepressed AD; ○ depressed AD.

Figure 2.

Stroke risk (i.e., ten-year probability of stroke) values for each participant group. Bars represent standard error. *Depressed AD demonstrated significantly greater stroke risk values relative to the cognitively normal group ($p = .03$).

Table 1

Means and standard deviations of demographic, vascular risk, and cognitive variables for the normal control and Alzheimer's disease (AD) groups

Demographic Characteristics	Normal control (n = 30)	Nondepressed AD (n = 30)	Depressed AD (n = 30)
Age	75.87 (10.19)	74.80 (6.08)	74.40 (5.58)
Years of education	15.40 (2.92)	14.30 (2.72)	13.73 (3.13)
Sex (women/men)	16/14	17/13	17/13
APOE genotype (ε4/non-ε4)	5/25	17/13	24/6
Vascular risk factors:			
Vascular risk (FSRP)	13.30 (8.12)	17.07 (11.17)	20.37 (12.15)*
Systolic blood pressure (mmHg)	133.33 (19.83)	144.60 (17.82)	142.27 (18.32)
Antihypertensive medication use (yes/no)	11/19	7/23	12/18
Diabetes mellitus (yes/no)	1/29	2/28	2/28
Cigarette smoking (yes/no)	1/29	4/26	4/26
Cardiovascular disease (yes/no)	5/25	9/21	15/15**
Atrial fibrillation (yes/no)	2/28	2/28	3/27
Total cholesterol (mg/dL)	208.73 (36.44)	221.07 (40.30)	227.43 (41.62)
Cognitive scores:			
DRS total score	139.40 (4.13)	106.37 (13.98)***	108.13 (19.90)***
Memory score	-0.10 (0.86)	-2.89 (.27)***	-2.74 (0.30)***
Attention score	0.00 (0.87)	-1.42 (1.29)*	-2.26 (2.87)***
Language score	0.02 (0.87)	-2.72 (1.88)***	-1.94 (1.59)***
Visuospatial score	0.01 (0.85)	-1.74 (1.18)***	-1.77 (1.65)***
Executive function score	-0.01 (0.54)	-2.55 (1.18)***	-2.57 (1.82)***
Speed of information processing score	0.07 (0.80)	-2.20 (1.25)***	-2.27 (1.41)***

Note: Statistically significant difference from cognitively normal participants.

*
p < 0.05;

**
p < 0.01;

p < 0.001.

DRS = Mattis dementia rating scale FSRP = Framingham Stroke Risk Profile. The two AD groups did not differ significantly on any of these vascular risk or cognitive measures (all p-values > 0.10). All cognitive domain scores are z-transformed summary scores.