



Dementia Risk in Veterans with PTSD and a History of Blast-Related TBI

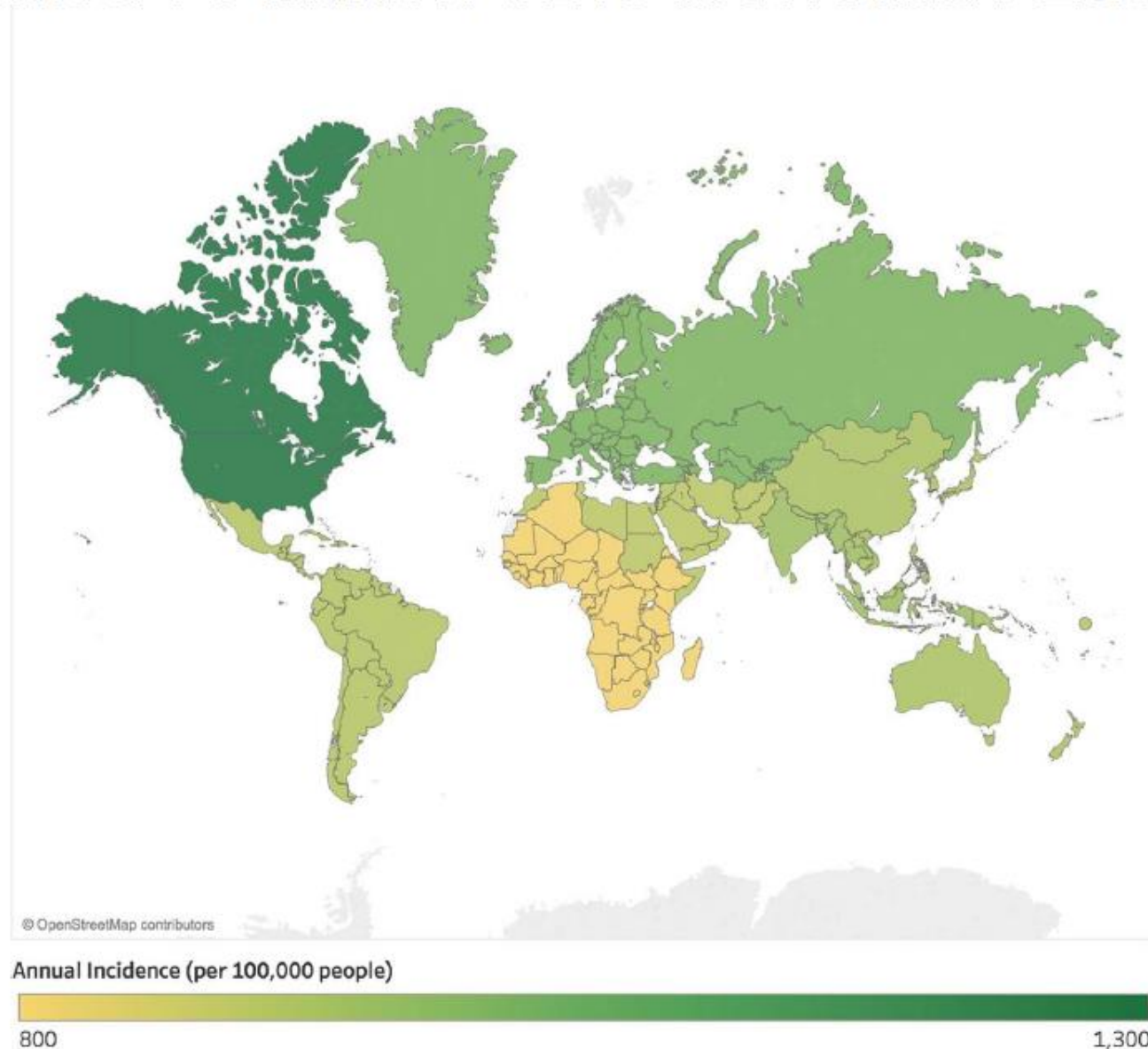
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Estimated 70 Million TBIs Worldwide Each Year



Estimate based on road traffic injuries, systematic review, and meta-analysis of TBI literature. Dewan et al, *J Neurosurg*, 2018.

TBI: Incidence in U.S. Veterans



DoD Numbers for Traumatic Brain Injury Worldwide - Incidence by Severity

No. of cases

30,000

25,000

20,000

15,000

10,000

5,000

0

'00 '01 '02 '03 '04 '05 '06 '07 '08 '09 '10 '11 '12 '13 '14 '15 '16

Calendar year

Mild

Moderate

Severe


Penetrating

Unclassified

Source: Defense Medical Surveillance System (DMSS), Theater Medical Data Store (TMDS)
provided by the Armed Forces Health Surveillance Branch (AFHSB).
Prepared by the Defense and Veterans Brain Injury Center (DVBIC)

2000-2016 as of May 10, 2017

How Did We Get Here?

- ▶ Humans have been sustaining mild TBI's (and experiencing PTSD) for millions of years, and yet we have no significant reports of related long-term effects in any great amount until the last 20 years.
 - ▶ High-contact athletes have been known to develop cognitive-behavioral issues for 100 years.
 - ▶ Combat-exposed Veterans have been known to develop behavioral issues for centuries.
 - ▶ NFL + OEF/OIF + \$\$\$ + Fame = Perfect Storm
- 

Combat-Induced Findings of Uncertainty (CIFU)

- ▶ The acute presentations of a range of physical and psychological stressors and injuries that result in combat may be missed (partially or entirely), misinterpreted, misconflated, misapportioned, misconstrued, misnamed, or otherwise MIA!
- ▶ While missed, delayed or mistaken diagnoses are not uncommon in healthcare, the demands of military conflict, the vastness and complexity of the defense health system, the challenges of multifactorial disorders, the variable training and expertise of health care professionals for CIFU, and the desire to explain (“diagnose”) symptoms and difficulties with singular labels all contribute to worsening difficulty.
- ▶ Okay, CIFU doesn’t exist....but, what about mTBI, Blast Injury, CTE?

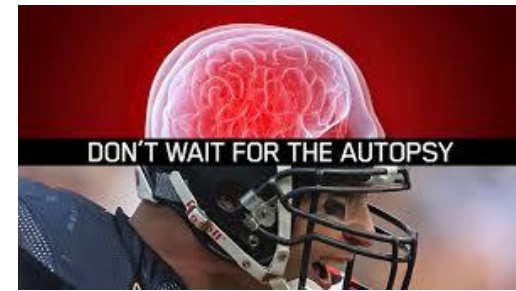
Concussion = mTBI



- ▶ **Concussion** (= mild TBI) is a complex pathophysiologic process induced by traumatic forces secondary to direct or indirect impulsive forces to the head that disrupts the function of the brain.
- ▶ Concussion is defined as an alteration or loss of consciousness for up to 30 minutes with associated loss of memory surrounding the event (post-traumatic amnesia) for up to 24 hours.
- ▶ Transient (<24 hours) neurologic sequelae may also be present, including numbness, dizziness, cognitive deficits, discoordination, and alterations in special senses.
- ▶ This disturbance of brain function is typically associated with normal structural neuroimaging findings.



Potentially Concussive Event

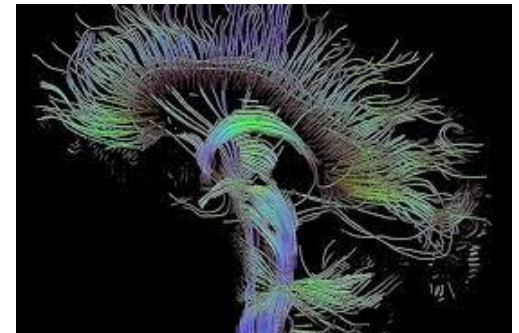


- ▶ A PCE is defined as an impulsive force to the head of sufficient intensity that results in acute or chronic symptoms in some individuals, but remain asymptomatic (“subclinical”) in others – no demonstrable neurologic or symptomatic effect.
- ▶ No available diagnostic testing available – new blood biomarker test or BrainScope EEG are of no value.
- ▶ Some have expressed concern about the long-term effects of this potential cumulative trauma disorder.

? Is this a CIFU

Challenges to Management

- ▶ Uncertainty of diagnosis
 - Gold standard test is question concerning AOC
 - Imaging (CT Scan) normal >95% of time or high false positive rate (50%) or poor clinical correlations.
 - Few clinicians specialty trained
 - Carpenters like to use wood for everything!
 - Overlap of symptoms with pain, depression, PTSD, fatigue, stress and life.



Challenges to Management

- ▶ Range of Treatment Options
 - Benign neglect successful >90% of the time
 - Majority of complaints are related to either musculoskeletal or stress-related factors.
 - Army of “specialists” and charlatans
 - Musculoskeletal
 - Vision
 - Vestibular
 - Cognitive
 - Catalogues full of remedies

Lots of CIFU here!!



Management of Concussion (and PCE)

- ▶ Explanation – transient minimal disruption of some signals in the brain.
- ▶ Education – range of symptoms predominantly related to the physical trauma, stress from injury, and concern over recovery
- ▶ Reassurance– Rapid and full recovery likely, wide range of effective treatments, supportive clinicians available for care
- ▶ Reactivation – Return to physical and cognitive activity within 1–2 days. Contact when able to perform tasks.

Post-Concussive Symptoms

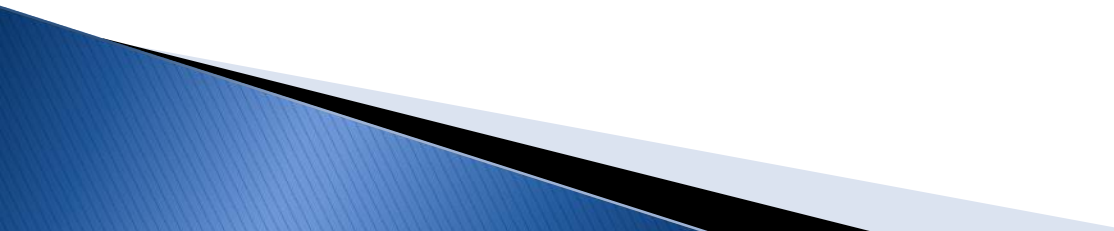


- ▶ Acute symptoms resolve in $>85\%$ by 2 weeks
- ▶ As with any mild traumatic injury, patients who are acutely and uniformly treated by experienced clinicians respond rapidly ($>90\%$ musculoskeletal origin), however benign neglect can also get some/many better.
- ▶ Symptoms presenting >2 weeks post-injury are not related to injury

Post-Concussive Symptoms

- “Post-Concussive Syndrome”
 - Label used if symptoms persist for 3+ months
 - May be seen in 15–30% of concussions and continue for >1 year in 5%.
- No clear central physiologic reason for symptoms after 2–6 weeks.
 - Axonal disconnection of <5% of white matter tracts
- ? Chronic pain, PTSD, anxiety, learned behavior, CIFU

Challenges to Management

- ▶ Individuals bring beliefs, fears and biases
 - Media is replete with concussion and dementia stories
 - Anxiety, misunderstanding, variable compliance, and symptom attribution affect efficacy
 - Differing opinions, prior experiences and outside influences (internet!) affect level of self-efficacy
 - Healthcare system favors testing and illness
- 

Post-Concussive Management – Integrative Medicine

► Education

- Diagnosis – explain multiple contributors
- Prognosis – optimism, self-actualization
- Health Management – Fitness, Sleep, Diet, Mind/Body

► Interventions

- Sleep – sleep hygiene, CBT-I, medications
- Pain – pain management, non-narcotic medications (short term)
- Behavior – counseling, mood stabilizers (at full dosing)
- Cognition – adaptive strategies, assistive technology
- Fatigue – sleep, fitness, diet, counseling

► Goals

- Normalization
- Deinstitutionalization
- Return to productivity and activity
- Reintegrate into social roles and activities



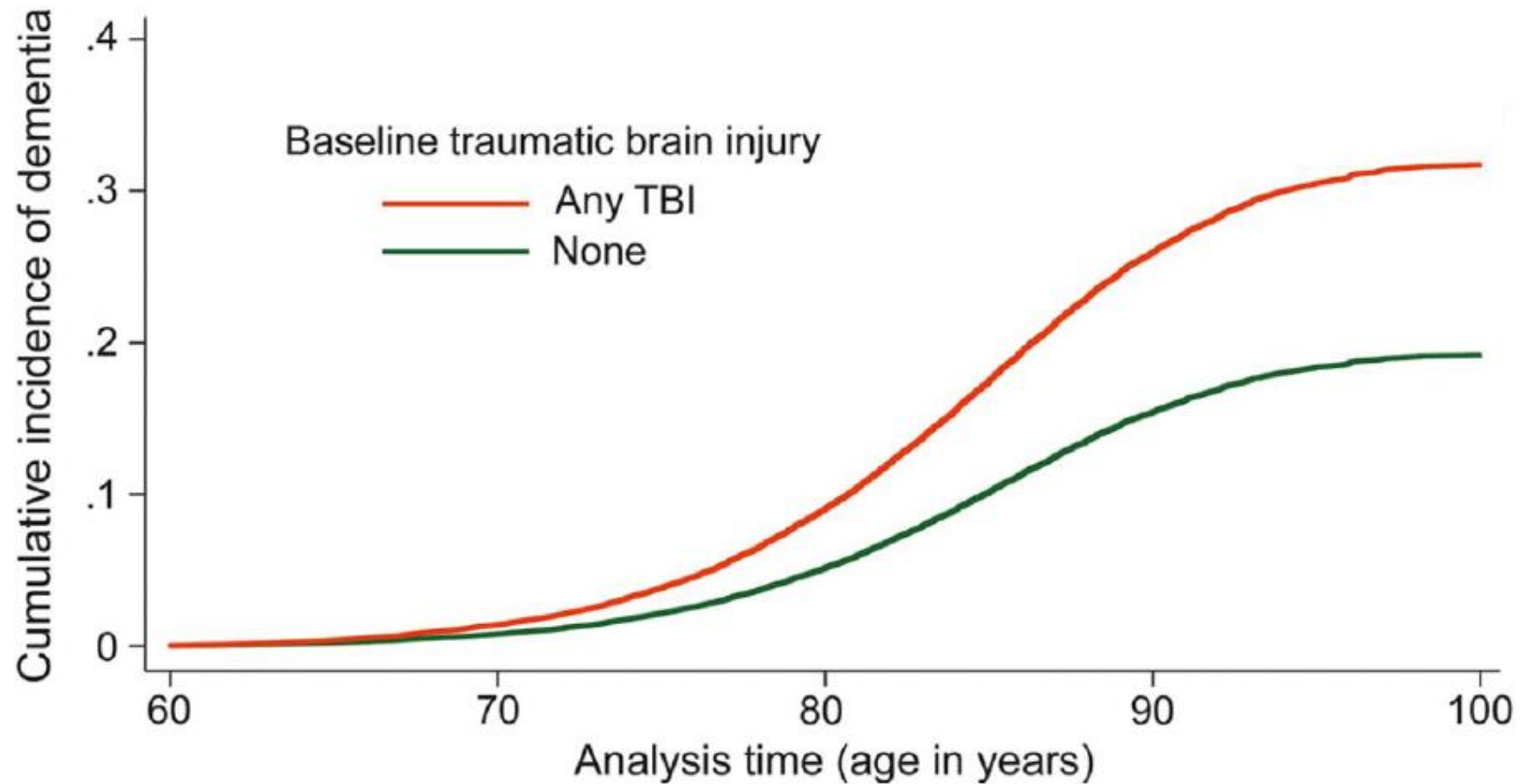
Long-term Effects of TBI & Dementia Risk in US Veterans

- ▶ Significant focus on acute effects of TBI
- ▶ Long-term effects of TBI are unclear
- ▶ There is a large population of older U.S. Veterans at risk for dementia
 - 40% of Veterans are >65 years of age
- ▶ PTSD itself is a risk factor for dementia
- ▶ Dementia associated with increased healthcare utilization and costs (3x greater)
- ▶ Veterans have a unique constellation of military-related risk factors

Possible Mechanisms Linking TBI to Cognitive Impairment

- ▶ Mechanical injury resulting in diffuse axonal injury
- ▶ Axonal swelling and degeneration
- ▶ Accumulation of proteins
- ▶ Breakdown of blood–brain barrier
- ▶ Synaptic dysfunction
- ▶ Cell death
- ▶ Microglial activation and inflammatory responses

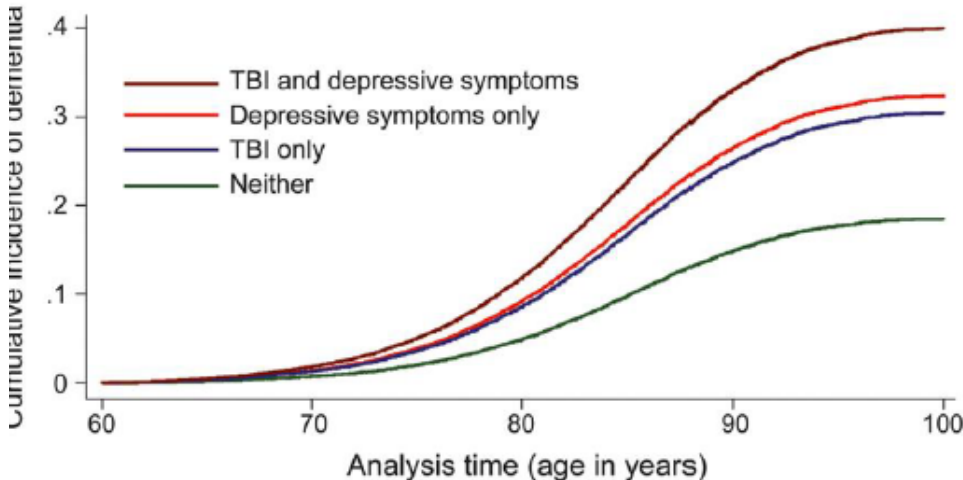
60% Increased Risk of Dementia with TBI



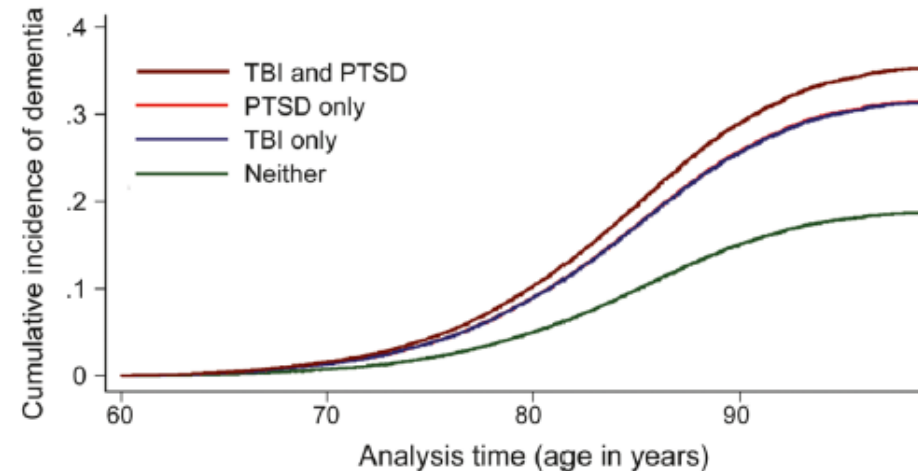
Adjusted HR:1.57; 95% CI (1.35–1.83)

Comorbidities Have an Additive Effect on Dementia Risk

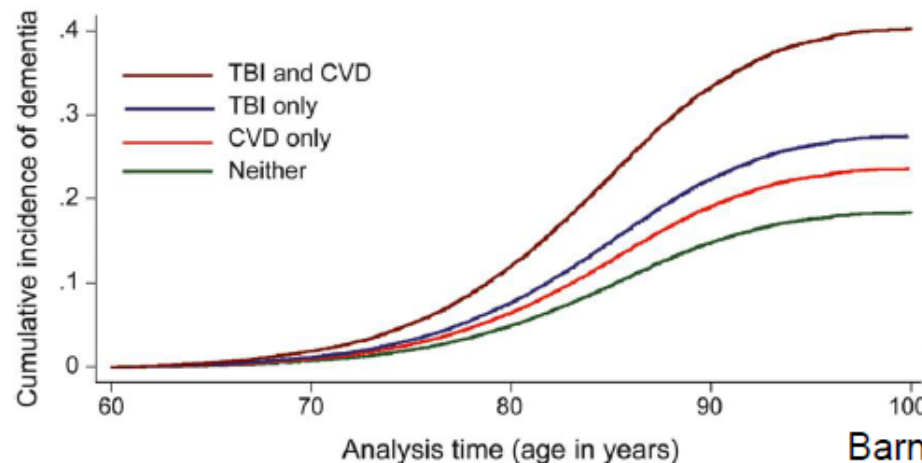
Depression



PTSD



Cerebrovascular Disease



Summary of Recent Epidemiological Studies

- Strong epidemiological evidence for TBI as a risk factor for dementia
- Emerging data for the role of mild TBI and neurodegenerative outcomes
- Inclusion of objective TBI measures
- Large studies with long follow up to address issues of power and reverse causation
- Age and medical and psychiatric comorbidities are critical factors

One Explosion/Blast has Multiple Mechanisms of Injury



Wall of Air (Primary)



Blast Wind (Primary)



Flying Debris
(Secondary)

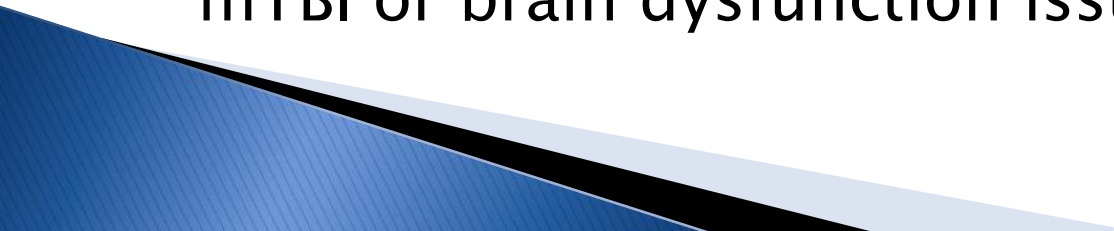


Displacement
(Tertiary)



Collapse Building
(Quaternary)

What is a blast-related mTBI?

- ▶ Per DoD, there have been approximately 10 “pure” blast mTBI from OEF/OIF, but it’s not clear what this even means.
 - ▶ No definitive literature supporting the existence of a blast-related mTBI without physical forces on head.
 - ▶ The head and/or body are moving in >99% of blasts.
 - ▶ Breacher research (munitions experts) that features repeated blast exposure has NOT revealed definitive mTBI or brain dysfunction issues.
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Combat Concussions



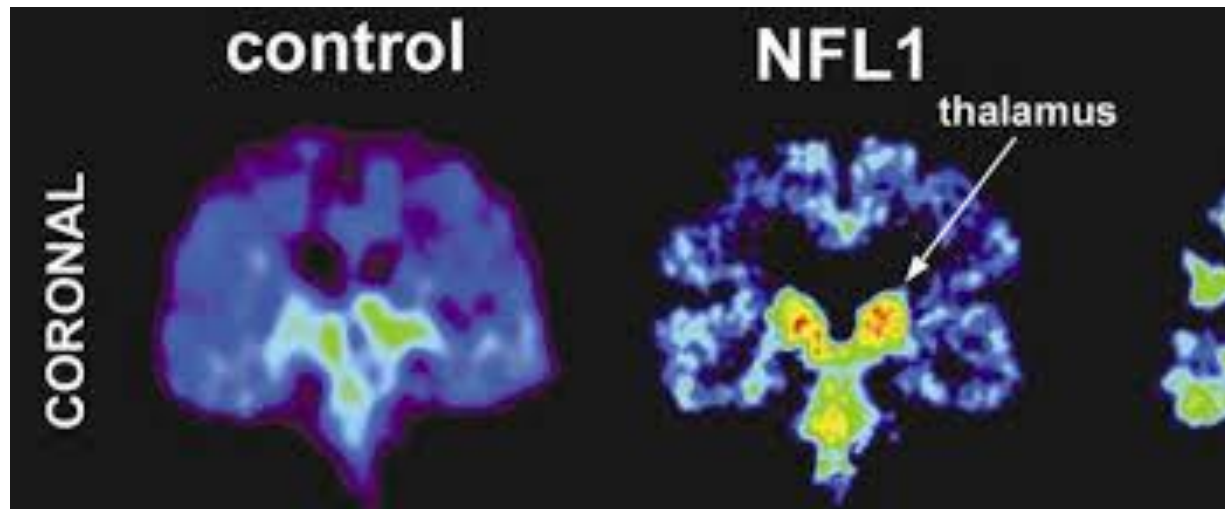
- ▶ 16–20% of OEF–OIF–OND Veterans who received VA medical care have confirmed TBI and 8% were still symptomatic when initiating care at VA
 - ~200,000 total (>1,100,000 screened) in VA
 - 90,000 symptomatic
 - >98% mild
 - <2% moderate–severe
 - >50% due to MVC
- ▶ 75% of Veterans with symptomatic mild TBI also have at least one mental health diagnosis, most commonly Post Traumatic Stress Disorder (PTSD)
- ▶ 90% will have either PTSD or chronic pain disorder



How is blast-related mTBI unique?

- ▶ Definitive research findings identifying the presence of any blast-specific contributions to mTBI without blast forces (i.e., head acceleration-deceleration) is lacking. Similarly, no blast-related PCE research findings!
- ▶ No literature supporting the existence of a blast-related mTBI without physical forces on head.
- ▶ Psychologic stressors of concussion resulting all or in part from a blast exposure must be considered.
- ▶ Unclear if further research is needed or CIFU?

Chronic Traumatic Encephalopathy





Iraq War combatants (U.S.) with mTBI
report 1–150 mTBIs (~4 average).

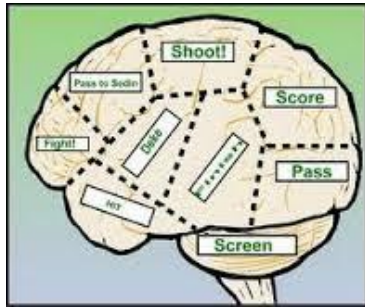
NFL players sustain 3,000–8,000
concussions during a lifetime of sports.

Your speaker has sustained 5–6
concussions in his timid, little life



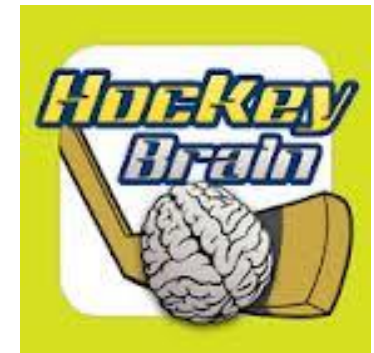
Veterans
& Brain Injury





Q: Do TBI's predispose for late life degeneration?

A: Yes



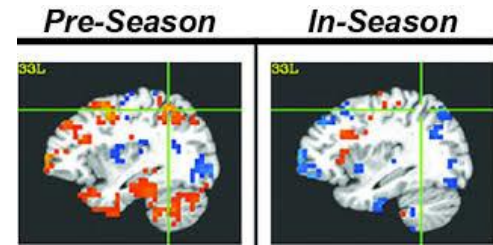
Q: Is someone who has sustained 5–6 mTBI's going to develop CTE?

A: *(Um, what was the question again?)* **NO!!!**

Chronic Traumatic Encephalopathy

- ▶ CTE (Punch Drunk, Dementia Pugilistica) begins insidiously, usually many years (5–20) after the patients have stopped playing sports, with inattention, mood and behavior disturbances, confusion, and memory loss, and progresses over many years (5+) to a stage of full blown dementia and Parkinsonism.
- ▶ The brain, in CTE, shows atrophy, dilatation of the lateral and third ventricles, and thinning of the corpus callosum.
- ▶ Microscopic examination reveals neuronal loss and **tau deposition** in neurons (**neurofibrillary tangles–NFTs**) and in astrocytes. This pathology involves the cerebral cortex (perivascular areas, deep), white matter, deep nuclei, and the brainstem.
- ▶ Beta amyloid deposition in the form of diffuse and less frequently neuritic plaques is seen inconstantly (unlike AD)


McKee CTE Staging



- ▶ Stage I, headaches and issues related to attention and concentration are common
- ▶ Stage II, the symptoms expanded to include depression, explosivity and short-term memory impairment
- ▶ Stage III, reported symptoms include cognitive impairment and problems with executive functions, specifically planning, organization, multitasking and judgment.
- ▶ Stage IV, there was evidence of full-blown dementia (i.e., memory and cognitive impairments severe enough to impact daily living).



CENC 1.0

- ▶ CENC multicenter, VA/DoD research collaboration funded in 2013, linking basic, translational, and clinical neuroscience researchers from the VA, military, academia, and the private sector to effectively address the diagnostic and therapeutic ramifications of mTBI and its long-term effects.
 - ▶ The overarching goal is understanding the lifetime impacts of military service, combat-associated concussions and being a Veteran, in particular with respect to the development of mental health disorders, Alzheimer's dementia and related neurodegeneration.
 - ▶ Research linkages between 15 major VA Centers, 12 DoD Military Treatment Facilities/Research Sites, and more than 30 academic research centers in 20 States and the D.C.
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CENC Findings

- ▶ More than two-thirds of Servicemembers and Veterans with persistent difficulties after combat concussions and related issues are high functioning, employed and managing well in the community more than 7 years after injury.
- ▶ One-third are demonstrating ongoing and increasing difficulties that are requiring significant health care utilization.
- ▶
- ▶ None of the subjects is exhibiting signs of dementia on average 9 years from last mTBI.
- ▶ Female subjects have greater symptoms than male.
- ▶ Servicemembers and Veterans with combat-related concussions and associated conditions (PTSD, pain, depression, substance use, elevated suicide risk) represent a unique and high-risk population.

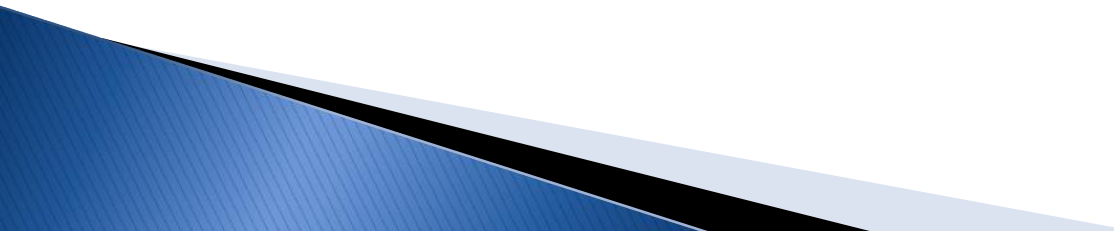
CENC Findings

- ▶ Linkages have been identified between elevated lifetime risks for neuro-degeneration, including Alzheimer's dementia and Parkinson's disease, chronic pain, opioid misuse, and PTSD in Servicemembers and Veterans who have experienced TBI.
- ▶ Multi-modal research assessment techniques have been developed that allow for more accurate diagnoses and clinical characterization. As of yet, these techniques and technologies (e.g. biomarker, imaging, eye-tracking, qEEG) are not appropriate for every day, clinical usage, and the existing diagnostic, assessment and intervention protocols that exist in the VA Polytrauma System of Care are state-of-the-art and clinically appropriate.

CENC Findings

- ▶ While evidence-based, comprehensive clinical services for the care of Servicemembers and Veterans with persistent difficulties due to military service and combat-related concussion exist across VA's Polytrauma System of Care, a number of individuals are not aware and/or accessing these services.
- ▶ While there exist a range of novel techniques and technologies (e.g., hyperbaric oxygen, transcranial magnetic stimulation, neurofacilitation) that are being either advocated or researched for the clinical care of Servicemembers and Veterans with military service and combat-related concussions, none of these newer treatments are yet appropriate for recommended for this population.
- ▶ The comprehensive, symptom-based, team-directed care provided through the VA Polytrauma System is the gold standard.

Clinical Practice Guideline–directed,
comprehensive approach to the clinical
management for individuals with
combat–related exposure to blast
repetitive mild TBI, and/or PTSD who
believe they are at risk for or have CTE.



Dementia-related Factors

- ▶ Nine modifiable lifestyle factors account for up to 50% of all cases of dementia
 - Limited education in early life
 - hearing loss
 - Hypertension
 - Obesity
 - Smoking
 - Depression
 - Physical inactivity
 - Social isolation
 - Diabetes
- ▶ No single risk or protective factor is dominant.

Ashby-Mitchell: Alzheimer Res Ther 2017

Norton: Lancet Neurology 2014

Dementia-related Factors

- ▶ Repeated TBI's may play a small role (1%) in increasing the risk for dementia.
- ▶ The presence of the apolipoprotein E (APOE) ϵ 4 allele may increase AD risk by 8%.
- ▶ In addition to depression, intermittent or persistent mental illness likely increases risk.
- ▶ Spending enough time getting tests and seeing doctors likely also increase the risk for dementia (? in the doctors)

Diagnosing Dementia

- ▶ The chance you will ever see CTE in your lifetime is about the same as Kuru, Jakob–Creutzfeldt or Cerebral Trichinosis (0%) – ? CIFU
- ▶ While unusual, early-onset (Alzheimer's-type) dementia is not uncommon, however it has NOT been associated with concussion.
- ▶ On the other hand, there is extreme value to acknowledging that the individual is having difficulties that
 - warrant an evaluation,
 - can be definitively diagnosed, and
 - have a range of evidence-based treatments

Diagnosing Dementia

- ▶ A patient who presents to a TBI or MH clinic with persistent or worsening cognitive (or behavioral) deficits should be evaluated the same way as any individual;
 - History – Neurologic change, new TBI/trauma, new MH symptoms, SA/EtOH, Medications, Life Stressors, Sleep, Diet, Activity, Work, Metabolic
 - Exam – MMSE, MOCA, Weight, Cardiovascular, Pulmonary, Behavioral, Neurological, Endocrine
 - Function – Activity/Exercise, Leisure Activity
 - Testing – Limited (n.b.: Role of Imaging, NeuroPsychological, EP)
 - Management – If you feel that you have nothing to offer, then reconsider your role!!

Using the Rehab Model to “Treat” Dementia

- ▶ Research efforts in dementias focus on
 - preventative strategies for dementia risk factors
 - pharmaceutical interventions to slow progression
- ▶ Rehabilitation strategies have demonstrated similar/better efficacy than medications for prevention or treatment
 - symptom management
 - lifestyle modifications
 - physical exercise
 - cognitive exercise
 - formal rehabilitation therapy

Implementing Brain Health

- ▶ FINGER study:
 - Double-blind, randomized clinical trial of 1260 individuals 60–77 years with normal cognition for age and a high risk of dementia
 - Assignment to a 2-year multidomain intervention (diet, exercise, cognitive training, social stimulation, and management of vascular and metabolic risk factors)
- ▶ Interventions are feasible and safe
- ▶ Interventions associated with significant beneficial effect on overall cognition, executive functioning, and processing speed, as well as body mass index, dietary habits, and physical activity.

Ngandu: Lancet 2015

Using the Rehab Model to “Treat” Dementia

- ▶ First, do the obvious
 - ▶ Reassure the individual and family
 - ▶ Treat medical and psychological issues
 - ▶ Optimize medication regimes
 - ▶ Identify “symptom specific” approaches
 - ▶ Establish a therapeutic alliance

Wheel Of Health



Self Care

Professional Care

Duke Integrative Medicine

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- ▶ Second, do the hard part
 - ▶ Identify short- and long-term cognitive wellness and brain health goals
 - ▶ Create a path to engagement (IM, MI, MIMI?)

Physical Fitness and Dementia

- ▶ Critical review of literature from 2006–2010 on role of physical fitness on health.
- ▶ Apart from not smoking, being physically active is the most powerful lifestyle choice any individual can make to improve their health.
- ▶ Individuals have an element of control over some of these factors, including obesity, diet, smoking and physical activity.
- ▶ Regular moderate to intense physical activity is associated with decreased risk of coronary heart disease, ischemic and hemorrhagic stroke, cancers (and exercise can enhance cancer recovery), osteoporosis, type 2 diabetes, depression, obesity and high blood pressure.
- ▶ There is growing evidence that physical activity could decrease the risk of dementia in the elderly.

Alford: Intl J Clin Pract 2010;64(13):1731–1734

Cognitive Fitness and Dementia


- ▶ The literature supports maintaining general cognitive fitness in dementia, especially when combined with acetylcholinesterase inhibitors
 - slow the rate of cognitive decline
 - slow the rate of functional decline
 - decrease negative emotional

- ▶ Cognitive fitness may be maintained via
 - Leisure skills training and activities
 - Individual training
 - Group training and Day Care
 - Internet-based training

Counseling on TBI (PTSD) and CTE

- ▶ Acknowledge their issues and concerns.
- ▶ Don't over explain or hedge your answer.
- ▶ The risk of developing dementia from a single concussion is zero. The risk of developing dementia from 10 concussions is just barely above zero.
- ▶ Undertreated symptoms (post-concussion, mental health, pain) may be a more relevant risk factor for dementia. Treating PTSD with an evidence-based treatment can help!
- ▶ Lifestyle factors, general wellness, and integration into society are biggest risk factors

Ten Commandments of Concussion

1. Concussions are events not diagnoses.
 2. >98% of concussions either go unnoticed or have full recovery.
 3. The management of concussion remains the same acutely or chronically – reassure, normalize, activate, treat symptomatically.
 4. Musculoskeletal factors are the key acutely and mental health factors chronically after traumatic events.
 5. Given the focus on concussions, they represent a unique avenue to care.
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Ten Commandments of Concussion

6. Cognitive wellness and brain health should be in every clinician's bag of tricks.
7. CTE and dementia are not really clinical issues related to concussion (risk is $<1\%$).
8. A large percentage of patients WILL develop cognitive difficulties, MCI, or AD; the "prevention" is what we have to offer.
9. Rehabilitation approaches and interventions are effective for acute AND chronic cognitive issues associated with concussion.
10. Diet, Exercise, Sleep, Stress Management, Pain Care, Productivity, Social Integration, Family, and Faith-Based Life are central tenets.

Summary: TBI and Dementia

- ▶ TBI is associated with an increased risk of dementia
 - ▶ But there is a critical interaction of TBI with other dementia risk factors including PTSD
 - ▶ Many questions still remain regarding chronic traumatic encephalopathy
 - ▶ We need more research: rigorous prospective studies of TBI to understand outcomes, exploration of mechanisms through biomarkers and treatment/rehabilitation.
- 