The Journal of Prevention of Alzheimer's Disease 13 (2026) 100710

Contents lists available at ScienceDirect

The Journal of Prevention of Alzheimer's Disease

journal homepage: www.elsevier.com/locate/tjpad

Editorial

Are cerebral microbleeds a marker for clinical progression in preclinical Alzheimer's disease? A question of mediation vs. effect modification

Despite the importance of vascular contributions to cognitive impairment and dementia (VCID), its relationship to Alzheimer's disease (AD) pathology has yet to be fully elucidated. Cerebral microhemorrhages (CMHs) have been considered an exemplar for how AD pathology and cerebrovascular disease may share a common pathway, as lobar CMHs are a hallmark of cerebral amyloid angiopathy (CAA), caused by β-amyloid deposition in vessel walls [1]. CMHs are also commonly caused by chronic hypertension, which usually result in deep CMHs where perforating small vessels are located. In the context of new amyloid targeting therapies, this relationship becomes more complicated, as CMHs are also part of the amyloid-related imaging abnormalities-haemorrhagic (ARIA-H) spectrum that are caused by the treatments themselves. One way to disentangle this relationship is to examine how CMHs are related to cognitive function in preclinical AD, as Baldaranov et al. have expertly done in this issue of the *Journal of Prevention of Alzheimer's Disease* [2]. The authors posited that their analysis potentially supports CMH accumulation as a marker of early clinical progression in preclinical AD. Ultimately, to make this claim, the underlying relationship between AD pathology and CMH needs to be interrogated – in other words, is CMH accumulation on a causal pathway between AD pathology and cognitive outcomes? Or do CMH accumulation and AD pathology interact to potentiate risk of cognitive decline? These two different but related mechanisms can be conceptualized as mediation vs. effect modification, respectively, and can help us frame how to evaluate whether CMHs are a marker of clinical progression in preclinical AD.

In the present study, Baldaranov et al. leveraged data from the A4 clinical trial [3], which originally was designed to test whether solanezumab prevents cognitive decline in preclinical AD patients compared to placebo. Baldaranov et al. examined associations between incident CMHs and global cognitive and functional performance in the A4 cohort with both treatment arms combined into one sample. They found that greater CMH accumulation was associated with worse global cognitive and functional status as measured by self- or informant-reported measures, but not objective measures of cognitive decline or activities of daily living. This evidence is compelling given the self- or informant-reported measures were significantly associated with incident CMHs as opposed to the objective measures, highlighting the importance of patient-centered outcomes when monitoring AD progression. Baldaranov et al. argue these data support the notion that CMHs may be related to early clinical progression in preclinical AD. For CMHs to act as a marker for clinical progression, we can think about whether CMH accumulation is on a causal pathway between amyloid deposition and clinical progression (i.e. mediation) vs. whether the presence of CMH accumulation increases risk of clinical progression in preclinical AD (i.e. effect modification).

When considering potential mediation in the context of the present study, Baldaranov et al.'s analysis provided a key first step, as their models were adjusted for baseline amyloid burden, implying that amyloid deposition may confound this association. This is a reasonable assumption given lobar CMHs in particular may be caused by β-amyloid deposition into vessel walls. Crude mediation could potentially be evaluated if estimates from the present models were compared to models without baseline amyloid burden via the Baron-Kenny method. One potential limitation of this present analysis is a lack of location-specific analyses, as incident CMHs were aggregated together regardless of their lobar or deep location, which may have aided in informing mechanisms. One way to more formally address the question of mediation would be to conduct a causal mediation analysis [4], which could estimate whether randomization to treatment with an anti-amyloid medication would reduce risk of cognitive decline through reduction of CMH accumulation, or alternatively, whether reducing CMH accumulation in the presence of stable amyloid deposition would reduce risk of cognitive decline. A restriction to this type of analysis in the A4 data specifically is the lack of clinical progression, which was shown in a recent mediation analysis to greatly limit the extent to which an effect could be detected [5]. Therefore, other individual-level clinical trials data with a larger sample size could be considered to approach this research question with a causal mediation framework in mind.

When considering potential effect modification in the context of the present study, Baldaranov et al. took key steps to examine interactions between CMH accumulation, time, and treatment. The next step in this line of work would be to examine interactions with baseline amyloid burden, which could tell us whether these pathologies work synergistically with risk of cognitive decline. Stratified analyses by levels of amyloid deposition would also be informative and could tell us whether the effect of CMHs on cognitive decline vary by levels of baseline amyloid, though residual confounding would be an issue to consider when interpreting stratified results. By considering effect modification in this case, one would be considering how cerebrovascular disease impacts one's cognitive or brain reserve, which explains how the clinical syndrome of dementia can be heterogeneous despite similar amyloid burden across participants.

Baldaranov et al.'s exploratory analysis of the A4 dataset the stage for future evaluation of CMH accumulation as a signal for early clinical progression in preclinical AD. Future work is required to validate their claims and triangulate evidence across different populations and study designs. Their data supports the notion that CMH accumulation is

https://doi.org/10.1016/j.tjpad.2026.100710
Received 10 November 2026; Accepted 16 November 2026
Available online 21 November 2026
2274-5807/© 2026 The Authors. Published by Elsevier Masson SAS on behalf of SERDI Publisher. This is an open access article under the CC BY license (http://creativecommons.org/licenses/by/4.0/).

associated with self- and informant-reported measures of cognitive and functional status, highlighting the importance of these reports as indicators of clinical decline. If CMH accumulation is on a causal pathway, then MRI screening for such pathology may aid in prognosticating clinical trajectories. If CMH accumulation modifies the effect of amyloid deposition on clinical outcomes, then they can be used to risk-stratify patients. Both relationships could exist, and moderated mediation can also be formally evaluated in future analyses. Ultimately, future work should consider these analyses from a causal perspective, as answering these causal questions will help inform mechanisms and clinical practice.

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

None.

CRediT authorship contribution statement

Michelle R. Caunca: Conceptualization, Writing – original draft, Writing – review & editing. **Sarah F. Ackley:** Conceptualization, Writing – review & editing. **Jane S. Paulsen:** Conceptualization, Writing – review & editing.

Declaration of competing interest

The authors have no competing interests to declare. This work was funded by the Alzheimer's Association P0590624 and National Institute Of Neurological Disorders And Stroke K23NS151370.

References

[1] Greenberg SM, Bacskai BJ, Hernandez-Guillamon M, Pruzin J, Sperling R, van Veluw SJ. Cerebral amyloid angiopathy and Alzheimer disease - one peptide, two pathways. Nat Rev Neurol 2020;16(1):30–42. https://doi.org/10.1038/s41582-019-0281-2.

[2] Baldaranov D, Wang S, Raman R, et al. Cerebral microhemorrhage and cognition in preclinical Alzheimer's disease. J Prevent Alzheimer's Dis 2026;13(10):100681. https://doi.org/10.1016/j.tjpad.2026.100681.

[3] 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.

[4] Rudolph KE, Goin DE, Paksarian D, Crowder R, Merikangas KR, Stuart EA. Causal mediation analysis with observational data: considerations and illustration examining mechanisms linking neighborhood poverty to adolescent substance use. Am J Epidemiol 2019;188(3):598–608. https://doi.org/10.1093/aje/kwy248.

[5] Ackley SF, Flanders MD, Murchland A, et al. Evaluation of amyloid change as a surrogate for cognitive decline: demonstration in individual-level data from the A4 study of solanezumab. A&D Transl Res Clin Interv 2026;12(1):e70205. https://doi.org/10.1002/trc2.70205.

Michelle R. Caunca[a,*], Sarah F. Ackley[b], Jane S. Paulsen[a]

[a] *Department of Neurology, University of Wisconsin-Madison, Madison, WI, United States*

[b] *Department of Epidemiology, Brown University, Providence, RI, United States*

[*] Corresponding author at: University of Wisconsin-Madison, Madison, WI, United States.

E-mail address: caunca@wisc.edu (M.R. Caunca).