

RELATIONSHIP OF DEPLOYMENT-RELATED MILD TRAUMATIC BRAIN INJURY TO POSTTRAUMATIC STRESS DISORDER, DEPRESSIVE DISORDERS, SUBSTANCE USE DISORDERS, SUICIDAL IDEATION, AND ANXIETY DISORDERS: A SYSTEMATIC REVIEW

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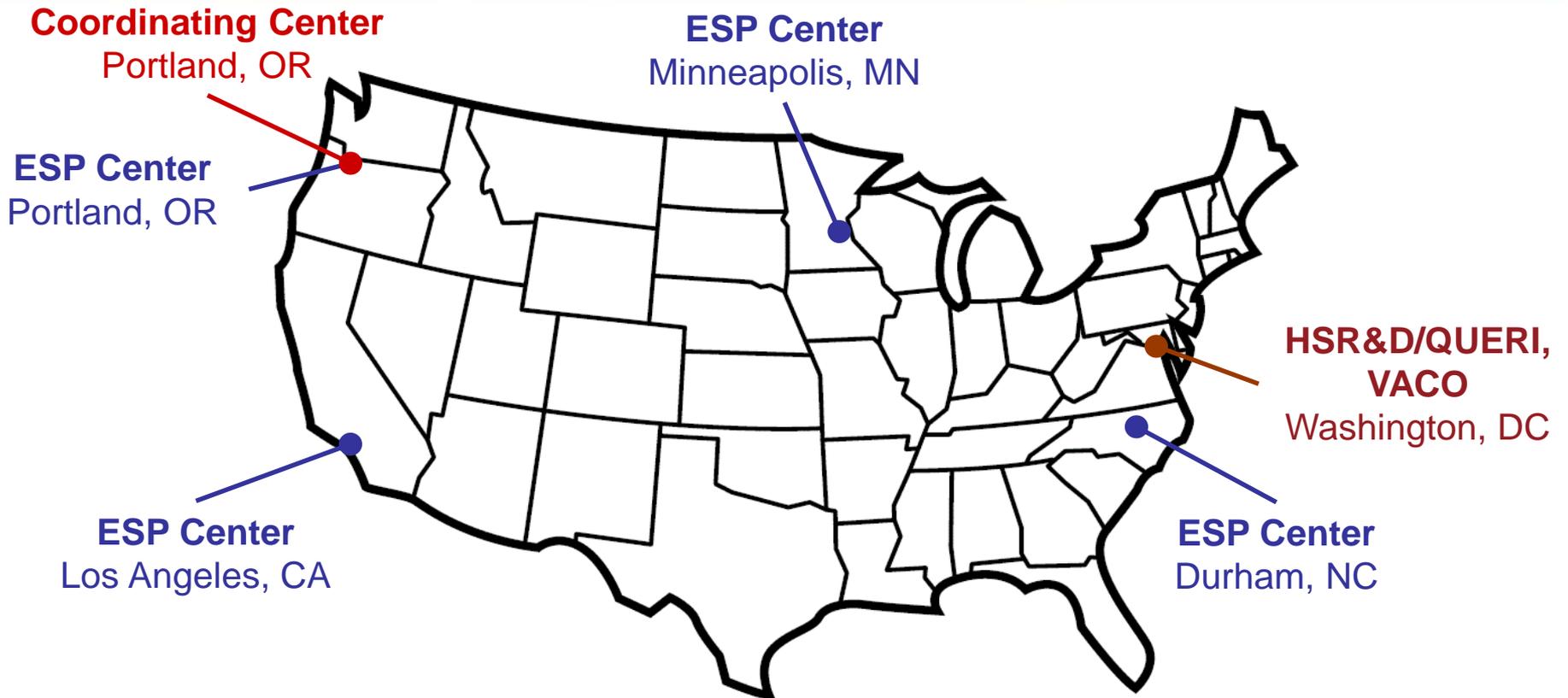
Disclosure

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VA Evidence-based Synthesis Program (ESP) Overview

- Sponsored by VA Office of Research and Development and the Quality Enhancement Research Initiative (QUERI)
- Established to provide timely and accurate syntheses/reviews of healthcare topics identified by VA clinicians, managers, and policy-makers, as they work to improve the health and healthcare of Veterans
- Reports conducted by internationally recognized VA clinician methodologists
- Builds on staff and expertise already in place at the Evidence-based Practice Centers (EPC) designated by AHRQ

ESP Center Locations



VA Evidence-based Synthesis Program (ESP) Overview

- ESP reports help:
 - develop clinical policies informed by evidence
 - the implementation of effective services to improve patient outcomes and to support VA clinical practice guidelines and performance measures
 - guide the direction of future research to address gaps in clinical knowledge
- Broad topic nomination process – *eg*, VACO, VISNs, field staff – facilitated by the ESP Coordinating Center (Portland) through an online process:

<http://www.hsrd.research.va.gov/publications/esp/TopicNominationForm.pdf>

Current Report

RELATIONSHIP OF DEPLOYMENT-RELATED MILD TRAUMATIC BRAIN INJURY TO POSTTRAUMATIC STRESS DISORDER, DEPRESSIVE DISORDERS, SUBSTANCE USE DISORDERS, SUICIDAL IDEATION AND ANXIETY DISORDERS: A SYSTEMATIC REVIEW

(June 2018)

Full-length report available on ESP website:

<http://www.hsrd.research.va.gov/publications/esp/reports.cfm>

Poll Question #1

- What percentage of individuals, deployed during OEF/OIF/OND and receiving VA medical care, sustained a confirmed combat-related TBI?
 - 8%
 - 20%
 - 33%
 - 50%

Background

- More than 2 million US service members deployed to Iraq and Afghanistan since September 11, 2001¹
- ~20% of OEF/OIF/OND Veterans who received VA medical care have a confirmed combat-related TBI²
- VHA began required screening for TBI in 2007; through September 2016:
 - 1,066,474 Veterans screened
 - 201,997 screened positive
 - 147,744 completed VA Comprehensive TBI Evaluation
 - 83,318 confirmed TBI diagnoses, mostly mTBI³
- Are psychiatric conditions more common in service members and Veterans with a deployment-related TBI? Are mental health treatments effective and safe for those with a history of TBI?

¹Defense and Veterans Brain Injury Center. Service Members and Veterans; ²Cifu 2018; ³Hoffman et al, Brain Inj 2017

Poll Question #2

- Which best describes your experience with systematic reviews?
 - Lead author and/or methodologist on a review
 - Participated on research team or taken systematic review coursework
 - Read systematic reviews
 - No experience with systematic reviews

Key Questions

- **Key Question 1a.** Is the prevalence of psychiatric conditions (posttraumatic stress disorder [PTSD], depressive disorders, substance use disorders, suicidal ideation or attempts, and anxiety disorders) different in service members and Veterans with and without deployment-related mild traumatic brain injury (mTBI) (one or more)?
- **Key Question 1b.** How do severity and persistence of psychiatric conditions (PTSD, depressive disorders, substance use disorders, suicidal ideation or attempts, and anxiety disorders) differ in service members and Veterans with and without deployment-related mTBI?

Key Questions

- **Key Question 2.** What are the effectiveness and comparative effectiveness and harms of interventions for treatment of PTSD, depressive disorders, substance use disorders, suicidal ideation or attempts, and anxiety disorders in service members and Veterans with history of deployment-related mTBI?

PICOT

Population: OEF/OIF/OND active duty service members and Veterans with 1 or more deployment-related mTBI(s)

Intervention: Deployment-related mTBI(s)

KQ2: Pharmacological or non-pharmacological interventions for the management of psychiatric conditions

Comparator: No deployment-related mTBI(s)

KQ2: Placebo or alternative pharmacological or non-pharmacological interventions including wait-list controls

Outcomes:

KQ1: Prevalence, severity, and symptom persistence of psychiatric conditions

KQ2: Clinically important changes in symptoms (improvement, loss of diagnosis, harms) following treatment; changes in function and quality of life

Timing: Any time post-deployment

Methods

- Protocol registered in PROSPERO
- Literature search:
 - MEDLINE, PsycINFO, & PILOTS databases
 - VA HSR&D & DVBIC websites
 - Reference lists of included studies and relevant systematic reviews
- Dual independent review of abstracts and full text articles

Methods

- **Inclusion (KQ1a/1b):**
 - Nationally representative or geographically diverse sample of US service members and/or Veterans (OEF/OIF/OND era)
 - Reported prevalence, severity, or symptom persistence of identified psychiatric conditions
 - Enrolled those with and without a history of mTBI (at least one incurred during deployment)
 - NOTE: Included studies that did not specify TBI severity based on prior research¹

¹Taylor et al, J Neurotrauma 2017

Methods

- **Inclusion (KQ2):**
 - Intervention for psychiatric condition(s) of interest
- **Exclusion (all KQs)**
 - Non-US service members
 - >75% not OEF/OIF/OND era
 - Not reporting outcomes of interest
 - Case reports, narrative reviews, etc.

Methods

Risk of Bias

- Criteria adapted from existing checklists
- KQ1: Joanna Briggs Institute Critical Appraisal Checklist for Studies Reporting Prevalence Data (<http://joannabriggs.org/research/critical-appraisal-tools.html>)
- KQ2: Joanna Briggs Institute Critical Appraisal Tool for Quasi-Experimental Studies (experimental studies without random allocation) (<http://joannabriggs.org/research/critical-appraisal-tools.html>)

Methods

- **Data Synthesis**

- KQ1: qualitative synthesis; considered subsets (active duty vs Veteran, time since TBI, etc.) where feasible
- KQ2:
 - Within study effect sizes using pre- to post-treatment data, if reported
 - Between group effect sizes based on mean change from baseline for each group, if reported

- **Strength of Evidence**

- Prevalence of psychiatric conditions – national sample data only (KQ1)
- Effectiveness of interventions for psychiatric conditions (KQ2)

Results - Literature Flow

Abstracts Reviewed: 1,215 citations



Excluded: 740 citations



Full Text Review: 475 articles
Excluded: 434 articles



Included: 41 articles
Key Question 1: 34 articles (33 studies)
Key Question 2: 7 articles

Results – Key Question 1 – Prevalence and Severity/Persistence

- National Samples – 11 studies:
 - Service members (2007-2011) (k=4)
 - Veterans (2007-2014) (k=7)
 - **Sample size:** 9,258 to 684,133
 - **Data sources:** medical records (k=3), surveys/questionnaires (k=3), administrative databases (k=5)
 - **TBI severity:** mTBI (k=5), unspecified (k=6)
 - **Etiology:** 100% blast (k=1), 74-80% blast or blast plus other (k=2), 60% blunt force (k=1)
 - **Time since TBI:** mean 4.8 years (k=1)
 - **Risk of bias:** low (k=1), moderate (k=9), high (k=1)

Results – Key Question 1 – Prevalence and Severity/Persistence

- Geographically Diverse Studies – 22 studies:
 - Service members (k=15), Veterans (k=6), Service members and Veterans (k=1)
 - **Sample size:** 65 to 11,828 (15 with < 1,000)
 - **Data sources:** medical evaluation (k=7), self-report/interview (k=12), administrative databases (k=3)
 - **TBI severity:** mTBI (k=20), unspecified (k=2)
 - **Etiology:** 100% blast (k=5), 65-95% blast (k=6)
 - **Time since TBI:** <14 days (k=5), <1 year (k=3), >1 year (k=1)
 - **Risk of bias:** low (k=1), moderate (k=16), high (k=5)

KQ1a - Prevalence of Psychiatric Conditions – National Samples

	PTSD	Depressive Disorders	Substance Use Disorders	Suicidal Ideation/ Attempts	Anxiety Disorders
SERVICE MEMBERS (4 studies)		↑ 1 study PHQ	↑ 2 studies ICD-9 or PDHA		
VETERANS (7 studies)	↑ 7 studies ICD-9 or CTBIE	↑ 5 studies ↔ 1 study ICD-9 or CTBIE	↑ 3 studies ↔ 1 study ICD-9 or CTBIE	↑ 1 study ICD-9	↑ 3 studies ↔ 1 study ICD-9 or CTBIE
TOTAL	↑ 7 studies 63-77% vs 10-64%	↑ 6 studies 31-50% vs 11-35% ↔ 1 study 47% vs 45%	↑ 5 studies a. binge drinking 28% vs 19% b. alcohol/drug 4% vs 2% c. alcohol 8-13% vs 4-11% and drug (k=2) d. substance (incl nicotine) 38% vs 21% ↔ 1 study alcohol or drug abuse	↑ 1 study attempts 0.5% vs 0.1%	↑ 3 studies (17-31% vs 8-16%) ↔ 1 study (24% vs 26%)

KQ1a - Prevalence of Psychiatric Conditions – Geographically Diverse Samples

	PTSD	Depressive Disorders	Substance Use Disorders	Suicidal Ideation	Anxiety Disorders
SERVICE MEMBERS (15 studies)	↑ 9 studies ↔ 2 studies Mixed 1 study	↑ 3 studies ↔ 1 study Mixed 1 study	↑ 1 study ↔ 2 studies	↑ 2 studies	↔ 1 study
VETERANS (7 studies)	↑ 5 studies	↑ 2 studies	↑ 3 studies		↑ 2 studies
TOTAL	↑ 14 studies ↔ 2 studies Mixed 1 study PCL-M, PCL-C, PCL-17, CAPS-IV, ICD-9, PC-PTSD, PDHA	↑ 5 studies ↔ 1 study Mixed 1 study PHQ-9, PHQ-15, PDHRA, BDI-II, ICD-9, MADRS	↑ 4 studies ↔ 2 studies AUDIT, CAGE, ICD-9	↑ 2 studies (ideation) SBQ-R, PHQ-9	↑ 2 studies ↔ 1 study BAI, ICD-9

KQ1b – Severity/Persistence of Psychiatric Conditions – National Samples

	PTSD	Depressive Disorders	Substance Use Disorders	Suicidal Ideation	Anxiety Disorders
SERVICE MEMBERS (4 studies)	↑ 1 study (PCL-M)				
VETERANS (7 studies)			↑ 1 study (AUDIT)		
TOTAL	↑ 1 study		↑ 1 study		

KQ1b – Severity/Persistence of Psychiatric Conditions – Geographically Diverse Samples

	PTSD	Depressive Disorders	Substance Use Disorders	Suicidal Ideation	Anxiety Disorders
SERVICE MEMBERS (15 studies)	↑ 4 studies Mixed 2 studies	↑ 2 studies ↔ 1 study Mixed 2 studies	↔ 1 study Mixed 1 study	↑ 1 study	
VETERANS (7 studies)	↑ 2 studies	↑ 2 studies	↑ 1 study		
TOTAL	↑ 6 studies Mixed 2 studies PCL, PCL-M, CAPS-IV	↑ 4 studies ↔ 1 study Mixed 2 studies BHM-20, MADRS, BDI-II, CESD	↑ 1 study ↔ 1 study Mixed 1 study AUDIT, MAST	↑ 1 study SBQ-R	

Key Question 1

Summary of Findings – National Samples

- ***PTSD***: more prevalent in Veterans with a history of mTBI (moderate strength evidence)
- ***Depressive disorders***: more prevalent in Veterans and service members with a history of mTBI (low strength evidence)
- ***Substance use disorders (including alcohol, drug, and tobacco)***: more prevalent in Veterans and service members (low strength evidence)
- ***Suicidal ideation or attempts***: more prevalent in Veterans (insufficient evidence)
- ***Anxiety disorders***: generally more prevalent in Veterans (low strength evidence)
- ***Severity or persistence***: rarely reported (insufficient evidence)

Results – Key Question 2 – Effectiveness and Harms of Treatments for Mental Health Conditions in Service Members and Veterans with mTBI

- No randomized controlled trials
- 7 non-randomized studies
 - 3 compared outcomes in service members or Veterans with a history of TBI vs no history
 - 4 reported outcomes for service members or Veterans with a history of TBI
- 6 studies of behavioral therapies for PTSD, depressive disorders, or anxiety disorders
 - 4 pre- to post-treatment; 2 secondary analyses of randomized trials
 - Sample size: 10 to 129
 - Population: mostly Veterans, 78-100% male, mean ages 33-35 years
 - Risk of bias: moderate to high
- 1 proof-of-concept study of hyperbaric oxygen therapy, n=16
 - ESP Evidence Brief: *Hyperbaric Oxygen Therapy (HBOT) for Traumatic Brain Injury and/or Post-traumatic Stress Disorder*
<https://www.hsrd.research.va.gov/publications/esp/hbot.cfm>

Results – Key Question 2 - Studies with TBI and No-TBI Groups

- ***Cognitive Processing Therapy (CPT)*** and ***Prolonged Exposure Therapy (PE)***
 - Retrospective study, Veterans, clinical data from medical records, n=19
 - Therapies reduced PTSD symptoms (PCL-S) in Veterans with a history of TBI and PTSD-only groups
 - PE but not CPT reduced symptoms of depression (BDI-II) - both groups
- ***Acceptance and Commitment Therapy (ACT)*** and ***Present Centered Therapy (PCT)***
 - Secondary analysis of multi-site RCT, n=129
 - Modest reductions in BSI-18 scores (depression and anxiety symptoms) for both treatments and both TBI and no-TBI groups
 - Modest reductions in SF-12 Mental Health Component scores for both treatments and both TBI and no-TBI groups
 - Physical Health Component scores unchanged
- ***PE*** or ***PCT*** (Groups combined for analysis)
 - Secondary analysis of RCT, n=22
 - CAPS-IV scores reduced from pre-treatment in TBI and PTSD-only groups

Results – Key Question 2 - Studies with TBI Group Only

- ***Cognitive Processing Therapy (CPT)***
 - Pre- to post-treatment, residential program, n=28
 - History of mTBI meeting CAPS-IV criteria for PTSD
 - CAPS-IV and PCL-S scores improved significantly from pre-treatment
- ***Prolonged Exposure Therapy***
 - Inpatient and outpatient clinical care at 2 VA medical centers, n=69
 - PTSD and history of TBI (75% mild, 25% moderate/severe)
 - PCL and BDI-II scores improved from pre-treatment
 - PCL: clinically significant change for 61% (86% of completers)
 - BDI-II: clinically significant change for 45% (55% of completers)
 - Outpatient therapy, n=10
 - PTSD and history of mild/moderate TBI
 - PCL-M and BDI-II scores improved from pre-treatment
 - PCL-M: clinically significant change for 90% (no longer met criteria for PTSD)
 - BDI-II: clinically significant reduction in depressive symptom scores for 40%

Key Question 2

Summary of Findings – Behavioral Therapies

- Strength of Evidence: Insufficient
 - 4 small non-randomized studies with pre-post design, 2 secondary analyses of RCTs
 - Improvements in PTSD and depressive symptoms scale scores observed with all therapies; exceeded minimal clinically important differences reported in the literature for PCL-M, CAPS-IV, and BDI-II
 - Lack of usual care or wait-list control groups limits interpretation of effect
 - No differences in outcomes based on TBI status (3 studies) - studies not specifically designed to examine differential effectiveness
- No studies of treatments for substance use disorders or suicidal ideation
- No studies on pharmacological interventions for conditions of interest in service members or Veterans with and without a history of mTBI

Limitations/Future Research Recommendations

- Limitations:
 - KQ1: data largely from administrative database studies which lack information on TBI severity; wide range of outcome measures used; time of assessment post-injury varied (or not reported); data largely from VHA users only
 - KQ2: no RCTs; no studies of pharmacological interventions; no studies of treatments for substance use disorders or suicidal ideation; harms not reported
- Future Research Recommendations:
 - KQ1: cohort study, in-person data collection, validated measures, follow-up at regular time intervals, ideally starting at time of entering military service, details of TBI events and other exposures documented
 - Resource intensive, large sample size required
 - Alternative: existing longitudinal study registries
 - KQ2: randomized trials, both behavioral and pharmacological interventions, short- and long-term outcomes in addition to symptom measures, assess harms (physical, mental, financial)

Conclusions

KQ1: Reports from national and geographically diverse samples provide moderate strength evidence of increased prevalence of PTSD and low strength evidence of increased prevalence of depressive, substance use, and anxiety disorders in active duty service members and Veterans with a history of mTBI compared to those with no TBI. There was little reporting of prevalence of suicidal ideation or severity and persistence of symptoms for any of the psychiatric conditions.

KQ2: Behavioral treatments for PTSD achieved minimal clinically important differences for changes in PTSD and depressive symptoms in Veterans with a history of TBI with no indication of harm. Results from studies that included groups with and without a history of TBI suggest TBI status does not affect treatment outcomes. Lacking usual care or wait-list control groups in the predominantly pre- to post-treatment studies, the strength of the evidence for effectiveness of interventions for psychiatric conditions in service members and Veterans with a history of mTBI is insufficient.



Discussion and Questions

Combat-Related Concussions

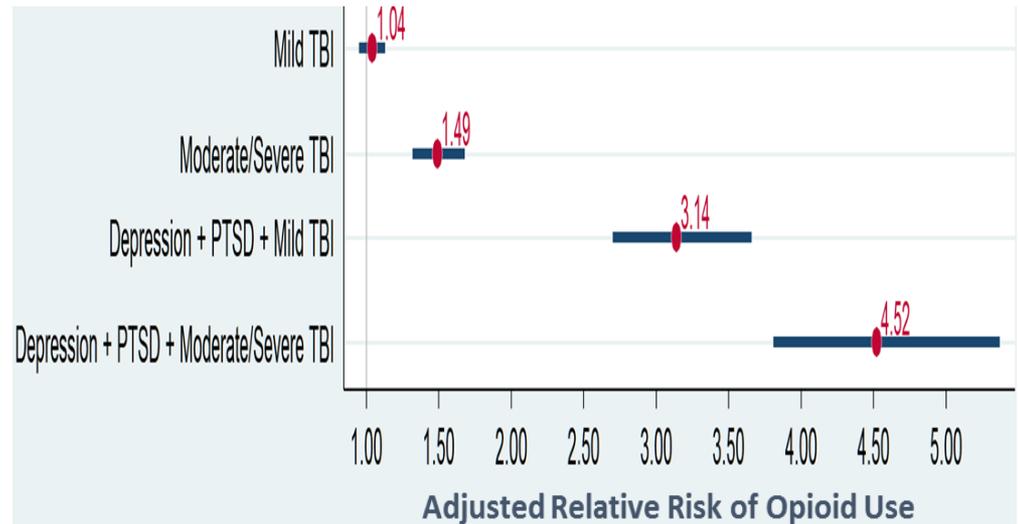
- ▶ Concussions (= mild TBI) are events that may or may not have short and/or long-term sequelae.
- ▶ ~20% of OEF-OIF-OND Veterans who received VA medical care have a confirmed combat-related TBI and, of these individuals, ~8% were still symptomatic when initiating care at VA
 - ~200,000 total (>1,100,000 screened) in VA
 - 90,000 symptomatic
 - >98% mild
 - <2% moderate-severe
 - >50% due to MVC in military theatre
- ▶ 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

CENC Findings: Short Term Outcomes and TBI

Aim: Determine the association between mTBI and Opioid Use in younger Veterans from the OEF-OIF-OND conflicts

- OEF/OIF/OND Veterans with TBI more likely to have chronic pain and disability and use opioids
- Risk of chronic pain and opioid use increase with severity of TBI and mental health burden
- Findings may help prevent adverse outcomes, including overdose death, and may help design opioid safety interventions
- CENC Epidemiology Study (Seal, Yaffe)

Risk of Opioid Use Increases with Greater TBI Severity and Mental Health Burden



CENC Findings: Long-Term Findings and TBI

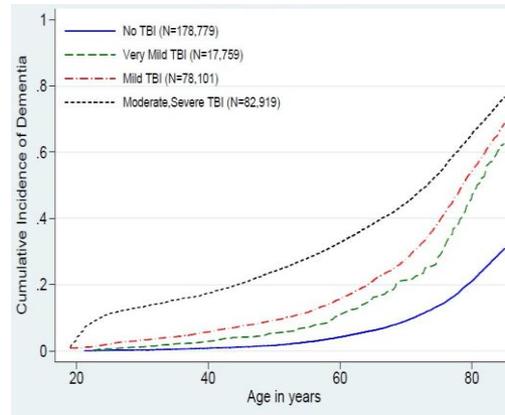
Aim: Determine the association between mTBI and neurologic outcomes in Veterans from all eras

- Veterans with TBI of any severity are at high risk of long-term neurologic outcomes, including dementia, Parkinson's, and suicide (including overdose and firearm deaths)
- One of the first studies to look at mild TBI with these outcomes
- Clinicians and patients should be aware that even mild TBI without LOC may increase risk of adverse neurologic outcomes
- CENC Epidemiology Study (Yaffe)

Next Steps:

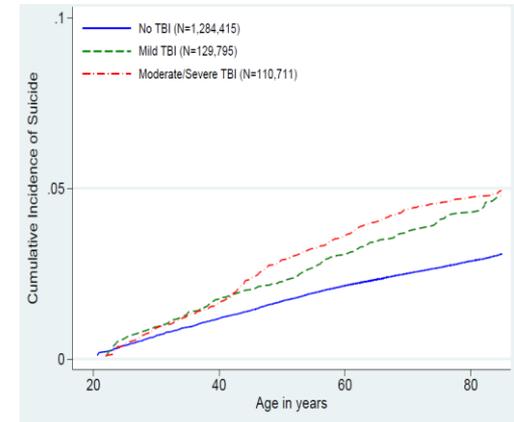
- TBI and sleep disorders
- TBI and cause-specific mortality

Risk of dementia increases with TBI severity

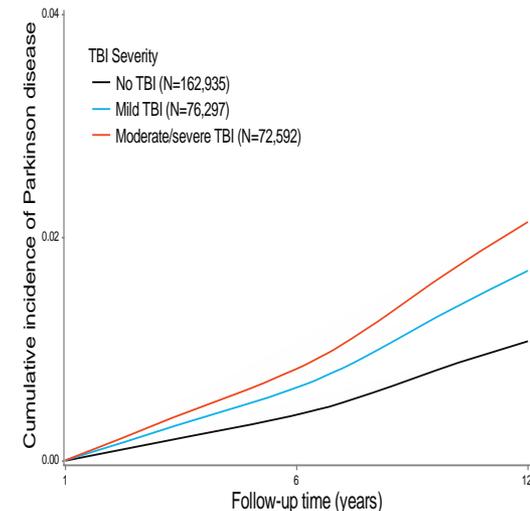


Adjusted HR = 1.57; 95% CL (1.35-1.83)

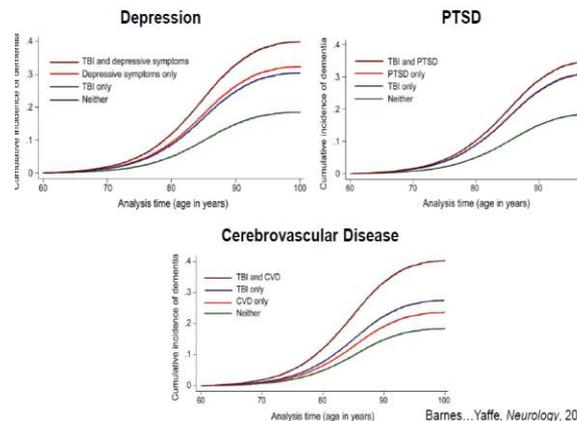
Risk of suicide increases with TBI severity



Risk of Parkinson's disease increases with TBI severity



Comorbidities Have an Additive Effect on Dementia Risk



Risk Communicating to Veterans with a TBI history and active Mental Health Disorders

- Acknowledge the Veteran's (and families') issues and concerns.
- Don't over explain or hedge your answers – you are the expert!
- The risk of developing dementia from a single concussion is **zero**. The risk of developing dementia from 10 concussions is also just barely above **zero**.
- Undertreated symptoms (post-concussion, mental health, pain) may be a more relevant risk factor for dementia than the TBI event.
- Treating PTSD, depression and other MH conditions with an evidence-based treatments is effective and can lower dementia risk!
- Lifestyle factors, general wellness, and integration into society are the biggest risk factors for dementia development.

Questions?

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