

Updates on the Relationship between Traumatic Brain Injury and Dementia

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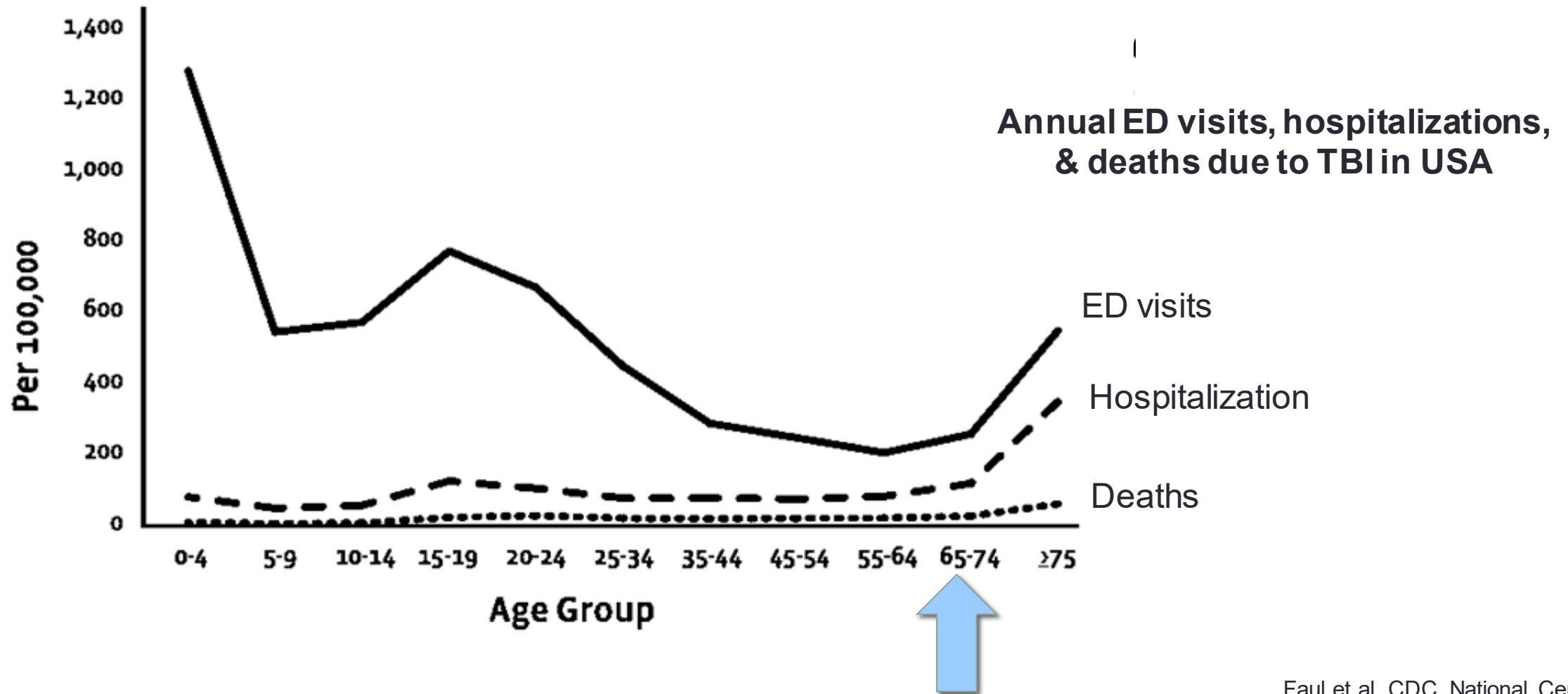
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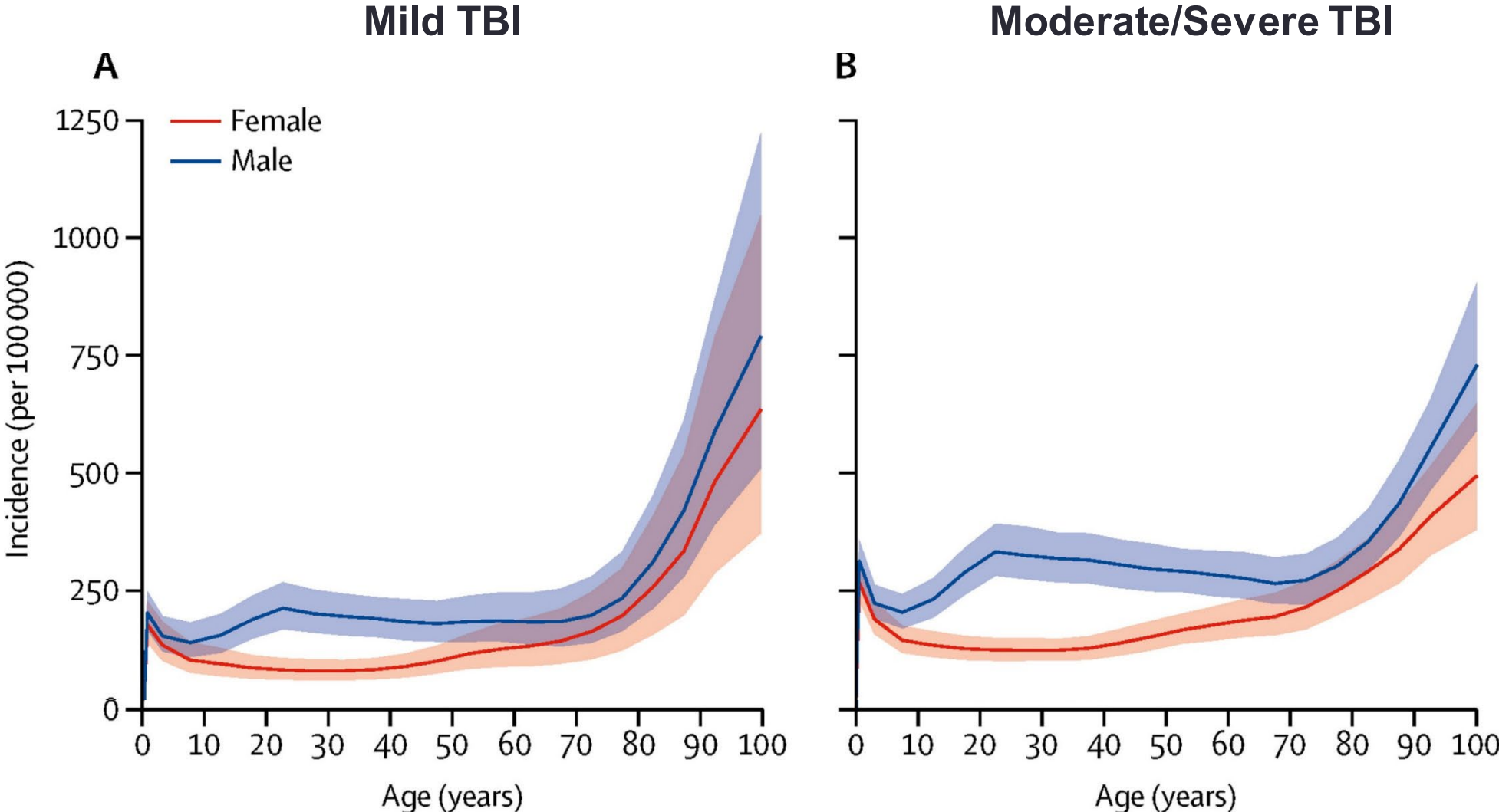


TBI is Common in Older Adults

LATE LIFE PEAK IN TBI INCIDENCE



Global Incidence of TBI in Men and Women



GBD 2016 Traumatic Brain Injury and Spinal Cord Injury Collaborators, *The Lancet Neurology*, 2019.

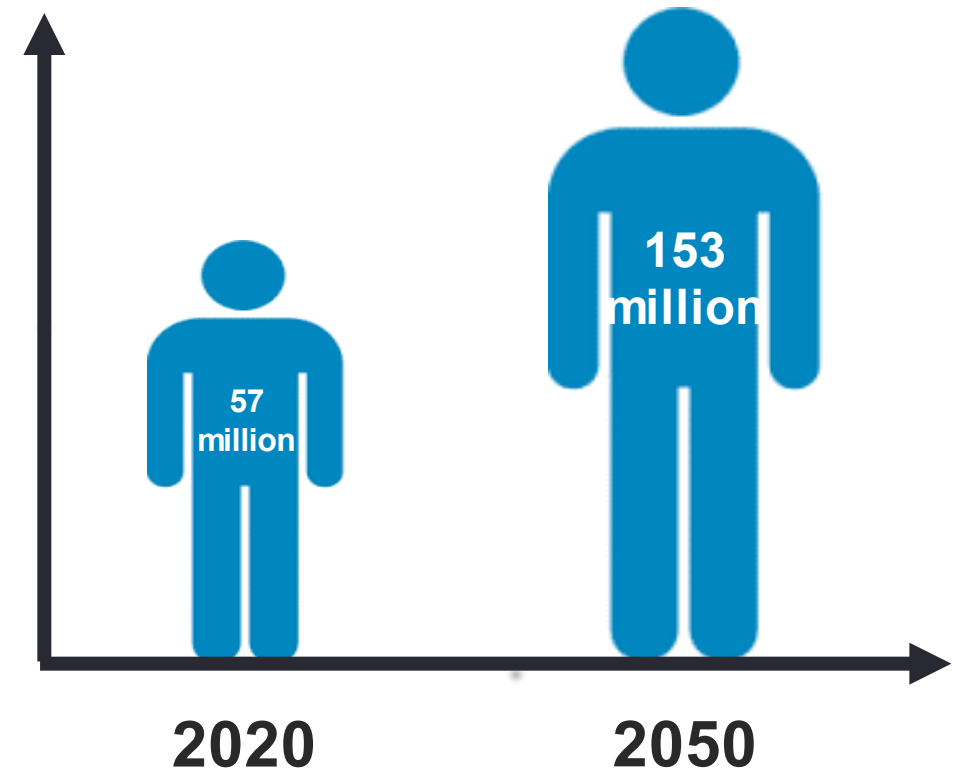
TBI Leads to Poor Outcomes, Especially in Older Adults

- Older adults, who are at high risk of TBI, often have poor outcomes
- Outcomes are complicated by pre-existing medical comorbidities
- Studies have shown an increased risk of neurological and psychological disorders, including dementia

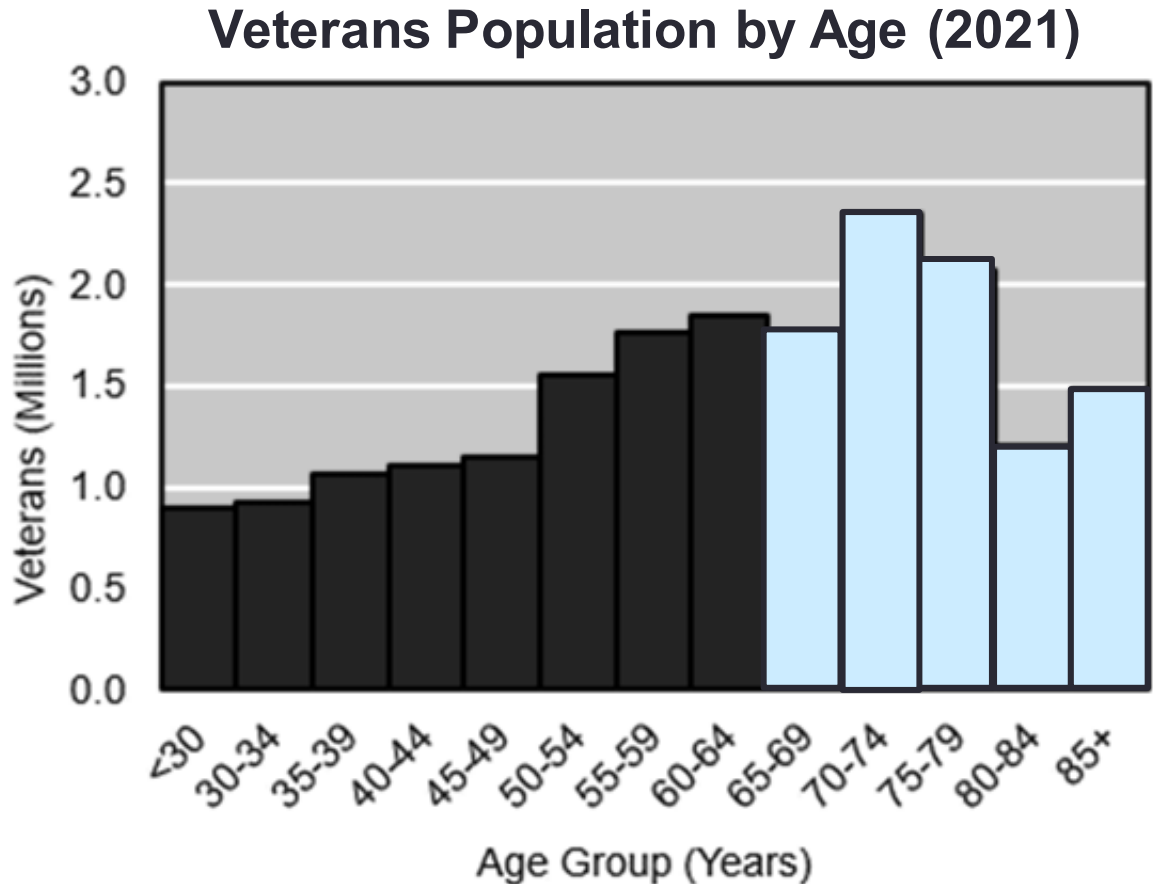
Dementia Prevalence is an Increasing Problem

- Dementia prevalence increasing with aging population
- Risk driven by age, genetics, and risk factors
- Multiple types of dementia
 - Alzheimer's Disease (~60%)
 - Vascular (15%)
 - Mixed (10%)
 - Others (Frontotemporal, Lewy Body, etc.)

Prevalence Projected to Triple Worldwide



U.S. Veteran Population is Aging



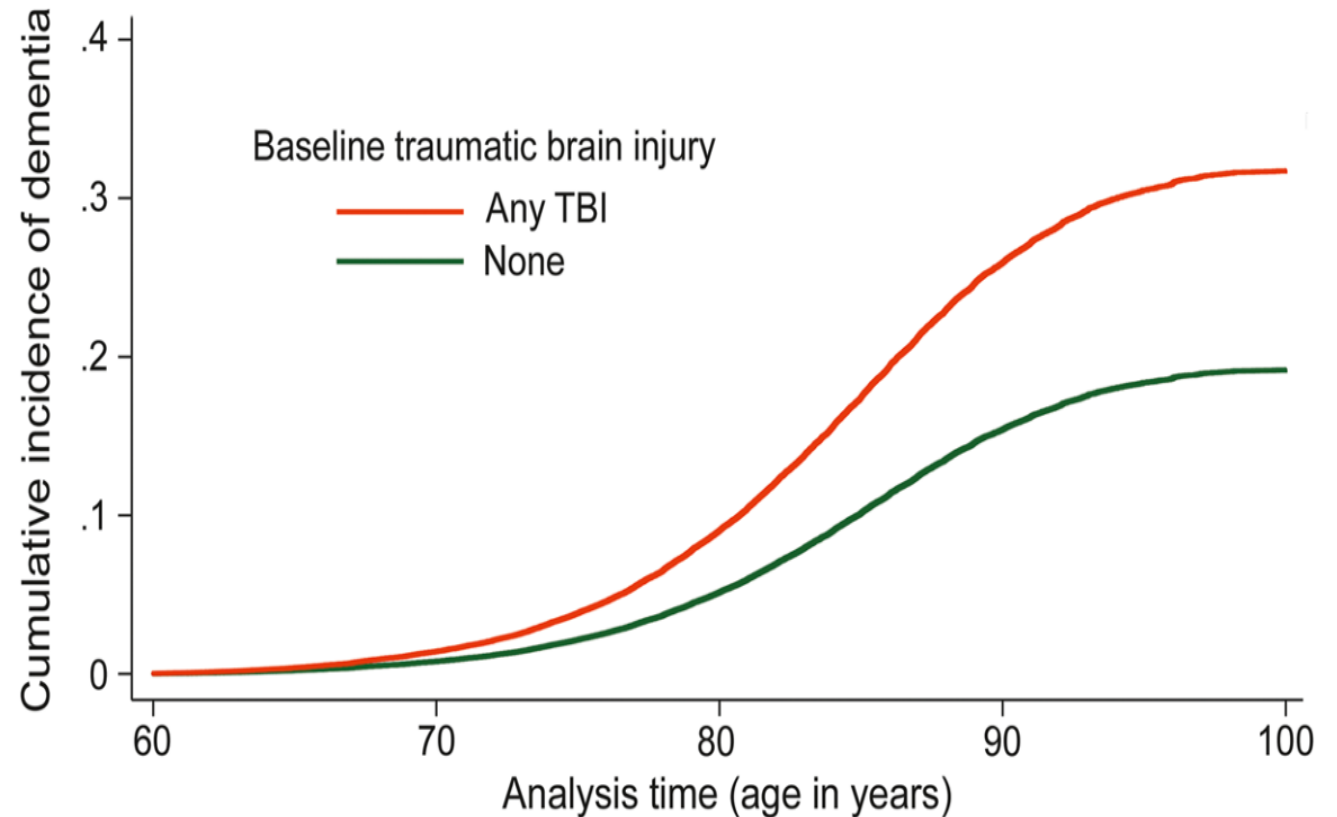
- The Veteran population is aging; almost 50% of Veterans are older than 65
- Veterans are at risk of dementia like older adults in the general population
- Veterans also face a unique set of military risk factors for dementia
- An estimated half a million veterans have Alzheimer's disease (AD)

Veterans: TBI & Dementia

- Military service increases risk of TBI; 15-20% of deployed service members report at least 1 TBI
- Veterans also incur more TBIs than non-Veterans during civilian life
- As the Veteran population ages, with higher prevalence of TBI and military risk factors, they are at increased risk of dementia and other long-term outcomes

60% Increased Risk of Dementia in Veterans with TBI

- We studied 188,764 Veterans
- All ≥ 55 years old and without dementia
- Around 1% had TBI diagnosis (ICD-9) during 3-year baseline
- Dementia diagnoses (ICD-9) over 9 years of follow-up

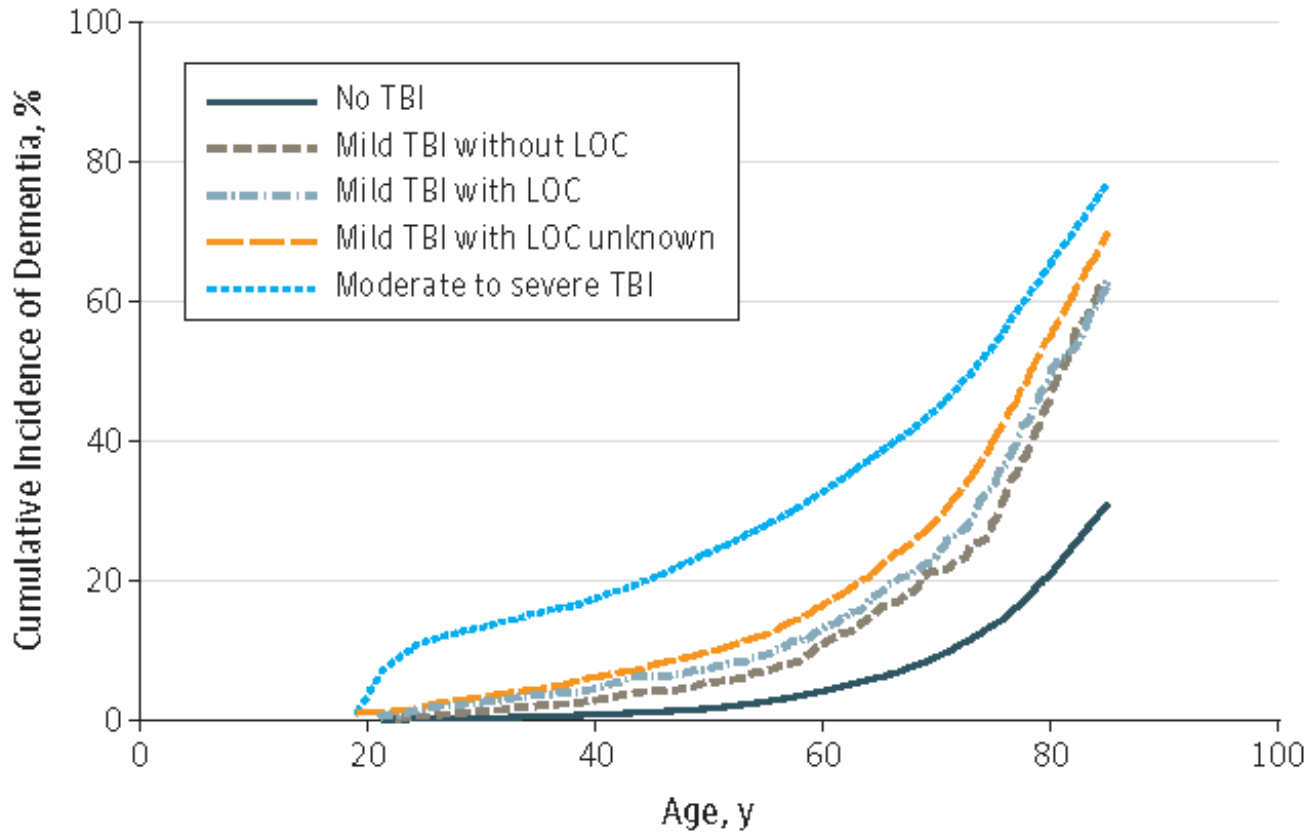


Adjusted HR:1.57; 95% CI (1.35–1.83)

Mild TBI & Dementia Risk in U.S. Veterans

- 357,558 Veterans ≥ 55 years old and dementia free
- 178,779 Veterans with TBI and propensity-matched comparison sample of 178,779 Veterans without TBI
- TBI diagnosis from Comprehensive Traumatic Brain Injury database or ICD-9 codes using Defense and Veterans Brain Injury Center 2012 Criteria
- Severity classified as none, mild, moderate, or severe
- mTBI categorized as without LOC, with LOC (≤ 30 min), or LOC status unknown
- Dementia diagnosis by ICD-9 codes

Mild TBI Even Without LOC Increases Risk of Dementia



Adjusted for demographic, medical conditions, and psychiatric disorders

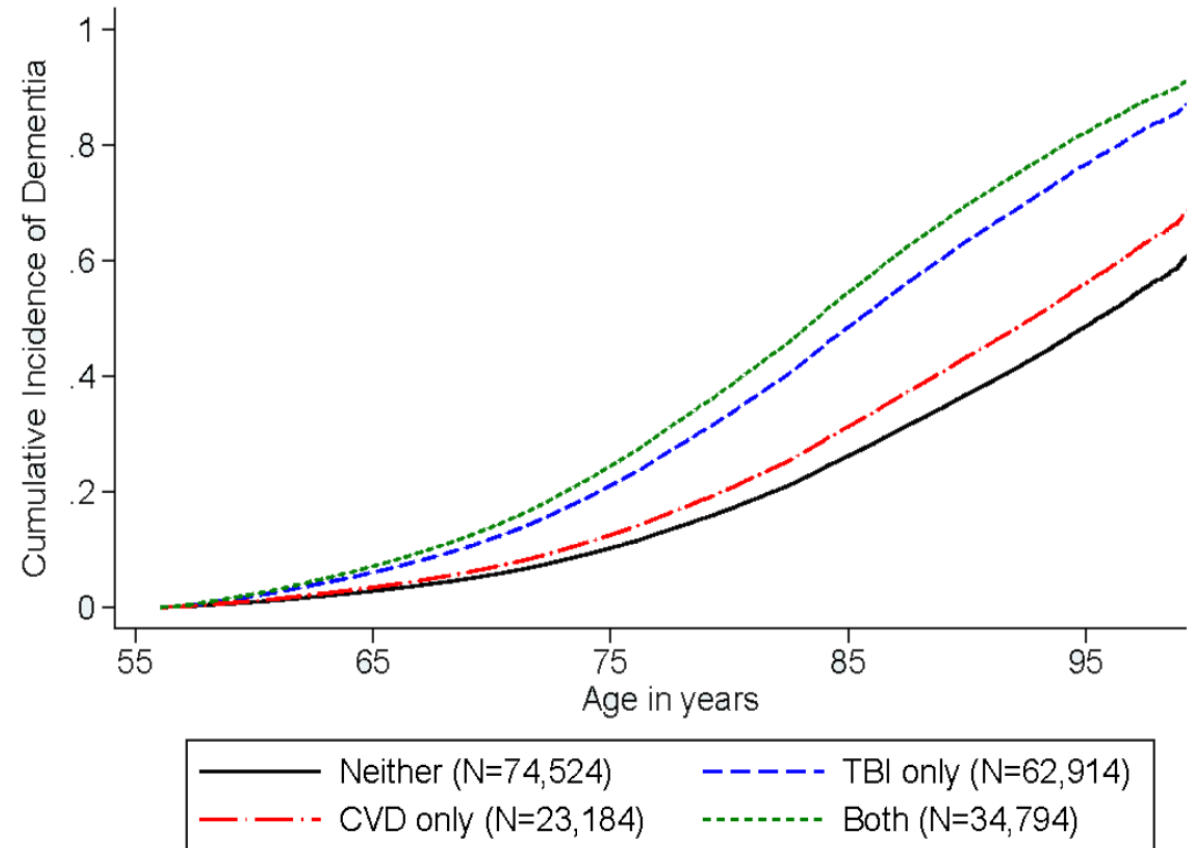
TBI Severity	Adjusted Hazard Ratios of Dementia (95% CI)
No TBI	Ref
Mild TBI, without LOC	2.36 (2.10, 2.66)
Mild TBI, with LOC	2.51 (2.29, 2.76)
Mild TBI, LOC unknown	3.19 (3.05, 3.33)
Moderate/Severe TBI	3.77 (3.63, 3.91)

TBI and Risk of Dementia: Effects of Comorbid CVD

- TBI is associated with elevated rates of cardiovascular disease (CVD)
- CVD and TBI are both important risk factors for dementia; however, little is known about how (or if) they interact
- Age, sex, and race-matched sample of Veterans aged 55+ with and without TBI (mean age=67 years), with no dementia at baseline
 - N=195,416 per group
 - At least 1 year of follow-up; average=6.6 years

TBI and Risk of Dementia: Effects of Comorbid CVD

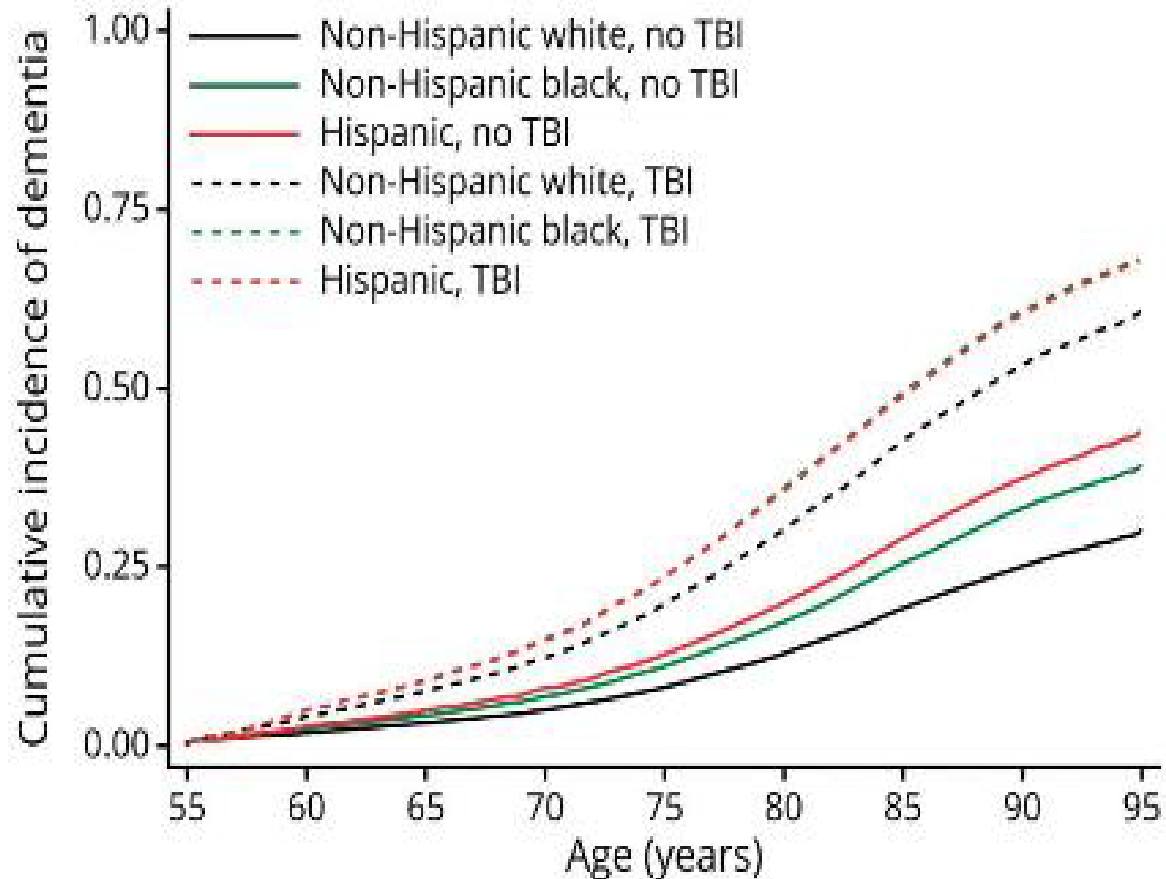
- CVD and cardiovascular risk factors are more prevalent in people with TBI
- Risk of dementia:
TBI only: HR=2.35 (2.26-2.43)
CVD only: HR=1.26 (1.20-1.33)
TBI + CVD : HR=2.83 (2.72-2.94)
- Additive effect between TBI and CVD; no interaction
- More research is needed to determine causal links among CVD, TBI, and dementia



TBI and Risk of Dementia: Disparities by Race

- Studies, including some of our own, found race differences in dementia incidence, but is the same true in dementia after TBI?
- We investigated incident dementia with TBI exposure by race
 - 1 million Veterans aged 55+ with data from 2001-2015; prevalent dementia excluded
 - 82% White, 12% Black, and 1% Hispanic
 - 96,178 with TBI
 - Fine-Gray regression models, adjusted for demographics and comorbid conditions

TBI and Risk of Dementia: Disparities by Race



HR of Dementia (95% CI) TBI vs no TBI	
Non-Hispanic White	2.71 (2.64, 2.77)
Non-Hispanic Black	2.15 (2.02, 2.30)
Hispanic	1.74 (1.51, 2.01)

- Findings may be due to differences in dementia risk, diagnosis rates, or an effect of differences in APOE
- Racial differences are a novel and important finding that deserve future study

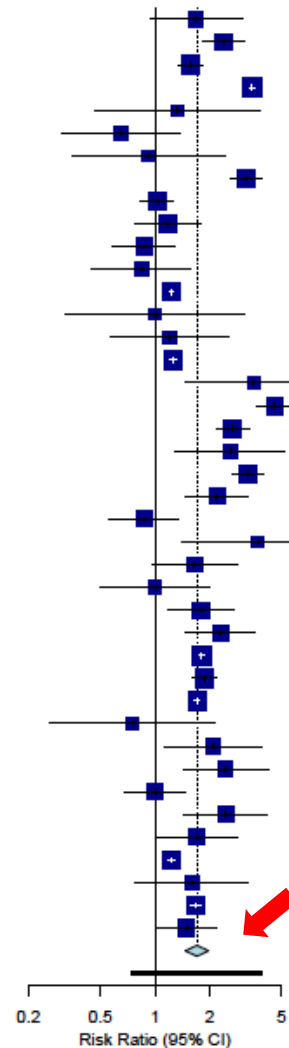
Meta-analysis of Dementia Associated with TBI

- Our studies and others find TBI as a risk factor for dementia, but the magnitude of risk is variable across studies
- We conducted a systematic review and meta-analysis of risk of all-cause dementia after all-severity TBI
- 32 studies met inclusion criteria. Data were pooled using random effects models

Systematic review and meta-analysis of dementia associated with TBI

Source	RR (95% CI)
Abner et al. 2014	1.89 [0.94; 3.03]
Bachman et al. 2003	2.40 [1.83; 3.15]
Barnes et al. 2014	1.57 [1.35; 1.83]
Barnes et al. 2018	3.45 [3.33; 3.57]
Broe et al. 1990	1.33 [0.46; 3.84]
Cations et al. 2018a (mild TBI)	0.65 [0.31; 1.37]
Cations et al. 2018b (moderate and severe TBI)	0.92 [0.35; 2.43]
Chu et al. 2016	3.21 [2.65; 3.89]
Crane et al. 2016a (ACT: LOC < 1 hr)	1.03 [0.83; 1.27]
Crane et al. 2016b (ACT: LOC > 1hr)	1.18 [0.78; 1.79]
Crane et al. 2016c (ROS: LOC < 1hr)	0.87 [0.58; 1.30]
Crane et al. 2016d (ROS: LOC > 1hr)	0.84 [0.44; 1.59]
Fann et al. 2018	1.24 [1.21; 1.27]
Ferini Strabi et al. 1990	1.00 [0.32; 3.11]
Forester et al. 1995	1.20 [0.57; 2.54]
Gardner et al. 2014	1.26 [1.21; 1.32]
Graves et al. 1990	3.50 [1.49; 8.23]
Guo et al. 2000a (probands)	4.80 [3.84; 5.81]
Guo et al. 2000b (parent and siblings)	2.70 [2.20; 3.31]
Guo et al. 2000c (spouses)	2.80 [1.30; 5.20]
Lee et al. 2013	3.26 [2.69; 3.95]
Lin et al. 2017	2.20 [1.48; 3.27]
Lindsay et al. 2002	0.87 [0.56; 1.38]
Mayeux et al. 1993	3.70 [1.41; 9.74]
McDowell et al. 1994	1.86 [0.97; 2.84]
Mehta et al. 1999	1.00 [0.50; 2.00]
Nordstrom et al. 2014a (mild TBI)	1.80 [1.18; 2.75]
Nordstrom et al. 2014b (severe TBI)	2.30 [1.48; 3.58]
Nordstrom et al. 2018a (cohort)	1.81 [1.76; 1.87]
Nordstrom et al. 2018b (sibling pairs)	1.89 [1.61; 2.21]
Nordstrom et al. 2018bc (case control)	1.71 [1.66; 1.76]
Ogunniyi et al. 2006 (U.S. Cohort)	0.75 [0.26; 2.15]
Omeara et al 1997	2.10 [1.13; 3.90]
Plassman et al. 2000	2.46 [1.43; 4.24]
Rippon et al. 2006	1.00 [0.68; 1.48]
Salib et al. 1997	2.46 [1.45; 4.18]
Suhanov et al. 2006	1.70 [1.02; 2.84]
Tolppanen et al. 2017	1.23 [1.18; 1.29]
Van Duijn et al. 1992	1.80 [0.78; 3.30]
Wang et al. 2012	1.88 [1.57; 1.80]
Yaffe et al. 2019	1.49 [1.01; 2.20]
Total	1.71 [1.47; 1.98]
95% PI	[0.74; 3.92]

Heterogeneity: $\chi^2_{40} = 2898.83$ ($P = 0$), $I^2 = 99\%$



70% increased risk for all-cause dementia

- Search window 1/1990-1/2019
- 41 risk estimates
- N=7,736,173 individuals

TBI and Cognitive Aging Among Older Veteran Men – A Twin Study Accounting for Genetics and Medical Conditions

- From our recent meta-analysis, TBI increases dementia risk by 70%, but few studies have examined cognitive decline
- We wanted to understand the association between TBI and rate of cognitive decline using Duke Twins Study of Memory in Aging (WWII Veteran male twins born between 1917 and 1927)
- Twin study design accounts for
 - Genetics; monozygotic (MZ) twins share 100% of genes while dizygotic (DZ) share ≈half
 - Early life experiences, such as home environment and socioeconomic status

TBI and Cognitive Aging Among Older Veteran Men – A Twin Study Accounting for Genetics and Medical Conditions

Study Population:

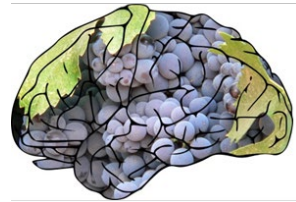
- N = 2,390 twin pairs discordant for TBI (one twin is used as the matched control for the other twin; gives the most control of confounding from genetics and early life shared environmental factors)
- Cognition measured every 3-4 years by Modified Telephone Interview Cognitive Status (TICS-m)
- Self-report of common medical diagnoses, including cardiovascular, neurologic, and psychiatric

TBI and Cognitive Aging Among Older Veteran Men – A Twin Study Accounting for Genetics and Medical Conditions

- Within MZ twin pairs discordant for TBI, >1 TBI and older age of TBI was associated with faster cognitive decline, compared to their co-twin without TBI
- The twin result in MZ pairs is evidence of a causal relationship between TBI and poorer late life cognitive outcomes
- TBI led to faster rates of cognitive decline in late-life, regardless of shared genetics, early-life exposures, and medical conditions

Phenotypes of Cognitive Impairment after TBI in Veterans

- Multiple lines of evidence suggest that TBI increases risk of cognitive decline and dementia in older adulthood
- But is it Alzheimer's disease? Something else?



The BRAVE Study

- Cohort study of 146 older Veterans living in 2 VA retirement homes, half with history of (mostly remote) TBI
- Examined cognitive profile and blood-based biomarkers

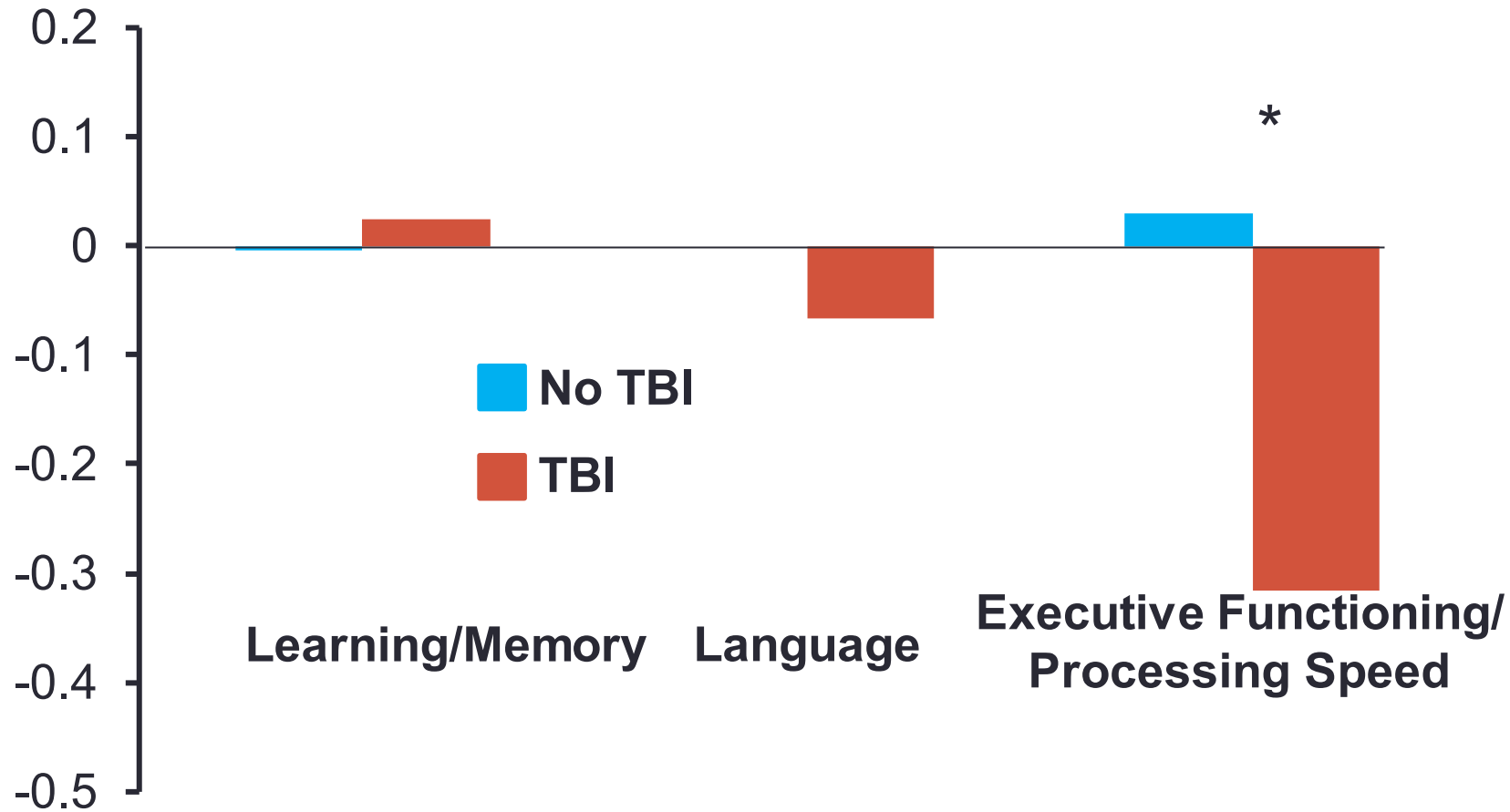


Veterans Home of California
Yountville, CA



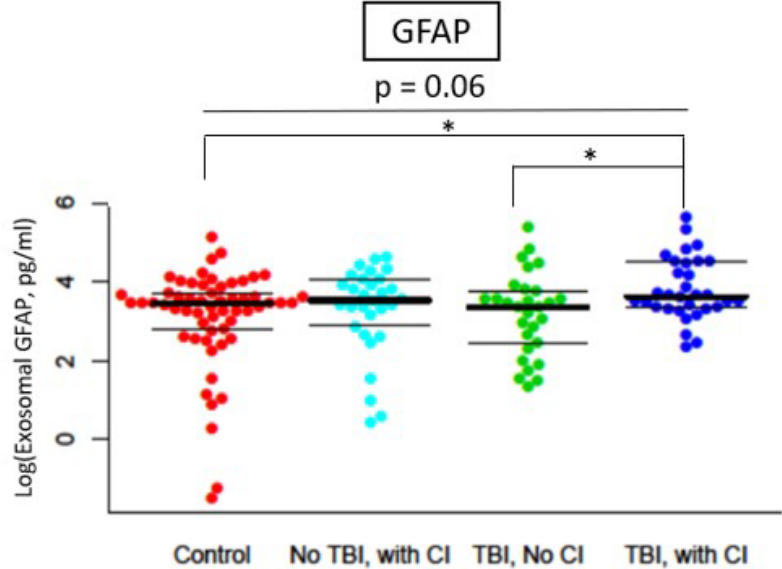
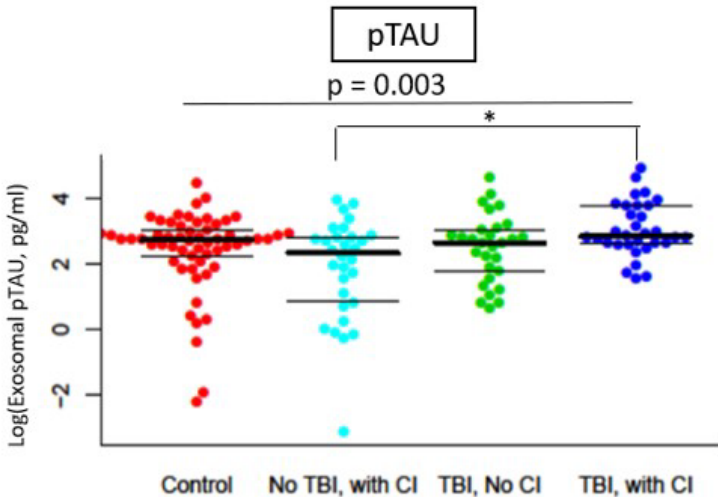
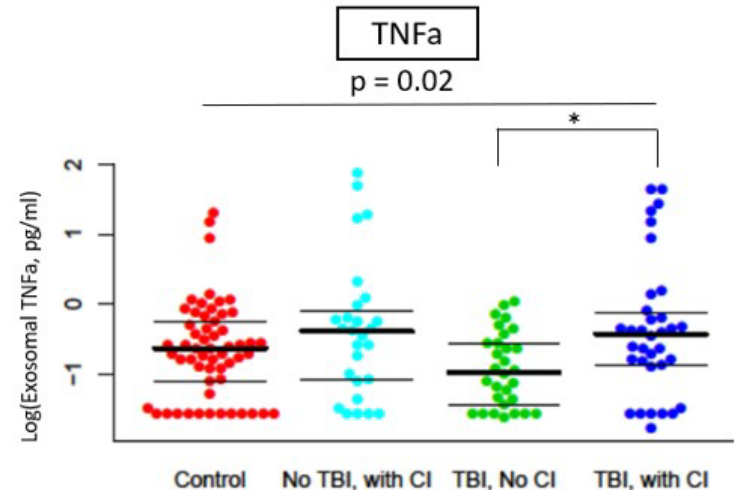
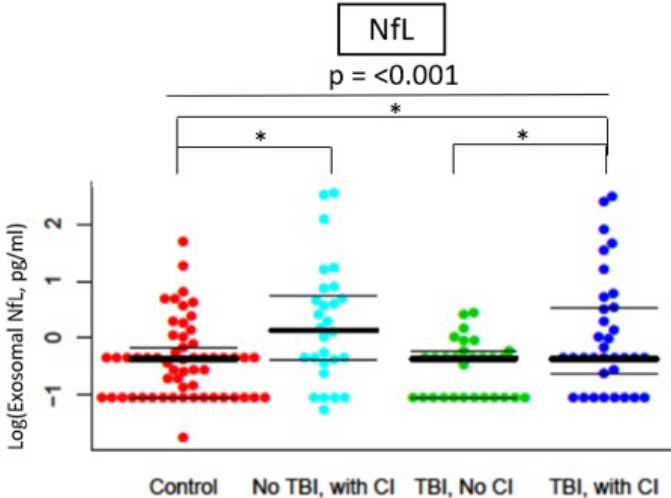
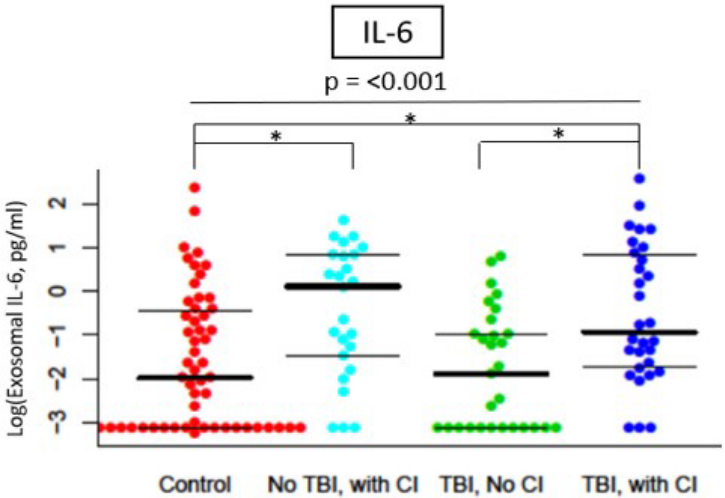
Armed Forces Retirement
Home
Washington, DC

Worse Executive Function in Older Veterans with Remote TBI



* P < 0.05 adjusted for demographics, diabetes, site, substance abuse history, depression symptoms, and PTSD symptoms

Veterans with TBI-CI have higher levels of IL6, NfL, GFAP, and pTAU but not amyloid



Results suggest early neurodegeneration in TBI-CI group

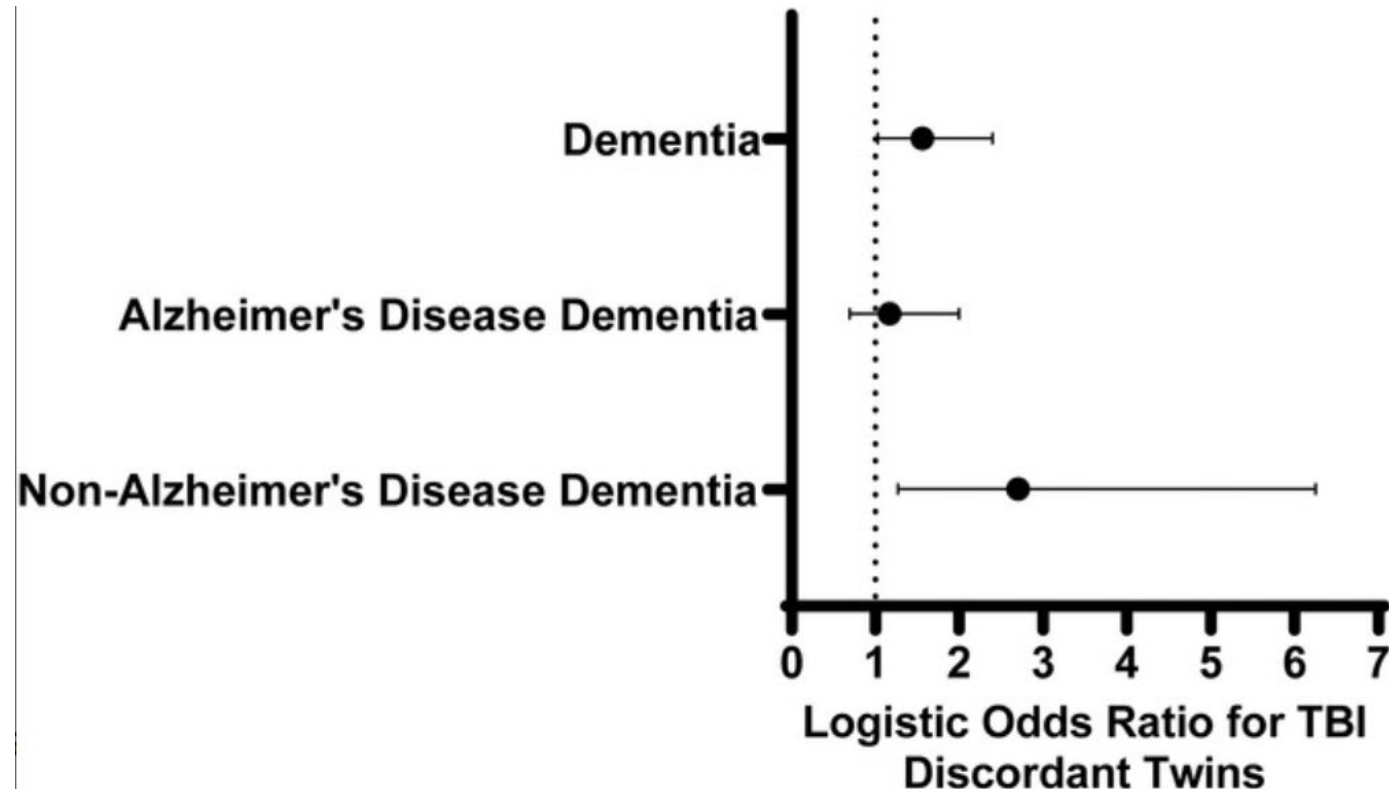
Cognitive Impairment after TBI in Veterans

- In this group of older Veterans, we found that remote TBI was associated with lower executive function, but found no differences in memory or language
- Veterans with TBI had higher levels of inflammatory protein markers and tau, but not amyloid
- Taking the cognitive and biomarker results together, the profile of the cognitive impairment differs from AD

Increasing Evidence Showing Not AD Dementia: A Twins Study of Veterans

In 100 twin pairs discordant for both TBI and onset of dementia:

- Increased risk of all-cause dementia in twin with TBI
OR = 1.56; 95% CI=1.03-2.40
- Mainly due to twin pairs with non-AD dementia
OR = 2.70; 95% CI=1.27-6.25



Summary

- Much of our research focus has been dedicated to Veterans who are at high risk of TBI and dementia
- Our studies show that people with TBI have a 71% higher risk of dementia; this is even true for mild TBI
- Comorbidities, such as CVD, and factors associated with racial differences can increase the risk of dementia after TBI even further
- The twin pair design study, controlling for genetics and early environment, suggests TBI as a causal mechanism

Conclusions

- TBI is a significant risk factor for dementia, particularly in Veteran populations
- Presented evidence that dementia after TBI may be non-AD dementia, which may have implications for prevention or treatment
- Veterans with TBI are an important population to monitor for cognitive decline and future dementia
- Veterans also may be an excellent target for both TBI and dementia prevention

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