

Perivascular spaces reflect neuropathological severity of Cerebral Amyloid Angiopathy in Alzheimer's disease



Mario Ricciardi Serra^{1,2}, Iván Burgueño-García¹, Elizabeth Valeriano-Lorenzo^{1,2}, María Ascensión Zea-Sevilla¹, Meritxell Valentí¹, Belén Frades¹, Isabel López Torres¹, Marta Anton¹, Francisco López-González¹, Paloma Ruiz¹, Laura Saiz¹, Alicia Uceda¹, Linda Zhang¹, Eva Alfayate Sáez¹, Marta Molero Cartón¹, María José López-Martínez¹, Michel Grothe¹, Alberto Rábano¹, Teodoro Del Ser¹, Pascual Sánchez-Juan¹.

1. Reina Sofía Alzheimer Center, **CIEN Foundation**, ISC III, Madrid, Spain. **2.** PhD programme in Medicine, **Universidad Autónoma de Madrid**, Madrid, Spain.

Enlarged perivascular spaces in the centrum semiovale (CSO-EPVS) burden is an independent MRI biomarker of neuropathological cerebral amyloid angiopathy (CAA) severity in Alzheimer's disease (AD), even in the absence of hemorrhagic MRI markers of CAA.

INTRODUCTIONMETHODSRESULTSCONCLUSIONSREFERENCES

Hemorrhagic lesions associated with **CAA** represent late manifestations of vascular damage. However, reliable **biomarkers for identifying CAA at earlier stages are still lacking**.

CSO-EPVS have emerged as an MRI marker associated with CAA and may reflect vascular alterations that precede and persist throughout the development of hemorrhagic lesions or occur in non-hemorrhagic forms of CAA.

Nevertheless, clinicopathological evidence directly linking CSO-EPVS burden on MRI with the neuropathological burden of CAA in **AD** remains limited.

We investigated whether CSO-EPVS burden on MRI is associated with the neuropathological burden of CAA in individuals with AD, whether this association is independent of AD neuropathological burden. In addition, we explored the influence of APOE $\epsilon 4$.

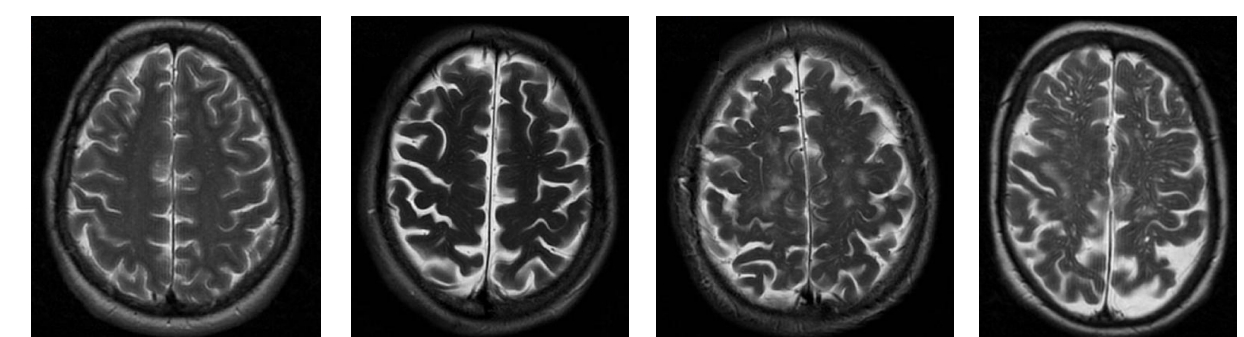


Figure 1. Representative MRI examples of CSO-EPVS burden according to the Potter scale.

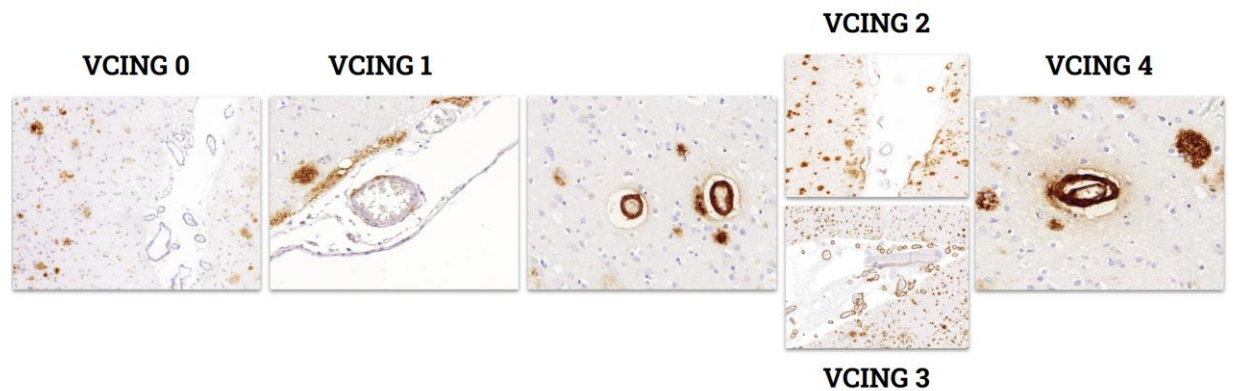
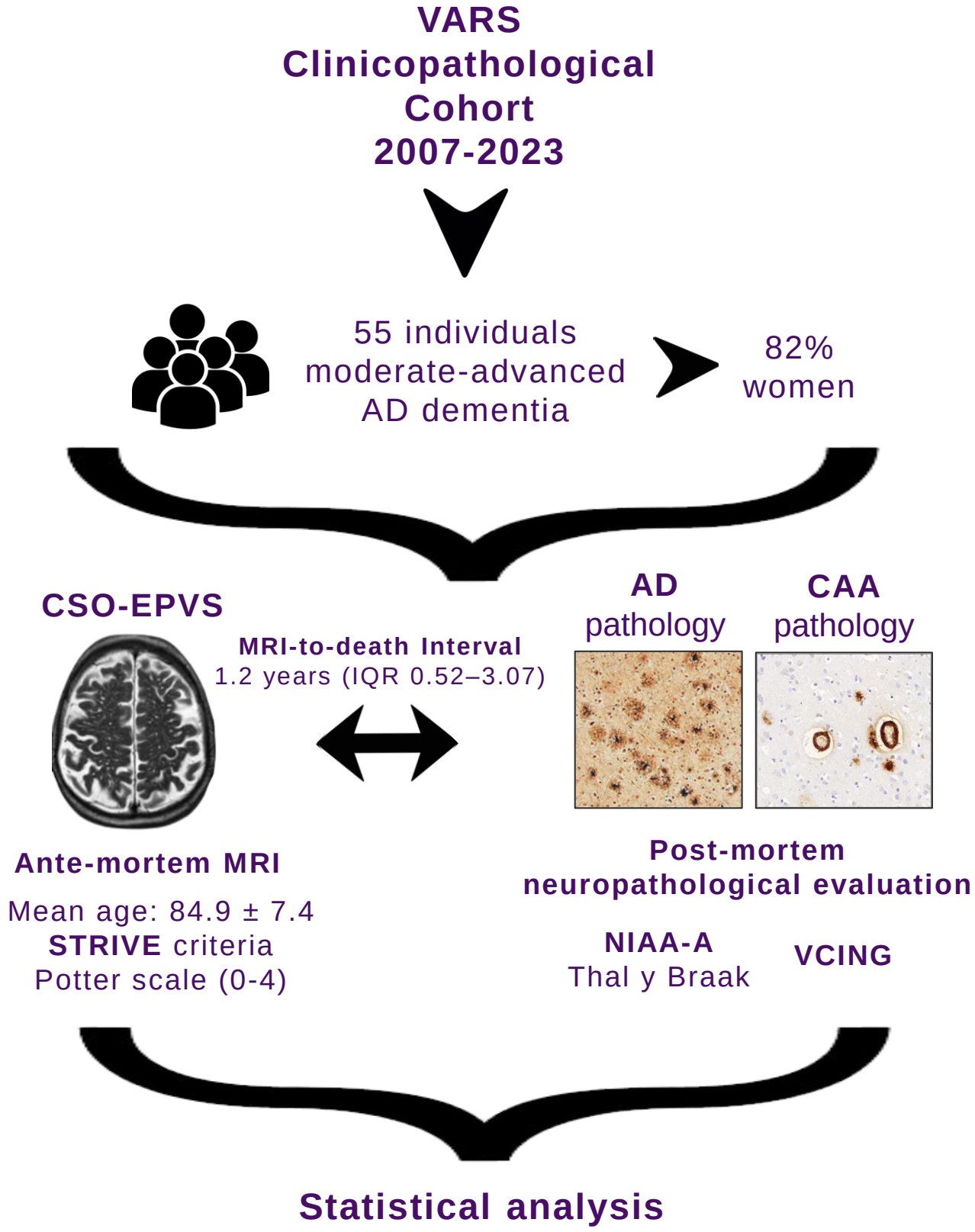


Figure 2. Neuropathological assessment of CAA according to VCING score



Partial Spearman correlations
Ordinal logistic regression

Adjusted for:

- Age at MRI
- MRI-to-death interval
- Thal stage
- Braak stage

Exploratory analyses:

- APOE $\epsilon 4$ allele burden.

Additional analyses:

- Sensitivity analysis: MRI ≤ 2 years (n = 33).
- Subanalysis: MRI without hemorrhagic lesions.

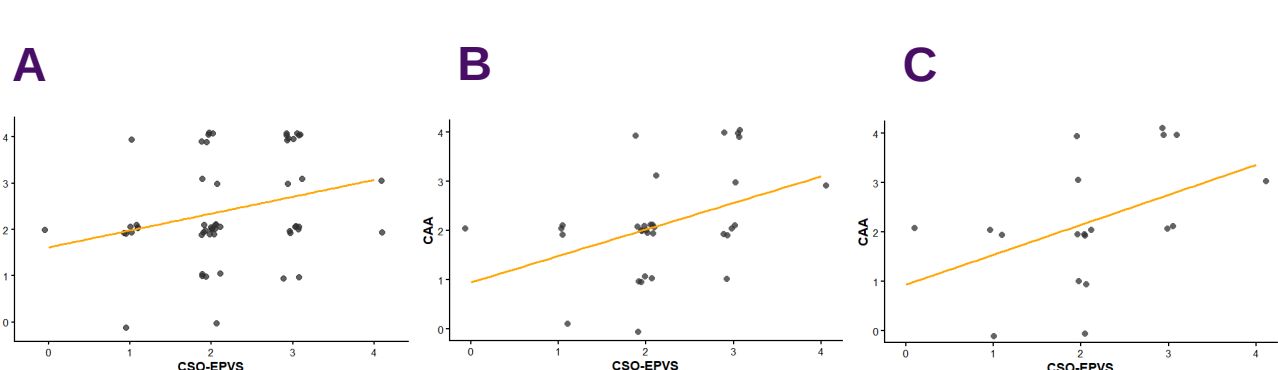


Figure 3. CSO-EPVS burden is associated with neuropathological CAA severity. Each point represents one participant. Solid lines illustrate the overall positive trend. **A)** Overall cohort (N=55). **B)** Subgroup with MRI ≤ 2 years before death (N=33). **C)** Subgroup without hemorrhagic MRI markers (N=19).

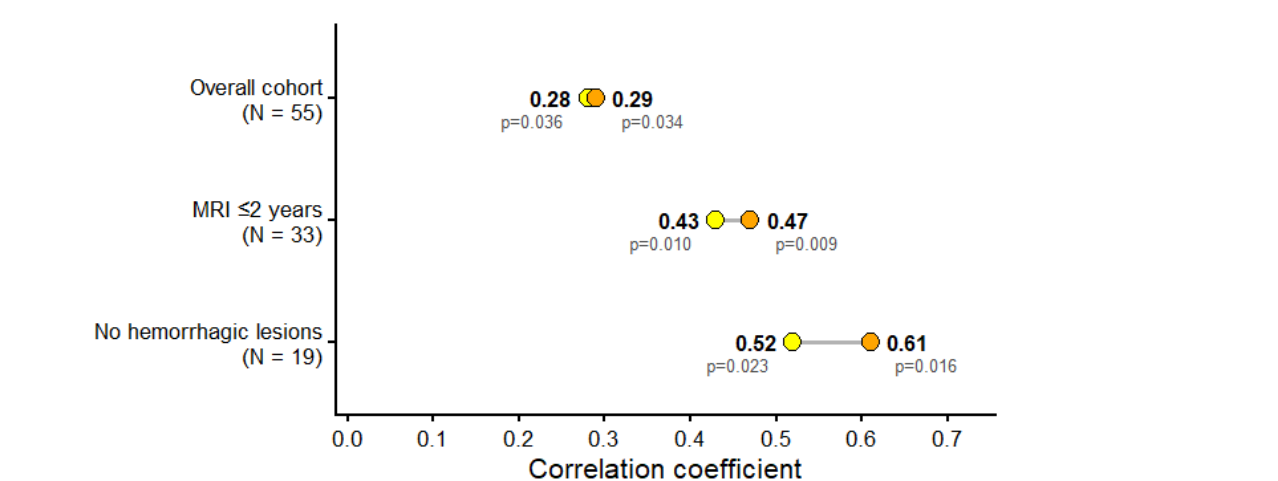


Figure 4. Spearman and partial correlation coefficients across the overall cohort and sensitivity analyses.

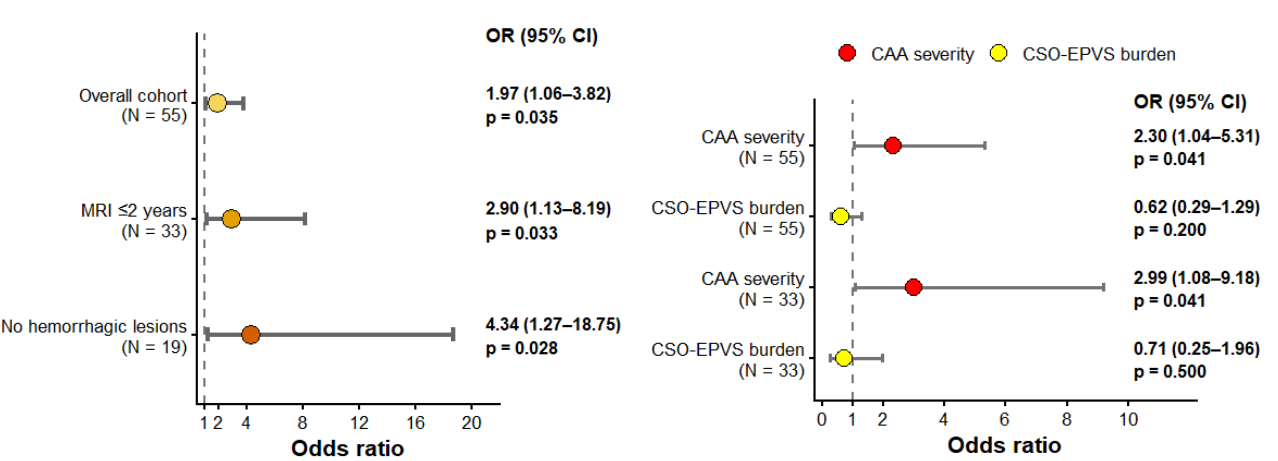


Figure 5. Ordinal logistic regression across the overall cohort and sensitivity analyses. Consistent association between CSO-EPVS burden and neuropathological CAA severity.

CSO-EPVS burden is independently associated with the neuropathological severity of **CAA** in **AD**.

This association remains significant after adjustment for age, MRI-to-death interval, and AD neuropathological burden, and becomes stronger when MRI and neuropathological assessment are temporally closer.

The association persists in patients without hemorrhagic lesions, suggesting that CSO-EPVS reflect underlying CAA pathology beyond hemorrhagic manifestations.

These findings support **CSO-EPVS** as a **MRI biomarker of CAA** in **AD** **in vivo**, particularly in non-hemorrhagic forms or at earlier stages of CAA.

Future studies should evaluate its potential role in clinical decision-making and in identifying patients at increased risk of ARIA before anti-amyloid therapies.

Exploratory analyses showed that APOE $\epsilon 4$ is associated with greater neuropathological CAA severity but not with CSO-EPVS burden.

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CONTACT



CIEN Foundation
C. de Valderrebollo, 5
Vallecas, 28031 Madrid, Spain
Mario Ricciardi Serra
mricciardi@fundacioncien.es

