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Brief Report

Cerebral microhemorrhage and cognition in preclinical Alzheimer's disease

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ABSTRACT

Background: Clarifying whether incident cerebral microhemorrhages (CMHs) contribute to early cognitive or functional decline is increasingly important in the context of anti-amyloid therapies.
Objective: To determine whether incident CMHs are associated with longitudinal changes in cognition and function in cognitively unimpaired individuals with elevated cerebral amyloid.
Design, Setting, and Participants: Post hoc analysis of individuals enrolled in the A4 study. Participants underwent serial MRI and cognitive assessments. Natural cubic spline models adjusted for baseline amyloid PET burden, age, sex, education, and APOE ε4 status.
Measurements: Longitudinal change in the Preclinical Alzheimer Cognitive Composite (PACC), Clinical Dementia Rating–Sum of Boxes (CDR-SB), Cognitive Function Index (CFI), and Activities of Daily Living.
Results: Participants who developed ≥2 incident CMHs demonstrated greater longitudinal worsening in CDR-SB (estimate = 0.44; 95% CI, 0.09–0.80; P = .009) and CFI (estimate = 1.37; 95% CI, 0.11–2.60; P = .03), but not in PACC or ADCS ADL.
Conclusions: Incident CMH accumulation was associated with greater longitudinal worsening in global clinical status and participant-reported functional change, but not objective cognitive performance, among cognitively unimpaired individuals with elevated cerebral amyloid.

1. Introduction

Cerebral microhemorrhages (CMHs) are common imaging findings in aging and Alzheimer's disease (AD) and have assumed increasing clinical importance with the introduction of anti-amyloid therapies, in which amyloid-related imaging abnormalities–hemosiderin (ARIA-H) is a recognized treatment-associated adverse events. Although CMHs have been extensively described in symptomatic AD, their clinical significance during the preclinical stage of the disease, when individuals have biomarker evidence of AD but remain cognitively unimpaired, is less well understood [1].

Understanding whether CMH accumulation is associated with early cognitive and functional decline is important for identifying individuals at greater risk of clinical progression and for informing monitoring strategies in cognitively unimpaired, amyloid-positive individuals. This question has become increasingly relevant with the introduction of anti-amyloid therapies, in which ARIA-H CMH is recognized as treatment-associated imaging abnormality and baseline or incident CMHs may influence treatment eligibility, monitoring, and clinical decision-making. Prior studies, including AGES–Reykjavik and DIAN-TU, have linked CMH burden to accelerated cognitive deterioration, but evidence in sporadic preclinical AD populations remains limited [2,3].

We examined whether incident CMH accumulation was associated with longitudinal changes in cognition, global clinical status, and daily functioning among cognitively unimpaired, amyloid-positive participants enrolled in the Anti-Amyloid Treatment in Asymptomatic Alzheimer's Disease (A4) Study [4].

A4 Study team (see: https://www.actcinfo.org/a4-study-team-lists/)
CMH and Cognition in Preclinical AD

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2. Methods

A4 study methods have been previously published [4]. The double-blind phase of the trial was conducted from 2014 through 2022, and database lock of this phase occurred in early 2023. This post hoc analysis was completed on June 19, 2025. Approval from an institutional review board was obtained at each of the trial sites, and all the participants and their study partners provided written informed consent. The trial was conducted in accordance with International Council for Harmonisation Good Clinical Practice guidelines. Each participant was required to have a partner who provided information about the participant's functioning. Here is a summary of the relevant aspects for this analysis.

2.1. Study population

Randomized participants were ages 65–85, cognitively unimpaired and living independently. At screening they all had a CDR-G score of 0 (range 0–3), Mini Mental State Exam score of 25–30 (range 0–30) and a Weschler Memory Scale-Revised Logical Memory Delayed Recall score of 6–18 (range 0–25). Participants were randomized 1:1 to either placebo (n = 591) or solanezumab (n = 578). All participants had a positive baseline 18F florbetapir- Positron Emission Tomography scan (FBP-PET) (standardized uptake value ratio (SUVr) 1.3 ± 0.2/ 1.3 ± 0.2 (Solanezumab arm /Placebo arm); Centiloid (CL) 66.2 ± 33.5/ 65.9 ± 32.1 (Solanezumab arm /Placebo arm) in a template-based set of cortical regions. Participants with more than four cerebral microhemorrhages at baseline MRI were excluded according to the A4 study eligibility criteria [4,5] All participants were required to have a study partner who was familiar with their functioning and consented to participate in data collection.

2.2. Exposure: incident CMHs post randomization

2.2.1. Magnetic resonance imaging (MRI)

MRI examinations were performed on qualified 3T scanners according to the standardized A4 study imaging protocol. Compliance with the standardized protocol parameters for each series is verified for each exam performed during the study. All scanners use the following parameters for the T2-weighted gradient-recalled echo (T2*GRE) acquisition which is used for CMH ascertainment: 1.0 × 0.8 × 4.0 mm, FoV 20 cm, TR 650 ms, TE 20.00 ms, Flip angle 20 degrees. Images were centrally reviewed to determine study eligibility and for longitudinal safety monitoring. Inter rater kappa scores among the experienced neuroradiologists at the Mayo Clinic for CMH detection are calculated periodically and range from .77 to .93. CMHs were identified as homogeneous hypointense lesions (≤10 mm) distinguishable from small vessels on T2*GRE [6] Although ARIA-H includes both cerebral microhemorrhages and superficial siderosis, superficial siderosis was not included in the analytic dataset for this post hoc analysis. Consequently, we were unable to evaluate the incidence of new superficial siderosis lesions or their association with longitudinal clinical outcomes.

Outcomes: Preclinical Alzheimer Cognitive Composite (PACC), Clinical Dementia Rating Scale Sum of Boxes (CDR-SB), Cognitive Function Index (CFI), ADCS Activities of Daily Living – Prevention Questionnaire [7–10]. PACC was assessed every 6 months, where CDR, ADL and CFI were assessed annually over the course of 4.5 years [4].

2.2.2. Statistical analysis

We used data from A4 study randomized participants who were MRI completers (participants who had both the baseline and last visit (week 240) MRI scan) [4]. The exposure of interest was incident ARIA H CMH accumulation, defined as the increase in maximum ARIA-H CMH count observed during follow-up relative to the baseline ARIA H CMH count, irrespective of baseline CMH burden. Participants were classified into three groups according to the change in CMH burden: Group 0 (no incident CMHs), Group 1 (one incident CMH), and Group2+ (two or more incident CMHs)., regardless of location in the brain.

Natural cubic spline mixed-effects models were used to evaluate the association between incident CMH accumulation and longitudinal clinical outcomes. The dependent variable was the raw longitudinal outcome score, including the baseline assessment (time = 0), thereby modeling each participant's trajectory from study entry.). The full model included main effects and interaction terms among time, treatment, and CMH change, with time treated as a continuous variable defined as days from baseline, and was adjusted for age, sex, education, APOE ε4 status, and baseline SUVr. Treatment assignment was evaluated in the initial models through treatment main effects and interaction terms with time and CMH change. Because the full model including treatment did not differ significantly from the reduced model based on a likelihood ratio test, treatment terms were omitted from the final models.

Continuous variables were compared using analysis of variance (ANOVA), and categorical variables were compared using the chi-square test.

Statistical analyses were conducted using statistical software R (Version 4.4.1) [11]. Because these analyses were exploratory, adjustments for multiple comparisons were not performed. A two-sided P value <0.05 was considered statistically significant.

3. Results

3.1. Participant characteristics

For this post hoc analysis, we included 754 of the 1169 in A4 study randomized participants, as they met the criteria of MRI completers (participants who had both the baseline and last visit (week 240) MRI scan). Their mean age was 71.5 (SD 4.5), 442 (58.6%) were female, mean FBP Centiloid of 65.6 (31.6), 466 (61.8%) had at least one APOE ε4 allele and 66 (8.8%) were homozygote. These variables differed significantly across the CMH groups. Among the clinical outcome measures, only the CFI Combined score differed significantly at baseline, whereas PACC, CDR-SB, and ADCS Activities of Daily Living did not. Table 1 shows the participants' demographics. APOE ε4 genotype distribution differed across incident CMH groups. Participants who developed two or more incident CMHs were more likely to be APOE ε4 homozygotes (24.2%) than participants with no incident CMHs (6.6%), whereas non-carriers were less frequent in the Group2+ (19.7%vs. 40.7%). In addition, baseline amyloid burden increased across groups, with participants who developed two or more incident CMHs demonstrating the highest baseline Centiloid values, Table 2.

3.2. MRI

Of these 754 participants 66 (8.8%) developed ≥2 new CMHs during the duration of the study. Those with incident CMHs were slightly older, more likely to be APOE ε4 carriers, had a greater amyloid burden and higher CFI combined. The distribution of incident CMHs was similar between the placebo and solanezumab treatment groups (overall comparison, p = 0.787), with 8.7% and 8.8% of participants, respectively, developing two or more new CMHs.

3.3. Functional and global clinical status

Participants who developed ≥2 new CMHs had a greater baseline amyloid burden (Fig. 1) and demonstrated significantly greater worsening compared to participants who did not develop any new CMHs post randomization after adjusting for demographic and biomarker covariates on: CDR-SB (estimate = 0.44, SE=0.15, p = 0.009, 95%CI [0.09,0.8]) (Fig. 2) and CFI Total (estimate = 1.37, SE=0.53, p = 0.03, 95%CI [0.11, 2.6]) (Fig. 3). No significant associations were observed between incident CMH and longitudinal change in PACC (estimate = −1.16, SE=0.4960871, p = 0.0502, 95%CI [−2.324418,

Table 1
Demographics.

	Group 0 (N = 587)	Group 1 (N = 101)	Group 2+ (N = 66)	Total (N = 754)	p value
Treatment group					0.787
Placebo	292 (49.7%)	54 (53.5%)	33 (50.0%)	379 (50.3%)	
Solanezumab	295 (50.3%)	47 (46.5%)	33 (50.0%)	375 (49.7%)	
Age (y)					0.017
Mean (SD)	71.3 (4.4)	72.1 (4.8)	72.7 (4.5)	71.5 (4.5)	
Range	65.0 - 84.7	65.0 - 85.3	66.1 - 84.7	65.0 - 85.3	
Education y					0.183
Mean (SD)	16.6 (2.7)	16.5 (2.8)	15.9 (2.8)	16.5 (2.7)	
Range	7.0 - 26.0	12.0 - 30.0	9.0 - 22.0	7.0 - 30.0	
FBP SUVr					< 0.001
Mean (SD)	1.3 (0.2)	1.3 (0.2)	1.4 (0.2)	1.3 (0.2)	
Range	1.0 - 2.1	1.0 - 1.8	1.1 - 1.8	1.0 - 2.1	
FBP CL					< 0.001
Mean (SD)	63.5 (31.1)	68.3 (29.5)	80.0 (35.2)	65.6 (31.6)	
Range	4.0 - 201.7	0.3 - 143.1	16.8 - 159.6	0.3 - 201.7	
Sex					0.017
Male	228 (38.8%)	54 (53.5%)	30 (45.5%)	312 (41.4%)	
Female	359 (61.2%)	47 (46.5%)	36 (54.5%)	442 (58.6%)	
Racial categories					0.602
American Indian or Alaskan Native	1 (0.2%)	0 (0.0%)	0 (0.0%)	1 (0.1%)	
Asian	12 (2.0%)	4 (4.0%)	1 (1.5%)	17 (2.3%)	
Black or African American	8 (1.4%)	4 (4.0%)	2 (3.0%)	14 (1.9%)	
More than one race	5 (0.9%)	0 (0.0%)	1 (1.5%)	6 (0.8%)	
Unknown or Not Reported	5 (0.9%)	0 (0.0%)	0 (0.0%)	5 (0.7%)	
White	556 (94.7%)	93 (92.1%)	62 (93.9%)	711 (94.3%)	
Ethnicity					0.199
Hispanic or Latino	16 (2.7%)	3 (3.0%)	1 (1.5%)	20 (2.7%)	
Not Hispanic or Latino	567 (96.6%)	95 (94.1%)	65 (98.5%)	727 (96.4%)	
Unknown or Not reported	4 (0.7%)	3 (3.0%)	0 (0.0%)	7 (0.9%)	
Marital Status					0.442
Divorced	88 (15.0%)	9 (8.9%)	13 (19.7%)	110 (14.6%)	
Married	422 (71.9%)	74 (73.3%)	48 (72.7%)	544 (72.1%)	
Never married	15 (2.6%)	4 (4.0%)	2 (3.0%)	21 (2.8%)	
Unknown or Not Reported	11 (1.9%)	3 (3.0%)	0 (0.0%)	14 (1.9%)	
Widowed	51 (8.7%)	11 (10.9%)	3 (4.5%)	65 (8.6%)	
Retirement Status	142 (24.2%)	24 (23.8%)	13 (19.7%)	179 (23.7%)	0.658
No	10 (1.7%)	0 (0.0%)	1 (1.5%)	11 (1.5%)	
Not Applicable					
Yes	435 (74.1%)	77 (76.2%)	52 (78.8%)	564 (74.8%)	
Family history of dementia (parent or sibling)	142 (24.2%)	16 (15.8%)	15 (22.7%)	173 (22.9%)	0.183
No	445 (75.8%)	85 (84.2%)	51 (77.3%)	581 (77.1%)	
Yes					
Current Tobacco User at Baseline					0.084
No	570 (97.1%)	101 (100.0%)	66 (100.0%)	737 (97.7%)	
Yes	17 (2.9%)	0 (0.0%)	0 (0.0%)	17 (2.3%)	
Systolic BP at Baseline	1	1	0	2	0.167
Missing					
Mean (SD)	132.6 (16.0)	134.0 (16.1)	136.4 (17.3)	133.1 (16.1)	
Range	90.0 - 191.0	101.0 - 181.0	100.0 - 177.0	90.0 - 191.0	
BMI at Baseline					0.714
Missing	0	1	1	2	
Mean (SD)	27.3 (5.0)	26.9 (5.0)	27.1 (3.9)	27.2 (4.9)	
Range	17.5 - 49.4	17.7 - 51.0	18.7 - 39.6	17.5 - 51.0	
Blood pressure being treated with medicines at Baseline	573 (97.6%)	98 (97.0%)	65 (98.5%)	736 (97.6%)	0.834
No					
Yes	14 (2.4%)	3 (3.0%)	1 (1.5%)	18 (2.4%)	
APO E Genotype					< 0.001
ε2/ ε 2	1 (0.2%)	0 (0.0%)	0 (0.0%)	1 (0.1%)	
ε 2/ ε 3	29 (4.9%)	3 (3.0%)	1 (1.5%)	33 (4.4%)	
ε 2/ ε 4	21 (3.6%)	3 (3.0%)	0 (0.0%)	24 (3.2%)	
ε 3/ ε 3	209 (35.6%)	33 (32.7%)	12 (18.2%)	254 (33.7%)	
ε 3/ ε 4	288 (49.1%)	51 (50.5%)	37 (56.1%)	376 (49.9%)	
ε 4/ ε 4	39 (6.6%)	11 (10.9%)	16 (24.2%)	66 (8.8%)	
APO E e4					0.003
No	239 (40.7%)	36 (35.6%)	13 (19.7%)	288 (38.2%)	
Yes	348 (59.3%)	65 (64.4%)	53 (80.3%)	466 (61.8%)	
PACC					0.326
Mean (SD)	0.2 (2.7)	−0.1 (2.7)	−0.2 (2.6)	0.1 (2.7)	
Range	−12.5 - 7.8	−8.2 - 4.6	−7.7 - 4.6	−12.5 - 7.8	
CDR-SB					0.778
Mean (SD)	0.1 (0.2)	0.0 (0.2)	0.1 (0.2)	0.1 (0.2)	
Range	0.0 - 2.0	0.0 - 0.5	0.0 - 0.5	0.0 - 2.0	
CFI Combined					0.024
Missing	1	0	0	1	
Mean (SD)	3.6 (3.3)	4.0 (3.4)	4.7 (4.1)	3.7 (3.4)	
Range	0.0 - 22.0	0.0 - 14.5	0.0 - 20.5	0.0 - 22.0	
CFI Participant					0.101
Mean (SD)	2.2 (2.1)	2.4 (2.2)	2.8 (2.2)	2.3 (2.1)	
Range	0.0 - 14.0	0.0 - 8.5	0.0 - 8.5	0.0 - 14.0	
CFI Partner					0.062
Missing	1	0	0	1	
Mean (SD)	1.4 (1.9)	1.6 (1.9)	2.0 (2.7)	1.5 (2.0)	
Range	0.0 - 14.0	0.0 - 9.0	0.0 - 12.0	0.0 - 14.0	
ADL Participant					0.503
Mean (SD)	43.4 (2.4)	43.2 (2.8)	43.0 (2.4)	43.3 (2.4)	
Range	29.0 - 45.0	26.0 - 45.0	35.0 - 45.0	26.0 - 45.0	
ADL Partner					0.488
Mean (SD)	43.5 (2.6)	43.6 (2.2)	43.1 (2.7)	43.5 (2.6)	
Range	26.8 - 45.0	34.0 - 45.0	33.0 - 45.0	26.8 - 45.0	

Values are means (SD) unless otherwise stated. Percentages are based on the numbers of participants with non-missing data. Age is defined as the age at randomization. Continuous variables were compared using analysis of variance

(ANOVA), and categorical variables were compared using the chi-square test. Abbreviations: FBP SUVr: Florbetapir-F18 Positron Emission Tomography (PET) Standardized Uptake Value Ratio; FBP CL: FBP PET Centiloid; PACC: Preclinical Alzheimer's Cognitive Composite, CDR-SB: Clinical Dementia Rating Scale Sum of Boxes, CFI: Cognitive Function Index, ADL: Activities of Daily Living. N, total number of participants in each treatment group; Group 0 included individuals with no change, Group 1 included individuals with an increase of 1 ARIA-H CMH, and Group2+ included participants with an increase of 2 or more ARIA-H CMH from baseline. Race and ethnicity were reported by the participants.

Table 2
Distribution of APOE ε4 genotype by group.

	Group 0 (N = 587)	Group 1 (N = 101)	Group 2+ (N = 66)	Total (N = 754)
E4				
Heterozygotes	309 (52.6%)	54 (53.5%)	37 (56.1%)	400 (53.1%)
Homozygotes	39 (6.6%)	11 (10.9%)	16 (24.2%)	66 (8.8%)
Non-carriers	239 (40.7%)	36 (35.6%)	13 (19.7%)	288 (38.2%)

Participants were classified according to the number of incident CMHs identified during follow-up: no incident CMHs (Group 0), one incident CMH (Group 1), and two or more incident CMHs (Group 2+). Data is presented as number (percentage) of participants in each group. APOE, apolipoprotein E; CMH, cerebral microhemorrhage.

0.0009417] or ADCS Activities of Daily Living (ADL Total: estimate = −2.1182744, SE=1.0044226, p = 0.088, 95%CI [−4.472340, 0.2357914] (data not shown). These results indicate that CMH accumulation is associated with functional and global clinical status.

4. Discussion

In this cohort of cognitively unimpaired older adults with elevated cerebral amyloid, the development of two or more incident cerebral microhemorrhages (CMHs) was independently associated with greater longitudinal worsening in global clinical status, as measured by the Clinical Dementia Rating–Sum of Boxes (CDR-SB), and participant-reported functional change, as measured by the Cognitive Function Index (CFI). These associations persisted after adjustment for age, sex, education, APOE ε4 status, and baseline amyloid burden. In contrast, no significant associations were observed for the Preclinical Alzheimer Cognitive Composite (PACC) or the ADCS Activities of Daily Living questionnaire. Together, these findings suggest that incident CMH accumulation is associated with early clinical progression in preclinical Alzheimer's disease. These results may have implications for risk stratification and monitoring, particularly in settings where the risk of ARIA-H is elevated. The emergence of ≥2 new CMHs may represent a clinically relevant threshold for surveillance and treatment decision-making.

Importantly, incident CMH accumulation occurred at similar frequencies in the placebo and solanezumab groups (overall comparison, $p = 0.787$), and inclusion of treatment assignment in the longitudinal models did not materially influence the observed associations. Specifically, 8.7% of placebo-treated participants and 8.8% of solanezumab-treated participants developed two or more incident CMHs. These findings suggest that the relationship between incident CMH accumulation and clinical decline was not driven by treatment allocation within the A4 study.

Our findings are consistent with several major studies in non-demented participants such as AGES–Reykjavik Study and the Rotterdam Scan Study [2,12]. The former study demonstrated that CMHs

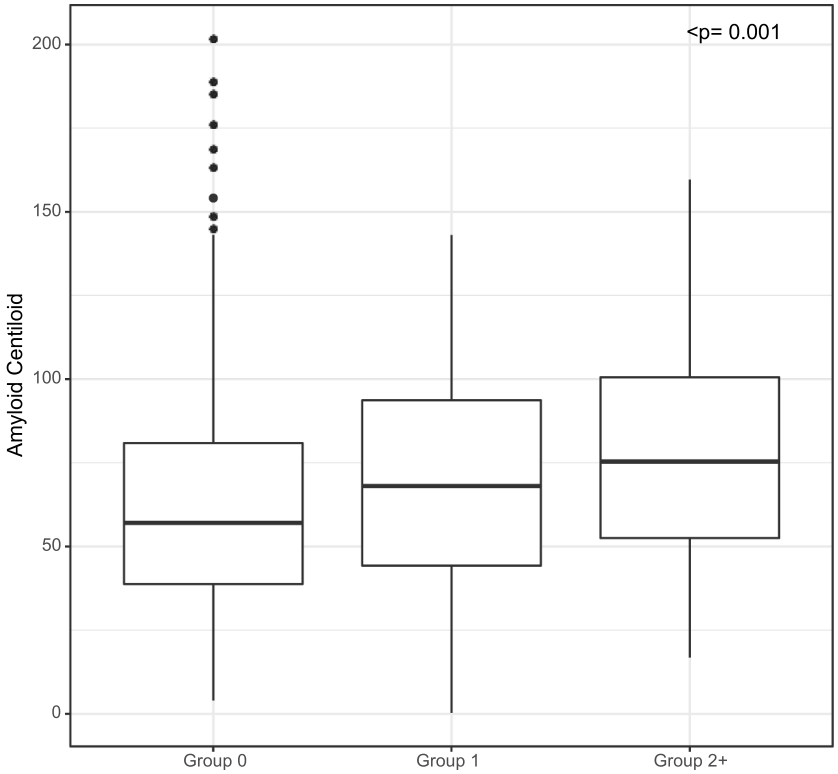

Fig. 1. Amyloid burden at baseline in the different groups:
Association between Amyloid burden at baseline and CMH accumulation in A4 study completers, categorized by accumulated CMH from baseline: none (Group 0; n = 587), one (Group 1; n = 101), two and more CMHs (Group2+; n = 66), with range for Group2+ shown in brackets. Baseline Amyloid burden was higher in A4 study completers how developed two end more CMHs CFI Totals score during the study. The middle line shows the median, the upper hinge is 75% quantile, the lower hinge is 25% quantile, lower and upper whiskers correspond to the smallest and largest observations, respectively. Group 0 included individuals with no change, Group 1 included individuals with an increase of 1 ARIA-H CMH, and Group2+ included participants with an increase of 2 or more ARIA-H CMH (in brackets the range of accumulated CMH) from baseline.

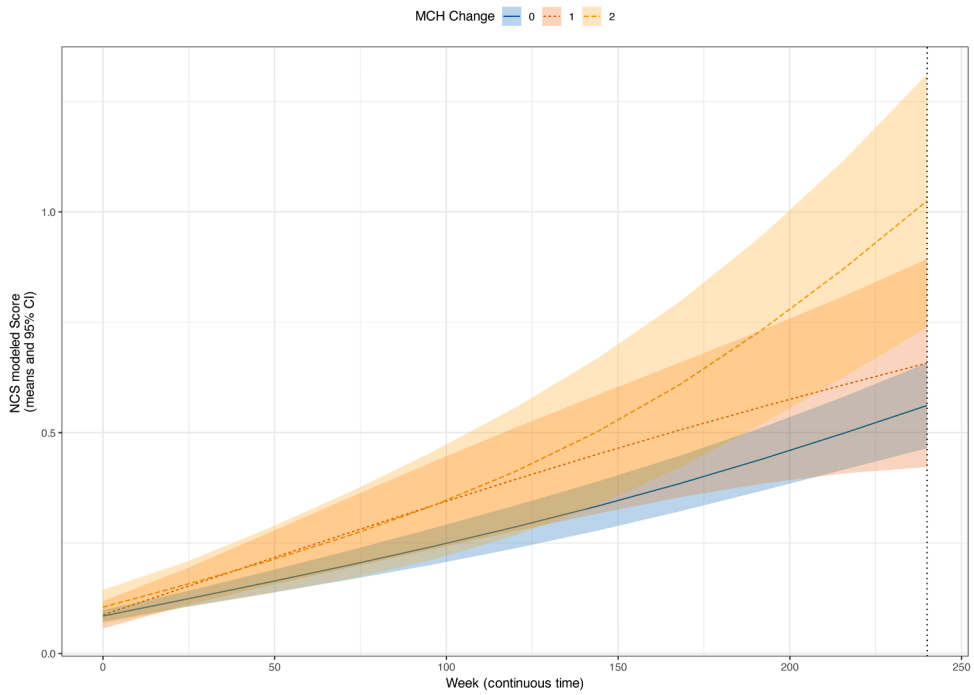

Fig. 2. CDR Sum of Boxes Change from Baseline to week 240 Between Groups: Modeled CDR Sum of Boxes scores over 240 weeks using natural cubic spline regression. Curves represent mean trajectories with 95% confidence intervals for each CMH change group. Contrast= omparison, SE = Standard Error, 95% CI = 95% confidence interval. Number of participants per group (Group 0 = 587, Group 1 = 101, Group 2 = 66). At Week 240, participants in Group2+ had significantly higher CDR SB score compared to Group 0 (Estimate = 0.443, 95% CI: 0.09–0.70, p = 0.008). No significant difference was observed between Group2+ and 1.

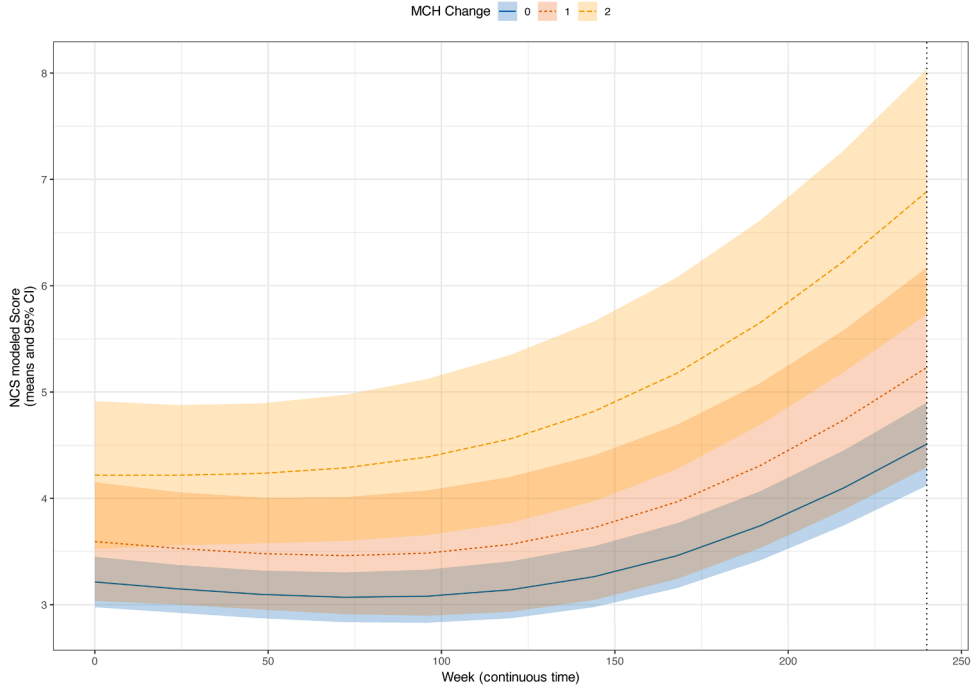

Fig. 3. CFI Total Change from Baseline to week 240 Between Groups:
Modeled CFI scores over 240 weeks using natural cubic spline regression. Curves represent mean trajectories with 95% confidence intervals for each CMHchange group. Contrast= Comparison, SE = Standard Error, 95% CI = 95% confidence interval. Number of participants per group (Group 0 = 587, Group 1 = 101, Group 2 = 66). At Week 240, participants in Group 2 had significantly higher CFI Total score compared to Group 0 (Estimate = 1.37, 95% CI: 0.11–2.63, p = 0.03). No significant difference was observed between Group2+ and 1.

predict greater cognitive decline across multiple domains over five years. Mixed-location CMHs (deep + lobar) were most strongly associated with declines in memory and processing speed. Individuals with >3 CMHs showed steeper global cognitive decline [2]. The latter study showed that higher number of CMHs was associated with lower Mini-Mental State Examination (MMSE) score and worse performance on tests of information processing speed and motor speed. In addition, the presence of >5 CMHs was associated with worse performance in all

cognitive domains, except memory [12].

Similarly, our findings are consistent with the DIAN-TU Study, where in autosomal dominant AD mutation carriers the increase in CMH burden was associated with faster annual worsening on the CDR-SB, reinforcing the link between CMH accumulation and clinical decline across distinct AD populations [3].

Participants who developed two or more incident CMHs exhibited greater baseline amyloid burden and were more likely to be APOE ε4 homozygotes, supporting the concept that more advanced Alzheimer's disease pathology may increase susceptibility to CMH accumulation. However, adjustment for baseline amyloid PET burden did not eliminate the association between incident CMHs and longitudinal clinical outcomes, indicating that amyloid burden alone does not fully explain these findings. Together, these observations suggest that vascular injury and amyloid pathology contribute through complementary, rather than entirely overlapping, mechanisms during the earliest stages of Alzheimer's disease. This interpretation is consistent with previous studies demonstrating persistent associations between CMHs and cognitive decline after adjustment for cerebrospinal fluid Aβ levels and cerebral amyloid angiopathy severity [13–15]. Supporting this hypothesis, a recent 3T MRI study found that individuals who developed ≥5 incident CMHs exhibited reduced global network efficiency, increased characteristic path length, and disruption of white matter structural networks, changes that were associated with slower information processing speed and impaired attention [16].

These findings have potential implications for the interpretation of vascular imaging abnormalities in preclinical Alzheimer's disease, particularly in the era of anti-amyloid therapies, where ARIA-H is a recognized imaging abnormality.

However, although the development of two or more new CMHs was independently associated with significant statistical longitudinal worsening in global clinical status (CDR-SB) and participant-reported functional change (CFI), the present study was not designed to establish thresholds for clinical significance, and these findings should be interpreted as evidence of early disease progression rather than definitive clinically meaningful decline.

Strengths of the present study include the large, well-characterized cohort of cognitively unimpaired individuals with biomarker-confirmed Alzheimer's disease pathology, standardized longitudinal MRI acquisition with centralized image review, repeated cognitive and functional assessments over 240 weeks, and adjustment for key demographic, genetic, and biomarker covariates. These features provide a unique opportunity to evaluate the clinical relevance of incident CMH accumulation during the preclinical stage of Alzheimer's disease.

The A4 study cohort provides a unique opportunity to study these relationships because participants exhibit biomarker evidence of AD pathology but no overt cognitive impairment. Demonstrating that CMHs predict early decline in this population highlights their potential value as early markers of clinically meaningful change.

5. Limitations

Several limitations should be considered. Incident CMHs were analyzed as cumulative burden irrespective of anatomical location, precluding assessment of whether lobar, deep, or infratentorial CMHs differentially influence clinical progression. In addition, CMHs were identified using T2*-GRE rather than susceptibility-weighted imaging, which may have underestimated the burden of small CMHs.

Although incident CMH accumulation was defined relative to baseline CMH burden, baseline CMH count was not modeled as an independent covariate. Pre-existing CMHs may represent an underlying marker of cerebrovascular vulnerability and could independently influence both subsequent CMH accumulation and longitudinal clinical outcomes. Furthermore, participants with more than four baseline CMHs were excluded by the A4 study eligibility criteria, limiting the range of prevalent CMH burden within this cohort. Future studies should evaluate the independent effects of baseline and incident CMH burden on clinical progression.

Another limitation is that we did not model a comprehensive set of cardiovascular and cerebrovascular risk factors. Although baseline descriptors such as systolic blood pressure, body mass index, current tobacco use, and blood pressure treatment status were available, the present post hoc analysis was not designed to adjust for broader vascular comorbidity, including diabetes, antithrombotic use, prior cerebrovascular disease, or other related factors. Therefore, we cannot determine the extent to which the observed associations are independent of overall vascular risk burden.

Finally, the predominantly white, highly educated A4 study cohort may limit the generalizability of these findings to broader populations.

Our findings suggest that CMH accumulation may represent a marker of cerebrovascular injury associated with early clinical progression in preclinical Alzheimer's disease. However, because other markers of cerebral small vessel disease, including white matter hyperintensity burden, were not included in the present analysis, we cannot determine whether these associations are independent of other cerebrovascular abnormalities. Future studies integrating multiple vascular imaging biomarkers are needed to clarify their relative contributions to disease progression.

6. Conclusions

In cognitively unimpaired individuals with elevated cerebral amyloid, incident CMH accumulation was associated with greater longitudinal worsening in global clinical status and participant-reported functional change. These findings support further investigation of CMHs as imaging markers of early disease progression in preclinical Alzheimer's disease

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

ChatGPT was used to assist with text formatting, typos.

Data statement

Publicly released data from A4 and LEARN studies can be requested at https://www.a4studydata.org

Role of the funder/sponsor

The sponsors had no role in the design and conduct of the study; in the collection, analysis, and interpretation of data; in the preparation of the manuscript; or in the review or approval of the manuscript.

CRediT authorship contribution statement

Dobri Baldaranov: Writing – original draft, Validation, Project

administration, Methodology, Data curation, Conceptualization. **Shunran Wang:** Writing – review & editing, Methodology, Formal analysis. **Rema Raman:** Writing – review & editing, Supervision, Methodology, Formal analysis, Data curation, Conceptualization. **Karin Ernstrom:** Writing – review & editing, Supervision, Methodology, Formal analysis. **Kejal Kantarci:** Writing – review & editing, Methodology, Data curation. **Clifford R. Jack:** Writing – review & editing, Methodology, Formal analysis, Data curation, Conceptualization. **Reisa A Sperling:** Writing – review & editing, Supervision, Resources, Investigation, Funding acquisition, Data curation, Conceptualization. **Paul S Aisen:** Writing – review & editing, Supervision, Resources, Methodology, Investigation, Funding acquisition. **Michael S Rafii:** Writing – review & editing, Supervision, Methodology, Data curation, Conceptualization.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

Reisa A Sperling reports was provided by National Institute on Aging. Reisa Sperling reports a relationship with National Institutes of Health that includes: funding grants. The A4 study was supported by a public–private–philanthropic partnership, including funding from the National Institute on Aging of the National Institutes of Health (R01AG063689, U19AG010483, and U24AG057437), Eli Lilly (also the supplier of active medication and placebo), the Alzheimer's Association, the Accelerating Medicines Partnership through the Foundation for the National Institutes of Health, the GHR Foundation, the Davis Alzheimer Prevention Program, the Yugilbar Foundation, an anonymous foundation, and additional private donors to Brigham and Women's Hospital, with in-kind support from Avid Radiopharmaceuticals, Cogstate, Albert Einstein College of Medicine, and the Foundation for Neurologic Diseases. If there are other authors, they declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.tjpad.2026.100681.

References

[1] Li X, Yang S, Li Y, Qin W, et al. The performance of patients with cerebral microbleeds in different cognitive tests: a cross-sectional study. Front Aging Neurosci 2023;15:1114426. https://doi.org/10.3389/fnagi.2023.1114426.
[2] Ding J, Sigurðsson S, Jónsson PV, et al. Space and location of cerebral microbleeds, cognitive decline, and dementia in the community. Neurology 2017;88(22):2089–97. https://doi.org/10.1212/WNL.0000000000003983.
[3] Joseph-Mathurin N, Wang G, Kantarci K, et al. Dominantly inherited Alzheimer network. Longitudinal accumulation of cerebral microhemorrhages in Dominantly inherited Alzheimer disease. Neurology 2021;96(12):e1632–45. https://doi.org/10.1212/WNL.0000000000011542.
[4] Sperling RA, Donohue MC, Raman R, et al. Trial of Solanezumab in preclinical Alzheimer's disease. N Engl J Med 2023;389(12):1096–107. https://doi.org/10.1056/NEJMoa2305032.
[5] Fleisher AS, Chen K, Liu X, et al. Using positron emission tomography and Florbetapir F 18 to image cortical amyloid in patients with mild cognitive impairment or dementia due to Alzheimer disease. Arch Neurol 2011;68(11):1404. https://doi.org/10.1001/archneurol.2011.150.
[6] Kantarci K, Gunter JL, Tosakulwong N, et al. Focal hemosiderin deposits and β-amyloid load in the ADNI cohort. Alzheimers Dement 2013;9(5 Suppl):S116–23. https://doi.org/10.1016/j.jalz.2012.10.011.
[7] Donohue MC, Sperling RA, Salmon DP, et al. The preclinical Alzheimer cognitive composite: measuring amyloid-related decline. JAMA Neurol 2014;71(8):961. https://doi.org/10.1001/jamaneurol.2014.803.
[8] Cedarbaum JM, Jaros M, Hernandez C, et al. Rationale for use of the clinical dementia rating sum of boxes as a primary outcome measure for Alzheimer's disease clinical trials. Alzheimers Dement 2013;9(Suppl):S45–55. https://doi.org/10.1016/j.jalz.2011.11.002.
[9] Amariglio RE, Donohue MC, Marshall GA, et al. Alzheimer's disease cooperative study. Tracking early decline in cognitive function in older individuals at risk for Alzheimer disease dementia: the Alzheimer's disease cooperative study cognitive function instrument. JAMA Neurol 2015;72(4):446. https://doi.org/10.1001/jamaneurol.2014.3375.
[10] Galasko D, Bennett DA, Sano M, et al. Alzheimer's disease cooperative study. ADCS Prevention instrument project: assessment of instrumental activities of daily living for community-dwelling elderly individuals in dementia prevention clinical trials. Alzheimer Dis Assoc Disord 2006;20(4 Suppl 3):S152–69. https://doi.org/10.1097/01.wad.0000213873.25053.2b.
[11] R Core Team. R: a language and environment for statistical computing. Vienna, Austria: R Foundation for Statistical Computing; 2019. https://www.R-project.org/.
[12] Poels MM, Ikram MA, van der Lugt A, et al. Cerebral microbleeds are associated with worse cognitive function: the Rotterdam Scan Study. Neurology 2012;78(5):326–33. https://doi.org/10.1212/WNL.0b013e3182452928.
[13] van der Vlies AE, Goos JD, Barkhof F, et al. Microbleeds do not affect rate of cognitive decline in Alzheimer disease. Neurology 2012;79(8):763–9. https://doi.org/10.1212/WNL.0b013e3182661f91.
[14] Chiang GC, Cruz Hernandez JC, Kantarci K, et al. Alzheimer's disease neuroimaging initiative. Cerebral microbleeds, CSF p-tau, and cognitive decline: significance of anatomic distribution. AJNR Am J Neuroradiol 2015;36(9):1635–41. https://doi.org/10.3174/ajnr.A4351.
[15] Arvanitakis Z, Leurgans SE, Wang Z, et al. Cerebral amyloid angiopathy pathology and cognitive domains in older persons. Ann Neurol 2011;69(2):320–7. https://doi.org/10.1002/ana.22112.
[16] Yin J, Zhou X, Chen Y, et al. Cerebral microbleeds linked to structural network disruption and cognitive impairment in white matter hyperintensities. Neuroscience 2025;564:31–40. https://doi.org/10.1016/j.neuroscience.2024.11.027. Epub 2024 Nov 15.