education, race/ethnicity, number of *APOE* ε4 status, or cognitive diagnosis (all p's > .027). **Conclusions:** In this matched case-control design, our findings suggest that a history of TBI, regardless of demographic factors, *APOE* ε4 status, and cognitive diagnosis, does not significantly alter the course of neurocognitive functioning later-in-life in older adults with and without cognitive impairment. Future clinicopathological longitudinal studies with well characterized TBI histories and the associated clinical course are needed to help clarify the mechanism by which TBI may increase dementia risk for some individuals, without affecting course of decline.

Categories: Aging
Keyword 1: brain injury
Keyword 2: cognitive course
Keyword 3: dementia - Alzheimer's disease
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5 Rejuvenating Blood Factor TIMP2 Relates to Physical Activity and Cognitive Functioning in Older Adults on The Alzheimer's Disease Continuum

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Objective: Tissue inhibitor of metalloproteinases 2 (TIMP2) is produced peripherally, crosses the blood-brain barrier, and improves synaptic plasticity and hippocampal-dependent cognition in aged mice; however, the role of TIMP2 in human cognitive aging is unclear. We examined associations of circulating TIMP2 levels in blood with a known plasticity-inducing behavior, physical activity, and cognitive functioning among older adults along the Alzheimer's disease continuum. **Participants and Methods:** Participants included 84 community-dwelling older adults ($mean_{age}$ = 78.8; 57% female; 82% cognitively normal; 14% MCI; 4% mild dementia; 35% PET Aß+) enrolled in the UC San Francisco Memory and Aging Center. All participants completed 30 days of observational Fitbit™ monitoring to quantify physical activity (average daily steps), as well as a comprehensive in-person visit including blood draw (proteins assayed on SOMAscan platform), [18F]AV-45 positron emission tomography (PET) to quantify brain beta-amyloid (centiloids), and neuropsychological assessment. Composite cognitive z-scores were calculated for memory (California Verbal Learning Test-II [CVLT-II] and Benson Figure Recall), semantic processing (animal fluency and Boston Naming Test), and executive functioning (digits backwards span, Stroop inhibition, modified trail making test, lexical fluency, and design fluency). Multiple linear regression examined TIMP2 as a function of physical activity, covarying for age and PET centiloids. Additional regression models separately examined cognitive z-scores as a function of TIMP2, covarying for age, sex, education, PET centiloids, and body mass index (BMI).
Results: TIMP2 was not significantly correlated with age, sex, education, or PET centiloids (*p*s > 0.05); however, TIMP2 was negatively correlated with BMI (r = -0.23, p = 0.036). Greater average daily steps related to higher levels of TIMP2 (b = 0.30, *95%CI* = 0.04-0.55, p = 0.022). TIMP2 also related to better semantic processing (b = 0.28, *95%CI* = 0.04-0.51, p = 0.021) and executive functioning (b = 0.26, *95%CI* = 0.03-0.49, p = 0.028). TIMP2 did not significantly relate to memory (p > 0.05).
Conclusions: Greater physical activity was associated with higher concentrations of blood factor TIMP2, which in turn related to better cognitive functioning independent of Alzheimer's disease pathology burden. These results support previous mouse models by broadly replicating relationships between TIMP2 and cognition in humans, while also uniquely demonstrating an association between TIMP2 and physical activity, a modifiable protective factor in both typical and diseased cognitive aging. Our domain-specific results, however, suggest that benefits of TIMP2 in humans may involve a broader neuroanatomical network than the hippocampal-specific effects previously shown in mice. Although exact mechanisms of TIMP2 need further examination, TIMP2 is known to be enriched in human umbilical cord plasma, has been shown to be involved in cell-growth promoting activities, and may relate to increased neural plasticity in older age. Further examination of TIMP2 and other novel blood-based proteins as potential therapeutic targets

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for improved cognitive aging, including in the presence of Alzheimer's disease, is warranted.

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6 Pulse Pressure and APOE ε4 Dose Interact to Affect Cerebral Blood Flow in Older Adults Without Dementia

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Objective: Alterations in cerebral blood flow (CBF) are associated with risk of cognitive decline and Alzheimer's disease (AD). Although apolipoprotein E (APOE) ε4 and greater vascular risk burden have both been linked to reduced CBF in older adults, less is known about how APOE ε4 status and vascular risk may interact to influence CBF. We aimed to determine whether the effect of vascular risk on CBF varies by gene dose of APOE ε4 alleles (i.e., number of ε4 alleles) in older adults without dementia.
Participants and Methods: 144 older adults without dementia from the Alzheimer's Disease Neuroimaging Initiative (ADNI) underwent arterial spin labeling (ASL) and T1-weighted MRI, APOE genotyping, fluorodeoxyglucose positron emission tomography (FDG-PET), lumbar puncture, and blood pressure assessment. Vascular risk was assessed using pulse pressure (systolic blood pressure – diastolic blood pressure), which is thought to be a proxy for arterial stiffening. Participants were classified by number of APOE ε4 alleles ($n_{0\ alleles}$ = 87, $n_{1\ allele}$ = 46, $n_{2\ alleles}$ = 11). CBF in six FreeSurfer-derived *a priori* regions of interest (ROIs) vulnerable to AD were examined: entorhinal cortex, hippocampus, inferior temporal cortex, inferior parietal cortex, rostral middle frontal gyrus, and medial orbitofrontal cortex. Linear regression models tested the interaction between categorical APOE ε4 dose (0, 1, or 2 alleles) and continuous pulse pressure on CBF in each ROI, adjusting for age, sex, cognitive diagnosis (cognitively unimpaired vs. mild cognitive impairment), antihypertensive medication use, cerebral metabolism (FDG-PET composite), reference CBF region (precentral gyrus), and AD biomarker positivity defined using the ADNI-optimized phosphorylated tau/β-amyloid ratio cut-off of > 0.0251 pg/ml.
Results: A significant pulse pressure X APOE ε4 dose interaction was found on CBF in the entorhinal cortex, hippocampus, and inferior parietal cortex (*p*s ≤ .005). Among participants with two ε4 alleles, higher pulse pressure was significantly associated with lower CBF (*p*s ≤ .001). However, among participants with zero or one ε4 allele, there was no significant association between pulse pressure and CBF (*p*s ≥ .234). No significant pulse pressure X APOE ε4 dose interaction was found in the inferior temporal cortex, rostral middle frontal gyrus, or medial orbitofrontal cortex (*p*s ≥ .109). Results remained unchanged when additionally controlling for general vascular risk assessed via the modified Hachinski Ischemic Scale.
Conclusions: These findings demonstrate that the cross-sectional association between pulse pressure and region-specific CBF differs by APOE ε4 dose. In particular, a detrimental effect of elevated pulse pressure on CBF in AD-vulnerable regions was found only among participants with the ε4/ε4 genotype. Our findings suggest that pulse pressure may play a mechanistic role in neurovascular unit dysregulation for those genetically at greater risk for AD. Given that pulse pressure is just one of many potentially modifiable vascular risk factors for AD, future studies should seek to examine how these other factors (e.g., diabetes, high cholesterol) may interact with APOE genotype to affect cerebrovascular dysfunction.

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