

BACKGROUND

- Cerebral microhemorrhages (CMHs) are recognized imaging biomarkers of cerebral small vessel disease and cerebral amyloid angiopathy and are a key manifestation of ARIA-H in anti-amyloid trials.
- However, their clinical significance in cognitively unimpaired individuals remains uncertain.

OBJECTIVE

- To determine whether accumulation of CMHs is associated with longitudinal cognitive and functional decline in amyloid-positive older adults enrolled in the A4 Study.

METHODS

PARTICIPANTS

- 754 A4 MRI completers
- Cognitively unimpaired
- Elevated amyloid PET at baseline
- Mean age: 71.5 ± 4.5 years
- 58.6% female

A4
STUDY

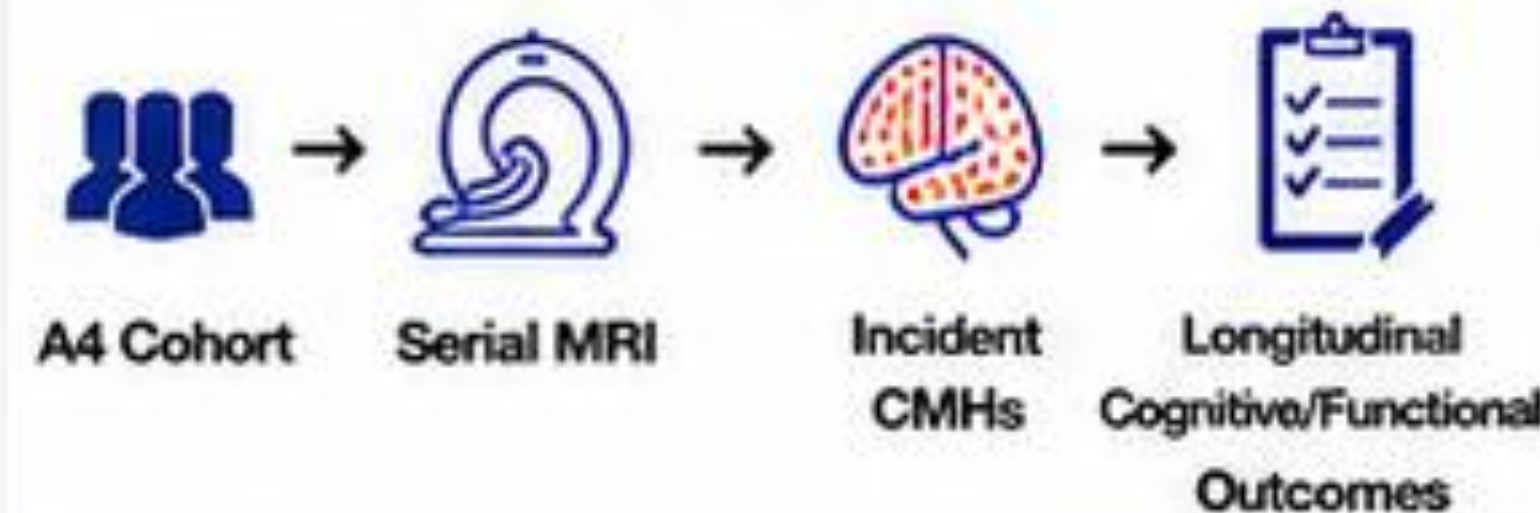
OUTCOMES



STATISTICAL ANALYSIS

- Natural cubic spline mixed models adjusted for:
- Age • Sex • Education • APOE ε4 status
 - Baseline amyloid burden

STUDY DESIGN OVERVIEW



DEFINITION OF INCIDENT CMHs

New CMHs identified on follow-up MRI that were not present on baseline MRI. Groups based on total number of new CMHs:

- 0 = No new CMHs
- 1 = One new CMH
- 2 = Two or more new CMHs

KEY TAKEAWAY



Participants developing **≥2 new CMHs** experienced significantly greater worsening in CDR-SB and CFI Total.



Associations persisted after adjustment for age, sex, education, APOE ε4 status, and baseline amyloid burden.

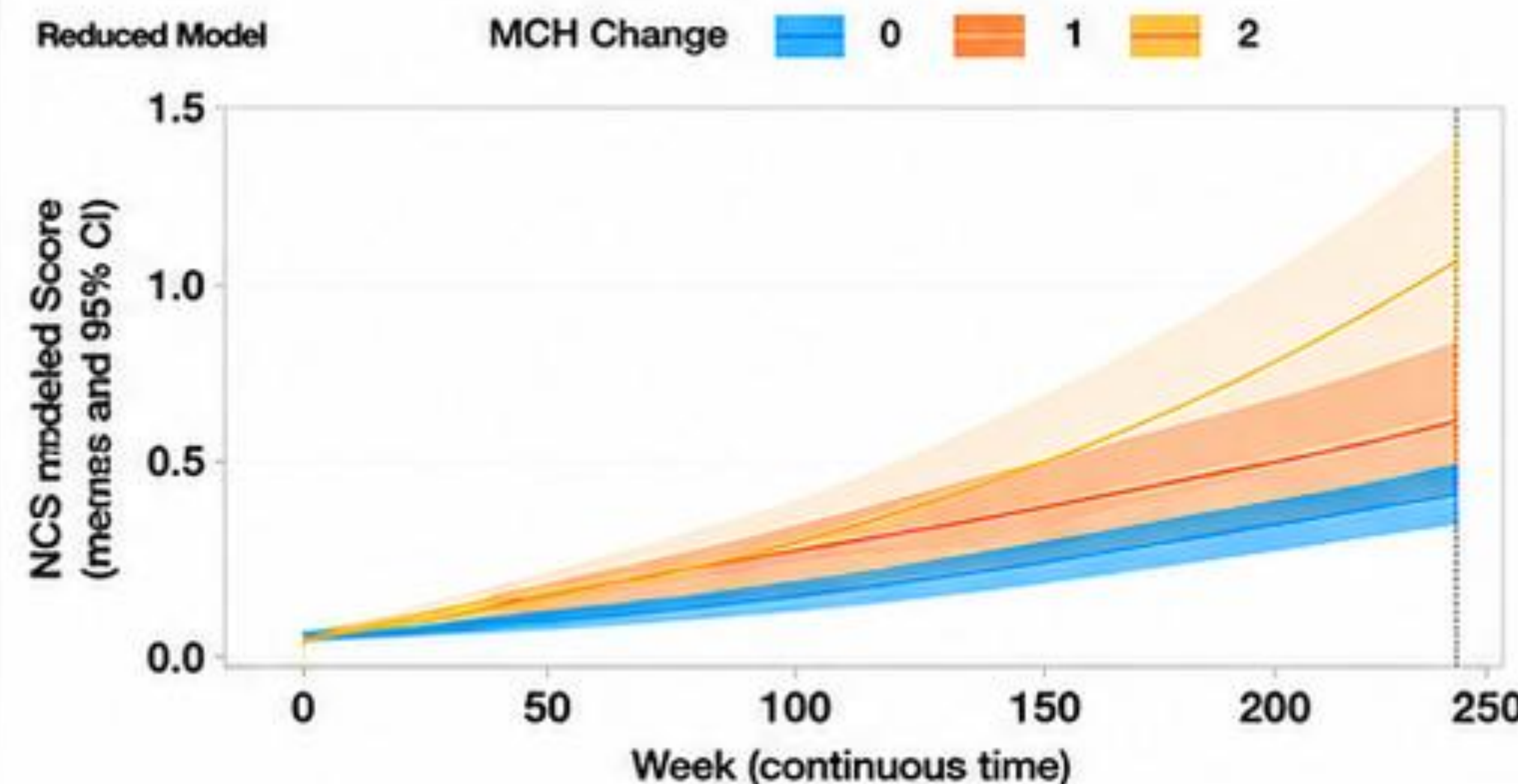


CMH accumulation may represent an early marker of clinically meaningful decline in preclinical Alzheimer's disease.

RESULTS – PARTICIPANT CHARACTERISTICS

	N = 754
Age, mean (SD), years	71.5 (4.5)
Female, n (%)	442 (58.8)
APOE ε4 carrier, n (%)	466 (61.8)
APOE ε4 homozygote, n (%)	66 (8.8)
Centiloid, mean (SD)	65.6 (31.6)
Years of education, mean (SD)	16.2 (2.6)

RESULTS – CLINICAL DEMENTIA RATING SUM OF BOXES (CDR-SB)

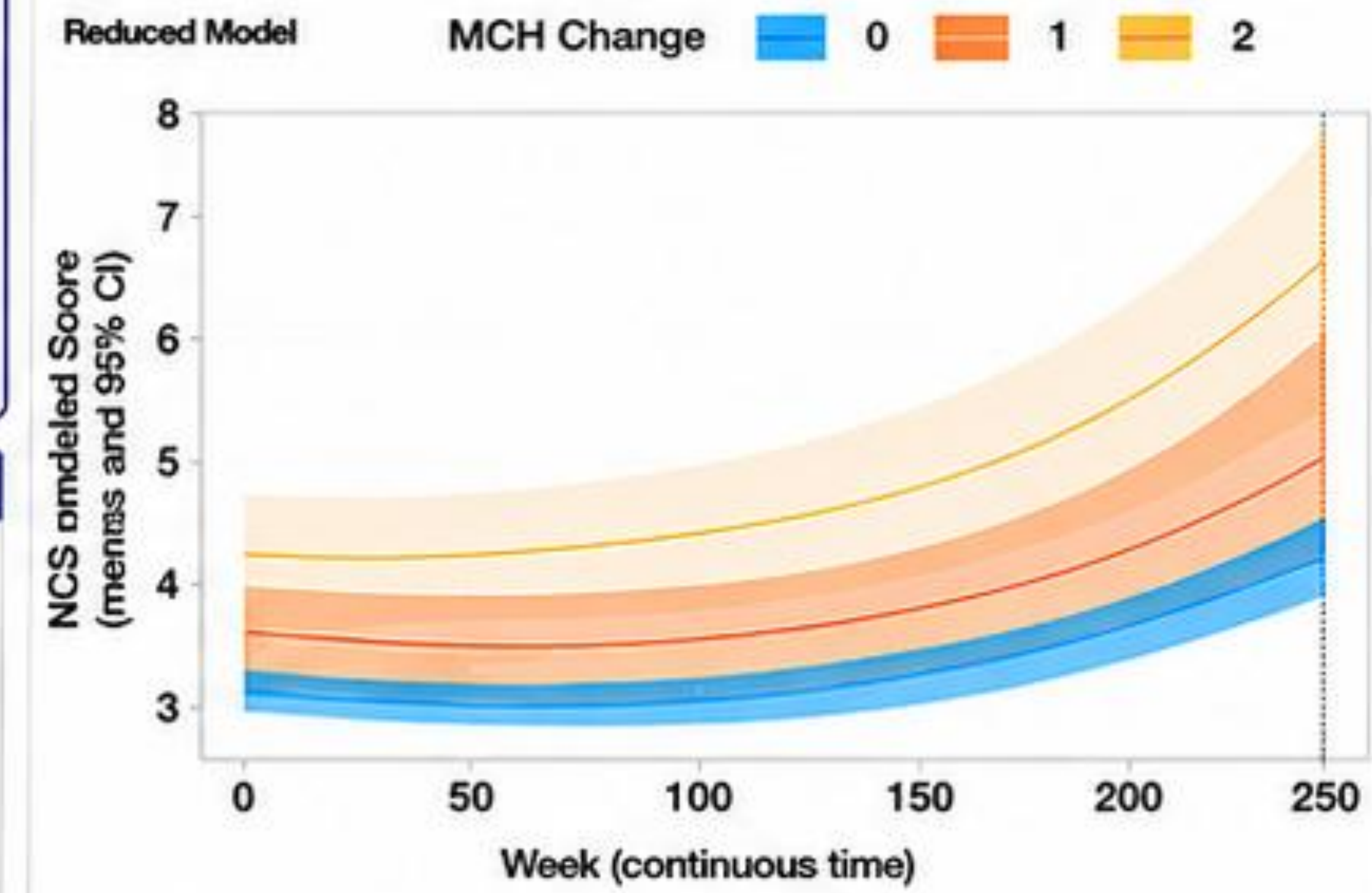


Contrast between MCH Groups at Week 240					
contrast	estimate	SE	p.value	lower.CL	upper.CL
1 - 0	0.3410	0.4497	0.729	-0.7129	1.3949
2 - 0	1.3702	0.5366	0.029*	0.1128	2.6276
2 - 1	1.0292	0.6568	0.260	-0.5102	2.5686



Participants with ≥2 incident CMHs showed significantly greater worsening in CDR-SB vs. those with no new CMHs (estimate = 0.44, 95% CI 0.09 – 0.80, p = 0.009).

RESULTS – COGNITIVE FUNCTION INDEX TOTAL (CFI TOTAL)



Contrast between MCH Groups at Week 240					
contrast	estimate	SE	p.value	lower.CL	upper.CL
1 - 0	0.3410	0.4497	0.729	-0.7129	1.3949
2 - 0	1.3702	0.5366	0.029*	0.1128	2.6276
2 - 1	1.0292	0.6568	0.260	-0.5102	2.5686



Participants with ≥2 incident CMHs showed significantly greater worsening in CFI Total vs. those with no new CMHs (estimate = 1.37, 95% CI 0.11 – 2.63, p = 0.029).

INTERPRETATION

- Accumulation of incident CMHs was associated with measurable worsening in global clinical status (CDR-SB) and participant/informant-reported cognitive function (CFI Total).
- These associations remained significant after adjustment for demographic factors, APOE ε4 status, and baseline amyloid burden, suggesting an effect independent of established AD risk factors.
- The absence of significant differences among participants with only one incident CMH suggests that the cumulative burden of CMHs, rather than isolated events, is associated with clinically meaningful decline.
- These findings support CMHs as a potential marker of progressive cerebrovascular injury contributing to early clinical decline in preclinical AD.

CLINICAL IMPLICATIONS

- Incident CMH accumulation may provide a practical imaging biomarker for longitudinal monitoring in individuals with preclinical AD.
- Development of ≥2 new CMHs may represent a clinically meaningful threshold for identifying individuals at increased risk of subsequent clinical decline.
- These findings support incorporating CMH trajectories into safety monitoring and risk stratification during anti-amyloid treatment.
- Future studies should determine whether prevention of CMH accumulation translates into improved long-term cognitive outcomes.

REFERENCES

- Sperling RA, Donohue MC, Raman R, et al. Trial of Solanezumab in Preclinical Alzheimer's Disease. N Engl J Med. 2023;389(12):1096–1107. doi: 10.1056/NEJMoa2305032.
- Baldaranov D, Wang S, Raman R, Ernstrom K, Kantarci K, Jack CR Jr., Sperling RA, Aisen PS, Rafii MS. Cerebral Microhemorrhage and Cognition in Preclinical Alzheimer's Disease. Under review.

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