Post-TBI Dementia

UCSF x 14 years →

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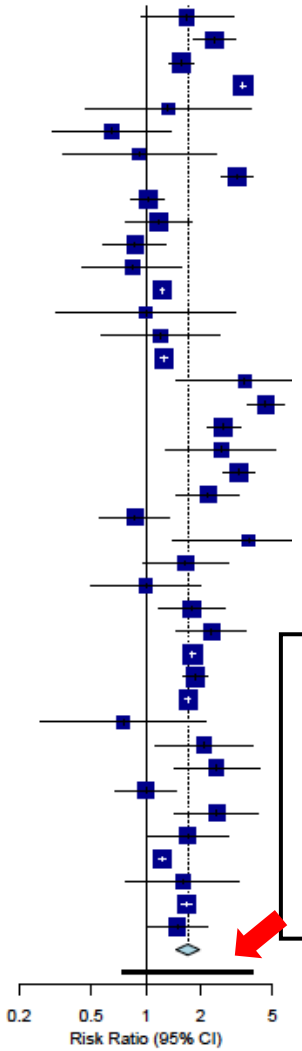
Meta-Analysis: Risk of All-Cause Dementia after TBI

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

Source	RR (95% CI)
Abner et al. 2014	1.69 [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)	4.60 [3.64; 5.81]
Guo et al. 2000b (parent and siblings)	2.70 [2.20; 3.31]
Guo et al. 2000c (spouses)	2.60 [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; 1.36]
Mayeux et al. 1993	3.70 [1.41; 9.74]
McDowell et al. 1994	1.66 [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; 3.56]
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; 1.46]
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	1.60 [0.78; 3.30]
Wang et al. 2012	1.68 [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: χ^2_{40} = 2898.83 (P = 0), I^2 = 99%



71% increased risk for all-cause dementia

Gardner...Yaffe. J Neurotrauma 2022

In U.S. military Veterans Even TBI without LOC associated with increased dementia risk

JAMA Neurology | Original Investigation

Association of Mild Traumatic Brain Injury With and Without Loss of Consciousness With Dementia in US Military Veterans

Deborah E. Barnes, PhD, MPH; Amy L. Byers, PhD, MPH; Raquel C. Gardner, MD; Karen H. Seal, MD, MPH; W. John Boscardin, PhD; Kristine Yaffe, MD

Figure. Cumulative Incidence of Dementia by Traumatic Brain Injury (TBI) Severity

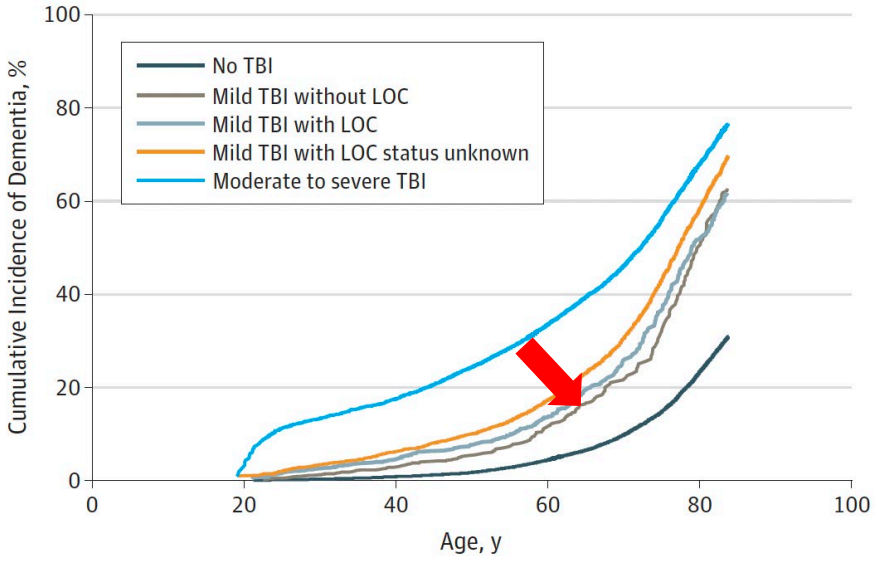


Table 2. Unadjusted and Adjusted Risk of Dementia by Traumatic Brain Injury Severity (N = 357 558)

Model	Individuals Without TBI (n = 178 779)	Individuals With ≥1 TBI (n = 178 779)	Participant Group, Hazard Ratio (95% CI)[a]			
			Mild TBI Without LOC (n = 17 759)	Mild TBI With LOC (n = 23 097)	Mild TBI With LOC Status Unknown (n = 55 004)	Moderate to Severe TBI (n = 82 919)
Unadjusted	1 [Reference]	3.41 (3.29-3.53)	2.29 (2.04-2.58)	2.48 (2.26-2.72)	3.11 (2.97-3.25)	3.75 (3.61-3.89)
1[b]	1 [Reference]	3.41 (3.30-3.53)	2.32 (2.06-2.61)	2.49 (2.27-2.73)	3.14 (3.00-3.28)	3.73 (3.60-3.88)
2[c]	1 [Reference]	3.41 (3.29-3.53)	2.34 (2.08-2.63)	2.50 (2.28-2.75)	3.16 (3.02-3.31)	3.71 (3.57-3.85)
3[d]	1 [Reference]	3.45 (3.33-3.57)	2.36 (2.10-2.66)	2.51 (2.29-2.76)	3.19 (3.05-3.33)	3.77 (3.63-3.91)

Lancet Commission on Dementia Prevention

	Relative risk for dementia (95% CI)	Risk factor prevalence	Communality	Unweighted PAF	Weighted PAF*
Early life (<45 years)					
Less education	1·6 (1·3–2·0)	40·0%	61·2%	19·4%	7·1%
Midlife (age 45–65 years)					
Hearing loss	1·9 (1·4–2·7)	31·7%	45·6%	22·2%	8·2%
TBI	1·8 (1·5–2·2)	12·1%	55·2%	9·2%	3·4%
Hypertension	1·6 (1·2–2·2)	8·9%	68·3%	5·1%	1·9%
Alcohol (>21 units/week)	1·2 (1·1–1·3)	11·8%	73·3%	2·1%	0·8%
Obesity (body-mass index ≥30)	1·6 (1·3–1·9)	3·4%	58·5%	2·0%	0·7%
Later life (age >65 years)					
Smoking	1·6 (1·2–2·2)	27·4%	62·3%	14·1%	5·2%
Depression	1·9 (1·6–2·3)	13·2%	69·8%	10·6%	3·9%
Social isolation	1·6 (1·3–1·9)	11·0%	28·1%	4·2%	3·5%
Physical inactivity	1·4 (1·2–1·7)	17·7%	55·2%	9·6%	1·6%
Diabetes	1·5 (1·3–1·8)	6·4%	71·4%	3·1%	1·1%
Air pollution	1·1 (1·1–1·1)	75·0%	13·3%	6·3%	2·3%

Data are relative risk (95% CI) or %. Overall weighted PAF=39·7%. PAF=population attributable fraction. TBI=traumatic brain injury. *Weighted PAF is the relative contribution of each risk factor to the overall PAF when adjusted for communality.

Table 1: **PAF for 12 dementia risk factors**

Dementia prevention, intervention, and care: 2020 report of the *Lancet* Commission

Gill Livingston, Jonathan Huntley, Andrew Sommerlad, David Ames, Clive Ballard, Sube Banerjee, Carol Brayne, Alistair Burns, Jiska Cohen-Mansfield, Claudia Cooper, Sergi G Costafreda, Amit Dias, Nick Fox, Laura N Gitlin, Robert Howard, Helen C Kales, Mika Kivimäki, Eric B Larson, Adesola Ogunniyi, Vasiliki Orgeta, Karen Ritchie, Kenneth Rockwood, Elizabeth L Sampson, Quincy Samus, Lon S Schneider, Geir Selbæk, Linda Teri, Naaheed Mukadam

Executive summary

against dementia. Using hearing aids appears to reduce

Lancet 2020; 396: 413–46

- For the first time, head trauma included in list of modifiable dementia risk factors.

Do we need to **triage "modifiable risk factors"** for post-TBI dementia differently than "regular" dementia?

Medical and Psychiatric Risk Factors for Dementia in Veterans with and without Traumatic Brain Injury (TBI): A Nationwide Cohort Study

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- Risk from each modifiable risk factor is LOWER in those with prior TBI
- Due to HIGH PREVALENCE of these risk factors in Veterans with prior TBI, aggressive screening & treatment is critical for population-level dementia risk reduction

Risk Factor Prevalence		TBI	No TBI
Hypertension	1.2 x	66%	53%
Coronary artery disease	1.6 x	35%	22%
Diabetes	1.4 x	30%	22%
Cerebrovascular disease	3 x	16%	5%
Epilepsy	7 x	7%	1%
Depression	2.5 x	35%	14%
PTSD	3 x	22%	7%

Table 3. Population attributable fraction (PAF) of dementia due to each comorbidity among Veterans with and without TBI

Characteristic	No TBI (N=190,278)		TBI (N=95,139)	
	HR (95%CI)*	PAF (95%CI)	HR (95%CI)*	PAF (95%CI)
Medical Comorbidities				
Hypertension	1.12 (1.08-1.17)	6.0% (4.1%-8.3%)	1.11 (1.07-1.16)	6.7% (4.4%-9.5%)
CAD	1.23 (1.18-1.28)	4.7% (3.7%-5.7%)	1.17 (1.13-1.21)	5.6% (4.4%-6.9%)
Diabetes	1.22 (1.17-1.27)	4.6% (3.6%-5.6%)	1.08 (1.04-1.12)	2.3% (1.2%-3.4%)
CVD	1.60 (1.50-1.71)	3.0% (2.5%-3.5%)	1.30 (1.24-1.36)	4.6% (3.7%-5.4%)
Epilepsy	2.13 (1.89-2.40)	1.4% (1.1%-1.8%)	1.37 (1.29-1.46)	2.5% (2.0%-3.1%)
Psychiatric comorbidities				
Depression	1.72 (1.64-1.81)	9.0% (8.1%-10.0%)	1.31 (1.26-1.36)	9.8% (8.4%-11.2%)
PTSD	1.50 (1.40-1.61)	3.5% (2.8%-4.2%)	1.15 (1.10-1.21)	3.2% (2.2%-4.4%)

*FG model using age as time scale, adjusted for race, sex, income, and education.

Gardner et al. J Prev Alz Dis 2023

What is the pathology?
Is it Alzheimer's or not Alzheimer's?
The answer is probably: YES

Original Investigation | Neurology

Association of Traumatic Brain Injury With and Without Loss of Consciousness With Neuropathologic Outcomes in Community-Dwelling Older Persons

Sonal Agrawal, PhD; Sue E. Leurgans, PhD; Bryan D. James, PhD; Lisa L. Barnes, PhD; Rupal I. Mehta, MD; Kristen Dams-O'Connor, PhD; Jesse Mez, MD; David A. Bennett, MD; Julie A. Schneider, MD

- Lewy body pathology
- Microvascular ischemia
- Amyloid Beta

Original Investigation

September 2016

Association of Traumatic Brain Injury With Late-Life Neurodegenerative Conditions and Neuropathologic Findings

Paul K. Crane, MD, MPH[1]; Laura E. Gibbons, PhD[1]; Kristen Dams-O'Connor, PhD[2]; et al

» Author Affiliations | Article Information

JAMA Neurol. 2016;73(9):1062-1069. doi:10.1001/jamaneurol.2016.1948

Next Steps for Treatment/Prevention of Post-TBI Dementia

- Post-TBI Dementia = multiple different pathologies. Which specific pathology/ies an individual person develops likely depends very much on:

  TBI dose

  Genetics

  Other lifetime exposures that increase or reduce risk

- We need specific precision-medicine disease-modifying interventions for the specific chronic and potentially progressive processes that are triggered from a TBI event.

- Now that we have entered the dementia treatment era with anti-amyloid drugs for Alzheimer's disease specifically, we must embark on:

  → SCREENING / DIAGNOSIS / TREATMENT FOCUSED RESEARCH for POST-TBI DEMENTIA to determine generalizability of these emerging therapies to post-TBI dementia.

  →Can we use the same biomarkers to screen for AD in TBI-exposed?

  →Do anti-amyloid drugs work as well in TBI-exposed?

Do we need to **diagnose** post-TBI dementia differently than “regular” dementia?

DoD-ADBI

Dept. of Defense Alzheimer’s Disease Blood Testing Initiative

US DoD CDMRP W81XWH-21-PRARP-ADRA

UCSF OHSU SHEBA Tel HaShomer City of Health

FUJIREBIO Roche Lilly Quanterix The Science of Precision Health

Accuracy of Leading Commercial AD (A/T) Blood Biomarkers

Military Relevant Exposures

TBI PTSD CSVD

Gold-Standard AD (A/T) PET Biomarkers

Impact

Guide appropriate use of AD (A/T) blood biomarkers in VETERANS as the field enters the treatment era.