
Article:
Wharton, S.B., Richardson, C.D., Ashford, B. et al. (2026) VCING scoring and white matter arteriolosclerosis show relationships to dementia status and white matter damage in an unselected ageing brain cohort. Neuropathology and Applied Neurobiology, 52 (3). e70081. ISSN: 0305-1846

https://doi.org/10.1111/nan.70081

Neuropathology and Applied Neurobiology

WILEY

Neuropathology and Applied Neurobiology
JOURNAL OF THE BRITISH NEUROPATHOLOGICAL SOCIETY

ORIGINAL ARTICLE OPEN ACCESS

VCING Scoring and White Matter Arteriolosclerosis Show Relationships to Dementia Status and White Matter Damage in an Unselected Ageing Brain Cohort

S. B. Wharton[1] | C. D. Richardson[2] | B. Ashford[1] | H. Brooke[1] | S. U. Ahamed[1] | D. J. Fillingham[1] | J. E. Simpson[1] | S. Francis[3] | C. Brayne[4] | F. E. Matthews[5] | on behalf of CFAS

[1]Sheffield Institute for Translational Neuroscience, University of Sheffield, Sheffield, UK | [2]Centre for Clinical Brain Sciences, University of Edinburgh, Edinburgh, UK | [3]School of Medicine and Population Health, University of Sheffield, Sheffield, UK | [4]Cambridge Public Health, School of Clinical Medicine, University of Cambridge, Cambridge, UK | [5]Institute for Clinical and Applied Health Research, University of Hull, Hull, UK

Correspondence: S. B. Wharton (s.wharton@sheffield.ac.uk)

Received: 5 February 2026 | **Revised:** 16 April 2026 | **Accepted:** 29 April 2026

Keywords: Alzheimer's neuropathology | cerebrovascular disease | dementia | staging scheme | vascular dementia | VCING score | white matter

ABSTRACT

Introduction: Vascular disease is associated with late-life dementia and other morbidities during life and commonly coexists with neurodegenerative pathologies. A complex variety of lesions can be documented, which has made development of standardised operationalised criteria difficult. A semiquantitative approach, vascular cognitive impairment neuropathology guidelines (VCING), has been developed that provides a score based on assessment of occipital white matter arteriolosclerosis, occipital leptomeningeal cerebral amyloid angiopathy (CAA) and the presence of any macroscopic infarct.

Methods: We applied VCING assessment to an ageing population-derived neuropathology cohort derived from two subcentres of the cognitive function and ageing study ($n = 158$, 63.7% female and 36.3% male).

Results: Vascular pathology using this method was common in this UK ageing population sample with 75% of individuals having a score of 1 or more. VCING score was associated with the presence of dementia at death, even accounting for Alzheimer's disease neuropathological change (ADNC). Of the VCING components, white matter arteriolosclerosis, but not CAA or infarcts, was associated with dementia (after adjustment for ADNC). VCING score was not associated with vascular risk factors during life, but males were at greater risk of a higher VCING score than females. VCING and arteriolosclerosis were associated with white matter pallor and perivascular space widening as markers of white matter damage. Venous collagenosis was also associated with white matter pallor. There was an association between VCING score and ADNC in regression analysis, and the association was particularly strong for the CAA component.

Conclusions: VCING is a straightforward method to assess vascular pathology in neuropathology cohorts and retains its association with dementia. The arteriolosclerosis component, in particular, is related to dementia and to white matter damage, whereas venous-side effects may also be important for the latter. The strong association of the CAA component with ADNC measures, however, raises the question of whether the VCING approach may have some confounding effects with ADNC.

Wharton SB and Richardson CD are joint first authors.

Summary

- VCING criteria provide a score to assess cerebrovascular disease based on the presence of any infarct > 10 mm, occipital leptomeningeal CAA and occipital white matter arteriolosclerosis.
- We assessed VCING in a UK population-representative neuropathology cohort from the Cognitive Function and Ageing Neuropathology Study.
- VCING and its arteriolosclerosis component are associated with dementia status at death and with other occipital white matter pathologies, whereas venous collagenosis may also be important white matter pathology.

1 | Introduction

Vascular disease is one of the commonest causes of late-life dementia, after Alzheimer's disease [1]. Vascular pathologies are common in population-, community-based and large unselected autopsy series, where they often coexist with neurodegenerative pathologies, such as Alzheimer's disease neuropathological change (ADNC), Lewy body disease and TDP-43 pathology, contributing to dementia as part of mixed pathologies [2–8]. Vascular disease has potentially modifiable risk factors, whereas changes in brain vascular disease may account for changing dementia prevalences across birth cohorts [9], so its assessment is of high importance. However, the pathology of vascular brain disease is complicated and does not have a stereotypical neuroanatomical hierarchy of progression that enables clear staging, such as is seen in the neurodegenerative causes of dementia. Consequently, there are inconsistencies in the assessment of vascular pathology, with a lack of harmonisation between studies [10].

Broadly, brain vascular disease can be divided into pathologies associated with large vessel disease and small vessel disease (SVD) [11]. Large vessel disease due to atherosclerosis causes cerebral infarcts, the volume and/or strategic locations of which correlate with dementia. However, even small strokes may be associated with a progressive poststroke dementia that is associated with gliovascular dysfunction in frontal white matter [12]. SVD, which may be due to arteriolosclerosis or cerebral amyloid angiopathy (CAA), is increasingly recognised as an important cause of progressive dementia that may mimic Alzheimer's disease clinically [13, 14].

Research into vascular cognitive impairment has been impaired by lack of clear operationalised criteria for assessment. Approaches to vascular brain disease include classification according to the type of vascular pathology present [11]. Consensus papers have emphasised the need to assess multiple types of pathology [15, 16]. Semiquantitative approaches to SVD include assessment of the severity of arteriolosclerosis and assessment of tissue effects related to SVD [17, 18]. The latter includes a constellation of lesion types considered to be related to SVD, such as lacunar infarcts, microinfarcts, cerebral microbleeds, perivascular lacunes and white matter myelin loss, changes that have also been used for in-life imaging-based assessment of SVD [19]. However, a well-accepted, simple, reproducible, (semi-)quantitative scheme has been difficult to achieve.

A recent approach has been the development of vascular cognitive impairment neuropathology guidelines (VCING) [20]. This study took a Delphi expert approach to identify potential vascular lesions for assessment and then to empirically test the various measures against dementia status in a cohort of 113 individuals. Regression modelling identified the best predictive model of cognitive impairment, which was comprised of (1) moderate/severe arteriolosclerosis in occipital white matter; (2) moderate/severe occipital leptomeningeal CAA; (3) the presence of at least one large infarct (> 10 mm). Assessment of these criteria gives a score of 0, 1, 2 or 3 that showed a relationship to cognitive impairment. The study was performed in a cohort selected to not have concurrent neurodegenerative pathology, so that the interaction with common pathologies such as ADNC was not assessed. VCING has since been used to assess vascular pathology in an ageing cohort [21] and in a cohort with Braak and Braak Stages III–IV tau pathology [22]. However, VCING still requires validation in additional cohorts and particular in a more general population setting.

We aimed to validate the VCING criteria in a population neuropathology cohort and to determine whether this provides predictive information for dementia in a general setting. We used the cognitive function and ageing study (CFAS) neuropathology cohort, as this provides a general 65 years. and over UK population-representative cohort allowing an epidemiological perspective [23]. The cohort includes a spectrum of age-related pathologies, allowing assessment of VCING criteria in the presence of ADNC. Our study therefore avoids biases inherent in preselection into clinicopathological groups for pathologies that show a continuum in the ageing population. This study defines the frequency of brain vascular disease as assessed by VCING, examines the relationship to other local SVD-related pathologies and to ADNC and determines the relationship of VCING score to dementia.

2 | Methods

2.1 | Cohort

Archival brain donations from the Newcastle and Cambridge centres of the CFAS neuropathology cohort were used for this study ($n = 158$, Table S1) and research ethics committee approval was granted (19/WM/0255). The CFAS cohort is a population-representative cohort aged 65 years and above on recruitment with strengths in the length of study and richness of its data. The study has been previously described. In brief, dementia status at death was determined from in-life structured interviews using the AGECAT algorithmic assessment, death certificate information and a retrospective informant interview [2, 3, 23, 24]. Measures of ADNC were assessed by neuropathologists including CERAD and Braak neurofibrillary tangle (NFT) stage, supplemented by Thal phase and assessment of CAA based on numbers of brain areas involved and severity [25, 26].

2.2 | Assessment of VCING Criteria

VCING criteria were assessed as previously described [20]. Using available formalin-fixed paraffin embedded haematoxylin and eosin-stained sections from the occipital lobe, white matter arteriolosclerosis was assessed as 0, *Normal*; 1, *Mild thickening of the vessel media, mild fibrosis*; 2, *Partial loss of smooth muscle cells in the media, moderate hyaline fibrosis*; and 3, *Complete loss of smooth muscle cells in media, severe hyaline fibrosis, lumen stenosis* (Figure 1). As per the approach detailed in Table S4 in Skrobot et al., we gave this score based on overall impression in the section rather than the worst vessel. Data on severity of occipital leptomeningeal CAA, based on the criteria of Love et al. [27] and assessment of macroscopical infarcts (> 1 cm diameter) in sections from nine brain areas was available on the cohort [26, 28]. We used the latter measure of infarcts because this was available on all the cases. For comparison, we also carried out an additional repeat analysis using infarcts documented as part of the macroscopical assessment of CFAS cases at donation; this information was available for 45 of our donations. VCING score (0 to 3) was then assessed as the presence of moderate/severe leptomeningeal CAA, moderate/severe arteriolosclerosis and any large infarct.

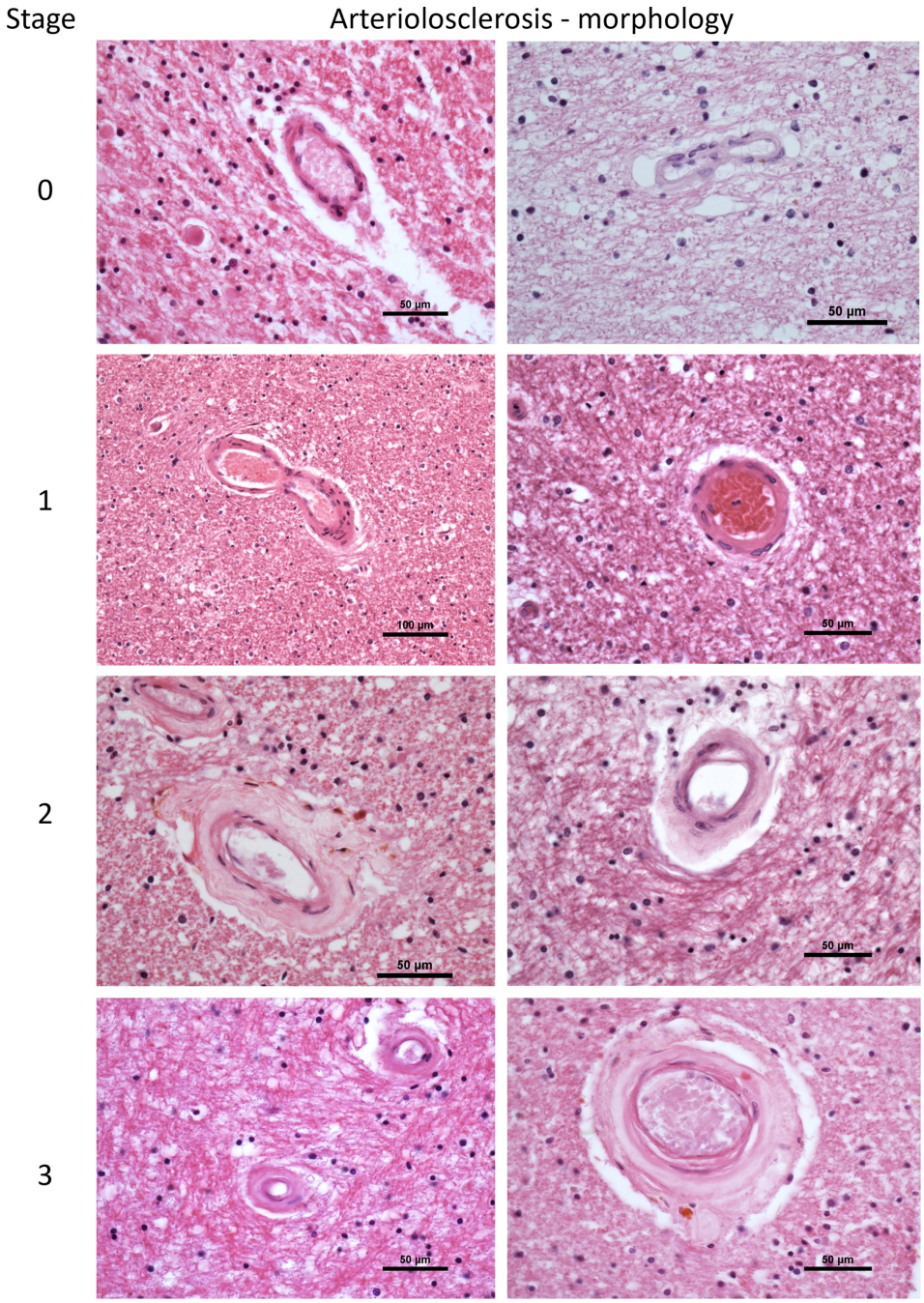

FIGURE 1 | Morphology and staging of occipital white matter arteriolosclerosis. Two example images shown for each m orphological stage: 0—normal, 1—mild thickening of vessel wall without collagenisation, 2—partial sclerosis but with preservation of some smooth muscle and 3—complete wall sclerosis with loss of smooth muscle.

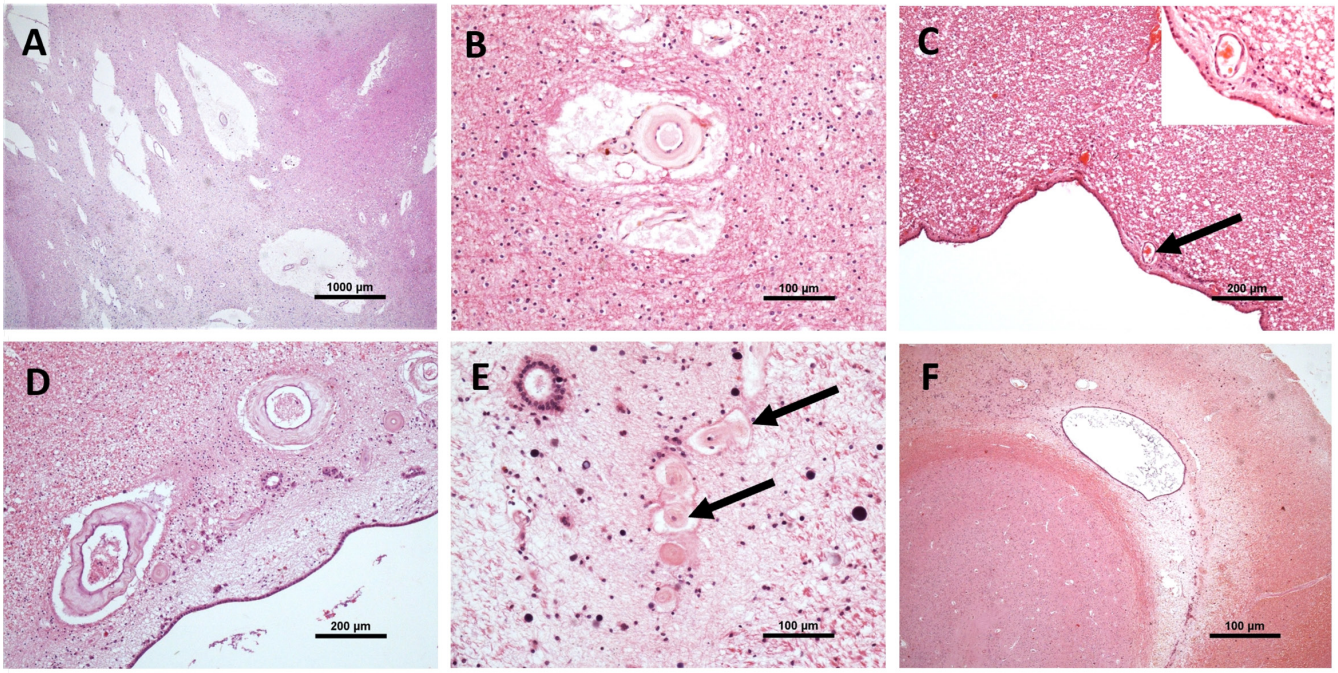

FIGURE 2 | Other vascular-associated pathology in white matter. (A) Severely dilated perivascular spaces. A central vessels can be discerned in each of these. (B) Mild perivascular space widening. The associated arteriole shows severe arteriolosclerosis and there is pallor of surrounding white matter. (C) Normal periventricular white matter and periventricular vein (arrow and inset detail). (D) Venous collagenosis in periventricular region. (E) Collagenosis of small veins in periventricular region (arrows). (F) Moderate periventricular white matter pallor.

We also assessed other features of vascular pathology in the occipital region, namely, widening of perivascular spaces in white matter (scored 0 to 3), white matter pallor (0 to 3) and the presence of venous collagenosis in small or large veins (Figure 2).

2.3 | Statistical Analysis

Statistical analysis was performed and plots prepared using R Studio version 2025.5.1.513.3 (Posit team (2025). RStudio: Integrated Development Environment for R. Posit Software, PBC, Boston, MA). As VCING score had very small numbers at the highest stage, the score was collapsed into three levels of 0, 1 and 2–3 combined for analysis. Similarly, the medium and high levels (2 and 3) for white matter pallor and perivascular space widening were combined. Chi-square tests were used to compare relationships between variables and ordinal and binary logistic regression to examine the effects VCING score had on the risks of the various white matter pathologies and ADNC. Regression modelling was used to investigate the effect of VCING on increased risk of dementia risk factors; ordinal models for categorical outcomes and logistic models for binary outcomes. *APOE*-genotype was made a binary variable for ε4-allele carrier or not to retain statistical power.

The relationship of VCING to dementia status was modelled univariately to assess the effect of VCING only and multivariately, adjusted for Braak NFT stage and Thal phase. VCING pathology was analysed using three classification schemes: (i) a binary variable (no pathology vs. any pathology), (ii) a collapsed three-level score (no pathology, 1 pathology and 2+ pathologies) and (iii) the original four-level score (no pathology, 1 pathology present, 2 pathologies present and 3 pathologies present). Fall prevalence was summarised by VCING category. Associations were tested using Pearson's χ^2 test, with Fisher's exact test applied when expected cell counts were <5. Linear trends in proportions were assessed with the Cochran–Armitage test. Unadjusted logistic regression models were fitted with VCING as a categorical predictor (reference = no pathology) to estimate odds ratios (ORs) and 95% confidence intervals (CIs).

3 | Results

3.1 | Frequency of Vascular Pathology as Assessed by VCING

VCING score was determined for 158 donations; demographic data for this cohort are shown in Table S1. Dementia status was known for 150 of these, with 57.3% having dementia at death. Approximately 75% of the cohort had some pathology present by VCING assessment, with the presence of one (out of three) pathology being most frequent (49%). As there were very small numbers in the highest VCING stage of three (< 2% of donations), VCING Stages 2 and 3 were collapsed into a single stage for further analysis. Distributions of VCING scores and of the individual components are shown in Figure S1 and Table S1. The distribution of VCING score and of the individual components did not differ between the two centres ($\chi^2 = 3.63$ 3df $p = 0.304$).

3.2 | Relationship of VCING and of Venous Collagenosis to White Matter Pathology

White matter pallor and perivascular space widening are important markers of white matter pathology. Other vascular-associated

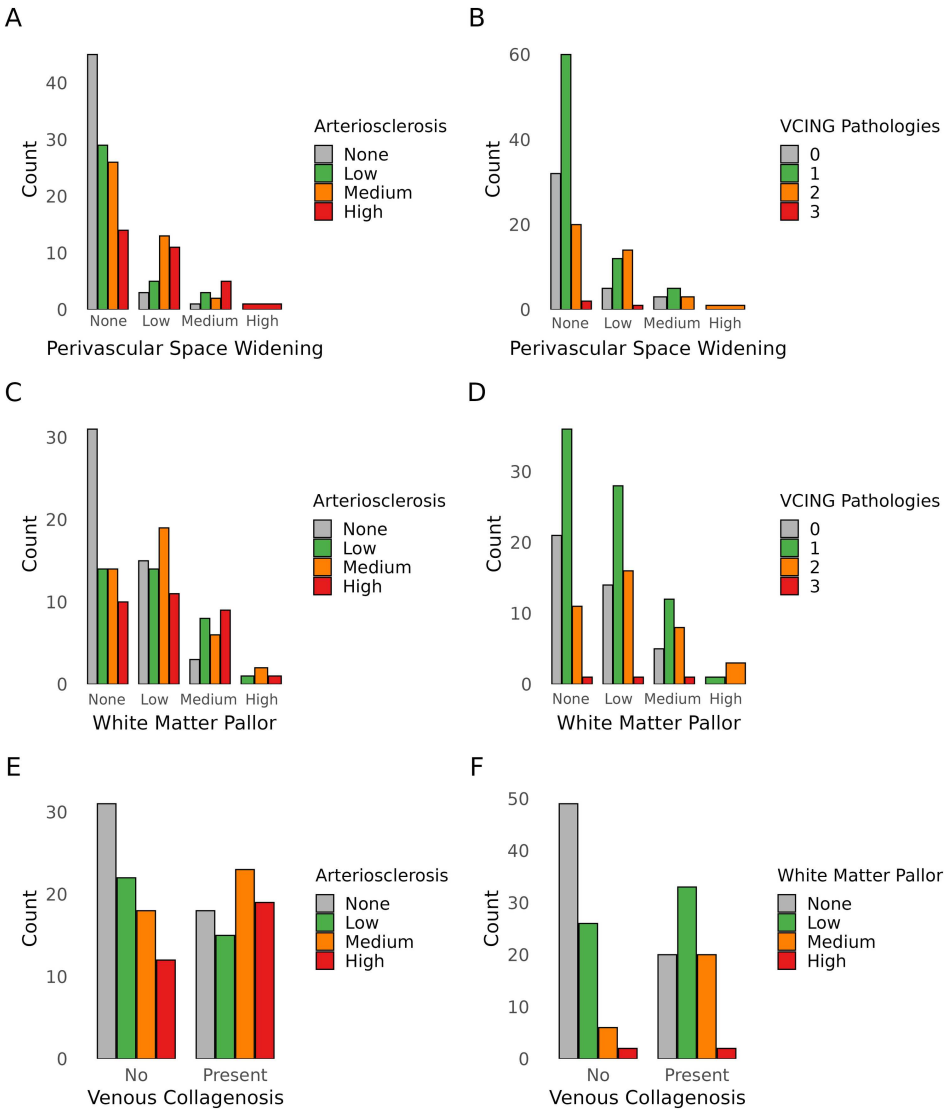

FIGURE 3 | Relationship of VCING and its component pathologies to white matter pathologies. Perivascular space widening shows relationships to arteriolosclerosis (A) $p < 0.01$ and VCING score (B) $p = 0.03$. White matter pallor shows a relationship to arteriolosclerosis (C) $p = 0.02$ but not VCING score (D) $p = 0.017$. Using logistic regression, severe arteriolosclerosis (E) OR = 2.7 and white matter pallor (F) OR = 6.7 for medium/high white matter pallor showed relationships to venous collagenosis. The *y*-axes show number of individuals.

pathologies were also noted and semiquantified in the occipital white matter (Figure 2 and Figure S2). Perivascular space widening was noted in 28% of cases. Venous collagenosis, affecting small or large vessels, was most noted in the periventricular region and was present in 48% of cases. White matter pallor was present in 56% of cases and was moderate or severe in 19%. Dilated venous structures and perivascular haemosiderin were noted in an occasional case but not quantified. For white matter pallor and perivascular space widening, high and medium levels of pathology were combined for further analysis due to low numbers in the respective highest stage. Venous collagenosis was assessed as present or absent.

To investigate how vascular pathology, as assessed by VCING criteria, affects white matter, we investigated the relationships between VCING score and its component measures versus white matter pallor and white matter perivascular space widening (Figure 3A–D) as measures of tissue effect. Initially using chi-square to assess associations (Table S2), perivascular space formation showed an association with white matter arteriolosclerosis ($p = <0.001$) and with VCING score ($p = 0.03$) but not with leptomeningeal CAA or infarcts. White matter pallor also showed an association with arteriolosclerosis ($p = 0.02$), but not with VCING score, leptomeningeal CAA score or the presence of any infarct > 10 mm.

We now used ordinal and binary logistic regression to investigate the effect of VCING and its components on the risk of white matter pathologies (Table 1). For perivascular space widening, moderate and severe arteriolosclerosis carried very high odds (OR: 6.0, [95% CI: 2.2–22.8] and OR: 14.0, [95% CI: 4.4–54.3]) of worse perivascular widening whilst having ≥2 VCING lesions tripled the odds (Table 3). For white matter pallor, a similar effect was seen. Even mild arteriolosclerosis tripled the odds of worse pallor rising to 4× at severe levels (OR: 4.4 [95% CI: 1.8–11.0]). A burden of ≥2 VCING lesions also doubled the odds. For both of these white matter pathologies, CAA and infarcts showed no effect.

TABLE 1 | Relationship of VCING and of venous collagenosis to white matter pathology.

Model	Level	OR	95% CI
Risk of perivascular space widening			
Arteriolosclerosis	*Low* vs. *none*	*3.2*	*(0.9–13)*
	Medium vs. *none*	*6.0**	*(2–22.8)*
	High vs. *none*	*14.0**	*(4.4–54.3)*
	Medium/high vs. *none/low*	*4.7**	*(2.2–10.3)*
Leptomeningeal CAA	*Low* vs. *none*	*1.3*	*(0.3–4.7)*
	Medium vs. *none*	*0.8*	*(0.4–1.9)*
	High vs. *none*	*1.5*	*(0.6–3.8)*
	Medium/high vs. *none/low*	*1.0*	*(0.5–2.0)*
VCING	*1 path* vs. *none*	*1.1*	*(0.4–3.0)*
	2+ path vs. *none*	*3.1**	*(1.2–8.5)*
	2+ path vs. *none/1 path*	*2.9**	*(1.4–6.0)*
Large infarct	*Present* vs *no infarct*	*0.7*	*(0.2–2.2)*
Risk of white matter pallor			
Arteriolosclerosis	*Low* vs. *none*	*3.2**	*(1.4–7.4)*
	Medium vs. *none*	*3.1**	*(1.4–7.1)*
	High vs. *none*	*4.4**	*(1.8–11.0)*
Leptomeningeal CAA	*Low* vs. *none*	*1.4*	*(0.4–4.1)*
	Medium vs. *none*	*0.8*	*(0.4–1.6)*
	High vs. *none*	*1.8*	*(0.8–4.1)*
VCING (ordinal)	*1 pathology* vs. *none*	*1.3*	*(0.6–2.7)*
	2+ pathologies vs. *none*	*2.7**	*(1.2–6.3)*
Large infarct	*Present* vs. *no infarct*	*1.4*	*(0.6–3.6)*
Risk of venous collagenosis			
White matter pallor	*Low* vs. *none*	*3.1**	*(1.5–6.6)*
	Medium/high vs. *none*	*6.7**	*(2.7–18.5)*
Perivascular space widening	*Low* vs. *none*	*0.6*	*(0.3–1.4)*
	Medium/high vs. *none*	*1.5*	*(0.4–5.2)*
VCING score	*1 pathology* vs. *none*	*1.5*	*(0.7–3.4)*
	2+ pathologies vs. *none*	*2.1*	*(0.9–5.3)*
Arteriolosclerosis	*Low* vs. *none*	*1.2*	*(0.5–2.8)*
	Medium vs. *none*	*2.2**	*(1.0–5.2)*
	High vs. *none*	*2.7**	*(1.1–7.1)*
Leptomeningeal CAA	*Low* vs. *none*	*0.5*	*(0.2–1.8)*
	Medium vs. *none*	*0.7*	*(0.3–1.4)*
	High vs. *none*	*0.7*	*(0.3–1.6)*
Large infarct	*Present* vs. *no infarct*	*3.3 **	*(1.2–10.6)*

Note: Categorical outcomes modelled using ordinal regression, and binary outcomes modelled using logistic regression. Results presented as odds ratios (OR) with 95% confidence intervals (95% CI). OR considered significant marked with *.

VCING is essentially composed of arterial side pathologies, so we also investigated the association of venous collagenosis with white matter effects. Venous collagenosis affecting large or small vessels was present in 47% of the overall cohort. Venous collagenosis showed a borderline association with infarcts >10 mm ($p=0.05$) but not with either arteriolosclerosis or VCING score (Table S2). Using logistic regression modelling, we found that white matter pallor staged at low (OR: 3.1 [95% CI: 1.5–6.6]) and medium/high (OR: 6.7 [95% CI: 1.8–2.7–18.5]), severe arteriolosclerosis (OR: 2.7 [95% CI: 1.1–7.1]) and the presence of a large infarct (OR: 3.3 [95% CI: 10.6]) predicted venous collagenosis, whereas risk estimates increased with VCING score and perivascular space widening; confidence intervals included no effect (Table 1 and Figure 3E,F).

3.3 | VCING and the CAA Component of Its Score Show a Relationship to Measures of ADNC

We next determined how VCING and its components relate to measures of ADNC using χ^2. VCING score did not show an association with either Thal phase ($p=0.06$) or Braak NFT stage ($p=0.79$). However, leptomeningeal CAA showed an association with both Thal phase ($p<0.001$) and Braak NFT stage ($p=0.01$). The present of any infarct >10 mm also showed associations with Thal phase ($p=0.01$) but not Braak NFT stage. Arteriolosclerosis was not significantly associated with either ADNC measure.

We further investigated these associations using regression modelling (Table 2). Leptomeningeal CAA score showed a very strong dose–response to Thal phases, with medium (OR: 6.3

TABLE 2 | Relationship of VCING to ADNC. Modelled using ordinal regression.

	Predictor	OR	95% CI
Thal phase			
VCING score	*1 pathology* vs. *none*	*2.0**	*(1.0–4.1)*
	2+ pathologies vs. *none*	*3.0**	*(1.3–7.1)*
Leptomeningeal CAA	*Low* vs. *none*	*2.4*	*(0.7–8.3)*
	Medium vs. *none*	*6.3**	*(3–13.8)*
	High vs. *none*	*13.6**	*(5.3–39.3)*
Arteriolosclerosis	*Low* vs. *none*	*0.7*	*(0.3–1.6)*
	Medium vs. *none*	*0.7*	*(0.3–1.6)*
	High vs. *none*	*0.7*	*(0.3–1.5)*
Large infarct	*Present* vs. *no infarct*	*0.6*	*(0.3–1.4)*
Braak stage			
VCING score	*1 pathology* vs. *none*	*1.2*	*(0.6–2.4)*
	2+ pathologies vs. *none*	*1.6*	*(0.7–3.6)*
Leptomeningeal CAA	*Low* vs. *none*	*1.3*	*(0.4–4)*
	Medium vs. *none*	*1.7*	*(0.9–3.5)*
	High vs. *none*	*5.2**	*(2.2–12.7)*
Arteriolosclerosis	*Low* vs. *none*	*1.7*	*(0.7–3.8)*
	Medium vs. *none*	*1.2*	*(0.6–2.5)*
	High vs. *none*	*0.8*	*(0.3–1.9)*
Large infarct	*Present* vs. *no infarct*	*0.7*	*(0.3–1.7)*

Note: Results presented as odds ratios (OR) with 95% confidence intervals (95% CI). OR considered significant marked with *.

[95% CI: 3.0–13.8]) and high CAA (OR: 13.6 [95% CI: 5.3–39.3]). VCING showed an increasing trend, strongest with 2 or more pathologies present (OR: 3.0 [95% CI: 1.3–7.1]). Large infarcts and atherosclerosis did not independently predict Thal phase. For Braak NFT stage, only leptomeningeal CAA emerged as a predictor of advanced tau pathology (OR: 5.2 [95% CI: 2.2–12.7]). For VCING stage, although point estimates showed a trend for increased odds, 95% confidence intervals included no effect. Arteriolosclerosis and infarcts showed no effect on Braak NFT stage in this univariate analysis.

3.4 | VCING Score and Dementia Risk

Distributions of VCING stage and of its component lesions in relation to dementia are shown in Figure 4. The relationship of VCING to dementia was investigated in univariate modelling and multivariately, adjusted for the risk from Braak stage and Thal phase (Table 3). For VCING, having ≥2 pathologies present more than doubled the odds of dementia (OR: 2.6, CI 1.0–6.9) suggesting that higher VCING scores increase dementia risk. This persisted when adjusted for ADNC (OR: 2.4); however, the lower CI for this was just below 1 (95% CI 0.9–7.1). For the component lesions of the VCING score, severe arteriolosclerosis independently predicted dementia (OR 3.7) but not moderate or mild disease. Leptomeningeal CAA and infarct did not independently predict dementia once ADNC burden was accounted for.

We assessed the relationship of VCING score to dementia risk factors (Table S3). Infarct was included as a dementia risk factor in the model and showed a very large increase in the OR for higher VCING burden, unsurprising given its inclusion in the VCING score. Men were at an increased risk for higher VCING score compared to women (OR: 1.5, 95% CI: 1.11–5.0). However, hypertension, diabetes, angina, heart attack and *APOE-ε4* showed no independent association with VCING in these univariate models.

3.5 | Effect of Changing How Infarcts Are Assessed for VCING

This analysis to date was based on infarct assessment in microscopical sections. Within the CFAS dataset, there is also a macroscopical assessment of infarcts >10 mm, by naked eye at the time of dissection. We therefore repeated the analysis and compared the VCING scores using the two infarct assessments. Only 45 of the donations had macroscopic infarct data and therefore we did not generally use this measure of infarcts for our analysis. Nevertheless, the VCING score using this measure of infarcts also showed a relationship to dementia. In a binary analysis of VCING, having more than one pathology gave an odds ratio of 3.43 (95% CI: 0.84–14.66) for dementia prediction in a univariate model. In a multivariate model, adjusted for Braak stage and Thal phase, having more than one pathology gave an odds ratio for dementia of 7.7 (95% CI: 1.29–74.06).

4 | Discussion

Unlike neurodegenerative pathologies, which progress in stereotypical hierarchies that lend themselves to clear staging schemes using standard immunohistochemical approaches [29–31], brain vascular disease is complex with different types and anatomical patterns of disease [11]. The VCING criteria, developed using an unbiased data-based method, were developed as the most parsimonious model predictive of dementia in the original study [20]. VCING has also been applied to assess vascular pathology in 185 brains derived from the Brains for Dementia Research programme and the University of Manchester Longitudinal Study of Cognition in Healthy Old Age [22] and in an archival brain cohort of 63 cognitively intact individuals across a wide age spectrum [21]. VCING has the advantage of simplicity and reproducibility but requires testing in a broader range of settings. We here present an assessment of the application of VCING criteria in an unselected late-life (65 years and above) population-derived cohort in which both cognitively intact donors and those with

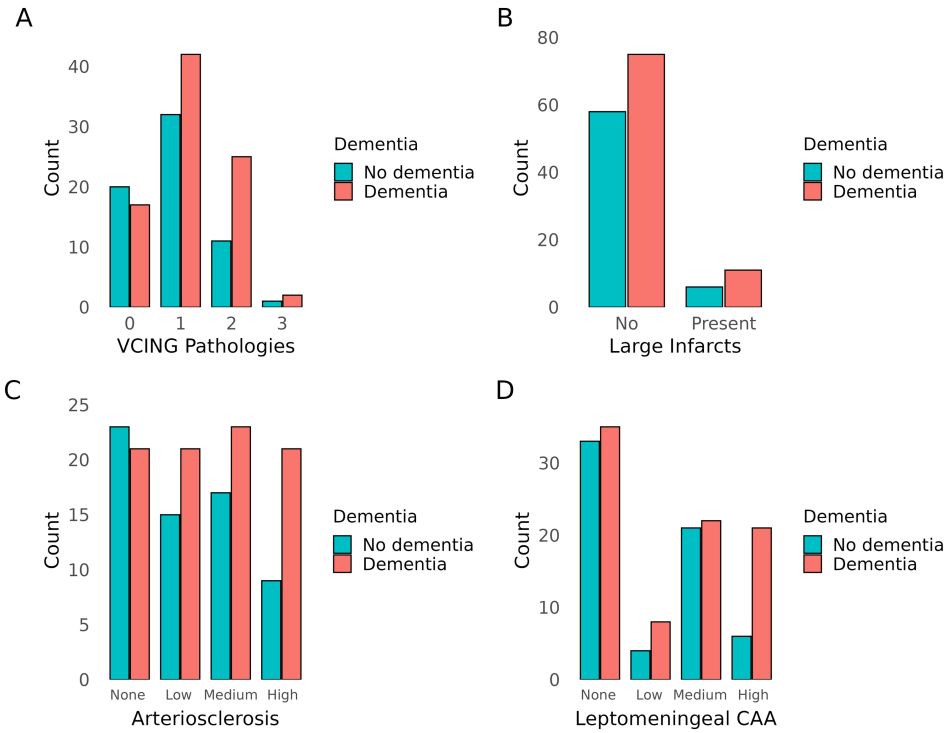

FIGURE 4 | Distributions of VCING and component pathology scores vs dementia status at death. VCING with ≥2 pathologies (A) OR 2.4 and severe arteriolosclerosis (C) OR 3.7 predicted dementia but not the presence of an infarct >1 cm (B) or leptomeningeal CAA (D). The *y*-axes show number of individuals. No dementia and dementia shown for each score level (*x*-axes) for respective pathologies.

TABLE 3 | Relationship of VCING to risk of dementia.

	Unadjusted		Adjusted	
Predictor	**OR**	**95% CI**	**OR**	**95% CI**
VCING no pathologies	1	.	1	.
VCING 1 pathology present	1.5	(0.7–3.4)	1.6	(0.6–3.8)
VCING 2+ pathologies present	2.6	(1.0–6.9)	2.4	(0.9–7.1)
Braak stage	.	.	3.2	(1.8–5.9)
Thal phase	.	.	1.1	(0.6–1.9)

Note: Modelled using logistic regression, univariate and multivariate (adjusted for Braak and Thal pathology). Results presented as odds ratios (OR) with 95% confidence intervals (95% CI).

dementia at death are represented, and where there is a mixture of pathologies typical of the ageing spectrum [23]. Given the important relationship of vascular disease to white matter pathology, we also looked at the relationship of VCING and its component scores to white matter pathology in the occipital region. Model outcomes from our statistical analyses are summarised in Table 4.

Our study has several limitations. It is based on a single cohort, CFAS, and ideally multiple cohorts should be investigated to determine the ranges of odds ratios for the dementia relationship. Although population-representative, there are limitations to the cohort related to its geography and ethnicity, which may impact vascular disease and risk factors. There is also a temporal effect such that later cohorts have different age-specific dementia prevalence rates, which could be due to changes in vascular disease [32, 33]. The study is limited to certain subcohorts of the CFAS study due to availability of some measures, thus reducing the study cohort size. The VCING analysis of CAA and arteriolosclerosis is limited to a single brain area, the occipital lobe, and so does not capture all of the potential vascular pathologies in a brain. Thus, although VCING may be valuable for large sample research studies, it is limited for the assessment of vascular pathology for diagnostic purposes in an individual, so that there is still a need to document all brain vascular pathologies for an individual case. Owing to the data available, our assessment of infarcts for this study was based on their detection in sections, which, although it may be proportional, is unlikely to detect all of the infarcts present. To address this, we carried out a sensitivity analysis by substituting data on infarcts from macroscopic analysis for the smaller number of donations for which this was available and found that this did not materially affect the relationship of VCING to dementia status.

The principal aim of this study was to determine whether VCING criteria retain their ability to predict dementia status in a general unselected late-life cohort that includes the range of both vascular and degenerative age-related pathologies. This was important to assess as the original study excluded cases with significant ADNC [20], thus potentially limiting general applicability particularly in community and population-based settings, where neurodegenerative and vascular pathologies commonly coexist to form the substrate for dementia [2, 5, 34–36]. In this context, we show that VCING retains an association with dementia risk at death, particularly when two or more of its constituent pathologies are present. However, it should be noted

TABLE 4 | Summary of model outcomes and predictors modelled.

	Predictors	
Outcome	**Associated**	**Not associated**
Perivascular space widening	*Arteriolosclerosis*	*Leptomeningeal CAA*
	VCING	*Large infarct*
White matter pallor	*Arteriolosclerosis*	*Leptomeningeal CAA*
	VCING	*Large infarct*
Venous collagenosis	*White matter pallor*	*Perivascular space widening*
	Arteriolosclerosis	*VCING*
	Large infarct	*Leptomeningeal CAA*
Thal phase	*VCING*	*Arteriosclerosis*
	Leptomeningeal CAA	*Large Infarct*
Braak stage	*Leptomeningeal CAA*	*VCING*
		Large infarct
		Arteriolosclerosis
Dementia	*VCING*	*Leptomeningeal CAA*
	Arteriolosclerosis	*Large infarct*
VCING	*Infarct*	*Hypertension*
	Age	*Diabetes*
	Male sex	*Angina*
		Heart attack
		APOE-ε4 carrier

Note: Associations divided by those with strong evidence of an association, based on point estimate and 95% confidence intervals, and those where no association was found.

that the confidence intervals for the odds ratio ranged from below 1 (in the adjusted), so that this relationship, although suggestive, is not proven in this cohort and greater power may be required. Nevertheless, the relationship to dementia was maintained in the smaller cohort where data on infarcts from macroscopic assessment was substituted. In a study of intermediate Braak NFT stage cases, VCING score did not differ between cognitively intact and impaired individuals, whereas CAA did [22], in contrast to our findings where arteriolosclerosis as well as VCING score, but not CAA showed a relationship to dementia. The robust significant link of severe arteriolosclerosis to dementia in our cohort suggests that this is a key measure to assess. An important question is how arteriolosclerosis varies between brain regions and whether occipital white matter arteriolosclerosis can be taken as a measure of general brain arteriolosclerosis, suggesting that its assessment in the occipital lobe may have value as a measure of global brain arteriolosclerotic disease in an individual case assessment. The third previous study using VCING assessment was limited to cognitively intact individuals [21]. Given the importance of being able to assess vascular pathology and the simplicity of use of VCING, assessment of the performance of this metric and of its composite parts to predict dementia in cohorts that reflect different patient and population groups is therefore warranted.

Given that VCING in our study showed a relationship to dementia, we further investigated whether VCING increased with dementia risk factors. As vascular dementia, cardiovascular disease and Alzheimer's disease share similar risk factors and some mechanisms [37–40], they might operate through either the infarct/arteriolosclerosis measures or through the CAA component given the latter's association with ADNC. We demonstrate an association with sex with an apparent protective effect of female sex, which may interact with dementia risk and cardiovascular risk factors in a complex way [41, 42]. A larger study, specifically powered, would be valuable to address the potential effect of sex. However, we did not demonstrate a relationship to other vascular risk factors, including possession of the *APOE* ε4 allele. The lack of a relationship in this study may reflect cohort size or the selectivity of the measures used in the VCING criteria.

In a late-life context, direct damage to small vessels is mainly due to either arteriolosclerosis or βA4-related CAA, with consequent tissue effects including lacunar infarcts, microinfarcts, cerebral microbleeds, perivascular space dilatation, perivascular rarefaction and white matter pallor forming the basis of in-life the basis of MRI assessment of SVD [19, 43]. We therefore examined the relationship of VCING and its criteria to local tissue damage effects in the occipital white matter. Arteriolosclerosis

in this cohort was the strongest driver of white matter pallor and perivascular space dilatation. VCING also predicted white matter pallor and PVS dilatation when two or more pathologies were present. We did not observe an effect of CAA on these measures, whereas CAA has been shown to be associated with white matter and PVS dilatation in other studies, and such an effect might be expected mechanistically through white matter ischaemia and impaired periarterial drainage [44, 45]. These relationships need clarification in pathological studies in different brain regions. Venous collagenosis of larger and smaller vessels was present at high frequency in our cohort and was associated with white matter pallor. This supports previous work showing that periventricular collagenosis is associated with white matter hyperintensities [46, 47]. This suggests that, in addition to arterial supply-side insufficiency [48], venous-side insufficiency and oedema are also important contributors to the pathogenesis of white matter damage.

VCING score showed an association with ADNC in regression modelling, particularly when two or more component pathologies were present. The association between VCING and ADNC *herein* appears mainly driven by the association between CAA and ADNC. Although CAA is a small vessel pathology, it is an Aβ-deposition disorder. Although in individual cases it may or may not be associated with parenchymal Alzheimer's lesions, in a population-cohort setting CAA is highly correlated with ADNC, and in particular other Aβ measures, such as Thal phase [26, 49]. This has implications for VCING as a relationship to dementia may be confounded by its association with ADNC in a setting where this is present and suggests a need for separate measures of vascular pathologies of arteriosclerotic versus CAA pathologies for mechanistic and therapeutic studies.

In conclusion, VCING is an easy-to-apply scheme that maintains its value as an assessment in a general population setting. We show that, in this context, it maintains a relationship to dementia and also to tissue effects of SVD. White matter arteriolosclerosis in particular has a more robust relationship to dementia in this setting. However, further correlative studies are needed to determine whether VCING is also a surrogate measure of subcortical vascular pathology and whether it has predictive value for subcortical clinical patterns of dementia that are an important outcome of vascular brain disease.

Author Contributions

Study conception and design: S.B.W. Neuropathological analysis and data collection: S.B.W. Design and conduct of statistical analysis: C.D.R. Writing first draft of paper: S.B.W. and C.D.R. Tissue archiving and preparation: S.U.A. and D.J.F. Project discussion and planning: All authors. Statistical oversight: F.E.M. Epidemiological interpretation: C.B. Development of final paper draft: All authors.

Acknowledgements

This study was support by a project grant from the British Heart Foundation (PG22/11008) and CFAS neuropathology cohort was supported by grants from the MRC (MRC/G9901400, U.1052.00.0013, G0900582). H.B. was/is supported by an Alzheimer's Society studentship. C.D.R. was/is the recipient of a postdoctoral fellowship from the National Institute for Health and Care Research (NIHR) Applied Research Collaboration Northeast and North Cumbria; this fellowship is part of an initiative funded by the NIHR and Alzheimer's Society to support postdoctoral capacity building in applied dementia research. The views expressed are those of the author(s) and not necessarily those of the Alzheimer's Society, NIHR or the Department of Health and Social Care. Work in the individual CFAS centres was supported by the UK NIHR Biomedical Research Centre for Ageing and Age—awarded to Newcastle upon Tyne Hospitals Foundation Trust; Cambridge Brain Bank supported by the NIHR Cambridge Biomedical Research Centre; Nottingham University Hospitals NHS Trust; University of Sheffield, Sheffield Teaching Hospitals NHS Foundation Trust and Sheffield NIHR Biomedical Research Centre; The Thomas Willis Oxford Brain Collection, supported by the Oxford Biomedical Research Centre; The Walton Centre NHS Foundation Trust, Liverpool. We would like to acknowledge the essential contribution of the liaison officers, the general practitioners, their staff and nursing and residential home staff. We are grateful to our respondents and their families for their generous gift to medical research, which has made this study possible.

Funding

This work was supported by the British Heart Foundation (PG22/11008), Medical Research Council (MRC/G9901400, U.1052.00.0013 and G0900582), Alzheimer's Society (AS-PhD-21-006) and National Institute for Health and Care Research.

Ethics Statement

Research ethics committee approval was granted for the study.

Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

References

1. C. Iadecola, M. Duering, V. Hachinski, et al., "Vascular Cognitive Impairment and Dementia: JACC Scientific Expert Panel," *Journal of the American College of Cardiology* 73 (2019): 3326–3344.

2. F. Matthews, C. Brayne, J. Lowe, I. McKeith, S. Wharton, and P. Ince, "Epidemiological Pathology of Dementia: Attributable-Risks at Death in the MRC Cognitive Function and Ageing Study," *PLoS Medicine* 6 (2009): e1000180, https://doi.org/10.1371/journal.pmed.

3. MRC-CFAS, "Pathological Correlates of Late-Onset Dementia in a Multicentre, Community-Based Population in England and Wales," *Lancet* 357 (2001): 169–175.

4. A. Kapasi, C. De Carli, and J. Schneider, "Impact of Multiple Pathologies on the Threshold for Clinically Overt Dementia," *Acta Neuropathologica* 134 (2017): 171–186.

5. L. R. White, S. D. Edland, L. S. Hemmy, et al., "Neuropathologic Comorbidity and Cognitive Impairment in the Nun and Honolulu-Asia Aging Studies," *Neurology* 86 (2016): 1000–1008.

6. J. Robinson, M. Corrada, G. Kovacs, et al., "Non-Alzheimer's Contributions to Dementia and Cognitive Resilience in the 90+ Study," *Acta Neuropathologica* 136 (2018): 377–388.

7. J. Rahimi and G. Kovacs, "Prevalence of Mixed Pathologies in the Aging Brain," *Alzheimer's Research & Therapy* 6 (2014): 82.

8. L. R. White, M. M. Corrada, C. H. Kawas, et al., "Neuropathologic Changes of Alzheimer's Disease and Related Dementias: Relevance to Future Prevention," *Journal of Alzheimer's Disease* 95 (2023): 307–316.

9. F. Grodstein, S. E. Leurgans, A. W. Capuano, J. A. Schneider, and D. A. Bennett, "Trends in Postmortem Neurodegenerative and Cerebrovascular Neuropathologies Over 25 Years," *JAMA Neurology* 80 (2023): 370–376.

10. E. Nichols, R. Merrick, S. I. Hay, et al., "The Prevalence, Correlation, and Co-Occurrence of Neuropathology in Old Age: Harmonisation of 12 Measures Across Six Community-Based Autopsy Studies of Dementia," *Lancet Healthy Longevity* 4 (2023): e115–e125.

11. R. Kalaria, "Neuropathological Diagnosis of Vascular Cognitive Impairment and Vascular Dementia With Implications for Alzheimer's Disease," *Acta Neuropathologica* 131 (2016): 659–685.

12. A. Chen, R. Akinyemi, Y. Hase, et al., "Frontal White Matter Hyperintensities, Clasmatodendrosis and Gliovascular Abnormalities in Ageing and Post-Stroke Dementa," *Brain* 139 (2016): 242–258.

13. Y. Inoue, F. Shue, G. Bu, and T. Kanekiyo, "Pathophysiology and Probable Etiology of Cerebral Small Vessel Disease in Vascular Dementia and Alzheimer's Disease," *Molecular Neurodegeneration* 18 (2023): 46.

14. A. H. Hainsworth, H. S. Markus, and J. A. Schneider, "Cerebral Small Vessel Disease, Hypertension, and Vascular Contributions to Cognitive Impairment and Dementia," *Hypertension* 81 (2024): 75–86.

15. K. McAleese, I. Alafuzoff, A. Charidimou, et al., "Post-Mortem Assessment in Vascular Dementia: Advances and Aspirations," *BMC Medicine* 14 (2016): 129.

16. I. Alafuzoff, E. Gelpi, S. Al-Saraj, et al., "The Need to Unify Neuropathological Assessments of Vascular Alterations in the Ageing Brain Multicentre survey by the BrainNet Europe consortium," *Experimental Gerontology* 47 (2012): 825–833.

17. V. Deramecourt, J. Slade, A. Oakley, et al., "Staging and Natural History of Cerebrovascular Pathology in Dementia," *Neurology* 78 (2012): 1043–1050.

18. K. McAleese, M. Firbank, D. Hunter, et al., "Magnetic Resonance Imaging of Fixed Post Mortem Brains Reliably Reflects Subcortical Vascular Pathology of Frontal, Parietal and Occipital White Matter," *Neuropathology and Applied Neurobiology* 39 (2013): 485–497.

19. J. M. Wardlaw, C. Smith, and M. Dichgans, "Small Vessel Disease: Mechanisms and Clinical Implications," *Lancet Neurology* 18 (2019): 684–696.

20. O. Skrobot, J. Attems, M. Esiri, et al., "Vascular Cognitive Impairment Neuropathology Neuropathology Guidelines (VCING): The Contribution of Cerebrovascular Pathology to Cognitive Impairment," *Brain* 139 (2016): 2957–2969.

21. C. Dallaire-Theroux, S. Saikali, M. Richer, O. Potvin, and S. Duchesne, "Histopathological Analysis of Cerebrovascular Lesions Associated With Aging," *Journal of Neuropathology and Experimental Neurology* 81 (2022): 97–105.

22. A. C. Robinson, F. Roncaroli, S. Chew-Graham, et al., "The Contribution of Vascular Pathology Toward Cognitive Impairment in Older Individuals With Intermediate Braak Stage Tau Pathology," *Journal of Alzheimer's Disease* 77 (2020): 1005–1015.

23. S. B. Wharton, J. E. Simpson, P. G. Ince, et al., "Insights Into the Pathological Basis of Dementia From Population Based Neuropathology Studies," *Neuropathology and Applied Neurobiology* 49 (2023): e12923.

24. MRC-CFAS, "Cognitive Function and Dementia in Six Areas of England and Wales: The Distribution of MMSE and Prevalence of GMS Orgnanicity Level in the MRC CFA Study," *Psychological Medicine* 28 (1998): 319–335.

25. S. Wharton, T. Minett, D. Drew, et al., "Epidemiological Pathology of Tau in the Ageing Brain: Application of Staging for Neuropil Threads (BrainNet Europe Protocol) to the MRC Cognitive Function and Ageing Brain Study," *Acta Neuropathologica Communications* 4 (2016): 11.

26. S. Wharton, D. Wang, C. Parikh, F. Matthews, C. Brayne, and P. Ince, "Epidemiological Pathology of Aβ Deposition in the Ageing Brain in CFAS: Addition of Multiple Aβ-Derived Measures Does not Improve Dementia Assessment Using Logistic Regression and Machine Learning Approaches," *Acta Neuropathologica Communications* 7 (2019): 198.

27. S. Love, K. Chalmers, P. Ince, et al., "Development, Appraisal, Validation And Implementation of a Consensus Protocol for the Assessment of Cerebral Amyloid Angiopathy in Post-Mortem Brain Tissue," *American Journal of Neurodegenerative Disease* 3 (2014): 19–32.

28. P. Ince, T. Minett, G. Forster, C. Brayne, and S. Wharton, "Microinfarcts in an Older Population-Representative Brain Donor Cohort (MRC-CFAS): Prevalence, Relation to Dementia and Mobility, and Implications for the Evaluation of Cerebral Small Vessel Disease," *Neuropathology and Applied Neurobiology* 43 (2017): 409–418.

29. H. Braak, I. Alafuzoff, T. Arzberger, H. Kretaschmar, and K. del Tredici, "Staging of Alzheimer Disease-Associated Neurofibrillary Pathology Using Paraffin Sections and Immunocytochemistry," *Acta Neuropathologica* 112 (2006): 389–404.

30. H. Braak, K. Del Tredici, U. Rub, R. de Vos, E. Jansen-Steur, and E. Braak, "Staging of Brain Pathology Related to Sporadic Parkinson's Disease," *Neurobiology of Aging* 24 (2003): 197–211.

31. D. Thal, U. Rub, M. Orantes, and H. Braak, "Phases of Aβ-Deposition in the Human Brain and Its Relevance for the Development of AD," *Neurology* 58 (2002): 1791–1800.

32. F. Matthews, A. Arthur, L. Barnes, et al., "A Two-Decade Comparison of Prevalence of Dementia in Individuals Aged 65 Years and Older From Three Geographical Areas of England: Results of the Cognitive Function and Ageing Study I and II," *Lancet* 382 (2013): 1405–1412.

33. F. Matthews, B. Stephan, L. Robinson, et al., "A Two Decade Dementia Incidence Comparison From the Cognitive Function and Ageing Studies I and II," *Nature Communications* 7 (2016): 11398.

34. J. A. Sonnen, E. B. Larson, S. Haneuse, et al., "Neuropathology in the Adult Changes in Thought Study: A Review," *Journal of Alzheimer's Disease* 18 (2009): 703–711.

35. D. A. Bennett, A. S. Buchman, P. A. Boyle, L. L. Barnes, R. S. Wilson, and J. A. Schneider, "Religious Orders Study and Rush Memory and Aging Project," *Journal of Alzheimer's Disease* 64 (2018): S161–S189.

36. M. Tanskanen, M. Makela, I. L. Notkola, et al., "Population-Based Analysis of Pathological Correlates of Dementia in the Oldest Old," *Annals of Clinical Translational Neurology* 4 (2017): 154–165.

37. A. Nelson, M. Sweeney, A. Sagare, and B. Zlokovic, "Neurovascular Dysfunction and Neurodegeneration in Dementia and Alzheimer's Disease," *Biochimica et Biophysica Acta* 1862 (2016): 887–900.

38. A. Kapasi and J. Schneider, "Vascular Contributions to Cognitive Impairment, Clinical Alzheimer's Disease, and Dementia in Older Persons," *Biochimica et Biophysica Acta* 1862 (2016): 878–886.

39. C. Iadecola, "Vascular and Metabolic Factors in Alzheimer's Diseases and Related Dementias: Introduction," *Cellular and Molecular Neurobiology* 36 (2016): 151–154.

40. A. Toyli, A. Shaik, C. Zhao, Q. H. Chen, Q. Sha, and W. Zhou, "The Heart-Brain Axis: Unraveling the Interconnections Between Cardiovascular and Alzheimer's Diseases," *Frontiers in Cardiovascular Medicine* 12 (2025): 1685461.

41. F. Akhter, A. Persaud, Y. Zaokari, Z. Zhao, and D. Zhu, "Vascular Dementia and Underlying Sex Differences," *Frontiers in Aging Neuroscience* 13 (2021): 720715.

42. A. M. Wood, J. Paterson, Z. Arvanitakis, et al., "Cardiovascular Contributions to Dementia: Examining Sex Differences and Female-Specific Factors," *Alzheimer's & Dementia: The Journal of the Alzheimer's Association* 21 (2025): e70610.

43. H. S. Markus and F. E. de Leeuw, "Cerebral Small Vessel Disease: Recent Advances and Future Directions," *International Journal of Stroke* 18 (2023): 4–14.

44. V. Perosa, J. Oltmer, L. Munting, et al., "Perivascular Space Dilation is Associated With Vascular Amyloid-β Accumulation in the Overlying Cortex," *Acta Neuropathologica* 143 (2022): 331–348.

45. R. O. Weller, C. A. Hawkes, R. N. Kalaria, D. J. Werring, and R. O. Carare, "White Matter Changes in Dementia: Role of Impaired Drainage of Interstitial Fluid," *Brain Pathology* 25 (2015): 63–78.

46. S. Black, F. Gao, and J. Bilbao, "Understanding White Matter Disease. Imaging-Pathological Correlations in Vascular Cognitive Impairment," *Stroke* 40, no. suppl (2009): S48–S52.

47. J. Keith, F. Gao, R. Noor, et al., "Collagenosis of the Deep Medullary Veins: An Underrecognized Pathologic Correlate of White Matter Hyperintensities and Periventricular Infarction?," *Journal of Neuropathology and Experimental Neurology* 76 (2017): 299–312.

48. M. Fernando, J. Simpson, F. Matthews, et al., "White Matter Lesions in an Unselected Cohort of the Elderly: Molecular Pathology Suggests Origin From Chronic Hypoperfusion Injury," *Stroke* 37 (2006): 1391–1398.

49. M. D. Rajab, E. Jammeh, T. Taketa, et al., "Assessment of Alzheimer-Related Pathologies of Dementia Using Machine Learning Feature Selection," *Alzheimer's Research & Therapy* 15 (2023): 47.

Supporting Information

Additional supporting information can be found online in the Supporting Information section. **Table S1:** Descriptive statistics for demographic and pathological variables used in the analysis. **Table S2:** Associations between VCING score and white matter pathologies, *p*-values determined using chi-square tests. **Table S3:** Relationship of VCING score to dementia risk factors. Categorical outcomes modelled using ordinal regression, binary outcomes modelled using logistic regression. Results presented as odds ratios (OR) of having higher VCING score with 95% confidence intervals (95% CI). **Figure S1:** Distribution of scores for VCING criteria (A) and for individual VCING pathologies (C–E). Comparison of distributions of VCING scores between the two CFAS centres is also shown (B). The *y*-axes show number of individuals and *x*-axes the score categories. **Figure S2:** Distributions of scores of the additional occipital white matter pathologies. The *y*-axes show number of individuals, *x*-axes the score categories.