UNIVERSITY OF CALIFORNIA SAN DIEGO

SAN DIEGO STATE UNIVERISTY

The buffering role of social contact on risk factors for later-life cognitive decline

A Dissertation submitted in partial satisfaction of the requirements
for the degree Doctor of Philosophy

in

Public Health (Epidemiology)

by

Alexander Ivan Barbadillo Posis

Committee in charge:

University of California, San Diego

Professor Linda K. McEvoy, Chair
Professor William S. Kremen
Professor Aladdin H. Shadyab

San Diego State University

Professor John E. Alcaraz
Professor Humberto Parada, Jr.

2023

The Dissertation of Alexander Ivan Barbadillo Posis is approved, and it is acceptable in quality and form for publication on microfilm and electronically.

_____

_____

_____

_____

_____

Chair

University of California San Diego

San Diego State University

2023

Dedication

To my mom, dad, brother, and sister.

Table of Contents

List of Figures

List of Tables

Acknowledgements

I would first like to acknowledge the chair of my committee, Dr. Linda McEvoy. Thank you for your positive enthusiasm, mentorship, and support which has shaped me into a stronger and more thoughtful researcher. I thank my committee members Drs. William Kremen, Aladdin Shadyab, John Alcaraz, and Humberto Parada Jr. for their valuable expertise and support on my dissertation research. Thank you for your guidance and encouragement during this program. I would also like to thank my mentors, family, and friends, especially my classmates, who have made our doctoral experience so much more fun. Lastly, I would like to thank my mom, dad, brother, sister, and corgi, Alfie, for their love, patience, and support. This dissertation would not be possible without you.

Chapter 2, in part, is currently being prepared for submission for publication of the material. Posis, Alexander Ivan B.; Alcaraz, John E.; Parada Jr., Humberto; Shadyab, Aladdin H.; Elman, Jeremy A; Panizzon, Matthew S.; Reynolds, Chandra A.; Franz, Carol E.; Kremen, William S.; McEvoy, Linda K. The dissertation author was the primary researcher and author of this paper.

Chapter 3, in part, is currently being prepared for submission for publication of the material. Posis, Alexander Ivan B.; Elman, Jeremy A.; Alcaraz, John E.; Parada Jr., Humberto; Shadyab, Aladdin H.; Fennema-Notestine, Christine; Hagler Jr., Donald J.; Lyons, Michael J.; Panizzon, Matthew S.; Reynolds, Chandra A.; Franz, Carol E; Kremen, William S.; McEvoy, Linda K. The dissertation author was the primary researcher and author of this material.

Chapter 4, in full, has been submitted for publication of the material as it may appear in the Journal of Alzheimer's Disease. Posis, Alexander Ivan B.; Shadyab, Aladdin H.; Parada Jr.,

Humberto; Alcaraz, John E.; Kremen, William S.; McEvoy, Linda K. The dissertation author was the primary investigator and author of this paper.

Vita

2015 Bachelor of Science in Neuroscience, University of California Santa Cruz

2018 Master of Public Health in Epidemiology, San Diego State University

2023 Doctor of Philosophy in Public Health (Epidemiology), University of California San Diego and San Diego State University

Publications

Kassem NOF, Kassem NO, Liles S, Jackson SR, **Posis AIB**, Chatfield DA, Hovell MF. Levels of Urine Cotinine from Hookah Smoking and Exposure to Hookah Tobacco Secondhand Smoke in Hookah Lounges and Homes. Int J High Risk Behav Addict. 2018 Mar;7(1):e67601. doi: 10.5812/ijhrba.67601. Epub 2018 Feb 19. PMID: 29805963; PMCID: PMC5967845.

Kassem NOF, Jackson SR, Kassem NO, Liles S, **Posis AIB**, Hovell MF. College Student Beliefs and Behavior Regarding Sharing When Smoking Hookahs. Am J Health Behav. 2019 Jan 1;43(1):133-144. doi: 10.5993/AJHB.43.1.11. PMID: 30522572; PMCID: PMC6662911.

Posis A, Bellettiere J, Liles S, Alcaraz J, Nguyen B, Berardi V, Klepeis NE, Hughes SC, Wu T, Hovell MF. Indoor cannabis smoke and children's health. Prev Med Rep. 2019 Mar 16;14:100853. doi: 10.1016/j.pmedr.2019.100853. PMID: 30976488; PMCID: PMC6441784.

Kassem NO, Kassem NO, Liles S, Reilly E, Kas-Petrus F, **Posis AIB**, Hovell MF. Waterpipe device cleaning practices and disposal of waste associated with waterpipe tobacco smoking in homes in the USA. Tob Control. 2020 Feb;29(Suppl 2):s123-s130. doi: 10.1136/tobaccocontrol-2019-054959. Epub 2019 Jul 20. PMID: 31326957; PMCID: PMC6980180.

Bellettiere J, Liles S, **Posis AIB**, Anuskiewicz B, Tripathi O, Nguyen B, Chavez P, Zhu SH, Park JY, Winstock A, Ferris J. In-home cannabis smoking more prevalent than in-home tobacco smoking among 2019 Global Drug Survey respondents. Addict Behav. 2022 Feb;125:107130. doi: 10.1016/j.addbeh.2021.107130. Epub 2021 Oct 1. PMID: 34674905.

Posis AIB, Tarraf W, Gonzalez KA, Soria-Lopez JA, Léger GC, Stickel AM, Daviglus ML, Lamar M, Zeng D, González HM. Anticholinergic Drug Burden and Neurocognitive Performance in the Study of Latinos-Investigation of Neurocognitive Aging. J Alzheimers Dis. 2022;86(1):53-65. doi: 10.3233/JAD-215247. PMID: 35001889; PMCID: PMC9632492.

Bañuls-Mirete M, Lombardi AF, **Posis AIB**, Shadyab AH, Chang EY, Lane NE, Guma M. Effusion-synovitis worsening mediates the association between body mass index and Kellgren-Lawrence progression in obese individuals: data from the Osteoarthritis Initiative. Osteoarthritis Cartilage. 2022 Sep;30(9):1278-1286. doi: 10.1016/j.joca.2022.05.011. Epub 2022 Jun 14. PMID: 35714760; PMCID: PMC9910445.

Posis AIB, Bellettiere J, Salem RM, LaMonte MJ, Manson JE, Casanova R, LaCroix AZ, Shadyab AH. Associations of Accelerometer-Measured Physical Activity and Sedentary Time With All-Cause Mortality by Genetic Predisposition for Longevity. J Aging Phys Act. 2022 Aug 24;31(2):265-275. doi: 10.1123/japa.2022-0067. PMID: 36002033; PMCID: PMC9950283.

Giudicessi AJ, Saelzler UG, Shadyab AH, **Posis AIB**, Sundermann EE, Banks SJ, Panizzon MS. The mediating role of socioeconomic status on the relationship between pregnancy history and later-life cognition. Climacteric. 2022 Oct 11:1-7. doi: 10.1080/13697137.2022.2129004. Epub ahead of print. PMID: 36218124.

Tripathi O, **Posis AIB**, Thompson CA, Ferris J, Anuskiewicz B, Nguyen B, Liles S, Berardi V, Zhu SH, Winstock A, Bellettiere J. In-Home Cannabis Smoking Among a Cannabis-Using Convenience Sample from the Global Drug Survey: With Weighted Estimates for U.S. Respondents. Cannabis Cannabinoid Res. 2022 Nov 1. doi: 10.1089/can.2022.0139. Epub ahead of print. PMID: 36318789.

Posis AIB, Yarish NM, McEvoy LK, Jain P, Kroenke CH, Saquib N, Ikramuddin F, Schnatz PF, Bellettiere J, Rapp SR, Espeland MA, Shadyab AH. Association of Social Support with Mild Cognitive Impairment and Dementia Among Older Women: The Women's Health Initiative Memory Study. J Alzheimers Dis. 2023;91(3):1107-1119. doi: 10.3233/JAD-220967. PMID: 36565123; PMCID: PMC9905323.

Ryu RH, Larsen B, LaCroix A, Nguyen S, **Posis AIB**, Schumacher BT, Danhauer SC, Tindle HA, Bellettiere J. Associations of Physical Activity and Sedentary Behavior with Optimism and Positive Affect in Older Women. Journal of Happiness Studies. 2023 Jan 10:1-27.

Posis AIB, Yarish NM, Ryu RH, Tindle HA, Michael YL, Wactawski-Wende J, Bellettiere J. Psychometric Analysis of the Modified Differential Emotions Scale and the Six-Item Life Orientation Test-Revised in a Cohort of Older Women from the Women's Health Initiative. J Womens Health (Larchmt). 2023 Sep;32(9):992-1005. doi: 10.1089/jwh.2023.0056. Epub 2023 Jul 17. PMID: 37449819; PMCID: PMC10510696.

Thai NQN, LaCroix AZ, Haring B, Wactawski-Wende J, Manson JE, **Posis AIB**, Shadyab AH. The association of leukocyte telomere length with exceptional longevity among older women. Geroscience. 2023 Oct 16. doi: 10.1007/s11357-023-00964-6. Epub ahead of print. PMID: 37843740.

Abstract of the Dissertation

The buffering role of social contact on risk factors for later-life cognitive decline

by

Alexander Ivan Barbadillo Posis

Doctor of Philosophy in Public Health (Epidemiology)

University of California San Diego, 2023

San Diego State University, 2023

Professor Linda K. McEvoy, Chair

Background: Traumatic brain injury (TBI), multimorbidity, and lower social contact are associated with worse cognitive health outcomes among older adults. While greater social contact is associated with lower risk of dementia, it is unknown if aspects of social connection buffer the relationships of TBI or multimorbidity with cognitive and brain health in aging.

Methods: This dissertation includes three studies. Using Vietnam Era Twin Study of Aging data, we tested prospective associations of TBI with cognitive performance trajectories in Study 1, and cross-sectional associations between TBI and markers of brain health in Study 2. In Study 3, we tested prospective associations of multimorbidity with cognitive performance trajectories in the Rancho Bernardo Study of Healthy Aging. In all studies, we tested for effect measure modification (EMM) by measures of social connectedness.

Results: In Study 1, TBI was associated with greater decline in executive function, primarily among *APOE* ε4 carriers (β=-0.017; 95% CI=-0.033,-0.0019) compared to non-carriers (β=-0.0036; 95% CI=-0.013,0.0063; $P_{\text{Interaction}}$=0.03). Relative to no TBI, TBI prior to military induction was associated with greater executive function decline (β=-0.011; 95% CI=-0.021,-7e-04). In Study 2, TBI was associated with microstructural differences in a white matter tract connecting occipital and temporal lobes, compared to no TBI (β=-0.017; SE=0.005; FDR-corrected p-value<0.01). There was no evidence of EMM by social connectedness (defined as loneliness) in Studies 1 or 2. In Study 3, multimorbidity was associated with faster declines in scores on the Mini-Mental State Examination (MMSE; β=-0.20; 95% CI=-0.35,-0.04), Trail-Making Test Part B (β=10.02; 95% CI=5.77,14.27), and Category Fluency (β=-0.42; 95% CI=-0.72,-0.13). There was EMM by social engagement; multimorbidity was associated with faster MMSE declines among those with low compared to medium or high social engagement ($P_{\text{Interaction}}$<0.01).

Conclusion: These results highlight the role of multimorbidity and remote TBI on cognitive health in aging. While our results do not support a buffering role of loneliness on effects of remote TBI on cognitive or brain health, they suggest that social engagement may support reducing adverse cognitive consequences of multimorbidity. These findings can inform

efforts focused on increasing social contact to reduce cognitive decline and improve wellbeing, particularly among those with multimorbidity.

Chapter 1 Introduction

1.1 Public health impact of Alzheimer's disease and other dementias

More than 55 million people live with dementia globally, and this prevalence is expected to increase to 78 million by the year 2030.[1] The annual global cost of dementia is estimated at $1 trillion and is forecasted to reach $2 trillion by 2030.[2] The prevalence of dementia increases with age, which is concerning given the growing older adult population. In 2011, Alzheimer's disease prevalence among older adults in the United States (US) was estimated to be 0.7 million among those aged 65-74 years, 2.3 million for 75-84 years, and 1.8 million for ≥85 years.[3] Therefore, there is a strong need to identify potentially modifiable risk factors to inform interventions and policies to reduce risk of dementia and cognitive decline in aging.

1.2 Modifiable risk factors for dementia

The Lancet Commission in 2020 proposed 12 modifiable risk factors for dementia which included traumatic brain injury (TBI) and social contact.[4] Additionally, multimorbidity (i.e., the presence of 2 or more chronic conditions) is increasingly prevalent among older adults.[5] Older adults with multimorbidities may have faster declines in cognitive function.[6] and increased risk of dementia.[7–9]

1.3 Risk factors under the lifecourse framework

The effects of TBI, multimorbidity, and social contact at different points in life with later-life cognitive decline and markers of brain health can be contextualized using a lifecourse framework.[10,11] Under this framework, TBI and multimorbidity can affect, or be affected by, social contact, which in turn affects later-life cognitive decline and markers of brain health.

However, there is no research on how social contact at mid-to-later life affects the relationships between TBI and multimorbidity with later-life cognitive decline and markers of brain health.

1.4 Traumatic brain injury (TBI)

Approximately 1.5 million Americans sustain a TBI annually and TBI is a major cause of death and disability in the US.[12] TBI is typically caused by direct impact or jolt to the head, or a penetrating injury. The most common mechanisms of injury include vehicular crashes and blast exposure.[13,14] TBIs are an important outcome to monitor given 176 TBI-related deaths daily in 2020 and over 223,000 hospitalizations in 2019.[13] However, the prevalence of TBI is likely underestimated for several reasons, including undiagnosed injuries and low care-seeking behaviors.[15] Additionally, those with TBI may have earlier onset of Alzheimer's disease and related dementias (ADRD) compared to those without TBI,[16–18] highlighting the need to study these injuries in relation to cognitive aging outcomes. Given the ubiquity of these injuries, it is important to understand TBI's effect on cognitive trajectories and brain health, especially at later life.

1.5 TBI and dementia

In terms of pathology, TBI is associated with tau pathology in human and mice models[19] as well as greater hippocampal hyper-phosphorylated tau among mice with the *APOE* ε4 genotype.[20] These findings along with others suggest shared mechanisms between Alzheimer's disease and TBI-related neurodegeneration.[21] However, there is inconsistent epidemiologic evidence on the associations between TBI with dementia and cognitive decline.

Some have found relations between TBI with incident dementia.[22–29] The Lancet Commission 2020 reported that those with TBI compared to no TBI had an 84% higher risk of dementia.[4] This high risk is consistent with studies of US veteran cohorts. One cohort study

among 188,764 US veterans found that 16% of those with TBI history developed dementia compared to 10% among those without TBI history.[22] Another study of 357,558 veterans found that those with mild TBI history had a 2.36 times higher risk of dementia relative to those without mild TBI after an average of 4.2 years of follow up.[23] In another study of 999,640 veterans with a median 4.3 years of follow, those with TBI had a 74%, 115%, and 171% higher risk of dementia diagnosis for Hispanic, Black, and White veterans, respectively.[26] In a large Danish cohort of 2,794,852 with an average 9.89 years follow up, those with history of TBI had 24% higher risk of all-cause dementia compared to those with no TBI history.[24] Similarly, in a retrospective cohort study of 164,661 participants identified in a California administrative health database, those with TBI history had a 26% higher risk of dementia compared to no TBI history after 5-7 years of follow-up.[25]

In contrast, others found no associations between TBI with Alzheimer's disease pathology,[30–32] any ADRD,[33] and changes in midlife cognition.[34] For example, in a cohort study of 7,310 using pooled data from the Adult Changes in Thought (ACT) study, the Religious Orders Study (ROS), and the Memory and Aging Project (MAP), self-reported TBI with LOC compared to those without TBI with loss of consciousness (LOC) was not associated with incident dementia after 45,190 person-years of follow up (Hazard Ratio [HR] range = 0.84-1.18).[30] Within the ACT study, examination of 4,225 dementia-free older adults with an average 7.4 years of follow-up, showed that self-reported first TBI at ages <25 years, 25-54 years and ≥55 years compared to no TBI was not associated with any dementia (Time Ratios [95% CI]: 1.02 [0.87-1.20], 1.04 [0.78-1.38], 1.06 [0.81-1.39], respectively).[33] The authors also did not find a significant interaction between APOE e4 and TBI with risk of dementia (likelihood ratio p = 0.60) or probable Alzheimer's disease (likelihood ratio p = 0.82).[33]

1.6 TBI and cognitive performance

Many studies relied on ICD or autopsy-confirmed diagnoses of Alzheimer's disease and related dementias. However, few examined TBI's association with cognitive performance.[31,34–39] This would clarify which domains of cognition would be most affected by TBI over time.

One cross-sectional study of 169 older veterans found that those with prior TBI had lower processing speed (beta [β] = -0.52, $p = 0.01$) and executive functioning (β = -0.41, $p = 0.02$).[40] They also found a significant interaction with post-traumatic stress and depressive symptoms, suggesting that those with TBI and these conditions may have greater cognitive deficits.[40] These findings are similar to a cross-sectional study of 146 veterans living in retirement communities that found significant differences in executive function and processing speed ($p < 0.01$).[41] Inferences from these studies could be improved upon with a longitudinal design, which allows for assessment of within-participant change.

In a 3-year cohort study of 52 older adults with TBI and 102 without TBI from the Australian Imaging, Biomarkers and Lifestyle (AIBL) Study of Ageing, self-reported TBI was not associated with primary memory, perceptual speed, verbal memory, visuospatial function, visual memory, verbal ability, and interference (all 95% high density intervals contained 0).[42] The TBI group generally had more pronounced declines on most outcomes, albeit differences were not statistically significant.[42] These results are similar to a cross-sectional study of 4,384 from the Vietnam Experience Study (VES) that found no differences across multiple neuropsychological measures.[37] However, the AIBL cohort ascertained head injuries via medical records, potentially underestimating TBI,[31] and the VES study did not use repeated measures to account for changes in cognitive performance over time.[37]

Two recent prospective studies examined the association between TBI and cognitive decline among middle-to-older aged adults.[38,39] Among 8,662 males (mean baseline age = 67 years; 2,168 with TBI) from the National Academy of Sciences-National Research Center (NAS-NRC) Twin Registry of World War II veterans, TBI was associated with faster declines in Telephone Interview for Cognitive Status–modified (TICS-m) scores over up to a 12 year follow-up (β = -0.56; 95% CI -0.73, -0.39), but did not assess specific cognitive domains.[39] In a study of 15,764 participants (average age = 62.7 years; 6,235 with TBI) from the PROTECT-TBI cohort study, TBI was associated with lower baseline measures of executive function, working memory, episodic memory, and processing speed, but not with differences in longitudinal trajectories across a brief follow-up period of up to 4 years.[38]

In summary, current literature on the relationship between TBI and cognitive performance remains mixed. These results suggest that TBI may have the most effect on executive functioning. However, these hypotheses should be tested in a larger cohort with extended follow up and consider the effects of social contact as a potentially modifiable moderator in the relationship between TBI and cognitive performance.

1.7 TBI and brain health

TBIs may contribute to premature changes to the brain as well.[43,44] In one study of 99 TBI patients and 113 controls, those with TBI had a higher mean predicted brain age difference based on grey matter (4.66 +/- 10.8 years) and white matter (5.97 +/- 11.22 years) compared to controls (grey matter = 0.07 +/- 7.41 years; white matter = 2.06 +/- 7.41 years).[43]

In a study of 28 patients in the post-acute/chronic phase following traumatic brain injury and in 26 age-matched controls, there were significant differences for all cognitive domains (p's<0.01; except word reading processing speed) and those with TBI had white matter

abnormalities.[45] One substudy of 51 participants with prior concussion and 150 controls from the Baltimore Longitudinal Study of Aging did not find significant differences in memory, attention, executive function, language or visuospatial domains.[46] They did find differences in the temporal and frontal regions, including the hippocampus, orbitofrontal cortex and cingulate cortex limbic regions,[46] which play a role in executive function.[47,48] In a case-control study of 92 patients with moderate to severe TBI (mean age = 42.9 years; 21% female) and 105 controls, there were significant differences for intellectual ability, information processing, executive functioning, and memory (p's<0.05).[49] Another case-control study of 30 veterans and 15 controls found that TBI cases with loss of consciousness had reduced executive function performance and altered white matter integrity.[50] However, these studies used smaller samples and did not consider the effect of different measures of social contact. It is plausible that other factors such as social contact may play a role in buffering (i.e., mediating or moderating) these associations.[51]

In contrast, a cross-sectional study of 4,761 participants from the National Alzheimer's Coordinating Center (NACC) found that self-reported TBI was not associated with differences in Alzheimer's disease neuropathologic changes ($\chi^2 = 0.12$; $p = 0.73$) and did not predict these changes (OR = 0.92; 95% CI 0.72-1.14) after controlling for APOE e4 status, age, race, sex, and education.[31] In a pooled study of 7,130 from the ACT, ROS, and MAP, TBI was not associated with dementia, neurotic plaques and neurofibrillary tangles, but was associated with Lewy body accumulation, Parkinsonian progression, and Parkinson disease risk.[30]

In summary, TBI has been associated with older predicted brain age than chronological age, and greater abnormal white matter.[43] Prior studies have identified several neuroimaging-based markers of brain health among mostly younger-aged participants and within shorter temporal proximity to the TBI event.[43,45,52,53] However, research on post-TBI neuroimaging

outcomes among older adults with remote injury are developing,[46] but the mechanisms in which earlier TBI affects later-life outcomes are still not well-understood.[54] Therefore, it is important to assess whether these TBI-related differences are apparent at older age and years after the initial injury.

1.8 Multimorbidity

Multimorbidity is defined as the presence of 2 or more chronic conditions. The aging of our populations has coincided with a growing proportion of those with multimorbidities.[5,55] Approximately 42% of US adults had multimorbidity between 2008-2014, with the prevalence rising to 81% among older adults.[5] It is associated with increased risk of disability and other adverse health outcomes compared to those without multimorbidity.[5] Additionally, multimorbidity is increasingly prevalent among older adults.[5]

In a 7-year cohort study of 2,176 in the Mayo Clinic Study of Aging (MCSA), multimorbidity was associated with 38% higher risk of MCI or dementia compared to those with ≤1 chronic condition.[9] One 12-year study in the Swedish National Study on Aging and Care in Kungsholmen (SNAC-K) found that cardiometabolic-specific multimorbidity was associated with 73% higher risk of cognitive impairment and 86% higher risk of progression to dementia.[8] Older adults with multimorbidity may have faster declines in cognitive function.[6]

1.9 Multimorbidity and cognitive performance

In terms of cognitive performance, multimorbidity is associated with declines in global cognition.[56] In a 14-year cohort study in the Health and Retirement Study (HRS), increases in a multimorbidity weighted index was associated with faster declines in global cognition, immediate recall, and working memory, but not delayed recall.[57] One BLSA study of 756 participants with an average of 3 years of follow up found that faster accumulation of

multimorbidity was associated with greater declines in verbal fluency (Category fluency: β = -0.13 [0.05], $p = 0.15$; Letter fluency: β = -0.16 [0.06], $p = 0.013$).[6] These analyses had limited follow-up and did not account for the potentially moderating effect of social engagement. One study found that every 5-year earlier onset of multimorbidity was associated with 18% higher risk of dementia compared to those without multimorbidity.

1.10 Differences in defining multimorbidity

Definitions of multimorbidity vary widely which makes comparisons across studies difficult. This may be due in part to data availability and how each condition relates to an outcome of interest. A widely cited review by Fortin et al[55] concluded that multimorbidity indices should include at least 12 conditions. Similar to others who have reviewed multimorbidity studies,[5] they do not provide a precise list of diseases to include but suggest including conditions believed to have the most impact in a study population.[55] To show the different operationalizations of multimorbidity, Table 1.1 outlines conditions that were included in a selection of prior studies of cognitive performance, dementia, and mild cognitive impairment.

Table 1.1 Morbidities included in studies of cognitive performance, dementia, and mild cognitive performance

Morbidity	Hassen et al. 2022[7]	Fabbri et al. 2016[6]	Lee et al. 2021[58]	Vassilaki et al. 2015[9]	Wei et al. 2020[57]	Espeland et al. 2021[56]	Dove et al. 2022[8]	Salive 2013[5]
Angina					●			
Arthritis/rheumatoid arthritis	●		●	●				●
Asthma				●				●
Atrial fibrillation							●	●
Cancer	●	●	●	●	●	●		●
Cardiac arrhythmias				●		●		
Chronic kidney disease	●			●		●		●
Chronic obstructive pulmonary disease	●	●	●	●	●			●
Coronary heart disease/ischemic heart disease	●	●				●	●	●
Depression	●		●	●		●		●
Diabetes	●	●	●	●	●		●	●
Dyslipidemia						●		
Hearing loss								
Heart failure	●	●		●	●	●	●	●
Heart attack/myocardial infarction					●			
Hepatitis				●				
Hip fracture		●						
Hyperlipidemia				●				●
Hypertension	●	●	●	●	●	●		●
Liver disease	●		●					
Lower extremity joint disease		●						
Mental disorders other than depression	●							
Osteoporosis				●				●
Parkinson's disease	●	●						
Schizophrenia				●				
Stroke	●	●		●	●	●	●	●

Note: Salive 2013 studied the relationship of multimorbidity with mortality and other health outcomes. Alzheimer's disease was included in their multimorbidity definition.

1.11 Social contact as a mediator or moderator

Social contact consists of multiple factors that affect well-being which include social isolation, loneliness, and social engagement. Social isolation is an objective measure of social interactions and relationships.[59] Loneliness is a subjective measure of feeling socially isolated.[59] Social engagement is the maintenance of social connection and participation in social activities.[60]

These factors may play a strong role in risk of dementia and cognitive decline.[4] Decreasing levels of social connection are of public health concern, as highlighted by the recent U.S. Surgeon General's Advisory report, "Our Epidemic of Loneliness and Isolation: The U.S. Surgeon General's Advisory on the Healing Effects of Social Connection and Community."[61]

There are several potential mechanisms in which social contact can buffer the relationship of multimorbidity or TBI with cognitive aging. Fratiglioni et al [62] posit a socially active and integrated lifestyle can reduce dementia risk via common pathways through the cognitive reserve, vascular, and stress hypotheses. Under the stress hypothesis, social engagement can lead to positive emotion states that reduce stress,[62] which, in turn, can reduce Alzheimer's disease risk.[63] Perry et al[64] hypothesize that social connectedness, via social bridging and bonding, can affect neurodegenerative, neuroendocrine, and hypothalamic-pituitary-adrenal stress response pathways related to the onset and course of cognitive aging.

The Lancet Commission reported that later life (age >65 years) social isolation is associated with 60% higher risk of all-cause dementia.[4] Individual aspects of social contact, such as loneliness,[65] and social engagement[66] have been associated with cognitive function. Conversely, others have shown non-significant associations between social isolation, social support and loneliness with incident dementia[67] as well as social support with longitudinal cognitive decline.[68] It is plausible that the Lancet Commission's recommended risk factors for dementia are interrelated.[4] However, social contact represents many aspects of social connection and well-being that need to be individually assessed. It would be beneficial for researchers to explicitly define what construct they are examining. Clear definitions of social contact are needed given that these constructs may affect different domains of cognition.[69] This would allow

researchers and policymakers to understand which aspects of social contact may be most impactful to intervene on.

TBI has been associated with lower levels of community integration, life satisfaction and social support[70] as well as increased loneliness.[71,72] Older adults with less frequent social engagement may have a greater accumulation of morbidities.[58,73] Therefore, different measures of social contact may act as mediators or moderators in the association between TBI and multimorbidity with cognitive decline.[51] However, no studies have examined whether social contact, and its specific factors, affect the relationship between TBI or multimorbidity with cognitive decline.

1.12 The Buffering Hypothesis

Social contact may play a role in buffering (i.e., mediating or moderating) the associations of TBI and multimorbidity with later-life cognitive decline using the Buffering Hypothesis framework.[51] The Buffering Hypothesis posits that there is some form of social contact or support system that can buffer an individual from the harmful effects of a stressful event.[51] Using this framework, TBI or multimorbidity can be framed as the harmful event, cognitive decline or brain markers as the outcome, and social contact as the buffer between the harmful event and outcome.

1.13 Overview of dissertation studies

In this dissertation, it is hypothesized that social contact acts as a buffer between TBI and multimorbidity (i.e., the stressful events) with multiple measures of cognitive health. This hypothesis was tested in the following three chapters, spanning three separate studies among middle-to-older aged adults:

Study 1: Estimate associations between TBI and later-life cognitive performance trajectories and test for effect measure modification by loneliness in the Vietnam Era Twin Study of Aging (VETSA).

Study 2: Test the cross-sectional relationship between TBI and markers of later-life brain health and test for effect measure modification by loneliness in VETSA.

Study 3: Test the association of multimorbidity with cognitive performance trajectories and test for effect measure modification by social engagement in the Rancho Bernardo Study of Healthy Aging (RBS).

Increases in social contact are theorized to reduce the risk of dementia.[4] However, it is unknown if social contact buffers the relationship between TBI or multimorbidity with different markers of cognitive decline and aging. Given the projected increase in dementia prevalence,[1] the results of this dissertation are timely and relevant to the recent US Surgeon General's Advisory on the poor health outcomes of declining social connection.[61]

Chapter 2 Association between traumatic brain injury and cognitive decline among middle-to-older aged men in the Vietnam Era Twin Study of Aging

2.1 Abstract

Traumatic brain injury (TBI) is associated with increased risk of dementia. However, associations of TBI with declines in specific cognitive domains over extended follow-up are not well understood. This prospective cohort study used data from 1,476 male Vietnam Era Twin Study of Aging participants (average age at study entry = 57.9 years, range = 51-71 years; 97.6% non-Hispanic; 92.5% white) collected from 2003 to 2019, who had complete information on prior TBI. Participants completed a comprehensive neuropsychological assessment at up to 3 visits over up to a 12-year follow-up period during which they also self-reported their history of TBI. Multivariable linear mixed-effects models were used to estimate betas (βs) and 95% confidence intervals (CIs) for associations between TBI and cognitive performance trajectories. Effect measure modification by *APOE* ε4 genotype status was assessed in a subset of participants. Thirty-one percent of participants reported a history of TBI; 29.4% were *APOE* ε4 carriers. There were no statistically significant associations of TBI with episodic memory, executive function, or processing speed, among participants overall. In models stratified by *APOE* ε4 carrier status, TBI was associated with larger magnitude of decline in executive function for *APOE* ε4 carriers (β=-0.0171; 95% CI= -0.0326, -0.0019) compared to non-carriers (β=-0.0036; 95% CI= -0.0134, 0.0063; $P_{Interaction}$=0.03). In sensitivity analyses, TBI prior to military induction (average age = 20 years) was associated with faster declines in executive function compared to no TBI, irrespective of *APOE* ε4 status. In this sample of middle-to-older aged men, TBI was associated with faster declines in executive function among *APOE* ε4 carriers and among those who reported remote TBI, prior to military induction. Moreover, these

findings support the importance of a life course perspective when considering factors that may influence cognitive health in aging.

2.2 Introduction

Traumatic brain injury (TBI) is a major cause of death and disability in the United States (US), with approximately 1.5 million Americans sustaining a TBI annually.[12] The incidence of TBI is notable in the context of cognitive and brain aging because the Lancet Commission considers it to be a modifiable risk factor for dementia and estimates that TBI of any severity is associated with 84% higher risk of all-cause dementia.[4] Additionally, those with TBI may have earlier onset of dementia and cognitive impairment.[16–18] Therefore, given the ubiquity of these injuries,[13,14] it is crucial to understand the effect of TBI on cognitive trajectories at later life.[74]

While TBI is associated with dementia,[4] associations between TBI and performance on neurocognitive tests in individuals without dementia are mixed.[34–42,45] For example, some smaller cross-sectional and case-control studies have found that participants with TBI performed worse on tests of memory, executive function, and processing speed relative to those without history of TBI.[40,41,45] In contrast, a study of older adults (53 with TBI and 104 controls, mean age = 70.2 years) from the Australian Imaging, Biomarkers and Lifestyle Study of Ageing (AIBL) and a cross-sectional study of 4,384 men from the Vietnam Experience Study (mean age = 70.2 years; 254 with mild TBI) found no differences in performance across multiple cognitive measures.[37,42] Two larger and more recent prospective studies examined the association between TBI and cognitive decline among middle-to-older aged adults.[38,39] Among 8,662 men (mean baseline age = 67 years; 2,168 with TBI) from the National Academy of Sciences-National Research Center (NAS-NRC) Twin Registry of World War II veterans, TBI was associated with faster declines in Telephone Interview for Cognitive Status–modified (TICS-m) scores over up to a 12 year follow-up, but specific cognitive domains were not assessed.[39] In a study of 15,764 participants (average age = 62.7 years; 6,235 with TBI) from the PROTECT-TBI cohort study,

TBI was associated with lower baseline measures of executive function, working memory, episodic memory, and processing speed, but not with differences in longitudinal trajectories across a brief follow-up period of up to 4 years.[38] Given these study design limitations, new insights may be gained by using repeated outcome measures spanning a range of cognitive domains over extended follow-up. Additionally, this association may differ by genetic susceptibility to dementia such as the apolipoprotein E (*APOE*) epsilon 4 (ε4) polymorphism,[75] which confers a greater risk for late onset Alzheimer's disease.[76] While *APOE* ε4 has been shown to modify vulnerability to a variety of stressors, results are mixed on *APOE* ε4's role in TBI-related cognitive decline.[77–79]

To further probe the relationship between TBI and cognition, the objective of the present study was to leverage longitudinal follow-up in the Vietnam Era Twin Study of Aging (VETSA) to test the associations between lifetime TBI and later-life cognitive trajectories among this well-characterized cohort of men beginning in midlife, with comprehensive cognitive assessment. Although prior cross-sectional work in VETSA found no main effect of TBI on cognitive outcomes,[34] longitudinal trajectories of cognitive performance as a function of TBI status have not been examined. We hypothesized that TBI would be associated with faster declines in episodic memory, executive function, and processing speed. We also examined whether associations differed by *APOE* ε4 carrier status. We hypothesized greater declines in cognitive performance over time among TBI participants who were *APOE* ε4 carriers compared to non-carriers.

2.3 Methods

2.3.1 Study population

This prospective cohort study used data from VETSA, an ongoing longitudinal study of men that began in 2001, with data collection initiated in 2003.[80,81] The study design is described in detail elsewhere.[80,81] Briefly, VETSA includes 1,608 men who were recruited from the Vietnam Era Twin Registry (VETR), a nationally representative registry, which includes male twins, who were in the military at some time during the Vietnam era (1965-1975). VETSA participants were recruited at random from the 1992 Harvard Twin Study of Substance Abuse among VETR twins, a study that did not select participants on the basis of any substance use or other characteristics.[82] Because VETSA was designed to assess cognitive changes during the critical transition period from middle-age to early older age, recruitment into wave 1 was restricted to a narrow age range of 51-60 years, and participants were followed at planned intervals (wave 2 occurred approximately 6 years after wave 1; wave 3 occurred an average of 12 years after wave 1). VETSA was also designed to address biases due to attrition and practice effects by enrolling new participants from the VETR at waves 2 and 3 who were of similar age to VETSA participants (for further details see Elman et al. 2018).[83] A total of 1,237 men (age range = 51-61 years) were enrolled at wave 1 from 2003 to 2007. At wave 2 (2009- 2013), a total of 247 new participants (age range = 55-67 years) were enrolled, and at wave 3 (2016-2019), 124 new participants were enrolled (age range = 63-71 years). This resulted in 1,608 unique participants. At the time of enrollment, VETSA participants had similar health and lifestyle characteristics compared to US men in their age cohort.[84] Approximately 80% of VETSA participants did not report combat exposure.[85]

Of the 1,608 VETSA participants, we excluded 131 with incomplete data on lifetime TBI and 1 missing cognitive outcome data. This yielded a final analytic sample of 1,476 participants. Baseline was defined as the participant's time of enrollment into VETSA, regardless of wave of enrollment.

Data collection occurred at two sites (San Diego, CA and Boston, MA) using identical protocols. This study was approved by the University of California, San Diego and Boston University Institutional Review Boards. All participants provided written informed consent.

2.3.2 Outcomes: cognitive test performance

We focused on three primary cognitive domains based on prior literature: 1) episodic memory, 2) executive function, and 3) processing speed.[34–42,45] VETSA participants were administered a comprehensive neurocognitive battery at each wave, with multiple tests assessing each cognitive domain. Using genetically-informed multivariate analyses, latent constructs for the domains of episodic memory, executive function, and processing speed were created.[86–89] Methods are described briefly below and in Supplementary Methods 2.1.

Episodic memory was derived using the California Verbal Learning Test-2 (CVLT-II) short and long delay free recall,[90] the Wechsler Memory Scale-III (WMS-III) Logical Memory immediate and delayed recall[91] and the Visual Reproductions tests immediate and delayed recall.[86,87,91] Executive function was derived from multiple tests as follows: Number correct on color-word test, adjusted for performance on color naming and word reading tests from the Stroop Test,[92] letter-number sequencing and digit span tests from the WMS-III,[91] reading span task,[93] and letter-number switching time adjusted for time on letter and number sequencing tasks from the Delis-Kaplan Executive Function System (D-KEFS) Trail Making Test, and category-switching score after adjusting for category fluency score on the D-KEFS Category switching

tests.[88,94] Processing speed was derived from scores on the number and letter sequencing task of the D-KEFS Trail-Making Test,[94] color naming and word reading subtests of the Stroop Test,[92] and a Simple Reaction Time task.[89]

In secondary analyses, we examined associations of TBI with working memory, (a subcomponent of executive function),[88] verbal fluency,[95] and semantic fluency (a subcomponent of verbal fluency).[95] Methods for deriving all cognitive test performance outcomes are summarized in Supplementary Methods 1.

Domain-specific factor scores, corrected for effects of practice and selective attrition, were derived for each participant at all 3 waves and standardized based on the means and standard deviations of scores at wave 1, as described previously.[83,96]

2.3.3 Main exposure: traumatic brain injury (TBI)

Lifetime TBI for VETSA participants was defined based on methods described previously.[34] Briefly, participants were asked four questions regarding prior head injury at each wave: 1) "Have you ever had a severe head injury that was associated with loss of consciousness or confusion?"; 2) "Did that head injury (any of those head injuries) result in your staying overnight in the hospital?"; 3) "Have you ever been told by a doctor that you had a concussion? (If 'Yes,' how many times?)"; and 4) "Altogether, how many different head injuries or concussions (all total) have you had?" Starting in wave 2, participants who reported having had a head injury were asked details of each head injury including age, cause of injury, receipt of medical attention or hospitalization. Data on the presence/duration of loss of consciousness (LOC) and/or posttraumatic amnesia (PTA) were used to classify TBI severity. For the present study, history of lifetime symptomatic TBI was defined as a binary variable (any/none). We also considered variables for severity (mild; moderate/severe; unclassifiable), multiple TBI (0; 1; ≥2),

and history of TBI before military induction (none; before military induction; after military induction). If multiple TBIs were reported, the highest severity was considered.

2.3.4 Effect modifier: apolipoprotein E genotype

We also examined effect modification by *APOE* ε4 carrier status among the 1,342 participants with *APOE* genotype and TBI history data. Genotyping methods in VETSA are described in detail elsewhere.[97] Due to the low number of homozygous ε4 (n = 26), participants were classified as an APOE ε4 carrier if they had at least one ε4 allele (i.e., ε2/ε4, ε3/ε4, or ε4/ε4; n = 394), and as non-carriers otherwise.

2.3.5 Covariates

Covariate information was derived from medical interviews and questionnaires that were completed at each wave. Covariates of interest were selected based on prior literature[23,34] and included age at enrollment into VETSA (i.e. at participant's baseline), race/ethnicity (non-Hispanic or Latino and white; other), years of education (as an additional socioeconomic status index; ≤12 years; 13-14 years; 15-16 years; >16 years), young adult general cognitive ability as measured by the Armed Forces Qualification Test (AFQT), and annual family income (<$40,000; $40,000-$89,999; ≥$90,000). The AFQT was administered at an average age of 20 years.[98,99] The AFQT is a 100-item multiple choice test, administered to service members prior to military induction and is highly correlated with standard IQ (r = 0.84).[100] AFQT scores were recorded as percentiles based on military norms, then scaled and normalized. We considered the following time-varying covariates at each wave: standardized body mass index (BMI; kg/m^2), smoking status (never; former; current), alcohol use (never; former; light; moderate; heavy), substance abuse (no; yes), relationship status (none; married or in a relationship), participation in religious activities (≤2 times a month; ≥3 times a month), number of close friends (≤2, ≥3),

loneliness (rarely or none of the time; at least 1 day in the past week), social isolation (at least 1 confidant; no confidants), and depressive symptom severity, as measured by the Center for Epidemiologic Studies Depression Scale (CES-D).[101] For the CES-D, scores of ≥16 suggest significant depressive symptom severity.[101] Social isolation was assessed using the following question, "How many people do you know who you can trust and confide in?" as defined in a prior VETSA study.[102] Loneliness was measured using a single item from the CES-D,[101] which is moderately correlated with the three-item University of California, Los Angeles Loneliness Scale ($r = 0.49$; $p < 0.01$).[103] Analyses with CES-D did not include loneliness as a separate covariate given its inclusion in the depressive symptom severity measure.

2.3.6 Statistical analysis

Participant characteristics at baseline (i.e., VETSA study entry) were summarized by TBI status. Continuous characteristics were described using median (range) and categorical variables were described using counts (percentages). Group differences were assessed using linear mixed-effects models for continuous variables and mixed-effects multinomial logistic regression models for categorical variables. Models included a random intercept to adjust for the correlation between twin pairs.

We fit linear mixed-effects models to estimate associations of TBI status with longitudinal cognitive performance trajectories, with separate models for episodic memory, executive function, and processing speed. Linear mixed-effect models accommodate missing data as well as inconsistent measurement intervals, which allowed us to use all available data under the assumption that data were missing at random. We assessed this assumption by plotting the pattern of missingness between variables of interest. For all models, time from baseline was calculated as the difference in age from the participant's first VETSA visit to subsequent visits,

such that time at the first visit is 0 years. We used three successively adjusted models: Model 1 included the fixed effects of TBI, time, and a TBI-by-time interaction term, and adjusted for age at baseline (centered at 57.86 years, the average age at study entry), race/ethnicity, education, annual family income, and young adult cognitive ability (AFQT at age 20); Model 2 additionally adjusted for time-varying health-related and social characteristics which included BMI (standardized), smoking status, alcohol use, substance abuse, relationship status, participation in religious activities, number of close friends, social isolation, and depressive symptom severity; and Model 3 additionally adjusted for *APOE* ε4 carrier status. All models included random intercepts and a family-relatedness random effect to adjust for the correlation between twin pairs. We plotted predicted values of Model 2 for all three outcomes by TBI status over years since baseline (i.e., the participant's first VETSA visit). We did not include random slopes given that our analyses were limited to 3 timepoints.[104] We used time from baseline, instead of age, as the temporal variable for linear mixed-effects models to reflect within-participant change. Age-based models may bias within-participant change estimates because cognitive trajectories would depend on the age of participants' entry into the study.[105–107]

To assess effect measure modification, we stratified Model 2 by *APOE* ε4 carrier status. *P* values for interaction ($P_{\text{Interaction}}$) were calculated using likelihood ratio tests to compare fully adjusted models with and without a 3-way interaction of *APOE* ε4 carrier status-by-TBI-by-time. In secondary analyses, we repeated linear mixed-effects models and assessment of effect measure modification by *APOE* ε4 carrier status with the following secondary outcomes: working memory, verbal fluency, and semantic fluency.

We performed several sensitivity analyses. We repeated primary analyses excluding those with unclassifiable TBI (n = 28) and using an indicator variable of injury severity (none;

mild; moderate/severe). To assess whether there were differences by age at injury, we repeated Model 3 using a three-level TBI variable indicating the timing of the injury (no TBI; TBI before military induction; TBI after military induction). To examine multiple TBI, we repeated Model 3 using a three-level TBI variable indicating the number of reported TBIs (no TBI; 1 TBI; ≥2 TBIs). Since ε2 and ε4 alleles may confer opposing risk for Alzheimer's disease,[108] we repeated *APOE* ε4 stratified analyses with ε2/ε4 participants excluded from the analysis (n=50). Given recent evidence that suggests the importance of social connection on later-life health,[61] Model 2, without adjustment for CES-D, was also stratified by loneliness reported at the participant's first visit.

All statistical analyses were conducted in R (version 4.2.2; R Core Team, 2022). The *lme4* package was used for linear mixed-effects analyses,[109] and the *sjPlot* package was used for visualization.[110] Statistical tests were two-tailed, and *P* values were considered significant at $P < 0.05$. We did not correct for multiple comparisons given our interest in only 3 primary outcomes.

2.4 Results

2.4.1 Participant characteristics at study entry

Of the 1,476 men in our study sample, 462 (31.3%) reported at least one lifetime TBI between the ages of 2 and 69 years. Of those with TBI, 162 (36.4%) reported ≥2 TBIs. The most common TBI severity was mild (65.8%), 28.1% were moderate/severe, and 6.1% were unclassifiable. The median age of the first TBI was 18 (range = 2-69) years. The majority of those with TBI reported history prior to military induction (56.9%; age range of first TBI: prior to military induction = 2-22 years, after military induction = 18-69 years). At study entry, the median age of participants was 58 (range = 51.1-71.1) years (Table 2.1). Most were non-

Hispanic/Latino (97.6%) and white (92.4%). Compared to no TBI history, those reporting TBI were more likely to have completed more than 12 years of education (65.6% vs 58.3%; p = 0.03), felt lonely 1 day in the past week (28.3% vs. 21.8%; p = 0.01), had significant depressive symptom severity as defined by the CES-D (18.6% vs. 13.3%; p = 0.03), and had symptoms of PTSD (18.2% vs. 12.4%; $p < 0.01$). Compared to those who completed follow-up of at least 2 visits (n=1,192), those who did not return for their final follow-up visit (n=284) were less likely to report TBI (25.4% vs. 32.7%; $p < 0.01$) but there were no significant differences across several characteristics, including age, race/ethnicity, AFQT, income, or *APOE* ε4 status between these groups (Supplementary Table 2.1).

2.4.2 TBI status and cognitive function by time

Over the 12-year follow-up period, there were statistically significant decreases in episodic memory, executive function, and processing speed after adjustment for socio-demographics and health behaviors in Models 1 and 2 (βs for Time < -0.03; Table 2.2). Neither the main effect of TBI nor the TBI-by-time interaction was statistically significant in any model (Table 2.2; Figure 2.1).

2.4.3 Effect measure modification by APOE ε4 carrier status

In the 1,342 participants with APOE genotype data, 29.4% were *APOE* ε4 carriers. Approximately 25.9% of those with TBI were *APOE* ε4 carriers compared to 30.8% of those without TBI; this difference was not statistically significant (p = 0.31). In models stratified by *APOE* ε4 carrier status, TBI was associated with larger magnitudes of decline in executive function for *APOE* ε4 carriers (β = -0.0171; 95% CI -0.0325, -0.0018) compared to non-carriers (β = -0.0036; 95% CI -0.0134, 0.0062; $P_{\text{Interaction}}$ = 0.03; Table 2.3; Figure 2.2).

2.4.4 Sensitivity analysis

In sensitivity analyses, exclusion of 28 individuals with unclassifiable TBI severity did not change the results (Supplementary Tables 2.3 and 2.4). When assessing the influence of TBI severity, the main effects of TBI-by-severity were not significant (Supplementary Table 2.5). However, mild TBI was associated with declines in executive function among *APOE* ε4 carriers (β = -0.0287; 95% CI -0.0466, -0.0108; $P_{\text{Interaction}} < 0.01$; Supplementary Table 2.6). After repeating analyses using an indicator for first occurrence of TBI to assess the effect of remote injury, TBI prior to military induction (n = 263; 56.9% of TBIs) was associated with faster declines in executive function compared to no TBI (β = -0.0111; 95 % CI -0.0214, -7e-04; Supplementary Table 2.7); this was not modified by *APOE* ε4 carrier status ($P_{\text{Interaction}} > 0.10$, all; Supplementary Figure 2.1). There were no substantial differences in the magnitude of effect for 1 TBI or ≥2 TBIs, relative to no TBI, for all outcomes (Supplementary Table 2.8). Excluding ε2/ε4 participants from the ε4 carrier group, did not materially affect the results: TBI remained associated with faster declines in executive function compared to no TBI in those with an ε4 allele (β = -0.0202; 95% CI -0.0364, -0.0039; $P_{\text{Interaction}} = 0.01$; Supplementary Table 2.9). In our analyses of secondary cognitive outcomes, TBI was associated with faster declines in semantic fluency (β = -0.0105; 95% CI -0.0208, -2e-04) compared to no TBI (Supplementary Table 2.10; Supplementary Figure 2.2). There was no evidence to suggest effect measure modification by *APOE* ε4 for any of the exploratory outcomes ($P_{\text{Interaction}} > 0.10$, all; Supplementary Table 2.11; Supplementary Figure 2.3). The interaction of TBI-by-time-by-loneliness was not statistically significant ($P_{\text{Interaction}} > 0.40$, all; Supplementary Table 2.12).

2.5 Discussion

In this prospective cohort study of middle-to-older aged men, TBI was associated with significantly steeper declines in executive function, by 0.2 SD per decade, among *APOE* ε4 carriers. Greater TBI-related decline in executive function was observed primarily among those reporting TBI prior to military induction, highlighting the importance of monitoring earlier-life TBIs. TBI was not associated with change in episodic memory or processing speed over a 12-year follow-up period. Overall, these findings contribute to our understanding of the role of TBI with cognitive health in aging, including the impact of *APOE* ε4 and timing of injury.

We found no statistically significant main effect associations of TBI with trajectories of cognitive decline in the domains of episodic memory, executive function, and processing speed. These results are similar to studies with brief follow-up periods ranging from 3 to 4 years.[38,42] For example, a study of 15,764 participants (average age = 62.7 years) from the PROTECT-TBI cohort study with up to 4 year of follow-up, TBI was not associated with longitudinal declines in executive function, working memory, episodic memory, and processing speed.[38] In a 3-year cohort study of 52 older adults with TBI and 102 without TBI (average age for both groups = 70.2 years) from the Australian Imaging, Biomarkers and Lifestyle (AIBL) Study of Ageing, self-reported TBI was not associated with verbal working memory, perceptual speed, verbal memory, visuospatial function, visual memory, verbal ability, or interference.[42] In contrast, a study with up to 12 years of follow-up of 8,662 men (mean baseline age = 67 years) from NAS-NRC Twin Registry, TBI was associated with faster declines in TICS-m scores.[39] These results suggest that TBI-related declines in cognition may not become pronounced until individuals are much older.

Although we did not find a main effect of TBI or APOE status on cognitive decline, participants who were *APOE* ε4 carriers had faster TBI-related decline in executive function than non-carriers. One meta-analysis of 14 studies suggests that having an ε4 allele may have a negative association with long-term neurocognitive recovery from TBI.[77] Our results are in line with this suggestion. Our results differ from those of the NAS-NRC Twin Registry study which did not find significant effect measure modification by *APOE*.[39] However, the NAS-NRC study only used TICS-m, which may be best described as a screening measure of global cognitive function with little assessment of executive function.[39] With more extensive neuropsychological testing, we found effect modification by *APOE* in TBI-related cognitive decline that was specific to executive function.

APOE may contribute to dementia risk via multiple mechanisms. In prior work with this sample, we found that *APOE* ε4 was associated with thinner frontal cortex,[111] and, in separate studies, the ε4 genotype conferred more pronounced vulnerability based on associations with higher vascular burden and lower general cognitive ability maintenance[112] as well as lower testosterone and lower hippocampal volume.[113] Neuronal cell injury or stress from events such as TBI influence the generation of neurotoxic fragments that result in mitochondrial dysfunction and cytoskeletal altercations to affect neurodegeneration, and *APOE* ε4 can accelerate these processes.[75] APOE ε4 may also affect compensatory mechanisms that may put ε4 carriers at greater risk of TBI-related cognitive deficits compared to non-carriers.[114]

In sensitivity analyses, TBI prior to military induction, relative to no TBI, was significantly associated with declines in executive function. The association of TBI after military induction, relative to no TBI, and executive function was not significant. This suggests that TBI events during childhood and adolescence may have stronger associations with later life cognition

than TBIs that occur later in life. It is possible that the stronger effect of TBIs during this period may be due to interference with neurodevelopment, but more work is needed. Conversely, the NAS-NRC Twin Registry study found that TBI after age 25 (vs. prior to age 25) had stronger associations with TICS-m scores.[39] This difference may be due in part to the older age of this World War II veteran cohort compared to VETSA or the lack of executive function measures in the TICS-m; however, further investigation is needed to examine the effects of TBI at different life stages. Unexpectedly, given that repetitive TBI is hypothesized to accelerate dementia-related pathology,[44] we did not find that those who had reported ≥2 TBIs had faster cognitive decline, partially due to a low number of participants with multiple TBIs and the fact that these were mostly mild cases.

There were several limitations. First, TBI in this study was self-reported, potentially contributing to information bias. It is plausible that not all TBI events were captured in our self-report derived measure, potentially underestimating the prevalence of lifetime TBI in this cohort. However, TBI information was derived from detailed items regarding the nature and plausibility of the injury events. Second, while there is potential for selection bias due to loss to follow-up, there were minimal demographic differences between those with complete and incomplete follow-up. Additionally, VETSA included age-matched attrition-replacement participants at each wave by design to account for attrition effects across tests.[83] Lastly, this cohort comprised primarily non-Hispanic and white males, which reduces generalizability to other populations. Although VETSA participants were comparable to US men in their age cohort in terms of health and lifestyle characteristics,[84] more work is needed to assess these associations in cohorts of different sexes and diverse socio-demographic backgrounds.

This study had several strengths, which included longitudinal follow-up over a 12-year period. We assessed cognitive change using a rigorous neuropsychological battery administered at each VETSA wave and controlled for practice effects.[83] In contrast to many prior studies, our measures comprised multiple tests in each domain rather than single brief tests, which we and others have shown provides substantial increases in sensitivity.[87,115] We were also able to control for young adult cognitive ability, which is a predictor of later-life cognitive function and cognitive decline and allows for improved assessment of domain-specific decline,[116] and time-varying covariates that may confound the relationship between TBI and cognitive trajectories.

In this prospective cohort study of middle-to-older aged male veterans, TBI history was associated with small but faster declines in executive functioning among *APOE* ε4 carriers. Remote TBIs, primarily in childhood and adolescence, had stronger associations than TBIs that occurred in adulthood, suggesting the importance of preventing earlier life TBIs, which occur during periods of substantial brain development. Given the small magnitudes of association in this study and presumed accelerated cognitive decline at older age, the observed associations may be more pronounced with further follow-up at later ages in this cohort. Additionally, further study among diverse populations with extended follow-up are needed to understand the mechanisms of TBI-related cognitive decline.

ACKNOWLEDGEMENTS

The content is the sole responsibility of the authors and does not necessarily represent official views of the National Institute on Aging, National Institutes of Health, or the Veteran's Administration.

U.S. Department of Veterans Affairs, Department of Defense; National Personnel Records Center, National Archives and Records Administration; Internal Revenue Service; National Opinion Research Center; National Research Council, National Academy of Sciences; and the Institute for Survey Research, Temple University provided invaluable assistance in the conduct of the VET Registry. The Cooperative Studies Program of the U.S. Department of Veterans Affairs provided financial support for development and maintenance of the Vietnam Era Twin Registry.

We would also like to acknowledge the continued cooperation and participation of the members of the VET Registry and their families.

FUNDING

This work was supported by a National Institutes of Health, National Institute on Aging, T32 Predoctoral Training Fellowship (T32 AG058529 to A.I.B.P.). A.H.S. and L.K.M. were supported by National Institute on Aging grants RF1AG079149 and RF1AG074345. H.P. was supported by the National Cancer Institute (K01 CA234317), the SDSU/UCSD Comprehensive Cancer Center Partnership (U54 CA132384 & U54 CA132379), and the Alzheimer's Disease Resource Center for Advancing Minority Aging Research at the University of California San Diego (P30 AG059299). VETSA was supported by grants from the National Institute on Aging at the National Institutes of Health: R01 AG050595, ROI AG022381, ROI AG076838, ROI AG037985, ROI AG064955, and P01 AG055367.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE:

University of California, San Diego Office of IRB Administration and the Boston University Institutional Review Boards approved the study protocols. The study was performed in accordance with ethical standards as laid down in the 1964 Declaration of Helsinki. Participants provided written informed consent.

AUTHOR DISCLOSURE STATEMENT

No completing financial interests exist.

Table 2.1 Participant characteristics at first visit by traumatic brain injury (TBI) status

Characteristic		TBI status		*p*-value
		No (N=1014)	Yes (N=462)	
Age	Median [Min, Max]	57.9 [51.1, 71.1]	58.1 [51.1, 70.9]	0.17
Ethnicity	Non-Hispanic or Non-Latino	983 (96.9%)	457 (98.9%)	0.73
Race	White	930 (91.7%)	435 (94.2%)	
Education years	≤12	423 (41.7%)	159 (34.4%)	0.03
	13-14	283 (27.9%)	137 (29.7%)	
	15-16	220 (21.7%)	122 (26.4%)	
	>16	88 (8.7%)	44 (9.5%)	
AFQT	Median [Min, Max]	0.270 [-1.29, 3.50]	0.300 [-1.13, 2.32]	0.20
Income	<$40,000	145 (17.9%)	65 (19.9%)	0.46
	$40,000-$89,999	432 (53.3%)	168 (51.4%)	
	≥$90,000	233 (28.8%)	94 (28.7%)	
BMI	Median [Min, Max]	28.8 [17.8, 48.9]	29.3 [19.5, 54.7]	0.17
Smoking status	Never	332 (32.9%)	170 (36.8%)	0.12
	Former	473 (46.9%)	200 (43.3%)	
	Current	204 (20.2%)	92 (19.9%)	
Alcohol use	Never	62 (6.1%)	24 (5.2%)	0.69
	Former	299 (29.6%)	140 (30.4%)	
	Light	416 (41.2%)	175 (38.0%)	
	Moderate	91 (9.0%)	58 (12.6%)	
	Heavy	141 (14.0%)	64 (13.9%)	
Relationship status	Married or in a relationship	797 (78.9%)	356 (77.4%)	0.61
Participation in religious activities	≥3 times a month	462 (45.8%)	184 (40.1%)	0.11
Close friends	≥3	930 (92.9%)	424 (92.6%)	0.14
Loneliness	At least 1 day in the past week	220 (21.8%)	130 (28.3%)	0.01
Social isolation	No confidants	27 (2.7%)	18 (3.9%)	0.76
Alcohol or drug abuse	Yes	45 (4.4%)	27 (5.8%)	0.76
Depressive symptoms	Yes	129 (13.3%)	83 (18.6%)	0.03
APOE ε4 carrier	Yes	290 (30.8%)	104 (25.9%)	0.31

P-values were derived from linear mixed-effects models for continuous variables and mixed-effects multinomial logistic regression models for categorical variables. Models included a random intercept to adjust for the correlation between twin pairs. n missing: income = 339 (23.0%), BMI = 3 (0.2%), smoking status = 5 (0.3%), alcohol use = 6 (0.4%), relationship status = 6 (0.4%), participation in religious activities =9 (0.6%), loneliness = 8 (0.5%), social isolation = 12 (0.8%), close friends = 17 (1.2%), alcohol or drug abuse = 1 (0.1%), AFQT = 20 (1.4%), depressive symptoms = 63 (4.3%), APOE ε4 carrier = 134 (9.1%)

Table 2.2 Association of any traumatic brain injury with cognitive performance trajectories over a 12 year follow up (n=1476)

Outcome	Model	Term	β (95% CI)
Episodic memory	1	TBI	0.0045 (-0.1056; 0.1145)
		Time	-0.0455 (-0.0502; -0.0408)
		TBI by time	-0.0041 (-0.0126; 0.0045)
	2	TBI	0.015 (-0.0966; 0.1267)
		Time	-0.0445 (-0.0495; -0.0395)
		TBI by time	-0.0053 (-0.0142; 0.0036)
	3	TBI	0.0144 (-0.0974; 0.1263)
		Time	-0.0442 (-0.0493; -0.0392)
		TBI by time	-0.0055 (-0.0144; 0.0034)
Executive function	1	TBI	0.0428 (-0.0592; 0.1449)
		Time	-0.067 (-0.0715; -0.0625)
		TBI by time	-0.0064 (-0.0145; 0.0017)
	2	TBI	0.0587 (-0.0451; 0.1625)
		Time	-0.0665 (-0.0712; -0.0618)
		TBI by time	-0.0073 (-0.0156; 0.001)
	3	TBI	0.0606 (-0.0431; 0.1643)
		Time	-0.0662 (-0.0708; -0.0615)
		TBI by time	-0.0076 (-0.0158; 7e-04)
Processing speed	1	TBI	-0.0547 (-0.1721; 0.0628)
		Time	-0.0946 (-0.0992; -0.0899)
		TBI by time	0.0031 (-0.0054; 0.0116)
	2	TBI	-0.0333 (-0.1485; 0.0818)
		Time	-0.0921 (-0.0971; -0.0872)
		TBI by time	2e-05 (-0.0088; 0.0089)
	3	TBI	-0.0386 (-0.1541; 0.0769)
		Time	-0.0925 (-0.0975; -0.0875)
		TBI by time	5e-04 (-0.0084; 0.0093)

Note: Beta (β) and 95% confidence intervals (CI) are derived from linear mixed-effects models that included random intercepts and family-relatedness a random effect to adjust for correlation between twin pairs. Time is defined as years from baseline. Model 1 fixed effects of TBI, time, and a TBI by time interaction term, and adjusted for baseline age (centered at 57.86 years, the average age of entry into VETSA), race/ethnicity, education, annual family income, and young adult cognitive ability (AFQT at age 20). Model 2 additionally adjusted for time-varying BMI (standardized), smoking status, alcohol use, substance abuse, relationship status, participation in religious activities, number of close friends, social isolation, and depressive symptom severity. Model 3 additionally adjusted for APOE ε4 carrier status among the subset of participants with APOE genotype data (n= 1342).

Table 2.3 Association of any traumatic brain injury with cognitive performance trajectories by APOE ε4 carrier status over a 12 year follow up

			APOE ε4 carrier status		
			No (n=948)	Yes (n=394)	
Outcome	Model	Term	β (95% CI)	β (95% CI)	$P_{Interaction}$
Episodic memory	1	TBI	-0.027 (-0.1573; 0.1034)	0.1421 (-0.06; 0.3441)	0.48
		Time	-0.0442 (-0.0499; -0.0385)	-0.0474 (-0.0559; -0.0389)	
		TBI by time	-0.0021 (-0.0124; 0.0082)	-0.0103 (-0.0258; 0.0052)	
	2	TBI	-0.0104 (-0.143; 0.1221)	0.1518 (-0.0546; 0.3583)	
		Time	-0.0431 (-0.0491; -0.0372)	-0.0463 (-0.0555; -0.0371)	
		TBI by time	-0.0037 (-0.0142; 0.0069)	-0.0105 (-0.0269; 0.0059)	
Executive function	1	TBI	0.0547 (-0.0654; 0.1748)	0.0494 (-0.1458; 0.2446)	0.03
		Time	-0.065 (-0.0704; -0.0597)	-0.0706 (-0.0786; -0.0627)	
		TBI by time	-0.0026 (-0.0123; 0.007)	-0.0169 (-0.0314; -0.0023)	
	2	TBI	0.0678 (-0.0537; 0.1893)	0.054 (-0.1492; 0.2573)	
		Time	-0.0645 (-0.07; -0.0589)	-0.0706 (-0.0792; -0.062)	
		TBI by time	-0.0036 (-0.0134; 0.0063)	-0.0173 (-0.0326; -0.0019)	
Processing speed	1	TBI	-0.0537 (-0.1919; 0.0845)	-0.0336 (-0.255; 0.1879)	0.73
		Time	-0.0964 (-0.1021; -0.0907)	-0.0913 (-0.0996; -0.0829)	
		TBI by time	0.0031 (-0.0071; 0.0133)	0.0036 (-0.0116; 0.0187)	
	2	TBI	-0.0279 (-0.1665; 0.1107)	-0.0411 (-0.2556; 0.1734)	
		Time	-0.0938 (-0.0999; -0.0877)	-0.0897 (-0.0986; -0.0808)	
		TBI by time	2e-04 (-0.0106; 0.0109)	0.0017 (-0.0141; 0.0175)	

Note: Beta (β) and 95% confidence intervals (CI) are derived from linear mixed-effects models that included random intercepts and family-relatedness a random effect to adjust for correlation between twin pairs. Time is defined as years from baseline. Model 1 fixed effects of TBI, time, and a TBI by time interaction term, and adjusted for baseline age (centered at 57.86 years, the average age of entry into VETSA), race/ethnicity, education, annual family income, and young adult cognitive ability (AFQT at age 20). Model 2 additionally adjusted for time-varying BMI (standardized), smoking status, alcohol use, substance abuse, relationship status, participation in religious activities, number of close friends, social isolation, and depressive symptom severity. P values for interaction ($P_{Interaction}$) were calculated using likelihood ratio tests to compare fully adjusted models with and without a 3-way interaction of APOE ε4 carrier status by TBI by time.

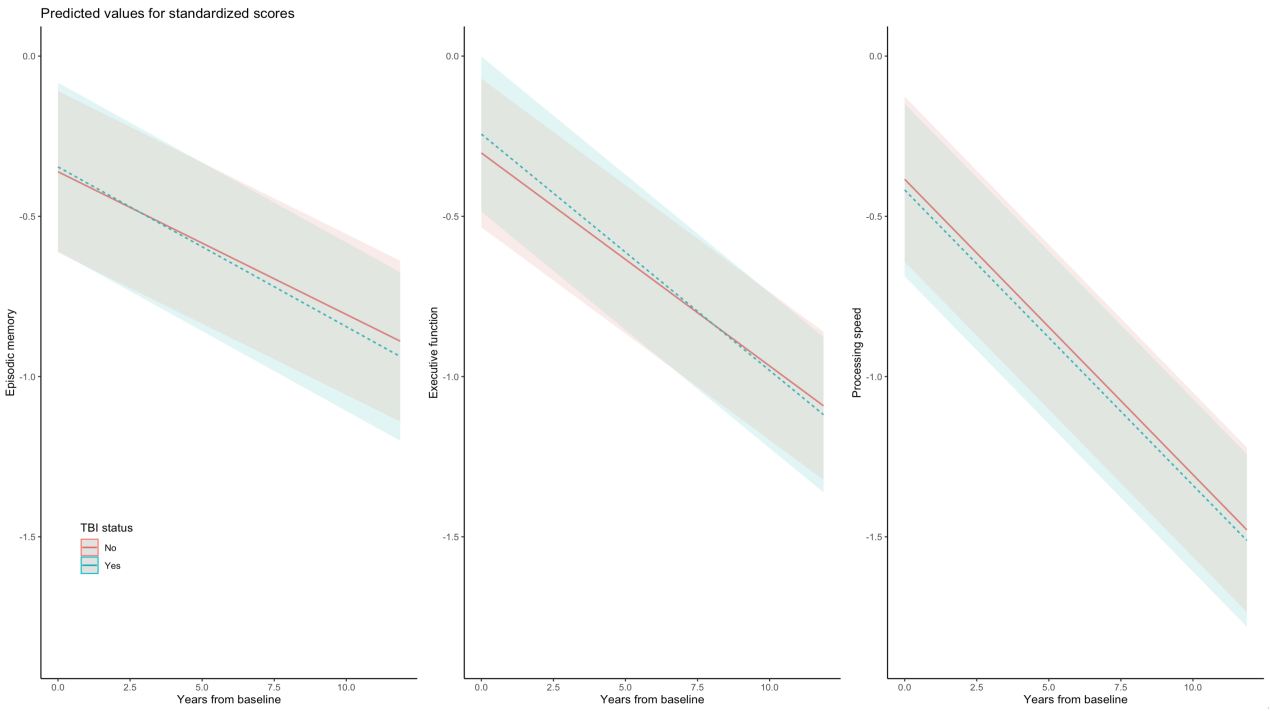


Figure 2.1 Trajectories of cognition function test performance over years from baseline by TBI. Plots are based on linear mixed-effects models adjusted for baseline age (centered at 57.86 years, the average age of entry into VETSA), race/ethnicity, education, annual family income and young adult cognitive ability (AFQT at age 20) as well as time-varying BMI (standardized), smoking status, alcohol use, substance abuse, relationship status, participation in religious activities, number of close friends, social isolation, and depressive symptom severity.

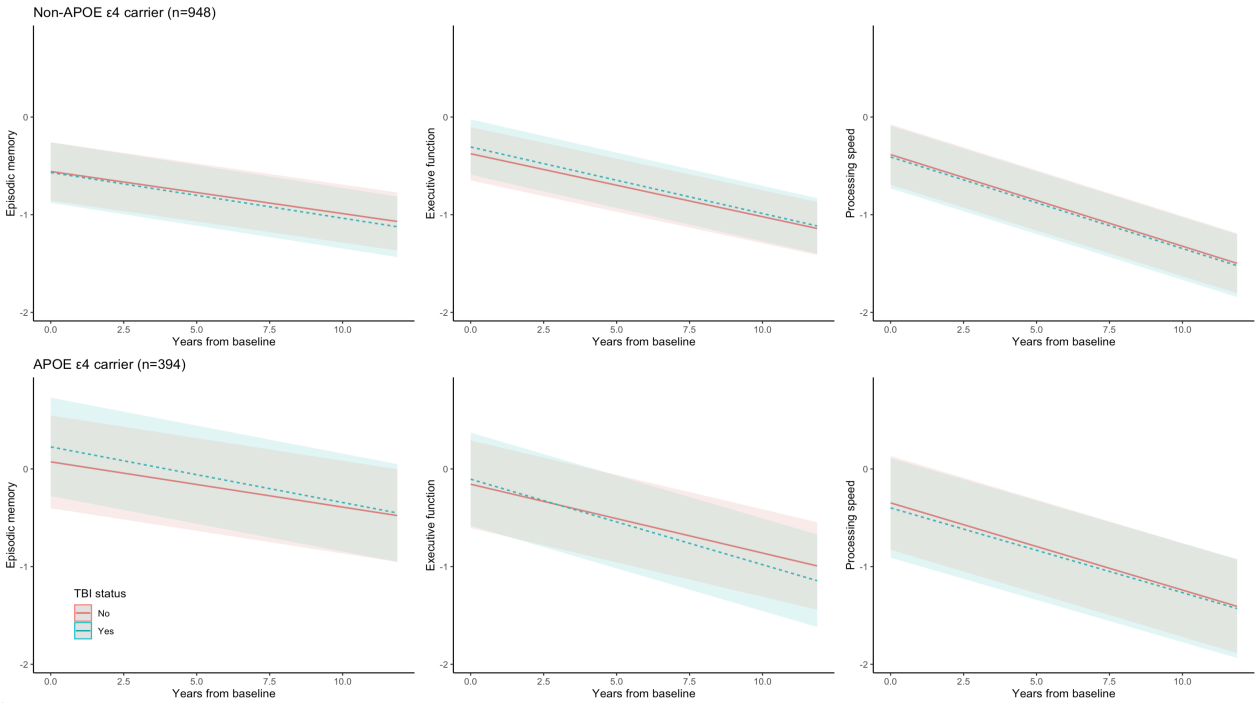


Figure 2.2 Trajectories of cognition function test performance over years from baseline by TBI stratified by APOE ε4 carrier status. Plots are based on linear mixed-effects models adjusted for baseline age (centered at 57.86 years, the average age of entry into VETSA), race/ethnicity, education, annual family income and young adult cognitive ability (AFQT at age 20) as well as time-varying BMI (standardized), smoking status, alcohol use, substance abuse, relationship status, participation in religious activities, number of close friends, social isolation, and depressive symptom severity.

Supplementary Methods 2.1: Description of cognitive outcome methods

VETSA participants were administered a comprehensive neurocognitive battery at each wave, with multiple tests assessing multiple cognitive domains of interest. Latent constructs for the domains of episodic memory,[1,2] executive function,[3] processing speed,[4] working memory,[3] verbal fluency,[5] and semantic fluency[5] were created using genetically-informed multivariate analyses. For the present study, we focused on 3 outcomes: 1) episodic memory, executive function, and processing speed. We also included 3 secondary outcomes: 1) working memory, 2) verbal fluency, and 3) semantic fluency.

Episodic memory was derived using the California Verbal Learning Test-2 (CVLT-II) short and long delay free recall,[6] the Wechsler Memory Scale (WMS)-III Logical Memory immediate and delayed recall,[7] and the Visual Reproductions tests immediate and delayed recall.[1,2]

Executive function was derived from multiple tests as follows: Number correct on color-word test, adjusted for performance on color naming and word reading tests from the Stroop Test,[8] letter-number sequencing and digit span tests from the WMS-III,[7] reading span task,[9] and letter-number switching time adjusted for time on letter and number sequencing tasks from the Delis-Kaplan Executive Function System (D-KEFS) Trail Making Test, and category-switching score after adjusting for category fluency score on the D-KEFS Category switching tests.[3,10] The working memory factor explains the variance related to working memory span that was not captured by the executive factor score.[3] While the working memory and executive function scores are correlated, we analyzed them separately to allow for comparability with other studies.

Processing speed was derived from scores on the number and letter sequencing task of the D-KEFS Trail-Making Test,[10] color naming and word reading subtests of the Stroop Test,[8] and the Simple Reaction Time task.[4]

Verbal fluency was derived from Letter fluency (F, A, and S), semantic fluency (Animals and Boys' Names) category switching subtest (fruits and items of furniture) from the D-KEFS.[5] The semantic fluency factor explains the variance related to category fluency that was not captured by general verbal fluency factor score.[5]

References for Supplementary Methods 2.1:

1. Kremen WS, Panizzon MS, Franz CE, et al. Genetic complexity of episodic memory: a twin approach to studies of aging. Psychol Aging. 2014;29(2):404-417. doi:10.1037/a0035962

2. Gustavson DE, Elman JA, Sanderson-Cimino M, et al. Extensive memory testing improves prediction of progression to MCI in late middle age. Alzheimers Dement (Amst). 2020;12(1):e12004. doi:10.1002/dad2.12004

3. Gustavson DE, Panizzon MS, Franz CE, et al. Genetic and environmental architecture of executive functions in midlife. Neuropsychology. 2018;32(1):18-30. doi:10.1037/neu0000389

4. Sanderson-Cimino M, Panizzon MS, Elman JA, et al. Genetic and environmental architecture of processing speed across midlife. Neuropsychology. 2019;33(6):862-871. doi:10.1037/neu0000551

5. Gustavson DE, Panizzon MS, Elman JA, et al. Genetic and environmental influences on verbal fluency in middle age: a longitudinal twin study. Behav Genet. 2018;48(5):361-373. doi:10.1007/s10519-018-9910-6

6. Delis DC, Kaplan E, Kramer JH, Ober BA. California Verbal Learning Test (CVLT). Psychological Corporation; 2000.

7. Wechsler D. Wechsler Memory Scale (WMS-III). Psychological Corporation; 1997.

8. Golden CJ, Freshwater SM. Stroop Color and Word Test: A Manual for Clinical and Experimental Uses.; 2002.

9. Daneman M, Carpenter PA. Individual differences in working memory and reading. Journal of Verbal Learning and Verbal Behavior. 1980;19(4):450-466. doi:10.1016/S0022-5371(80)90312-6

10. Delis DC, Kaplan E, Kramer JH. Delis-Kaplan Executive Function System (D-KEFS). Psychological Corporation; 2001.

Supplementary Table 2.1 Participant characteristics by follow up status

Characteristic		Followed for 2nd or 3rd visit		
		No (N=284)	Yes (N=1192)	*p*-value
TBI	Yes	72 (25.4%)	390 (32.7%)	<0.01
Age	Median [Min, Max]	57.7 [51.8, 65.9]	58.0 [51.1, 71.1]	0.82
Ethnicity	Non-Hispanic or Non-Latino	276 (97.2%)	1164 (97.7%)	0.73
Race	White	265 (93.3%)	1100 (92.3%)	
Education years	≤12	131 (46.1%)	451 (37.8%)	0.03
	13-14	74 (26.1%)	346 (29.0%)	
	15-16	58 (20.4%)	284 (23.8%)	
	>16	21 (7.4%)	111 (9.3%)	
AFQT	Median [Min, Max]	0.250 [-1.13, 3.50]	0.300 [-1.29, 2.32]	0.51
Income	<$40,000	46 (19.5%)	164 (18.2%)	0.52
	$40,000-$89,999	129 (54.7%)	471 (52.3%)	
	≥$90,000	61 (25.8%)	266 (29.5%)	
BMI	Median [Min, Max]	29.4 [17.8, 48.7]	28.9 [19.3, 54.7]	0.48
Smoking status	Never	77 (27.1%)	425 (35.8%)	0.01
	Former	118 (41.5%)	555 (46.8%)	
	Current	89 (31.3%)	207 (17.4%)	
Alcohol use	Never	19 (6.7%)	67 (5.6%)	0.91
	Former	96 (33.9%)	343 (28.9%)	
	Light	95 (33.6%)	496 (41.8%)	
	Moderate	25 (8.8%)	124 (10.4%)	
	Heavy	48 (17.0%)	157 (13.2%)	
Relationship status	Married or in a relationship	214 (76.4%)	939 (78.9%)	0.32
Participation in religious activities	≥3 times a month	114 (40.7%)	532 (44.8%)	0.22
Close friends	≥3	249 (89.9%)	1105 (93.5%)	0.50
Loneliness	At least 1 day in the past week	73 (26.0%)	277 (23.3%)	0.41
Social isolation	No confidants	10 (3.6%)	35 (3.0%)	0.57
Alcohol or drug abuse	Yes	19 (6.7%)	53 (4.4%)	0.82
Depressive symptoms	Yes	49 (17.9%)	163 (14.3%)	*
APOE ε4 carrier	Yes	92 (32.6%)	302 (28.5%)	0.14

P-values were derived from linear mixed-effects models for continuous variables and mixed-effects multinomial logistic regression models for categorical variables. Models included a random intercept to adjust for the correlation between twin pairs. The test for race and ethnicity were combined given sparse cell counts. *No test was reported for depressive symptom severity due to model fit.

n missing: income = 339 (23.0%), BMI = 3 (0.2%), smoking status = 5 (0.3%), alcohol use = 6 (0.4%), relationship status = 6 (0.4%), participation in religious activities =9 (0.6%), loneliness = 8 (0.5%), social isolation = 12 (0.8%), close friends = 17 (1.2%), alcohol or drug abuse = 1 (0.1%), AFQT = 20 (1.4%), depressive symptoms = 63 (4.3%), APOE ε4 carrier = 134 (9.1%)

Supplementary Table 2.2 Association of classifiable traumatic brain injury with cognitive performance trajectories over a 12 year follow up

Outcome	Model	Term	β (95% CI)
Episodic memory	1	TBI	0.0175 (-0.0956; 0.1306)
		Time	-0.0455 (-0.0502; -0.0408)
		TBI by time	-0.0058 (-0.0145; 0.003)
	2	TBI	0.0282 (-0.0866; 0.1429)
		Time	-0.0446 (-0.0495; -0.0396)
		TBI by time	-0.0072 (-0.0163; 0.0018)
	3	TBI	0.0276 (-0.0873; 0.1425)
		Time	-0.0443 (-0.0493; -0.0393)
		TBI by time	-0.0075 (-0.0165; 0.0016)
Executive function	1	TBI	0.0438 (-0.0611; 0.1487)
		Time	-0.067 (-0.0715; -0.0626)
		TBI by time	-0.0066 (-0.015; 0.0017)
	2	TBI	0.0613 (-0.0454; 0.168)
		Time	-0.0665 (-0.0712; -0.0618)
		TBI by time	-0.0076 (-0.0161; 0.001)
	3	TBI	0.0639 (-0.0427; 0.1705)
		Time	-0.0662 (-0.0708; -0.0615)
		TBI by time	-0.0079 (-0.0163; 6e-04)
Processing speed	1	TBI	-0.075 (-0.1939; 0.0439)
		Time	-0.0946 (-0.0992; -0.0899)
		TBI by time	0.0036 (-0.0051; 0.0123)
	2	TBI	-0.0515 (-0.1677; 0.0648)
		Time	-0.092 (-0.097; -0.087)
		TBI by time	0.001 (-0.0081; 0.0101)
	3	TBI	-0.0571 (-0.1737; 0.0594)
		Time	-0.0924 (-0.0974; -0.0874)
		TBI by time	0.0014 (-0.0077; 0.0105)

Note: Classifiable traumatic brain injury (TBI) includes TBIs that were deemed mild or moderate/severe by loss of consciousness and/or post traumatic amnesia. Beta (β) and 95% confidence intervals (CI) are derived from linear mixed-effects models that included random intercepts and family-relatedness a random effect to adjust for correlation between twin pairs. Time is defined as years from baseline. Model 1 fixed effects of TBI, time, and a TBI by time interaction term, and adjusted for baseline age (centered at 57.86 years, the average age of entry into VETSA), race/ethnicity, education, annual family income, and young adult cognitive ability (AFQT at age 20). Model 2 additionally adjusted for time-varying BMI (standardized), smoking status, alcohol use, and substance abuse, relationship status, participation in religious activities, number of close friends, social isolation, and depressive symptom severity. Model 3 additionally adjusted for APOE ε4 carrier status

Supplementary Table 2.3 Association of classifiable traumatic brain injury with cognitive performance trajectories by among those with and without an APOE e4 allele.

			APOE ε4 carrier status		
			No (n=979)	Yes (n=336)	
Outcome	Model	Term	β (95% CI)	β (95% CI)	$P_{Interaction}$
Episodic memory	1	TBI	-0.0194 (-0.1533; 0.1145)	0.1761 (-0.0345; 0.3867)	0.3660
		Time	-0.0443 (-0.05; -0.0386)	-0.0474 (-0.0559; -0.0389)	
		TBI by time	-0.004 (-0.0145; 0.0064)	-0.0118 (-0.0278; 0.0042)	
	2	TBI	-0.0034 (-0.1395; 0.1326)	0.1908 (-0.0249; 0.4065)	
		Time	-0.0431 (-0.0491; -0.0372)	-0.0465 (-0.0557; -0.0373)	
		TBI by time	-0.0055 (-0.0163; 0.0053)	-0.0129 (-0.0299; 0.004)	
Executive function	1	TBI	0.0467 (-0.0759; 0.1692)	0.0711 (-0.1328; 0.275)	0.0651
		Time	-0.065 (-0.0704; -0.0597)	-0.0707 (-0.0786; -0.0627)	
		TBI by time	-0.003 (-0.0129; 0.0068)	-0.0172 (-0.0322; -0.0022)	
	2	TBI	0.0619 (-0.062; 0.1859)	0.0787 (-0.1339; 0.2913)	
		Time	-0.0645 (-0.07; -0.0589)	-0.0708 (-0.0794; -0.0621)	
		TBI by time	-0.0044 (-0.0145; 0.0056)	-0.0167 (-0.0326; -8e-04)	
Processing speed	1	TBI	-0.0817 (-0.2214; 0.058)	-0.0397 (-0.2663; 0.1869)	0.6797
		Time	-0.0964 (-0.1021; -0.0907)	-0.0913 (-0.0996; -0.083)	
		TBI by time	0.0031 (-0.0073; 0.0136)	0.0052 (-0.0104; 0.0208)	
	2	TBI	-0.0547 (-0.1947; 0.0854)	-0.0403 (-0.2599; 0.1792)	
		Time	-0.0937 (-0.0998; -0.0876)	-0.0893 (-0.0982; -0.0805)	
		TBI by time	6e-04 (-0.0104; 0.0116)	0.0039 (-0.0124; 0.0201)	

Note: Classifiable traumatic brain injury (TBI) includes TBIs that were deemed mild or moderate/severe by loss of consciousness and/or post traumatic amnesia. Beta (β) and 95% confidence intervals (CI) are derived from linear mixed-effects models that included random intercepts and family-relatedness a random effect to adjust for correlation between twin pairs. Time is defined as years from baseline. Model 1 fixed effects of TBI, time, and a TBI by time interaction term, and adjusted for baseline age (centered at 57.86 years, the average age of entry into VETSA), race/ethnicity, education, annual family income, and young adult cognitive ability (AFQT at age 20). Model 2 additionally adjusted for time-varying BMI (standardized), smoking status, alcohol use, substance abuse, relationship status, participation in religious activities, number of close friends, loneliness, social isolation, and depressive symptom severity. *P* values for interaction ($P_{Interaction}$) were calculated using likelihood ratio tests to compare fully adjusted models with and without a 3-way interaction of APOE ε4 carrier status by TBI by time.

Supplementary Table 2.4 Association of traumatic brain injury by severity with cognitive performance trajectories over a 12 year of follow up

Outcome	Term		β (95% CI)
Episodic memory	TBI (ref = no TBI)	Mild	-0.0075 (-0.1378; 0.1227)
		Moderate/severe	0.1119 (-0.074; 0.2978)
	Time		-0.0443 (-0.0493; -0.0393)
	TBI by time (ref = no TBI)	Mild	-0.0077 (-0.0179; 0.0026)
		Moderate/severe	-0.007 (-0.022; 0.0081)
Executive function	TBI (ref = no TBI)	Mild	0.0628 (-0.0582; 0.1838)
		Moderate/severe	0.0647 (-0.1085; 0.2379)
	Time		-0.0662 (-0.0708; -0.0615)
	TBI by time (ref = no TBI)	Mild	-0.0093 (-0.0188; 3e-04)
		Moderate/severe	-0.0043 (-0.0185; 0.0098)
Processing speed	TBI (ref = no TBI)	Mild	-0.0448 (-0.1767; 0.0872)
		Moderate/severe	-0.0816 (-0.27; 0.1067)
	Time		-0.0924 (-0.0974; -0.0874)
	TBI by time (ref = no TBI)	Mild	0.0052 (-0.0051; 0.0154)
		Moderate/severe	-0.0079 (-0.0231; 0.0072)

Note: Beta (β) and 95% confidence intervals (CI) are derived from linear mixed-effects models that included random intercepts and family-relatedness a random effect to adjust for correlation between twin pairs. Time is defined as years from baseline. Models include fixed effects of TBI, time, and a TBI by time interaction term, and are adjusted for baseline age (centered at 57.86 years, the average age of entry into VETSA), race/ethnicity, education, annual family income, young adult cognitive ability (AFQT at age 20) and APOE ε4 carrier status.as well as time-varying BMI (standardized), smoking status, alcohol use, substance abuse, relationship status, participation in religious activities, number of close friends, social isolation, and depressive symptom severity.

Supplementary Table 2.5 Association of traumatic brain injury by severity with cognitive performance trajectories by among those with and without an APOE e4 allele

			APOE ε4 carrier status		
			No (n=948)	Yes (n=394)	
Outcome	Term		β (95% CI)	β (95% CI)	$P_{Interaction}$
Episodic memory	TBI (ref = no TBI)	Mild	-0.0345 (-0.1888; 0.1198)	0.1446 (-0.0964; 0.3857)	0.601
		Moderate/severe	0.0698 (-0.1506; 0.2902)	0.306 (-0.0384; 0.6504)	
	Time		-0.0432 (-0.0491; -0.0372)	-0.0464 (-0.0557; -0.0372)	
	TBI by time (ref = no TBI)	Mild	-0.0068 (-0.019; 0.0054)	-0.0127 (-0.0319; 0.0066)	
		Moderate/severe	-0.0023 (-0.0202; 0.0156)	-0.0139 (-0.042; 0.0143)	
Executive function	TBI (ref = no TBI)	Mild	0.0572 (-0.0835; 0.198)	0.0971 (-0.1403; 0.3345)	0.005
		Moderate/severe	0.0762 (-0.1249; 0.2774)	0.0248 (-0.3223; 0.372)	
	Time		-0.0645 (-0.07; -0.0589)	-0.0708 (-0.0794; -0.0622)	
	TBI by time (ref = no TBI)	Mild	-0.0019 (-0.0132; 0.0094)	-0.0286 (-0.0465; -0.0107)	
		Moderate/severe	-0.0109 (-0.0277; 0.0059)	0.0127 (-0.0136; 0.0391)	
Processing speed	TBI (ref = no TBI)	Mild	-0.0304 (-0.1891; 0.1282)	-0.0819 (-0.3271; 0.1633)	0.750
		Moderate/severe	-0.108 (-0.3348; 0.1188)	0.0681 (-0.2814; 0.4176)	
	Time		-0.0937 (-0.0998; -0.0876)	-0.0893 (-0.0981; -0.0804)	
	TBI by time (ref = no TBI)	Mild	0.0042 (-0.0083; 0.0166)	0.0088 (-0.0097; 0.0272)	
		Moderate/severe	-0.0085 (-0.0269; 0.0099)	-0.0083 (-0.0353; 0.0188)	

Note: Beta (β) and 95% confidence intervals (CI) are derived from linear mixed-effects models that included random intercepts and family-relatedness a random effect to adjust for correlation between twin pairs. Time is defined as years from baseline. Models included fixed effects of TBI, time, and a TBI by time interaction term, and adjusted for baseline age (centered at 57.86 years, the average age of entry into VETSA), race/ethnicity, education, annual family income, and young adult cognitive ability (AFQT at age 20) as well as time-varying BMI (standardized), smoking status, alcohol use, substance abuse, varying relationship status, participation in religious activities, number of close friends, social isolation, depressive symptom severity, and APOE ε4 carrier status. *P* values for interaction ($P_{Interaction}$) were calculated using likelihood ratio tests to compare fully adjusted models with and without a 3-way interaction of APOE ε4 carrier status by TBI by time.

Supplementary Table 2.6 Association of traumatic brain injury before and after military induction with cognitive performance trajectories over a 12 year follow up

Outcome	Term		β (95% CI)
Episodic memory	TBI (ref = no TBI)	Before military induction	0.0336 (-0.1058; 0.173)
		After military induction	-0.0096 (-0.1611; 0.142)
	Time		-0.0441 (-0.0491; -0.0391)
	TBI by time (ref = no TBI)	Before military induction	-0.0062 (-0.0173; 0.005)
		After military induction	-0.005 (-0.0169; 0.007)
Executive function	TBI (ref = no TBI)	Before military induction	0.0912 (-0.038; 0.2205)
		After military induction	0.0255 (-0.1154; 0.1664)
	Time		-0.0661 (-0.0708; -0.0615)
	TBI by time (ref = no TBI)	Before military induction	-0.0111 (-0.0214; -7e-04)
		After military induction	-0.0035 (-0.0147; 0.0077)
Processing speed	TBI (ref = no TBI)	Before military induction	-0.0209 (-0.1647; 0.1228)
		After military induction	-0.0598 (-0.2162; 0.0965)
	Time		-0.0926 (-0.0976; -0.0876)
	TBI by time (ref = no TBI)	Before military induction	0.0045 (-0.0066; 0.0156)
		After military induction	-0.0042 (-0.0162; 0.0078)

Note: Beta (β) and 95% confidence intervals (CI) are derived from linear mixed-effects models that included random intercepts and family-relatedness a random effect to adjust for correlation between twin pairs. Time is defined as years from baseline. Models include fixed effects of TBI, time, and a TBI by time interaction term, and are adjusted for baseline age (centered at 57.86 years, the average age of entry into VETSA), race/ethnicity, education, annual family income, young adult cognitive ability (AFQT at age 20) and APOE ε4 carrier status as well as time-varying BMI (standardized), smoking status, alcohol use, substance abuse, relationship status, participation in religious activities, number of close friends, social isolation, and depressive symptom severity.

Supplementary Table 2.7 Association of traumatic brain injury count with cognitive performance trajectories over a 12 year of follow up

Outcome	Term		β (95% CI)
Episodic memory	TBI (ref = no TBI)	1 TBI	-0.0611 (-0.1894; 0.0673)
		≥2 TBIs	0.1708 (-0.0024; 0.344)
	Time		-0.0442 (-0.0492; -0.0392)
	TBI by time (ref = no TBI)	1 TBI	-0.0041 (-0.0144; 0.0061)
		≥2 TBIs	-0.0085 (-0.0223; 0.0052)
Executive function	TBI (ref = no TBI)	1 TBI	0.0172 (-0.102; 0.1364)
		≥2 TBIs	0.1486 (-0.0124; 0.3096)
	Time		-0.0662 (-0.0708; -0.0615)
	TBI by time (ref = no TBI)	1 TBI	-0.0093 (-0.0189; 2e-04)
		≥2 TBIs	-0.0042 (-0.017; 0.0085)
Processing speed	TBI (ref = no TBI)	1 TBI	-0.013 (-0.1459; 0.1199)
		≥2 TBIs	-0.0922 (-0.2714; 0.0869)
	Time		-0.0925 (-0.0975; -0.0875)
	TBI by time (ref = no TBI)	1 TBI	-0.0011 (-0.0113; 0.0092)
		≥2 TBIs	0.0036 (-0.0101; 0.0173)

Note: Beta (β) and 95% confidence intervals (CI) are derived from linear mixed-effects models that included random intercepts and family-relatedness a random effect to adjust for correlation between twin pairs. Time is defined as years from baseline. Models include fixed effects of TBI, time, and a TBI by time interaction term, and are adjusted for baseline age (centered at 57.86 years, the average age of entry into VETSA), race/ethnicity, education, annual family income, young adult cognitive ability (AFQT at age 20) and APOE ε4 carrier status as well as time-varying BMI (standardized), smoking status, alcohol use, substance abuse, relationship status, participation in religious activities, number of close friends, social isolation, and depressive symptom severity.

Supplementary Table 2.8 Association of any traumatic brain injury with cognitive performance trajectories by APOE ε4 carrier status (excluding ε2/ε4 from ε4 carrier group) over a 12 year of follow up

			APOE ε4 carrier status		
			No (n=948)	Yes (n=344)	
Outcome	Model	Term	β (95% CI)	β (95% CI)	$P_{Interaction}$
Episodic memory	1	TBI	-0.027 (-0.1573; 0.1034)	0.1634 (-0.0513; 0.3782)	0.2452
		Time	-0.0442 (-0.0499; -0.0385)	-0.0483 (-0.0574; -0.0391)	
		TBI by time	-0.0021 (-0.0124; 0.0082)	-0.0127 (-0.0292; 0.0037)	
	2	TBI	-0.0104 (-0.143; 0.1221)	0.1855 (-0.0309; 0.4018)	
		Time	-0.0431 (-0.0491; -0.0372)	-0.0465 (-0.0564; -0.0366)	
		TBI by time	-0.0037 (-0.0142; 0.0069)	-0.014 (-0.0314; 0.0035)	
Executive function	1	TBI	0.0547 (-0.0654; 0.1748)	0.1172 (-0.0851; 0.3194)	0.0106
		Time	-0.065 (-0.0704; -0.0597)	-0.0729 (-0.0814; -0.0644)	
		TBI by time	-0.0026 (-0.0123; 0.007)	-0.0188 (-0.0341; -0.0035)	
	2	TBI	0.0678 (-0.0537; 0.1893)	0.1272 (-0.0832; 0.3376)	
		Time	-0.0645 (-0.07; -0.0589)	-0.0717 (-0.081; -0.0625)	
		TBI by time	-0.0036 (-0.0134; 0.0063)	-0.0202 (-0.0364; -0.0039)	
Processing speed	1	TBI	-0.0537 (-0.1919; 0.0845)	0.0505 (-0.184; 0.285)	0.2583
		Time	-0.0964 (-0.1021; -0.0907)	-0.0873 (-0.096; -0.0787)	
		TBI by time	0.0031 (-0.0071; 0.0133)	0.0017 (-0.0139; 0.0172)	
	2	TBI	-0.0279 (-0.1665; 0.1107)	0.0445 (-0.1777; 0.2668)	
		Time	-0.0938 (-0.0999; -0.0877)	-0.0854 (-0.0946; -0.0763)	
		TBI by time	2e-04 (-0.0106; 0.0109)	9e-04 (-0.0152; 0.0169)	

Note: Beta (β) and 95% confidence intervals (CI) are derived from linear mixed-effects models that included random intercepts and family-relatedness a random effect to adjust for correlation between twin pairs. Time is defined as years from baseline. Model 1 fixed effects of TBI, time, and a TBI by time interaction term, and adjusted for baseline age (centered at 57.86 years, the average age of entry into VETSA), race/ethnicity, education, annual family income, and young adult cognitive ability (AFQT at age 20). Model 2 additionally adjusted for time-varying BMI (standardized), smoking status, alcohol use, and substance abuse, relationship status, participation in religious activities, number of close friends, social isolation, and depressive symptom severity. Model 3 additionally adjusted for APOE ε4 carrier status. P values for interaction ($P_{Interaction}$) were calculated using likelihood ratio tests to compare fully adjusted models with and without a 3-way interaction of APOE ε4 carrier status by TBI by time.

Supplementary Table 2.9 Secondary outcomes for the association of any traumatic brain injury with cognitive performance trajectories over a 12 year of follow up

Outcome	Model	Term	β (95% CI)
Working memory	1	TBI	0.0116 (-0.0859; 0.1091)
		Time	-0.0346 (-0.0386; -0.0306)
		TBI by time	-0.0047 (-0.0119; 0.0025)
	2	TBI	0.0234 (-0.0757; 0.1225)
		Time	-0.0341 (-0.0383; -0.0299)
		TBI by time	-0.0051 (-0.0126; 0.0023)
	3	TBI	0.0239 (-0.0751; 0.1229)
		Time	-0.0341 (-0.0383; -0.0299)
		TBI by time	-0.0051 (-0.0126; 0.0024)
Verbal fluency	1	TBI	-0.0021 (-0.1123; 0.1081)
		Time	-0.0253 (-0.0296; -0.0209)
		TBI by time	-0.0055 (-0.0133; 0.0023)
	2	TBI	0.0169 (-0.0942; 0.1279)
		Time	-0.0241 (-0.0287; -0.0194)
		TBI by time	-0.0077 (-0.0159; 4e-04)
	3	TBI	0.0142 (-0.0971; 0.1255)
		Time	-0.0242 (-0.0288; -0.0196)
		TBI by time	-0.0076 (-0.0158; 6e-04)
Semantic fluency	1	TBI	0.053 (-0.0603; 0.1664)
		Time	-0.031 (-0.0364; -0.0255)
		TBI by time	-0.0079 (-0.0177; 0.002)
	2	TBI	0.0811 (-0.0331; 0.1953)
		Time	-0.0305 (-0.0362; -0.0247)
		TBI by time	-0.0105 (-0.0208; -2e-04)
	3	TBI	0.0788 (-0.0357; 0.1934)
		Time	-0.0304 (-0.0362; -0.0246)
		TBI by time	-0.0105 (-0.0208; -2e-04)

Note: Beta (β) and 95% confidence intervals (CI) are derived from linear mixed-effects models that included random intercepts and family-relatedness a random effect to adjust for correlation between twin pairs. Time is defined as years from baseline. Model 1 fixed effects of TBI, time, and a TBI by time interaction term, and adjusted for baseline age (centered at 57.86 years, the average age of entry into VETSA), race/ethnicity, education, annual family income, and young adult cognitive ability (AFQT at age 20). Model 2 additionally adjusted for time-varying BMI (standardized), smoking status, alcohol use, substance abuse, relationship status, participation in religious activities, number of close friends, social isolation, and depressive symptom severity. Model 3 additionally adjusted for APOE ε4 carrier status

Supplementary Table 2.10 Secondary outcomes for the association of any traumatic brain injury with cognitive performance trajectories by APOE ε4 carrier status over a 12 year follow up

			APOE ε4 carrier status		
			No (n=948)	Yes (n=394)	
Outcome	Model	Term	β (95% CI)	β (95% CI)	$P_{Interaction}$
Working memory	1	TBI	0.0398 (-0.0758; 0.1553)	-0.0108 (-0.1933; 0.1717)	0.12
		Time	-0.0351 (-0.0399; -0.0303)	-0.0332 (-0.0404; -0.026)	
		TBI by time	-5e-04 (-0.0091; 0.0081)	-0.015 (-0.0281; -0.0019)	
	2	TBI	0.0475 (-0.0695; 0.1645)	0.0086 (-0.1814; 0.1987)	
		Time	-0.0343 (-0.0394; -0.0292)	-0.0339 (-0.0416; -0.0262)	
		TBI by time	-9e-04 (-0.0099; 0.0081)	-0.0149 (-0.0286; -0.0012)	
Verbal fluency	1	TBI	0.0576 (-0.0747; 0.19)	-0.1429 (-0.3414; 0.0555)	0.11
		Time	-0.0241 (-0.0294; -0.0188)	-0.0287 (-0.036; -0.0214)	
		TBI by time	-0.0087 (-0.0183; 8e-04)	0.0027 (-0.0106; 0.016)	
	2	TBI	0.0819 (-0.0513; 0.2152)	-0.1522 (-0.3557; 0.0513)	
		Time	-0.0214 (-0.0271; -0.0158)	-0.0307 (-0.0387; -0.0227)	
		TBI by time	-0.0129 (-0.0229; -0.0029)	0.0056 (-0.0086; 0.0198)	
Semantic fluency	1	TBI	0.0911 (-0.0442; 0.2264)	-0.0744 (-0.2809; 0.1322)	0.53
		Time	-0.0314 (-0.038; -0.0248)	-0.0297 (-0.0395; -0.0198)	
		TBI by time	-0.0105 (-0.0223; 0.0014)	-0.0021 (-0.0201; 0.016)	
	2	TBI	0.1185 (-0.0183; 0.2553)	-0.0791 (-0.2917; 0.1336)	
		Time	-0.0305 (-0.0374; -0.0236)	-0.0295 (-0.0403; -0.0186)	
		TBI by time	-0.0138 (-0.0261; -0.0016)	-0.0019 (-0.0213; 0.0175)	

Note: Beta (β) and 95% confidence intervals (CI) are derived from linear mixed-effects models that included random intercepts and family-relatedness a random effect to adjust for correlation between twin pairs. Time is defined as years from baseline. Model 1 fixed effects of TBI, time, and a TBI by time interaction term, and adjusted for baseline age (centered at 57.86 years, the average age of entry into VETSA), race/ethnicity, education, annual family income, and young adult cognitive ability (AFQT at age 20). Model 2 additionally adjusted for time-varying BMI (standardized), smoking status, alcohol use, substance abuse, relationship status, participation in religious activities, number of close friends, social isolation, and depressive symptom severity. *P* values for interaction ($P_{Interaction}$) were calculated using likelihood ratio tests to compare fully adjusted models with and without a 3-way interaction of APOE ε4 carrier status by TBI by time.

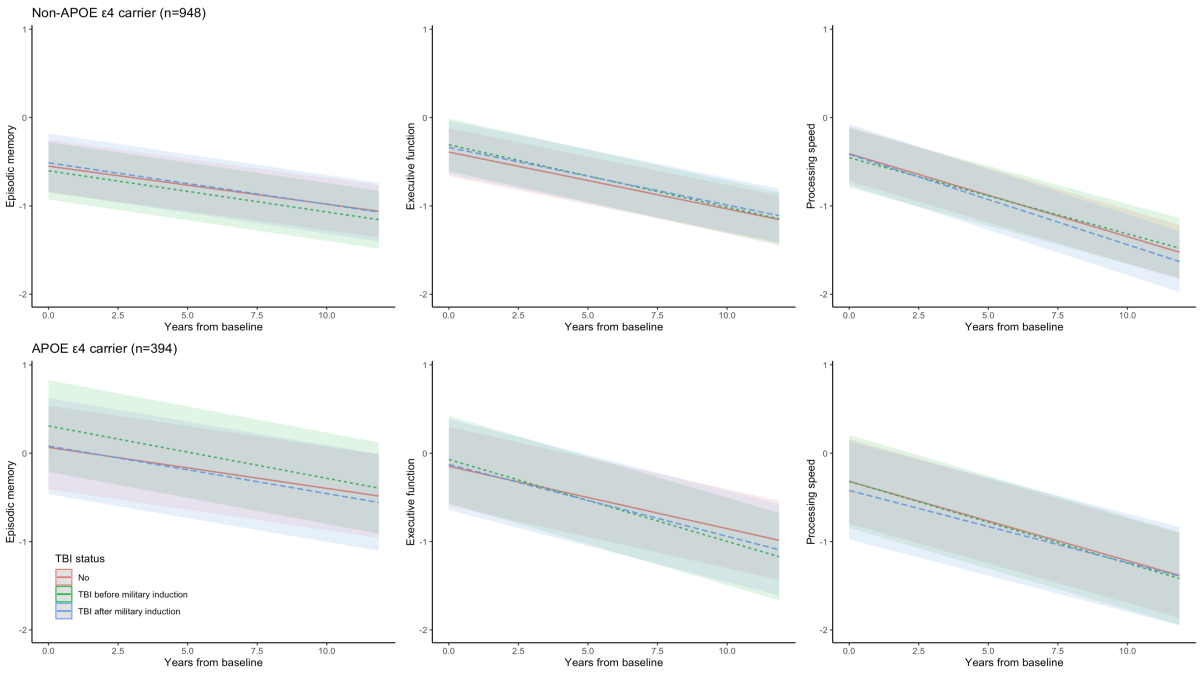
Supplementary Table 2.11 Association of any traumatic brain injury with cognitive performance trajectories by loneliness at the first visit over a 12 year follow up

			Loneliness at first visit		
			No (n=1118)	Yes (n=350)	
Outcome	Model	Term	β (95% CI)	β (95% CI)	$P_{Interaction}$
Episodic memory	1	TBI	0.0218 (-0.1033; 0.147)	0.1221 (-0.1307; 0.3749)	0.498
		Time	-0.0461 (-0.0515; -0.0408)	-0.0427 (-0.0528; -0.0325)	
		TBI by time	-9e-04 (-0.0108; 0.0091)	-0.0142 (-0.0309; 0.0026)	
	2	TBI	0.0306 (-0.0957; 0.157)	0.1601 (-0.0981; 0.4183)	
		Time	-0.0455 (-0.051; -0.04)	-0.0431 (-0.0533; -0.0328)	
		TBI by time	-0.0025 (-0.0126; 0.0077)	-0.0143 (-0.0311; 0.0025)	
	3	TBI	0.0306 (-0.0961; 0.1574)	0.1559 (-0.102; 0.4138)	
		Time	-0.0452 (-0.0507; -0.0396)	-0.0428 (-0.0532; -0.0325)	
		TBI by time	-0.0027 (-0.0128; 0.0075)	-0.0145 (-0.0313; 0.0024)	
Executive function	1	TBI	0.0904 (-0.0314; 0.2122)	-0.0483 (-0.2526; 0.156)	0.461
		Time	-0.0675 (-0.0724; -0.0625)	-0.066 (-0.0762; -0.0557)	
		TBI by time	-0.0077 (-0.017; 0.0016)	-0.0031 (-0.0201; 0.0139)	
	2	TBI	0.0925 (-0.0303; 0.2153)	-0.0489 (-0.2513; 0.1535)	
		Time	-0.0679 (-0.073; -0.0628)	-0.0653 (-0.0758; -0.0548)	
		TBI by time	-0.0073 (-0.0166; 0.0021)	-0.0035 (-0.0208; 0.0137)	
	3	TBI	0.0937 (-0.0291; 0.2165)	-0.0459 (-0.2478; 0.156)	
		Time	-0.0678 (-0.0729; -0.0627)	-0.0642 (-0.0744; -0.054)	
		TBI by time	-0.0074 (-0.0168; 0.002)	-0.0046 (-0.0213; 0.0122)	

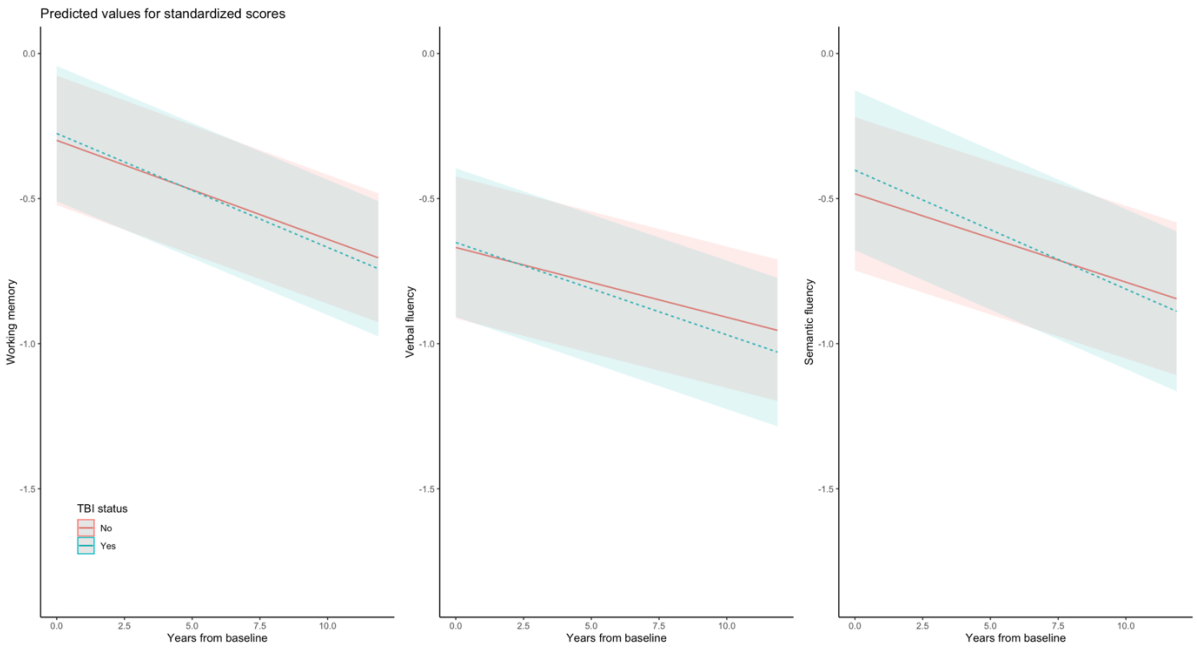
Supplementary Table 2.11 (cont'd) Association of any traumatic brain injury with cognitive performance trajectories by loneliness at the first visit over a 12 year follow up

			Loneliness at first visit		
			No (n=1118)	Yes (n=350)	
Outcome	Model	Term	β (95% CI)	β (95% CI)	$P_{Interaction}$
Processing speed	1	TBI	0.0024 (-0.1326; 0.1375)	-0.1748 (-0.433; 0.0834)	0.389
		Time	-0.0952 (-0.1003; -0.09)	-0.0923 (-0.1031; -0.0815)	
		TBI by time	0.0073 (-0.0024; 0.0169)	-0.009 (-0.0268; 0.0088)	
	2	TBI	0.0261 (-0.105; 0.1571)	-0.1648 (-0.4295; 0.0999)	
		Time	-0.0939 (-0.0993; -0.0886)	-0.0907 (-0.1018; -0.0796)	
		TBI by time	0.007 (-0.0028; 0.0168)	-0.0123 (-0.0305; 0.0058)	
	3	TBI	0.0212 (-0.1102; 0.1526)	-0.1807 (-0.4466; 0.0852)	
		Time	-0.0942 (-0.0995; -0.0888)	-0.0918 (-0.1029; -0.0807)	
		TBI by time	0.0072 (-0.0026; 0.0171)	-0.0111 (-0.0292; 0.007)	

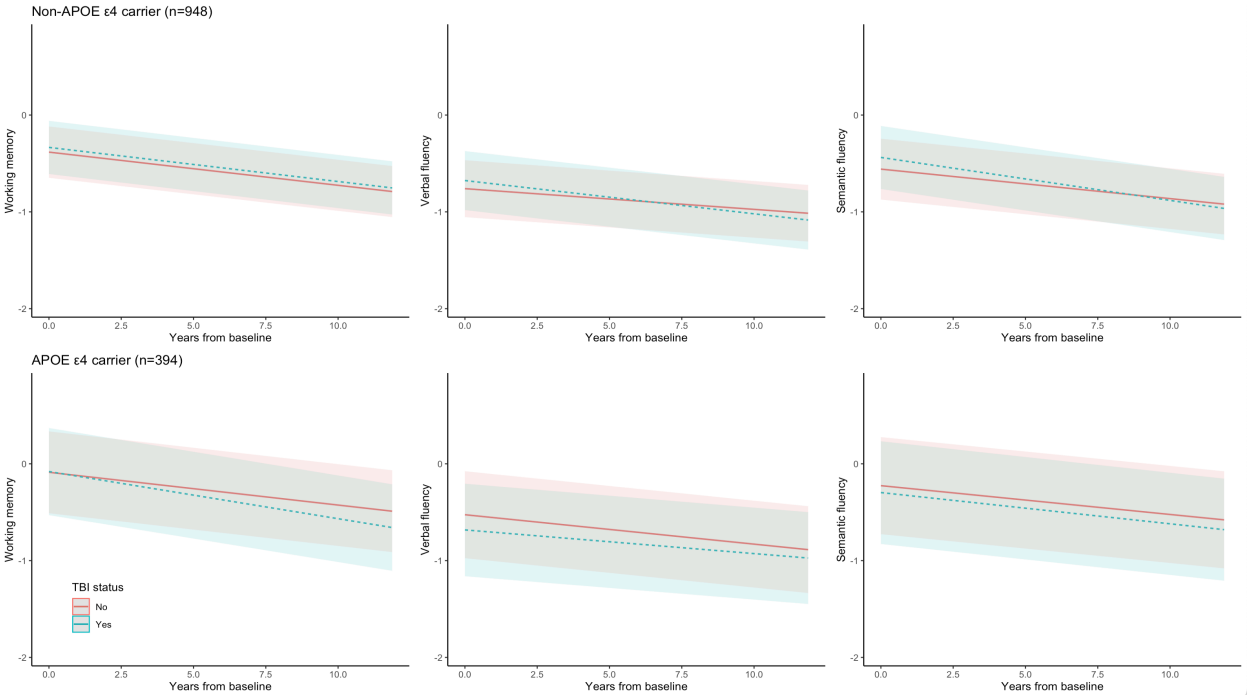
Note: Beta (β) and 95% confidence intervals (CI) are derived from linear mixed-effects models that included random intercepts and family-relatedness a random effect to adjust for correlation between twin pairs. Time is defined as years from baseline. Model 1 fixed effects of TBI, time, and a TBI by time interaction term, and adjusted for baseline age (centered at 57.86 years, the average age of entry into VETSA), race/ethnicity, education, annual family income, and young adult cognitive ability (AFQT at age 20). Model 2 additionally adjusted for time-varying BMI (standardized), smoking status, alcohol use, and substance abuse, relationship status, participation in religious activities, number of close friends, and social isolation. Model 3 additionally adjusted for APOE ε4 carrier status. *P* values for interaction ($P_{Interaction}$) were calculated using likelihood ratio tests to compare fully adjusted models with and without a 3-way interaction of APOE ε4 carrier status by TBI by time.



Supplementary Figure 2.1 Trajectories of cognition function test performance over years from baseline by TBI before or after military induction vs. no TBI, stratified by APOE ε4 carrier status. Plots are based on linear mixed-effects models adjusted for baseline age (centered at 57.86 years, the average age of entry into VETSA), race/ethnicity, education, annual family income and young adult cognitive ability (AFQT at age 20) as well as time-varying BMI (standardized), smoking status, alcohol use, substance abuse, relationship status, participation in religious activities, number of close friends, loneliness, social isolation, and depressive symptom severity.



Supplementary Figure 2.2 Trajectories of secondary cognition function test performance outcomes over years from baseline by TBI. Plots are based on linear mixed-effects models adjusted for baseline age (centered at 57.86 years, the average age of entry into VETSA), race/ethnicity, education, annual family income and young adult cognitive ability (AFQT at age 20) as well as time-varying BMI (standardized), smoking status, alcohol use, substance abuse, relationship status, participation in religious activities, number of close friends, loneliness, social isolation, and depressive symptom severity.



Supplementary Figure 2.3 Trajectories of secondary cognition function test performance outcomes over years from baseline by TBI stratified by APOE ε4 carrier status. Plots are based on linear mixed-effects models adjusted for baseline age (centered at 57.86 years, the average age of entry into VETSA), race/ethnicity, education, annual family income and young adult cognitive ability (AFQT at age 20) as well as time-varying BMI (standardized), smoking status, alcohol use, substance abuse, relationship status, participation in religious activities, number of close friends, loneliness, social isolation, and depressive symptom severity.

Chapter 2, in part, is currently being prepared for submission for publication of the material. Posis, Alexander Ivan B.; Alcaraz, John E.; Parada Jr., Humberto; Shadyab, Aladdin H.; Elman, Jeremy A; Panizzon, Matthew S.; Reynolds, Chandra A.; Franz, Carol E.; Kremen, William S.; McEvoy, Linda K. The dissertation author was the primary researcher and author of this paper.

Chapter 3 Associations of traumatic brain injury with markers of brain health among older men in the Vietnam Era Twin Study of Aging

3.1 Abstract

Background: Traumatic brain injury (TBI) is a major cause of disability and mortality and is associated with increased risk of dementia. However, it is unclear whether TBI exacerbates changes in markers of brain health in aging.

Methods: This cross-sectional study included 517 male Vietnam Era Twin Study of Aging participants at Wave 3 from 2016 to 2019 (median age=68 [range=61-72] years; 96.7% non-Hispanic; 90.2% white). The Brain-Age Regression Analysis and Computation Utility Software (BARACUS) was used on structural MRIs to calculate predicted brain age difference (PBAD) scores. A multichannel segmentation approach measured and quantified abnormal white matter (AWM). Restriction spectrum imaging (RSI) was used to characterize white matter microstructure and model diffusion in restricted and free water compartments. Multivariable linear mixed-effects models were used to estimate associations of TBI with PBAD, AWM, and RSI outcomes. We also assessed differences by apolipoprotein E epsilon 4 (*APOE* ε4) status, psychiatric symptoms based on depressive and posttraumatic stress symptom severity, and loneliness.

Results: Thirty-four percent of participants reported a history of TBI. TBI was not associated with PBAD or AWM (p-values > 0.05). In region-specific RSI analyses, TBI was associated with lower restricted diffusion in the inferior longitudinal fasciculus bilaterally and the left inferior occipital fasciculus compared to no TBI, after adjusting for age and scanner (p-values < 0.05). Main effects for TBI were not significant in any other region after correction for

multiple comparisons. There was no evidence to suggest effect measure modification by *APOE* ε4 status, elevated psychiatric symptoms, or loneliness for all primary outcomes.

Conclusions: Findings suggest that there are subtle white matter microstructural changes after a TBI event that persist years after the initial injury.

3.2 Introduction

There were an estimated 210,110 traumatic brain injury (TBI)-related hospitalizations in the United States in 2020.[117] Furthermore, TBI was associated with an 84% higher risk of dementia in a meta-analysis by the Lancet Commission.[4] Brain atrophy following TBI may contribute to this elevated dementia risk.[44] Potential mechanisms include accelerated brain aging by neuronal damage caused by a TBI,[74] and earlier onset of age-related neurodegenerative processes such as white matter degredation.[118]

Given that TBI is associated with higher risk of dementia[4] and may deplete neuronal resources and exacerbate the brain atrophy process,[43] it is of public health interest to identify sensitive biomarkers indicative of reduced structural integrity after a TBI. Prior studies among mostly younger-aged participants and within relatively short temporal proximity to the TBI event reported evidence of adverse brain associations, including older predicted brain age difference (PBAD) scores[43] and altered white matter microstructure.[45,52,53] For example, one study reported that compared to non-TBI participants, those with TBI (n = 99; mean age = 38 years; mean time since injury = 28 months) had an older predicted brain age based on grey and white matter models, with larger predicted brain age differences observed among older participants.[43] Others have reported differences in white matter microstructure. For example, one study of 40 participants with TBI (mean age = 48 +/- 17 years; mean time since injury = 73 months) reported altered white matter microstructure in the inferior longitudinal fasciculus (ILF), and in the forceps minor.[52] Another study (n with TBI = 30; mean age = 38.5 +/- 10.1 years; median time since injury = 34 months) found that TBI was associated with altered diffusion metrics for the corpus callosum, ILF bilaterally, as well as the anterior regions of the fronto-occipital tracts.[53]

The longer term (i.e., over decades) consequences of TBI on brain health in aging are not well understood,[54] and few studies have examined associations of remote TBI with neuroimaging measures in later life.[46] A study of 51 older adults with mild TBI (mean age = 65.1 years; average age of injury = 33.1 years) found smaller volumes of temporal white matter compared to controls.[46] More research on whether earlier life TBI is associated with differences in measures of brain health at older age is warranted.

The objective of this study was to test the association between lifetime history of TBI and three different neuroimaging-based measures of brain health including PBAD, abnormal white matter (AWM), and restriction spectrum imaging (RSI) white matter metrics among a well-characterized cohort of older aged men (age range = 61-72 years). We hypothesized that TBI would be associated with greater PBAD, a higher proportion of AWM to total white matter, and with altered white matter microstructure based on RSI in regions such as the ILF. We also examined group differences (i.e., effect measure modification) by apolipoprotein E epsilon 4 (*APOE* ε4) genotype, given that this polymorphism confers higher risk for Alzheimer's disease.[76] With evidence showing the importance of social connection in health-related outcomes,[61] we also examined effect measure modification by depressive and post-traumatic stress symptom severity, and loneliness.

3.3 Methods

3.3.1 Study Population

The Vietnam Era Twin Study of Aging (VETSA) is an ongoing longitudinal study of men that began in 2001; the study design is described in detail elsewhere.[80,81] At the time of enrollment, VETSA participants had similar health and lifestyle characteristics compared to US men in their age cohort according to Center for Disease Control and Prevention data,[84] and

approximately 80% of VETSA participants did not report combat exposure.[85] The present cross-sectional study used data from the Wave 3 MRI component (n=525) of VETSA, which occurred between 2016 to 2019.[80,81]

For the present study, we excluded participants based on poor image quality (e.g., due to excessive motion) or cerebral abnormalities (e.g., tumors, large strokes) that resulted in poor image segmentation accuracy (Figure 1). For PBAD, we excluded 5 participants with abnormal radiological findings and 10 with poor image quality resulting in an analytic sample of 510. For AWM, there were 475 participants with multichannel imaging data to compute global volumes; we excluded 4 participants with abnormal radiological findings resulting in an analytic sample of 471. There were 505 participants with diffusion imaging data to compute RSI outcomes; we excluded 5 participants with abnormal radiological findings, and 41 whose data failed quality assurance resulting in an analytic sample of 459. There were 517 unique participants across all analyses. This study was approved by the University of California, San Diego Institutional Review Board. All participants provided written informed consent.

3.3.2 Outcomes

3.3.2.1 MRI acquisition and processing

Methods for MRI acquisition and processing in VETSA are described in detail elsewhere.[119,120] T1-, T2-, proton-density (PD)-, and diffusion-weighted images were obtained using standardized protocols in VETSA. Images were acquired on two GE 3 T Discovery 750x scanners (GE Healthcare, Waukesha, WI, USA) with 8-channel phased array head coils. Anatomical data were acquired with a sagittal 3D fast spoiled gradient echo (FSPGR) T1-weighted (T1w) volume, optimized for maximum gray/white contrast (TE = 3.2 ms, TR = 8.1 ms, TI = 600 ms, flip angle = 8 degrees, matrix = 256 × 192, in-plane resolution = 1 × 1 mm,

slice thickness = 1.2 mm, slices = 172), and a coronal 2D FRFSE-XL T2 with 2 mm slice thickness, FOV = 24 cm, TE = 94 ms, TR = 4.6 s, ETL = 16, frequency = 256, phase = 256, 2 NEX; and a coronal 2D FSE-XL PD with 2 mm slice thickness, FOV = 24 cm, TE = min/full, TR = 3 s, ETL = 4, frequency = 256, phase = 256. Diffusion data were acquired with a multi-shell diffusion-weighted scan (54-directions, b values = [0 (x3), 666 (x6), 1333 (x15), 2666 (x15), 4000 (x15)] s/mm^2, integrated with a pair of b = 0 images with opposite phase-encode polarity, TR = 6600 msec, TE = 81.1 msec, matrix = 96x96, in-plane resolution = 2.5x2.5 mm, slice thickness = 2.5 mm, 54 slices). T1w structural images were processed using the FreeSurfer software package,[121] as described previously to obtain measures of subcortical gray matter volume, cortical thickness and cortical surface area.[119,120]

3.3.2.2 Predicted brain age difference score (PBAD)

The Brain-Age Regression Analysis and Computation Utility Software (BARACUS) v0.9.4 was used to calculate predicted brain age based on structural MRIs,[122] as previously described for VETSA participants.[123,124] Based on each participant's cortical thickness, cortical surface area, and subcortical volume measures derived from FreeSurfer, BARACUS used linear support vector regression models to create a composite brain age score. The predicted brain age difference (PBAD) score was calculated as the difference between the participant's chronological age and predicted brain age, such that more negative PBAD values suggest an older brain age compared to an individual's chronological age. Residualized PBAD scores, adjusted for scanner, were used as the outcome variable. To account for age-dependent bias in predicted brain age (because brain age may be overestimated for younger participants and underestimated for older participants), analyses adjusted for chronologic age.[125]

3.3.2.3 Abnormal white matter (AWM)

A multi-segmentation approach was used to measure and quantify global abnormal white matter (AWM; i.e., regions within the white matter that are hyperintense on T2-weighted images) volume based on methods described previously.[120] Briefly, combining information from T1-, T2-, and PD-weighted images, the tissue segmentation was performed using the statistical classification framework of the open source Insight Segmentation and Registration Toolkit (ITK),[126] leveraging Scott's L2E method[127] to determine robust means and covariances, and in combination with anatomical considerations via ITK's morphological operators.[128] Since partial voluming of fluid and white matter along the edges of ventricles results in voxels with AWM-like signal, any voxels that touched a ventricular fluid voxel were excluded from the estimated volumes. Due to the non-normal distribution of AWM data, the values were transformed using the natural log. The outcome measure used was the proportion of total white matter that was abnormal, a ratio of global AWM to total white matter.

3.3.2.4 Diffusion MRI processing and restriction spectrum imaging (RSI)

Diffusion MRI (dMRI) images were pre-processed as previously described in VETSA.[129] Briefly, dMRI images were corrected for eddy current distortions,[130] head motion,[131] B_0 susceptibility distortion,[132–134] and gradient nonlinearity distortion.[135] and T2-weighted b=0 images were registered to T1-weighted structural images. Registration quality of the images was manually reviewed. Diffusion-weighted images were resampled into a standard orientation with 2mm isotropic resolution using cubic interpolation. White matter tracts were labeled using a probabilistic atlas (AtlasTrack[136]; Hagler et al., 2009[131]).

Restriction spectrum imaging (RSI) was used to characterize white matter microstructure by modeling diffusion in the restricted, hindered, and free water compartments,[137–139] which

roughly correspond to intracellular, extracellular, and fluid filled spaces, respectively. RSI methods are described in detail elsewhere.[119] RSI metrics, representing the total diffusion signal (i.e., both isotropic and anisotropic) in each of the three compartments, were calculated as the square root of the sum of squares of model fit parameters for each compartment. Normalized signal fractions were calculated by dividing by the square root of the sum of squares for all model fit parameters, resulting in unitless measures that range from 0 to 1.

Our primary RSI outcomes of interest were the normalized signal fractions of the restricted and free water compartments, averaged across all white matter tract voxels. We focused on restricted diffusion given its improved characterization of fiber architecture compared to hindered diffusion.[137] To investigate the potential for regionally specific vulnerabilities to TBI, we examined diffusion parameters within white matter tracts previously found to be affected by TBI,[52,53] which included the corpus callosum, forceps major and minor, inferior frontal fasciculus (ILF) bilaterally, and the inferior frontal occipital fasciculus (IFOF) bilaterally.

3.3.3 Main exposure: traumatic brain injury (TBI)

Lifetime TBI, reported at any VETSA wave, was defined based on methods described in prior work in VETSA.[34] Briefly, participants were asked four questions regarding prior head injury at each VETSA Wave: 1) “Have you ever had a severe head injury that was associated with loss of consciousness or confusion?”; 2) “Did that head injury (any of those head injuries) result in your staying overnight in the hospital?”; 3) “Have you ever been told by a doctor that you had a concussion? (If ‘Yes,’ how many times?)”; and 4) “Altogether, how many different head injuries or concussions (all total) have you had?” Starting in Wave 2 of VETSA, participants who reported having had a head injury were asked details of each head injury which included age, cause of injury, receipt of medical attention or hospitalization, presence/duration of

loss of consciousness (LOC), posttraumatic amnesia (PTA), confusion or memory loss, and seizures related to the injury. For the present study, history of lifetime symptomatic TBI was defined as a binary variable (any/none). We also considered variables for severity based on LOC and/or PTA (mild; moderate/severe; unclassifiable), multiple TBI (0; 1; ≥2), and history of TBI before military induction (none; before military induction; after military induction).

3.3.4 Effect modifiers: apolipoprotein E, elevated psychiatric symptoms, and loneliness

We tested for effect measure modification among a subset of the study population with data on *APOE* ε4 carrier status, depressive symptom severity, posttraumatic stress symptom severity, and loneliness. Genotyping methods in VETSA are described in detail elsewhere.[97] Participants were classified as an *APOE* ε4 carrier if they had at least one ε4 allele or as non-carriers otherwise. There was a high correlation between depressive and posttraumatic symptom severity ($r = 0.75$; $p < 0.01$). Therefore, we created a composite binary variable for psychiatric symptoms, indicating the presence or absence of depressive and posttraumatic stress symptoms.[101,140] As defined in our prior work,[34] scores ≥36 on the PTSD Checklist – Civilian version[140] or ≥16 on the Center for Epidemiologic Studies Depression Scale (CES-D)[101] were classified as clinically significant symptoms. Loneliness was measured using a single item from the CES-D which asked how often the participant felt lonely in the past week.[101] The loneliness item is moderately correlated with the three-item University of California, Los Angeles Loneliness Scale ($r = 0.49$; $p < 0.01$).[103]

3.3.5 Covariates

Covariate information was derived from medical interviews and questionnaires that were completed at VETSA Wave 3. Covariates of interest were selected based on prior literature[23,34] and included age at the VETSA Wave 3 visit, race/ethnicity, years of education (as a

socioeconomic status index), young adult general cognitive ability as measured by the Armed Forces Qualification Test (AFQT), and annual family income (<$40,000; $40,000-$89,999; ≥$90,000). The AFQT, administered at an average age of 20 years,[98,99] is a 100-item multiple choice test administered to service members prior to military induction and is highly correlated with Wechsler IQ ($r = 0.84$).[100] AFQT scores were recorded as percentiles based on military norms, then converted to z-scores (i.e., quantiles from the standard normal distribution). We also considered the following covariates assessed at Wave 3: body mass index (BMI; kg/m^2), smoking status (never; former; current), alcohol use (never; former; light; moderate; heavy), relationship status (none; married or in a relationship), participation in religious activities (≤2 times a month; ≥3 times a month), number of close friends (≤2; ≥3), social isolation (at least 1 confidant; no confidants), and elevated psychiatric symptoms (yes; no). Social isolation was assessed using the following question, "How many people do you know who you can trust and confide in?" as defined in a prior report.[102]

3.3.6 Statistical analysis

Participant characteristics at VETSA Wave 3 were summarized by TBI status. Continuous characteristics were described using median (range) and categorical variables were described using counts (percentages). Differences in characteristics by TBI groups were assessed using linear mixed-effects models for continuous variables and multinomial logistic regression models for categorical variables. Race and ethnicity were combined for group comparisons given sparse cell sizes. Models included a random intercept of family relatedness to account for the correlation between twin pairs.

For our primary analyses, we fit multivariable linear mixed-effects models to estimate cross-sectional associations of TBI status with PBAD, AWM ratio, and RSI outcomes,

separately. We used four successively adjusted models: Model 1 included the fixed effects of TBI and adjusted for age (and scanner for RSI models; potential scanner differences were accounted for in the computation of PBAD and AWM). Model 2 additionally adjusted for socio-demographic characteristics including race/ethnicity, education, annual family income, and young adult cognitive ability; Model 3 additionally adjusted for health- and social-related characteristics that may potentially operate as mediators and included BMI (standardized), smoking status, alcohol use, relationship status, participation in religious activities, number of close friends, social isolation, and psychiatric symptoms; Model 4 additionally adjusted for *APOE* ε4 carrier status. We separately assessed effect measure modification by *APOE* ε4 carrier status, psychiatric symptom severity, and loneliness. *P* values for interaction ($P_{\text{Interaction}}$) were calculated using likelihood ratio tests comparing fully adjusted models with and without a 2-way interaction of the effect modifier-by-TBI.

We performed several sensitivity analyses building on Model 1. To assess whether there were differences by timing of injury, we used a three-level TBI variable indicating when a TBI occurred relative to military induction (no TBI; TBI before military induction; TBI after military induction). To assess the potential impact of greater TBI severity, we repeated analyses by TBI severity (no TBI; mild TBI; moderate/severe TBI). Because repetitive TBI is hypothesized to accelerate dementia-related pathology,[44] we used a three-level TBI variable indicating the number of reported TBIs (no TBI; 1 TBI; ≥2 TBIs).

All statistical analyses were conducted in R (version 4.2.2; R Core Team, 2022). The *lme4* package was used for linear mixed-effects analyses.[109] Statistical tests were two-tailed, and *P* values were considered significant at $p < 0.05$. Given that we considered 16 outcomes for our

RSI analyses across the free and restricted diffused compartments, we corrected for multiple comparisons using the Li and Ji method for false discovery rate (FDR) adjustment.[141]

3.4 Results

3.4.1 Participant characteristics at study entry

Of the 517 men included in this study, 34% reported lifetime TBI and 12.7% reported ≥2 TBIs. The most common TBI severity was mild (67%) while 29% were moderate/severe and 4% were unclassifiable (i.e., did not have data on presence of LOC, confusion or memory loss, seizures, medical attention, or hospitalization due to injury). The majority of those with TBI reported history prior to military induction (59%) and the median age at first TBI was 18 (range=2-69) years. At Wave 3, the median age of participants was 68.7 (range=61-72) years old (Table 3.1). Most men were non-Hispanic/Latino (96.7%) and white (90.2%). A higher proportion of those with TBI history had >12 years of education (70.6% vs. 60.3% , p-value = 0.03), were more likely to be heavy alcohol users (16% vs. 10.1%; p-value < 0.01), less likely to participate in religious activities ≥3 times a month (39.0% vs. 49.6%; p-value < 0.01), more likely to report feeling lonely in the past week (26.0% vs. 17.5%; p-value = 0.03), and more likely to have significant depressive symptom severity (15.3% vs. 7.3%; p-value = 0.02).

3.4.2 PBAD and AWM by TBI status

There were no statistically significant associations of TBI status with PBAD (Table 3.2) or AWM (Table 3.3) in any model. Additionally, *APOE* ε4 carrier status did not modify the association between TBI and PBAD or AWM (PBAD $P_{\text{Interaction}} = 0.44$; AWM $P_{\text{Interaction}} = 0.59$).

3.4.3 White matter microstructure by TBI status

There were no statistically significant associations of TBI with restricted diffusion averaged across all white matter tracts (Table 3.4; Figure 3.2). Increased age was associated with

lower total diffusion in the restricted compartment averaged across all tracts (β = -0.002; SE = 0.0008; p-value = 0.04). In region-specific analyses, TBI was associated with lower restricted diffusion in bilateral ILF (left IFL: β = -0.017, SE = 0.005; right ILF: β = -0.013, SE = 0.005), and left IFOF (β = -0.013, SE = 0.005) in minimally adjusted models. Associations of TBI with restricted diffusion were of similar magnitude after further adjustment in Models 2, 3, and 4, but were not significant after multiple comparisons adjustment, except for the left ILF for Model 2. Increased age was associated with lower restricted diffusion in the left ILF controlling for TBI (β = -0.0028; SE = 0.0012; p-value = 0.02). There were no significant associations between TBI and free water diffusion in any tract. Increased age was associated with higher total free water diffusion (β = 0.002; SE = 0.0007; p-value < 0.01), averaged across all tracts after controlling for TBI. There was no evidence to suggest effect measure modification by *APOE* ε4 carrier status in the association between TBI with all white matter tract ROIs ($P_{\text{Interaction}} > 0.12$, all).

3.4.4 Effect measure modification by elevated psychiatric symptoms, and loneliness

There was no evidence to suggest effect measure modification by elevated psychiatric symptoms or loneliness in the associations of TBI with PBAD, AWM, and RSI outcomes ($P_{\text{Interaction}} > 0.22$, all; Supplementary Tables 3.5-3.7). There were also no significant interactions between TBI with elevated psychiatric symptoms ($P_{\text{Interaction}} = 0.72$) or loneliness ($P_{\text{Interaction}} = 0.90$) in relation to total restricted diffusion in the left ILF (Supplementary Table 3.8).

3.4.5 Sensitivity analysis

In sensitivity analyses, there were no statistically significant associations of timing, severity, or number of TBIs with PBAD or AWM (Supplementary Table 3.1). Associations did not differ by the timing of the TBI (i.e., before or after military induction), the severity of the TBI, or the number of TBIs in relation to white matter ROIs (Supplementary Tables 3.2-3.4).

3.5 Discussion

In this cross-sectional study of older men, history of TBI was not associated with predicted brain age difference or proportion of abnormal white matter in older adulthood. Using sensitive measures of white matter microstructure, TBI was associated with lower restricted diffusion in the ILF bilaterally and left IFOF compared to no TBI. There was no evidence of differences according to the timing, severity, or number of TBI. We did not find effect measure modification by *APOE* ε4 carrier status, elevated psychiatric symptoms, or loneliness with any of the primary outcomes. While TBIs were not associated with more global neuroimaging-based measures of brain health, these findings suggest that earlier life TBI has subtle effects on long-range white matter tracts in later life.

We did not find significant differences in PBAD scores by participants' TBI status. In a prior study of younger adults that modeled PBAD based on white and grey matter volumetric measures separately, participants with TBI had a greater PBAD compared to controls in both models.[43] Participants were scanned on an average of 28.4 months post-TBI.[43] Most injuries were moderate/severe TBI (82.8%), and the authors did not find significant differences among those with mild TBI compared to controls.[43] In our study, participants were scanned an average of 45.3 years after their first TBI and most injuries were mild (67.2%). Our null findings may be indicative of the mild severity of injury and potential attenuation of the effects of TBI over time. Additionally, the brain age measure generated by BARACUS is based on gray matter measures, and is not sensitive to differences in white matter which, as suggested by our results, may be more vulnerable to TBI-related effects.

TBI, relative to no TBI, was associated with lower restricted diffusion in the ILF bilaterally and the left IFOF. Lower restricted diffusion may be indicative of lower structure

integrity due that may, for example, reflect breakdown in cellular membranes. The ILF is a long-range white matter tract which connects the occipital and temporal lobes to the anterior temporal areas of the brain.[142] The IFOF connects the parietal and occipital lobes to the frontal lobe.[143] Our findings are generally in line with two smaller studies of mostly younger adults that used a similar diffusion approach (i.e., neurite orientation dispersion and density imaging), which has analogs to the restricted and free water measures we present here.[52,53] TBIs may cause loss of white matter integrity in these regions and have further effects on cognitive function.[45] In a previous report on this sample, we found that greater executive function ability was associated with less free water.[144] In a study of 52 participants (age range = 25-82 years), fractional anisotropy in the left ILF was positively correlated with visual spatial and memory performance.[145] While there were no significant differences in macrostructural measures of PBAD and AWM by TBI status, our results add to the current evidence base by showing that differences in TBI-associated white matter microstructure injury measured by RSI are apparent at later life, many years after injury.

We did not find significant interactions of elevated psychiatric symptoms or loneliness with TBI in relation to any outcomes of interest. These are important to consider given that depressive and posttraumatic stress symptoms, in addition to other conditions, are often present following a TBI event.[146] Future work in larger and more diverse samples should consider clarifying whether psychiatric symptoms mediate the relationship between TBI and brain health given that posttraumatic stress disorder and depression are common outcomes following a TBI,[147] and depression may be a symptom or prodrome of dementia.[148]

This study has several strengths, which included a large and well-characterized study sample with multimodal neuroimaging data. There was also information on potentially

confounding characteristics, and we were able to examine effect measure modification by *APOE* status and multiple aspects of social contact. However, there were several limitations to consider. First, this study was cross-sectional, which does not allow for assessment of within-participant change for the outcomes of interest. Further follow-up of the VETSA cohort should assess these relationships over the life course and probe if TBI accelerates ongoing age-related structural changes to the brain. Second, data on lifetime TBI were derived from retrospective reports of often remote events, possibly contributing to information bias. There is also potential for selection bias due to survival bias given that participants needed to have lived to middle-to-older age to be included in the present study. Lastly, while our study population was representative of US men in this age cohort with respect to education and health characteristics,[84] there is limited generalizability of our findings to women and populations of diverse race and ethnicity, requiring future study among these populations.

In this study of community-dwelling men who were in early older age, we found small and regionally specific associations of TBI with lower restricted diffusion, primarily in the ILF and IFOF. Our findings suggest that there are subtle white matter microstructural effects after a TBI event that may have persisted decades after the initial injury. These changes may contribute to greater age-related cognitive decline, although we did not assess this in the present study. Because the Lancet Commission highlights TBI as a risk factor for dementia,[4] these results provide further rationale for public health interventions and policy intended to prevent TBI and to mitigate the impact of TBI-related cognitive decline and dementia risk in later life.

ACKNOWLEDGEMENTS

The content is the sole responsibility of the authors and does not necessarily represent official views of the National Institute on Aging, National Institutes of Health, or the Veteran's Administration.

U.S. Department of Veterans Affairs, Department of Defense; National Personnel Records Center, National Archives and Records Administration; Internal Revenue Service; National Opinion Research Center; National Research Council, National Academy of Sciences; and the Institute for Survey Research, Temple University provided invaluable assistance in the conduct of the VET Registry. The Cooperative Studies Program of the U.S. Department of Veterans Affairs provided financial support for development and maintenance of the Vietnam Era Twin Registry.

We would also like to acknowledge the continued cooperation and participation of the members of the VET Registry and their families.

FUNDING

This work was supported by a National Institutes of Health, National Institute on Aging, T32 Predoctoral Training Fellowship (T32 AG058529 to A.I.B.P.). A.H.S. and L.K.M. were supported by National Institute on Aging grants RF1AG079149 and RF1AG074345. H.P. was supported by the National Cancer Institute (K01 CA234317), the SDSU/UCSD Comprehensive Cancer Center Partnership (U54 CA132384 & U54 CA132379), and the Alzheimer's Disease Resource Center for Advancing Minority Aging Research at the University of California San Diego (P30 AG059299). Other support includes grants from the National Institute on Aging at the National Institutes of Health: R01 AG050595, ROI AG022381, ROI AG076838, ROI AG037985, ROI AG064955, R01 AG056410 and P01 AG055367.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE:

University of California, San Diego Office of IRB Administration and the Boston University Institutional Review Boards approved the study protocols. The study was performed in accordance with ethical standards as laid down in the 1964 Declaration of Helsinki. Participants provided written informed consent.

Table 3.1 Participant characteristics at Wave 3 by traumatic brain injury (TBI) status

Characteristic		TBI status		p-value
		No (N=340)	Yes (N=177)	
Age	Median [Min, Max]	68.9 [61.4, 71.7]	68.5 [62.6, 71.0]	0.67
Ethnicity	Non-Hispanic or Non-Latino	325 (95.6%)	175 (98.9%)	0.59
Race	White	305 (89.7%)	164 (92.7%)	
Education years	≤12	135 (39.7%)	52 (29.4%)	0.03
	13-14	100 (29.4%)	57 (32.2%)	
	15-16	73 (21.5%)	49 (27.7%)	
	>16	32 (9.4%)	19 (10.7%)	
Income	<$40,000	43 (16.7%)	23 (19.2%)	0.55
	$40,000-$89,999	139 (54.1%)	61 (50.8%)	
	≥$90,000	75 (29.2%)	36 (30.0%)	
AFQT	Median [Min, Max]	0.250 [-1.18, 2.05]	0.380 [-1.00, 2.32]	0.13
BMI	Median [Min, Max]	29.0 [16.0, 42.8]	29.1 [16.0, 40.9]	0.62
Smoking status	Never	126 (37.2%)	71 (40.1%)	0.48
	Former	159 (46.9%)	77 (43.5%)	
	Current	11 (3.2%)	3 (1.7%)	
Alcohol use	Never	35 (10.4%)	8 (4.6%)	<0.01
	Former	101 (29.9%)	50 (28.6%)	
	Light	132 (39.1%)	71 (40.6%)	
	Moderate	36 (10.7%)	18 (10.3%)	
	Heavy	34 (10.1%)	28 (16.0%)	
Relationship status	Married or in a relationship	272 (80.2%)	130 (73.4%)	0.09
Participation in religious activities	≥3 times a month	168 (49.6%)	69 (39.0%)	<0.01
Close friends	≥3	310 (92.0%)	162 (91.5%)	0.87
Social isolation	No confidants	13 (3.8%)	9 (5.1%)	0.80
Depressive symptoms	Yes	24 (7.3%)	27 (15.3%)	0.02
PTSD symptoms	Yes	42 (12.7%)	31 (17.7%)	0.32
Elevated psychiatric symptoms	Yes	49 (15.0%)	40 (22.9%)	0.06
APOE ε4 carrier	Yes	72 (24.1%)	35 (24.6%)	0.61

P-values were derived from linear mixed-effects models for continuous variables or multinomial logistic regression models for categorical variables, with a random intercept for family-related to account for the correlation between twin pairs. Race and ethnicity were combined for group comparisons given sparse cell sizes. n missing: income = 140 (27.1%), AFQT = 8 (1.5%), BMI = 1 (0.2%), smoking status = 1 (0.2%), alcohol use = 4 (0.8%), relationship status = 1 (0.2%), participation in religious activities =1 (0.2%), close friends = 3 (0.6%), social isolation = 2 (0.4%), depressive symptoms = 11 (2.1%), PTSD symptoms = 12 (2.3%), elevated psychiatric symptoms = 16 (3.1%), and APOE ε4 carrier = 76 (14.7%)

Table 3.2 Association of traumatic brain injury with predicted brain age difference score

Model	β (95% CI)	p-value
1	-0.25 (-1.10, 0.61)	0.57
2	-0.55 (-1.54, 0.45)	0.28
3	-0.40 (-1.44, 0.64)	0.45
4	-0.41 (-1.46, 0.63)	0.44

Note: Beta (β) and 95% confidence intervals (CI) are derived from linear mixed-effects models that included family-relatedness a random intercept to adjust for correlation between twin pairs. P-values are derived from type III analysis of variance with Satterthwaite's method. Model 1 include the fixed effect of traumatic brain injury, adjusted for age. Model 2 additionally adjusted for race/ethnicity, education, annual family income, and young adult cognitive ability (AFQT at age 20). Model 3 additionally adjusted for BMI (standardized), smoking status, alcohol use, relationship status, participation in religious activities, number of close friends, social isolation, and elevated psychiatric symptoms. Model 4 additionally adjusted for APOE ε4 carrier status.

Table 3.3 Association of traumatic brain injury with abnormal white matter ratio

Model	β (95% CI)	p-value
1	-0.0016 (-0.0085, 0.0054)	0.66
2	0.0019 (-0.0063, 0.010)	0.64
3	0.0013 (-0.0074, 0.010)	0.76
4	0.0011 (-0.0076, 0.0098)	0.81

Note: Beta (β) and 95% confidence intervals (CI) are derived from linear mixed-effects models that included family-relatedness a random intercept to adjust for correlation between twin pairs. P-values are derived from type III analysis of variance with Satterthwaite's method. Model 1 include the fixed effect of traumatic brain injury, adjusted for age. Model 2 additionally adjusted for race/ethnicity, education, annual family income, and young adult cognitive ability (AFQT at age 20). Model 3 additionally adjusted for BMI (standardized), smoking status, alcohol use, relationship status, participation in religious activities, number of close friends, social isolation, and elevated psychiatric symptoms. Model 4 additionally adjusted for APOE ε4 carrier status.

Table 3.4 Associations of traumatic brain injury with specific regions of interest derived from restriction spectrum imaging measures

		Model 1			Model 2			Model 3			Model 4		
Region of interest		β (SE)	t-statistic	p-value	β (SE)	t-statistic	p-value	β (SE)	t-statistic	p-value	β (SE)	t-statistic	p-value
Total restricted diffusion	All fibers	-0.0053 (0.0031)	-1.71	0.09	-0.0057 (0.0038)	-1.48	0.14	-0.0034 (0.004)	-0.86	0.39	-0.0033 (0.004)	-0.83	0.41
	CC	-0.0049 (0.0036)	-1.38	0.17	-0.0044 (0.0044)	-1.01	0.31	-0.0018 (0.0046)	-0.39	0.70	-0.0017 (0.0046)	-0.36	0.72
	Fmaj	-0.0059 (0.0038)	-1.55	0.12	-0.0051 (0.0045)	-1.12	0.26	-0.0013 (0.0048)	-0.28	0.78	-0.0013 (0.0048)	-0.27	0.79
	Fmin	-0.0092 (0.0048)	-1.93	0.05	-0.0121 (0.0059)	-2.05	0.04	-0.0102 (0.0065)	-1.58	0.12	-0.0102 (0.0065)	-1.58	0.12
	IFOF - Left	-0.0112 (0.0044)	-2.53	**0.01**	-0.0114 (0.0052)	-2.20	0.03	-0.0093 (0.0057)	-1.63	0.10	-0.0092 (0.0057)	-1.61	0.11
	ILF - Left	-0.0172 (0.005)	-3.45	**<0.01**	-0.0172 (0.0059)	-2.92	**<0.01**	-0.0155 (0.0064)	-2.43	0.02	-0.0155 (0.0064)	-2.41	0.02
	IFOF - Right	-0.008 (0.0046)	-1.73	0.09	-0.0062 (0.0056)	-1.11	0.27	-0.0038 (0.0059)	-0.64	0.52	-0.0037 (0.006)	-0.63	0.53
	ILF - Right	-0.0126 (0.0048)	-2.64	**0.01**	-0.0122 (0.0057)	-2.16	0.03	-0.0107 (0.006)	-1.80	0.07	-0.0108 (0.006)	-1.80	0.07
Isotropic-free water	All fibers	-0.002 (0.0027)	-0.72	0.47	-0.0018 (0.0034)	-0.54	0.59	-0.0048 (0.0036)	-1.33	0.18	-0.0047 (0.0036)	-1.30	0.19
	CC	-0.002 (0.0035)	-0.57	0.57	-0.0038 (0.0043)	-0.89	0.38	-0.0073 (0.0045)	-1.64	0.10	-0.0073 (0.0045)	-1.63	0.10
	Fmaj	-0.0015 (0.0041)	-0.36	0.72	-0.0058 (0.0048)	-1.20	0.23	-0.0092 (0.0051)	-1.82	0.07	-0.0092 (0.0051)	-1.80	0.07
	Fmin	-0.0013 (0.0046)	-0.27	0.79	1e-04 (0.0052)	0.03	0.98	-0.0038 (0.0055)	-0.69	0.49	-0.0036 (0.0055)	-0.66	0.51
	IFOF - Left	0.0018 (0.0041)	0.45	0.65	0.005 (0.0049)	1.01	0.31	0.0034 (0.0053)	0.64	0.52	0.0035 (0.0053)	0.67	0.50
	ILF - Left	0.0082 (0.005)	1.65	0.10	0.0125 (0.0059)	2.10	0.04	0.0117 (0.0064)	1.83	0.07	0.012 (0.0064)	1.86	0.06
	IFOF - Right	-0.0027 (0.0043)	-0.63	0.53	-0.0035 (0.0051)	-0.69	0.49	-0.0044 (0.0054)	-0.83	0.41	-0.0043 (0.0054)	-0.80	0.42
	ILF - Right	0.0012 (0.0048)	0.25	0.81	-5e-04 (0.0055)	-0.09	0.93	-3e-04 (0.0058)	-0.05	0.96	-1e-04 (0.0059)	-0.01	0.99

Notes: Beta (β) and 95% confidence intervals (CI) are derived from linear mixed-effects models that included family-relatedness a random intercept to adjust for correlation between twin pairs. P-values are derived from type III analysis of variance with Satterthwaite's method. P-values surviving FDR-correction are highlighted in bold. Model 1 includes the fixed effect of traumatic brain injury, adjusted for age and scanner. Model 2 additionally adjusted for race/ethnicity, education, annual family income, and young adult cognitive ability (AFQT at age 20). Model 3 additionally adjusted for BMI (standardized), smoking status, alcohol use, relationship status, participation in religious activities, number of close friends, social isolation, and elevated psychiatric symptoms. Model 4 additionally adjusted for APOE ε4 carrier status. β = beta. SE = standard error. CC = corpus callosum. Fmaj = forceps major. Fmin = forceps minor. IFOF = inferior frontal occipital fasciculus. ILF = inferior longitudinal fasciculus.

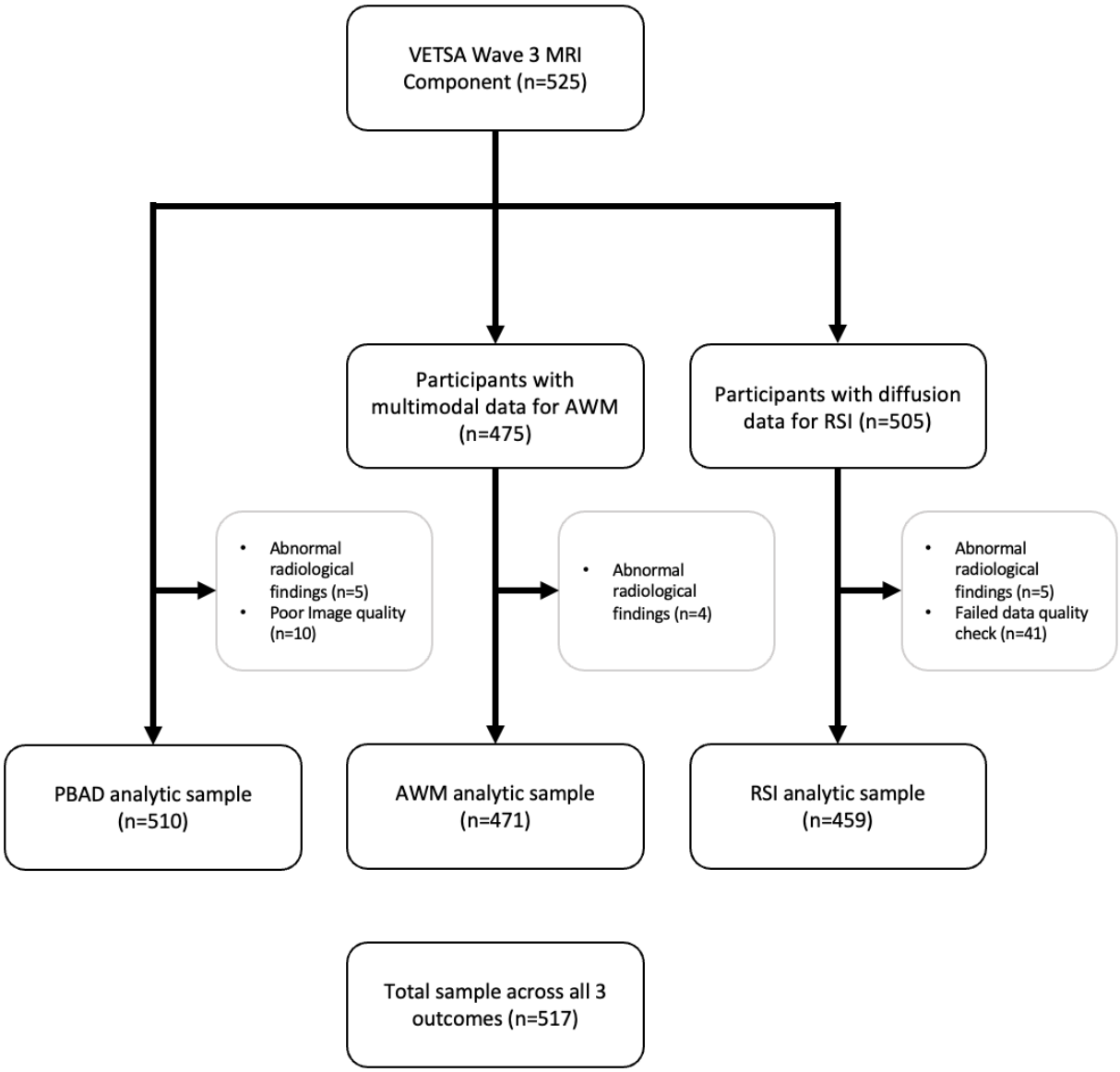


Figure 3.1 CONSORT diagram by study outcome. VETSA = Vietnam Era Twin Study of Aging; TBI = traumatic brain injury; PBAD = predicted brain age difference score; AWM = abnormal white matter; RSI = restriction spectrum imaging; MRI = magnetic resonance imaging

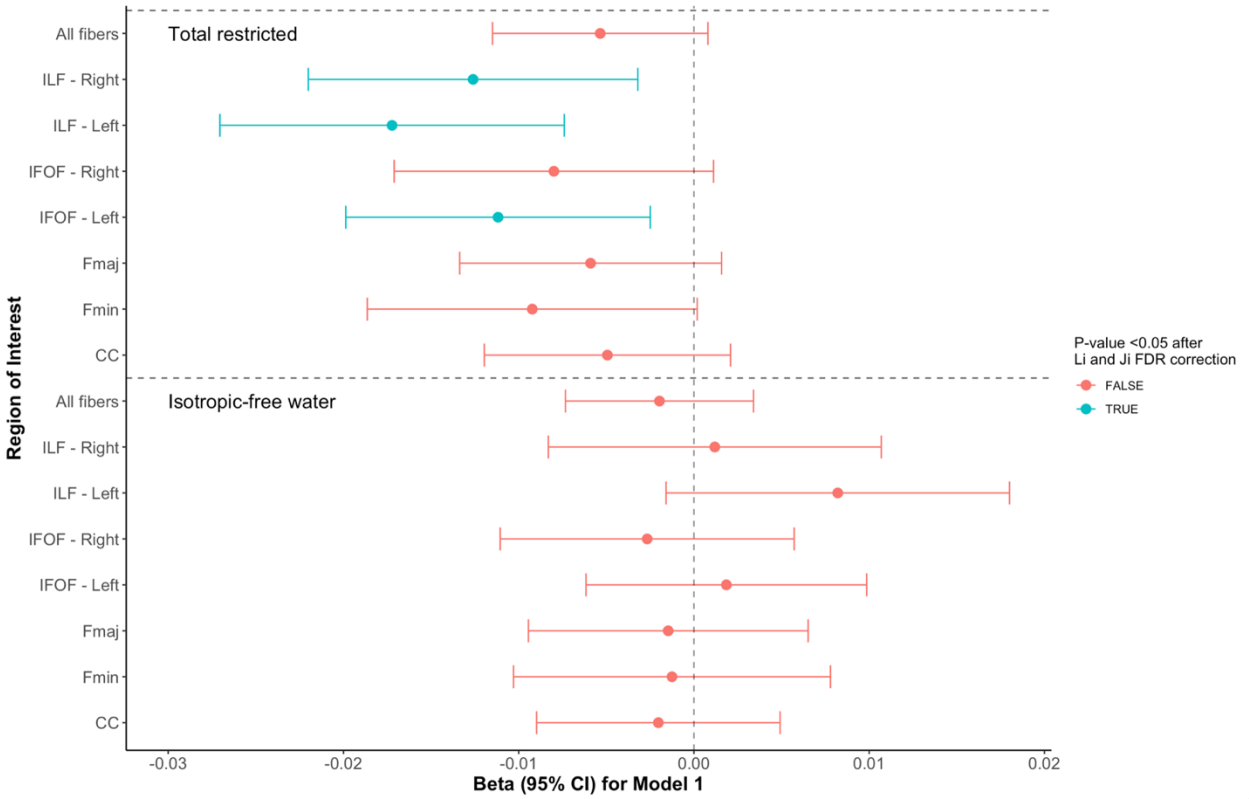


Figure 3.2 Associations of traumatic brain injury with specific regions of interest derived from restriction spectrum imaging measures. Beta (β) and 95% confidence intervals (CI) are derived from linear mixed-effects models that included family-relatedness a random intercept to adjust for correlation between twin pairs. P-values are derived from type III analysis of variance with Satterthwaite's method. Model 1 includes the fixed effect of traumatic brain injury, adjusted for age and scanner. CC = corpus callosum. Fmaj = forceps major. Fmin = forceps minor. IFOF = inferior frontal occipital fasciculus. ILF = inferior longitudinal fasciculus.

Supplementary Table 3.1 Associations with of traumatic brain injury (TBI) timing, severity, or number with predicted brain age difference score (PBAD) or abnormal white matter (AWM)

		Dependent variable			
		PBAD		AWM	
Independent variable		β (95% CI)	p-value	β (95% CI)	p-value
Timing of TBI	No TBI	1 (ref)		1 (ref)	
	Before military induction	-0.26 (-1.31, 0.79)	0.63	-0.002 (-0.0107, 0.0066)	0.64
	After military induction	-0.24 (-1.42, 0.95)	0.70	-0.001 (-0.0103, 0.0084)	0.84
Severity	No TBI	1 (ref)		1 (ref)	
	Mild	-0.72 (-1.65, 0.21)	0.13	-0.0011 (-0.009, 0.0068)	0.78
	Moderate/severe	-0.09 (-1.47, 1.3)	0.90	-0.0010 (-0.0123, 0.0104)	0.87
Number of TBI	No TBI	1 (ref)		1 (ref)	
	1 TBI	0.02 (-0.96, 1.01)	0.97	0.0015 (-0.0064, 0.0095)	0.70
	≥2 TBIs	-0.79 (-2.10, 0.51)	0.23	-0.0081 (-0.0189, 0.0027)	0.14

Beta (β) and 95% confidence intervals (CI) are derived from linear mixed-effects models that included family-relatedness a random intercept to adjust for correlation between twin pairs. P-values are derived from type III analysis of variance with Satterthwaite's method. Models included the fixed effect of traumatic brain injury and adjusted for age.

Supplementary Table 3.2 Associations of traumatic brain injury timing with regions of interest derived from restriction spectrum imaging measures

		No TBI	TBI prior to military induction	TBI after military induction
Region of interest		β (95% CI)	β (95% CI)	β (95% CI)
Total restricted diffusion	All fibers	1 (ref)	-0.0033 (-0.011, 0.0043)	-0.008 (-0.0165, 5e-04)
	CC	1 (ref)	-0.0028 (-0.0115, 0.0059)	-0.0077 (-0.0175, 0.002)
	Fmaj	1 (ref)	-0.0021 (-0.0113, 0.0072)	-0.0109 (-0.0212, -5e-04)
	Fmin	1 (ref)	-0.0045 (-0.0162, 0.0071)	-0.0154 (-0.0283, -0.0024)
	IFOF - Left	1 (ref)	-0.0099 (-0.0208, 9e-04)	-0.0128 (-0.0248, -8e-04)
	ILF - Left	1 (ref)	-0.0137 (-0.0258, -0.0015)	-0.0219 (-0.0355, -0.0083)
	IFOF - Right	1 (ref)	-0.0046 (-0.0159, 0.0067)	-0.0125 (-0.0251, 1e-04)
	ILF - Right	1 (ref)	-0.0097 (-0.0213, 0.0019)	-0.0165 (-0.0295, -0.0035)
Isotropic-free water	All fibers	1 (ref)	-0.0047 (-0.0113, 0.002)	0.0016 (-0.0058, 0.009)
	CC	1 (ref)	-0.0052 (-0.0138, 0.0034)	0.0022 (-0.0075, 0.0118)
	Fmaj	1 (ref)	-0.0068 (-0.0166, 0.003)	0.0056 (-0.0054, 0.0166)
	Fmin	1 (ref)	-0.0078 (-0.0189, 0.0033)	0.0074 (-0.0051, 0.0198)
	IFOF - Left	1 (ref)	-0.0014 (-0.0113, 0.0085)	0.0062 (-0.0049, 0.0172)
	ILF - Left	1 (ref)	0.0044 (-0.0077, 0.0164)	0.0134 (-2e-04, 0.0269)
	IFOF - Right	1 (ref)	-0.0085 (-0.0188, 0.0018)	0.0051 (-0.0065, 0.0167)
	ILF - Right	1 (ref)	-0.0072 (-0.0188, 0.0044)	0.0134 (-2e-04, 0.0269)

Notes: Beta (β) and 95% confidence intervals (CI) are derived from linear mixed-effects models that included family-relatedness a random intercept to adjust for correlation between twin pairs. Models include the fixed effect of traumatic brain injury, adjusted for age and scanner. β = beta. SE = standard error. FDR = false discovery rate. CC = corpus callosum. Fmaj = forceps major. Fmin = forceps minor. IFOF = inferior frontal occipital fasciculus. ILF = inferior longitudinal fasciculus.

Supplementary Table 3.3 Associations of traumatic brain injury severity with regions of interest derived from restriction spectrum imaging measures

		No TBI	Mild TBI	Moderate/Severe TBI
Region of interest		β (95% CI)	β (95% CI)	β (95% CI)
Total restricted diffusion	All fibers	1 (ref)	-0.0052 (-0.0122, 0.0018)	-0.0052 (-0.0157, 0.0053)
	CC	1 (ref)	-0.0034 (-0.0114, 0.0045)	-0.008 (-0.0199, 0.004)
	Fmaj	1 (ref)	-0.0031 (-0.0116, 0.0054)	-0.0105 (-0.0232, 0.0022)
	Fmin	1 (ref)	-0.0076 (-0.0182, 0.003)	-0.0115 (-0.0276, 0.0045)
	IFOF - Left	1 (ref)	-0.0106 (-0.0205, -7e-04)	-0.0119 (-0.0269, 0.0031)
	ILF - Left	1 (ref)	-0.0165 (-0.0277, -0.0053)	-0.0169 (-0.0337, -5e-05)
	IFOF - Right	1 (ref)	-0.0095 (-0.0198, 9e-04)	-0.004 (-0.0197, 0.0116)
	ILF - Right	1 (ref)	-0.0137 (-0.0245, -0.0029)	-0.009 (-0.0252, 0.0071)
Isotropic-free water	All fibers	1 (ref)	-0.0034 (-0.0094, 0.0027)	2e-04 (-0.0088, 0.0092)
	CC	1 (ref)	-0.0046 (-0.0124, 0.0031)	0.0036 (-0.0081, 0.0152)
	Fmaj	1 (ref)	-0.0057 (-0.0147, 0.0034)	0.006 (-0.0075, 0.0195)
	Fmin	1 (ref)	-0.0028 (-0.0131, 0.0074)	0.001 (-0.0143, 0.0163)
	IFOF - Left	1 (ref)	-1e-04 (-0.0092, 0.0089)	0.0041 (-0.0094, 0.0177)
	ILF - Left	1 (ref)	0.0034 (-0.0076, 0.0145)	0.0154 (-0.001, 0.0319)
	IFOF - Right	1 (ref)	-0.0038 (-0.0133, 0.0057)	-0.0027 (-0.0169, 0.0116)
	ILF - Right	1 (ref)	8e-04 (-0.01, 0.0115)	0.0154 (-0.001, 0.0319)

Notes: Beta (β) and 95% confidence intervals (CI) are derived from linear mixed-effects models that included family-relatedness a random intercept to adjust for correlation between twin pairs. P-values are derived from type III analysis of variance with Satterthwaite's method. P-values surviving FDR-correction are highlighted in bold. Models include the fixed effect of traumatic brain injury, adjusted for age and scanner. β = beta. SE = standard error. FDR = false discovery rate. CC = corpus callosum. Fmaj = forceps major. Fmin = forceps minor. IFOF = inferior frontal occipital fasciculus. ILF = inferior longitudinal fasciculus.

Supplementary Table 3.4 Associations of traumatic brain injury count with regions of interest derived from restriction spectrum imaging measures

		No TBI	1 TBI	≥2 TBIs
Region of interest		β (95% CI)	β (95% CI)	β (95% CI)
Total restricted diffusion	All fibers	1 (ref)	-0.0046 (-0.0116, 0.0025)	-0.007 (-0.0166, 0.0026)
	CC	1 (ref)	-0.0036 (-0.0117, 0.0045)	-0.0077 (-0.0186, 0.0032)
	Fmaj	1 (ref)	-0.0058 (-0.0145, 0.0028)	-0.006 (-0.0177, 0.0056)
	Fmin	1 (ref)	-0.0061 (-0.0169, 0.0047)	-0.0158 (-0.0305, -0.0011)
	IFOF - Left	1 (ref)	-0.0089 (-0.0188, 0.0011)	-0.0161 (-0.0298, -0.0025)
	ILF - Left	1 (ref)	-0.016 (-0.0273, -0.0046)	-0.0198 (-0.035, -0.0046)
	IFOF - Right	1 (ref)	-0.0088 (-0.0193, 0.0018)	-0.0064 (-0.0206, 0.0077)
	ILF - Right	1 (ref)	-0.0134 (-0.0243, -0.0026)	-0.0109 (-0.0255, 0.0036)
Isotropic-free water	All fibers	1 (ref)	-0.001 (-0.0072, 0.0052)	-0.0039 (-0.0122, 0.0044)
	CC	1 (ref)	-0.0025 (-0.0105, 0.0055)	-0.0011 (-0.0118, 0.0097)
	Fmaj	1 (ref)	-0.0013 (-0.0105, 0.008)	-0.0019 (-0.0142, 0.0104)
	Fmin	1 (ref)	-5e-04 (-0.011, 0.0099)	-0.0027 (-0.0167, 0.0113)
	IFOF - Left	1 (ref)	0.0035 (-0.0058, 0.0127)	-0.0015 (-0.0138, 0.0109)
	ILF - Left	1 (ref)	0.0109 (-5e-04, 0.0222)	0.003 (-0.0119, 0.0179)
	IFOF - Right	1 (ref)	-0.0018 (-0.0115, 0.008)	-0.0045 (-0.0174, 0.0084)
	ILF - Right	1 (ref)	0.0046 (-0.0064, 0.0156)	0.003 (-0.0119, 0.0179)

Notes: Beta (β) and 95% confidence intervals (CI) are derived from linear mixed-effects models that included family-relatedness a random intercept to adjust for correlation between twin pairs. P-values are derived from type III analysis of variance with Satterthwaite's method. P-values surviving FDR-correction are highlighted in bold. Models include the fixed effect of traumatic brain injury, adjusted for age and scanner. β = beta. SE = standard error. FDR = false discovery rate. CC = corpus callosum. Fmaj = forceps major. Fmin = forceps minor. IFOF = inferior frontal occipital fasciculus. ILF = inferior longitudinal fasciculus.

Supplementary Table 3.5 Associations of traumatic brain injury and predicted brain age difference score by elevated psychiatric symptoms or loneliness status.

Effect modifier					$P_{Interaction}$
Elevated psychiatric symptoms	No (n=405)		Yes (n=89)		0.73
	β (SE)	p-value	β (SE)	p-value	
TBI (ref = no TBI)	-0.257 (0.504)	0.61	0.214 (1.09)	0.85	
Loneliness	No (n=403)		Yes (n=105)		0.89
	β (SE)	p-value	β (SE)	p-value	
TBI (ref = no TBI)	-0.224 (0.489)	0.65	-0.111 (1.10)	0.92	

Note: Beta (β) and 95% confidence intervals (CI) are derived from linear mixed-effects models that included family-relatedness a random intercept to adjust for correlation between twin pairs. P-values are derived from type III analysis of variance with Satterthwaite's method. Models include the fixed effect of traumatic brain injury, adjusted for age and scanner. $P_{Interaction}$ was calculated using likelihood ratio tests to compare fully adjusted models with and without a 2-way interaction of the effect modifier-by-TBI. Elevated psychiatric symptoms were defined as the presence of absence of post-traumatic stress disorder (PTSD) and depressive symptom severity. For the PTSD Checklist – Civilian version, scores ≥36 suggest PTSD symptoms (n missing = 8). Significant depressive symptom severity was defined by scores of ≥16 on the Center for Epidemiologic Studies Depression Scale (CES-D). Loneliness was measured using a single item from the CES-D.

Supplementary Table 3.6 Associations of traumatic brain injury and abnormal white matter ratio by elevated psychiatric symptoms or loneliness status.

Effect modifier					$P_{Interaction}$
Elevated psychiatric symptoms	No (n=376)		Yes (n=83)		0.25
	β (SE)	p-value	β (SE)	p-value	
TBI (ref = no TBI)	-0.00324 (0.00401)	0.42	0.00741 (0.00912)	0.42	
Loneliness	No (n=376)		Yes (n=94)		0.22
	β (SE)	p-value	β (SE)	p-value	
TBI (ref = no TBI)	-0.00201 (0.00396)	0.61	0.00669 (0.00789)	0.40	

Note: Beta (β) and 95% confidence intervals (CI) are derived from linear mixed-effects models that included family-relatedness a random intercept to adjust for correlation between twin pairs. P-values are derived from type III analysis of variance with Satterthwaite's method. Models include the fixed effect of traumatic brain injury, adjusted for age and scanner. $P_{Interaction}$ was calculated using likelihood ratio tests to compare fully adjusted models with and without a 2-way interaction of the effect modifier-by-TBI. Elevated psychiatric symptoms were defined as the presence of absence of post-traumatic stress disorder (PTSD) and depressive symptom severity. For the PTSD Checklist – Civilian version, scores ≥36 suggest PTSD symptoms (n missing = 8). Significant depressive symptom severity was defined by scores of ≥16 on the Center for Epidemiologic Studies Depression Scale (CES-D). Loneliness was measured using a single item from the CES-D.

Supplementary Table 3.7 Associations of traumatic brain injury and total restricted, hindered, and free water diffusion by elevated psychiatric symptoms or loneliness status.

Outcome	Effect modifier					$P_{Interaction}$
Total restricted diffusion averaged across all fibers	Elevated psychiatric symptoms	No (n=367)		Yes (n=79)		0.99
		β (SE)	p-value	β (SE)	p-value	
	TBI (ref = no TBI)	-0.00407 (0.00349)	0.24	-0.00807 (0.00892)	0.37	
	Loneliness	No (n=363)		Yes (n=95)		0.86
		β (SE)	p-value	β (SE)	p-value	
	TBI (ref = no TBI)	-0.00570 (0.00361)	0.12	-0.00652 (0.00704)	0.36	
Isotropic-free water averaged across all fibers	Elevated psychiatric symptoms	No (n=367)		Yes (n=79)		0.91
		β (SE)	p-value	β (SE)	p-value	
	TBI (ref = no TBI)	-0.00199 (0.00317)	0.53	-0.00717 (0.00625)	0.26	
	Loneliness	No (n=363)		Yes (n=95)		0.65
		β (SE)	p-value	β (SE)	p-value	
	TBI (ref = no TBI)	-0.00212 (0.00314)	0.50	-0.00583 (0.00635)	0.36	

Note: Beta (β) and 95% confidence intervals (CI) are derived from linear mixed-effects models that included family-relatedness a random intercept to adjust for correlation between twin pairs. P-values are derived from type III analysis of variance with Satterthwaite's method. Models include the fixed effect of traumatic brain injury, adjusted for age and scanner. $P_{Interaction}$ was calculated using likelihood ratio tests to compare fully adjusted models with and without a 2-way interaction of the effect modifier-by-TBI. Elevated psychiatric symptoms were defined as the presence of absence of post-traumatic stress disorder (PTSD) and depressive symptom severity. For the PTSD Checklist – Civilian version, scores ≥36 suggest PTSD symptoms (n missing = 8). Significant depressive symptom severity was defined by scores of ≥16 on the Center for Epidemiologic Studies Depression Scale (CES-D). Loneliness was measured using a single item from the CES-D.

Supplementary Table 3.8 Associations of traumatic brain injury and total restricted diffusion in the left inferior longitudinal fasciculus by elevated psychiatric symptoms or loneliness status.

Effect modifier					$P_{Interaction}$
Elevated psychiatric symptoms	No (n=367)		Yes (n=79)		0.72
	β (SE)	p-value	β (SE)	p-value	
TBI (ref = no TBI)	-0.0123 (0.00587)	0.04	-0.00339 (0.0138)	0.81	
Loneliness	No (n=363)		Yes (n=95)		0.90
	β (SE)	p-value	β (SE)	p-value	
TBI (ref = no TBI)	-0.0143 (0.00583)	0.01	-0.00675 (0.0126)	0.60	

Note: Beta (β) and 95% confidence intervals (CI) are derived from linear mixed-effects models that included family-relatedness a random intercept to adjust for correlation between twin pairs. P-values are derived from type III analysis of variance with Satterthwaite's method. Models include the fixed effect of traumatic brain injury, adjusted for age and scanner. $P_{Interaction}$ was calculated using likelihood ratio tests to compare fully adjusted models with and without a 2-way interaction of the effect modifier-by-TBI. Elevated psychiatric symptoms were defined as the presence of absence of post-traumatic stress disorder (PTSD) and depressive symptom severity. For the PTSD Checklist – Civilian version, scores ≥36 suggest PTSD symptoms (n missing = 8). Significant depressive symptom severity was defined by scores of ≥16 on the Center for Epidemiologic Studies Depression Scale (CES-D). Loneliness was measured using a single item from the CES-D.

Chapter 3, in part, is currently being prepared for submission for publication of the material. Posis, Alexander Ivan B.; Elman, Jeremy A.; Alcaraz, John E.; Parada Jr., Humberto; Shadyab, Aladdin H.; Fennema-Notestine, Christine; Hagler Jr., Donald J.; Lyons, Michael J.; Panizzon, Matthew S.; Reynolds, Chandra A.; Franz, Carol E; Kremen, William S.; McEvoy, Linda K. The dissertation author was the primary researcher and author of this material.

Chapter 4 Multimorbidity, social engagement, and age-related cognitive decline in adults from the Rancho Bernardo Study of Healthy Aging

4.1 Abstract

Background: Multimorbidity is associated with increased rate of cognitive decline with age. It is unknown whether social engagement, which is associated with reduced risk of dementia, modifies associations between multimorbidity and cognitive decline.

Objective: To examine the associations of multimorbidity with longitudinal cognitive test performance among community-dwelling older adults, and to determine whether associations differed by levels of social engagement.

Methods: We used data from the Rancho Bernardo Study of Healthy Aging, a community-based prospective cohort study. Starting in 1992-1996, participants completed a battery of cognitive function tests at up to 6 study visits over 23.7 (mean=7.2) years. Multimorbidity was defined as ≥2 of 14 chronic diseases. Social engagement was assessed using items based on the Berkman-Syme Social Network Index. Multivariable linear mixed-effects models were used to test associations of multimorbidity and cognitive performance trajectories. Effect measure modification by social engagement was evaluated.

Results: Among 1,381 participants (mean age=74.5 years; 60.8% women; 98.8% non-Hispanic White), 37.1% had multimorbidity and 35.1% had low social engagement. Multimorbidity was associated with faster declines in Mini-Mental State Examination (MMSE; β=-0.20; 95%CI -0.35, -0.04), Trail-Making Test Part B (β=10.02; 95%CI 5.77, 14.27), and Category Fluency (β=-0.42; 95%CI -0.72, -0.13) after adjustment for socio-demographic and health-related characteristics. Multimorbidity was associated with faster declines in MMSE among those with low compared to medium and high social engagement (*p*-interaction<0.01).

Conclusion: Multimorbidity was associated with faster declines in cognition among community-dwelling older adults. Higher social engagement may mitigate multimorbidity-associated cognitive decline.

Keywords: Alzheimer's disease; cognitive aging; epidemiology; morbidity; multimorbidities

4.2 Introduction

Approximately 62% of adults aged 65 to 74 years in the United States (US) have multimorbidity, which is defined as the presence of at least two chronic conditions, such as diabetes and arthritis.[5,55] In a study of multimorbidity among Medicare beneficiaries, the most prevalent combination of 3 conditions was hypertension, hyperlipidemia, and ischemic heart disease.[5] Multimorbidity is associated with 38% higher risk of mild cognitive impairment (MCI) or dementia.[9] Multimorbidity may represent the accumulation of conditions that, for example, affect dysregulation in cardiovascular- and stress-related systems that increase susceptibility to aging-related outcomes such as cognitive decline.[6] Older adults with less frequent social engagement, defined as the maintenance of social connections and participation in social activities,[60] may have a higher number of morbidities.[73] Social engagement includes elements of one's social network, such as marital status, contact with friends and family as well as church involvement and group activities, that affect health and well-being.[149,150] Involvement in these types of social activities has been associated with lower risk of dementia,[4,62,151] which can operate through mechanisms such as stress reduction.[62]

Multimorbidity has been associated with higher risk of dementia in multiple longitudinal cohort studies of women and men, ranging from 2,176 to 10,095 participants.[7–9] For example, a multimorbidity index comprising 17 chronic conditions was associated with 38% higher risk of mild cognitive impairment or dementia among 2,176 older community-dwelling adults in the Mayo Clinic Study of Aging (mean age = 78.5 +/- 5.2 years).[9] One 12-year study in the Swedish National Study on Aging and Care in Kungsholmen (SNAC-K) found that cardiometabolic-specific multimorbidity was associated with 73% higher risk of cognitive impairment and 86% higher risk of progression to dementia.[8] Several longitudinal studies have found that

multimorbidity (derived from 9 to 16 conditions, such as cancer, hypertension and stroke) was associated with lower cognitive performance across multiple domains as well as indices of global cognitive ability.[6,56,57] However, it is unknown if these associations are modified by social engagement. Understanding whether social engagement plays a role in multimorbidity-associated cognitive decline would be important in the context of the US Surgeon General's Advisory on the poor health outcomes of declining social connection.[61] This would inform the development of dementia prevention strategies that are focused on increasing social engagement.

The objective of this study was to examine the associations of multimorbidity with longitudinal cognitive test performance among community-dwelling older adults, and to determine whether associations differed by levels of social engagement. We hypothesized that multimorbidity would be associated with faster declines in the cognitive measures that were administered to these study participants, and that declines would be faster among those with lower levels of social engagement than among those who report more frequent social engagement. The available cognitive tests are presumed measures of global cognition, executive function/speed, and category fluency.

4.3 Methods

4.3.1 Study population

This prospective cohort study used data from the Rancho Bernardo Study of Healthy Aging (RBS).[152] The RBS is a community-based prospective cohort study that began in 1972–1974 when residents of Rancho Bernardo, a suburb of San Diego, California were enrolled in a nationwide lipid research study. Beginning in 1984, surviving, community-dwelling participants were followed at approximately 4-year intervals, completing detailed demographic and health assessments. Cognitive assessment was first included in Visit 5 (1988-1992) and included in all

subsequent visits. For the present study, we used data from Visit 7 (1992-1996; n = 1,781) as our baseline, with follow-up to the most recent visit, Visit 12 (2014-2016; n = 221; for a maximum follow-up time of 24 years). Visit 7 was chosen as the baseline because it contained relevant data on comorbidities. We excluded 400 participants who did not have complete cognitive data at baseline, which resulted in a final analytic sample of 1,381. Excluded participants, relative to included participants, were less likely to have multimorbidity (26.3% vs 37.1%; $p < 0.01$), had a lower mean age of 61.2 (SD = 12) years ($p < 0.01$), but did not differ by sex ($p = 0.95$) or social engagement ($p = 0.25$).

This study was approved by the University of California, San Diego Institutional Review Board. All RBS participants provided written informed consent prior to participating at each study visit.

4.3.2 Measures

4.3.2.1 Cognitive outcomes

Cognitive function was assessed at each visit using a short battery of standardized neuropsychological tests, including the Mini Mental State Exam (MMSE; global cognitive function); 2) Trail-Making Test Part B of the Halsted Reitan Battery (Trails B; executive function/speed); and 3) Category Fluency Test (CFT). The MMSE assesses orientation, registration, attention, calculation, language, and recall, and is scored from 0 to 30, with higher scores indicating higher global cognitive function.[153,154] MMSE scores <24 suggest cognitive impairment or dementia.[155] For Trails B, participants are instructed to draw a line to connect, in ascending order, an alternating series of letters and numbers on a page.[156] Trails B performance was measured as time (seconds) needed to complete this task, with shorter time suggesting better executive function (set shifting) and faster processing speed. The CFT assesses semantic

memory.[157] CFT performance was defined as the number of unique animals named within 1 minute; a greater number of animals named suggests higher category fluency.

4.3.2.2 Multimorbidity

It has been recommended that multimorbidity indices should contain at least 12 chronic conditions.[55] Therefore, we defined multimorbidity as the presence of ≥2 of the following 14 common chronic conditions at baseline: arthritis, asthma, cancer (excluding skin cancer), chronic kidney disease, chronic obstructive pulmonary disease (COPD), depression, diabetes, dyslipidemia, heart attack, heart failure, hypertension, liver disease, osteoporosis, and stroke. Similar diseases have been included in other multimorbidity indices in prior literature.[6–9,56,57,158] Dyslipidemia was defined as the presence of all the following conditions at baseline: abnormal total cholesterol (>200 mg/dL), high-density lipoprotein (HDL; <40 mg/dL for men, <50 mg/dL for women), low-density lipoprotein (>100 mg/dL), and non-HDL (>130 mg/dL).[159] In sensitivity analyses, we considered a cardiovascular disease multimorbidity variable defined as the presence of at least 2 related conditions at baseline (i.e., heart attack, heart failure, hypertension, stroke) versus 1 or none of these conditions. All outcomes were self-reported, excluding dyslipidemia which was based on clinical laboratory measures.

4.3.2.3 Social engagement

As described in prior RBS work,[160] social engagement was assessed at Visit 7 using questions adapted from the Berkman-Syme Social Network Index.[149] We examined four different sources of self-reported social engagement based on a prior analysis in the Framingham Heart Study[161]: 1) social group involvement (0 = not active or inactive; 1 = somewhat active or very active); 2) participation in religious meetings or services (0 = not active or inactive; 1 = somewhat active or very active); 3) number of close family and friends (0 = ≤2 friends and

relatives; 1 = ≥3 friends and relatives); and 4) marital status (0 = separated/divorced/widowed/single; 1 = married). All questions and responses are provided in Supplementary Table 4.1. We summed the four sources of social engagement (range = 0-4) and then categorized to three levels (low = ≤2; medium = 3; or high = 4), such that higher scores suggest greater social engagement.

4.3.2.4 Covariates

Covariate data were collected at baseline. We selected covariates for the present study based on prior literature that examined the association between multimorbidity and cognitive decline or dementia.[6–9,56,57,158] Covariates of interest included age, sex, body mass index (BMI), education, smoking status, alcohol use, and physical activity (regular physical activity ≥3 times per week). We also included a retest variable, which indicated whether a participant completed a cognitive test in a prior visit or not, to control for practice-related differences in performance.[162]

4.3.3 Statistical analysis

Participant characteristics were described using mean (standard deviation [SD]), median (range) or counts (percentages) by multimorbidity status. Comparisons by multimorbidity status were performed using Kruskal-Wallis tests for continuous variables and Pearson's chi-squared tests for categorical variables.

We used linear mixed-effects models to estimate associations of multimorbidity with each longitudinal cognitive test performance outcome. Linear mixed-effect models accommodate missing data as well as inconsistent measurement intervals within and across participants, which allowed us to use all available data under the assumption that data were missing at random.[163] Three successively adjusted models were fit with random effects for each participant and time to account for differences in cognitive performance at baseline (intercept) as well as rate of change (slope). Model 1 included the fixed effects of multimorbidity, time (years from baseline), time-

squared (to assess non-linear trends), and a multimorbidity by time interaction term, adjusted for the retest variable, age, sex, and education. Time was standardized by grand mean centering (grand mean = 5.3 years) and dividing by the standard deviation (SD = 5.2 years) across all observations for all participants. Model 2 additionally adjusted for BMI, smoking status, alcohol use, and physical activity. Model 3 additionally adjusted for social engagement. We did not adjust for race and ethnicity due to the homogeneity of the study sample. For visualization, we plotted predicted values of Model 3 over standardized time for each outcome.

To assess effect measure modification by social engagement, we stratified Model 2 by social engagement and plotted predicted values. *P* values for interaction ($P_{\text{Interaction}}$) were calculated using likelihood ratio tests to compare models with and without a 3-way interaction of multimorbidity by time by continuous social engagement. For the MMSE model among those with high social engagement, we only included random intercepts but not random slopes due to smaller variability in the MMSE in this subgroup compared to other tests. In exploratory analyses, we assessed effect measure modification by different sources of social engagement. Specifically, we stratified analyses for each of these variables: 1) social group involvement; 2) participation in religious meetings or services; 3) number and frequency of contact with family and friends; and 4) marital status. For these analyses, models included covariates in Model 2 as well as the three sources of social engagement that were not examined as the stratifying factor.

We performed several sensitivity analyses. Given evidence of associations between cardiometabolic multimorbidity and higher dementia risk,[8] we repeated our main analysis using the presence of at least 2 cardiovascular disease-related conditions at baseline (i.e., heart attack, heart failure, hypertension, stroke) versus 1 or none of these conditions. In exploratory analyses, we also tested effect measure modification by sex and marital status, given that the association of

marital status with cognition may differ by sex.[4,164] To evaluate potential bias due to reverse causation, we repeated analyses of Trails B and CFT trajectories among participants scoring ≥24 on the MMSE at Visit 7 (n = 1,351).[155] To assess selection bias due to loss to follow-up, we repeated Model 3 weighted by stabilized inverse probability of selection weights (IPSWs) for each participant at each visit.[165] Stabilized IPSW create a pseudo-population of similar size at each visit after censoring.[166] To construct the IPSW, we calculated the inverse of propensity scores based on logistic regression to predict being selected (i.e., uncensored) at each visit, conditional on baseline multimorbidity status, selection in the prior visit, sex, age, education, BMI, smoking status, alcohol use, physical activity, and social engagement. Weights were stabilized by the probability of selection at each visit, conditional on baseline multimorbidity status and selection at the prior visit, and then truncated at the 5th and 95th percentiles. To assess bias due to the competing risk of mortality, we used joint models where we simultaneously fit a Cox proportional hazards model for mortality during the follow-up period and linear mixed-effects Model 1 for each outcome.[167] To examine results among older adults only, analyses were repeated after excluding participants who were <50 years old at baseline (n=13). Finally, because those who did not report participation in religious activities could not have been categorized into the high level of social engagement based on our definition, we assessed effect measure modification using a social engagement variable that did not consider participation in religious activities.

All statistical analyses were conducted in R (version 4.2.2; R Core Team, 2022). The *lme4* package was used for linear mixed-effects analyses,[109] the *sjPlot* package was used for plotting predicted values,[110] and the *JM, survival* and *nlme* packages were used for joint

modeling.[168–170] Statistical tests were two-tailed, and *P* values were considered significant at $P < 0.05$.

4.4 Results

4.4.1 Participant characteristics

Of the 1,381 participants, 37.1% had multimorbidity at baseline (Table 4.1). Most participants were non-Hispanic White (98.8%), women (60.8%), and 74.5 years (SD = 9.4) of age, on average, at baseline. There were no differences between women and men by age at baseline (mean age 74.6 vs. 74.2 years; $p = 0.25$). Although the sample had a wide age range, most participants were aged 50 and older (n = 1368).

Compared to participants without multimorbidity, those with multimorbidity were older (mean age = 76.8 vs 73.1 years; $p < 0.01$), more likely to be former smokers (54.0% vs 49.1%; $p = 0.03$), less likely to report daily alcohol consumption (32.2% vs. 36.6%; $p < 0.01$), and less likely to be married (37.8% vs. 25.3%; $p < 0.01$) at baseline. The social engagement index did not differ by multimorbidity status ($p = 0.30$). Among those with multimorbidity, the three most common chronic conditions were hypertension (58.8%), arthritis (43.8%), and history of cancer (31.3%; Supplementary Table 4.2). Participants with multimorbidity had shorter mean follow up time of 5.5 (SD = 5.7) years compared to those without multimorbidity (mean = 8.2 [SD = 6.5] years). Follow up time also decreased as social engagement decreased (high engagement mean = 8.3 [SD = 6.4] years; medium engagement = 7.5 [SD = 6.2] years; low engagement = 6.3 [SD = 6.5] years). There were differences for baseline cognitive measures of Trails B ($p < 0.01$) and CFT ($p = 0.04$), but not MMSE ($p = 0.12$), by the social engagement index after adjustment for age, sex, and education (Supplementary Table 4.16).

4.4.2 Baseline multimorbidity and cognitive function by time

Over the average 7.2 (SD = 6.4) years of follow up for the sample, multimorbidity at baseline was associated with greater decline in cognitive performance (Table 4.2, Figure 4.1). In Model 1, multimorbidity was associated with faster declines in MMSE (β = -0.19; 95% CI -0.35, -0.04), Trails B (β = 9.75; 95% CI 5.51, 13.99), and CFT (β = -0.40; 95% CI -0.70, -0.11) after adjustment for the retest variable, age, sex, and education. Results were similar after adjustment for BMI, smoking status, alcohol use and physical activity in Model 2, and after further adjustment for social engagement in Model 3.

4.4.3 Effect measure modification by social engagement

In models stratified by social engagement, multimorbidity, relative to no multimorbidity was associated with greater decline on MMSE among those with low social engagement only (β = -0.38; 95% CI -0.70, -0.06; $P_{\text{Interaction}} < 0.01$, Table 4.3, Figure 4.2). There were no significant differences in rate of decline by multimorbidity among those with medium (β = -0.14; 95% CI -0.39, 0.12) or high (β = -0.12; 95% CI -0.35, 0.12) social engagement, adjusted for the retest variable, age, sex, education, BMI, smoking status, alcohol use, and physical activity. The multimorbidity by time by social engagement interaction was not statistically significant for Trails B ($P_{\text{Interaction}} = 0.07$) or CFT ($P_{\text{interaction}} = 0.35$).

4.4.4 Exploratory analysis: effect modification by individual sources of social engagement

There was no evidence to suggest effect measure modification by social group involvement ($P_{\text{interaction}} = 0.07$, Supplementary Table 4.3). Participants with ≤2 close friends and relatives had faster multimorbidity-associated declines in MMSE compared to participants with ≥3 close friends and relatives, adjusted for the retest variable, age, sex, education, BMI, smoking status, alcohol use, physical activity, social group involvement, participation in religious

meetings or services, and marital status ($P_{interaction} < 0.01$, Supplementary Table 4.4). Among those who were married, multimorbidity was associated with faster declines in Trails B ($P_{interaction} < 0.01$) adjusted for the retest variable, age, sex, education, BMI, smoking status, alcohol use, social group involvement, participation in religious meetings or services, and number of close family and friends (Supplementary Table 4.5). The multimorbidity by time by participation in religious meetings or services interactions were not significant for any outcome ($P's_{interaction} > 0.15$, Supplementary Table 4.6).

4.4.4 Sensitivity analysis

Cardiovascular disease multimorbidity was associated with faster declines in MMSE and Trails B, but not CFT in fully adjusted models (Supplementary Table 4.7). In sex-stratified analyses, women had faster multimorbidity-associated declines in MMSE, Trails B, and CFT than men (Supplementary Table 4.8). However, interactions by sex were not significant (Supplementary Table 4.8). In exploratory analyses further stratified by sex and marital status, multimorbidity was associated with faster Trails B declines among women who were married but not among those who were not married, whereas multimorbidity was associated with faster declines among non-married men vs. married men ($P_{interaction} < 0.01$, Supplementary Table 4.9). After restricting analyses to participants who scored ≥24 on the MMSE at baseline, multimorbidity was associated with faster declines for Trails B and CFT in fully adjusted models, consistent with our main analysis (Supplementary Table 4.10). Results were also similar after applying stabilized IPSWs to our analyses, suggesting minimal impact of selection bias due to loss to follow-up (Supplementary Table 4.11). Associations were similar in joint models that accounted for the increased risk of mortality among those with multimorbidity (vs. no multimorbidity) after controlling for age, sex, and education (HR = 1.61; 95% CI 1.41-1.85;

Supplementary Table 4.12). Excluding individuals <50 years of age (n=13) had minimal effects on the results (Supplementary Table 13), with the exception that the interaction of social engagement with multimorbidity status was significant for both MMSE ($P_{interaction} < 0.01$) and Trails B ($P_{interaction} = 0.01$, Supplementary Table 4.14). Multimorbidity-related declines in MMSE were only significant for those in the low social engagement group (Supplementary Table 4.14). Rates of multimorbidity-related Trails B decline were greater among the low social engagement group, followed by high and medium groups (Supplementary Table 4.14). In the full cohort, results were similar when examining effect modification by the social engagement index that excluded consideration of religious social activities (Supplementary Table 4.15). With this social engagement index, significant effect modification was observed for MMSE ($P_{interaction} < 0.01$) and Trails B ($P_{interaction}= 0.02$); multimorbidity-related declines in MMSE and Trails B were faster among those with low social engagement, followed by the medium then high social engagement groups (Supplementary Table 4.15).

4.5 Discussion

In this prospective cohort study of 1,381 older adults, multimorbidity was associated with faster declines in global cognitive function, executive function/speed, and category fluency over an average 7.2 years of follow-up. These findings varied by level of social engagement. Participants with lower social engagement had a larger magnitude of multimorbidity-associated declines in global cognitive function and executive function/speed (in those over 50 years of age) compared to those with medium and high social engagement. Findings for category fluency did not significantly vary by social engagement.

Our results are generally consistent with prior literature that multimorbidity relative to no multimorbidity is associated with greater cognitive decline.[6,56,57] However, results vary by

specific tests and study population. For example, in one analysis in the Health and Retirement Study of 12,265 participants with approximately 14 years of follow up, a multimorbidity-weighted index was associated with faster declines in global cognitive function, immediate recall, and working memory, but not delayed recall.[57] In contrast, in a study of 756 participants from the Baltimore Longitudinal Study of Aging with an average of 3 years of follow up, multimorbidity was associated with faster declines in verbal fluency, but not global function, executive function, spatial ability, or memory.[6] It is important to note that cross-study comparisons are challenging given differences in morbidities and tests of cognitive domains that were assessed. However, these studies, in conjunction with our own, support Fabbri et al's[171] hypothesis that multimorbidity coincides with multiple aging phenotypes, highlighting the importance of reducing multimorbidity in our aging populations.

The present study extends previous work by examining whether the associations of multimorbidity with cognitive function differ by social engagement, which has been associated with lower risk of dementia.[151] Among participants with low social engagement, multimorbidity was associated with faster declines in our measure of global cognitive function compared to those with higher social engagement. Multimorbidity was also associated with faster decline in our measure of executive function in analyses restricted to older adults (<50 years). This is consistent with meta-analyses that suggest that higher social engagement is associated with lower risk of dementia,[4,151] and a cross-sectional study of 838 older adults in the Rush Memory and Aging Project that found that higher frequency of social activity and perceived social support were associated with better global cognitive function.[66] In exploratory analyses that stratified by sources of social engagement, we found that the modifying effects of social engagement differed by type of social contact and by cognitive outcome. Participants with ≤2 close friends and

relatives had faster multimorbidity-associated declines than those with more close friends and relatives. Future studies should consider examining which features of social engagement activities have the most impact.

Although the interaction was not significant, likely due in part to lower power, we found that women generally had faster multimorbidity-associated cognitive decline compared to men. Conversely, one study of 2,176 participants in the Mayo Clinic Study of Aging found that multimorbidity was associated with higher MCI risk among men compared to women over a median 4 years of follow up.[9] Older women may be more impacted by changes to marital status if they outlive their husbands and become widowed, potentially reducing their social contact or engagement.[4] Unexpectedly, after stratifying by marital status, we found that multimorbidity was associated with faster declines in executive function/speed among women who were married compared to not married. This is at odds with others who found that being married is associated with lower risk of dementia compared to being widowed or single.[164] After we stratified by sex, we observed faster declines among married women and unmarried men. However, it is important to note that the sample sizes were low in our stratified analyses. These interactions need to be investigated in larger study populations.

Social engagement may contribute to slower cognitive decline through several mechanisms. Participating in enriching social activities that are intellectually stimulating or meaningful may promote slower cognitive decline, especially among older adults.[172] Fratiglioni et al[62] posit that the social, mental, and physical lifestyle components in late life operate via common pathways through the cognitive reserve, vascular, and stress hypotheses to affect dementia risk. Under the stress hypothesis, for example, social engagement can lead to positive emotion states that reduce stress.[62] Reducing chronic stress can lower Alzheimer's disease risk.[63]

According to the glucocorticoid cascade hypothesis, stress can induce corticosterone hypersecretion, potentially resulting in loss of hippocampal neurons.[173] More work is needed to understand the mechanisms by which different sources of social engagement may mitigate multimorbidity-associated cognitive decline.

There are several limitations to our study. First, bias due to reverse causation is possible if cognitive impairment resulted in lower levels of social engagement. However, results were similar after excluding participants with evidence of cognitive impairment at baseline, as determined by a score <24 on the MMSE.[155] Second, there was differential follow-up time by baseline multimorbidity status and potential for selection bias due to loss to follow-up. However, results were similar after applying stabilized IPSW and joint modelling. Third, there is no standard method of operationalizing multimorbidity.[5,171] Results may differ for multimorbidity indices including different diseases. Although we were underpowered to examine specific combinations of morbidities, we found similar results using a multimorbidity index that considered cardiovascular disease conditions only. Fourth, it is likely that multimorbidity and social engagement change over time. Additionally, the relationships between multimorbidity, social engagement and cognitive decline may follow a different temporal path than we have hypothesized and tested here. For example, multimorbidity or lower baseline cognitive function may affect one's ability to partake in certain types of social contact or activities, and thus affect cognitive function downstream. The wide range of potential mechanisms make it difficult to determine which aspects of social engagement play the most prominent role in these associations. Lastly, the RBS population is primarily non-Hispanic, White, and well-educated, and results may not generalize to other populations.

There were several strengths to our study, including up to 23.7 years of longitudinal follow-up. This allowed us to leverage repeated assessments of cognitive function and assess longitudinal associations between multimorbidity and cognitive decline. We also considered morbidities that were included in multimorbidity indices in other study populations.

In this study of community-dwelling older adults, participants with multimorbidity had faster declines in global cognitive ability, executive function/speed, and category fluency, relative to those without multimorbidity. Multimorbidity-associated declines in global cognitive function and executive function/speed (among participants >50 years of age) were more pronounced among those with lower social engagement compared to those with higher levels of social engagement. These findings contribute to the US Surgeon General's call for more research on social connection indicators that influence health outcomes.[61] With the projected rise in older adults with multimorbidity and dementia,[174,175] further study is needed to confirm these findings in more diverse populations, and to determine whether social engagement interventions may mitigate multimorbidity-associated cognitive decline.

ACKNOWLEDGEMENTS

The authors have no acknowledgments to report.

FUNDING

This work was supported by a National Institutes of Health, National Institute on Aging, T32 Predoctoral Training Fellowship (T32 AG058529 to A.I.B.P.). A.H.S. was supported by National Institute on Aging grants RF1AG079149 and RF1AG074345. H.P. was supported by the National Cancer Institute (K01 CA234317), the SDSU/UCSD Comprehensive Cancer Center Partnership (U54 CA132384 & U54 CA132379), and the Alzheimer's Disease Resource Center for Advancing Minority Aging Research at the University of California San Diego (P30 AG059299). Data collection for the Rancho Bernardo Study of Healthy Aging was provided primarily by the National Institutes of Health (including grant numbers: HV012160, AA021187, AG028507, AG007181, DK31801, HL034591, HS06726 and HL089622). Archiving and sharing of RBS data was supported by AG054067. RBS data is available through the RBS website: https://knit.ucsd.edu/ranchobernardostudy/.

CONFLICT OF INTEREST

Alexander Ivan B. Posis is an Editorial Board Member of this journal, but was not involved in the peer-review process nor had access to any information regarding its peer-review.

All other authors have no conflict of interest to report.

DATA AVAILABILITY

The data supporting the findings of this study are openly available from The Rancho Bernardo Study (RBS) of Healthy Aging at https://knit.ucsd.edu/ranchobernardostudy/.

Table 4.1 Baseline characteristics by multimorbidity status of participants in the Rancho Bernardo Study of Health Aging

Characteristic		Multimorbidity status at baseline		
		No (N=869)	Yes (N=512)	Overall (N=1381)
Age (years)	Mean (SD)	73.1 (9.75)	76.8 (8.25)	74.5 (9.39)
	Median [Min, Max]	73.9 [30.9, 93.5]	77.8 [41.4, 96.1]	75.0 [30.9, 96.1]
Sex	Female	512 (58.9%)	328 (64.1%)	840 (60.8%)
Education	<12 years	44 (5.1%)	14 (2.8%)	58 (4.2%)
	12 years	212 (24.7%)	115 (22.6%)	327 (23.9%)
	13-15 years	271 (31.6%)	162 (31.9%)	433 (31.7%)
	16 years	197 (23.0%)	138 (27.2%)	335 (24.5%)
	≥17 years	134 (15.6%)	79 (15.6%)	213 (15.6%)
Body mass index (kg/m^2)	Median [Min, Max]	24.6 [15.5, 45.9]	24.6 [16.2, 44.6]	24.6 [15.5, 45.9]
Smoking status	Never	367 (42.6%)	210 (41.1%)	577 (42.1%)
	Former	423 (49.1%)	276 (54.0%)	699 (50.9%)
	Current	71 (8.2%)	25 (4.9%)	96 (7.0%)
Alcohol consumption	Non-drinker	108 (12.5%)	100 (19.5%)	208 (15.1%)
	Daily	318 (36.9%)	165 (32.2%)	483 (35.2%)
	2-4 per week	95 (11.0%)	47 (9.2%)	142 (10.3%)
	1-2 per week	125 (14.5%)	60 (11.7%)	185 (13.5%)
	1-2 per month	108 (12.5%)	74 (14.5%)	182 (13.3%)
	<1 per month	107 (12.4%)	66 (12.9%)	173 (12.6%)
Physical activity	≥3 times/week	651 (75.4%)	347 (67.8%)	998 (72.6%)
Social engagement index	Low (score ≤ 2)	295 (34.3%)	190 (37.3%)	485 (35.5%)
	Medium (score = 3)	357 (41.6%)	202 (39.6%)	559 (40.8%)
	High (score = 4)	207 (24.1%)	118 (23.1%)	325 (23.7%)
Social group activity	Somewhat or very active	664 (77.0%)	410 (80.1%)	1074 (78.2%)
Participation in religious meetings or services	Somewhat or very active	359 (41.6%)	239 (46.7%)	598 (43.5%)
Close friends and relatives	≥3	747 (86.7%)	447 (87.5%)	1194 (87.0%)
Marital Status	Married	648 (74.7%)	318 (62.2%)	966 (70.1%)

n missing: education = 15 (1.1%); body mass index = 3 (0.2%); smoking status = 9 (0.7%); alcohol consumption = 8 (0.6%); physical activity = 6 (0.4%); social engagement index = 12 (0.9%); group activity = 7 (0.5%); participation in religious meetings or services = 7 (0.5%); close friends and relatives = 8 (0.6%); marital status = 3 (0.2%)

Table 4.2 Associations of multimorbidity with longitudinal cognitive test performance among participants of the Rancho Bernardo Study of Healthy Aging

Outcome	Model	Term	β (95% CI)
MMSE	1	Multimorbidity	0.02 (-0.18; 0.22)
		Time	-0.50 (-0.59; -0.41)
		$Time^2$	0.18 (0.13; 0.22)
		Multimorbidity x time	-0.19 (-0.35; -0.04)
	2	Multimorbidity	<0.01 (-0.20; 0.20)
		Time	-0.5 (-0.59; -0.42)
		$Time^2$	0.17 (0.13; 0.22)
		Multimorbidity x time	-0.20 (-0.35; -0.04)
	3	Multimorbidity	0.01 (-0.19; 0.21)
		Time	-0.50 (-0.59; -0.41)
		$Time^2$	0.18 (0.13; 0.22)
		Multimorbidity x time	-0.20 (-0.36; -0.04)
Trails B	1	Multimorbidity	11.21 (4.83; 17.59)
		Time	11.66 (9.35; 13.98)
		$Time^2$	3.71 (2.59; 4.83)
		Multimorbidity x time	9.75 (5.51; 13.99)
	2	Multimorbidity	11.29 (4.87; 17.71)
		Time	11.76 (9.43; 14.09)
		$Time^2$	3.68 (2.56; 4.80)
		Multimorbidity x time	10.02 (5.77; 14.27)
	3	Multimorbidity	10.78 (4.39; 17.17)
		Time	11.80 (9.46; 14.13)
		$Time^2$	3.68 (2.55; 4.80)
		Multimorbidity x time	9.91 (5.66; 14.17)
CFT	1	Multimorbidity	-0.44 (-0.89; 0.02)
		Time	-1.36 (-1.53; -1.19)
		$Time^2$	-0.05 (-0.14; 0.04)
		Multimorbidity x time	-0.40 (-0.7; -0.11)
	2	Multimorbidity	-0.39 (-0.85; 0.06)
		Time	-1.36 (-1.53; -1.19)
		$Time^2$	-0.05 (-0.14; 0.04)
		Multimorbidity x time	-0.42 (-0.72; -0.13)
	3	Multimorbidity	-0.37 (-0.83; 0.09)
		Time	-1.36 (-1.54; -1.19)
		$Time^2$	-0.05 (-0.14; 0.04)
		Multimorbidity x time	-0.42 (-0.72; -0.13)

Note: Time is defined as time from baseline in years, standardized by centering using the grand mean and dividing by the standard deviation. Model 1 adjusted for retest(yes; no), age (years), sex (female; male), and education years (<12; 12; 13-15; 16; ≥17). Model 2 adjusted for BMI (kg/m2; standardized), smoking status (never; former; current), alcohol use (non-drinker; daily; 2-4 per week; 1-2 per month; <1 per month), and physical activity (<3 times/week; ≥3 times/week). Model 3 adjusted for social engagement (≤2; 3; 4).

Table 4.3 Associations of multimorbidity with longitudinal cognitive test performance by social engagement among participants of the Rancho Bernardo Study of Healthy Aging

		Social engagement			
		Low (n=485)	Medium (n=559)	High (n=325)	
Outcome	Term	β (95% CI)	β (95% CI)	β (95% CI)	$P_{interaction}$
MMSE	Multimorbidity	0.27 (-0.07; 0.62)	-0.18 (-0.49; 0.12)	-0.12 (-0.51; 0.28)	0.0064
	Time	-0.55 (-0.73; -0.36)	-0.51 (-0.65; -0.37)	-0.43 (-0.58; -0.29)	
	$Time^2$	0.15 (0.07; 0.23)	0.15 (0.07; 0.22)	0.19 (0.11; 0.27)	
	Multimorbidity x time	-0.38 (-0.70; -0.06)	-0.14 (-0.39; 0.12)	-0.12 (-0.35; 0.12)	
Trails B	Multimorbidity	6.55 (-5.06; 18.16)	11.57 (1.83; 21.30)	17.50 (4.50; 30.50)	0.0691
	Time	13.96 (9.34; 18.59)	11.59 (7.76; 15.42)	10.10 (6.54; 13.67)	
	$Time^2$	3.48 (1.30; 5.67)	5.66 (3.83; 7.48)	1.43 (-0.31; 3.18)	
	Multimorbidity x time	12.13 (3.89; 20.37)	8.20 (1.05; 15.35)	10.13 (3.82; 16.45)	
CFT	Multimorbidity	-0.01 (-0.79; 0.77)	-0.24 (-0.96; 0.49)	-1.04 (-1.98; -0.10)	0.3513
	Time	-1.27 (-1.58; -0.96)	-1.55 (-1.83; -1.28)	-1.19 (-1.51; -0.87)	
	$Time^2$	-0.14 (-0.31; 0.02)	-0.14 (-0.29; 0.01)	0.14 (-0.03; 0.31)	
	Multimorbidity x time	-0.45 (-0.97; 0.08)	-0.21 (-0.70; 0.27)	-0.68 (-1.22; -0.14)	

Note: Time is defined as time from baseline in years, standardized by centering using the grand mean and dividing by the standard deviation. Models are adjusted for retest (yes; no), age (years), sex (female; male), education years (<12; 12; 13-15; 16; ≥17), BMI (kg/m2; standardized), smoking status (never; former; current), alcohol use (non-drinker; daily; 2-4 per week; 1-2 per month; <1 per month), and physical activity (<3 times/week; ≥3 times/week). $P_{interaction}$ is derived from likelihood ratio tests comparing models with and without a 3-way interaction of multimorbidity by time by continuous social engagement.

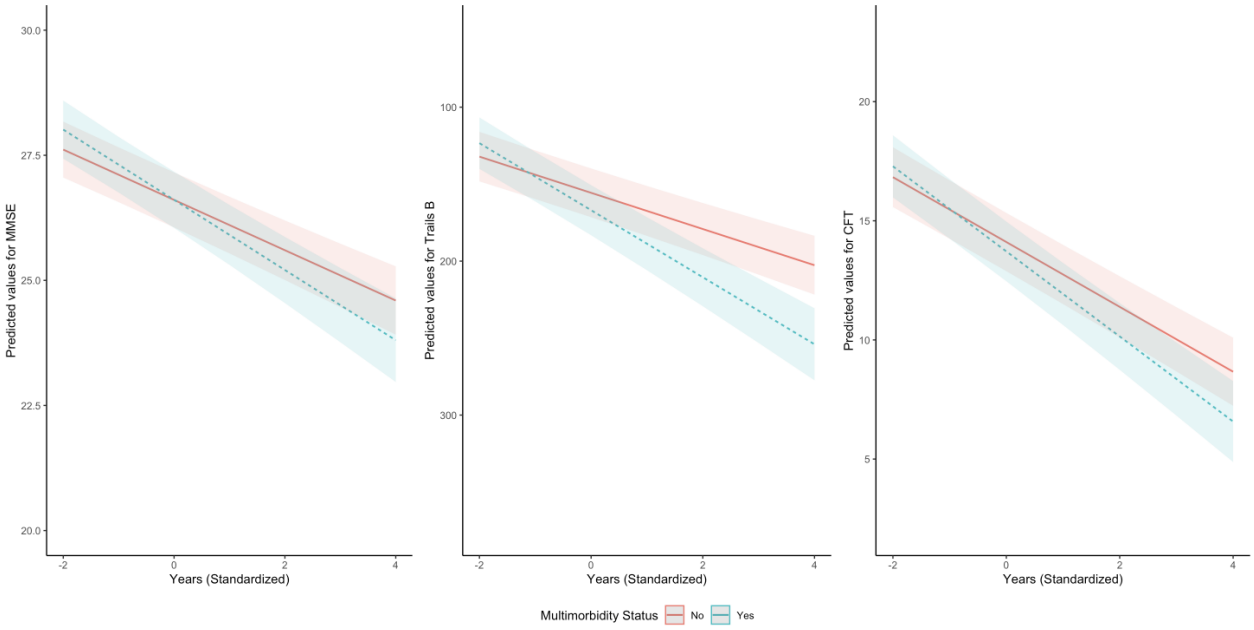


Figure 4.1 Trajectories of cognition function test performance over years since baseline (standardized) by multimorbidity status at baseline in the Rancho Bernardo Study of Healthy Aging. Plots are based on model coefficients adjusted for the retest variable, age, sex, education, body mass index (standardized), smoking, alcohol use, physical activity, and social engagement. The y-axis for Trails B is inverted so that for all graphs, steeper downward sloping lines indicate poorer performance.

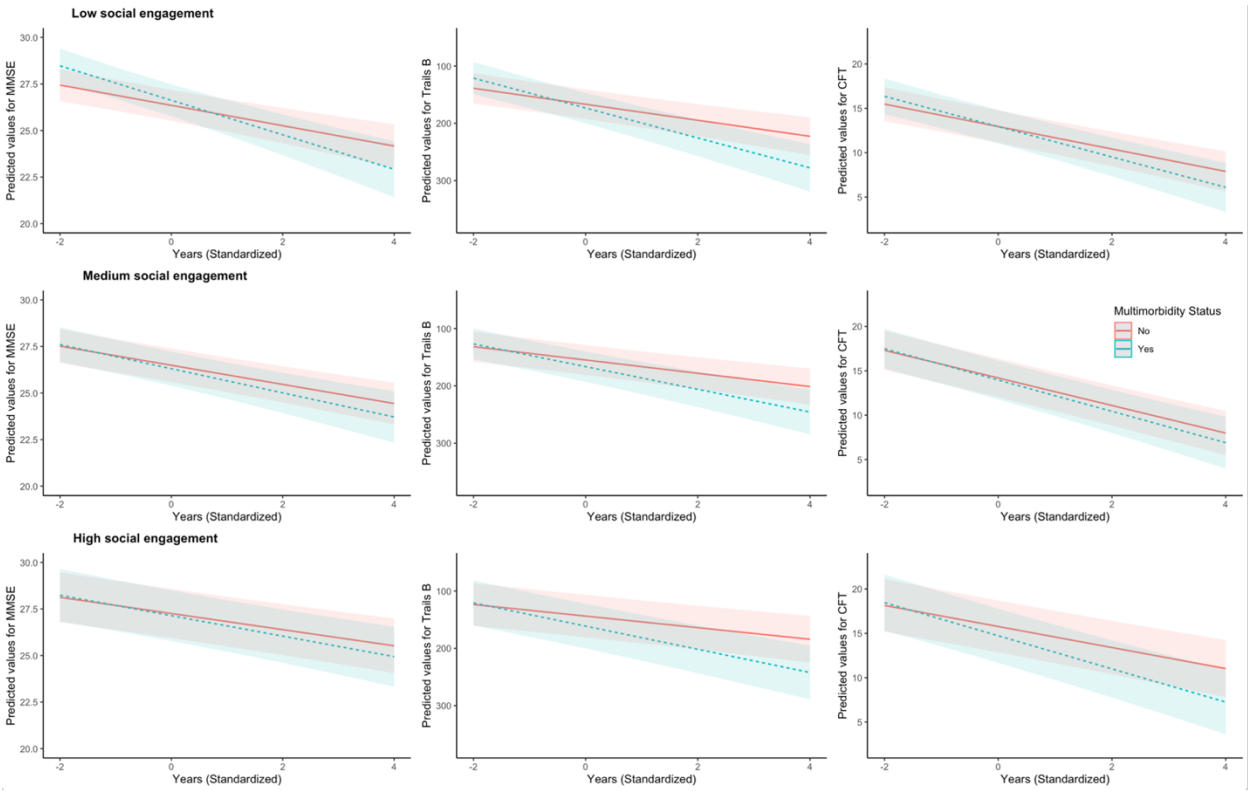


Figure 4.2 Trajectories of cognition function test performance over years since baseline (standardized) by multimorbidity status at baseline (red = no; blue = yes) stratified by social engagement level in the Rancho Bernardo Study of Healthy Aging. Plots are based on model coefficients adjusted for the retest variable, age, sex, education, body mass index (standardized), smoking, alcohol use, and physical activity. The y-axis for Trails B is inverted so that for all graphs, steeper downward sloping lines indicate poorer performance.

Supplementary Table 4.1 Sources of social engagement at baseline in the Rancho Bernardo Study of Healthy Aging

Source of social engagement	Question
Social group involvement (Not active or inactive; Somewhat active or very active)	Belong to a social or recreational group?
	Belong to a union, commercial group, or professional association?
	Belong to a political group or club?
	Belong to a group concerned with children?
	Belong to a group concerned with community betterment, charity, or service?
	Belong to a group concerned with self-improvement that meets regularly?
	Belong to an exercise group or class?
	Belong to any other group?
Participation in religious meetings or services (Not active or inactive; Somewhat active or very active)	Belong to a church or synagogue group?
Number of close family and friends (≤2 friends and relatives; ≥3 friends and relatives)	How many close friends do you have?
	How many close relatives do you have (excluding spouse, including children)?
Marital status (separated/divorced/widowed/single; married)	Marital status

Supplementary Table 4.2 Chronic conditions by multimorbidity status at baseline

Condition		Multimorbidity at baseline		
		No (N=869)	Yes (N=512)	Total (N=1381)
Arthritis	No	788 (90.7%)	288 (56.3%)	1076 (77.9%)
	Yes	76 (8.7%)	224 (43.8%)	300 (21.7%)
	Missing	5 (0.6%)	0 (0%)	5 (0.4%)
Asthma	No	845 (97.2%)	449 (87.7%)	1294 (93.7%)
	Yes	18 (2.1%)	63 (12.3%)	81 (5.9%)
	Missing	6 (0.7%)	0 (0%)	6 (0.4%)
Cancer (excluding skin)	No	803 (92.4%)	352 (68.8%)	1155 (83.6%)
	Yes	60 (6.9%)	160 (31.3%)	220 (15.9%)
	Missing	6 (0.7%)	0 (0%)	6 (0.4%)
COPD	No	855 (98.4%)	432 (84.4%)	1287 (93.2%)
	Yes	8 (0.9%)	80 (15.6%)	88 (6.4%)
	Missing	6 (0.7%)	0 (0%)	6 (0.4%)
Depression	No	845 (97.2%)	456 (89.1%)	1301 (94.2%)
	Yes	19 (2.2%)	56 (10.9%)	75 (5.4%)
	Missing	5 (0.6%)	0 (0%)	5 (0.4%)
Diabetes	No	845 (97.2%)	439 (85.7%)	1284 (93.0%)
	Yes	18 (2.1%)	73 (14.3%)	91 (6.6%)
	Missing	6 (0.7%)	0 (0%)	6 (0.4%)
Dyslipidemia	No	824 (94.8%)	416 (81.3%)	1240 (89.8%)
	Yes	41 (4.7%)	96 (18.8%)	137 (9.9%)
	Missing	4 (0.5%)	0 (0%)	4 (0.3%)
Heart attack	No	853 (98.2%)	416 (81.3%)	1269 (91.9%)
	Yes	16 (1.8%)	96 (18.8%)	112 (8.1%)
Heart failure	No	859 (98.8%)	474 (92.6%)	1333 (96.5%)
	Yes	4 (0.5%)	37 (7.2%)	41 (3.0%)
	Missing	6 (0.7%)	1 (0.2%)	7 (0.5%)
Hypertension	No	706 (81.2%)	211 (41.2%)	917 (66.4%)
	Yes	157 (18.1%)	301 (58.8%)	458 (33.2%)
	Missing	6 (0.7%)	0 (0%)	6 (0.4%)
Kidney disease	No	860 (99.0%)	496 (96.9%)	1356 (98.2%)
	Yes	3 (0.3%)	16 (3.1%)	19 (1.4%)
	Missing	6 (0.7%)	0 (0%)	6 (0.4%)
Liver disease	No	846 (97.4%)	460 (89.8%)	1306 (94.6%)
	Yes	23 (2.6%)	52 (10.2%)	75 (5.4%)
Osteoporosis	No	840 (96.7%)	444 (86.7%)	1284 (93.0%)
	Yes	24 (2.8%)	68 (13.3%)	92 (6.7%)
	Missing	5 (0.6%)	0 (0%)	5 (0.4%)
Stroke	No	855 (98.4%)	471 (92.0%)	1326 (96.0%)
	Yes	8 (0.9%)	41 (8.0%)	49 (3.5%)
	Missing	6 (0.7%)	0 (0%)	6 (0.4%)

Supplementary Table 4.3 Associations of multimorbidity with longitudinal cognitive test performance by social group involvement among participants of the Rancho Bernardo Study of Healthy Aging

		Social group involvement		
		Somewhat or very active (n=1074)	Not active (n=300)	
Outcome	Term	β (95% CI)	β (95% CI)	$P_{interaction}$
MMSE	Multimorbidity	-0.06 (-0.28; 0.16)	<0.01 (-0.53; 0.54)	0.0717
	Time	-0.54 (-0.64; -0.45)	-0.42 (-0.63; -0.21)	
	Time^2	0.17 (0.12; 0.22)	0.18 (0.09; 0.27)	
	Multimorbidity x time	-0.12 (-0.29; 0.05)	-0.57 (-0.98; -0.16)	
Trails B	Multimorbidity	10.24 (3.11; 17.37)	20.17 (5.36; 34.98)	0.1860
	Time	12.43 (9.74; 15.13)	9.94 (5.37; 14.51)	
	Time^2	3.91 (2.60; 5.22)	2.78 (0.65; 4.92)	
	Multimorbidity x time	7.95 (3.14; 12.76)	19.43 (10.36; 28.49)	
CFT	Multimorbidity	-0.32 (-0.83; 0.20)	-0.77 (-1.83; 0.29)	0.7153
	Time	-1.42 (-1.61; -1.22)	-1.19 (-1.54; -0.83)	
	Time^2	-0.01 (-0.12; 0.10)	-0.18 (-0.37; 0.01)	
	Multimorbidity x time	-0.41 (-0.74; -0.07)	-0.52 (-1.19; 0.15)	

Note: Time is defined as time from baseline in years, standardized by subtracting the sample mean and dividing by sample standard deviation. Models are adjusted for retest (yes; no), age (years), sex (female; male), education years (<12; 12; 13-15; 16; ≥17), BMI (kg/m2; standardized), smoking status (never; former; current), alcohol use (non-drinker; daily; 2-4 per week; 1-2 per month; <1 per month), physical activity (<3 times/week; ≥3 times/week), participation in religious meetings or services (not active or inactive; somewhat active or very active), number of close family and friends (≤2 friends and relatives; ≥3 friends and relatives), and marriage (separated/divorced/widowed/single; married). $P_{interaction}$ is derived from likelihood ratio tests comparing models with and without a 3-way interaction of multimorbidity by time by social group involvement.

Supplementary Table 4.4 Associations of multimorbidity with longitudinal cognitive test performance by number of friends and relatives among participants of the Rancho Bernardo Study of Healthy Aging

		Friends and relatives		
		≥3 (n=1194)	≤2 (n=179)	
Outcome	Term	β (95% CI)	β (95% CI)	$P_{interaction}$
MMSE	Multimorbidity	-0.08 (-0.28; 0.13)	0.27 (-0.48; 1.02)	0.0032
	Time	-0.48 (-0.57; -0.40)	-0.71 (-1.08; -0.35)	
	$Time^2$	0.18 (0.13; 0.22)	0.11 (-0.04; 0.26)	
	Multimorbidity x time	-0.16 (-0.31; -0.01)	-0.76 (-1.53; 0.01)	
Trails B	Multimorbidity	12.19 (5.60; 18.78)	-0.66 (-26.00; 24.68)	0.7198
	Time	11.4 (8.93; 13.86)	15.32 (7.60; 23.04)	
	$Time^2$	3.93 (2.75; 5.11)	2.43 (-1.36; 6.22)	
	Multimorbidity x time	10.24 (5.82; 14.65)	9.58 (-8.76; 27.92)	
CFT	Multimorbidity	-0.47 (-0.95; 0.02)	-0.19 (-1.82; 1.44)	0.4459
	Time	-1.37 (-1.55; -1.19)	-1.29 (-1.86; -0.72)	
	$Time^2$	-0.03 (-0.12; 0.07)	-0.31 (-0.62; -0.01)	
	Multimorbidity x time	-0.39 (-0.70; -0.08)	-1.34 (-2.61; -0.06)	

Note: Time is defined as time from baseline in years, standardized by subtracting the sample mean and dividing by sample standard deviation. Models are adjusted for retest (yes; no), age (years), sex (female; male), education years (<12; 12; 13-15; 16; ≥17), BMI (kg/m2; standardized), smoking status (never; former; current), alcohol use (non-drinker; daily; 2-4 per week; 1-2 per month; <1 per month), physical activity (<3 times/week; ≥3 times/week), social group involvement (not active or inactive; somewhat active or very active), participation in religious meetings or services (not active or inactive; somewhat active or very active), and marriage (separated/divorced/widowed/single; married). $P_{interaction}$ is derived from likelihood ratio tests comparing models with and without a 3-way interaction of multimorbidity by time by friends and relatives.

Supplementary Table 4.5 Associations of multimorbidity with longitudinal cognitive test performance by marital status among participants of the Rancho Bernardo Study of Healthy Aging

		Marital Status		
		Yes (n=966)	No (n=412)	
Outcome	Term	β (95% CI)	β (95% CI)	$P_{interaction}$
MMSE	Multimorbidity	-0.13 (-0.38; 0.12)	0.19 (-0.16; 0.54)	0.0699
	Time	-0.46 (-0.56; -0.37)	-0.63 (-0.85; -0.41)	
	$Time^2$	0.18 (0.13; 0.23)	0.15 (0.03; 0.26)	
	Multimorbidity x time	-0.26 (-0.44; -0.09)	-0.05 (-0.39; 0.29)	
Trails B	Multimorbidity	17.28 (9.68; 24.88)	-1.13 (-13.52; 11.26)	0.0016
	Time	10.93 (8.50; 13.36)	16.75 (10.38; 23.11)	
	$Time^2$	2.92 (1.73; 4.11)	7.64 (4.69; 10.59)	
	Multimorbidity x time	9.60 (4.88; 14.33)	7.72 (-2.02; 17.47)	
CFT	Multimorbidity	-0.62 (-1.18; -0.07)	0.01 (-0.82; 0.84)	0.2023
	Time	-1.38 (-1.58; -1.19)	-1.35 (-1.72; -0.98)	
	$Time^2$	-0.01 (-0.11; 0.10)	-0.24 (-0.45; -0.04)	
	Multimorbidity x time	-0.32 (-0.67; 0.03)	-0.67 (-1.23; -0.10)	

Note: Time is defined as time from baseline in years, standardized by subtracting the sample mean and dividing by sample standard deviation. Models are adjusted for retest (yes; no), age (years), sex (female; male), education years (<12; 12; 13-15; 16; ≥17), BMI (kg/m2; standardized), smoking status (never; former; current), alcohol use (non-drinker; daily; 2-4 per week; 1-2 per month; <1 per month), physical activity (<3 times/week; ≥3 times/week), social group involvement (not active or inactive; somewhat active or very active), participation in religious meetings or services (not active or inactive; somewhat active or very active), and number of close family and friends (≤2 friends and relatives; ≥3 friends and relatives). $P_{interaction}$ is derived from likelihood ratio tests comparing models with and without a 3-way interaction of multimorbidity by time by marital status.

Supplementary Table 4.6 Associations of multimorbidity with longitudinal cognitive test performance by participation in religious meetings or services among participants of the Rancho Bernardo Study of Healthy Aging

		Participation in religious meetings or services		
		Active (n=598)	Not active (n=776)	
Outcome	Term	β (95% CI)	β (95% CI)	$P_{interaction}$
MMSE	Multimorbidity	-0.05 (-0.38; 0.29)	0.01 (-0.24; 0.26)	0.5681
	Time	-0.53 (-0.66; -0.39)	-0.49 (-0.61; -0.38)	
	$Time^2$	0.20 (0.13; 0.27)	0.15 (0.10; 0.21)	
	Multimorbidity x time	-0.10 (-0.33; 0.13)	-0.29 (-0.50; -0.07)	
Trails B	Multimorbidity	11.90 (1.93; 21.86)	11.66 (3.18; 20.13)	0.7403
	Time	11.26 (7.97; 14.54)	12.17 (8.90; 15.45)	
	$Time^2$	2.56 (1.00; 4.12)	4.55 (2.96; 6.13)	
	Multimorbidity x time	11.94 (6.18; 17.71)	9.12 (2.98; 15.27)	
CFT	Multimorbidity	-0.63 (-1.33; 0.08)	-0.19 (-0.80; 0.42)	0.1585
	Time	-1.26 (-1.52; -1.00)	-1.43 (-1.66; -1.20)	
	$Time^2$	0.02 (-0.12; 0.16)	-0.10 (-0.23; 0.02)	
	Multimorbidity x time	-0.75 (-1.19; -0.31)	-0.18 (-0.59; 0.22)	

Note: Time is defined as time from baseline in years, standardized by subtracting the sample mean and dividing by sample standard deviation. Models are adjusted for retest (yes; no), age (years), sex (female; male), education years (<12; 12; 13-15; 16; ≥17), BMI (kg/m2; standardized), smoking status (never; former; current), alcohol use (non-drinker; daily; 2-4 per week; 1-2 per month; <1 per month), physical activity (<3 times/week; ≥3 times/week), social group involvement (not active or inactive; somewhat active or very active), number of close family and friends (≤2 friends and relatives; ≥3 friends and relatives), and marriage (separated/divorced/widowed/single; married). $P_{interaction}$ is derived from likelihood ratio tests comparing models with and without a 3-way interaction of multimorbidity by time by participation in religious meetings or services.

Supplementary Table 4.7 Supplementary Table 4.7 Associations of cardiovascular disease multimorbidity with longitudinal cognitive test performance among participants of the Rancho Bernardo Study of Healthy Aging

Outcome	Model	Term	β (95% CI)
MMSE	1	Multimorbidity	-0.41 (-0.89; 0.08)
		Time	-0.54 (-0.62; -0.47)
		$Time^2$	0.18 (0.13; 0.22)
		Multimorbidity x time	-0.50 (-0.94; -0.07)
	2	Multimorbidity	-0.41 (-0.89; 0.07)
		Time	-0.55 (-0.62; -0.47)
		$Time^2$	0.18 (0.13; 0.22)
		Multimorbidity x time	-0.51 (-0.95; -0.07)
	3	Multimorbidity	-0.41 (-0.89; 0.08)
		Time	-0.55 (-0.62; -0.47)
		$Time^2$	0.18 (0.13; 0.22)
		Multimorbidity x time	-0.52 (-0.96; -0.08)
Trails B	1	Multimorbidity	34.55 (19.96; 49.14)
		Time	14.06 (12.04; 16.09)
		$Time^2$	3.65 (2.53; 4.77)
		Multimorbidity x time	16.48 (4.58; 28.39)
	2	Multimorbidity	33.56 (18.93; 48.19)
		Time	14.23 (12.20; 16.27)
		$Time^2$	3.62 (2.49; 4.74)
		Multimorbidity x time	16.90 (4.96; 28.84)
	3	Multimorbidity	33.33 (18.76; 47.89)
		Time	14.25 (12.21; 16.29)
		$Time^2$	3.61 (2.48; 4.74)
		Multimorbidity x time	16.86 (4.92; 28.80)
CFT	1	Multimorbidity	-0.40 (-1.44; 0.64)
		Time	-1.48 (-1.63; -1.33)
		$Time^2$	-0.04 (-0.13; 0.06)
		Multimorbidity x time	0.20 (-0.66; 1.05)
	2	Multimorbidity	-0.27 (-1.31; 0.78)
		Time	-1.49 (-1.64; -1.34)
		$Time^2$	-0.04 (-0.13; 0.06)
		Multimorbidity x time	0.18 (-0.67; 1.04)
	3	Multimorbidity	-0.26 (-1.31; 0.78)
		Time	-1.50 (-1.65; -1.34)
		$Time^2$	-0.04 (-0.13; 0.06)
		Multimorbidity x time	0.17 (-0.68; 1.03)

Note: Time is defined as time from baseline in years, standardized by subtracting the sample mean and dividing by sample standard deviation. Model 1 adjusted for retest(yes; no), age (years), sex (female; male), and education years (<12; 12; 13-15; 16; ≥17). Model 2 adjusted for BMI (kg/m2; standardized), smoking status (never; former; current), alcohol use (non-drinker; daily; 2-4 per week; 1-2 per month; <1 per month), and physical activity (<3 times/week; ≥3 times/week). Model 3 adjusted for social engagement (≤2; 3; 4).

Supplementary Table 4.8 Associations of multimorbidity with longitudinal cognitive test performance by sex among participants of the Rancho Bernardo Study of Healthy Aging

		Gender		
		Women (n=840)	Men (n=541)	
Outcome	Term	β (95% CI)	β (95% CI)	$P_{interaction}$
MMSE	Multimorbidity	<-0.01 (-0.25; 0.25)	-0.04 (-0.37; 0.29)	0.8654
	Time	-0.49 (-0.60; -0.38)	-0.51 (-0.65; -0.36)	
	$Time^2$	0.21 (0.16; 0.27)	0.12 (0.05; 0.19)	
	Multimorbidity x time	-0.23 (-0.41; -0.05)	-0.18 (-0.47; 0.11)	
Trails B	Multimorbidity	8.38 (0.13; 16.63)	12.70 (2.43; 22.97)	0.1100
	Time	12.66 (9.38; 15.95)	10.73 (7.61; 13.84)	
	$Time^2$	4.05 (2.51; 5.59)	3.02 (1.45; 4.59)	
	Multimorbidity x time	11.03 (5.34; 16.73)	6.43 (0.23; 12.63)	
CFT	Multimorbidity	-0.38 (-0.95; 0.19)	-0.35 (-1.14; 0.45)	0.2233
	Time	-1.25 (-1.48; -1.03)	-1.51 (-1.78; -1.24)	
	$Time^2$	-0.04 (-0.16; 0.07)	-0.06 (-0.21; 0.09)	
	Multimorbidity x time	-0.59 (-0.96; -0.22)	-0.18 (-0.68; 0.33)	

Note: Time is defined as time from baseline in years, standardized by subtracting the sample mean and dividing by sample standard deviation. Models are adjusted for retest (yes; no), age (years), education years (<12; 12; 13-15; 16; ≥17), BMI (kg/m2; standardized), smoking status (never; former; current), alcohol use (non-drinker; daily; 2-4 per week; 1-2 per month; <1 per month), physical activity (<3 times/week; ≥3 times/week), and social engagement (≤2; 3; 4). $P_{interaction}$ is derived from likelihood ratio tests comparing models with and without a 3-way interaction of multimorbidity by time by gender.

Supplementary Table 4.9 Associations of multimorbidity with longitudinal cognitive test performance by sex and marital status among participants of the Rancho Bernardo Study of Healthy Aging

		Female		Male		
		Not married (n=350)	Married (n=489)	Not married (n=62)	Married (n=477)	
Outcome	Term	β (95% CI)	β (95% CI)	β (95% CI)	β (95% CI)	$P_{interaction}$
MMSE	Multimorbidity	0.19 (-0.20; 0.57)	-0.23 (-0.59; 0.12)	0.16 (-1.05; 1.38)	-0.07 (-0.43; 0.29)	0.3598
	Time	-0.63 (-0.87; -0.39)	-0.43 (-0.55; -0.31)	-0.74 (-1.31; -0.16)	-0.49 (-0.65; -0.34)	
	$Time^2$	0.19 (0.07; 0.31)	0.22 (0.16; 0.29)	-0.04 (-0.30; 0.22)	0.14 (0.06; 0.21)	
	Multimorbidity x time	-0.02 (-0.38; 0.33)	-0.38 (-0.59; -0.16)	-0.39 (-1.55; 0.77)	-0.16 (-0.46; 0.14)	
Trails B	Multimorbidity	-4.90 (-18.75; 8.94)	18.65 (7.80; 29.51)	8.83 (-28.41; 46.08)	14.32 (3.44; 25.20)	0.0033
	Time	20.28 (12.80; 27.76)	10.94 (7.40; 14.47)	8.25 (-3.13; 19.63)	11.01 (7.75; 14.26)	
	$Time^2$	9.60 (6.27; 12.92)	2.54 (0.84; 4.24)	0.91 (-4.88; 6.70)	3.27 (1.64; 4.90)	
	Multimorbidity x time	4.14 (-6.95; 15.23)	12.18 (5.45; 18.92)	13 (-10.58; 36.58)	5.87 (-0.58; 12.32)	
CFT	Multimorbidity	0.06 (-0.82; 0.93)	-0.79 (-1.55; -0.03)	0.36 (-2.86; 3.58)	-0.44 (-1.27; 0.40)	0.2717
	Time	-1.45 (-1.86; -1.03)	-1.22 (-1.49; -0.96)	-1.11 (-2.05; -0.16)	-1.56 (-1.85; -1.27)	
	$Time^2$	-0.26 (-0.48; -0.03)	0.02 (-0.12; 0.16)	-0.26 (-0.77; 0.25)	-0.05 (-0.20; 0.11)	
	Multimorbidity x time	-0.55 (-1.17; 0.06)	-0.50 (-0.97; -0.03)	-1.58 (-3.65; 0.50)	-0.09 (-0.62; 0.43)	

Note: Time is defined as time from baseline in years, standardized by subtracting the sample mean and dividing by sample standard deviation. Models are adjusted for retest (yes; no), age (years), sex (female; male), education years (<12; 12; 13-15; 16; ≥17), BMI (kg/m2; standardized), smoking status (never; former; current), alcohol use (non-drinker; daily; 2-4 per week; 1-2 per month; <1 per month), physical activity (<3 times/week; ≥3 times/week), social group involvement (not active or inactive; somewhat active or very active), participation in religious meetings or services (not active or inactive; somewhat active or very active), and number of close family and friends (≤2 friends and relatives; ≥3 friends and relatives). $P_{interaction}$ is derived from likelihood ratio tests comparing models with and without a 4-way interaction of multimorbidity by time by sex by marital status.

Supplementary Table 4.10 Associations of multimorbidity with longitudinal cognitive test performance among participants of the Rancho Bernardo Study of Healthy Aging who scored >24 on the Mini Mental State Examination at baseline

Outcome	Term	β (95% CI)
Trails B	Multimorbidity	11.99 (5.66; 18.32)
	Time	12.13 (9.78; 14.48)
	$Time^2$	3.67 (2.55; 4.78)
	Multimorbidity x time	9.87 (5.59; 14.15)
CFT	Multimorbidity	-0.45 (-0.90; 0.01)
	Time	-1.39 (-1.56; -1.22)
	$Time^2$	-0.05 (-0.14; 0.05)
	Multimorbidity x time	-0.40 (-0.69; -0.10)

Note: Time is defined as time from baseline in years, standardized by centering using the grand mean and dividing by the standard deviation. Models are adjusted for retest (yes; no), age (years), sex (female; male), education years (<12; 12; 13-15; 16; ≥17), BMI (kg/m2; standardized), smoking status (never; former; current), alcohol use (non-drinker; daily; 2-4 per week; 1-2 per month; <1 per month), physical activity (<3 times/week; ≥3 times/week), and social engagement (≤2; 3; 4).

Supplementary Table 4.11 Stabilized inverse probability of selection weighted associations of multimorbidity with longitudinal cognitive test performance among participants of the Rancho Bernardo Study of Healthy Aging

		Non-weighted	Weighted
Outcome	Term	β (95% CI)	β (95% CI)
MMSE	Multimorbidity	0.01 (-0.19; 0.21)	-0.01 (-0.22; 0.20)
	Time	-0.50 (-0.59; -0.41)	-0.55 (-0.64; -0.45)
	$Time^2$	0.18 (0.13; 0.22)	0.17 (0.12; 0.22)
	Multimorbidity x time	-0.20 (-0.36; -0.04)	-0.21 (-0.38; -0.04)
Trails B	Multimorbidity	10.78 (4.39; 17.17)	11.31 (4.78; 17.83)
	Time	11.80 (9.46; 14.13)	12.28 (9.88; 14.68)
	$Time^2$	3.68 (2.55; 4.80)	4.50 (3.31; 5.69)
	Multimorbidity x time	9.91 (5.66; 14.17)	10.37 (5.97; 14.78)
CFT	Multimorbidity	-0.37 (-0.83; 0.09)	-0.39 (-0.85; 0.07)
	Time	-1.36 (-1.54; -1.19)	-1.38 (-1.55; -1.21)
	$Time^2$	-0.05 (-0.14; 0.04)	-0.11 (-0.21; -0.02)
	Multimorbidity x time	-0.42 (-0.72; -0.13)	-0.45 (-0.75; -0.15)

Note: Weights were truncated at the 5th and 95th percentiles. Time is defined as time from baseline in years, standardized by centering using the grand mean and dividing by the standard deviation. Models are adjusted for retest (yes; no), age (years), sex (female; male), education years (<12; 12; 13-15; 16; ≥17), BMI (kg/m2; standardized), smoking status (never; former; current), alcohol use (non-drinker; daily; 2-4 per week; 1-2 per month; <1 per month), physical activity (<3 times/week; ≥3 times/week), and social engagement (≤2; 3; 4).

Supplementary Table 4.12 Longitudinal joint modelling associations of multimorbidity with longitudinal cognitive test performance among participants of the Rancho Bernardo Study of Healthy Aging

		Linear mixed-effects model	Joint model
Outcome	Term	β (95% CI)	β (95% CI)
MMSE	Multimorbidity	0.02 (-0.18; 0.22)	-0.05 (-0.17; 0.08)
	Time	-0.50 (-0.59; -0.41)	-0.57 (-0.64; -0.50)
	$Time^2$	0.18 (0.13; 0.22)	0.17 (0.14; 0.21)
	Multimorbidity x time	-0.19 (-0.35; -0.04)	-0.18 (-0.29; -0.07)
Trails B	Multimorbidity	11.21 (4.83; 17.59)	13.22 (7.64; 18.81)
	Time	11.66 (9.35; 13.98)	13.12 (11.15; 15.09)
	$Time^2$	3.71 (2.59; 4.83)	1.43 (0.36; 2.50)
	Multimorbidity x time	9.75 (5.51; 13.99)	9.57 (6.22; 12.93)
CFT	Multimorbidity	-0.44 (-0.89; 0.02)	-0.35 (-0.80; 0.09)
	Time	-1.36 (-1.53; -1.19)	-1.57 (-1.72; -1.42)
	$Time^2$	-0.05 (-0.14; 0.04)	0.05 (-0.04; 0.13)
	Multimorbidity x time	-0.40 (-0.70; -0.11)	-0.28 (-0.50; -0.07)

Note: In linear mixed-effects models, time is defined as time from baseline in years, standardized by centering using the grand mean and dividing by the standard deviation. Models are adjusted for retest (yes; no; for linear-mixed models only), age (years), sex (female; male), and education years (<12; 12; 13-15; 16; ≥17).

Supplementary Table 4.13 Associations of multimorbidity with longitudinal cognitive test performance among participants >50 years old from the Rancho Bernardo Study of Healthy Aging

Outcome	Model	Term	β (95% CI)
MMSE	1	Multimorbidity	0.03 (-0.17; 0.23)
		Time	-0.51 (-0.60; -0.42)
		$Time^2$	0.18 (0.13; 0.22)
		Multimorbidity x time	-0.19 (-0.35; -0.03)
	2	Multimorbidity	0.02 (-0.19; 0.22)
		Time	-0.51 (-0.60; -0.42)
		$Time^2$	0.17 (0.13; 0.22)
		Multimorbidity x time	-0.2 (-0.35; -0.04)
	3	Multimorbidity	0.02 (-0.18; 0.22)
		Time	-0.51 (-0.60; -0.42)
		$Time^2$	0.17 (0.13; 0.22)
		Multimorbidity x time	-0.20 (-0.35; -0.04)
Trails B	1	Multimorbidity	10.87 (4.47; 17.27)
		Time	12.04 (9.69; 14.40)
		$Time^2$	3.87 (2.72; 5.01)
		Multimorbidity x time	9.63 (5.34; 13.92)
	2	Multimorbidity	10.82 (4.38; 17.27)
		Time	12.11 (9.75; 14.48)
		$Time^2$	3.84 (2.69; 4.98)
		Multimorbidity x time	9.89 (5.59; 14.19)
	3	Multimorbidity	10.3 (3.88; 16.71)
		Time	12.16 (9.79; 14.53)
		$Time^2$	3.83 (2.68; 4.98)
		Multimorbidity x time	9.78 (5.48; 14.09)
CFT	1	Multimorbidity	-0.41 (-0.87; 0.04)
		Time	-1.39 (-1.56; -1.22)
		$Time^2$	-0.06 (-0.16; 0.03)
		Multimorbidity x time	-0.39 (-0.69; -0.09)
	2	Multimorbidity	-0.36 (-0.82; 0.10)
		Time	-1.39 (-1.57; -1.22)
		$Time^2$	-0.06 (-0.16; 0.03)
		Multimorbidity x time	-0.41 (-0.70; -0.11)
	3	Multimorbidity	-0.34 (-0.79; 0.12)
		Time	-1.40 (-1.57; -1.22)
		$Time^2$	-0.06 (-0.16; 0.03)
		Multimorbidity x time	-0.40 (-0.70; -0.11)

Note: Time is defined as time from baseline in years, standardized by centering using the grand mean and dividing by the standard deviation. Model 1 adjusted for retest (yes; no), age (years), sex (female; male), and education years (<12; 12; 13-15; 16; ≥17). Model 2 adjusted for BMI (kg/m2; standardized), smoking status (never; former; current), alcohol use (non-drinker; daily; 2-4 per week; 1-2 per month; <1 per month), and physical activity (<3 times/week; ≥3 times/week). Model 3 adjusted for social engagement (≤2; 3; 4).

Supplementary Table 4.14 Associations of multimorbidity with longitudinal cognitive test performance by social engagement among participants >50 years old of the Rancho Bernardo Study of Healthy Aging

		Social engagement			
		Low (n=482)	Medium (n=554)	High (n=320)	
Outcome	Term	β (95% CI)	β (95% CI)	β (95% CI)	$P_{interaction}$
MMSE	Multimorbidity	0.27 (-0.07; 0.62)	-0.16 (-0.47; 0.14)	-0.12 (-0.51; 0.28)	0.0045
	Time	-0.55 (-0.74; -0.37)	-0.52 (-0.67; -0.38)	-0.43 (-0.58; -0.29)	
	$Time^2$	0.15 (0.07; 0.23)	0.14 (0.07; 0.21)	0.19 (0.11; 0.27)	
	Multimorbidity x time	-0.38 (-0.70; -0.06)	-0.13 (-0.39; 0.13)	-0.12 (-0.35; 0.12)	
Trails B	Multimorbidity	6.36 (-5.31; 18.03)	10.8 (1.03; 20.56)	16.96 (4.1; 29.81)	0.0138
	Time	14.26 (9.57; 18.95)	11.89 (8.01; 15.76)	10.44 (6.81; 14.06)	
	$Time^2$	3.61 (1.38; 5.85)	5.77 (3.92; 7.62)	1.57 (-0.21; 3.36)	
	Multimorbidity x time	11.9 (3.59; 20.21)	8.25 (1.01; 15.49)	9.61 (3.24; 15.98)	
VFT	Multimorbidity	0.01 (-0.77; 0.79)	-0.18 (-0.91; 0.55)	-1.04 (-1.98; -0.09)	0.4480
	Time	-1.29 (-1.60; -0.98)	-1.58 (-1.86; -1.31)	-1.23 (-1.55; -0.91)	
	$Time^2$	-0.16 (-0.33; 0.01)	-0.15 (-0.30; -0.0041)	0.14 (-0.03; 0.31)	
	Multimorbidity x time	-0.43 (-0.96; 0.10)	-0.21 (-0.70; 0.28)	-0.63 (-1.17; -0.1)	

Note: Time is defined as time from baseline in years, standardized by centering using the grand mean and dividing by the standard deviation. Models are adjusted for retest (yes; no), age (years), sex (female; male), education years (<12; 12; 13-15; 16; ≥17), BMI (kg/m2; standardized), smoking status (never; former; current), alcohol use (non-drinker; daily; 2-4 per week; 1-2 per month; <1 per month), and exercise (<3 times/week; ≥3 times/week). $P_{interaction}$ is derived from likelihood ratio tests comparing models with and without a 3-way interaction of multimorbidity by time by continuous social engagement.

Supplementary Table 4.15 Associations of multimorbidity with longitudinal cognitive test performance by social engagement (excluding participation in religious activities) among participants of the Rancho Bernardo Study of Healthy Aging

		Social engagement (not including religious activities)			
		Low (n=164)	Medium (n=545)	High (n=660)	
Outcome	Term	β (95% CI)	β (95% CI)	β (95% CI)	$P_{interaction}$
MMSE	Multimorbidity	0.65 (-0.04; 1.33)	0.0015 (-0.32; 0.32)	-0.20 (-0.47; 0.08)	0.0047
	Time	-0.41 (-0.67; -0.15)	-0.60 (-0.79; -0.42)	-0.45 (-0.55; -0.35)	
	$Time^2$	0.26 (0.12; 0.40)	0.13 (0.05; 0.21)	0.18 (0.13; 0.24)	
	Multimorbidity x time	-0.32 (-0.79; 0.16)	-0.23 (-0.55; 0.08)	-0.14 (-0.31; 0.04)	
Trails B	Multimorbidity	0.94 (-19.89; 21.78)	11.98 (0.88; 23.08)	14.34 (5.92; 22.76)	0.0151
	Time	10.27 (2.61; 17.92)	14.9 (10.43; 19.38)	10.37 (7.52; 13.23)	
	$Time^2$	4.44 (0.62; 8.27)	4.16 (2.12; 6.19)	3.35 (1.93; 4.77)	
	Multimorbidity x time	20.10 (5.61; 34.58)	9.19 (1.51; 16.88)	8.3 (2.93; 13.67)	
CFT	Multimorbidity	-0.64 (-2.09; 0.81)	-0.02 (-0.77; 0.72)	-0.72 (-1.37; -0.08)	0.4394
	Time	-0.71 (-1.22; -0.20)	-1.57 (-1.87; -1.27)	-1.36 (-1.59; -1.14)	
	$Time^2$	-0.54 (-0.82; -0.26)	-0.06 (-0.22; 0.10)	0.03 (-0.10; 0.15)	
	Multimorbidity x time	-1.36 (-2.32; -0.40)	-0.34 (-0.84; 0.15)	-0.31 (-0.72; 0.09)	

Note: Time is defined as time from baseline in years, standardized by centering using the grand mean and dividing by the standard deviation. Models are adjusted for retest (yes; no), age (years), sex (female; male), education years (<12; 12; 13-15; 16; ≥17), BMI (kg/m2; standardized), smoking status (never; former; current), alcohol use (non-drinker; daily; 2-4 per week; 1-2 per month; <1 per month), and exercise (<3 times/week; ≥3 times/week). $P_{interaction}$ is derived from likelihood ratio tests comparing models with and without a 3-way interaction of multimorbidity by time by continuous social engagement.

Supplementary Table 4.16 Baseline cognitive outcome scores by social engagement level

	Social engagement			
Outcome	Low (n=485)	Medium (n=559)	High (n=325)	p-value
MMSE, mean (SD)	27.9 (2.05)	28.1 (1.63)	28.3 (1.62)	0.12
Trails B, mean (SD)	145 (66.5)	130 (55.6)	123 (58.8)	<0.01
CFT, mean (SD)	16.8 (4.74)	17.8 (4.74)	18.2 (4.80)	0.04

Note: P-values were derived from analysis of covariance models that were adjusted for age, sex, and education.

Chapter 4, in full, has been submitted for publication of the material as it may appear in the Journal of Alzheimer's Disease. Posis, Alexander Ivan B.; Shadyab, Aladdin H.; Parada Jr., Humberto; Alcaraz, John E.; Kremen, William S.; McEvoy, Linda K. The dissertation author was the primary investigator and author of this paper.

Chapter 5 Discussion

5.1 Summary of dissertation research

The global prevalence of dementia is expected to increase to 78 million,[1] with an estimated cost of $2 trillion,[2] by the year 2030. Thus, it is crucial to identify modifiable risk factors for dementia to inform interventions and policy to promote healthy cognitive aging. However, it is unknown if these risk factors interplay in such a manner that social contact moderates (i.e., buffers) the associations of TBI or multimorbidity with cognitive health. By studying the buffering effects of social contact, this dissertation addresses the World Health Organization's action area "Dementia awareness and friendliness" to understand the role of the social and physical environments.[176] Understanding the effects of TBI and multimorbidity on brain health and changes in cognitive performance over time will provide valuable insights into the cognitive aging processes.

In Chapter 2 (Study 1), we tested the association between TBI and trajectories of episodic memory, executive function, and processing speed among 1,476 men in VETSA. Contrary to our hypotheses, there was no evidence to suggest effect measure modification by loneliness in the association between TBI with measures of episodic memory, executive function, and processing speed. However, we found that history of TBI was associated with small but faster declines in executive functioning among *APOE* ε4 carriers, which aligns with hypotheses that the allele affects compensatory mechanisms that places ε4 carriers at greater risk of TBI-related cognitive deficits compared to non-carriers.[114] Additionally, we expanded on the current evidence base by showing that remote TBIs, prior to military induction, was associated with decline in executive function relative to no TBI, suggesting the importance of preventing earlier life TBIs. This study

highlights the need for future studies to consider the role of earlier TBI in relation to later life cognitive outcomes.

In Chapter 3 (Study 2), we tested the association of TBI with measures of predicted brain age, global white matter abnormalities, and specific white matter tracts among 517 men in VETSA. While we did not find significant associations of TBI with predicted brain age difference or the presence of abnormal white matter, TBI was associated with lower restricted diffusion in the inferior longitudinal fasciculus (ILF) bilaterally and left inferior frontal occipital fasciculus (IFOF) compared to no TBI. There was no evidence to suggest effect measure modification by loneliness or by *APOE* carrier status. Prior studies have identified several TBI-related differences in neuroimaging-based markers of brain health, but these studies involved mostly younger-aged participants who were imaged within shorter temporal proximity to the TBI event.[43,45,52,53]

Overall our findings in Chapters 2 and 3 expanded upon the current evidence base in two ways: 1) highlighting the effect of remote, or earlier life, TBI on later-life executive function, particularly among *APOE* e4 carriers and those reporting TBI before military induction; and 2) showing that there are subtle white matter microstructural changes after a TBI event, that may be apparent even years after the initial injury. These insights are important because sensitive neuroimaging measures, such as restriction spectrum imaging (RSI), can uncover microstructural changes that are associated with early Alzheimer's disease neuropathology.[177]

The results of Chapters 2 and 3 correspond with each other in highlighting the role of TBI in executive function decline and changes to the brain's microstructure. Specifically, we found that the TBI primarily affected the ILF bilaterally and left IFOF. The ILF is a long-range white matter tract which connects the occipital and temporal lobes,[142] and the IFOF connects the

parietal and occipital lobes to the frontal lobe.[143] In a separate study, differences in white matter anisotropy in fronto-parietal tracts, including the IFOF, were associated with lower executive function.[178] While our main effect of TBI for free water diffusion in the ILF bilaterally was positive but not significant (see Figure 3.2), this corresponds with prior work in VETSA which found that greater free water diffusion in the ILF was associated with lower executive function (β = -0.15; FDR-corrected p-value =0.007).[144] This aligns with a review of the literature which suggests that age-related declines in white matter integrity are associated with declines in processing speed, episodic memory, and executive function.[179] This is also consistent with a case-control study of 30 veterans and 15 controls that found that TBI cases with loss of consciousness had reduced executive function performance and altered white matter integrity.[50]

Results on the association between TBI and lower restricted diffusion in the ILF bilaterally can inform potential hypotheses that we were not able to examine in this dissertation. For example, disruptions to the ILF white matter tract were implicated with visual and memory impairments in other studies.[142,145,180] TBI may impact vision function through mechanisms such as axonal injury, loss of retinal ganglion cells, and optic neuropathy.[181] Therefore, the evidence we present in Chapter 3 should motivate investigations into whether TBI affects longitudinal trajectories of visual memory and reasoning performance.

The findings of Chapter 2 and 3 are consistent with other research that suggests that those with TBI may have earlier onset of dementia and cognitive impairment.[16–18] However, the results of TBI in relation to dementia and pathology vary by study population. The Lancet Commission Report[4] and other studies in populations primarily comprised of veterans[22–29] support the association between TBI with incident dementia. Whereas studies, in mostly non-Veteran populations, found no associations between TBI with Alzheimer's disease pathology,[30–32] any

ADRD,[33] and changes in midlife cognition.[34] Discrepancies in findings may partly be explained by study population characteristics and different TBI definitions or underreport or misdiagnosis of TBI, especially mild injury.[182]

In Chapter 4 (Study 3), we tested the association between multimorbidity and multiple measures of cognitive performance, and assessed effect measure modification by social engagement, in a prospective study of 1,381 participants from the RBS cohort. We found that multimorbidity was associated with faster declines in measures of global cognitive function, executive function/speed, and category fluency during an average 7.2 years of follow-up. These results were generally consistent with prior literature.[6,56,57] Participants with lower social engagement had a larger magnitude of multimorbidity-associated declines in a test of global cognitive function compared to those with medium and high social engagement. Effect measure modification for executive function/speed was significant when considering a higher type I error threshold of alpha of 0.10 as well as in sensitivity analyses where the social engagement index was redefined and after restricting the analytic sample to older adults. Results on the modifying effects of social engagement on multimorbidity-associated cognitive decline are highly relevant given the projected rise in older adults with multimorbidity and dementia.[174,175] Additionally, these results add to the literature of negative health outcomes associated with lower levels of social connection, which was emphasized by the recent U.S. Surgeon General's Advisory report, "Our Epidemic of Loneliness and Isolation: The U.S. Surgeon General's Advisory on the Healing Effects of Social Connection and Community".[61]

Although the Lancet Commission classifies social contact as a modifiable risk factor for dementia,[4] there was no evidence to suggest effect measure modification in the associations of TBI with cognitive decline and markers of brain health by loneliness in Chapters 2 and 3. We

were underpowered to assess the effect of social isolation, another risk factor highlighted in the Lancet Report,[4] in this study population given its low prevalence in VETSA. While we used an index score in the RBS study in Chapter 4, the two VETSA studies assessed social contact via a single item pertaining to how often the participant felt in the past week. There is opportunity to expand upon this topic by testing different social connectedness-related scales in VETSA and RBS. Additionally, it is plausible that other forms of social contact may be more impactful in these populations.

In Chapter 4, we found that those with low social engagement had stronger multimorbidity-related declines in global cognitive function compared to those with higher levels of social engagement. These findings align with meta-analyses that suggest that higher social engagement is associated with lower risk of dementia,[4,151] and supports our hypothesis of the buffering effect of social contact on risk factors for cognitive decline. We also elucidated which aspects of social engagement may be most impactful by showing that participants who had ≤2 close friends and relatives had faster multimorbidity-associated declines.

In summary, the results of this dissertation advance the dementia and cognitive aging field in several ways. Chapter 2 outlined the impact of TBI in early life (i.e., prior to military induction) and *APOE* ε4 carrier status in relation to faster executive function decline among middle-to-older aged men. Chapter 3 leveraged multiple neuroimaging-based biomarkers, spanning predicted brain age, global white matter abnormalities and white matter microstructure derived from RSI, to assess the impact of TBI in later life. However, we did not find evidence to suggest effect measure modification by loneliness in Chapters 2 and 3. Chapter 4 outlined the modifying effect of social engagement on multimorbidity-related cognitive decline, supporting social engagement as a potentially modifiable and actionable factor among older adults.[4]

Additionally, we leveraged inverse probability of selection weights[165] and joint models[167] to assess the impact of selection bias due to loss to follow-up and bias due to the competing risk of mortality, respectively, which are techniques that can be applied in similar longitudinal contexts.

5.2 Limitations and recommendation for future work

There are several limitations to this dissertation to consider. First, given the longitudinal design of the studies outlined in Chapters 2 and 4, selection bias due to loss to follow up may affect our results. We assessed the impact of the effect of this bias by using inverse probability of selection weights in our last study among RBS participants in Chapter 4. Additionally, the VETSA design included age-matched attrition-replacement participants at each wave to compare cognitive test scores between returnees and replacements,[83] and there were few demographic differences between those with complete and incomplete follow-up in Chapter 2 (see Supplementary Table 2.1).

Second, there may be measurement error due to recall bias of self-reported TBI, multimorbidity and measures of social contact, contributing to information bias. Future studies should consider multiple data sources to ascertain TBI and multimorbidity. For example, they may incorporate medical record data to confirm self-reported TBI and morbidity history. Given the differences in defining multimorbidity (see Table 1.1), it may also be beneficial for further collaboration into defining morbidities that have the most impact on cognitive aging,[55] as well as considering different clusters of multimorbidity categories such as cardiometabolic multimorbidity.[8] Additionally, time-varying TBI and multimorbidity should be considered to assess the impact of timing and severity throughout the lifecourse. Data on the timing of injury and morbidity diagnosis would allow for a clearer timeline of events to elucidate the mechanisms by which these risk factors affect cognitive outcomes.

Third, the VETSA study sample is predominantly non-Hispanic White and male, and the RBS is predominantly white and middle class from a single region, which limits generalizability of our findings. Future work must include populations of diverse race, ethnicity, and socio-demographic backgrounds, especially because there are major racial and ethnic disparities in dementia incidence.[183] Additionally, sex differences should be assessed given evidence indicating worse recovery after TBI[184] and higher prevalence of multimorbidity[5] among women compared to men.

Given our interests in multiple domains of cognition with repeated measures over time in Papers 1 and 3, there may be bias due to practice effects. Both VETSA and RBS have outlined analytic approaches to address this bias. VETSA, by design, addressed biases due to attrition and practice effects by enrolling new participants from the Vietnam Era Twin Registry (VETR) at waves 2 and 3 who were of similar age to VETSA participants (see Elman et al. 2018).[83] Briefly, the practice effect for each cognitive outcome was calculated as the difference in scores between returnees and replacements (i.e., the difference score), subtracted by the difference in scores between returnees and all participants (i.e., the attrition effect).[83] Although the adjustment for practice effects in RBS was not as robust, due in part to study design, including a covariate indicating whether a test had been previously administered to the participant may be beneficial.[162]

It is possible that the risk factors we have assessed follow a different temporal path than we have posited and assessed here. For example, cognitive impairment may result in decreased social engagement and higher levels of loneliness. It is also possible that having multimorbidity or TBI may reduce one's social contact, and in turn, impact cognitive outcomes. Additionally, while yet to be examined, social contact (e.g., through lower loneliness, higher social

engagement, etc.) may have a more impactful role on cognitive health if implemented more proximal to the point of TBI or onset of morbidity. However, we were not able to examine these potentially mediating paths given the small magnitudes of effect in Chapters 2 and 3, and our definition of multimorbidity and social engagement Chapter 4. If provided time-varying measures of correct temporal sequence and confirmation of identifiability criteria, these mechanisms can be assessed using a causal mediation framework.[185] Moreover, we primarily focused on interpersonal and intrapersonal factors of social contact. Further research, while considering other pathways, can assess the impact of community and policy level factors, such as access to care, on the associations tested here.

Lastly, given the small magnitudes of association of TBI with different outcomes in Chapters 2 and 3, and presumed accelerated cognitive decline at older age, the observed associations may be more pronounced with further follow-up in VETSA. Further study is needed among older-aged cohorts to study the mechanisms in which TBI affects later-life health. Medical records-based studies may be able to assess these associations using a retrospective cohort design but may be limited by the quality of available data.

5.3 Conclusions

The results of this dissertation underscore the negative impact of multimorbidity and TBI on cognitive and brain health at later life but did not provide strong support for low loneliness as a buffer of TBI. Nonetheless, this work expands the current evidence base by highlighting the importance of TBI in early life and *APOE* ε4 carrier status in relation to cognitive decline, as well as the impact of TBI on white matter microstructures which are crucial to cognitive function. While loneliness was not a significant moderator of TBI with our outcomes of interest, social engagement modified the relationship between multimorbidity and cognitive decline.

There remains a strong need to elucidate these relationships given the limitations of this dissertation to date. Findings can inform subsequent efforts focused on increasing social engagement to reduce cognitive decline and improve wellbeing, particularly among those with multimorbidity.

References

1. Gauthier S, Rosa-Neto P, Morais J, Webster C. *World Alzheimer Report 2021: Journey through the Diagnosis of Dementia*.; 2021.

2. Patterson C. *World Alzheimer Report 2018 - The State of the Art of Dementia Research: New Frontiers*. Alzheimer's Disease International; 2018:48.

3. Hebert LE, Weuve J, Scherr PA, Evans DA. Alzheimer disease in the United States (2010-2050) estimated using the 2010 census. *Neurology*. 2013;80(19):1778-1783. doi:10.1212/WNL.0b013e31828726f5

4. Livingston G, Huntley J, Sommerlad A, Ames D, Ballard C, Banerjee S, Brayne C, Burns A, Cohen-Mansfield J, Cooper C, Costafreda SG, Dias A, Fox N, Gitlin LN, Howard R, Kales HC, Kivimäki M, Larson EB, Ogunniyi A, Orgeta V, Ritchie K, Rockwood K, Sampson EL, Samus Q, Schneider LS, Selbæk G, Teri L, Mukadam N. Dementia prevention, intervention, and care: 2020 report of the Lancet Commission. *Lancet*. 2020;396(10248):413-446. doi:10.1016/S0140-6736(20)30367-6

5. Salive ME. Multimorbidity in older adults. *Epidemiologic Reviews*. 2013;35(1):75-83. doi:10.1093/epirev/mxs009

6. Fabbri E, An Y, Zoli M, Tanaka T, Simonsick EM, Kitner-Triolo MH, Studenski SA, Resnick SM, Ferrucci L. Association of accelerated multi-morbidity and age-related cognitive decline in older, non-demented participants from the Baltimore Longitudinal Study of Aging. *J Am Geriatr Soc*. 2016;64(5):965-972. doi:10.1111/jgs.14092

7. Hassen CB, Fayosse A, Landré B, Raggi M, Bloomberg M, Sabia S, Singh-Manoux A. Association between age at onset of multimorbidity and incidence of dementia: 30 year follow-up in Whitehall II prospective cohort study. *BMJ*. 2022;376:e068005. doi:10.1136/bmj-2021-068005

8. Dove A, Marseglia A, Shang Y, Grande G, Vetrano DL, Laukka EJ, Fratiglioni L, Xu W. Cardiometabolic multimorbidity accelerates cognitive decline and dementia progression. *Alzheimers Dement*. Published online 2022. doi:10.1002/alz.12708

9. Vassilaki M, Aakre JA, Cha RH, Kremers WK, St. Sauver JL, Mielke MM, Geda YE, Machulda MM, Knopman DS, Petersen RC, Roberts RO. Multimorbidity and risk of mild cognitive impairment. *Journal of the American Geriatrics Society*. 2015;63(9):1783-1790. doi:10.1111/jgs.13612

10. Whalley LJ, Dick FD, McNeill G. A life-course approach to the aetiology of late-onset dementias. *The Lancet Neurology*. 2006;5(1):87-96. doi:10.1016/S1474-4422(05)70286-6

11. Liu S, Jones RN, Glymour MM. Implications of lifecourse epidemiology for research on determinants of adult disease. *Public health reviews*. 2010;32(2):489. doi:10.1007/BF03391613

12. Thurman D, Alverson C, Browne D, Dunn KA, Guerrero J, Johnson R, Johnson V, Langlois, Pilkey D, Sniezek JE, Toal S. Report to Congress on Traumatic Brain Injury in the United States: Understanding the Public Health Problem among Current and Former Military Personnel. Published online 1999.

13. Centers for Disease Control and Prevention. Traumatic brain injury & concussion. Published 2022. Accessed August 28, 2022. https://www.cdc.gov/traumaticbraininjury/index.html

14. Okie S. Traumatic Brain Injury in the War Zone. *New England Journal of Medicine*. 2005;352(20):2043-2047. doi:10.1056/NEJMp058102

15. Langlois JA, Rutland-Brown W, Wald MM. The epidemiology and impact of traumatic brain injury: a brief overview. *J Head Trauma Rehabil*. 2006;21(5):375-378. doi:10.1097/00001199-200609000-00001

16. Li W, Risacher SL, McAllister TW, Saykin AJ. Traumatic brain injury and age at onset of cognitive impairment in older adults. *J Neurol*. 2016;263(7):1280-1285. doi:10.1007/s00415-016-8093-4

17. LoBue C, Wadsworth H, Wilmoth K, Clem M, Hart J, Womack KB, Didehbani N, Lacritz LH, Rossetti HC, Cullum CM. Traumatic brain injury history is associated with earlier age of onset of Alzheimer disease. *Clinical Neuropsychologist*. 2017;31(1):85-98. doi:10.1080/13854046.2016.1257069

18. Schaffert J, LoBue C, White CL, Chiang HS, Didehbani N, Lacritz L, Rossetti H, Dieppa M, Hart J, Cullum CM. Traumatic brain injury history is associated with an earlier age of dementia onset in autopsy-confirmed Alzheimer's disease. *Neuropsychology*. 2018;32(4):410. doi:10.1037/NEU0000423

19. Zanier ER, Bertani I, Sammali E, Pischiutta F, Chiaravalloti MA, Vegliante G, Masone A, Corbelli A, Smith DH, Menon DK, Stocchetti N, Fiordaliso F, De Simoni MG, Stewart W, Chiesa R. Induction of a transmissible tau pathology by traumatic brain injury. *Brain*. 2018;141(9):2685-2699. doi:10.1093/brain/awy193

20. Cao J, Gaamouch FE, Meabon JS, Meeker KD, Zhu L, Zhong MB, Bendik J, Elder G, Jing P, Xia J, Luo W, Cook DG, Cai D. ApoE4-associated phospholipid dysregulation contributes to development of Tau hyper-phosphorylation after traumatic brain injury. *Scientific Reports*. 2017;7(1):11372-11372. doi:10.1038/s41598-017-11654-7

21. Shively S, Scher AI, Perl DP, Diaz-Arrastia R. Dementia resulting from traumatic brain injury: what is the pathology? *Archives of Neurology*. 2012;69(10):1245-1251. doi:10.1001/archneurol.2011.3747

22. Barnes DE, Kaup A, Kirby KA, Byers AL, Diaz-Arrastia R, Yaffe K. Traumatic brain injury and risk of dementia in older veterans. *Neurology*. 2014;83(4):312-319. doi:10.1212/WNL.0000000000000616

23. Barnes DE, Byers AL, Gardner RC, Seal KH, Boscardin WJ, Yaffe K. Association of Mild Traumatic Brain Injury With and Without Loss of Consciousness With Dementia in US Military Veterans. *JAMA Neurology*. 2018;75(9):1055-1061. doi:10.1001/JAMANEUROL.2018.0815

24. Fann JR, Ribe AR, Pedersen HS, Fenger-Grøn M, Christensen J, Benros ME, Vestergaard M. Long-term risk of dementia among people with traumatic brain injury in Denmark: a population-based observational cohort study. *The Lancet Psychiatry*. 2018;5(5):424-431. doi:10.1016/S2215-0366(18)30065-8

25. Gardner RC, Burke JF, Nettiksimmons J, Kaup A, Barnes DE, Yaffe K. Dementia risk after traumatic brain injury vs nonbrain trauma: the role of age and severity. *JAMA neurology*. 2014;71(12):1490-1497. doi:10.1001/JAMANEUROL.2014.2668

26. Kornblith E, Peltz CB, Xia F, Plassman B, Novakovic-Apopain T, Yaffe K. Sex, race, and risk of dementia diagnosis after traumatic brain injury among older veterans. *Neurology*. 2020;95(13):e1768. doi:10.1212/WNL.0000000000010617

27. Nordström A, Nordström P. Traumatic brain injury and the risk of dementia diagnosis: a nationwide cohort study. *PLoS Medicine*. 2018;15(1). doi:10.1371/JOURNAL.PMED.1002496

28. Snowden TM, Hinde AK, Reid HMO, Christie BR. Does mild traumatic brain injury increase the risk for dementia? A systematic review and meta-analysis. *Journal of Alzheimer's disease : JAD*. 2020;78(2):757-775. doi:10.3233/JAD-200662

29. Plassman BL, Chanti-Ketterl M, Pieper CF, Yaffe K, Francisco S. Traumatic brain injury and dementia risk in male veteran older twins—Controlling for genetic and early life non-genetic factors. *Alzheimer's & Dementia*. Published online February 2022. doi:10.1002/ALZ.12571

30. Crane PK, Gibbons LE, Dams-O'Connor K, Trittschuh E, Leverenz JB, Dirk Keene C, Sonnen J, Montine TJ, Bennett DA, Leurgans S, Schneider JA, Larson EB. Association of Traumatic Brain Injury With Late-Life Neurodegenerative Conditions and Neuropathologic Findings. *JAMA Neurology*. 2016;73(9):1062-1069. doi:10.1001/JAMANEUROL.2016.1948

31. Sugarman MA, McKee AC, Stein TD, Tripodis Y, Besser LM, Martin B, Palmisano JN, Steinberg EG, O'Connor MK, Au R, McClean M, Killiany R, Mez J, Weiner MW, Kowall NW, Stern RA, Alosco ML. Failure to detect an association between self-reported traumatic brain injury and Alzheimer's disease neuropathology and dementia. *Alzheimer's & dementia : the journal of the Alzheimer's Association*. 2019;15(5):686-698. doi:10.1016/J.JALZ.2018.12.015

32. Weiner MW, Harvey D, Landau SM, Veitch DP, Neylan TC, Grafman JH, Aisen PS, Petersen RC, Jack Jr CR, Tosun D, Shaw LM, Trojanowski JQ, Saykin AJ, Hayes J, De Carli C, for the Alzheimer's Disease Neuroimaging Initiative and the Department of Defense Alzheimer's Disease Neuroimaging Initiative. Traumatic brain injury and post-

traumatic stress disorder are not associated with Alzheimer's disease pathology measured with biomarkers. *Alzheimer's & Dementia*. 2022;n/a(n/a). doi:10.1002/alz.12712

33. Dams-O'Connor K, Gibbons LE, Bowen JD, McCurry SM, Larson EB, Crane PK. Risk for late-life re-injury, dementia and death among individuals with traumatic brain injury: A population-based study. *Journal of Neurology, Neurosurgery and Psychiatry*. 2013;84(2):177-182. doi:10.1136/JNNP-2012-303938

34. Kaup AR, Toomey R, Bangen KJ, Delano-Wood L, Yaffe K, Panizzon MS, Lyons MJ, Franz CE, Kremen WS. Interactive Effect of Traumatic Brain Injury and Psychiatric Symptoms on Cognition among Late Middle-Aged Men: Findings from the Vietnam Era Twin Study of Aging. *Journal of Neurotrauma*. 2019;36(2):338. doi:10.1089/NEU.2018.5695

35. Gardner RC, Langa KM, Yaffe K. Subjective and objective cognitive function among older adults with a history of traumatic brain injury: A population-based cohort study. *PLOS Medicine*. 2017;14(3):e1002246. doi:10.1371/journal.pmed.1002246

36. Himanen L, Portin R, Isoniemi H, Helenius H, Kurki T, Tenovuo O. Longitudinal cognitive changes in traumatic brain injury: A 30-year follow-up study. *Neurology*. 2006;66(2):187-192. doi:10.1212/01.wnl.0000194264.60150.d3

37. Vanderploeg RD, Curtiss G, Belanger HG. Long-term neuropsychological outcomes following mild traumatic brain injury. *J Int Neuropsychol Soc*. 2005;11(3):228-236. doi:10.1017/S1355617705050289

38. Lennon MJ, Brooker H, Creese B, Thayanandan T, Rigney G, Aarsland D, Hampshire A, Ballard C, Corbett A, Raymont V. Lifetime traumatic brain injury and cognitive domain deficits in late life: the PROTECT-TBI cohort study. *Journal of Neurotrauma*. 2023;40(13-14):1423-1435. doi:10.1089/neu.2022.0360

39. Marianne Chanti-Ketterl, Carl F Pieper, Kristine Yaffe, Brenda L Plassman. Associations between traumatic brain injury and cognitive decline among older veteran men - a twin study. *Neurology*. Published online September 6, 2023:10.1212/WNL.0000000000207819. doi:10.1212/WNL.0000000000207819

40. Kaup AR, Peltz C, Kenney K, Kramer JH, Diaz-Arrastia R, Yaffe K. Neuropsychological Profile of Lifetime Traumatic Brain Injury in Older Veterans. *Journal of the International Neuropsychological Society*. 2017;23(1):56-64. doi:10.1017/S1355617716000849

41. Peltz CB, Gardner RC, Kenney K, Diaz-Arrastia R, Kramer J, Yaffe K. Neurobehavioral Characteristics of Older Veterans with Remote Traumatic Brain Injury. *J Head Trauma Rehabil*. 2017;32(1):E8-E15. doi:10.1097/HTR.0000000000000245

42. Albrecht MA, Masters CL, Ames D, Foster JK. Impact of mild head injury on neuropsychological performance in healthy older adults: longitudinal assessment in the AIBL cohort. *Frontiers in Aging Neuroscience*. 2016;8(MAY). doi:10.3389/FNAGI.2016.00105/ABSTRACT

43. Cole JH, Leech R, Sharp DJ, for the Alzheimer's Disease Neuroimaging Initiative. Prediction of brain age suggests accelerated atrophy after traumatic brain injury. *Annals of Neurology*. 2015;77(4):571-581. doi:10.1002/ana.24367

44. Smith DH, Johnson VE, Stewart W. Chronic neuropathologies of single and repetitive TBI: substrates of dementia? *Nat Rev Neurol*. 2013;9(4):211-221. doi:10.1038/nrneurol.2013.29

45. Kinnunen KM, Greenwood R, Powell JH, Leech R, Hawkins PC, Bonnelle V, Patel MC, Counsell SJ, Sharp DJ. White matter damage and cognitive impairment after traumatic brain injury. *Brain*. 2011;134(Pt 2):449-463. doi:10.1093/brain/awq347

46. June D, Williams OA, Huang CW, An Y, Landman BA, Davatzikos C, Bilgel M, Resnick SM, Beason-Held LL. Lasting consequences of concussion on the aging brain: Findings from the Baltimore Longitudinal Study of Aging. *NeuroImage*. 2020;221:117182. doi:10.1016/j.neuroimage.2020.117182

47. Rolls ET, Everitt BJ, Roberts A, Roberts AC, Robbins TW, Weiskrantz L. The orbitofrontal cortex. *Philosophical Transactions of the Royal Society of London Series B: Biological Sciences*. 1996;351(1346):1433-1444. doi:10.1098/rstb.1996.0128

48. Vogt BA, Finch DM, Olson CR. Functional heterogeneity in cingulate cortex: the anterior executive and posterior evaluative regions. *Cereb Cortex*. 1992;2(6):435-443. doi:10.1093/cercor/2.6.435-a

49. Jolly AE, Scott GT, Sharp DJ, Hampshire AH. Distinct patterns of structural damage underlie working memory and reasoning deficits after traumatic brain injury. *Brain*. 2020;143(4):1158-1176. doi:10.1093/brain/awaa067

50. Sorg SF, Delano-Wood L, Luc N, Schiehser DM, Hanson KL, Nation DA, Lanni E, Jak AJ, Lu K, Meloy MJ, Frank LR, Lohr JB, Bondi MW. White Matter Integrity in Veterans With Mild Traumatic Brain Injury: Associations With Executive Function and Loss of Consciousness. *J Head Trauma Rehabil*. 2014;29(1):21-32. doi:10.1097/HTR.0b013e31828a1aa4

51. Cohen S, Wills TA. Stress, social support, and the buffering hypothesis. *Psychologkal Bulletin*. 1985;98(2):31.

52. Muller J, Middleton D, Alizadeh M, Zabrecky G, Wintering N, Bazzan AJ, Lang J, Wu C, Monti DA, Wu Q, Newberg AB, Mohamed FB. Hybrid diffusion imaging reveals altered white matter tract integrity and associations with symptoms and cognitive dysfunction in chronic traumatic brain injury. *NeuroImage: Clinical*. 2021;30:102681. doi:10.1016/j.nicl.2021.102681

53. Bourke NJ, Yanez Lopez M, Jenkins PO, De Simoni S, Cole JH, Lally P, Mallas EJ, Zhang H, Sharp DJ. Traumatic brain injury: a comparison of diffusion and volumetric magnetic resonance imaging measures. *Brain Commun*. 2021;3(2):fcab006. doi:10.1093/braincomms/fcab006

54. Gardner RC, Dams-O'Connor K, Morrissey MR, Manley GT. Geriatric traumatic brain injury: epidemiology, outcomes, knowledge gaps, and future directions. *Journal of Neurotrauma*. 2018;35(7):889-906. doi:10.1089/neu.2017.5371

55. Fortin M, Stewart M, Poitras ME, Almirall J, Maddocks H. A Systematic Review of Prevalence Studies on Multimorbidity: Toward a More Uniform Methodology. *Ann Fam Med*. 2012;10(2):142-151. doi:10.1370/afm.1337

56. Espeland MA, Justice JN, Bahnson J, Evans JK, Munshi M, Hayden KM, Simpson FR, Johnson KC, Johnston C, Kritchevsky SR, the Look AHEAD Research Group. Eight-year changes in multimorbidity and frailty in adults with type 2 diabetes mellitus: associations with cognitive and physical function and mortality. *The Journals of Gerontology: Series A*. Published online November 12, 2021:glab342. doi:10.1093/gerona/glab342

57. Wei MY, Levine DA, Zahodne LB, Kabeto MU, Langa KM. Multimorbidity and cognitive decline over 14 years in older Americans. *The Journals of Gerontology: Series A*. 2020;75(6):1206-1213. doi:10.1093/gerona/glz147

58. Lee SA, Joo S, Chai HW, Jun HJ. Patterns of multimorbidity trajectories and their correlates among Korean older adults. *Age and Ageing*. 2021;50(4):1336-1341. doi:10.1093/ageing/afab002

59. National Academies of Sciences, Engineering, and Medicine. *Social Isolation and Loneliness in Older Adults: Opportunities for the Health Care System*. National Academies Press; 2020.

60. Bassuk SS, Glass TA, Berkman LF. Social disengagement and incident cognitive decline in community-dwelling elderly persons. *Ann Intern Med*. 1999;131(3):165-173. doi:10.7326/0003-4819-131-3-199908030-00002

61. US Department of Health and Human Services. *Our Epidemic of Loneliness and Isolation: The US Surgeon General's Advisory on the Healing Effects of Social Connection and Community*.; 2023. https://www.hhs.gov/sites/default/files/surgeon-general-social-connection-advisory.pdf

62. Fratiglioni L, Paillard-Borg S, Winblad B. An active and socially integrated lifestyle in late life might protect against dementia. *Lancet Neurol*. 2004;3(6):343-353. doi:10.1016/S1474-4422(04)00767-7

63. Wilson RS, Evans DA, Bienias JL, Mendes de Leon CF, Schneider JA, Bennett DA. Proneness to psychological distress is associated with risk of Alzheimer's disease. *Neurology*. 2003;61(11):1479-1485. doi:10.1212/01.wnl.0000096167.56734.59

64. Perry BL, McConnell WR, Coleman ME, Roth AR, Peng S, Apostolova LG. Why the cognitive "fountain of youth" may be upstream: Pathways to dementia risk and resilience through social connectedness. *Alzheimer's & Dementia*. 2022;18(5):934-941. doi:10.1002/alz.12443

65. Freak-Poli R, Wagemaker N, Wang R, Lysen TS, Ikram MA, Vernooij MW, Dintica CS, Vernooij-Dassen M, Melis RJM, Laukka EJ, Fratiglioni L, Xu W, Tiemeier H. Loneliness, not social support, is associated with cognitive decline and dementia across two longitudinal population-based cohorts. *Journal of Alzheimer's Disease*. 2021;Preprint(Preprint):1-14. doi:10.3233/JAD-210330

66. Krueger KR, Wilson RS, Kamenetsky JM, Barnes LL, Bienias JL, Bennett DA. Social engagement and cognitive function in old age. *Experimental Aging Research*. 2009;35(1):45-60. doi:10.1080/03610730802545028

67. Joyce J, Ryan J, Owen A, Hu J, McHugh Power J, Shah R, Woods R, Storey E, Britt C, Freak-Poli R. Social isolation, social support, and loneliness and their relationship with cognitive health and dementia. *International Journal of Geriatric Psychiatry*. 2022;37(1). doi:10.1002/GPS.5644

68. Moreno GL, Ammann E, Kaseda ET, Espeland MA, Wallace R, Robinson J, Denburg NL. The influence of social support on cognitive health in older women: a Women's Health Initiative study. *https://doi.org/101080/0895284120211945368*. Published online 2021. doi:10.1080/08952841.2021.1945368

69. Kelly ME, Duff H, Kelly S, McHugh Power JE, Brennan S, Lawlor BA, Loughrey DG. The impact of social activities, social networks, social support and social relationships on the cognitive functioning of healthy older adults: a systematic review. *Systematic Reviews*. 2017;6(1). doi:10.1186/S13643-017-0632-2

70. Stålnacke BM, Lnacke BMS. Community integration, social support and life satisfaction in relation to symptoms 3 years after mild traumatic brain injury. *http://dx.doi.org/101080/02699050701553189*. 2009;21(9):933-942. doi:10.1080/02699050701553189

71. Kumar RG, Ornstein KA, Bollens-Lund E, Watson EM, Ankuda CK, Kelley AS, Dams-O'Connor K. Lifetime history of traumatic brain injury is associated with increased loneliness in adults: A US nationally representative study. *International Journal of Geriatric Psychiatry*. 2020;35(5):553-563. doi:10.1002/GPS.5271

72. Straus E, Norman SB, Tripp JC, Tsai J, Sippel LM, Jeste D V., Southwick SM, Pietrzak RH. Behavioral Epidemic of Loneliness in Older U.S. Military Veterans: Results From the 2019-2020 National Health and Resilience in Veterans Study. *The American Journal of Geriatric Psychiatry*. Published online July 24, 2021. doi:10.1016/J.JAGP.2021.07.006

73. Cherry KE, Walker EJ, Brown JS, Volaufova J, LaMotte LR, Welsh DA, Su LJ, Jazwinski SM, Ellis R, Wood RH, Frisard MI. Social Engagement and Health in Younger, Older, and Oldest-Old Adults in the Louisiana Healthy Aging Study. *J Appl Gerontol*. 2013;32(1):51-75. doi:10.1177/0733464811409034

74. Moretti L, Cristofori I, Weaver SM, Chau A, Portelli JN, Grafman J. Cognitive decline in older adults with a history of traumatic brain injury. *The Lancet Neurology*. 2012;11(12):1103-1112. doi:10.1016/S1474-4422(12)70226-0

75. Mahley RW, Huang Y. Apolipoprotein e sets the stage: response to injury triggers neuropathology. *Neuron*. 2012;76(5). doi:10.1016/j.neuron.2012.11.020

76. Corder EH, Saunders AM, Strittmatter WJ, Schmechel DE, Gaskell PC, Small GW, Roses AD, Haines JL, Pericak-Vance MA. Gene dose of apolipoprotein E type 4 allele and the risk of Alzheimer's disease in late onset families. *Science*. 1993;261(5123):921-923. doi:10.1126/science.8346443

77. McFadyen CA, Zeiler FA, Newcombe V, Synnot A, Steyerberg E, Gruen RL, Rosand J, Palotie A, Maas AIR, Menon DK. Apolipoprotein E4 polymorphism and outcomes from traumatic brain injury: a living systematic review and meta-analysis. *J Neurotrauma*. 2021;38(8):1124-1136. doi:10.1089/neu.2018.6052

78. Zhou W, Xu D, Peng X, Zhang Q, Jia J, Crutcher KA. Meta-analysis of APOE4 allele and outcome after traumatic brain injury. *J Neurotrauma*. 2008;25(4):279-290. doi:10.1089/neu.2007.0489

79. Padgett CR, Summers MJ, Skilbeck CE. Is APOE ε4 associated with poorer cognitive outcome following traumatic brain injury? A meta-analysis. *Neuropsychology*. 2016;30(7):775-790. doi:10.1037/neu0000270

80. Kremen WS, Franz CE, Lyons MJ. Current status of the Vietnam Era Twin Study of Aging (VETSA). *Twin Research and Human Genetics*. 2019;22(6):783-787. doi:10.1017/thg.2019.125

81. Kremen WS, Thompson-Brenner H, Leung YMJ, Grant MD, Franz CE, Eisen SA, Jacobson KC, Boake C, Lyons MJ. Genes, environment, and time: the Vietnam Era Twin Study of Aging (VETSA). *Twin Research and Human Genetics*. 2006;9(6):1009-1022. doi:10.1375/twin.9.6.1009

82. Tsuang MT, Bar JL, Harley RM, Lyons MJ. The Harvard Twin Study of Substance Abuse: What We Have Learned. *Harvard Review of Psychiatry*. 2001;9(6):267-279. doi:10.1080/10673220127912

83. Elman JA, Jak AJ, Panizzon MS, Tu XM, Chen T, Reynolds CA, Gustavson DE, Franz CE, Hatton SN, Jacobson KC, Toomey R, McKenzie R, Xian H, Lyons MJ, Kremen WS. Underdiagnosis of mild cognitive impairment: A consequence of ignoring practice effects. *Alzheimers Dement (Amst)*. 2018;10:372-381. doi:10.1016/j.dadm.2018.04.003

84. Schoenborn CA, Heyman KM. Health characteristics of adults aged 55 years and over: United States, 2004-2007. *Natl Health Stat Report*. 2009;(16):1-31.

85. Franz CE, Lyons MJ, O'Brien R, Panizzon MS, Kim K, Bhat R, Grant MD, Toomey R, Eisen S, Xian H, Kremen WS. A 35-year longitudinal assessment of cognition and midlife depression symptoms: the Vietnam Era Twin Study of Aging. *Am J Geriatr Psychiatry*. 2011;19(6):559-570. doi:10.1097/JGP.0b013e3181ef79f1

86. Kremen WS, Panizzon MS, Franz CE, Spoon KM, Vuoksimaa E, Jacobson KC, Vasilopoulos T, Xian H, McCaffery JM, Rana BK, Toomey R, McKenzie R, Lyons MJ. Genetic complexity of episodic memory: a twin approach to studies of aging. *Psychol Aging*. 2014;29(2):404-417. doi:10.1037/a0035962

87. Gustavson DE, Elman JA, Sanderson-Cimino M, Franz CE, Panizzon MS, Jak AJ, Reynolds CA, Neale MC, Lyons MJ, Kremen WS. Extensive memory testing improves prediction of progression to MCI in late middle age. *Alzheimers Dement (Amst)*. 2020;12(1):e12004. doi:10.1002/dad2.12004

88. Gustavson DE, Panizzon MS, Franz CE, Friedman NP, Reynolds CA, Jacobson KC, Xian H, Lyons MJ, Kremen WS. Genetic and environmental architecture of executive functions in midlife. *Neuropsychology*. 2018;32(1):18-30. doi:10.1037/neu0000389

89. Sanderson-Cimino M, Panizzon MS, Elman JA, Gustavson DE, Franz CE, Reynolds CA, Toomey R, Lyons MJ, Kremen WS. Genetic and environmental architecture of processing speed across midlife. *Neuropsychology*. 2019;33(6):862-871. doi:10.1037/neu0000551

90. Delis DC, Kaplan E, Kramer JH, Ober BA. *California Verbal Learning Test (CVLT)*. Psychological Corporation; 2000.

91. Wechsler D. *Wechsler Memory Scale (WMS-III)*. Psychological Corporation; 1997.

92. Golden CJ, Freshwater SM. *Stroop Color and Word Test: A Manual for Clinical and Experimental Uses*.; 2002.

93. Daneman M, Carpenter PA. Individual differences in working memory and reading. *Journal of Verbal Learning and Verbal Behavior*. 1980;19(4):450-466. doi:10.1016/S0022-5371(80)90312-6

94. Delis DC, Kaplan E, Kramer JH. *Delis-Kaplan Executive Function System (D-KEFS)*. Psychological Corporation; 2001.

95. Gustavson DE, Panizzon MS, Elman JA, Franz CE, Beck A, Reynolds CA, Jacobson KC, Xian H, Toomey R, Lyons MJ, Kremen WS. Genetic and environmental influences on verbal fluency in middle age: a longitudinal twin study. *Behav Genet*. 2018;48(5):361-373. doi:10.1007/s10519-018-9910-6

96. Sanderson-Cimino M, Elman JA, Tu XM, Gross AL, Panizzon MS, Gustavson DE, Bondi MW, Edmonds EC, Eglit GML, Eppig JS, Franz CE, Jak AJ, Lyons MJ, Thomas KR, Williams ME, Kremen WS, Alzheimer's Disease Neuroimaging Initiative. Cognitive practice effects delay diagnosis of MCI: Implications for clinical trials. *Alzheimers Dement (N Y)*. 2022;8(1):e12228. doi:10.1002/trc2.12228

97. Schultz MR, Lyons MJ, Franz CE, Grant MD, Boake C, Jacobson KC, Xian H, Schellenberg GD, Eisen SA, Kremen WS. Apolipoprotein E genotype and memory in the sixth decade of life. *Neurology*. 2008;70(19 Pt 2):1771-1777. doi:10.1212/01.wnl.0000286941.74372.cc

98. Bayroff AG, Anderson AA. *Development of Literacy Screening Scales for AFQT 7 and 8 Failures*. US Army Personnel Research Office; 1963. Accessed August 28, 2022. https://apps.dtic.mil/sti/pdfs/AD0411227.pdf

99. Uhlaner JE, Bolanovich DJ. *Development of the Armed Forces Qualification Test and Predecessor Army Screening Tests, 1946–1950*. Personnel Research Section, Department of the Army; 1952. Accessed August 28, 2022. https://apps.dtic.mil/sti/citations/AD0000191

100. Lyons MJ, Panizzon MS, Liu W, McKenzie R, Bluestone NJ, Grant MD, Franz CE, Vuoksimaa EP, Toomey R, Jacobson KC, Reynolds CA, Kremen WS, Xian H. A Longitudinal Twin Study of General Cognitive Ability over Four Decades. *Dev Psychol*. 2017;53(6):1170-1177. doi:10.1037/dev0000303

101. Radloff LS. The CES-D Scale: a self-report depression scale for research in the general population. *Applied Psychological Measurement*. 1977;1(3):385-401. doi:10.1177/014662167700100306

102. Xian H, Scherrer JF, Franz CE, McCaffery J, Stein PK, Lyons MJ, Jacobsen K, Eisen SA, Kremen WS. Genetic vulnerability and phenotypic expression of depression and risk for ischemic heart disease in the Vietnam Era Twin Study of Aging. *Psychosomatic medicine*. 2010;72(4):370-370. doi:10.1097/PSY.0B013E3181D28125

103. Hughes ME, Waite LJ, Hawkley LC, Cacioppo JT. A Short Scale for Measuring Loneliness in Large Surveys. *Res Aging*. 2004;26(6):655-672. doi:10.1177/0164027504268574

104. Wright DB. Some limits using random slope models to measure academic growth. *Frontiers in Education*. 2017;2. Accessed March 28, 2023. https://www.frontiersin.org/articles/10.3389/feduc.2017.00058

105. Hoffman L. Considering alternative metrics of time: Does anybody really know what "time" is? In: *Advances in Longitudinal Methods in the Social and Behavioral Sciences*. CILVR series on latent variable methodology. IAP Information Age Publishing; 2012:255-287.

106. Sliwinski M, Hoffman L, Hofer SM. Evaluating Convergence of Within-Person Change and Between-Person Age Differences in Age-Heterogeneous Longitudinal Studies. *Res Hum Dev*. 2010;7(1):45-60. doi:10.1080/15427600903578169

107. Weuve J, Proust-Lima C, Power MC, Gross AL, Hofer SM, Thiébaut R, Chêne G, Glymour MM, Dufouil C. Guidelines for reporting methodological challenges and evaluating potential bias in dementia research. *Alzheimer's and Dementia*. 2015;11(9):1098-1109. doi:10.1016/j.jalz.2015.06.1885

108. Corder EH, Saunders AM, Risch NJ, Strittmatter WJ, Schmechel DE, Gaskell PC, Rimmler JB, Locke PA, Conneally PM, Schmader KE. Protective effect of apolipoprotein

E type 2 allele for late onset Alzheimer disease. *Nat Genet*. 1994;7(2):180-184. doi:10.1038/ng0694-180

109. Bates D, Mächler M, Bolker B, Walker S. Fitting Linear Mixed-Effects Models using lme4. Published online June 23, 2014. Accessed November 18, 2022. http://arxiv.org/abs/1406.5823

110. Lüdecke D. sjPlot: Data Visualization for Statistics in Social Science. Published online 2022. https://CRAN.R-project.org/package=sjPlot

111. Fennema-Notestine C, Panizzon MS, Thompson WR, Chen CH, Eyler LT, Fischl B, Franz CE, Grant MD, Jak AJ, Jernigan TL, Lyons MJ, Neale MC, Seidman LJ, Tsuang MT, Xian H, Dale AM, Kremen WS. Presence of ApoE ε4 Allele Associated with Thinner Frontal Cortex in Middle Age. *J Alzheimers Dis*. 2011;26(Suppl 3):49-60. doi:10.3233/JAD-2011-0002

112. Eglit GML, Elman JA, Panizzon MS, Sanderson-Cimino M, Williams ME, Dale AM, Eyler LT, Fennema-Notestine C, Gillespie NA, Gustavson DE, Hatton SN, Hagler DJ, Hauger RL, Jak AJ, Logue MW, McEvoy LK, McKenzie RE, Neale MC, Puckett O, Reynolds CA, Toomey R, Tu XM, Whitsel N, Xian H, Lyons MJ, Franz CE, Kremen WS. Paradoxical cognitive trajectories in men from earlier to later adulthood. *Neurobiology of Aging*. 2022;109:229-238. doi:10.1016/j.neurobiolaging.2021.10.002

113. Panizzon MS, Hauger R, Dale AM, Eaves LJ, Eyler LT, Fischl B, Fennema-Notestine C, Franz CE, Grant MD, Jak AJ, Jacobson KC, Lyons MJ, Mendoza SP, Neale MC, Prom-Wormley EC, Seidman LJ, Tsuang MT, Xian H, Kremen WS. Testosterone modifies the effect of APOE genotype on hippocampal volume in middle-aged men. *Neurology*. 2010;75(10):874-880. doi:10.1212/WNL.0b013e3181f11deb

114. Han SD, Drake AI, Cessante LM, Jak AJ, Houston WS, Delis DC, Filoteo JV, Bondi MW. Apolipoprotein E and traumatic brain injury in a military population: evidence of a neuropsychological compensatory mechanism? *Journal of Neurology, Neurosurgery & Psychiatry*. 2007;78(10):1103-1108. doi:10.1136/jnnp.2006.108183

115. Jonaitis EM, Koscik RL, Clark LR, Ma Y, Betthauser TJ, Berman SE, Allison SL, Mueller KD, Hermann BP, Van Hulle CA, Christian BT, Bendlin BB, Blennow K, Zetterberg H, Carlsson CM, Asthana S, Johnson SC. Measuring longitudinal cognition: Individual tests versus composites. *Alzheimer's & Dementia: Diagnosis, Assessment & Disease Monitoring*. 2019;11:74-84. doi:10.1016/j.dadm.2018.11.006

116. Kremen WS, Beck A, Elman JA, Gustavson DE, Reynolds CA, Tu XM, Sanderson-Cimino ME, Panizzon MS, Vuoksimaa E, Toomey R, Fennema-Notestine C, Hagler DJ, Jr., Fang B, Dale AM, Lyons MJ, Franz CE. Influence of young adult cognitive ability and additional education on later-life cognition. *Proceedings of the National Academy of Sciences of the United States of America*. 2019;116(6):2021-2021. doi:10.1073/PNAS.1811537116

117. TBI Data | Concussion | Traumatic Brain Injury | CDC Injury Center. Published March 21, 2022. Accessed May 9, 2022. https://www.cdc.gov/traumaticbraininjury/data/index.html

118. Bigler E. Traumatic brain injury, neuroimaging, and neurodegeneration. *Frontiers in Human Neuroscience*. 2013;7. Accessed September 18, 2023. https://www.frontiersin.org/articles/10.3389/fnhum.2013.00395

119. Elman JA, Puckett OK, Hagler DJ Jr, Pearce RC, Fennema-Notestine C, Hatton SN, Lyons MJ, McEvoy LK, Panizzon MS, Reas ET, Dale AM, Franz CE, Kremen WS. Associations between MRI-assessed locus coeruleus integrity and cortical gray matter microstructure. *Cerebral Cortex*. 2022;32(19):4191-4203. doi:10.1093/cercor/bhab475

120. Fennema-Notestine C, McEvoy LK, Notestine R, Panizzon MS, Yau WYW, Franz CE, Lyons MJ, Eyler LT, Neale MC, Xian H, McKenzie RE, Kremen WS. White matter disease in midlife is heritable, related to hypertension, and shares some genetic influence with systolic blood pressure. *Neuroimage Clin*. 2016;12:737-745. doi:10.1016/j.nicl.2016.10.001

121. Fischl B. FreeSurfer. *NeuroImage*. 2012;62(2):774-781. doi:10.1016/j.neuroimage.2012.01.021

122. Liem F, Varoquaux G, Kynast J, Beyer F, Kharabian Masouleh S, Huntenburg JM, Lampe L, Rahim M, Abraham A, Craddock RC, Riedel-Heller S, Luck T, Loeffler M, Schroeter ML, Witte AV, Villringer A, Margulies DS. Predicting brain-age from multimodal imaging data captures cognitive impairment. *NeuroImage*. 2017;148:179-188. doi:10.1016/j.neuroimage.2016.11.005

123. Hatton SN, Franz CE, Elman JA, Panizzon MS, Hagler DJ, Fennema-Notestine C, Eyler LT, McEvoy LK, Lyons MJ, Dale AM, Kremen WS. Negative fateful life events in midlife and advanced predicted brain aging. *Neurobiology of Aging*. 2018;67:1-9. doi:10.1016/j.neurobiolaging.2018.03.004

124. Whitsel N, Reynolds CA, Buchholz EJ, Pahlen S, Pearce RC, Hatton SN, Elman JA, Gillespie NA, Gustavson DE, Puckett OK, Dale AM, Eyler LT, Fennema-Notestine C, Hagler Jr DJ, Hauger RL, McEvoy LK, McKenzie R, Neale MC, Panizzon MS, Sanderson-Cimino M, Toomey R, Tu XM, Williams MKE, Bell T, Xian H, Lyons MJ, Kremen WS, Franz CE. Long-term associations of cigarette smoking in early mid-life with predicted brain aging from mid- to late life. *Addiction*. 2022;117(4):1049-1059. doi:10.1111/add.15710

125. de Lange AMG, Cole JH. Commentary: Correction procedures in brain-age prediction. *Neuroimage Clin*. 2020;26:102229. doi:10.1016/j.nicl.2020.102229

126. Avants BB, Tustison NJ, Stauffer M, Song G, Wu B, Gee JC. The Insight ToolKit image registration framework. *Front Neuroinform*. 2014;8:44. doi:10.3389/fninf.2014.00044

127. Scott DW. Parametric statistical modeling by minimum integrated square error. *Technometrics*. 2001;43(3):274-285. doi:10.1198/004017001316975880

128. Yoo TS, Ackerman MJ, Lorensen WE, Schroeder W, Chalana V, Aylward S, Metaxas D, Whitaker R. Engineering and algorithm design for an image processing Api: a technical report on ITK--the Insight Toolkit. *Stud Health Technol Inform*. 2002;85:586-592.

129. Elman JA, Panizzon MS, Hagler DJ, Fennema-Notestine C, Eyler LT, Gillespie NA, Neale MC, Lyons MJ, Franz CE, McEvoy LK, Dale AM, Kremen WS. Genetic and environmental influences on cortical mean diffusivity. *NeuroImage*. 2017;146:90-99. doi:10.1016/j.neuroimage.2016.11.032

130. Zhuang J, Hrabe J, Kangarlu A, Xu D, Bansal R, Branch CA, Peterson BS. Correction of eddy-current distortions in diffusion tensor images using the known directions and strengths of diffusion gradients. *Journal of Magnetic Resonance Imaging*. 2006;24(5):1188-1193. doi:10.1002/jmri.20727

131. Hagler Jr. DJ, Ahmadi ME, Kuperman J, Holland D, McDonald CR, Halgren E, Dale AM. Automated white-matter tractography using a probabilistic diffusion tensor atlas: Application to temporal lobe epilepsy. *Human Brain Mapping*. 2009;30(5):1535-1547. doi:10.1002/hbm.20619

132. Chang H, Fitzpatrick JM. A technique for accurate magnetic resonance imaging in the presence of field inhomogeneities. *IEEE Transactions on Medical Imaging*. 1992;11(3):319-329. doi:10.1109/42.158935

133. Morgan PS, Bowtell RW, McIntyre DJO, Worthington BS. Correction of spatial distortion in EPI due to inhomogeneous static magnetic fields using the reversed gradient method. *Journal of Magnetic Resonance Imaging*. 2004;19(4):499-507. doi:10.1002/jmri.20032

134. Holland D, Kuperman JM, Dale AM. Efficient correction of inhomogeneous static magnetic field-induced distortion in Echo Planar Imaging. *NeuroImage*. 2010;50(1):175-183. doi:10.1016/j.neuroimage.2009.11.044

135. Jovicich J, Czanner S, Greve D, Haley E, van der Kouwe A, Gollub R, Kennedy D, Schmitt F, Brown G, MacFall J, Fischl B, Dale A. Reliability in multi-site structural MRI studies: Effects of gradient non-linearity correction on phantom and human data. *NeuroImage*. 2006;30(2):436-443. doi:10.1016/j.neuroimage.2005.09.046

136. NeuroImaging Tools and Resources Collaboratory: AtlasTrack Fiber Tract Atlas. Accessed November 8, 2023. https://www.nitrc.org/projects/atlastrack/

137. White NS, Leergaard TB, D'Arceuil H, Bjaalie JG, Dale AM. Probing tissue microstructure with restriction spectrum imaging: Histological and theoretical validation. *Hum Brain Mapp*. 2013;34(2):327-346. doi:10.1002/hbm.21454

138. White NS, McDonald CR, Farid N, Kuperman JM, Kesari S, Dale AM. Improved Conspicuity and Delineation of High-Grade Primary and Metastatic Brain Tumors Using "Restriction Spectrum Imaging": Quantitative Comparison with High B-Value DWI and ADC. *AJNR Am J Neuroradiol*. 2013;34(5):958-964. doi:10.3174/ajnr.A3327

139. White NS, McDonald C, McDonald CR, Farid N, Kuperman J, Karow D, Schenker-Ahmed NM, Bartsch H, Rakow-Penner R, Holland D, Shabaik A, Bjørnerud A, Hope T, Hattangadi-Gluth J, Liss M, Parsons JK, Chen CC, Raman S, Margolis D, Reiter RE, Marks L, Kesari S, Mundt AJ, Kane CJ, Kaine CJ, Carter BS, Bradley WG, Dale AM. Diffusion-weighted imaging in cancer: physical foundations and applications of restriction spectrum imaging. *Cancer Res*. 2014;74(17):4638-4652. doi:10.1158/0008-5472.CAN-13-3534

140. Blanchard EB, Jones-Alexander J, Buckley TC, Forneris CA. Psychometric properties of the PTSD checklist (PCL). *Behaviour Research and Therapy*. 1996;34(8):669-673. doi:10.1016/0005-7967(96)00033-2

141. Li J, Ji L. Adjusting multiple testing in multilocus analyses using the eigenvalues of a correlation matrix. *Heredity*. 2005;95(3):221-227. doi:10.1038/sj.hdy.6800717

142. Herbet G, Zemmoura I, Duffau H. Functional Anatomy of the Inferior Longitudinal Fasciculus: From Historical Reports to Current Hypotheses. *Frontiers in Neuroanatomy*. 2018;12. Accessed September 19, 2023. https://www.frontiersin.org/articles/10.3389/fnana.2018.00077

143. Conner AK, Briggs RG, Sali G, Rahimi M, Baker CM, Burks JD, Glenn CA, Battiste JD, Sughrue ME. A connectomic atlas of the human cerebrum—chapter 13: tractographic description of the inferior fronto-occipital fasciculus. *Oper Neurosurg (Hagerstown)*. 2018;15(Suppl 1):S436-S443. doi:10.1093/ons/opy267

144. Gustavson DE, Archer DB, Elman JA, Puckett OK, Fennema-Notestine C, Panizzon MS, Shashikumar N, Hohman TJ, Jefferson AL, Eyler LT, McEvoy LK, Lyons MJ, Franz CE, Kremen WS. Associations among executive function abilities, free water, and white matter microstructure in early old age. *Neuroimage Clin*. 2023;37:103279. doi:10.1016/j.nicl.2022.103279

145. Sasson E, Doniger GM, Pasternak O, Tarrasch R, Assaf Y. White matter correlates of cognitive domains in normal aging with diffusion tensor imaging. *Front Neurosci*. 2013;7:32. doi:10.3389/fnins.2013.00032

146. Rogers JM, Read CA. Psychiatric comorbidity following traumatic brain injury. *Brain Injury*. 2007;21(13-14):1321-1333. doi:10.1080/02699050701765700

147. Stein MB, Jain S, Giacino JT, Levin H, Dikmen S, Nelson LD, Vassar MJ, Okonkwo DO, Diaz-Arrastia R, Robertson CS, Mukherjee P, McCrea M, Mac Donald CL, Yue JK, Yuh E, Sun X, Campbell-Sills L, Temkin N, Manley GT, TRACK-TBI Investigators, Adeoye O, Badjatia N, Boase K, Bodien Y, Bullock MR, Chesnut R, Corrigan JD, Crawford K, Diaz-Arrastia R, Dikmen S, Duhaime AC, Ellenbogen R, Feeser VR, Ferguson A, Foreman B, Gardner R, Gaudette E, Giacino JT, Gonzalez L, Gopinath S, Gullapalli R, Hemphill JC, Hotz G, Jain S, Korley F, Kramer J, Kreitzer N, Levin H, Lindsell C, Machamer J, Madden C, Martin A, McAllister T, McCrea M, Merchant R, Mukherjee P, Nelson LD, Noel F, Okonkwo DO, Palacios E, Perl D, Puccio A, Rabinowitz M, Robertson CS, Rosand J, Sander A, Satris G, Schnyer D, Seabury S, Sherer M, Stein MB,

Taylor S, Toga A, Temkin N, Valadka A, Vassar MJ, Vespa P, Wang K, Yue JK, Yuh E, Zafonte R. Risk of Posttraumatic Stress Disorder and Major Depression in Civilian Patients After Mild Traumatic Brain Injury: A TRACK-TBI Study. *JAMA Psychiatry*. 2019;76(3):249-258. doi:10.1001/jamapsychiatry.2018.4288

148. Enache D, Winblad B, Aarsland D. Depression in dementia: epidemiology, mechanisms, and treatment. *Current Opinion in Psychiatry*. 2011;24(6):461-472. doi:10.1097/YCO.0b013e32834bb9d4

149. Berkman LF, Syme SL. Social networks, host resistance, and mortality: a nine-year follow-up study of Alameda County residents. *Am J Epidemiol*. 1979;109(2):186-204. doi:10.1093/oxfordjournals.aje.a112674

150. Bath PA, Deeg D. Social engagement and health outcomes among older people: introduction to a special section. *Eur J Ageing*. 2005;2(1):24-30. doi:10.1007/s10433-005-0019-4

151. Penninkilampi R, Casey AN, Singh MF, Brodaty H. The association between social engagement, loneliness, and risk of dementia: a systematic review and meta-analysis. Published online 2018. doi:10.3233/JAD-180439

152. Barrett-Connor E. The Rancho Bernardo Study: 40 years studying why women have less heart disease than men and how diabetes modifies women's usual cardiac protection. *Glob Heart*. 2013;8(2):10.1016/j.gheart.2012.12.002. doi:10.1016/j.gheart.2012.12.002

153. Folstein MF, Folstein SE, McHugh PR. "Mini-mental state": a practical method for grading the cognitive state of patients for the clinician. *Journal of Psychiatric Research*. 1975;12(3):189-198. doi:10.1016/0022-3956(75)90026-6

154. Teng EL, Chui HC. The Modified Mini-Mental State (3MS) examination. *Journal of Clinical Psychiatry*. 1987;48(8):314-318.

155. Tombaugh TN, McIntyre NJ. The mini-mental state examination: a comprehensive review. *J Am Geriatr Soc*. 1992;40(9):922-935. doi:10.1111/j.1532-5415.1992.tb01992.x

156. Reitan RM. Validity of the Trail Making Test as an Indicator of Organic Brain Damage. *Percept Mot Skills*. 1958;8(3):271-276. doi:10.2466/pms.1958.8.3.271

157. Butters N, Granholm E, Salmon DP, Grant I, Wolfe J. Episodic and semantic memory: A comparison of amnesic and demented patients. *Journal of Clinical and Experimental Neuropsychology*. 1987;9(5):479-497. doi:10.1080/01688638708410764

158. Bunn F, Burn AM, Goodman C, Rait G, Norton S, Robinson L, Schoeman J, Brayne C. Comorbidity and dementia: a scoping review of the literature. *BMC Med*. 2014;12:192. doi:10.1186/s12916-014-0192-4

159. Expert Panel on Detection E and Treatment of High Blood Cholesterol in Adults. Executive Summary of the Third Report of the National Cholesterol Education Program

(NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). *JAMA*. 2001;285(19):2486-2497. doi:10.1001/jama.285.19.2486

160. Alattar AA, Bergstrom J, Laughlin GA, Kritz-Silverstein D, Richard EL, Reas ET, Harris JP, Barrett-Connor E, McEvoy LK. Hearing Impairment and Cognitive Decline in Older, Community-Dwelling Adults. *The Journals of Gerontology: Series A*. 2020;75(3):567-573. doi:10.1093/GERONA/GLZ035

161. Loucks EB, Sullivan LM, D'Agostino Sr RB, Larson MG, Berkman LF, Benjamin EJ. Social networks and inflammatory markers in the Framingham Heart Study. *J Biosoc Sci*. 2006;38(6):835-842. doi:10.1017/S0021932005001203

162. Reas ET, Laughlin GA, Bergstrom J, Kritz-Silverstein D, Barrett-Connor E, Mcevoy LK. Effects of Sex and Education on Cognitive Change Over a 27-Year Period in Older Adults: The Rancho Bernardo Study HHS Public Access. *Am J Geriatr Psychiatry*. 2017;25(8):889-899. doi:10.1016/j.jagp.2017.03.008

163. Little RJA, Rubin DB. *Statistical Analysis with Missing Data*. 3rd ed. John Wiley & Sons; 2019.

164. Sommerlad A, Ruegger J, Singh-Manoux A, Lewis G, Livingston G. Marriage and risk of dementia: systematic review and meta-analysis of observational studies. *J Neurol Neurosurg Psychiatry*. 2018;89(3):231-238. doi:10.1136/jnnp-2017-316274

165. Cole SR, Hernán MA. Constructing inverse probability weights for marginal structural models. *Am J Epidemiol*. 2008;168(6):656-664. doi:10.1093/aje/kwn164

166. Hernán MA, Robins JM. *Causal Inference: What If*. Taylor & Francis; 2020.

167. Ibrahim JG, Chu H, Chen LM. Basic concepts and methods for joint models of longitudinal and survival data. *J Clin Oncol*. 2010;28(16):2796-2801. doi:10.1200/JCO.2009.25.0654

168. Rizopoulos D. JM: an R package for the joint modelling of longitudinal and time-to-event data. *Journal of Statistical Software*. 2010;35(9):1-33.

169. Pinheiro J, Bates D, DebRoy S, Sarkar D, R Core Team. nlme: Linear and Nonlinear Mixed Effects Models; R package version 3.1-152. Published online 2021.

170. Therneau TM. A package for survival analysis in R; R package version 3.5-5. Published online 2023. https://CRAN.R-project.org/package=survival

171. Fabbri E, Zoli M, Gonzalez-Freire M, Salive ME, Studenski SA, Ferrucci L. Aging and multimorbidity: new tasks, priorities, and frontiers for integrated gerontological and clinical research. *J Am Med Dir Assoc*. 2015;16(8):640-647. doi:10.1016/j.jamda.2015.03.013

172. Hertzog C, Kramer AF, Wilson RS, Lindenberger U. Enrichment effects on adult cognitive development: can the functional capacity of older adults be preserved and enhanced? *Psychol Sci Public Interest*. 2008;9(1):1-65. doi:10.1111/j.1539-6053.2009.01034.x

173. Sapolsky RM, Krey LC, McEwen BS. The neuroendocrinology of stress and aging: the glucocorticoid cascade hypothesis. *Endocr Rev*. 1986;7(3):284-301. doi:10.1210/edrv-7-3-284

174. Kingston A, Robinson L, Booth H, Knapp M, Jagger C, for the MODEM project. Projections of multi-morbidity in the older population in England to 2035: estimates from the Population Ageing and Care Simulation (PACSim) model. *Age and Ageing*. 2018;47(3):374-380. doi:10.1093/ageing/afx201

175. Gauthier S, Rosa-Neto P, Morais J, Webster C. *World Alzheimer Report 2021: Journey through the Diagnosis of Dementia*.; 2021. https://www.alzint.org/resource/world-alzheimer-report-2021/

176. World Health Organization. *Global Action Plan on the Public Health Response to Dementia 2017–2025*.; 2017. https://www.who.int/publications-detail-redirect/9789241513487

177. Reas ET, Hagler DJ, White NS, Kuperman JM, Bartsch H, Cross K, Loi RQ, Balachandra AR, Meloy MJ, Wierenga CE, Galasko D, Brewer JB, Dale AM, McEvoy LK. Sensitivity of restriction spectrum imaging to memory and neuropathology in Alzheimer's disease. *Alzheimers Res Ther*. 2017;9(1):55. doi:10.1186/s13195-017-0281-7

178. Hoagey DA, Lazarus LTT, Rodrigue KM, Kennedy KM. The effect of vascular health factors on white matter microstructure mediates age-related differences in executive function performance. *Cortex*. 2021;141:403-420. doi:10.1016/j.cortex.2021.04.016

179. Gunning-Dixon FM, Brickman AM, Cheng JC, Alexopoulos GS. Aging of cerebral white matter: a review of MRI findings. *International journal of geriatric psychiatry*. 2009;24(2):109. doi:10.1002/gps.2087

180. Gu L, Li J, Feng DF, Cheng ET, Li DC, Yang XQ, Wang BC. Detection of white matter lesions in the acute stage of diffuse axonal injury predicts long-term cognitive impairments: a clinical diffusion tensor imaging study. *J Trauma Acute Care Surg*. 2013;74(1):242-247. doi:10.1097/TA.0b013e3182684fe8

181. Sen N. An insight into the vision impairment following traumatic brain injury. *Neurochemistry International*. 2017;111:103-107. doi:10.1016/j.neuint.2017.01.019

182. Voss JD, Connolly J, Schwab KA, Scher AI. Update on the epidemiology of concussion/mild traumatic brain injury. *Curr Pain Headache Rep*. 2015;19(7):32. doi:10.1007/s11916-015-0506-z

183. Mayeda ER, Glymour MM, Quesenberry CP, Whitmer RA. Inequalities in dementia incidence between six racial and ethnic groups over 14 years. *Alzheimers Dement*. 2016;12(3):216-224. doi:10.1016/j.jalz.2015.12.007

184. Gupte R, Brooks W, Vukas R, Pierce J, Harris J. Sex differences in traumatic brain injury: what we know and what we should know. *J Neurotrauma*. 2019;36(22):3063-3091. doi:10.1089/neu.2018.6171

185. VanderWeele TJ. Mediation analysis: a practitioner's guide. *Annual Review of Public Health*. 2016;37:17-32. doi:10.1146/annurev-publhealth-032315-021402