Published in final edited form as:

Ann Neurol. 2010 August ; 68(2): 231–240. doi:10.1002/ana.22055.

Atherosclerosis, Dementia, and Alzheimer's Disease in the BLSA Cohort

Hillary Dolan³, Barbara Crain¹, Juan Troncoso¹, Susan M Resnick², Alan B Zonderman², and Richard J OBrien³

¹) Department of Pathology, Johns Hopkins University

²) National Institute on Aging, Intramural Research Program, Laboratory of Personality & Cognition, National Institutes of Health

³) Departments of Neurology and Medicine, Johns Hopkins Bayview Medical Center

Abstract

Objective—Although it is now accepted that asymptomatic cerebral infarcts are an important cause of dementia in the elderly, the relationship between atherosclerosis *per se* and dementia is controversial. Specifically, it is unclear whether atherosclerosis can cause the neuritic plaques and neurofibrillary tangles that define Alzheimer neuropathology and whether atherosclerosis, a potentially reversible risk factor, can influence cognition independent of brain infarcts.

Methods—We examined the relationship between systemic atherosclerosis, Alzheimer type pathology and dementia in autopsies from 200 participants in the Baltimore Longitudinal Study of Aging (BLSA), a prospective study of the effect of aging on cognition, 175 of whom had complete body autopsies.

Results—Using a quantitative analysis of atherosclerosis in the aorta, heart and intracranial vessels, we found no relationship between the degree of atherosclerosis in any of these systems and the degree of Alzheimer's type brain pathology. However, we found that the presence of intracranial but not coronary or aortic atherosclerosis significantly increased the odds of dementia, independent of cerebral infarction. Given the large number of individuals with intracranial atherosclerosis in this cohort (136/200), the population attributable risk of dementia related to intracranial atherosclerosis (independent of infarction) is substantial and potentially reversible.

Interpretation—Atherosclerosis of the intracranial arteries is an independent and important risk factor for dementia, suggesting potentially reversible pathways unrelated to Alzheimer's pathology and stroke through which vascular changes may influence dementia risk.

Introduction

Cerebral infarction and Alzheimer's disease (AD) are leading and independent causes of dementia in the elderly¹⁻⁸. Systemic atherosclerosis has also been suggested to play a role in cognitive deterioration in the elderly⁹⁻¹⁴, and several studies have proposed that systemic atherosclerosis can increase Alzheimer's pathology directly, thus making Alzheimer's pathology potentially remediable with the treatment of systemic atherosclerosis^{10-13,51,52}. The effect of atherosclerosis on dementia has also been attributed to its relation to cerebral infarction^{1,3,5,6,8} or to systemic or local factors that underlie both atherosclerosis and cognition¹⁴⁻¹⁷. Alternatively, atherosclerosis and AD pathology may reflect a common

underlying process leading to a relationship between the two pathologies. Prospective cohorts with postmortem brain evaluations have been important in attempts to understand the etiology of dementia in the elderly. Such studies are uniquely able to investigate associations between cognitive changes during life with a variety of pathological findings at autopsy, including AD pathology, atherosclerosis, macroscopic and microscopic infarcts and Lewy body pathology⁴. We report here the results of the Baltimore Longitudinal Study of Aging Autopsy Program, a prospective study of the effects of aging on cognition and dementia. The large number of subjects in this study with complete autopsies makes it an important resource for elucidating the contribution of systemic atherosclerosis to dementia and the mechanisms underlying these effects. We report that coronary, intracranial and aortic atherosclerosis are not correlated with brain AD pathology, although intracranial atherosclerosis uniquely and significantly increases the odds of dementia independent of cerebral infarcts.

Methods

Cohort

A total of 579 participants from the Baltimore Longitudinal Study of Aging (BLSA) have agreed to post-mortem brain exams. The rate of dementia and clinical stroke in the autopsy cohort is similar to that in the BLSA cohort as a whole¹⁸. As of January 2009, 216 subjects have died and underwent brain autopsy (88% autopsy rate). Of this group, we excluded 15 subjects who had other pathological explanations for cognitive impairment; nine had both a clinical and pathological diagnosis of Parkinson's disease (subjects with Parkinson's disease were specifically sought out for the autopsy cohort at its inception and are thus not representative of the cohort as a whole), one had a primary brain tumor, one had an inflammatory leukoencephalopathy, one had metastatic brain lesions, and three had hippocampal sclerosis combined with FTD. An additional participant was excluded because language deficits from a clinical stroke compromised assessment of cognition. These exclusions left 200 individuals for the present analysis (133 men, 67 women). Participants were predominantly white (94%) with a mean of 17.1 ± 3.9 (S.D.) years of education. The mean age at death was 87.6 ± 7.1 years.

All participants in the present study were cognitively and neurologically normal at the time of entry into the BLSA and the autopsy cohort. They were assessed at baseline, within 18 months of death (mean of 8.7 ± 6.3 months prior to death), and periodically in between. The majority were seen annually after age 70, although approximately 25% of the cohort had gaps in their follow-up of several years duration. Using Fisher's Exact Test, the percentages of subjects with dementia or any pathologic infarct did not differ significantly between the group with annual evaluations ($n=154$) and those with less intense follow up ($n=46$). Studies of this cohort are conducted under the auspices of the Johns Hopkins and MedStar Research Institute IRBs, and all participants provided written informed consent.

Neuropsychological and risk factor evaluation

Evaluations included neuropsychological tests, neurological exam, interval medical history, medication review, and a structured informant and subject interview as described¹⁹. A diagnosis of diabetes or hypertension required both a documented history and the use of at least one medication for that condition over more than one visit. A diagnosis of coronary artery disease (CAD) required a history of myocardial infarction or coronary artery disease plus medication prescribed to treat CAD. Smoking history (any history of smoking) was obtained from a BLSA questionnaire obtained during yearly assessment. ApoE genotype was obtained for 154 of the 200 subjects with brain autopsies and 133 of the 175 subjects

with complete autopsies. Fasting total cholesterol levels were obtained, off medication, upon entry into the study.

Diagnosis of dementia

All participants were reviewed at a consensus conference at time of death or, during life, if their Blessed Information Memory Concentration score²⁰ was 3 or above, if their informant or subject CDR²¹ score was 0.5 or above, or if the Dementia Questionnaire²² was abnormal. Diagnoses of dementia were based on DSM-III-R criteria. The diagnosis of dementia required evidence of a progressive cognitive syndrome, including memory decline.

General Autopsies

At the time of death, subjects underwent either complete (n= 175) or brain-only autopsy (n= 25). Information about atherosclerosis in the heart, aorta or brain was transcribed from the autopsy report by an assistant blinded to the purpose of the study and without information regarding the cognitive diagnosis, CERAD or Braak scores. In grading atherosclerosis we sought to divide the subjects into 3 groups, one with only minimal atherosclerosis (grade 1), one with severe atherosclerosis (grade 3), and those with an intermediate grade (grade 2). We defined severe atherosclerosis (grade 3) based on generally accepted criteria²³⁻²⁵ and attempted to include at least 35 subjects in each group to provide statistical power. We had no limit on the number of subjects categorized as grade 1. Subjects were divided into atherosclerosis groups without knowledge of the end organ damage or risk factors against which the atherosclerosis would be correlated (brain or myocardial infarcts, abdominal aneurysms, hypertension, cholesterol), and without knowledge of Braak and CERAD scores. Although there was variability in the pathologists performing the general autopsies, which is a limitation of our analysis, we found no significant variation in atherosclerosis grade that was dependent on the performing pathologist.

Cardiac atherosclerosis (n=175)

For all complete autopsies, serial 3-5 mm axial sections of all the major cardiac vessels along their length were taken and examined for atherosclerosis. Estimates of degree of stenosis were made visually by the performing pathologist. Old myocardial infarcts were diagnosed by the presence of discrete areas of fibrosis and replacement of muscular tissue. Coronary atherosclerosis was graded in the following 3 categories. Grade 1 (n=41) included subjects who had no atherosclerotic plaques or atherosclerotic plaques and no stenosis beyond 20% in a single vessel. Grade 3 (n=55) required greater than 50% stenosis in 2 of 4 major cardiac vessels (left main, circumflex, LAD, RCA). Grade 2 (n=77) included subjects intermediate to grades 1 and 3 and consisted mainly of subjects with high grade (>50%) disease in one vessel or more diffuse but less obstructing disease.

Aortic atherosclerosis (n=175)

All aorta were opened longitudinally along their entire length (ascending, thoracic and abdominal) and examined for the degree of atherosclerosis (confluent (extending circumferentially) or non-confluent) and the presence of complexities including ulcerations and protrusions. The presence of abdominal aneurysms were also noted. The presence of an aneurysm did not change the atherosclerosis grade. All subjects in the study had some degree of aortic atherosclerosis. A grade of 1 (n=39) was assigned if atherosclerotic aortic plaques were not confluent (extending around the circumference of the aorta) and if plaque ulceration and protrusions were absent. Grade 3 (n=69) required confluent plaques and either multifocal ulceration or protrusions. Grade 2 (n=61) was intermediate, and for the most part included subjects with confluent areas of plaques but either no ulceration or one area of ulceration and minimal protrusions.

Intracranial atherosclerosis (n=200)

All subjects had an examination of the intracranial circulation including the Circle of Willis, carotid siphon, distal Internal carotid arteries (ICA), intracranial vertebral arteries, basilar artery and the proximal portions of the middle (MCA), anterior (ACA) and posterior (PCA) cerebral arteries. We did not have data on the carotid bifurcation, as this was not included with the brain when it was removed from the body and was usually not described by the pathologist performing the autopsy. All vessels were inspected visually; areas of atherosclerosis were identified and then sectioned to determine the degree of stenosis (in most cases by visual estimation without measurement). Grade 1 intracranial atherosclerosis (n=51) required no stenotic lesions (defined as 20% or greater) in any vessel. Grade 3 (n=47) required a stenosis of 40% or greater in two vessels. Grade 2 (n=71) was assigned for intermediate lesions, which for the most part included single vessel disease or multiple low-grade stenoses. The extent and number of intracranial vessels which were examined in subjects with complete autopsies was identical to those examined in subjects with “brain only” autopsies, as in both cases the vessels examined were those that came with the brain when it was removed from the skull.

Composite atherosclerosis grade (n=175)

A composite atherosclerosis grade was generated by adding the grades of the 3 individual atherosclerosis scores (aortic, cardiac and intracranial; range 3-9) and then dividing them into 4 groups with similar numbers of subjects from minimal to severe systemic atherosclerosis. Grade 1 composite atherosclerosis had total atherosclerosis scores of 3 and 4 (n=39); grade 2 had total atherosclerosis scores of 5 and 6 (n=58); grade 3 had a total atherosclerosis score of 7 (n=45) and grade 4 had total atherosclerosis scores of 8 and 9 (n=37).

Brain pathology

Postmortem examination of all brains was performed at Johns Hopkins by a neuropathologist; neuritic plaques and neurofibrillary tangles were assessed as described⁸. Macroscopic infarcts were assessed on the basis of visual inspection of 1-cm coronal slices of both hemispheres. Microscopic infarcts were determined from 1.5 cm H&E stained sections obtained from the middle frontal, superior and middle temporal, parietal, occipital, cingulate, orbitofrontal, basal forebrain and entorhinal cortex, as well as the hippocampus, basal ganglia, amygdala, thalamus, midbrain, pons, medulla, and cerebellum. Infarcts judged acute or subacute, based on macroscopic and microscopic features, were not included in this analysis. Ninety of the 200 subjects had at least one old (cavitary) brain macroscopic or microscopic infarct. AD pathology was examined on silver stains and graded according to CERAD and Braak criteria^{26,27}. For CERAD scoring we determined both the maximum neuritic plaque score seen in all 4 cortical regions examined (peak CERAD score) and the mean of the peak scores in each of the 4 cortical regions examined (mean CERAD score). In addition, we generated a composite AD pathology score by summing the CERAD and Braak scores in equal measure. CERAD scores were assigned to 3 groups with 1= zero or mild neuritic plaques, 2= moderate neuritic plaques, and 3=frequent neuritic plaques. Braak scores were divided into 3 groups with 1= Braak stages 0, I and II; 2= Braak stages III and IV; and 3= Braak stages V and VI. The sum of the modified Braak and CERAD scores yielded a composite score ranging from 2 to 6. The composite AD pathology score has been shown to correlate closely with cognitive status in this cohort⁸. Systematic white matter ratings were not included in this analysis.

Statistics

Potential predictors of dementia were analyzed using univariate and stepwise multivariate logistic regression with dementia as the dependent variable. All models included age at death and sex as covariates. Age was examined as both a continuous variable and categorized in quartiles or tertiles without any difference in the results. Comparisons of mean AD pathology scores in different atherosclerosis groups were performed using a one-way ANOVA. Non-parametric correlations between discrete vascular risk factors and atherosclerosis and between atherosclerosis grades and AD pathology were made using Spearman's Rank Correlation and ordinal regression. Ordinal regression analyses were adjusted for age and sex. Power analyses using G*Power software demonstrated an 80% certainty of excluding one-way effects (increasing atherosclerosis leading to increasing AD pathology scores) of 30% or more both in the ANOVA (Group 1 vs. Group 3) and the Spearman Rank Test.

Results

Atherosclerosis grades correlate with end organ damage

Blinded atherosclerosis grades in each of the three vascular systems correlated with accepted atherosclerotic endpoints (Figure 1). After adjusting for age, sex, hypertension and the presence of diabetes, a unit increase in the cardiac atherosclerotic grade was associated with a 6.1 (3.3 – 11.2) fold increase in the odds of a myocardial infarction. Increasing aortic atherosclerosis grades were associated with a 3.0 (1.3 - 7.1) fold increase in the odds of an abdominal aortic aneurysm per unit increase in aortic atherosclerosis grade, while increasing intracranial atherosclerosis was associated with a 1.8 (1.2-2.7) fold increase in the odds of a cerebral infarct per unit increase whether analyzed in the 175 subjects with complete autopsies or the 200 subjects with complete or brain only autopsies. Interestingly, only aortic atherosclerosis showed a significant relationship with baseline cholesterol ($\rho = 0.26$; $p=0.001$; Spearman's Rank Test) and smoking history ($\rho = 0.20$; $p=0.01$). There was also a significant correlation between the degree of atherosclerosis in one vascular bed with the degree of atherosclerosis in another (mean $\rho = 0.25$; $p=0.001$; Spearman's Rank Test). It should be noted that although we corrected for age at death in all our analyses, there was no statistical difference in the mean age of death between those groups with minimal and maximal atherosclerosis grades.

Atherosclerosis grades do not correlate with AD pathology

To examine the association between atherosclerosis and Alzheimer's pathology we plotted intracranial, aortic, coronary and composite atherosclerosis grades against peak CERAD score, mean CERAD score, Braak score and Composite AD pathology score (Figure 2). Using analysis of variance or ordinal regression, adjusting for age at death and sex, or an unadjusted Spearman's rank test (Table 1), there were no significant relationships between any AD pathology score and any atherosclerosis grade. The lack of significant associations was observed in analyses of AD pathology scores in subjects with mild, moderate and severe atherosclerosis (grades 1-3) and in comparisons of subjects with mild versus severe atherosclerosis (grade 1 vs. grade 3; Table 1). Moreover there was no relationship between AD pathology scores and atherosclerotic outcomes such as stroke (below) and the presence of a myocardial infarction on autopsy (not shown). The presence of an ApoE4 allele had no effect on systemic atherosclerosis or on the relationship between atherosclerosis and AD pathology (not shown) although the number of ApoE4 positive subjects with total body autopsies in this cohort is small (35/133).

To look at local relationships between atherosclerosis and AD pathology we performed two additional analyses. In the first we compared the superior and middle temporal gyri

(SMTG) CERAD scores in subjects with 50% or greater stenoses of the ipsilateral distal internal carotid or proximal middle cerebral artery (n=27) with superior and middle temporal gyrus CERAD scores in subjects with minimal intracranial atherosclerosis (n=51). No difference was seen in the SMTG CERAD score distal to these severe ipsilateral stenoses (1.4+/- 1.2) compared to the SMTG CERAD score in subjects with minimal intracranial atherosclerosis (1.5+/- 1.1; mean +/- S.D; OR 1.0 (0.7-1.3)). Secondly, SMTG CERAD scores were no different in subjects with ipsilateral MCA territory infarcts (1.5+/-1.2; n=37) and no history of atrial fibrillation or congestive heart failure (to isolate the effect of atherosclerosis) than in subjects with minimal intracranial atherosclerosis, no cerebral infarcts and no history of atrial fibrillation or congestive heart failure (1.4+/-1.1; n=41).

Intracranial atherosclerosis correlates with dementia independent of brain infarcts

In spite of the lack of relation between atherosclerosis and AD pathology, we observed a relation between intracranial atherosclerosis and dementia that was independent of the presence of cerebral infarcts. As shown in Figure 3 and Table 2, increasing intracranial, but not aortic or cardiac, atherosclerosis significantly increased the odds for dementia. Univariate odds for dementia increased by a factor of 2.0 per unit increase in intracranial atherosclerosis grade or increased by a factor of 2.7 for any grade other than 1. The magnitude of the effect was not changed by including age, sex, AD pathology, stroke risk factors, and, most importantly, the presence of cerebral infarcts (including microscopic infarcts) as covariates (Table 2B). To further verify that the effect of intracranial atherosclerosis on dementia was independent of infarction, we analyzed the data from the 110 subjects without any cerebral infarcts (Table 2B) and found the same result.

Given the large number of individuals in our cohort with intracranial atherosclerosis grades greater than 1 (136/200), the population attributable risk of dementia related to intracranial atherosclerosis (independent of infarction) is substantial, in spite of the relatively modest odds ratio. The rate of dementia in subjects with atherosclerosis above grade 1 is 82/136; in subjects with grade 1 intracranial atherosclerosis it is 22/64. Given the total incidence of dementia in the cohort (104/200), the percent of dementia that is attributable to intracranial atherosclerosis, independent of cerebral infarcts, in this cohort is 34%. Looking at the same data using a multivariate logistic regression model (Table 2C), a intracranial atherosclerosis grade greater than 1, a composite AD pathology score >3, and any brain infarct were each independent predictors of dementia. While AD pathology was associated with the largest increase in the odds of dementia, intracranial atherosclerosis was still associated with a substantial increase in the odds of dementia, with a significantly higher population at risk than either stroke or high AD pathology score.

Discussion

The relationship between atherosclerosis and Alzheimer's disease

Using a series of 200 autopsies from prospectively followed subjects in the Baltimore Longitudinal Study of Aging, 175 of whom had total body autopsies, we have found that the presence of intracranial atherosclerosis uniquely increased the odds of dementia independent of Alzheimer's pathology or cerebral infarcts. There was no significant relationship between systemic or localized atherosclerosis and brain Alzheimer's disease (AD) pathology. The etiologic role of atherosclerosis in the development of AD pathology^{11,12} and the relationship between atherosclerosis and dementia independent of its association with stroke¹⁻⁸ has been controversial. Clinical studies of the association of atherosclerosis risk factors and dementia have shown positive associations between dementia and carotid atherosclerosis, ankle-brachial blood pressure ratio, cardiovascular risk factors, and EKG abnormalities¹⁴⁻¹⁷.

Two studies have looked at the relationship between ultrasound visualized atherosclerosis and dementia in vivo. The Rotterdam study¹⁵ found a correlation between carotid atherosclerosis, determined by ultrasound, and the diagnosis of Alzheimer's disease. Another group²⁸ found an association between atherosclerosis in the circle of Willis (measured by transcranial Doppler) and the diagnosis of Alzheimer's dementia. These studies are important but limited by their inability to exclude stroke, increasing AD pathology or other mechanisms as the proximate cause of the increased rate of dementia in subjects with intracranial atherosclerosis.

Autopsy studies^{13, 51-52} have found an association between circle of Willis atherosclerosis and "Alzheimer's Disease" in retrospective convenience samples of postmortem autopsies. However, because these studies were not prospective and lacked cognitively normal older subjects with AD pathology, who are common in most prospective studies of the elderly³⁰, they were not able to determine whether the increased atherosclerosis in subjects with Alzheimer's disease was due to an effect of atherosclerosis on AD pathology or was simply due to an additive effect of two independent pathologies (Alzheimer's pathology and atherosclerosis) on cognition. In addition, none of these studies controlled for microscopic infarcts, a significant cause of dementia in several prospective cohorts^{6,8-31-32}. While our data suggest that variations in atherosclerosis as seen in our cohort are not related to variations in AD pathology, we cannot exclude the possibility that extreme levels of atherosclerosis are related to increases in AD pathology scores in some cases.

The presence of intracranial atherosclerosis increases the odds of dementia but does not effect AD pathology

Our data are consistent with reports showing a relationship between atherosclerosis and dementia²⁹, and extends those results in several important ways. First, the relationship appears to be due to the atherosclerosis itself. Adjusting for diabetes, smoking, hypertension and cholesterol did not influence our findings. We were not able to adjust for homocysteine levels but suspect this is unrelated, as homocysteine is related to generalized atherosclerosis not specifically to intracranial atherosclerosis³³. Second, atherosclerosis and dementia are related only for intracranial atherosclerosis, but not for cardiac or aortic atherosclerosis. This implies that the effect of atherosclerosis on cognition is local and not mediated by more systemic underlying processes that might be common to atherosclerosis in all vascular beds. Atherosclerosis in the intracranial circulation is likely to have significant differences from atherosclerosis in other beds, as the prevalence of intracranial atherosclerosis shows a poor correlation with atherosclerosis at the carotid bifurcation^{34,35} and in the coronary arteries^{35,36}. Indeed, in our own cohort, the correlation between the severity of intracranial atherosclerosis and the severity of coronary and aortic atherosclerosis was only 25%, implying some degree of heterogeneity between atherosclerosis in these vascular beds as was also demonstrated in the CAPRIE study³⁷. Understanding the mechanisms for these heterogeneities and the unique risk factors for intracranial atherosclerosis are important future research endeavors.

Two possible explanations, *a priori*, for the unique association between intracranial atherosclerosis and dementia would be through an effect on the number of brain infarcts or an increase in AD pathology. However, we found neither of these two enticing possibilities was the explanation for our results, even though both AD pathology and infarcts are independent and powerful predictors of dementia in this cohort⁸. We observed no significant association between atherosclerosis in any vascular bed and measures of AD pathology such as Braak, CERAD or composite AD pathology score. Further we did not find that the presence of an ApoE4 allele influenced this relationship. This result is similar to that found by Itoh and colleagues⁴⁹ who found no association between AD pathology and aortic, cardiac or intracranial atherosclerosis in a convenience sample of autopsies from

elderly subjects, but differs from that of Beeri and colleagues³⁸ who found a relationship between neuritic plaques and coronary atherosclerosis (mostly in ApoE4 carriers) in a retrospective, convenience sample of 99 brains, 36 of whom were ApoE4 positive. We offer the prospective nature of our cohort, and its larger total numbers as an important addition to this debate.

Although intracranial atherosclerosis was related to the presence of cerebral infarcts, this effect did not account for the magnitude of the observed effect of atherosclerosis on dementia risk. While it is likely that some microscopic strokes were unaccounted for in our post mortem analysis, accounting for the presence of any infarct (microscopic or macroscopic) did not affect the association of intracranial atherosclerosis and dementia risk, making it unlikely that unidentified microscopic infarcts were the cause of the association between intracranial atherosclerosis and dementia, although we did not rigorously exclude a role for watershed infarcts in this association.

Intracranial atherosclerosis and dementia

Since intracranial atherosclerosis appears to be additive to, yet independent of, AD pathology in the etiology of dementia in the elderly, the question of its mechanism of action deserves consideration. As detailed in our prior work⁸, cerebral infarcts are a significant cause of dementia in the BLSA cohort. Our current study, however, suggests that there is an additional association between intracranial atherosclerosis and cognition that is independent of cerebral infarctions. Our results are similar to those recently described in a cohort of subjects selected on the basis of significant preexisting cerebrovascular disease, where pathological measures of intracranial atherosclerosis were predictors of gray matter volume independent of AD pathology, and are similar to a recent retrospective pathologic study which suggested that circle of Willis atherosclerosis is significantly related to dementia²⁹. Our results extend these observations to a larger, more generalizable, prospective cohort and emphasize the specific role of intracranial atherosclerosis in clinical dementia outcomes⁵⁰.

Possible explanations for the association between intracranial atherosclerosis and dementia include a common mechanism that results in intracranial atherosclerosis and cerebral dysfunction such as oxidative stress^{39,40}, white matter disease⁵⁵, toxic yet soluble A β species^{53,54}, or the expression of inflammatory mediators within blood vessels or brain parenchyma, including the receptor for advanced glycation end-products⁴¹⁻⁴³. Alternatively, large vessel intracranial atherosclerosis could be a marker for dysfunction of small cerebral vessels and their endothelium that might be the proximate cause of cognitive deterioration, either through disruption of the communication between neurons and blood vessels (the neurovascular unit) that underlies activity induced vasodilatation⁴⁴⁻⁴⁶, or through disruption of the blood-brain barrier⁴⁷. Clearly this deserves further investigation, as these represent processes that can be prevented.

Limitations of current study

Although our study is prospective, our participants are not generalizable to the entire population; the majority are Caucasian and well-educated. However, the relative uniformity of the sample lends strength in isolating particular interactions. Moreover we had no data on carotid bifurcation atherosclerosis, which would have added strength to this study. Finally, because our sample size is limited, small effects of severe atherosclerosis on AD pathology cannot be excluded. This analysis might have been facilitated if we had available more quantitative counts of plaque and tangle density. Nevertheless, our study indicates that intracranial atherosclerosis, which is potentially preventable and whose number one risk factor is hypertension⁴⁸, is significantly associated with the burden of dementia in the United States, independent of its effect on cerebral infarcts.

Acknowledgments

Supported by National Institute on Aging grant P50 AG05146, the Burroughs Wellcome Fund for Translational Research, and the Intramural Research Program, National Institute on Aging, National Institutes of Health.

References

1. Snowdon DA, Greiner LH, Mortimer JA, Riley KP, Greiner PA, Markesbery WR. Brain infarction and the clinical expression of Alzheimer disease. The Nun Study. *JAMA* 1997;277:813–17. [PubMed: 9052711]
2. Schneider JA, Wilson RS, Cochran EJ, Bienias JL, Arnold SE, Evans DA, Bennett DA. Relation of cerebral infarctions to dementia and cognitive function in older persons. *Neurology* 2003;60(7):1082–8. [PubMed: 12682310]
3. Schneider JA, Wilson RS, Bienias JL, Evans DA, Bennett DA. Cerebral infarctions and the likelihood of dementia from Alzheimer disease pathology. *Neurology* 2004;62:1148–55. [PubMed: 15079015]
4. Schneider JA, Arvanitakis Z, Bang W, Bennett DA. Mixed brain pathologies account for most dementia cases in community-dwelling older persons. *Annals of Neurology* 2007;69(24):2197–2204.
5. Esiri MM, Nagy Z, Smith MZ, Barnettson L, Smith AD. Cerebrovascular disease and threshold for dementia in the early stages of Alzheimer's disease. *Lancet* 1999;354:919–20. [PubMed: 10489957]
6. White L, Petrovitch H, Hardman J, Nelson J, Davis DG, Ross GW, Masaki K, Launer L, Markesbery WR. Cerebrovascular pathology and dementia in autopsied Honolulu-Asia Aging Study participants. *Ann N Y Acad Sci* 2002;977:9–23. [PubMed: 12480729]
7. Sonnen JA, Larson EB, Crane PK, Haneuse S, Li G, Schellenberg GD, Craft S, Leverenz JB, Montine TJ. Pathological correlates of dementia in a longitudinal, population-based sample of aging. *Ann Neurol* 2007;62(4):406–413. [PubMed: 17879383]
8. Troncoso JC, Zonderman AB, Resnick SM, Crain B, Pletnikova O, O'Brien RJ. Effect of infarcts on dementia in the Baltimore longitudinal study of aging. *Ann Neurol* Aug;2008 64(2):168–76. 2008. [PubMed: 18496870]
9. Viswanathan A, Rocca WA, Tzourio C. Vascular risk factors and dementia: how to move forward? *Neurology* 2009;72(4):368–74. [PubMed: 19171835]
10. Sparks DL. Coronary artery disease, hypertension, ApoE, and cholesterol: a link to Alzheimer's disease? *Ann N Y Acad Sci* 1997;826:128–46. [PubMed: 9329686]
11. Casserly I, Topol E. Convergence of atherosclerosis and Alzheimer's Disease: Inflammation, cholesterol, and misfolded proteins. *The Lancet* 2004;363:1139–1146.
12. de la Torre JC. Is Alzheimer's disease a neurodegenerative or a vascular disorder? Data, dogma, and dialectics. *Lancet Neurol* 2004;3(3):184–90. [PubMed: 14980533]
13. Roher AE, Esh C, Rahman A, Kokjohn TA, Beach TG. Atherosclerosis of cerebral arteries in Alzheimer Disease. *Stroke* 2004;35:2623–2627. [PubMed: 15375298]
14. Exel EV, Gussekloo J, Houx P, de Craen AJM, Macfarlane PW, Bootsma-van der Wiel A, Blauw GJ, Westendorp RGJ. Atherosclerosis and cognitive impairment are linked in the elderly. The Leiden 85- plus Study. *Atherosclerosis* 2002;165:353–359. [PubMed: 12417287]
15. Hofman A, Ott A, Breteler MMB, Bots ML, Slieter AJC, Harskamp FV, van Duijn CN, Van Broeckhoven C, Grobbee DE. Atherosclerosis, apolipoprotein E, and prevalence of dementia and Alzheimer's Disease in the Rotterdam Study. *The Lancet* 1997;349:151–154.
16. Laurin D, Masaki KH, White LR, Launer LJ. Ankle-to-brachial index and dementia: The Honolulu-Asia Aging Study. *Circulation* 2007;116:2269–2274. [PubMed: 17967779]
17. Newman AB, Fitzpatrick AL, Lopez O, Jackson S, Lyketsos C, Jagust W, Ives D, DeKosky ST, Kuller LH. Dementia and Alzheimer's disease in the cardiovascular health study cohort. *Journal of American Geriatrics Society* 2005;53:1101–1107.
18. Gamaldo A, Resnick S, Kilada S, Troncoso J, Zonderman A, O'Brien RJ. The Interaction between Stroke and Alzheimer Pathology on Dementia in the Baltimore Longitudinal Study of Aging. *Neurology* 2006;67:1363–1369. [PubMed: 17060561]

19. Kawas C, Gray S, Brookmeyer R, Fozard J, Zonderman A. Age-specific incidence rates of Alzheimer's disease: the Baltimore Longitudinal Study of Aging. *Neurology* 2004;54(11):2072–2077. [PubMed: 10851365]
20. Blessed G, Tomlinson BE, Roth M. The association between quantitative measures of dementia and of senile change in the cerebral grey matter of elderly subjects. *Br J Psychiatry* 1968;114(512):797–811. [PubMed: 5662937]
21. Morris JC. Clinical dementia rating: a reliable and valid diagnostic and staging measure for dementia of the Alzheimer type. *Int Psychogeriatr* 1997;9(Suppl 1):173–176. [PubMed: 9447441]
22. Kawas C, Segal J, Stewart WF, Corrada M, Thal LJ. A validation study of the Dementia Questionnaire. *Arch Neurol* 1994;51(9):901–906. [PubMed: 8080390]
23. Creager, M.; Dzau, VJ.; Loscalzo, J. *Vascular Medicine: A Companion to Braunwald's Heart Disease* Saunders. 2006.
24. Libby, P.; Bonow, R.; Mann, D.; Zipes, D. *Braunwald's Heart Disease: A Textbook of Cardiovascular Medicine*, Saunders. 2007.
25. Kim, JS.; Caplan, LR.; Wong, L. *Intracranial Atherosclerosis* Wiley-Blackwell. 2008.
26. Mirra SS, Heyman A, McKeel D, Sumi SM, Crain BJ, Brownlee LM. The Consortium to Establish a Registry for Alzheimer's Disease (CERAD). Part II. Standardization of the neuropathologic assessment of Alzheimer's disease. *Neurology* 1991;41(4):479–86. [PubMed: 2011243]
27. Braak H, Braak E. Neuropathological staging of Alzheimer-related changes. *Acta Neuropathologica* 1991;82:239–259. [PubMed: 1759558]
28. Roher AE, Garami Z, Alexandrov AV, Kokjohn TA, Esh CL, Kalback WM, Vedders LJ, Wilson JR, Sabbagh MN, Beach TG. Interaction of cardiovascular disease and neurodegeneration: transcranial Doppler ultrasonography and Alzheimer's disease. *Neurol Res* 2006;28(6):672–8. [PubMed: 16945221]
29. Beach TG, Wilson JR, Sue LI, Newell A, Poston M, Cisneros R, Pandya Y, Esh C, Connor DJ, Sabbagh M, Walker DG, Roher AE. Circle of Willis atherosclerosis: Association with Alzheimer's Disease, neuritic plaques and neurofibrillary tangles. *Acta Neuropathology* 2007;113:13–21.
30. Driscoll I, Resnick SM, Troncoso JC, An Y, O'Brien R, Zonderman AB. Impact of Alzheimer's pathology on cognitive trajectories in nondemented elderly. *Ann Neurol* 2006;60(6):688–95. [PubMed: 17192929]
31. Suter O-C, Sunthorn T, Kraftsik R, Straubel J, Darekar P, Khalili K, Miklossy J. Cerebral hypoperfusion generates cortical watershed microinfarcts in alzheimer disease. *Stroke* 2002;33:1986–1992. [PubMed: 12154250]
32. Miklossy J. Cerebral hypoperfusion induces cortical watershed microinfarcts which may further aggravate cognitive decline in alzheimer's disease. *Neurol Res* 2003;25:605–610. [PubMed: 14503014]
33. Milani R, Lavie C. Homocysteine: The Rubik's Cube of Cardiovascular Risk Factors. *Mayo Clin Proc* 2008;83(11):1200–1202. [PubMed: 18990317]
34. Suwanwela NC, Chutinet A. Risk factors for atherosclerosis of cervicocerebral arteries: intracranial versus extracranial. *Neuroepidemiology* 2003;22(1):37–40. [PubMed: 12566952]
35. Seo WK, Yong HS, Koh SB, Suh SI, Kim JH, Yu SW, Lee JY. Correlation of coronary artery atherosclerosis with atherosclerosis of the intracranial cerebral artery and the extracranial carotid artery. *Eur Neurol* 2008;59(6):292–8. [PubMed: 18408369]
36. Bae HJ, Yoon BW, Kang DW, Koo JS, Lee SH, Kim KB, Lee J, Roh JK. Correlation of coronary and cerebral atherosclerosis: difference between extracranial and intracranial arteries. *Cerebrovasc Dis* 2006;21(1-2):112–9. 2006. [PubMed: 16340186]
37. Ouriel K. Peripheral arterial disease. *Lancet* 2001;358:1257–1264. [PubMed: 11675083]
38. Beeri MS, Rapp M, Silverman JM, Schmeidler J, Grossman HT, Fallon JT, Purohit DP, Perl DP, Siddiqui A, Lesser G, Rosendorff C, Haroutunian V. Coronary artery disease is associated with AD Neuropathology in APOE 4 carriers. *Neurology* 2006;66:1399–1404. [PubMed: 16682673]
39. Cai H, Harrison DG. Endothelial dysfunction in cardiovascular diseases: the role of oxidant stress. *Circ Res* 2000;87:840–844. [PubMed: 11073878]
40. D'Armiento FP, Bianchi A, de Nigris F, Capuzzi DM, D'Armiento MR, Crimi G, Abete P, Palinski W, Condorelli M, Napoli C. Age-related effects on atherogenesis and scavenger enzymes

- of intracranial and extracranial arteries in men without classic risk factors for atherosclerosis. *Stroke* 2001;32(11):2472–9. 2001. [PubMed: 11692003]
41. Arenillas JF, Alvarez-Sabín J. Basic mechanisms in intracranial large-artery atherosclerosis: advances and challenges. *Cerebrovasc Dis* 2005;20(Suppl 2):75–83. [PubMed: 16327256]
 42. Hoshi T, Kitagawa K, Yamagami H, Furukado S, Hougaku H, Hori M. Relation between interleukin-6 level and subclinical intracranial large-artery atherosclerosis. *Atherosclerosis* 2008;197(1):326–32. [PubMed: 17604035]
 43. Maczurek A, Shanmugam K, Munch G. Inflammation and the redox-sensitive AGE-RAGE pathway as a therapeutic target in Alzheimer's disease. *Ann. NY Acad. Sci* 2008;1126:147–151. 2008. [PubMed: 18448809]
 44. Wollner L, McCarthy ST, Soper NDW, Macy DJ. Failure of cerebral autoregulation as a cause of brain dysfunction in the elderly. *British Medical Journal* 1979;1:1117–1118. [PubMed: 444957]
 45. Benarroch EE. Neurovascular unit dysfunction: a vascular component of Alzheimer disease? *Neurology* 2007;68(20):1730–2. [PubMed: 17502556]
 46. van Dijk EJ, Prins ND, Vrooman HA, Hofman A, Koudstaal PJ, Breteler MMB. Progression of cerebral small vessel disease in relation to risk factors and cognitive consequences: Rotterdam Scan Study. *Stroke* 2008;39:2712–2719. [PubMed: 18635849]
 47. Bell RD, Zlokovic BV. Neurovascular mechanisms and blood-brain barrier disorder in Alzheimer's disease. *Acta Neuropathol* Jul;2009 118(1):103–13. 2009. [PubMed: 19319544]
 48. Aboyans V, Lacroix P, Criqui MH. Large and small vessels atherosclerosis: similarities and differences. *Prog Cardiovasc Dis* 2007;50(2):112–25. [PubMed: 17765473]
 49. Itoh Y, Yamada M, Sodeyama N, Suematsu N, Matsushita M, Otomo E, Mizusawa H. Atherosclerosis is not implicated in association of APOE ε4 with AD. *Neurology* 1999;53:236–238. [PubMed: 10408574]
 50. Jagust WJ, Zheng L, Harvey DJ, Mack WJ, Vinters HV, Weiner MW, Ellis WG, Zarow C, Mungas D, Reed BR, Kramer JH, Schuff N, DeCarli C, Chui HC. Neuropathological basis of magnetic resonance images in aging and dementia. *Ann Neurol* 2008;63(1):72–80. [PubMed: 18157909]
 51. Honig LS, Kukull W, Mayeux R. Atherosclerosis and AD: analysis of data from the US National Alzheimer's Coordinating Center. *Neurology* 2005;64(3):494–500. [PubMed: 15699381]
 52. Roher AE, Esh C, Kokjohn TA, Kalback W, Luehrs DC, Seward JD, Sue LI, Beach TG. Circle of willis atherosclerosis is a risk factor for sporadic Alzheimer's disease. *Arterioscler Thromb Vasc Biol* 2003;23(11):2055–62. [PubMed: 14512367]
 53. Wen Y, Yu WH, Maloney B, Bailey J, Ma J, Marié I, Maurin T, Wang L, Figueroa H, Herman M, Krishnamurthy P, Liu L, Planel E, Lau LF, Lahiri DK, Duff K. Transcriptional regulation of beta-secretase by p25/cdk5 leads to enhanced amyloidogenic processing. *Neuron* 2008;57(5):680–90. [PubMed: 18341989]
 54. Walsh DM, Klyubin I, Fadeeva JV, Cullen WK, Anwyl R, Wolfe MS, Rowan MJ, Selkoe DJ. Naturally secreted oligomers of amyloid beta protein potently inhibit hippocampal long-term potentiation in vivo. *Nature* 2002;416(6880):535–9. [PubMed: 11932745]
 55. Frisoni GB, Galluzzi S, Pantoni L, Filippi M. The effect of white matter lesions on cognition in the elderly--small but detectable. *Nat Clin Pract Neurol* 2007;3(11):620–7. [PubMed: 17982432]

Figure 1. Relationship between regional atherosclerosis and regional vascular endpoints Intracranial, cardiac and aortic atherosclerosis grades are plotted $\pm$ S.E. against the rate of any coincident cerebral infarct, myocardial infarct or aortic aneurysm being present (respectively) in the same autopsy specimen. All relationships are significant at the 0.01 level using logistic regression. The odds ratio indicates the increase in odds of the indicated outcome with a step increase in the regional atherosclerosis grade, adjusting for age and sex. Relationships with intracranial atherosclerosis are based on 200 autopsies while aortic and cardiac atherosclerosis are based on 175.

Figure 2. The relationship between atherosclerosis and AD pathology

Multiple indicators of cerebral AD pathology are plotted against the degree of intracranial, cardiac, aortic (graded on a 3 point scale) and composite atherosclerosis (graded on a 4 point scale) $\pm$ S.E. None of the relationships are significant. Associations with intracranial atherosclerosis include data from 200 autopsies and associations with aortic and cardiac atherosclerosis include 175.

Figure 3. The relationship between atherosclerosis and dementia

Intracranial, cardiac and aortic atherosclerosis grades are plotted $\pm$ S.E. against the dementia rate for subjects with those grades. The odds ratio refers to the increase in odds of dementia for a step increase in the regional atherosclerosis grade, adjusting for age and sex. Associations with intracranial atherosclerosis include data from 200 autopsies while associations with aortic and cardiac atherosclerosis include 175.

Table 1
The relationship between systemic atherosclerosis and Alzheimer pathology

The significance of the relationship between increasing intracranial, cardiac, aortic and composite atherosclerosis grades and 4 measures of Alzheimer pathology was tested using several parametric and non parametric tests. We compared the entire spectrum of atherosclerosis for each vascular bed against the AD pathology endpoints, or simply compared the group with minimal atherosclerosis in each vascular bed against the group with the maximal atherosclerosis in each vascular bed (grade 1 vs. grade 3 in the case of intracranial, aortic and cardiac atherosclerosis, or grade 1 vs. grade 4 in the case of composite atherosclerosis). The intracranial atherosclerosis data is from 200 autopsies; the aortic and cardiac data is from 175. Spearman's rank test was not corrected for age and sex while ordinal regression and ANOVA were. None of the relationships are significant.

	Peak CERAD	Mean CERAD	Braak Score	Composite AD Score
ANOVA (Corrected for Age and Sex)	P Values			
Intracranial Atherosclerosis	0.52	0.48	0.74	0.77
Intracranial Atherosclerosis (Grade 1 vs. Grade 3)	0.72	0.69	0.83	0.49
Cardiac Atherosclerosis	0.41	0.59	0.33	0.26
Cardiac Atherosclerosis (Grade 1 vs. Grade 3)	0.76	0.99	0.32	0.39
Aortic Atherosclerosis	0.71	0.67	0.32	0.43
Aortic Atherosclerosis (Grade 1 vs. Grade 3)	0.44	0.39	0.20	0.24
Composite Atherosclerosis	0.28	0.17	0.30	0.48
Composite Atherosclerosis (Grade 1 vs. Grade 4)	0.69	0.62	0.71	0.88
Ordinal Regression (Corrected for Age and Sex)	Odds Ratio (C.I.)			
Intracranial Atherosclerosis	1.0 (0.7-1.5)	1.1 (0.8-1.6)	1.1 (0.8-1.5)	1.1 (0.8-1.6)
Intracranial Atherosclerosis (Grade 1 vs. Grade 3)	1.1 (0.6-2.2)	1.2 (0.6-2.4)	1.0 (0.6-2.1)	1.2 (0.6-2.3)
Cardiac Atherosclerosis	0.9 (0.6-1.4)	1.0 (0.7-1.3)	0.9 (0.6-1.3)	0.9 (0.6-1.3)
Cardiac Atherosclerosis (Grade 1 vs. Grade 3)	0.8 (0.4-1.7)	0.9 (0.5-1.9)	0.8 (0.4-1.7)	0.8 (0.4-1.6)
Aortic Atherosclerosis	0.9 (0.6-1.2)	0.9 (0.6-1.2)	0.8 (0.6-1.2)	0.9 (0.6-1.2)
Aortic Atherosclerosis (Grade 1 vs. Grade 3)	0.8 (0.4-1.6)	0.8 (0.4-1.4)	0.8 (0.4-1.4)	0.8 (0.4-1.4)
Composite Atherosclerosis	0.9 (0.7-1.2)	1.0 (0.7-1.3)	1.0 (0.8-1.3)	1.0 (0.7-1.3)
Composite Atherosclerosis (Grade 1 vs. Grade 4)	1.1 (0.5-2.7)	1.1 (0.8-1.5)	1.2 (0.6-2.3)	1.1 (0.5-2.8)
Spearman's Rank Test	rho (P Value)			
Intracranial Atherosclerosis	0.03 (0.68)	0.06 (0.39)	0.09 (0.24)	0.08 (0.32)
Intracranial Atherosclerosis (Grade 1 vs. Grade 3)	0.02 (0.84)	0.07 (0.43)	0.09 (0.34)	0.08 (0.38)
Cardiac Atherosclerosis	-0.03 (0.69)	-0.01 (0.93)	-0.01 (0.93)	-0.04 (0.62)
Cardiac Atherosclerosis (Grade 1 vs. Grade 3)	-0.04 (0.69)	0.00 (0.98)	-0.02 (0.83)	-0.06 (0.58)

	Peak CERAD	Mean CERAD	Braak Score	Composite AD Score
Aortic Atherosclerosis	-0.06 (0.42)	-0.05 (0.46)	-0.06 (0.40)	-0.06 (0.40)
Aortic Atherosclerosis (Grade 1 vs. Grade 3)	-0.08 (0.35)	-0.09 (0.33)	-0.10 (0.26)	-0.10 (0.29)
Composite Atherosclerosis	-0.05 (0.51)	-0.01 (0.85)	0.02 (0.78)	-0.01 (0.85)
Composite Atherosclerosis (Grade 1 vs. Grade 4)	0.01 (0.91)	0.08 (0.48)	0.11 (0.37)	0.03 (0.77)

Table 2
The relationship between systemic atherosclerosis and dementia

In A, a univariate logistic regression analysis examined the relationship between atherosclerosis in different vascular beds and dementia. For intracranial, aortic and cardiac atherosclerosis we calculated the increasing odds of dementia per step increase in atherosclerosis grade (1-3). For intracranial atherosclerosis we also determined the increase in the odds of dementia for any grade above 1 (1 vs 2+3). The intracranial atherosclerosis data was analyzed both in the 175 subjects who had complete autopsies and in the 200 who had complete or brain-only autopsies. In B, the odds of dementia per step increase in intracranial atherosclerosis grade was calculated using the indicated factors as covariates. In the subjects with no infarcts (n=110) the odds of dementia due to intracranial atherosclerosis was corrected for Age, Sex, DM, HTN, and AD pathology. In C, a logistic regression model using the indicated threshold variables is shown.

A	Odds of Dementia Per Step Increase in Atherosclerosis Grade
Univariate Analysis	
Intracranial Atherosclerosis (n=200)	2.0 (1.4-2.9)
Intracranial Atherosclerosis (1 vs 2+3; n=200)	2.9 (1.5-5.3)
Cardiac Atherosclerosis (n=175)	0.8 (0.6-1.2)
Aortic Atherosclerosis (n=175)	1.1 (0.8-1.6)
Intracranial Atherosclerosis (n=175)	1.9 (1.2-3.1)

B	Odds of Dementia Per Step Increase in Intracranial Atherosclerosis Grade
Multivariate Analysis - Covariates (n=200):	
Age, Sex	1.9 (1.3-2.8)
Age, Sex, DM, HTN	2.0 (1.3-3.0)
Age, Sex, DM, HTN, Any Brain Infarct	1.9 (1.3-2.8)
Age Sex, DM,HTN, CVA, Chol, Smoking	1.8 (1.2-3.0)
Age, Sex, DM,HTN, Any Cortical Infarct	1.9 (1.2-3.0)
Age, Sex, DM, HTN, CVA, AD Path	2.0 (1.4-3.4)
Subjects with No Infarcts (n=110)	1.9 (1.1-3.9)

C		
Multivariate Model (n=200)	Odds of Dementia	Number at Risk
Any Cerebral Infarct	3.4 (1.7-6.8)	90
Comp. AD Path Score >3	6.0 (3.0-12)	115
Intracranial Athero >1	2.7 (1.3-5.7)	135