



Impact of Cerebral Microhemorrhage Baseline Load on Cognition and Function in Preclinical Alzheimer's Disease

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BACKGROUND

Cerebral microhemorrhages (CMHs) are recognized as an important adverse event (ARIA-H) in clinical trials of anti-amyloid therapies for Alzheimer's disease (AD). They are also relevant in the general elderly population as markers of cerebrovascular disease. This analysis examined whether baseline CMH burden is associated with changes in cognition and daily functioning among participants in the Anti-Amyloid Treatment in Asymptomatic Alzheimer's Disease (A4) Study.

STUDY OBJECTIVE

To evaluate whether baseline CMH load is associated with longitudinal changes in cognition and function in cognitively normal older adults at elevated risk for AD.

METHODS

- MRI data from 754 A4 Study completers were analyzed.
- CMH burden categories: 0, 1, or ≥ 2 microhemorrhages.
- Outcomes: Preclinical Alzheimer Cognitive Composite (PACC), Clinical Dementia Rating–Sum of Boxes (CDR-SB), Cognitive Function Index (CFI), and Activities of Daily Living (ADL).
- Mixed-effects models with continuous time, adjusted for age, sex, education, APOE $\epsilon 4$ status, and baseline Centiloid.
- Participants underwent serial MRI and cognitive assessments throughout the study period.

BASILINE CHARACTERISTICS

Characteristic	0 CMH (N = 616)	1 CMH (N = 99)	≥ 2 CMH (N = 39)	p value*
Age, years, mean (SD)	71.3 (4.4)	72.3 (4.8)	72.4 (4.5)	0.048
Female, n (%)	373 (60.6)	49 (49.5)	20 (51.3)	0.074
Education, years, mean (SD)	16.6 (2.7)	16.2 (2.5)	15.7 (2.7)	0.047
APOE $\epsilon 4$ carrier, n (%)	382 (62.0)	66 (66.7)	18 (46.2)	0.080
Centiloid, mean (SD)	65.5 (32.0)	64.7 (30.1)	69.0 (29.6)	0.758
Baseline PACC, mean (SD)	0.2 (2.6)	-0.7 (2.8)	0.2 (2.2)	0.005

REFERENCE

Sperling RA, Donohue MC, Raman R, et al. Trial of Solanezumab in Preclinical Alzheimer's Disease. *N Engl J Med*. 2023 Sep 21;389(12):1096-1107. doi: 10.1056/NEJMoa2305032.

LONGITUDINAL PACC ANALYSIS

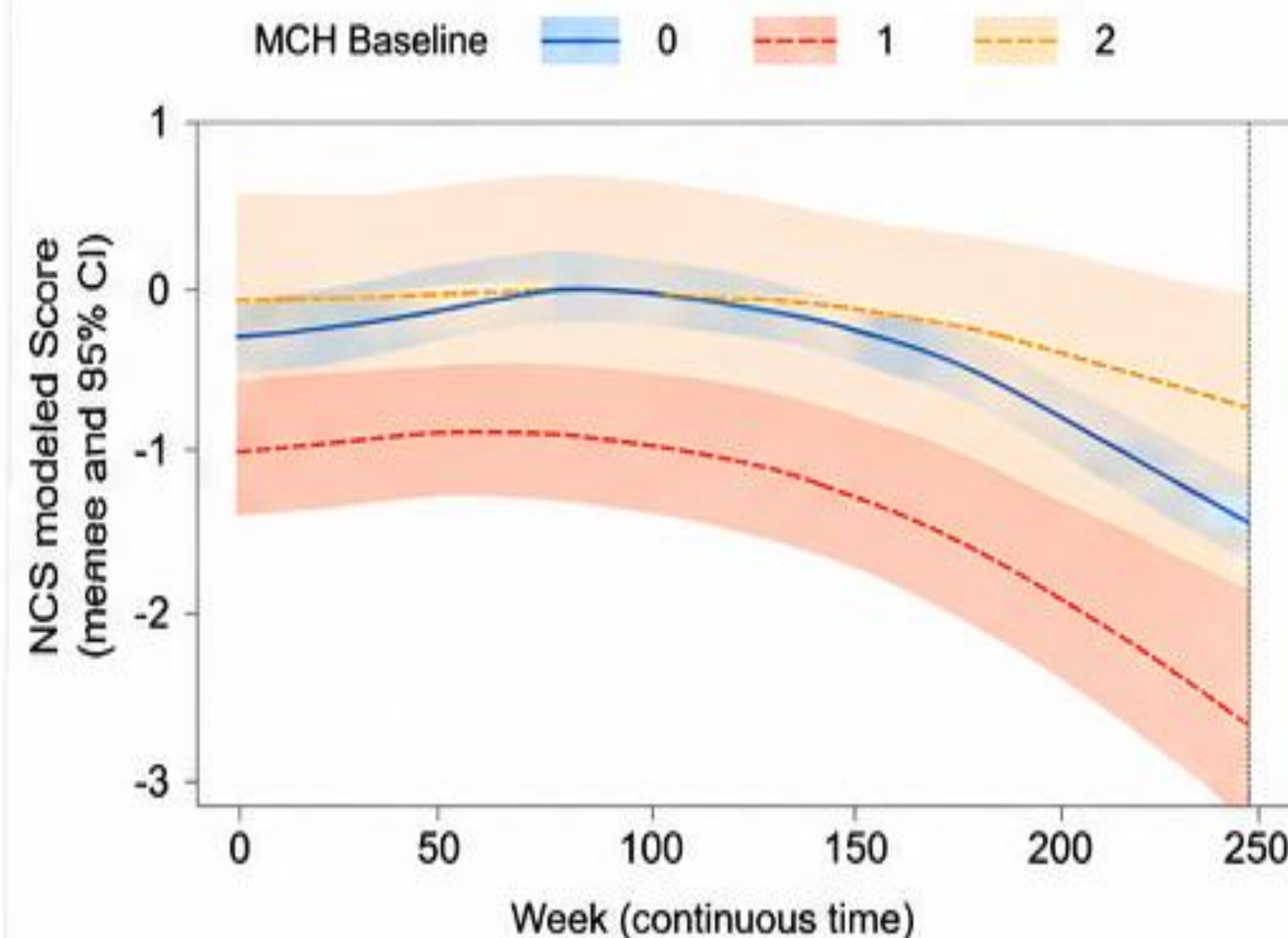
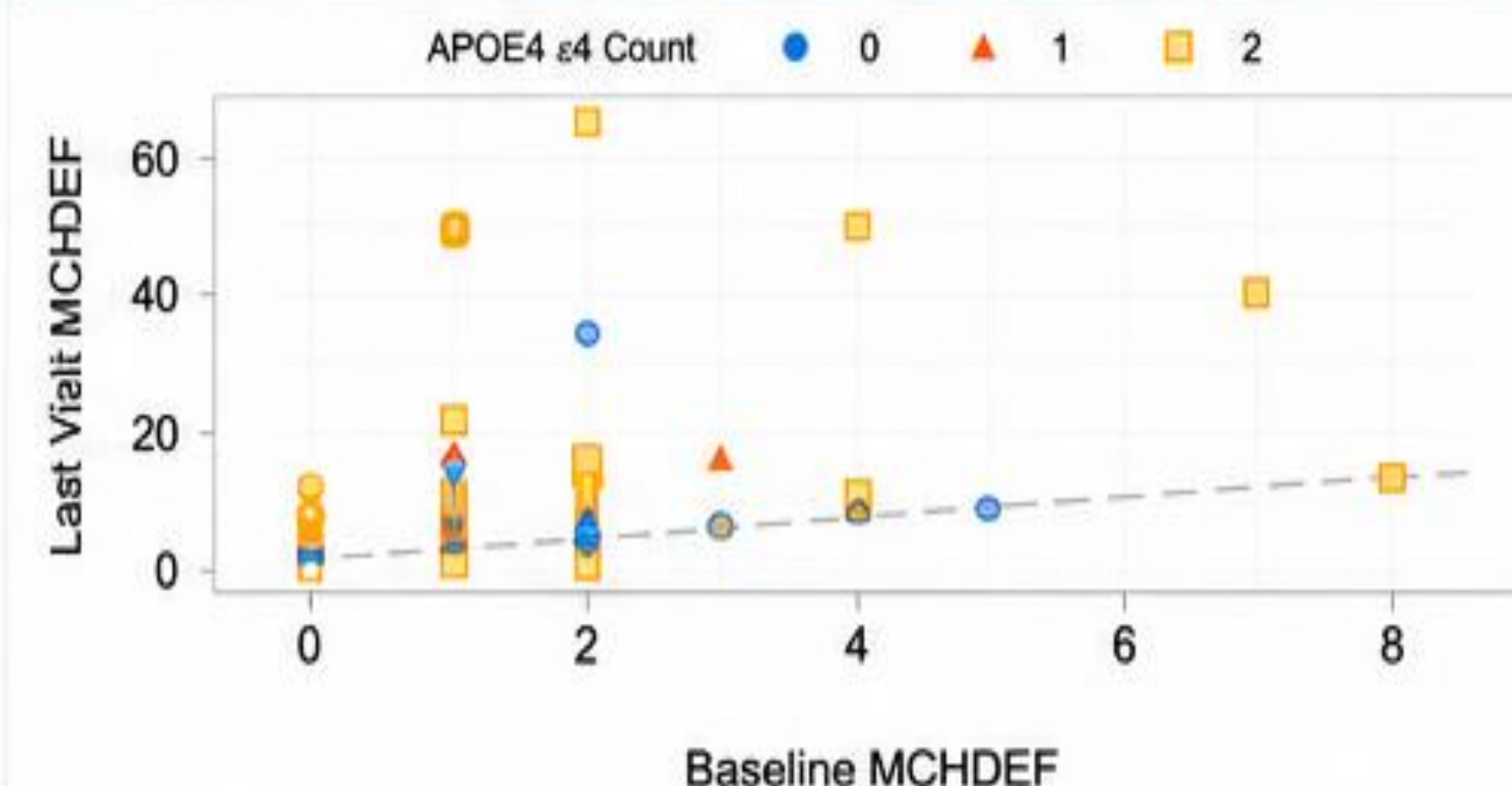


Table 2. PACC Change from Baseline Contrast between MCH Groups at Week 240

contrast	estimate	SE	p.value	lower.CL	upper.CL
1 - 0	-0.5410651	0.3662695	0.3019340	-1.3996479	0.3175177
2 - 0	0.6265408	0.5521146	0.4926160	-0.6676867	1.9207683
2 - 1	1.1676059	0.6341105	0.1562904	-0.3188306	2.6540424

At Week 240, no significant differences in PACC change from baseline were observed among baseline CMH groups. All pairwise comparisons were non-significant, and the 95% confidence intervals included zero.

BASILINE VS LAST VISIT CMH (COMPLETERS)



LONGITUDINAL CDR-SB ANALYSIS

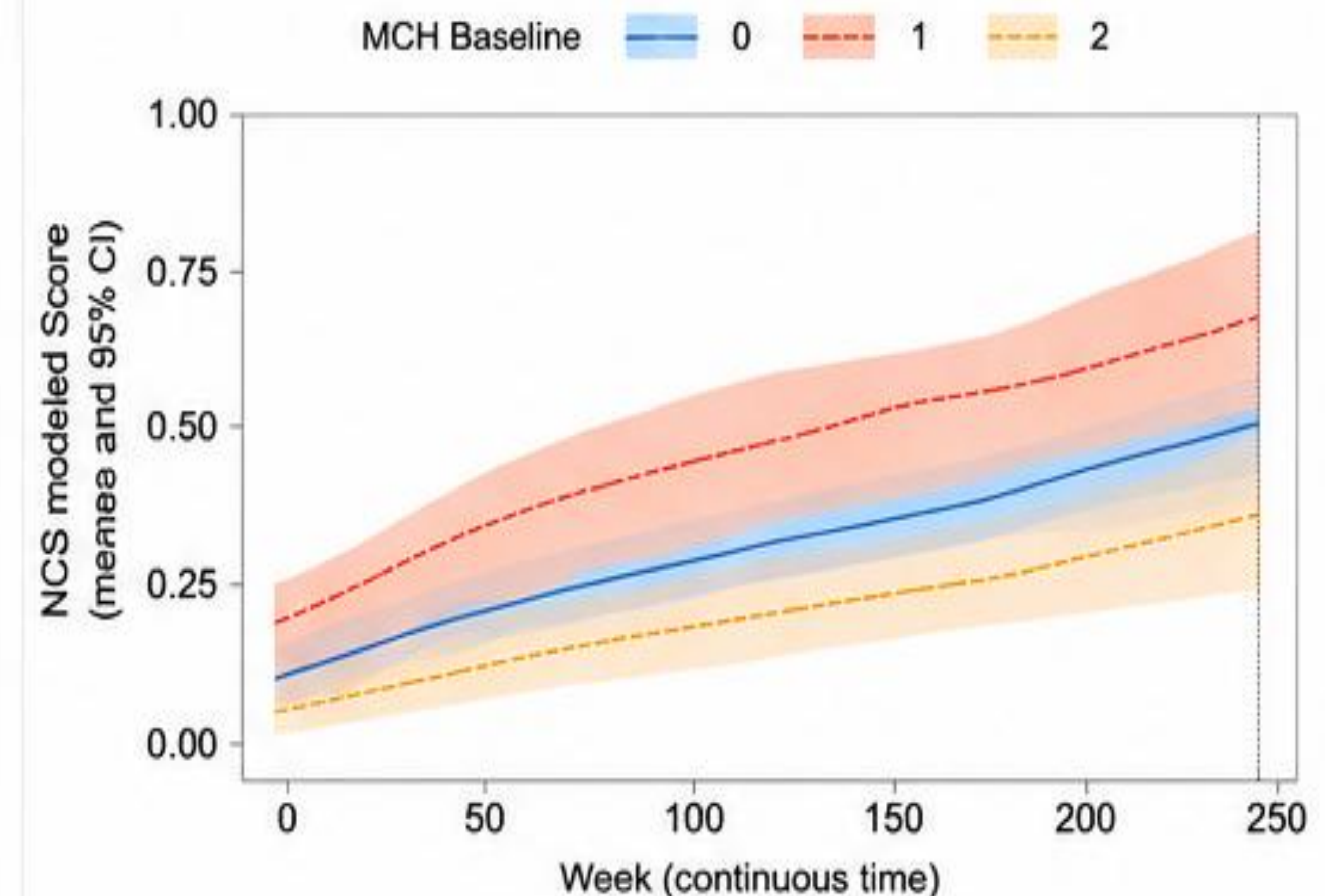


Table 3. CDR Sum of Boxes Change from Baseline Contrast between MCH Groups at Week 240

contrast	estimate	SE	p.value	lower.CL	upper.CL
1 - 0	0.1482330	0.1263322	0.4691263	-0.1478518	0.4443177
2 - 0	-0.1080564	0.1891949	0.8355048	-0.5514725	0.3355598
2 - 1	-0.2562893	0.2177219	0.4668459	-0.7665643	0.2539857

At Week 240, no significant differences in CDR-SB change from baseline were observed among baseline CMH groups. All pairwise comparisons were non-significant, and the 95% confidence intervals included zero.

KEY FINDINGS

- No significant differences in longitudinal change in PACC, CDR-SB, CFI, or ADL were observed between CMH groups at Week 240.
- Results were consistent after adjustment for age, sex, education, APOE $\epsilon 4$ status, and baseline Centiloid.

CONCLUSIONS

Baseline CMH burden is not associated with differences in cognitive or functional trajectories over 240 weeks in cognitively unimpaired older adults at elevated risk for Alzheimer's disease.

ACKNOWLEDGMENTS

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