

# Associations Of Regional White Matter Hyperintensities With Cognitive Impairment Onset And Decline In Alzheimer's Disease



Anthony S Gabay, Graeme McKinnley, Barbara Brito Vega, Robin Wolz, Richard Joules

P3-07

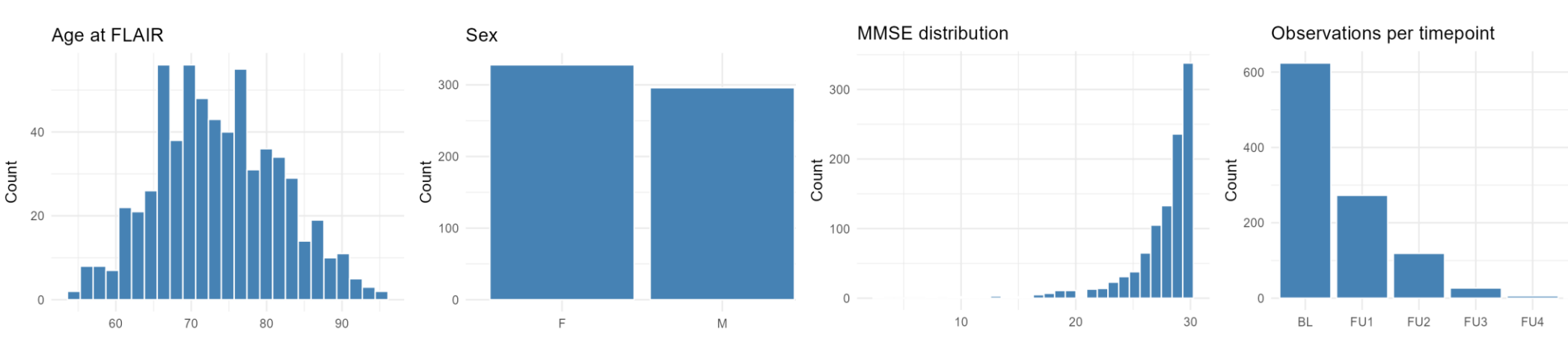
## SUMMARY

- Higher WMH burden accelerates the transition out of intact cognition (reduction from MMSE=30), but not the rate of decline once impairment is established
- Cross-sectional association of WMH with worse cognition is amyloid-dependent, and concentrated in amyloid-negative individuals
- In amyloid-positive individuals, lesion confluence, not total volume, tracks faster decline, underscoring that WMH is heterogeneous and that a single volume measure can be misleading

White-matter hyperintensities (WMH) are common in ageing and are linked to cognitive impairment<sup>1</sup>. Severe WMH is among the MRI exclusion criteria in anti-amyloid trials on ARIA-risk grounds<sup>2</sup>. The relationship between WMH and cognition in ageing and AD is heterogeneous, and there is limited data on their joint dependence on amyloid status and lesion morphology<sup>3</sup>

We characterise how WMHs relate to cross-sectional and longitudinal cognitive measures in a sample of ADNI participants, with particular focus on amyloid status and lesion morphology.

**Cohort:** 624 ADNI participants (mean age 73.6 (SD 8.1), 52.6% F, 1,051 scans, 273 with ≥2 visits); 510 with amyloid status, of which 264 had ≥2 visits (105 amyloid+, 159 amyloid-)



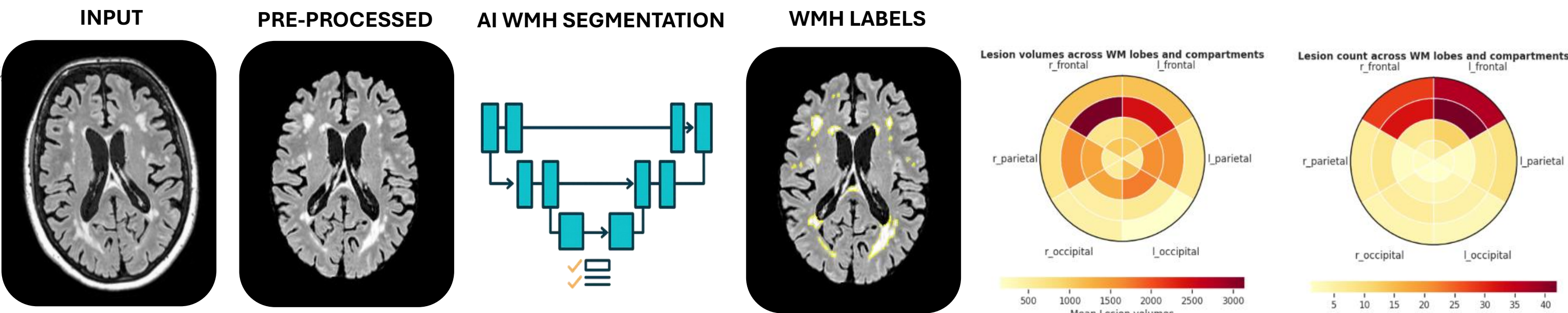
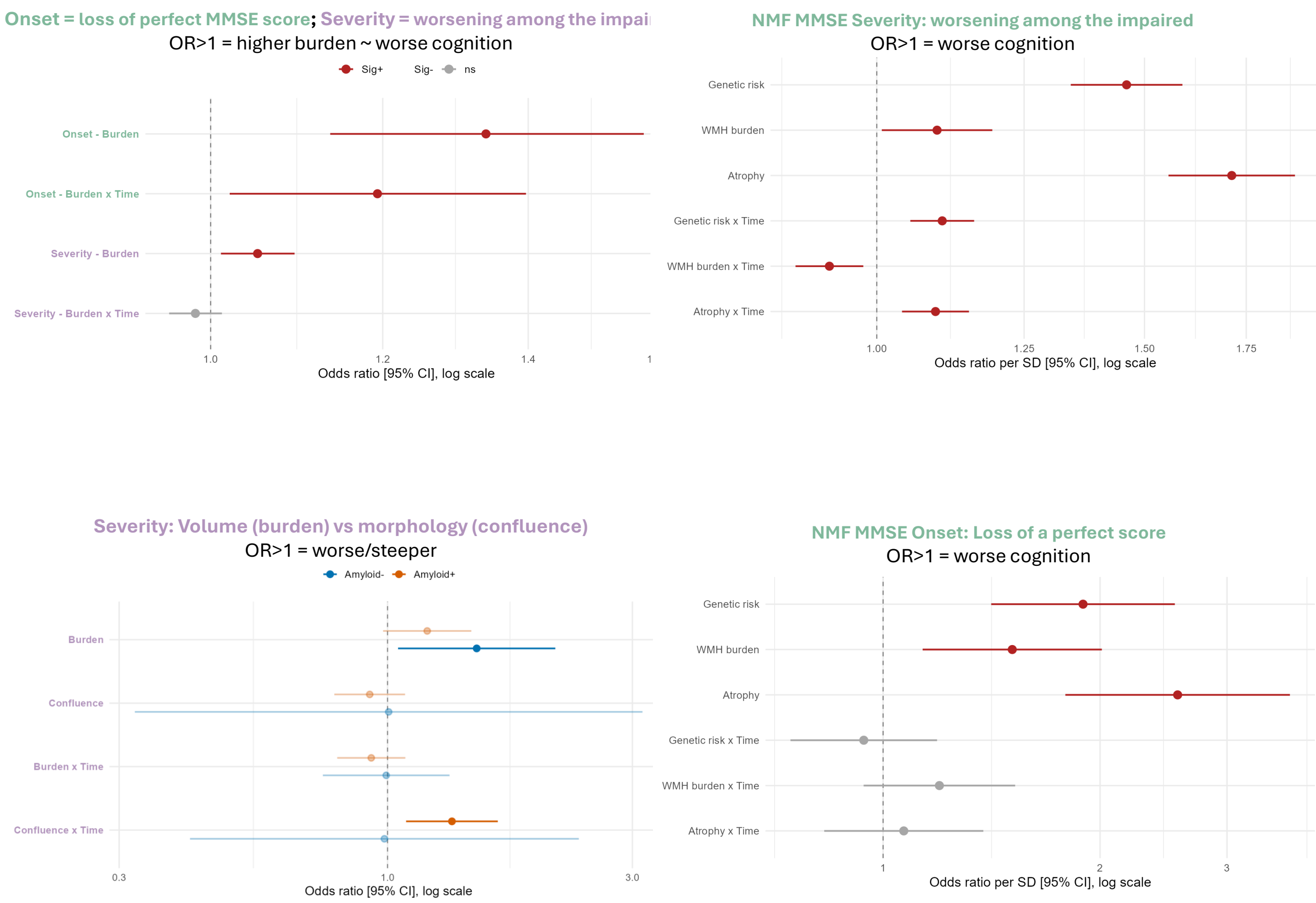
FLAIR images were processed with an in-house deep-learning WMH segmentation tool reporting DICE = 0.65 (±0.17) wrt to a mean manual rating and R<sup>2</sup>=0.96 for estimated volumes. Segmentations were used to derive regional **WMH burden** (per-compartment %WM across 10 partially overlapping regions) and **lesion confluence** (volume ÷ count = mean lesion size) measures

Across all subjects, WMH burden predicts both the probability of being cognitively impaired and the severity of impairment. Additionally, it appears to accelerate the first departure from intact cognition (onset interaction term)

Splitting by amyloid status and including lesion confluence in the model suggests that the effect of burden is restricted to Amyloid -ve individuals, and for the Amyloid +ve, confluence accelerates cognitive decline where burden does not

Non-negative matrix factorization (NMF) decomposed 16 baseline markers (regional WMH burden, lesion confluence, amyloid, hippocampal atrophy, APOE ε4; n = 487) into three pathology profiles (genetic risk, WMH burden, atrophy), with confluence spread across burden and atrophy profiles, and amyloid across genetic risk and atrophy.

Cross-sectionally, all three profiles were associated with worse MMSE — greater pathology of any kind (genetic/amyloid risk, WMH burden, or atrophy) accompanied lower scores. Longitudinally the picture separated: only the two Alzheimer's profiles (genetic risk and atrophy) predicted faster subsequent decline, whereas the WMH-burden profile — associated with worse cognition at baseline — did not accelerate it. In short, all three pathologies mark who is currently impaired, but only Alzheimer's pathology forecasts who declines fastest.



WMH segmentation pipeline with example bullseye plot displaying subject-specific lesion distributions

Cross-sectional and longitudinal associations between WMHs and cognition (MMSE) were assessed with a mixed-effect zero-inflated regression (zero-inflation ["onset"] = probability of a perfect score; conditional ["severity"] = worsening among already impaired)

All models included covariates for hippocampal volume, age and sex, with a participant-level random intercept

<sup>1</sup>Debette S, Markus HS. BMJ. 2010;341:c3666; <sup>2</sup>Cummings J et al J Prev Alzheimers Dis 2023 ; <sup>3</sup>Lam S et al. J Am Geriatr Soc. 2021;69(7):1906–1915.