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Letter to the Editor

# Beyond MRI associations: refining clinical interpretation in anti-amyloid therapy

To the Editor,

We read with interest Kujuro et al.'s real-world study linking pretreatment medial temporal atrophy to functional deterioration during lecanemab therapy and baseline cerebral microbleeds to amyloid-related imaging abnormalities with hemorrhage (ARIA-H) [1]. By examining routinely acquired magnetic resonance imaging (MRI), the authors address an important challenge in personalizing anti-amyloid therapy. While the meticulous work and significant contributions of this study are highly commended, we also offer some constructive suggestions for future developments.

First, the claim that MRI offers prognostic information beyond amyloid positron emission tomography (PET) should distinguish association from incremental prediction. Baseline atrophy correlated with 12-month change in Clinical Dementia Rating–Sum of Boxes ($r = 0.39$; $n = 40$), while the corresponding PET correlation was not significant ($r = 0.29$; $n = 19$). Statistical significance in one analysis but not another does not establish a difference between markers, especially across unequal samples. Moreover, adjustment for age, sex, and baseline function does not establish independence from amyloid burden. A common-sample model including both markers, with assessment of incremental predictive performance, would better support the proposed complementary role of MRI [2].

Second, interpretation of the cognitive-domain findings may be complicated by part–whole coupling. The authors adjusted individual Mini-Mental State Examination (MMSE) domains for MMSE total score, which already contains the domain being modeled. At a fixed total, poorer recall necessarily entails better performance elsewhere in aggregate. This constraint could accentuate apparent domain contrasts, particularly the counterintuitive positive association between atrophy and serial-sevens performance (adjusted $\beta = +0.43$; $P = .003$). This association might indicate relative preservation within an impaired cognitive profile, rather than a specific advantage in calculation. Analyses using an independent global cognition measure, or a total excluding the tested domain, would help clarify the interpretation [3].

Third, the pooled association between baseline microbleeds and ARIA-H (odds ratio, 14.0) may conceal clinically relevant variation in ascertainment. Among lecanemab recipients, ARIA-H occurred in 4 of 12 patients with microbleeds versus 1 of 77 without, compared with 2 of 13 versus 2 of 59 among donanemab recipients. Although directionally consistent, these contrasts arose under different MRI surveillance schedules, follow-up durations, and donanemab dose-titration regimens. For events detected exclusively through scheduled imaging, the opportunity for detection is integral to the observed risk. Harmonizing surveillance windows and accounting for scan timing and treatment exposure would clarify whether a single pooled estimate appropriately characterizes both treatment pathways.

We commend Kujuro and colleagues for their valuable contribution to understanding the prognostic and safety implications of routinely available MRI markers during anti-amyloid therapy. Together, these considerations offer ways to distinguish genuine prognostic information from analytical and observation-dependent effects.

## Declaration of the use of generative AI and AI-assisted technologies in scientific writing and in figures, images and artwork

The author declares that no generative AI or AI-assisted technologies were used in the preparation of the original manuscript. The manuscript contains no figures, images or artwork.

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## Declaration of competing interest

None of the authors has any conflicts of interest.

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## References

[1] Kujuro Y, Saito M, Maruko M, et al. Baseline MRI markers and clinical outcomes during anti-amyloid β therapy: a real-world study in a Japanese dementia center. J Prev Alzheimers Dis 2026;13(10):100686.

[2] Kim DH, Oh M, Kim JS. Prediction of conversion from mild cognitive impairment to Alzheimer's disease using amyloid PET and Brain MR imaging data: a 48-month follow-up analysis of the Alzheimer's Disease neuroimaging Initiative cohort. Diagnostics (Basel) 2023;13(21).

[3] Blance A, Tu YK, Gilthorpe MS. A multilevel modelling solution to mathematical coupling. Stat Methods Med Res 2005;14(6):553–65.

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