attention/executive functioning scores, but only in those with T2D (β=-.116, [-.225, -.006], p=.038). This interaction was not significant for language or memory.

Conclusions: The results show that Aβ may negatively impact attention/executive functioning, but this effect was only found in Veterans with T2D. Prior work has suggested that T2D may be more associated with tau biomarkers than markers of Aβ, so it is possible that the current results are due to a compounding effect of Aβ pathology plus microvascular and/or tau pathology. Notably, the sample was relatively young, a relatively large proportion had elevated PTSD symptoms and/or a TBI history (which have both been shown to relate to attention/executive function), and the measures that made up the attention/executive composite (Trail Making Test A and B) have been shown to be particularly sensitive – all of which may have contributed to the domain-specific effects. Future research is needed to investigate the role that tau and vascular pathology may play in cognition among individuals with T2D. Longitudinal studies are also needed to better understand the timing and progression of these relationships.

Categories: Aging
Keyword 1: diabetes
Keyword 2: dementia - Alzheimer's disease
Keyword 3: attention
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4 Traumatic Brain Injury Does Not Alter the Course of Neurocognitive Functioning Later in Life

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Objective: History of traumatic brain injury (TBI) is associated with increased risk of dementia, but few studies have evaluated whether TBI history alters the course of neurocognitive decline, and existing literature on this topic is limited to short follow-up and smaller samples. The primary aim of this study was to evaluate whether a history of TBI (TBI+) influences neurocognitive decline later-in-life among older adults with or without cognitive impairment [i.e., normally aging, Mild Cognitive Impairment (MCI), or dementia].

Participants and Methods: Participants included individuals from the National Alzheimer's Coordinating Center (NACC) who were at least 50 years old and with 3 to 6 visits (M number of visits = 4.43). Participants with any self-reported history of TBI (n = 1,467) were matched 1:1 to individuals with no reported history of TBI (TBI-) from a sample of approximately 45,000 participants using case-control matching based on age (+/- 2 years), sex, education, race, ethnicity, cognitive diagnosis [cognitively normal (CN), MCI, or all-cause dementia], etiology of cognitive impairment, functional decline (Clinical Dementia Rating Scale, CDR), number of Apolipoprotein E4 (*APOE* ϵ4) alleles, and number of annual visits (3 to 6). Mixed linear models were used to assess longitudinal neuropsychological test composites (using NACC normative data) of executive functioning/attention/speed (EFAS), language, and memory in TBI+ and TBI- participants. Interactions between TBI and demographics, *APOE* ϵ4 status, and cognitive diagnosis were also examined.

Results: Following matching procedures, TBI+ (n=1467) and TBI- (n=1467) groups were nearly identical in age (TBI+ M = 71.59, SD = 8.49; TBI- M = 71.63, SD = 8.44), education (TBI+ M = 16.12, SD = 2.59; TBI- M = 16.10, SD = 2.52), sex (both 55% male), race (both 90% White), ethnicity (both 98% non-Hispanic), *APOE* ϵ4 alleles (both 0 = 62%, 1 = 33%, 2 = 5%), baseline cognitive diagnoses (both CN = 60%, MCI = 18%, dementia = 12%), and global CDR (TBI+ M = 0.30, SD = 0.38, TBI- M = 0.30, SD = 0.38). At baseline, groups had similar Z-scores of in EFAS (TBI+ M_{EFAS} = -0.02, SD = 1.21; TBI- M_{EFAS} = -0.04, SD = 1.27), language (TBI+ $M_{Language}$ = -0.48, SD = 0.98; TBI- $M_{Language}$ = -0.55, SD = 1.05), and memory (TBI+ M_{Memory} = -0.45, SD = 1.28; TBI- M_{Memory} = -0.45, SD = 1.28). The course of change in neuropsychological functioning worsened longitudinally, but did not differ between TBI groups (p's > .110). There were no significant interactions between TBI history and age, sex,

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^{TM} 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 (ps > 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