

APOE genotype and baseline cerebral microbleed burden as determinants of microbleed accrual in older adults

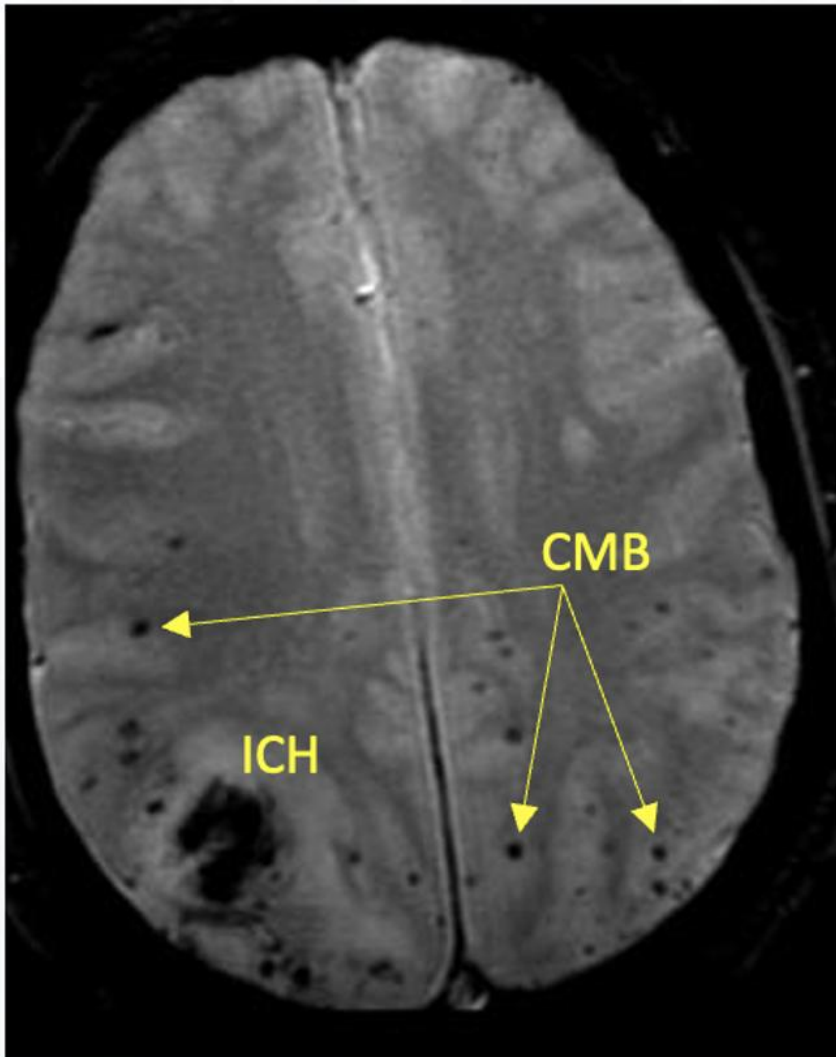
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Background

- Cerebral microbleeds (**Figure 1**) occur in the natural history of Alzheimer’s disease (AD),¹ and are a recognised risk factor for stroke and amyloid-related imaging abnormalities in individuals receiving anti-amyloid monoclonal antibodies for AD.²
- Understanding what drives microbleed progression can inform clinical trial design and treatment strategies.
- Previous research has suggested that *APOE* $\epsilon 4$ allele is associated with increased A β deposition, which may lead to formation and progression of white matter hypersensitivities and long-term detrimental effects in cerebral small-vessel disease.³
- This study investigated the impact of *APOE* genotype, baseline microbleed count, cerebral amyloid level (centiloid) and Clinical Dementia Rating Scale sum of boxes (CDR-SB) on microbleed progression in older adults.

Figure 1. Example of a cerebral microbleed



CMB, cerebral microbleed (in the lobar); ICH, intracerebral hematoma.

Methods

- Longitudinal data from 742 individuals in the Alzheimer’s Disease Neuroimaging Initiative (ADNI) were analysed and categorised by *APOE* genotype:
 - $\epsilon 3/\epsilon 3$ (n=354).
 - $\epsilon 3/\epsilon 4$ (n=290).
 - $\epsilon 4/\epsilon 4$ (n=98).
- APOE* $\epsilon 2$ individuals were excluded due to the small sample size.
- Microbleeds were counted (based on ADNI counts) from T2* gradient-recalled echo magnetic resonance imaging by expert neuroradiologists.
- Mixed-effects linear regression was used to model microbleed progression, with genotype, age, sex, baseline microbleed count, baseline centiloids and CDR-SB as predictors.
- A multivariate model was used to evaluate the joint effects of these predictors.
- Random intercepts and slopes for time were used to account for repeated measures and individual variation.

Results

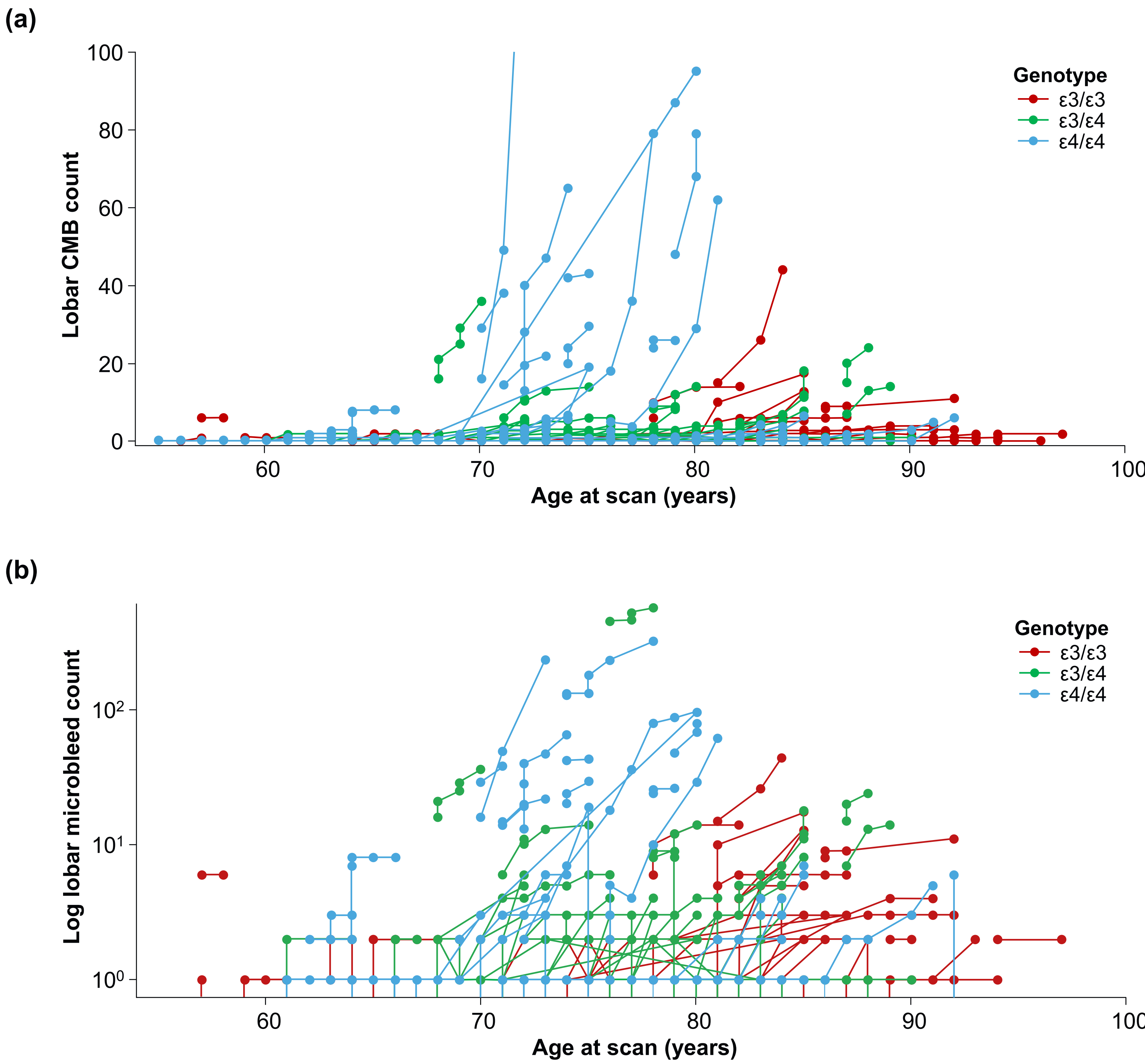
- Across 742 participants (**Table 1**), baseline microbleed count strongly predicted progression ($\beta=0.063$, 95% CI: 0.058–0.069; $P<0.001$).
- APOE* $\epsilon 4/\epsilon 4$ individuals tended to develop microbleeds at younger ages (**Figure 2**).
- APOE* $\epsilon 4/\epsilon 4$ individuals had a faster rate of microbleed accrual over time compared with both *APOE* $\epsilon 3/\epsilon 3$ and $\epsilon 3/\epsilon 4$ individuals ($\beta=0.222$, 95% CI: 0.107–0.338; $P<0.001$).
- Age, sex, baseline centiloids and CDR-SB were not significant predictors of microbleeds.

Table 1. Summary statistics and demographic information on the study participants

<i>APOE</i> genotype	Mean age, years (SD)	Sex, %	Mean baseline centiloid (SD)	Mean baseline CDR-SB (SD)	Mean baseline microbleed count (SD)	Annualised microbleed accrual mean (SD)	Mean duration of follow-up, months (SD)
$\epsilon 3/\epsilon 3$ (n=354)	74.7 (8.1)	Male: 53 Female: 47	32.8 (47.7)	1.5 (1.6)	0.4 (1.2)	0.1 (0.7)	40.8 (30.9)
$\epsilon 3/\epsilon 4$ (n=290)	72.9 (7.0)	Male: 55 Female: 45	69.2 (47.6)	2.2 (1.9)	2.1 (26.7)	0.5 (3.1)	36.3 (30.8)
$\epsilon 4/\epsilon 4$ (n=98)	70.3 (7.1)	Male: 61 Female: 39	75.9 (35.6)	2.5 (1.9)	3.8 (14.8)	2.7 (10.4)	34.0 (30.4)

CDR-SB, Clinical Dementia Rating Scale sum of boxes.

Figure 2. Cerebral microbleed count progression by age, grouped by *APOE* genotype, for Alzheimer’s Disease Neuroimaging Initiative participants: (a) raw number and (b) log-transformed.



Coloured lines connect data from the same participant. CMB, cerebral microbleed.

Conclusions

- APOE* $\epsilon 4/\epsilon 4$ genotype and baseline microbleed count were significant predictors of microbleed progression, highlighting the importance of these factors for identifying people at high risk of microbleed accrual.

References

1. Chin KS et al. *Neurobiol Aging*. 2024;134:74–83; 2. Oomens JE et al. *JAMA Network Open*. 2025;8:e2455571; 3. Luo X et al. *Oncotarget*. 2017;8:44477–44489.

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Disclosures

FS, EO, AC, JB, JD, AA, and OH are employees and shareholders of Regeneron Pharmaceuticals, Inc. LS was an employee of Regeneron Pharmaceuticals, Inc. at the time of generation of data reported in this poster. NSP and RD are employees and shareholders of Alnylam Pharmaceuticals.