

Accelerated epigenetic aging as a modifier of homocysteine-associated cognitive decline: Findings from NHANES

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KEY TAKE AWAY • Elevated homocysteine is linked to poorer cognitive processing speed; GrimAge2 and β 2-microglobulin mediate this association; folate appears protective mainly by lowering homocysteine rather than suppressing downstream inflammatory-aging pathways.

INTRODUCTION	METHODS	RESULTS	RESULTS	CONCLUSIONS
Background - Hyperhomocysteinemia (Hhcy) is a potentially modifiable risk factor for cognitive decline and dementia. - Elevated homocysteine (Hcy) may affect cognition through one-carbon metabolism, oxidative stress, vascular dysfunction, excitotoxicity, and inflammatory pathways. - The contribution of epigenetic aging to Hcy-related cognitive decline has not been systematically quantified. Objective To test whether epigenetic age acceleration and inflammatory components mediate the association between Hcy and cognitive performance in older adults.	Study population - NHANES 1999-2002, adults aged ≥ 60 years. - Main analytic sample: $n = 1,343$ with DNA methylation data, DSST, Hcy, folate, vitamin B12, and covariates. - Independent validation cohort: $n = 2,073$ with measured serum β2-microglobulin. Measurements and analyses - Exposure: log2-transformed serum homocysteine. - Epigenetic aging: HorvathAge, HannumAge, PhenoAge, GrimAge2, DunedinPoAm, DNAmTL. - Models: survey-weighted generalized linear models, restricted cubic splines, weighted mediation, serial mediation, moderated mediation, network pharmacology. - Fully adjusted models included demographics, BMI, smoking, alcohol, diabetes, folate, and vitamin B12.	Key findings - Hhcy participants showed lower DSST scores than non-Hhcy participants (35.0 ± 15.7 vs 40.9 ± 18.9; $P < 0.001$). - Each doubling of Hcy was associated with lower DSST score in the fully adjusted model ($\beta = -2.371$; 95% CI, -4.286 to -0.456; $P = 0.036$). - Higher Hcy was associated with accelerated GrimAge2 ($\beta = 1.661$; $P = 0.0007$) and PhenoAge ($\beta = 1.397$; $P = 0.0415$). - Grim2EAA mediated 33.3% of the Hcy-DSST association; PhenoEAA mediated 15.1%. β2-microglobulin was the strongest validated mediator: measured serum β2M mediated 38.8% of the total effect in the validation cohort. (A) $F_{total} = -0.801$ (95% CI: -1.098, -0.510) $PE = -0.175$ (0.177, -0.350) $F_{ind} = -1.517$ (95% CI: -2.309, -0.725) (B) $F_{total} = -0.375$ (95% CI: -0.691, -0.119) $PE = -0.175$ (0.225, -0.575) $F_{ind} = -1.561$ (95% CI: -3.335, -0.387) (C) $F_{total} = -0.376$ (95% CI: -0.577, -0.187) $PE = -0.175$ (0.185, -0.450) $F_{ind} = -1.591$ (95% CI: -2.295, -0.786) (D) $P = 0.001$ (95% CI: 0.001, 0.002) $P = 0.001$ (95% CI: 0.001, 0.002) $P = 0.001$ (95% CI: 0.001, 0.002) $P = 0.001$ (95% CI: 0.001, 0.002)	Interpretation - Epigenetic aging-associated inflammatory biology may provide a mechanistic bridge between Hcy elevation and poorer cognitive performance. β2-microglobulin emerged as a central component linking Hcy with cognitive aging, supporting an inflammatory-aging pathway. - Folate was associated with lower Hcy and better DSST performance, but it did not significantly moderate downstream Hcy $\rightarrow$ epigenetic aging/β2M $\rightarrow$ cognition pathways. Implications - Hcy control may be most valuable during primary prevention before downstream inflammatory-aging cascades become established. - Future studies should test combined strategies targeting Hcy reduction plus inflammatory or epigenetic aging pathways. (B) $F_{total} = -0.201$ (95% CI: -0.350, -0.052) $PE = -0.175$ (0.185, -0.450) $F_{ind} = -1.206$ (95% CI: -0.613, -1.900) (C) $F_{total} = -0.201$ (95% CI: -0.350, -0.052) $PE = -0.175$ (0.185, -0.450) $F_{ind} = -1.206$ (95% CI: -0.613, -1.900)	In conclusion, this study demonstrates that folate supplementation enhances cognitive function through homocysteine-lowering mechanisms. Importantly, epigenetic aging-related neuroinflammation emerges as a critical pathophysiological pathway linking Hhcy to cognitive deterioration, providing novel mechanistic insights that may inform precision prevention strategies and therapeutic target identification in elderly populations. CONTACT Correspondence Sha Li, PhD Department of Human Anatomy Hebei Medical University Email: lisha@hebmu.edu.cn ALZHEIMER'S ASSOCIATION AAIC 26