Aggregate effects of vascular risk factors on cerebrovascular changes in autopsy-confirmed Alzheimer's disease

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Abstract

We examined the relationships of ante-mortem vascular risk factors to post-mortem cerebrovascular and AD pathologies. Eighty-four AD patients underwent assessment of vascular risk (blood pressure, cholesterol, smoking, cardiovascular disease, diabetes, atrial fibrillation, transient ischemic attack [TIA] or stroke) and later underwent brain autopsy. Given our aim to examine mild cerebrovascular changes (CVC), individuals were excluded if autopsy revealed large stroke. The most common forms of CVC were circle of Willis atherosclerosis followed by arteriosclerosis, lacunes, and microinfarcts. Excluding history of TIA/clinical stroke, individual vascular risk factors were not associated with CVC. However, the presence of multiple vascular risk factors was associated with CVC. Further, presence of CVC was associated with lower Braak and Braak stage. Findings highlight the importance of aggregate risk in the vascular contribution to dementia. Interventions designed to maintain cerebrovascular health may represent important opportunities for preventing or delaying dementia, even when AD is the dominant pathology.

Keywords

Alzheimer's disease; vascular risk; cerebrovascular disease

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1. INTRODUCTION

Vascular risk factors are common and increase risk for Alzheimer's disease (AD) (1, 2). Most studies have focused on individual vascular risk factors, although multiple vascular risk factors often co-exist (3) and have been shown to incrementally increase risk for AD (1, 2). Studies commonly examine individual risk factors while adjusting for additional risk factors, but this approach may result in over-adjustment and underestimation of effects (1, 4).

Accumulating evidence suggests that vascular risk factors increase risk for AD via cerebrovascular disease (CVD) (5). Although the majority of evidence suggests that vascular risk factors do not increase plaques and tangles *per se* (5), some studies demonstrate positive correlations between CVD and AD pathology (6–8). Notably, most studies examining the association between vascular risk and AD have characterized participants as AD based on clinical data alone, without autopsy-based data to confirm clinical diagnosis and allow for assessment of multiple forms of neuropathology (e.g., neurofibrillary tangles, CVD, cerebral amyloid angiopathy [CAA]). Given that individuals with clinically diagnosed 'probable' AD commonly exhibit mixed pathologies (9, 10), previous findings may be explained in part by misclassification of participants with mixed or vascular pathologies as pure AD (1).

To improve our understanding of mechanisms linking vascular risk burden and AD, we assessed whether ante-mortem assessment of aggregate vascular risk factors is related to cerebrovascular changes (CVC), CAA, and AD pathology in individuals with autopsy-confirmed AD. We were particularly interested in whether vascular risk factors were associated with occult CVC (cerebral arteriosclerosis, circle of Willis atherosclerosis, lacunes, microinfarcts) at autopsy in patients with ante-mortem clinical diagnoses of AD. We hypothesized that greater vascular risk burden would be associated with the presence of CVC and that individual vascular risk factors would show attenuated associations with neuropathology. A secondary aim was to examine the association between CVC and AD pathology in autopsy-confirmed AD. Given evidence that CVC and AD pathology have additive effects on risk for AD, we expected that CVC would be associated with less severe AD pathology at a given level of dementia severity. The current study adds to the existing literature by including neuropathologic confirmation of AD diagnosis, examining both AD and CVC as underlying neuropathological substrates, focusing on AD patients with subclinical or mild CVC, and including a comprehensive vascular risk assessment and scoring system.

2. METHODS

2.1 Participants and clinical evaluation

Autopsy-based neuropathological data from 602 participants of various ages at autopsy (range=36–104 years) and with various neuropathological diagnoses (e.g., normal, Alzheimer's disease, Pick's disease) recruited through the University of California San Diego (UCSD) Alzheimer's Disease Research Center (ADRC) were initially reviewed. From the subset of individuals meeting criteria for probable or definite AD at autopsy based on semi-quantitative estimates of neuritic plaque density as recommended by Consortium to

Establish a Registry for Alzheimer's Disease (CERAD) (11) and Braak score as recommended by the National Institute on Aging-Reagan criteria (12) (*n*=277), we selected all individuals with "pure" AD on neuropathology (i.e., individuals who did not show evidence of CVC, medial temporal lobe sclerosis, Lewy body pathology, or Pick's disease at autopsy; *n*=34). We included all 34 individuals in this group given its relatively low prevalence (9). Participants with both AD and CVC (i.e., individuals who showed lacunes, cortical microinfarcts, cerebral arteriosclerosis, and/or circle of Willis atherosclerosis) were then randomly sampled (*n*=124). Individuals were excluded if autopsy revealed any significant pathological process other than AD or CVC. Also, given our aim to examine subclinical or mild CVC, individuals were excluded if autopsy revealed large (macroscopic) stroke. Twenty-seven individuals were excluded for significant Lewy body pathology, 8 for large infarcts (>10 mm in diameter), 7 for medial temporal lobe sclerosis, 6 for macroscopic cerebral hemorrhage, and none for Pick's disease. Clinical data were reviewed and those who underwent vascular risk assessment and met National Institute of Neurological and Communicative Diseases and Stroke/Alzheimer's Disease and Related Disorders Association criteria (13) for probable or possible AD at the time of the vascular risk assessment were included. Sixteen individuals were excluded for missing vascular risk data. Groups of AD patients with and without CVC (AD+CVC and AD-CVC, respectively) were matched on mean age. These inclusion and exclusion criteria resulted in a final sample of 84 participants (AD-CVC: *n*=34; AD+CVC: *n*=50).

On the day of vascular risk assessment, demographic and clinical data were recorded and the Mattis Dementia Rating Scale (DRS) was administered to estimate dementia severity. Apolipoprotein E (APOE) genotyping was performed. Data were collected in accordance with UCSD institutional review board-approved procedures.

2.2 Vascular risk assessment

Participants underwent clinical interview and physical examination to determine the presence or absence of vascular risk factors. Brachial artery blood pressure measures were obtained while the participant was seated. A blood draw was performed and plasma glucose and serum cholesterol levels were obtained.

The presence or absence of the following risk factors was determined from clinical interview, physical exam, and laboratory studies: cardiovascular disease (coronary artery disease, cardiac failure, or intermittent claudication); diabetes (self-reported diabetes, use of anti-diabetic therapy, or casual blood glucose ≥ 200 mg/dL); high total cholesterol (≥ 240 mg/dL); hypertension (untreated systolic blood pressure ≥ 140 mm Hg, untreated diastolic blood pressure ≥ 90 mm Hg, or use of antihypertensive medications (14, 15)); atrial fibrillation; and current smoking (16).

2.3 Aggregate vascular risk

Aggregate vascular risk was computed using a modified algorithm developed to predict lifetime risk for cardiovascular disease (17, 18). We modified this algorithm to be more relevant to CVC. Specifically, we included history of stroke/TIA, cardiovascular disease, and atrial fibrillation as additional major risk factors given that they have each been shown

to increase stroke risk (16). We classified participants into five mutually exclusive categories depending on whether they had (1) no risk factors above threshold levels, (2) 1 risk factor at mildly elevated levels, (3) 1 moderately-to-severely elevated risk factor(s), (4) 1 major risk factor only, or (5) 2 major risk factors. See Table 2 for specific criteria for each of the five aggregate risk categories.

We calculated a second vascular risk composite score based on the summation of individual vascular risk factors (1). First, each of the following risk factors was assigned a value of 0 if absent and 1 if present based on the criteria described above: cardiovascular disease, diabetes, high total cholesterol, hypertension, current smoking, atrial fibrillation, and history of TIA/stroke. We summed these seven vascular risk factors to create a composite score for each participant. Unlike the aggregate risk score described above, this sum score does not differentially weigh individual risk factors based on severity.

2.4 Brain autopsy procedures

Brain autopsies were performed at UCSD using established ADRC protocols (19) described elsewhere (20). Briefly, brains were staged for degree of neurofibrillary tangle pathology by one neuropathologist (L.A.H.) using a modification (21) of Braak and Braak's staging scheme (22). Semi-quantitative estimates of neuritic plaque density were calculated using methods recommended by CERAD (11). Brains were assessed for four forms of CVC: 1) lacunes (small [<10 mm in diameter] artery infarcts and/or hemorrhages), 2) cortical microinfarcts, 3) cerebral arteriosclerosis (small parenchymal arteriolar disease), and 4) atherosclerosis in the circle of Willis (20, 23). Severity of CAA was assessed semi-quantitatively on thioflavin-S stained preparations (24). See Appendix (part A) for a more detailed description of the brain autopsy procedures.

For each AD+CVC participant, a semi-quantitative measure of CVC severity was calculated using a modification of a published method (20). Briefly, four forms of CVC (cerebral arteriosclerosis, circle of Willis atherosclerosis, lacunes, and cortical microinfarcts) were each scored 0 if absent or 1 if present. The points were then summed to create a measure of CVC severity ranging from 0 to a maximum of 4 possible points.

2.5 Participant groupings

For analysis of neuropathologic variables, participants were classified in three ways depending on the presence and/or severity of different forms of pathology. First, participants were classified into AD+CVC (*n*=50) or AD-CVC (*n*=34) based on the presence or absence of CVC at autopsy. Second, participants were categorized as having CAA (AD+CAA, *n*=68) or no CAA (AD-CAA, *n*=15). Third, participants were grouped into less severe AD (Braak scores less than VI, *n*=25) or more severe AD (Braak score of VI, *n*=59).

2.6 Statistical analyses

Independent samples *t*-tests for continuous variables and χ^2 tests for categorical variables were performed. All statistical tests were two-tailed with a significance cutoff of $p < .05$.

3. RESULTS

3.1 Participant groupings

Of the 84 participants, 50 (59.5%) displayed CVC at autopsy whereas 34 (40.5%) did not. See Table 3 for frequencies of the individual forms of CVC. Among those with CVC, the mean semi-quantitative score for CVC severity was 1.34 (standard deviation=.63; range=1–3). Across the entire sample, CAA was present in 81.0% of participant brains. Brains of all participants demonstrated AD tangle pathology at Braak and Braak stage IV or higher (IV: 4.8%; V: 25.0, %; VI: 70.2%). Brains of participants demonstrated neuritic plaque density rated as sparse (3.6%), moderate (16.7%), or frequent (73.8%).

3.2 Demographic and clinical data

The AD+CVC and AD-CVC groups did not significantly differ in terms of mean age (at vascular risk assessment and DRS administration), mean years of education, sex distribution, APOE genotype, or cognitive functioning (Table 1). Compared to the AD-CVC group, the AD+CVC group was significantly older at estimated age of dementia onset and age at death, however, there were no significant differences between the two groups in terms of duration of dementia or dementia severity (based on DRS) or in clinical diagnosis (probable versus possible AD). Further, there were no significant differences between the AD+CVC and AD-CVC groups on DRS performance when additional analyses were conducted including age as a covariate (See Appendix [part B] for detailed results).

3.3 Individual vascular risk factors and CVC

At least one vascular risk factor was present in 70 participants across the entire sample (83.3%; Table 2). Seven of the AD+CVC participants and none of the AD-CVC participants had a self-reported history of possible stroke or TIA (p=.02). Although there were no other significant group differences in terms of frequencies of vascular risk factors (p-values > .05), there were trends toward the AD+CVC group having higher rates of cardiovascular disease and diabetes (p-values of .07 and .09, respectively).

3.4 Aggregate vascular risk and CVC

AD patients with the most severe aggregate risk (2 major risk factors) were more likely to have CVC compared to those with less severe aggregate risk (χ^2=5.14, p=.02, φ=.25; Table 2 and Figure 1). Among those participants with the most severe aggregate risk, 16 had 2 major risk factors (11 AD+CVC, 5 AD-CVC), 9 had 3 major risk factors (6 AD+CVC, 3 AD-CVC), 6 had 4 major risk factors (6 AD+CVC, 0 AD-CVC), and 1 had 5 major risk factors (1 AD+CVC, 0 AD-CVC). When different forms of CVC were analyzed separately, AD patients with the most severe aggregate vascular risk were significantly more likely to have arteriosclerosis/circle of Willis atherosclerosis (χ^2=3.90, p=.048, φ=.22) and nearly significantly more likely to have lacunes and/or infarcts (χ^2=3.50, p=.061, φ=.20). There were no significant differences between the AD+CAA and AD-CAA groups (χ^2=1.09, p=.30, φ=.12), between lower and higher Braak stage groups (χ^2=2.92, p=.09, φ=.19), or between neuritic plaque density groups (χ^2=5.24, p=.07, φ=.26) in terms of aggregate vascular risk.

When the sum of vascular risk factors based on the presence or absence of seven risk factors was assessed, the AD+CVC group showed significantly greater vascular risk burden relative to the AD-CVC group (Table 2 and Figure 2). Although having one or more vascular risk factor did not distinguish the AD+CVC and AD-CVC groups (χ^2=1.94, *p*=.16, φ=.15), significantly more individuals in the AD+CVC group had two or more vascular risk factors (χ^2=6.19, *p*=.01, φ=.27) and three or more vascular risk factors (χ^2=4.57, *p*=.03, φ=.23). Given that few individuals had four or more vascular risk factors (*n*=7), we did not compare groups in terms of aggregate risk beyond three or more risk factors. These analyses did not involve independent groups (e.g., the "two or more risk factors'" category includes participants from the "one or more risk factor(s)" category). There were no significant differences between the AD+CAA and AD-CAA groups, between the lower and higher Braak and Braak stage groups, or between neuritic plaque density groups in terms of the sum of vascular risk factors (*p*-values >.05).

Although we excluded potential participants for evidence of large (macroscopic) stroke on autopsy, to ensure that findings were not determined by a self-reported history of TIA or possible stroke, we computed the aggregate vascular risk composite withholding history of TIA/stroke as a risk factor. We conducted further χ^2 analyses to determine whether severity of aggregate risk was related to CVC and results remained identical to those described above. In addition, we conducted analyses excluding those participants with self-reported history of possible stroke and results remained qualitatively and statistically very similar.

3.5 Relationships among cerebrovascular pathology, Alzheimer's disease pathology, and cerebral amyloid angiopathy

The presence of CVC among AD patients was associated with a significantly lower Braak Stage (χ^2=6.19, *p*=.01; Figure 3). When excluding those with lacunar infarcts or cortical microinfarcts (n = 11), there was a marginally significant relationship between lower Braak stage and the presence of CVC (χ^2=3.39, *p*=.06, φ=.22). This suggests that infarcts play an important role in this relationship. However, this could also reflect a power issue given that, after these 11 participants are removed and the sample size of AD+CVC participants is reduced from 50 to 39, the effect size does not substantially differ (φ=.27 versus φ=.22). There was no relationship between the presence of CVC and CAA (χ^2=1.31, *p*=.25) or neuritic plaque density (χ^2=4.05, *p*=.26).

4. DISCUSSION

Results indicate that AD patients with multiple vascular risk factors are more likely to show CVC at autopsy. These observed relationships are consistent with our previously published report demonstrating that vascular risk factors are associated with CVD in AD patients (20), as well as neuroimaging studies showing that increased vascular risk burden is associated with MRI markers of CVD (e.g., white matter hyperintensities) in mild cognitive impairment (25) and AD (26). Of the 84 participants in the present sample, 50 (59.5%) displayed CVC at autopsy whereas 34 (40.5%) did not. Although this finding demonstrates a high comorbidity of CVC among AD patients in our sample, this ratio of AD+CVC to AD-CVC is not necessarily representative of the true prevalence of CVC given that we

deliberately selected all available cases of "pure" AD, which represented a minority of autopsy-confirmed AD cases in the broader sample. Nonetheless, our findings are consistent with a growing body of evidence indicating that CVC is a common co-morbidity and may be integrally involved in the development of AD (5, 9, 10). However, it should be noted that a methodological difference between these previous studies (9, 10) and the current study is that the former restricted their definitions of CVD to macroscopic cerebral infarcts whereas we excluded those with large infarcts and focused on mild forms of CVC (i.e., cerebral arteriosclerosis, circle of Willis atherosclerosis, lacunes, microinfarcts). In the present sample, which involved a relatively limited range of vascular risk burden, traditional vascular risk factors including cardiovascular disease, diabetes, hypertension, high cholesterol, atrial fibrillation, and current smoking were not associated with the presence of CVC when examined individually. In contrast, the presence of multiple vascular risk factors and aggregate vascular burden were associated with CVC. These findings highlight the potential importance of considering aggregate risk when examining the vascular contribution to cognitive impairment.

An area of continuing debate involves whether vascular risk factors directly increase AD pathology or whether the effect is mediated through CVD (5). Regarding the latter possibility, some evidence suggests that vascular dysfunction may reduce clearance of β-amyloid (Aβ) or indirectly increase deposition of Aβ (27). In the present study, aggregate vascular risk factors were associated with CVC but not severity of AD or presence of CAA. This finding is in contrast to some previous autopsy studies from AD/neurodegenerative disease brain banks reporting associations between increased atherosclerosis and greater plaque and tangle densities (8, 28, 29). However, it has been argued that such findings may reflect selection bias given that they are not confirmed when samples are drawn from non-dementia clinic/center findings (5). Further, such findings are not consistent with a growing body of evidence suggesting that vascular risk factors do not increase plaques and tangles *per se* (5).

We found that the presence of CVC was associated with lower Braak stage, yet there were no differences in severity of cognitive impairment (based on the DRS) between the AD +CVC and AD-CVC groups. The fact that the AD+CVC group showed the same degree of overall cognitive impairment as the AD-CVC group, despite having a significantly lower burden of neurofibrillary tangle pathology, suggests that vascular pathology has an additive effect on cognitive impairment, even in patients with autopsy-confirmed AD and relatively mild CVC. However, given the cross-sectional nature of the neuropathologic exam, causality of this association cannot be inferred. In addition, there was no difference between the groups in terms of neuritic plaque density. Although this lack of association is in line with previous studies demonstrating that CVD is not related to amyloid deposition (30), a recent neuroimaging study showed a relationship between vascular risk and amyloid deposition (31). However, the latter finding was reported in a sample of mainly cognitively normal and mildly impaired older adults and involved *in vivo* neuroimaging rather than autopsy findings from confirmed AD cases. Further, compared to tau, amyloid has been proposed to be an earlier marker during the course of AD and may be particularly sensitive prior to the onset of cognitive impairment (32). Taken together, the present results

corroborate previous findings demonstrating that AD patients with CVD have lower Braak stages than AD patients without CVD (33, 34).

In the present study, the AD+CVC group was significantly older than the AD-CVC group at dementia onset and at death. However, there was no difference between the two groups in terms of duration of dementia or severity of cognitive impairment. We found that the presence of CVC was associated with less AD pathology (i.e., lower Braak stage) among autopsy-confirmed AD patients. It is possible that less AD pathology is required to clinically unmask dementia in AD patients who also have some degree of cognitive impairment related to coexisting CVC (5, 20). Taken together with evidence that the prevalence of CVC increases with advancing age (35, 36), AD patients with a later age at dementia onset may be more likely to have both vascular and AD pathology contributing to their dementia. Future community-based, longitudinal studies may help elucidate potential differences in the course of AD with underlying CVC versus "pure" AD.

The prevalence of vascular risk factors and conditions is rising and, for many individuals, these risk factors are undiagnosed or undertreated (37). In the present study we were particularly interested in whether we could predict occult vascular disease in patients with a primary diagnosis of AD. This approach differs from many previous studies that have included participants with mixed or vascular dementias. We found that aggregate vascular risk was significantly associated with asymptomatic or mild forms of CVC. These findings suggest that aggregate vascular risk burden may be a useful predictor of occult CVC. Taken together with recent research suggesting that vascular pathology but not amyloid pathology is related to poorer cognition among older adults (30), these findings raise the possibility that aggregate vascular risk measures may be useful predictors of cognitive decline.

Although atherosclerosis may result in infarcts, most of the AD+CVC participants in the current sample evidenced atherosclerotic changes in the absence of ischemic brain damage. The mechanisms through which atherosclerotic cerebrovascular pathology may directly lead to cognitive impairment in the absence of infarcts are not well established. Proposed mechanisms include chronic cerebral hypoperfusion; cerebral embolism originating from ruptured or thrombotic plaques; increased parenchymal oxidative stress; or blood pressure dysregulation contributing to reduced integrity of the blood-brain barrier (38). In addition, evidence from a clinical-pathological-imaging study demonstrated significant associations between atherosclerosis/arteriosclerosis and cortical gray matter atrophy in an autopsy sample (39). Such findings suggest that vascular disease leads to cognitive decline not only through its effects on white matter and subcortical structures but also by contributing to cortical atrophy. When both AD and vascular pathologies are present, the two processes may converge to affect cortical structures involved in cognition (39).

The present study is not without limitations. First, data related to the age of onset of vascular risk factors were unavailable. The relationship between some vascular risk factors and dementia may be age-dependent (40) and midlife exposure may be most closely linked to late life cognitive impairment (41). We cannot be sure how findings may have differed if we examined exposure earlier in life or adequacy of treatment of vascular risk factors. Second, as is the case in all studies based on neuropathologic data, we cannot determine the

pathology at the time of ante-mortem assessment and examine how the relationship between vascular risk factors and neuropathology may differ over time. Third, the sample was selected for likely neurodegenerative rather than vascular dementia. Findings may have differed in a sample including individuals with more severe CVC. Also, we did not assess white matter integrity, which may have provided additional information regarding ischemic vascular pathology. Finally, as is common in neuropathology studies (9, 20, 42), we assessed only one hemisphere and, therefore, may have underestimated existing pathology.

Despite these limitations, the present study has several strengths. We collected extensive neuropathologic data from a well-characterized sample, and the ADRC has maintained an autopsy rate of 90% among subjects followed clinically. Pathologic diagnoses were made blind to clinical diagnoses. Given autopsy confirmation of diagnoses, we did not misclassify individuals with mixed or vascular dementia as AD and, therefore, are not positively biasing the relationships between the measured vascular risk factors and CVC. Further, unlike most previous studies, which have focused on individual vascular risk factors, we assessed several vascular risk factors, objectively measured multiple risk factors (blood pressure, glucose, cholesterol), and computed an aggregate burden score.

Growing evidence for vascular contributions to AD has potential implications for models of AD neuropathology, diagnostic criteria, and treatment (43). Given that many vascular risk factors are modifiable, together with the current lack of effective therapies to treat neurodegenerative cognitive impairment, interventions designed to target vascular risk factors in order to maintain cerebrovascular health may represent important opportunities for preventing or delaying the onset of AD (38). Future studies assessing ante-mortem vascular risk burden at time intervals from midlife to late life, incorporating ante-mortem MRI measures with neuropathologic data, and including participants with a wide range of vascular risk burden may further elucidate associations between vascular risk and AD and inform approaches for earlier identification and treatment for those at risk for dementia.

ACKNOWLEDGMENTS

APPENDIX

A. Description of Brain Autopsy Procedures

Brain autopsies were performed at University of California San Diego using established ADRC protocols (19). The left hemisphere was fixed in formalin for 5–7 days. After fixation, the hemibrain was examined grossly and cut into 1-cm thick coronal slabs. Tissue blocks were taken from the midfrontal cortex, inferior parietal cortex, superior temporal gyrus, inferior temporal gyrus, anterior cingulate gyrus, posterior cingulate gyrus, anterior hippocampus, posterior hippocampus, amygdala, basal ganglia including substantia innominata and adjacent insular cortex, mesencephalon, rostral pons, and cerebellar vermis as well as all gross lesions. Tissue blocks were embedded in paraffin, cut into 10-μm thick

sections, and stained with hematoxylin and eosin and thioflavin-S (44). For a subset of cases, selected tissue blocks were also stained with antibodies against ubiquitin or α-synuclein and a phosphorylated form of tau in order to rule out other forms of neurodegeneration. Diffuse plaques, neuritic plaques, and neurofibrillary tangles were counted in midfrontal, rostral superior temporal, inferior parietal, entorhinal, and hippocampal regions. Brains were then staged for the degree of neurofibrillary tangle pathology by one neuropathologist (L.A.H.) using a modification (21) of Braak and Braak's staging scheme (22). Participant brains were assessed for four forms of CVC: 1) lacunes (small [<10 mm in diameter] artery infarcts and/or hemorrhages), 2) cortical microinfarcts, 3) cerebral arteriosclerosis (small parenchymal arteriolar disease), and 4) atherosclerosis in the circle of Willis. Using a method previously described (24), the severity of CAA was assessed semiquantitatively on thioflavin-S stained preparations of the midfrontal cortex, superior temporal gyrus, inferior parietal cortex, and posterior hippocampus by the study neuropathologist (L.A.H.) using a four-point scale ranging from 0 to 3 (absent, mild, moderate, severe). Criteria for classification of non-AD pathologies used by the National Alzheimer's Disease Coordinating Center were applied (45–51).

B. Statistical Results from Regression Models Including Age as a Covariate

There were no significant differences between the AD+CVC and AD-CVC groups on DRS performance when analyses were conducted including age as a covariate. Results from the analyses including age as a covariate were as follows. When entered as the only predictor on step 1, age did not account for a significant amount of overall variance in DRS performance (DRS Total Score: $F = .05$, $p = .82$, $R^2 = .001$, $\beta = .03$; DRS Attention subscale: $F = 2.71$, $p = .10$, $R^2 = .03$, $\beta = .18$; DRS Initiation/Perseveration subscale: $F = .03$, $p = .86$, $R^2 = <.001$, $\beta = .02$; DRS Construction subscale: $F = 2.37$, $p = .13$, $R^2 = .03$, $\beta = .17$; DRS Conceptualization subscale: $F = .006$, $p = .94$, $R^2 = <.01$, $\beta = .008$; DRS Memory subscale: $F = 3.59$, $p = .06$, $R^2 = .04$, $\beta = -.21$). When entered on step 2, participant group (AD+CVC versus AD-CVC) did not account for a significant amount of overall variance in DRS performance (DRS Total Score: $F = .53$, $p = .59$, $R^2 = .01$; DRS Attention subscale: $F = 1.65$, $p = .20$, $R^2 = .04$; DRS Initiation/Perseveration subscale: $F = 1.32$, $p = .27$, $R^2 = .03$; DRS Construction subscale: $F = 1.31$, $p = .28$, $R^2 = .03$; DRS Conceptualization subscale: $F = .98$, $p = .38$, $R^2 = .02$; DRS Memory subscale: $F = 2.92$, $p = .06$, $R^2 = .07$). Further, participant group (AD+CVC versus AD-CVC) was not associated with cognitive performance (DRS Total Score: $\beta = .11$, $p = 32$; DRS Attention subscale: $\beta = .09$, $p = .45$; DRS Initiation/Perseveration subscale: $\beta = .18$, $p = 11$; DRS Construction subscale: $\beta = .06$, $p = .61$; DRS Conceptualization subscale: $\beta = .16$, $p = .17$; DRS Memory subscale: $\beta = .16$, $p = .14$.

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1. Systematic review: We reviewed the literature on the influence of vascular risk factors on cerebrovascular disease (CVD) and Alzheimer's pathology in patients with Alzheimer's disease (AD). We included neuropathological and neuroimaging studies.

2. Interpretation: The present findings highlight the potential relative importance of aggregate vascular risk burden compared to individual risk factors in terms of the vascular contribution to AD. Findings suggest that even relatively low vascular risk burden is associated with cerebrovascular changes (CVC). Taken together, results suggest that aggregate vascular risk measures may be a useful predictor of occult CVC and of AD risk.

3. Future directions: The role of vascular risk burden as a predictor of AD should be evaluated with longitudinal studies that assess vascular risk from midlife to late life, incorporate ante-mortem MRI measures with neuropathologic data, and include participants with a wide range of vascular risk burden.
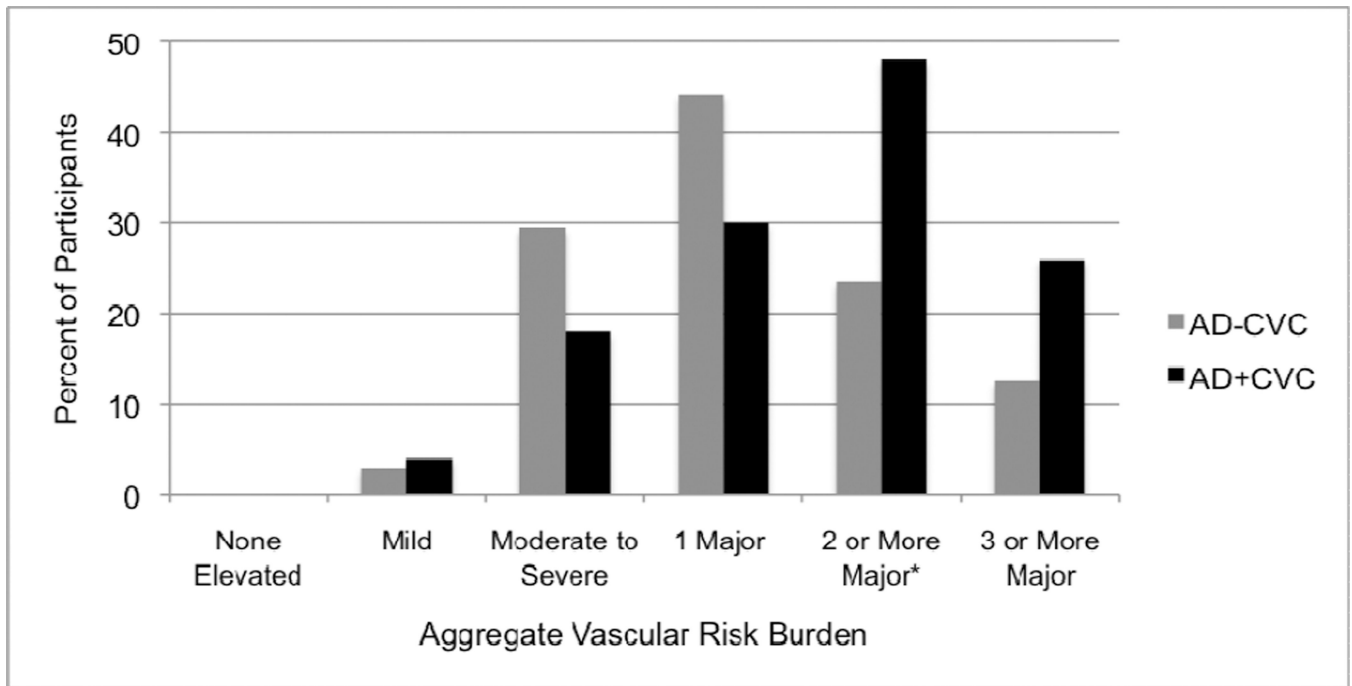
Figure 1. Aggregate vascular risk burden for Alzheimer's disease groups with cerebrovascular changes (AD+CVC) and without cerebrovascular changes (AD−CVC)

Bar graph showing the percent of participants in the AD-CVC and AD+CVC groups classified into each of six categories: (1) no elevated risk factor levels (0% of participants fit this category), (2) 1 mildly elevated risk factor, (3) 1 moderately-to-severely elevated risk factor(s), (4) 1 major risk factor only, (5) 2 major risk factors, and (6) 3 major risk factors.

* $\chi^2 = 5.14$ (p = .02) for comparison between AD-CVC and AD+CVC
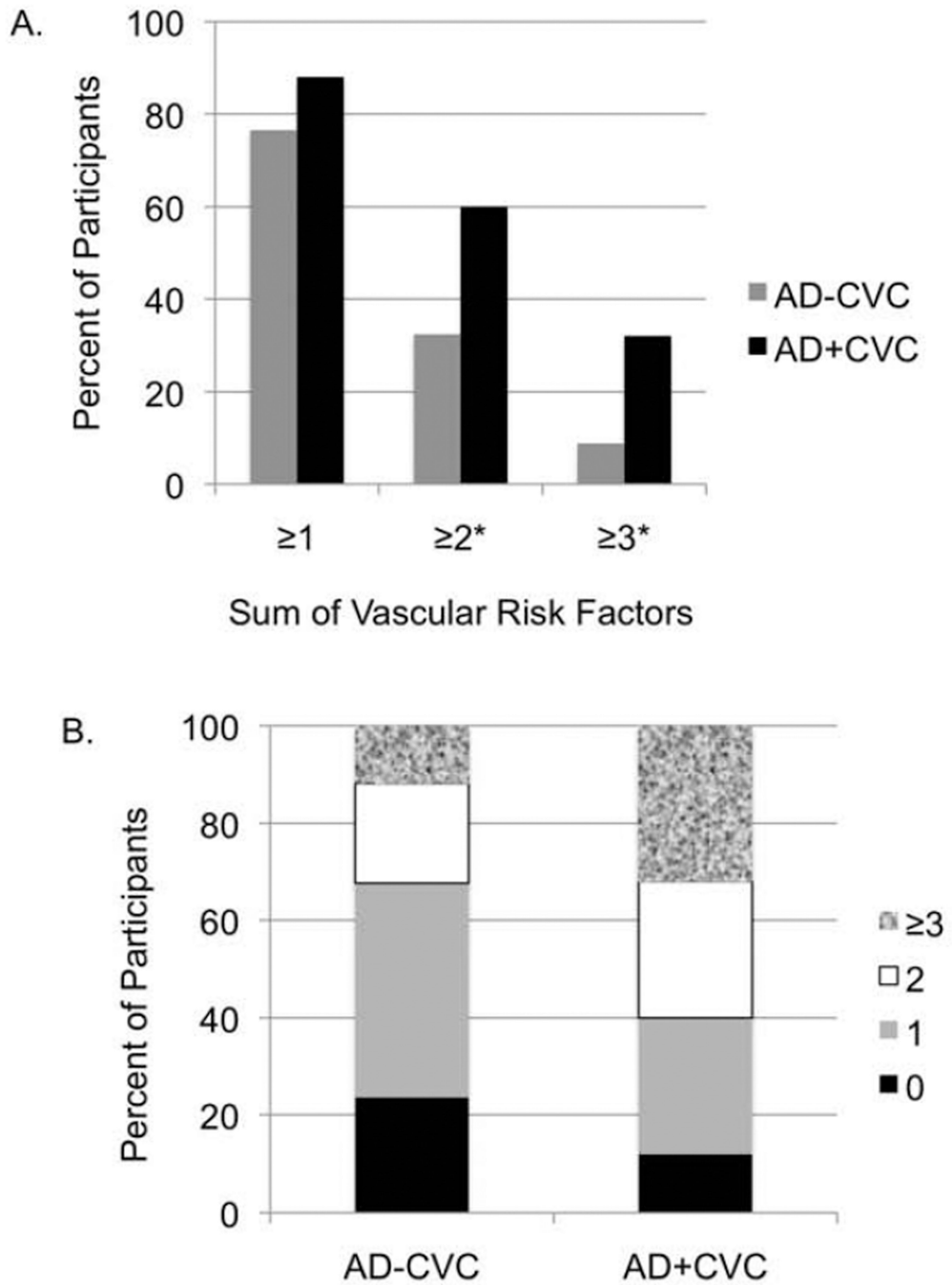
Figure 2. Sum of vascular risk factors for Alzheimer's disease groups with cerebrovascular changes (AD+CVC) and without cerebrovascular changes (AD−CVC)

A. Bar graph showing the percent of participants in the AD-CVC and AD+CVC groups classified based on the presence of: (1) one or more vascular risk factors, (2) two or more vascular risk factors, and (3) three or more vascular risk factors. Note that these analyses did not involve independent groups (e.g., the "one or more risk factor(s)" category includes participants from the "two or more risk factors" category.)

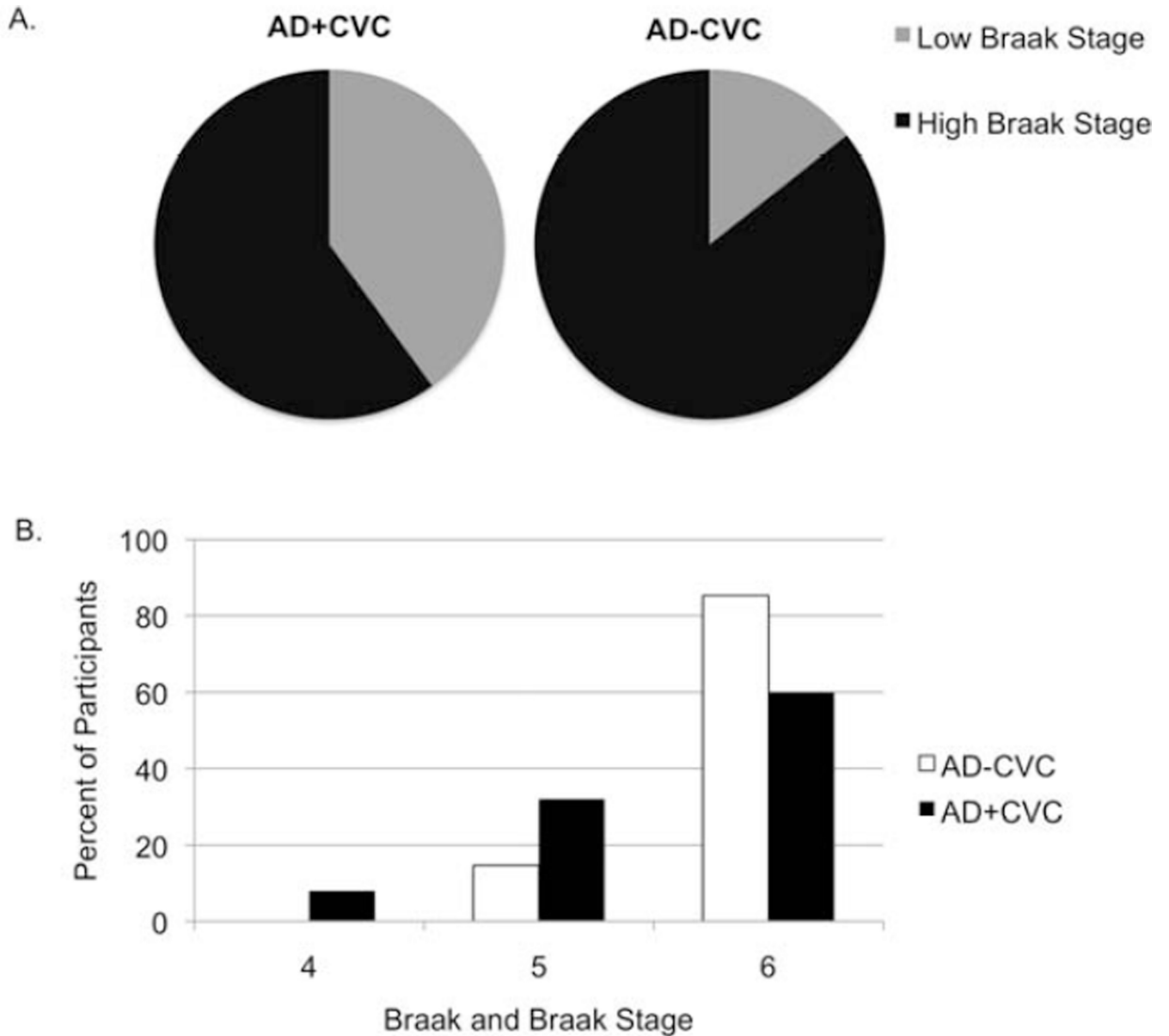*p < .05 for comparison between AD-CVC and AD+CVC

B. Stacked bar chart showing the percent of participants in the AD-CVC and AD+CVC groups with zero, one, two, or three or more vascular risk factors.

Figure 3. Braak and Braak stage for Alzheimer's disease groups with cerebrovascular changes (AD+CVC) and without cerebrovascular changes (AD−CVC)

A. Proportion of participants in the AD+CVC and AD-CVC groups with lower versus higher severity of neurofibrillary tangle pathology as determined by Braak and Braak stage. Braak and Braak stages were divided into Low (stages IV and V) and High (stage VI). $\chi^2 =$ 6.19 ($p = .01$) for comparison between AD-CVC and AD+CVC groups on low versus high Braak and Braak stages.

B. Proportion of participants in the AD+CVC and AD-CVC groups as a function of Braak and Braak stage (IV, V, or VI). $\chi^2 = 6.99$ ($p = .03$) for comparison between AD-CVC and AD+CVC groups on Braak and Braak stages (IV, V, or VI).

Table 1

Comparison of Alzheimer's disease groups with cerebrovascular changes (AD+CVC) and without cerebrovascular changes (AD–CVC) on demographic and clinical characteristics

	AD+CVC, n = 50 mean (sd)		AD–CVC, n = 34 mean (sd)		t or χ^2 value	p-value
Demographics						
Age at Vascular Risk Assessment, yrs	73.18	(7.97)	70.38	(6.33)	1.71	.09
Education, yrs	13.00	(3.21)	13.53	(2.67)	.79	.43
Women/men	26/24		16/18		.20	.66
APOE Genotype (ε4+/ε4−)	34/16		22/9		.08	.78
Diagnosis at Vascular Risk Assessment	40/10		28/6		.07	.79
(Probable AD/Possible AD)						
Age at Dementia Onset	69.24	(8.28)	64.85	(6.35)	2.59	.01
Age at Death	79.10	(8.07)	75.41	(6.01)	2.27	.03
Duration of Dementia	9.86	(4.14)	10.36	(2.98)	.60	.55
Time Between Vascular Risk Assessment and Death, yrs	6.11	(3.35)	5.21	(2.48)	1.50	.14
Cognitive Functioning (raw scores)						
DRS Total Score	104.42	(25.24)	98.56	(25.59)	1.04	.30
DRS Attention	32.47	(5.51)	30.91	(7.72)	1.07	.29
DRS Initiation/Perseveration	24.98	(9.10)	21.65	(9.22)	1.63	.11
DRS Construction	4.45	(1.67)	4.15	(1.69)	.81	.42
DRS Conceptualization	31.00	(6.64)	28.74	(8.11)	1.39	.17
DRS Memory	12.76	(5.20)	11.50	(5.55)	1.05	.30

Abbreviations: APOE = apolipoprotein E; DRS = Dementia Rating Scale

Table 2

Comparison of Alzheimer's disease groups with cerebrovascular changes (AD+CVC) and without cerebrovascular changes (AD−CVC) on vascular risk factors and neuropathologic measures

	AD+CVC, n = 50 mean (sd)	AD−CVC, n = 34 mean (sd)	t or χ^2 value	p-value
Individual Vascular Risk Factors, N (%)				
Cardiovascular Disease	23 (46.00%)	9 (26.47%)	3.27	.07
Diabetes	7 (14.00%)	1 (2.94%)	2.87	.09
Hypertension	33 (66.00%)	18 (53.00%)	1.48	.23
High Total Cholesterol	19 (38.00%)	9 (26.47%)	1.21	.27
Atrial Fibrillation	6 (12.00%)	1 (2.94%)	2.17	.14
Current smoker	3 (6.00%)	3 (8.82%)	.24	.62
TIA/Stroke	7 (14.00%)	0 (0.0%)	5.19	.02
Total cholesterol (mg/dL)	223.08 (46.86)	224.15 (35.33)	.11	.91
Triglycerides (mg/dL)	166.23 (99.94)	151.32 (64.45)	.82	.42
Systolic blood pressure (mm Hg)	140.21 (20.19)	138.18 (20.50)	.45	.65
Diastolic blood pressure (mm Hg)	79.26 (10.88)	81.44 (9.30)	.96	.34
Taking antihypertensive medication	17 (34.00%)	8 (23.53%)	1.06	.30
Casual glucose (mg/dL)	98.82 (34.38)	94.00 (19.72)	.74	.46
BMI	24.13 (3.71)	24.01 (4.17)	.14	.89
Aggregate Vascular Risk Profile [*]			5.54	.14
No elevated risk factors	0 (0%)	0 (0%)		
1 Mildly elevated risk factor	2 (4.00%)	1 (2.94%)		
1 Moderately-to-severely elevated risk factor	9 (18.00%)	10 (29.41%)		
1 Major risk factor	15 (30.00%)	15 (44.12%)		
2 Major risk factors	24 (48.00%)	8 (23.53%)		
Aggregate vascular risk (low/high) [†]	26/24	26/8	5.14	.02
Vascular Risk Factor Sum Score [‡]				
One or more risk factor(s)	44 (88.00%)	26 (76.47%)	1.94	.16
Two or more risk factors	30 (60.00%)	11 (32.35%)	6.19	.01
Three or more risk factors	16 (32.00%)	4 (11.76%)	4.57	.03

	AD+CVC, n = 50 mean (sd)	AD−CVC, n = 34 mean (sd)	t or χ^2 value	p-value
Neuropathology				
Braak and Braak stage (low/high)	20/30	5/29	6.19	.01
CAA (absent/present) §	11/39	4/29	1.31	.25

*
Participants were classified into five mutually exclusive categories depending on whether they had (1) no risk factors above threshold levels (total cholesterol<180 mg/dL; untreated systolic blood pressure<120 mm Hg; untreated diastolic blood pressure<80 mm Hg; no history of stroke/TIA, diabetes, cardiovascular disease, or atrial fibrillation; and nonsmoker), (2) 1 risk factor at mildly elevated levels (total cholesterol 180–199 mg/dL; untreated systolic blood pressure 120–139 mm Hg or untreated diastolic blood pressure 80–89 mm Hg; no history of stroke/TIA, diabetes, cardiovascular disease, or atrial fibrillation; and nonsmoker), (3) 1 moderately-to-severely elevated risk factor(s) (total cholesterol 200–239 mg/dL; untreated systolic blood pressure 140–159 mm Hg or untreated diastolic blood pressure 90–99 mm Hg; no history of stroke/TIA, diabetes, cardiovascular disease, or atrial fibrillation; and nonsmoker), (4) 1 major risk factor only (total cholesterol 240 mg/dL; treated hypertension, untreated systolic blood pressure 160 mm Hg, or untreated diastolic blood pressure 100 mm Hg; history of stroke/TIA, diabetes, cardiovascular disease, or atrial fibrillation; or current smoker), or (5) 2 major risk factors.

†
Aggregate vascular risk burden classified as Low (1 mildly elevated risk factor, 1 moderately-to-severely elevated risk factor(s), or 1 major risk factor only) or High (2 major risk factors)

‡
Vascular risk sum score is based on the presence or absence of the following seven risk factors: high total cholesterol, hypertension, history of TIA/stroke, diabetes, cardiovascular disease, atrial fibrillation, and current smoking

§
cerebral amyloid angiopathy was not assessed for one participant

Abbreviations: TIA = transient ischemic attack; BMI = body mass index; CAA = cerebral amyloid angiopathy

Table 3

Prevalence of the individual forms of cerebrovascular changes among Alzheimer's disease patients with cerebrovascular changes

Lacunes[*]	18%
Cortical microinfarcts	8%
Cerebral arteriosclerosis [†]	18%
Atherosclerosis in the circle of Willis	90%

[*] Small (<10 mm in diameter) artery infarcts and/or hemorrhages

[†] Small parenchymal arteriolar disease