Chronic Effects of Neurotrauma Consortium 2013–2019: Is Dementia a Common Endpoint after TBI?

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Hunter Holmes
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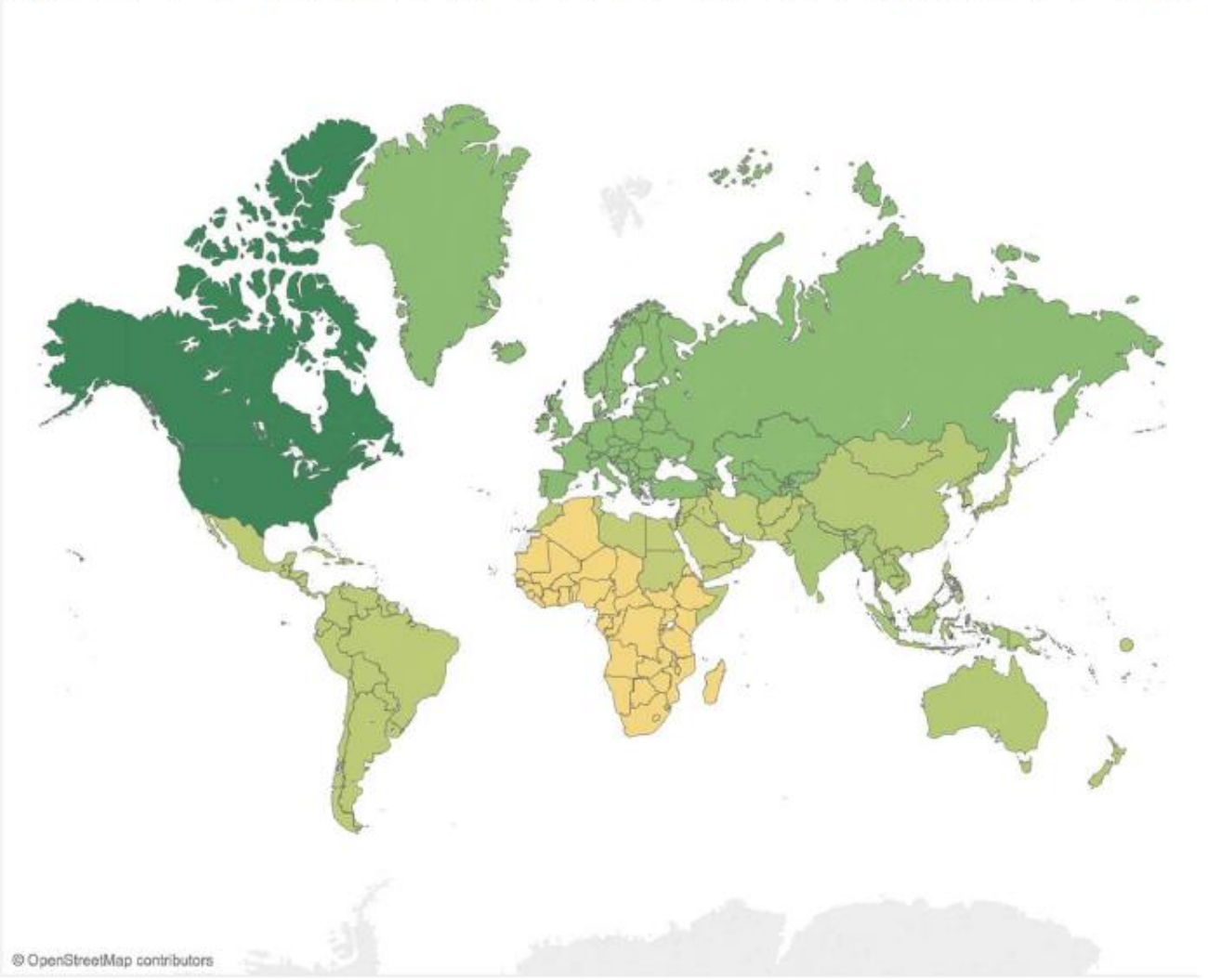
Veterans Day
Honoring All
Who Served

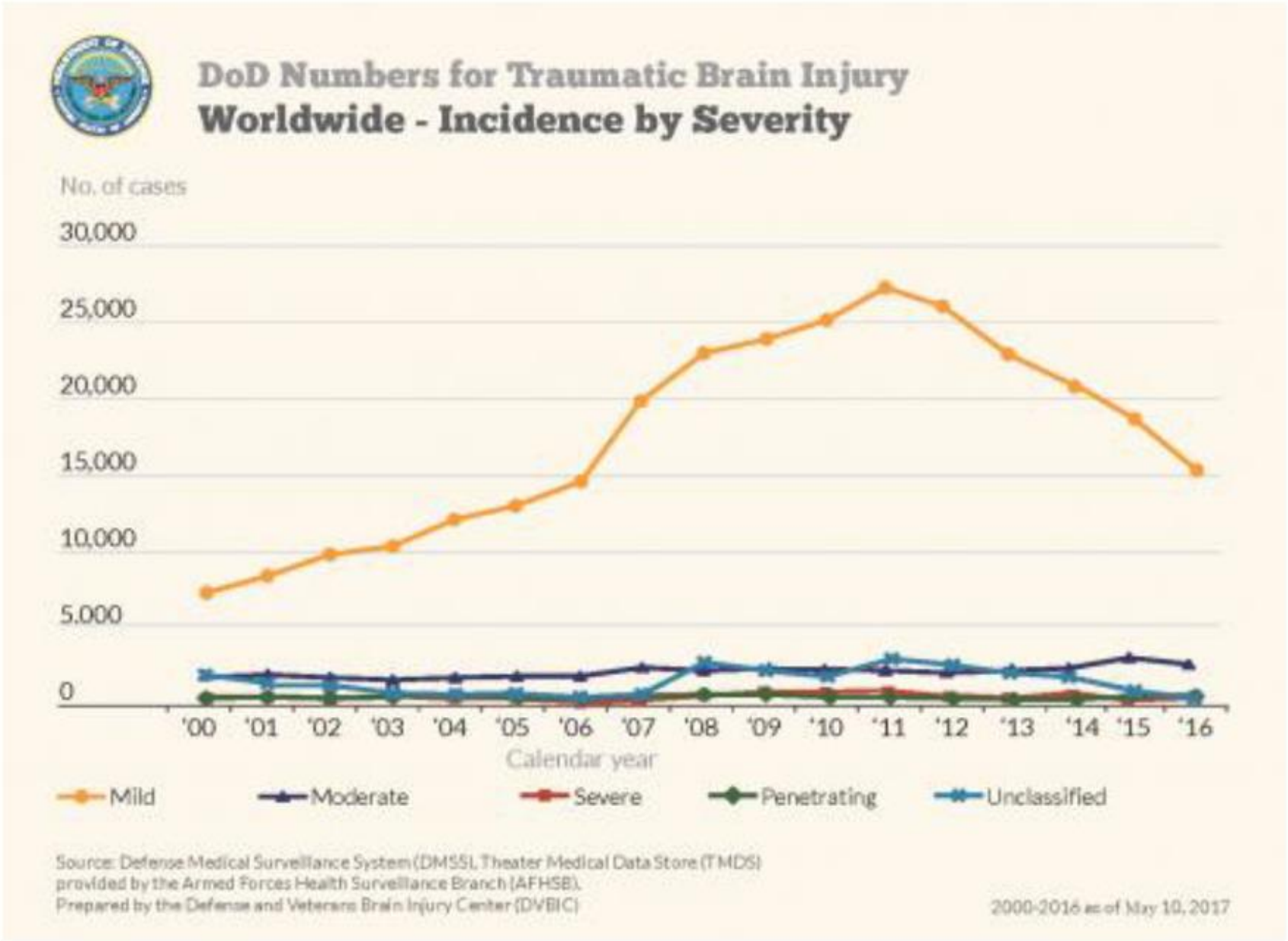

VCU

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



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.

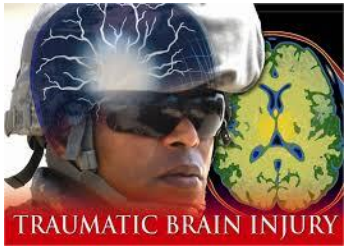
- Okay, CIFU doesn't exist….but, what about mTBI, Blast Injury, CTE?

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
- Concern about long-term effects of injury and persistent symptomatology

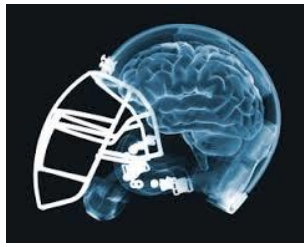
CENC 1.0



- CENC is a $62.2 million, 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.



CENC Sites

- Barrows Neurological Institute, Phoenix, AZ
- Baylor College of Medicine, Houston, TX
- Boston University, Boston, MA
- Brigham Young University, Provo, UT
- Duke University School of Medicine, Durham, NC
- Eisenhower Army Medical Center, Fort Gordon, GA
- Fort Belvoir Community Hospital, Alexandria, VA
- Fort Eustis, Fort Eustis, VA
- Fort Jackson, Columbia, SC
- Fort Lee, Fort Lee, VA
- Fort Stewart, Fort Stewart, GA
- Hunter Holmes McGuire VA, Richmond, VA
- James A. Haley Veterans Hospital, Tampa, FL
- Iowa City VA Health Care Center
- MacDill Air Force Base, MacDill AFB, FL
- Medical College of Wisconsin, Milwaukee, WI
- Medical University of South Carolina, Charleston, South Carolina
- Michael E. DeBakey VA Medical Center, Houston, TX
- Milwaukee VA Medical Center, Milwaukee, WI
- Minneapolis VA Health Care System
- Mountain Home VA Medical Center, Mountain Home, TN
- Northern California Institute of Research and Education, San Francisco, CA
- Roskamp Institute, Sarasota, FL
- RTI International, Durham, NC
- San Antonio Military Medical Center, San Antonio, TX
- San Francisco VA Medical Center, San Francisco, CA
- South Texas Veterans Healthcare Center, San Antonio, TX
- Uniformed Services University of the Health Sciences, Bethesda, MD
- University of Missouri St. Louis, MO

- University of Washington, Seattle, WA
- University of St. Louis, St. Louis, MO
- University of Hawaii, Manoa, HI
- University of Utah, Salt Lake City, UT
- University of Washington, Seattle, WA
- VA Boston Healthcare System
- VA Portland Health Care System
- VA San Diego Health Care System, San Diego, CA
- Virginia Commonwealth University, Richmond, VA
- WG Hefner VA Medical Center, Salisbury, NC

- Coordinating Center/ Research Site
- Research Core
- Research Site/ Core
- Research Site
- Recruiting Site

CENC Studies

- Longitudinal Study of 82% individuals with combat-concussion (+ other lifetime concussion) and 18% no-concussion who are comprehensively studied (history, symptoms and screens (PCS, depression, PTSD, pain, dementia), exam, MRI, electrophysiology, saliva and serum initially, phone f/u annually and in-person re-evaluation every 5 years for life (n=1,647).

- Retrospective database of 2 million Veterans with clinical care, healthcare utilization, and medications established

- 6 additional prospective, clinical studies completed (n= 600 participants)

- Basic science study of human-tau producing mouse exposed to repetitive concussions and aged.

- Development of a concussion-specific DTI phantom to standardize imaging platforms.

Summaries of Protocols and Results

- CENC Special Issue: *Brain Injury 2016;* 30(12): 1397–1514
  - Methodologies for 10 studies
  - Assessment Protocols and Tools

    https://www.tandfonline.com/toc/ibij20/30/12?nav=tocList

- CENC Special Issue *Brain Injury* 2018, 32:9, 1149–1294
  - Findings for 10 studies through Spring 2018
  - Integration of findings across 7 clinical studies

    https://www.tandfonline.com/toc/ibij20/32/10?nav=tocList

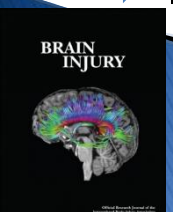


Figure 1. CENC Accomplishments and the Foundation/Experience for Serving as the Infrastructure for LIMBIC

CENC Infrastructure: At-the-Ready Forces to Deploy Research and Facilitate Knowledge Translation

Administrative Coordinating Center has successfully ensured the overall establishment, maturation and functioning of all CENC personnel, researchers, studies and Cores

Biomarker

- ~ **1,500** unique blood and saliva samples to-date
- Plasma, exosomal tau and p-tau associated with repetitive mTBI
- GWAS and exosome work underway on CENC and DVBIC **15-Year Study samples** (biomarker partners funded through NIH)

Neuroimaging

- Central reading of > **2,000** MRIs
- Ongoing specialty research analyses (volumetric, diffusion, perfusion, functional connectivity) of more than **1,400** MRIs
- Patented mTBI-specific, DTI Phantom for **standardization** across MRI scanners

Biostatistics, Data and Study Management

- **7** prospective human studies, including the **8-center Longitudinal Study's** highly standardized, human research protocol
- Knowledge translation of data from **10** studies into **>50** scientific publications, **100** abstracts and **150** presentations

Neuropathology-Brain Bank

- IRB-compliant protocol for dedicated brain bank (interdigitated with VA PTSD Brain Bank) for accepting brain donations from CENC human studies
- **12** brain donations to-date and **86** commitments

Multi-site, Multi-discliplinary Research Team

Geographic Diversity -- **21 States**

- **30** Academic Universities
- **15** Veterans Affairs Medical Centers
- **12** Military Treatment Facilities
- **75** multi-disciplinary neuroscience researchers to conduct a wide range of basic, translational, clinical, epidemiologic and biomedical sciences research
- Established links with researchers performing clinical trials to provide a **pipeline for referral of participants**

Uniform, Standardized Research Approaches across DoD, VA, and Academic Sites

"Gold Standards" in Concussion

Uniform, standardized research approaches to facilitate replication and validation of findings yielding "gold standards" for the field of concussion:

- Common Data Elements **(CDE)**
- Manualized methods of procedure **(MOP)**
- Best Practice approaches for all protocols
- CENC Longitudinal Study has been deployed with > **1,500** unique research subjects, is published, has been available on the CENC website since inception, and offers a multi-modal evaluation and monitoring model to address the complexity of brain functioning

CENC Findings

- Of the 2,200+ participants recruited:
  - more than two-thirds who still had persistent difficulties after combat concussions and related issues are high functioning, employed and managing well in the community more than 7 years after injury.
  - the remaining one-third of the cohort with post-concussion symptoms are demonstrating ongoing and increasing difficulties that are requiring significant health care utilization.

- None of the subjects is exhibiting signs of dementia 5-20 (mean = 9) years after most recent injury

- 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.

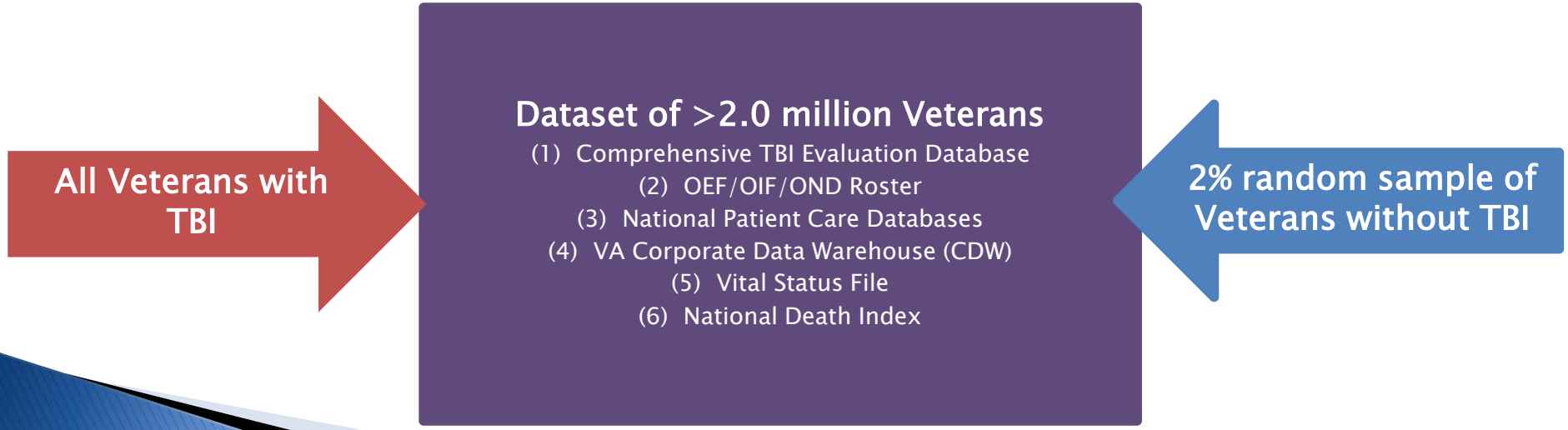
CENC Clinical Findings

- Retinal thickness does not correlate well with symptom burden, secondary conditions, vision or time post-injury.
- NeuroImaging (DTI, fMRI, McDESPOT, PRISM, MR Volumetrics, Fractional Anisotropy) do not correlate with symptom burden, secondary conditions, or activity
- Central otolith deficits are most disabling, but clinical approaches to diagnoses are limited.
- Computerized eye tracking can be used to differentiate normal from PTSD/mTBI and PTSD from TBI diagnoses.
- Serum biomarkers can differentiate those with 0-1 mTBI vs those with 3+ mTBI

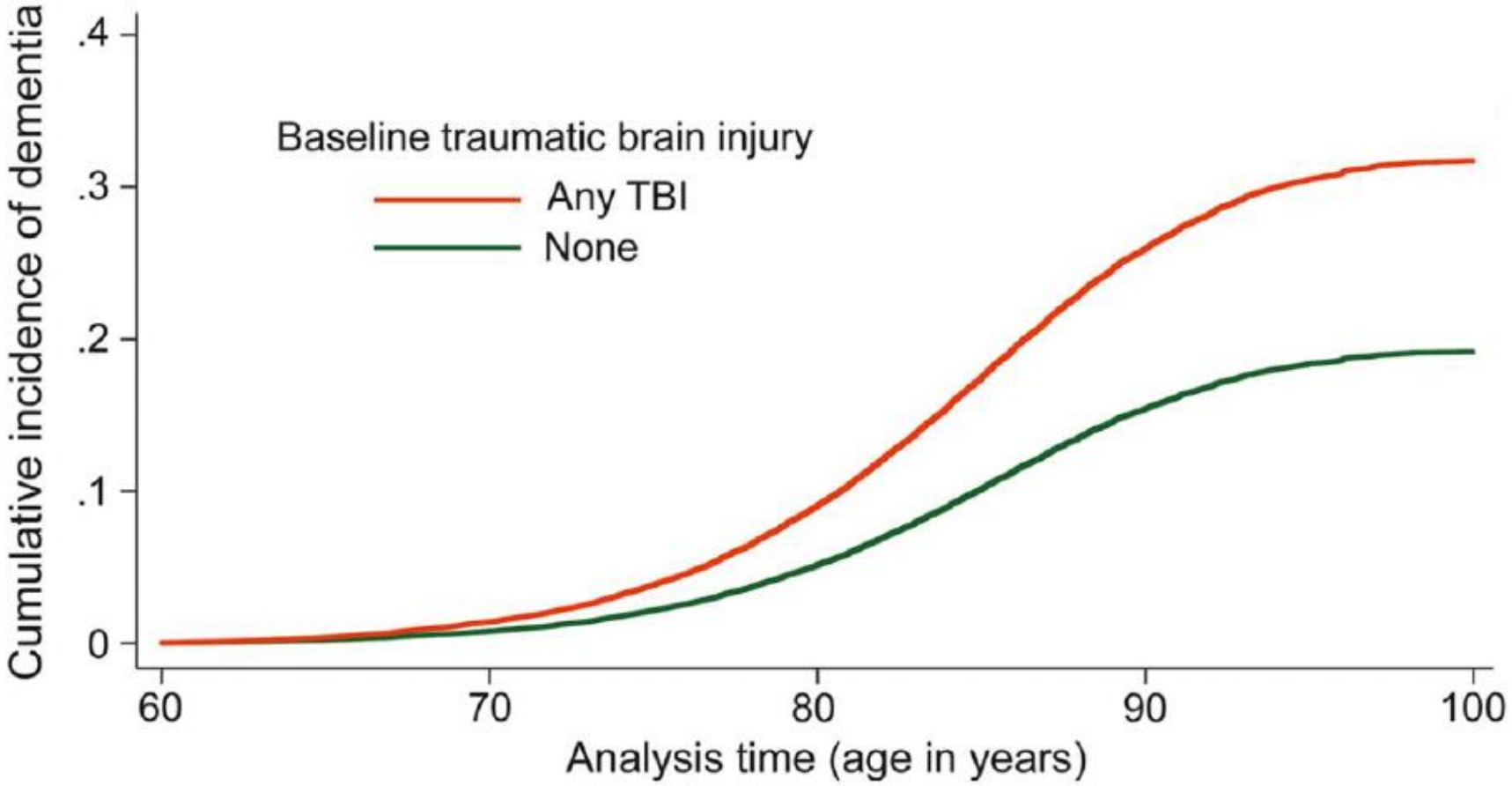
CENC Epidemiology Data

DoD and VA maintain large Veterans' health datasets

In an innovative and cost efficient way, we pooled DoD and VA datasets to determine the effects of TBI (by injury severity) in Service Members and Veterans



60% Increased Risk of Dementia with TBI

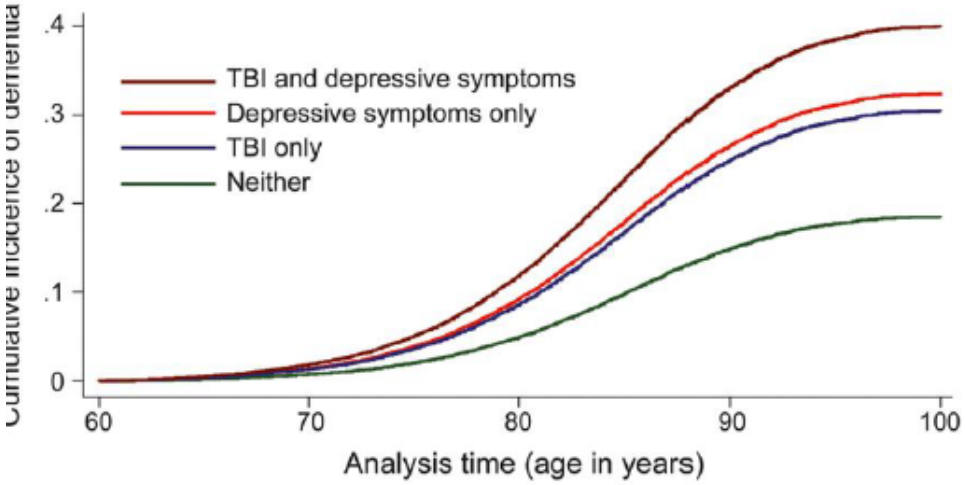


Adjusted HR:1.57; 95% CI (1.35–1.83)

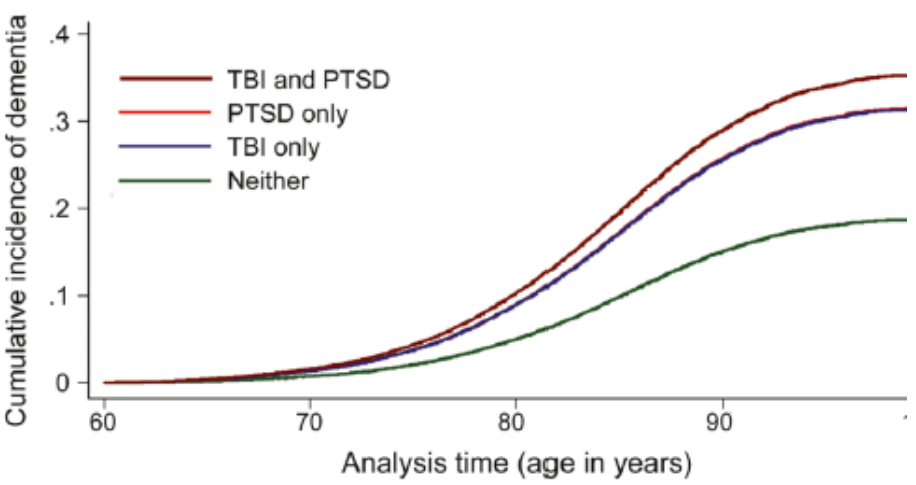
Barnes…Yaffe, *Neurology*, 2014.

Comorbidities Have an Additive Effect on Dementia Risk

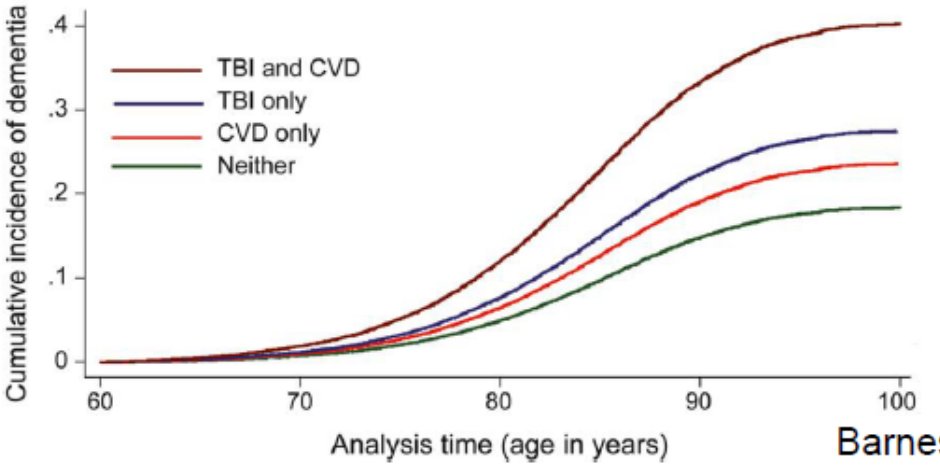
Depression



PTSD



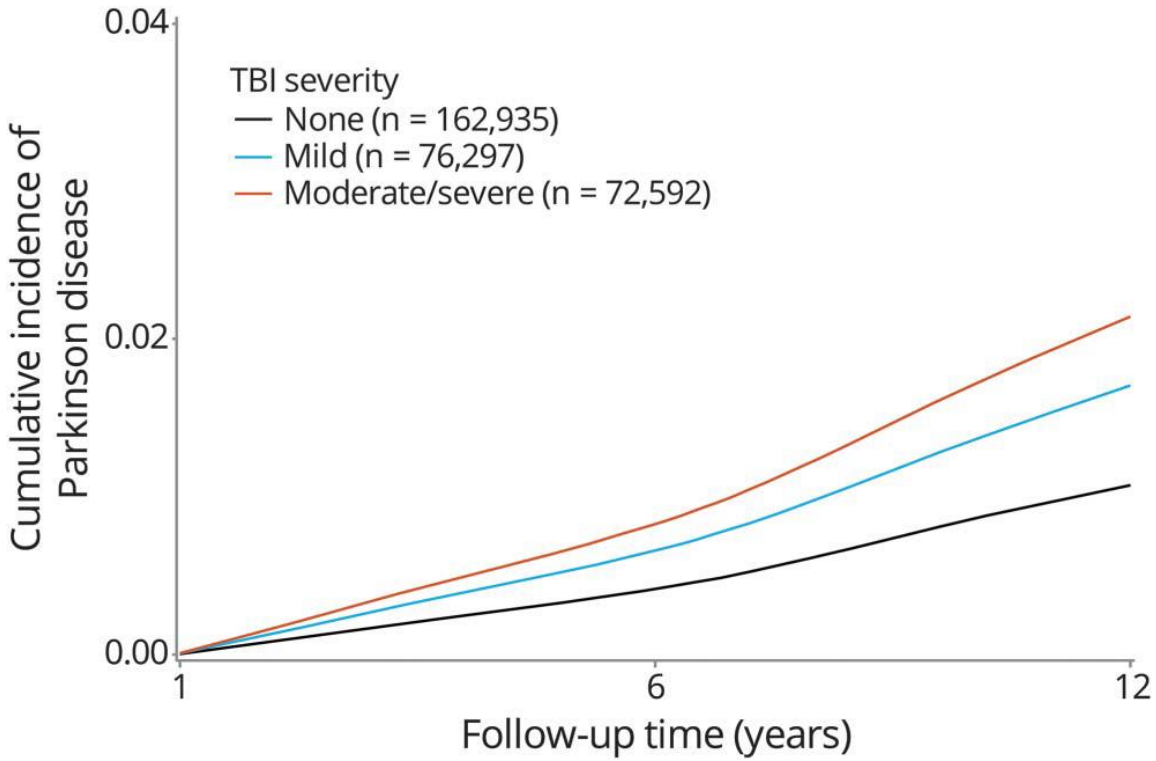
Cerebrovascular Disease



Barnes…Yaffe, *Neurology*, 2014.

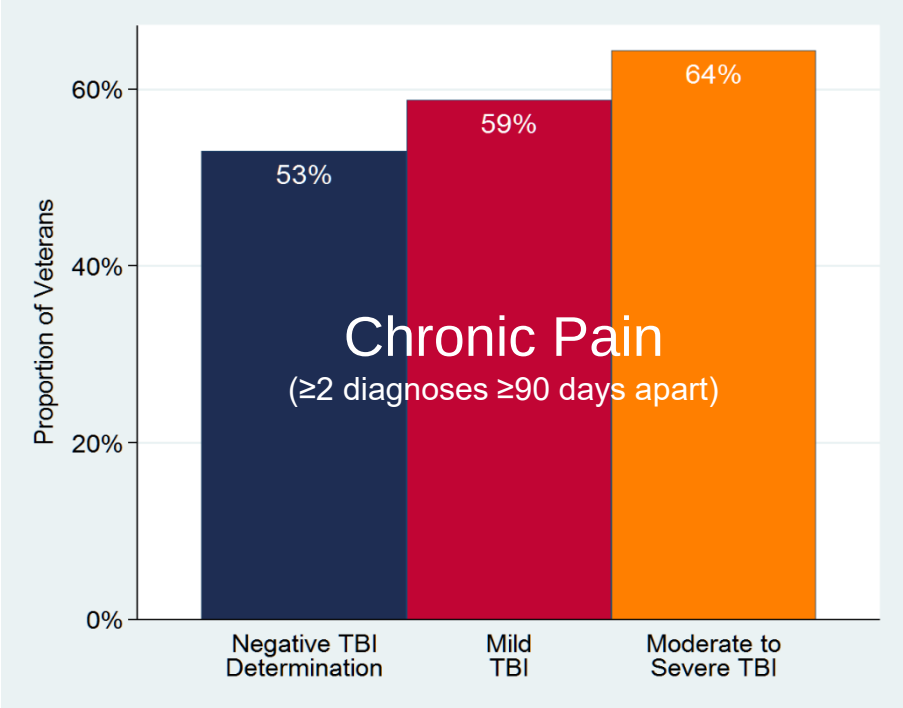
Risk of Parkinson's Disease Increases with TBI Severity

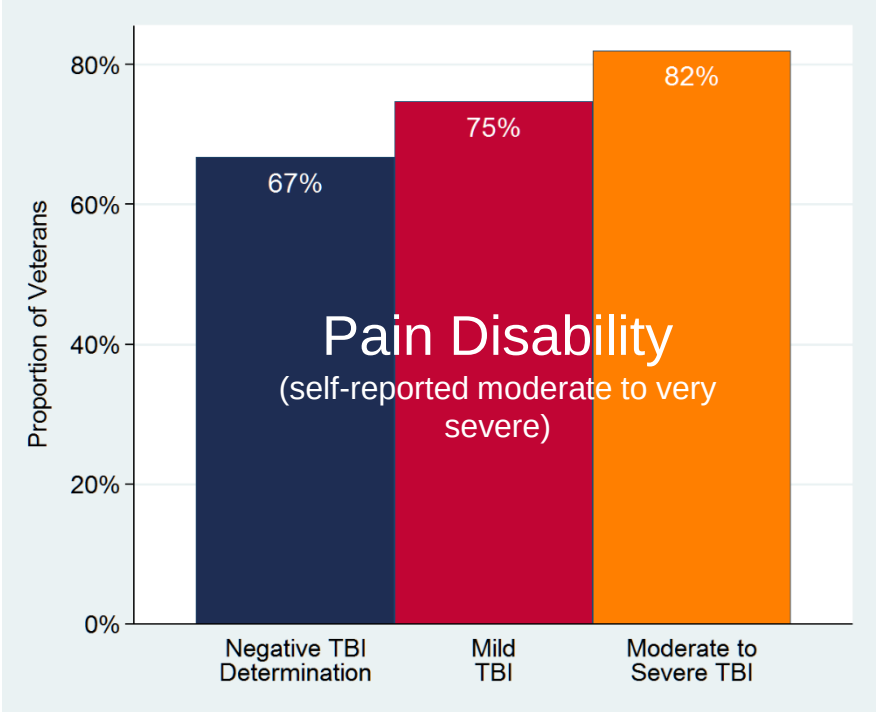
TBI Severity	Adjusted Hazard Ratios of Parkinson's (95% CI)
Mild	1.56 (1.35, 1.80)
Moderate/Severe	1.83 (1.37, 2.07)



Gardner et al, Neurology 2018

Chronic Pain and Pain Disability

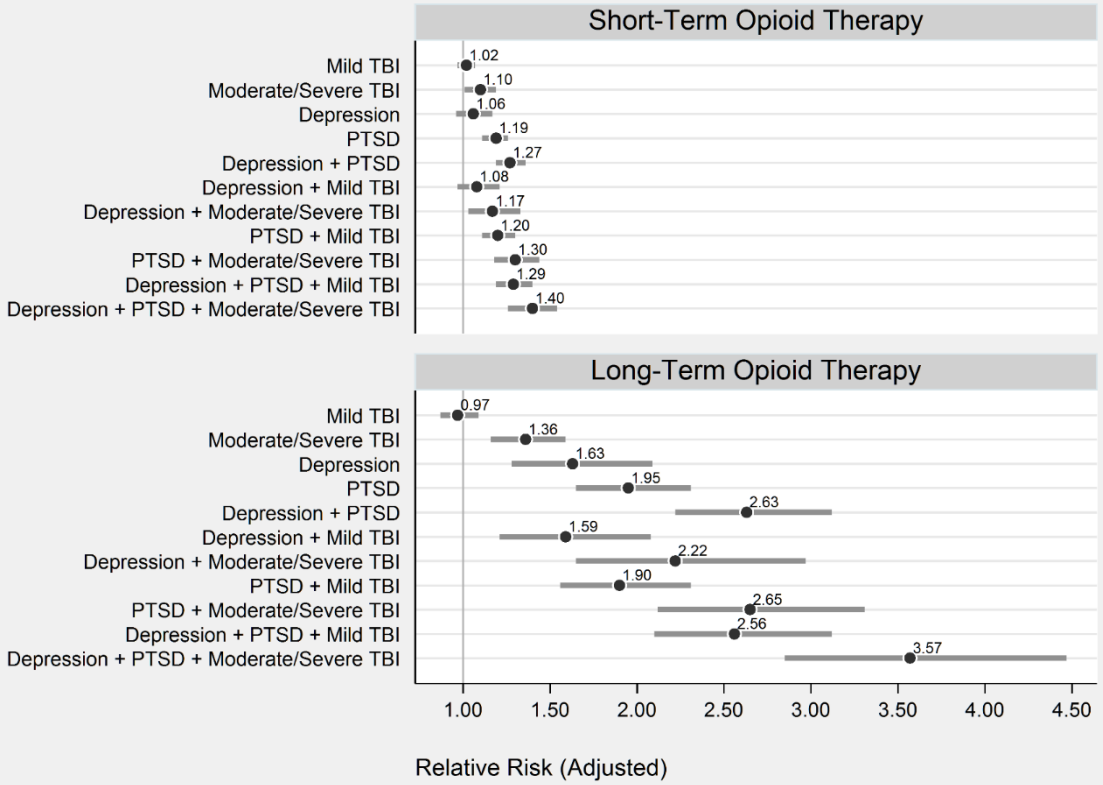




Study population: 116,913 Iraq/Afghanistan Veterans who received care from 2007-2015 and completed Comprehensive TBI Evaluation (CTBIE)

Seal et al., Arch Phys Med and Rehab, 2017.

Chronic Opioid Therapy Higher in mTBI + Depression/PTSD



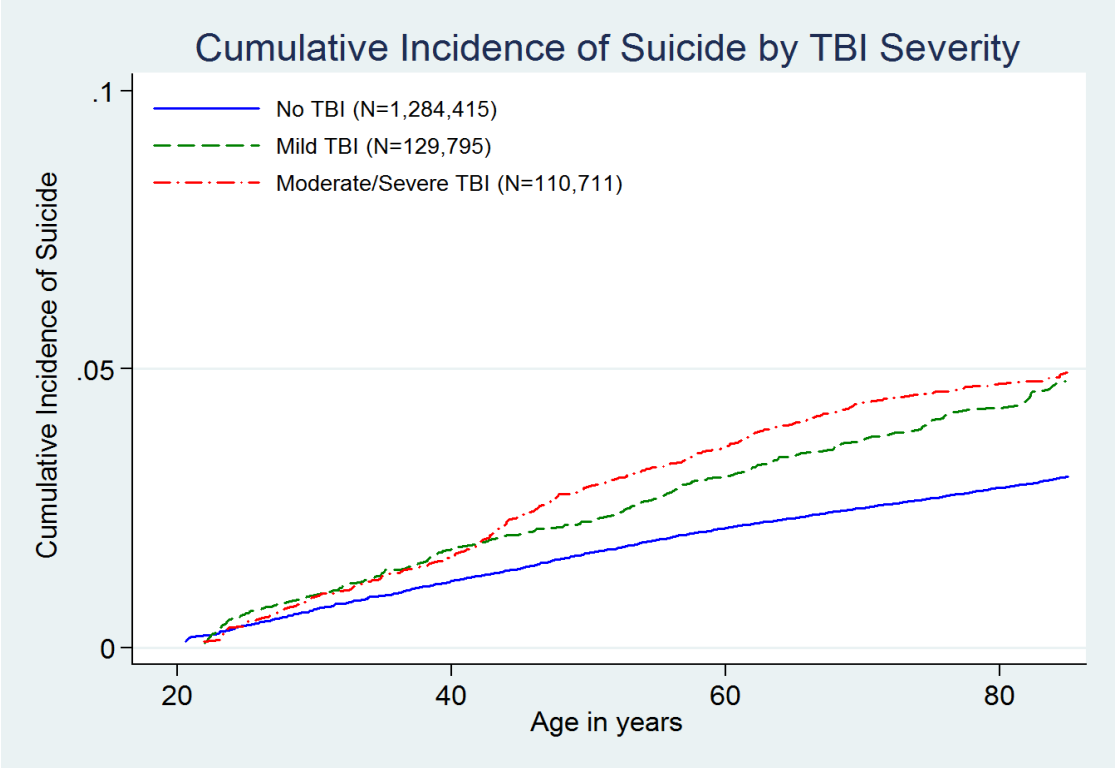
<u>Study population:</u>

53,124 Iraq/Afghanistan Veterans who completed CTBIE and had chronic pain and no opioid prescriptions in prior year

Seal et al., J Pain, 2018.

Risk of Suicide Increases with TBI Severity

TBI Severity	Adjusted Hazard Ratio of Suicide (95% CI)
Mild	1. 23 (1.08, 1.41)
Moderate/Severe	1.46 (1.29, 1.64)



Byers et al: under review

CENC Next Steps

- Longitudinal Observational Study (current n = 1,647) is expanding to 11 recruitment sites with annual re-assessment and monitoring for recovery and/or neurodegeneration patterns. Expansion of Biomarker and Imaging assessments.

- Epidemiologic Study (2 million unique subjects) will continue to explore associations between mTBI/co-morbidities and persistence of symptoms (pain, opioid usage, behavioral), recovery patterns, health care utilization, and neurodegeneration.

- Interventional trials will be implemented using the Longitudinal Cohort as appropriate management strategies and approaches are identified.

- $50 million renewal proposal (LIMBIC) submitted January 2019.

Dementia Risk After TBI

- Significant focus on acute effects of TBI
- Long-term effects of TBI are unclear
- There is a large population of older adults at risk for dementia
  - 40% of U.S. 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

Yaffee, 2018

Dementia-related Factors

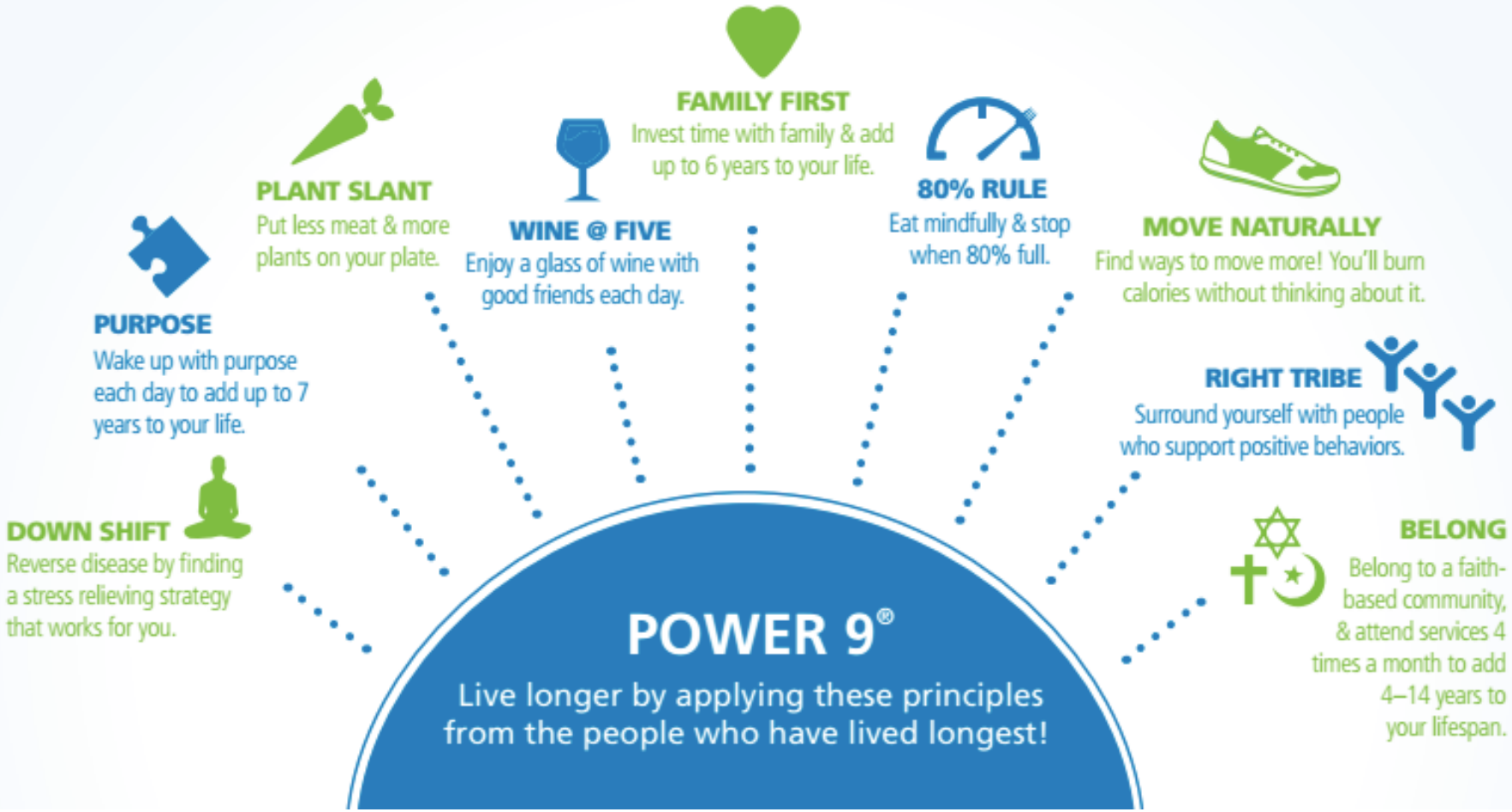
- Nine modifiable lifestyle factors account for up to 50% of all cases of dementia
  - Limited education in early life
  - hearing loss
  - Hypertension
  - Obesity
  - Smoking
  - Depression
  - Physical inactivity
  - Social isolation
  - Diabetes
- No single risk or protective factor is dominant.

Ashby-Mitchell: Alzheim 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) ϵ4 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)



75% of chronic diseases preventable

One-third of dementias preventable

Diet, Exercise, Sleep, Stress Management, Pain Care, Productivity, Social Integration, Family, Faith-Based Community

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.

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.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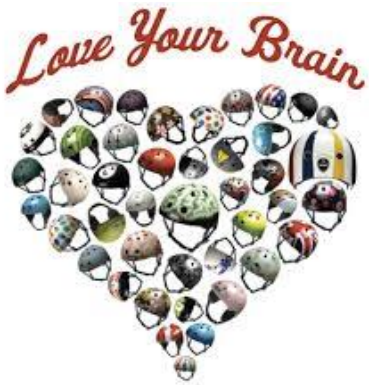
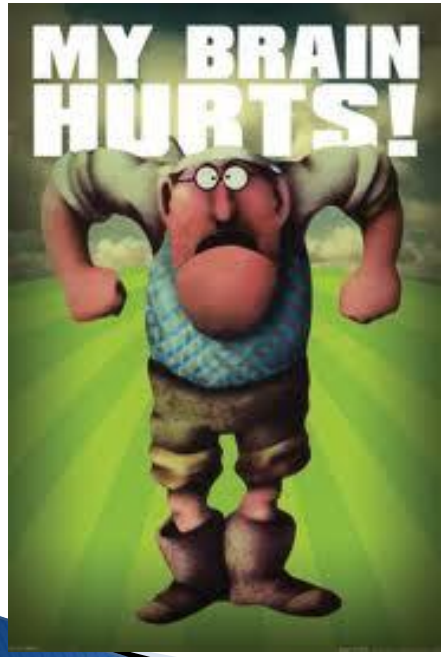
UNITED STATES OF AMERICA


Love Your Brain


DEPARTMENT OF DEFENSE
UNITED STATES OF AMERICA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