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# 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 antemortem vascular risk factors to postmortem cerebrovascular and Alzheimer's disease (AD) pathologies. Eighty-four AD patients underwent an 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 (CVCs), 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 the 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. Furthermore, the presence of CVC was associated with lower Braak and Braak stage. These 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.
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## 1. Introduction

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

Accumulating evidence suggests that vascular risk factors increase the risk for AD via cerebrovascular disease (CVD) [5]. Although most 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 the 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 the

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antemortem assessment of aggregate vascular risk factors is related to cerebrovascular changes (CVCs), 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, and microinfarcts) at autopsy in patients with antemortem 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 the evidence that CVC and AD pathology have additive effects on the risk for AD, we expected that CVC would be associated with less severe AD pathology at a given level of dementia severity. The present study adds to existing literature by including neuropathologic confirmation of AD diagnosis, examining both AD and CVC as underlying neuropathologic 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 neuropathologic data from 602 participants of various ages at autopsy (range, 36–104 years) and with various neuropathologic diagnoses (e.g., normal, AD, 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 the criteria for probable or definite AD at autopsy based on semiquantitative estimates of neuritic plaque density as recommended by Consortium to Establish a Registry for Alzheimer's Disease (CERAD) [11] and a 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 pathologic 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, eight for large infarcts (>10 mm in diameter), seven for medial temporal lobe sclerosis, six for macroscopic cerebral hemorrhage, and none for Pick's disease. Clinical data were reviewed, and those who underwent vascular risk assessment and met the 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 examination, and laboratory studies: cardiovascular disease (coronary artery disease, cardiac failure, or intermittent claudication), diabetes (self-reported diabetes, use of antidiabetic therapy, or casual blood glucose ≥200 mg/dL), high total cholesterol level (≥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 the history of stroke/transient ischemic attack (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) one or more risk factors at mildly elevated levels, (3) one or more moderately to severely elevated risk factor(s), (4) one major risk factor only, or (5) two or more 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