

LONG-TERM IMPACT OF MILITARY-RELEVANT BRAIN INJURY CONSORTIUM - CHRONIC EFFECTS OF NEUROTRAUMA CONSORTIUM (LIMBIC-CENC)

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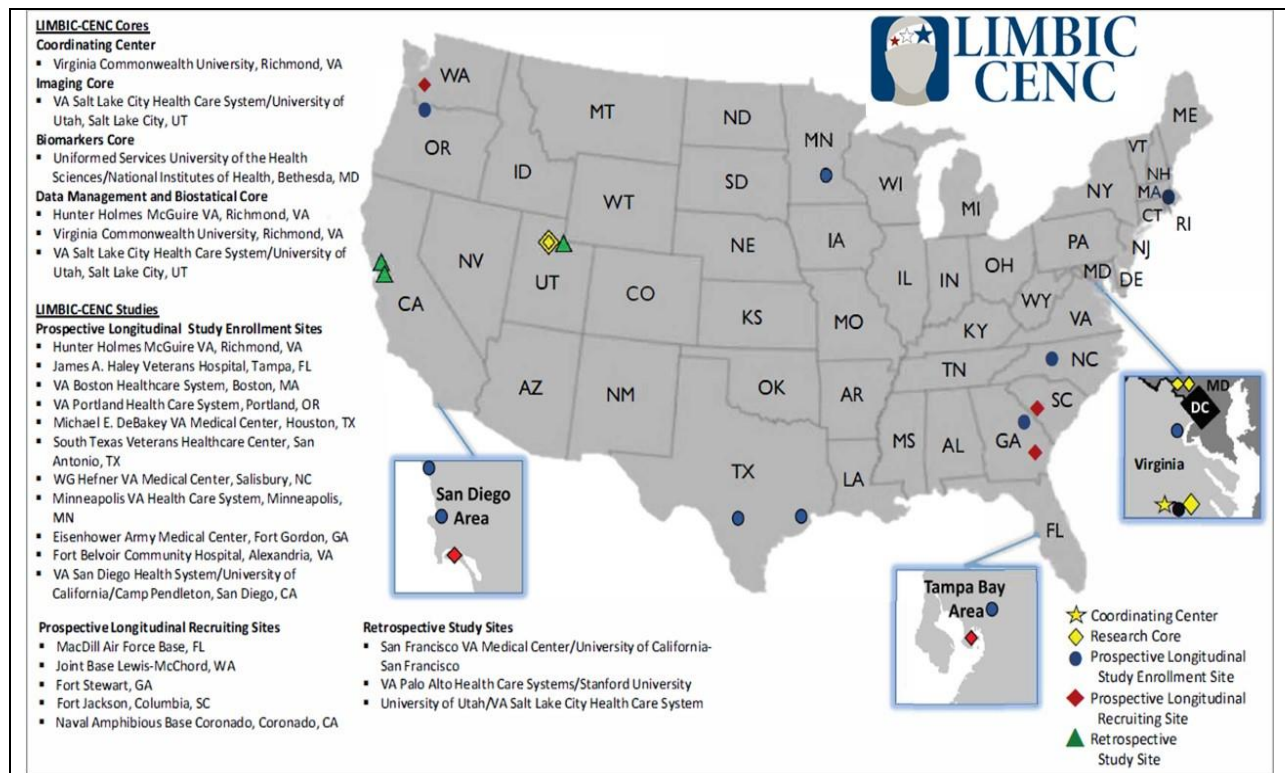
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- Mature, federal mTBI research consortium targeting long-term outcomes with robust infrastructure.
- Since 2013, 12 research studies have been completed with 200+ publications and 12 additional grants funded.
- Currently, supporting 6 active research studies
 - 2,000+ (target 3,000) participant Prospective Longitudinal Study
 - Prospective Biomarker Discovery and Novel Neuroimaging studies
 - 2.5+ million-participant Retrospective Database, Phenotypes and Health Economics big data studies using extant federal datasets
 - Also supporting 2 prospective intervention (sleep, cognitive dysfunction) trials
- Key deliverable: A range of Knowledge Translation products have been developed and additional ones are underway for consumers, family, clinicians and researchers.

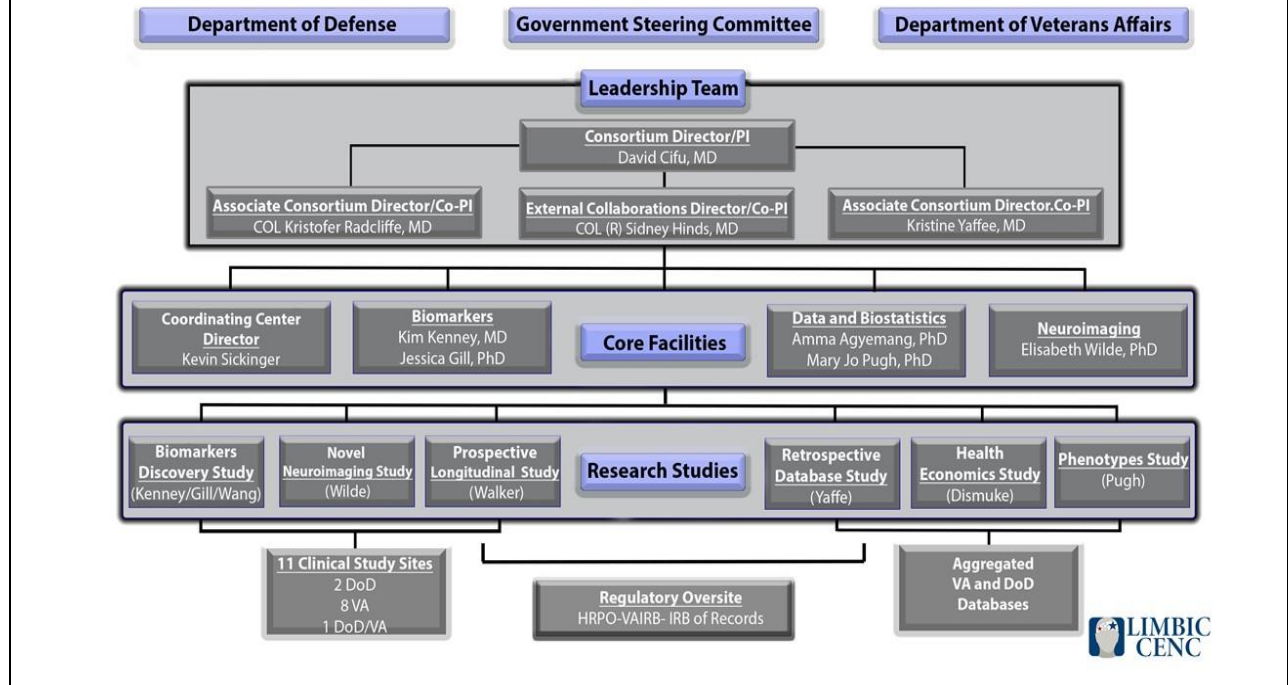


Summary of LIMBIC-CENC 2013-2022

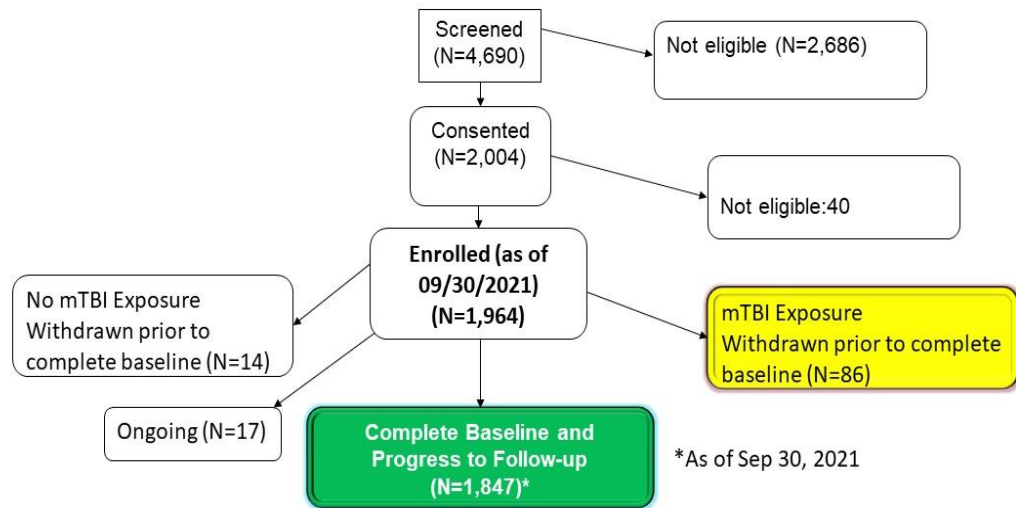
- The Chronic Effects of Neurotrauma Consortium (CENC 2013–19) identified a range of differences between SM's and Veterans with and w/o mild TBI in the 1,700+ participant Prospective Longitudinal Study (PLS).
- CENC derived a unique, combined mega-dataset from the VA and DoD's electronic medical, benefits, pharmacy and administrative records of 2+ million unique Veterans that revealed linkages between TBI and dementia, Parkinson's disease, chronic pain and suicide.
- The Long-term Impact of Military-relevant Brain Injury Consortium (LIMBIC 2019–24) commenced October 2019 and has grown the PLS to 2,000 (target 3,000) participants and also continues to analyze mega-dataset (2.5 million Veterans)
- LIMBIC-CENC's research teams have identified an association between TBI and dementia and biofluid markers of repetitive TBI, and confirmed that pain and mental health disorders worsen dysfunction after mTBI.



LIMBIC-CENC Organizational Chart



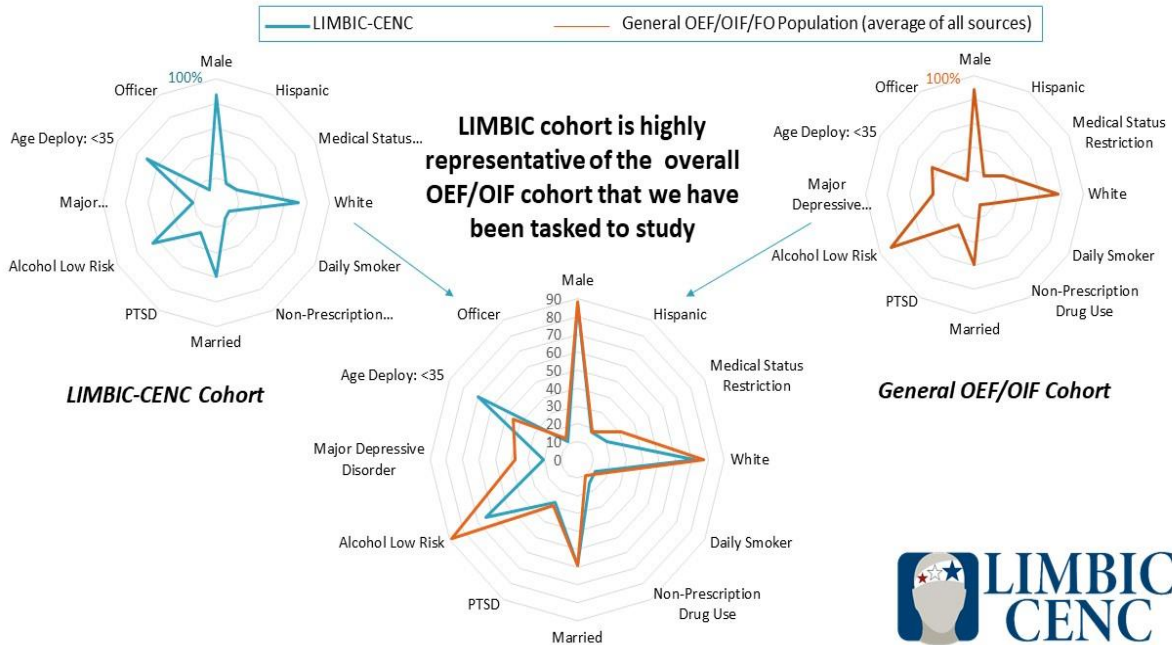
Study Consort Diagram for PLS Initial Evaluations



- Proportion with mTBI(s): 82%
- Median (IQR) # mTBIs per person: 2 (1,3).

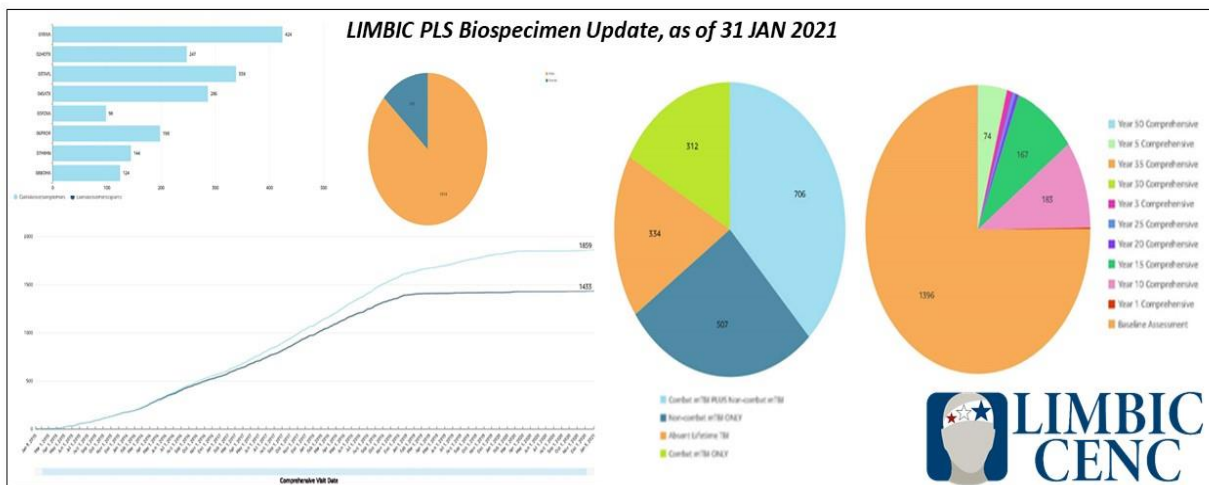


Comparison of Accrued Study Cohort to OEF/OIF Population



LIMBIC-CENC Biomarker Core

- Collated, stored, processed and aliquoted biospecimens from 1,859 Study 1 (426 F/U) participants and 163 samples from previous CENC studies for current total **28,223** aliquots of in the biorepository available for analysis.
- 4,202 have been distributed to LIMBIC Biomarker Discovery projects and to 3 collaborative projects approved by Research Committee.

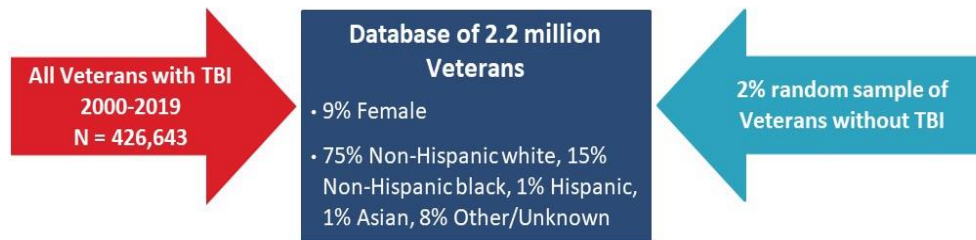


Creation of a Dashboard to Compare DoD, VA and Private Sector Inpatient Costs by Diagnosis Related Groups (DRG)

- Created a cohort of Veterans diagnosed with TBI in inpatient or outpatient VA administrative data based on DoD/VA ICD-9 codes between 2000-2015.
- Requested DoD data for those veterans who have records in DaVINCI.
- Followed utilization and cost of inpatient care in DoD Tricare and VA between 2004-2020 based on DRGs.
- For all inpatient discharges in DoD Tricare and VA 2004-2020, estimated the median DoD billing amount and VA MCA cost per TBI non-surgical DRG.
- Used AHRQ Health Care Utilization Project (HCUP) National Inpatient Sample (NIS) tool to calculate the median private sector hospital charge and hospital cost by TBI non-surgical DRG for 2017.
- Used the US Department of Labor Inflation Calculator to convert \$ to 2/2021 value.



Progress: LIMBIC-CENC Database

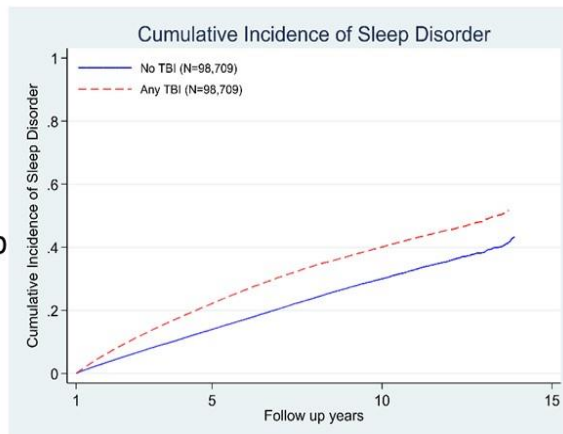


- Expanded and updated through 2020
- Contains inpatient/outpatient diagnosis codes and medication data for all 2.5 million Veterans, for use in defining outcomes, comorbidities, and examining treatment
- TBI and TBI severity defined using Defense and Veterans Brain Injury Center (DVBIC) definitions for TBI case detection
- TBI severity: 82% Mild, 17% Moderate, and 1% Severe/Penetrating



TBI and Risk of Sleep Disorders in Nearly 200,000 US Veterans

- Veterans with TBI were 41% more likely to develop any sleep disorder, adjusting for demographics and medical and psychiatric conditions: HR=1.41 (1.37-1.44)
- Veterans with TBI were more likely to develop
 - Sleep apnea HR=1.28 (1.24-1.32)
 - Insomnia HR=1.50 (1.45-1.55)
 - Hypersomnia HR=1.50 (1.39-1.61)
 - Sleep-related movement disorders HR=1.33 (1.16-1.52)



Leng et al., *Neurology*, 2021



Progress: TBI, Cardiovascular Disease, and Risk of Dementia among Older US Veterans

- CVD and TBI are both important risk factors for dementia; however, little is known about how they interact on this risk
- 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
- Preliminary Results:

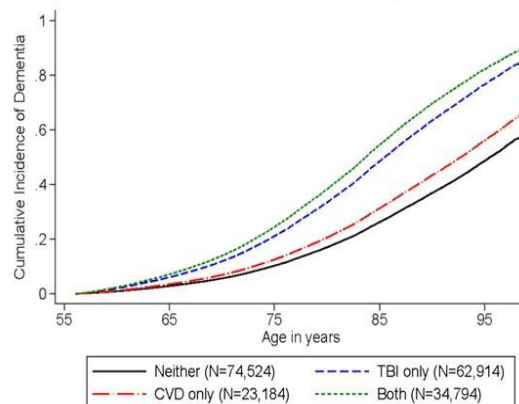
CVD and CV risk factors are 2X higher in people with TBI

TBI only: HR=2.35 (2.26-2.43)

CVD only: HR=1.26 (1.20-1.33)

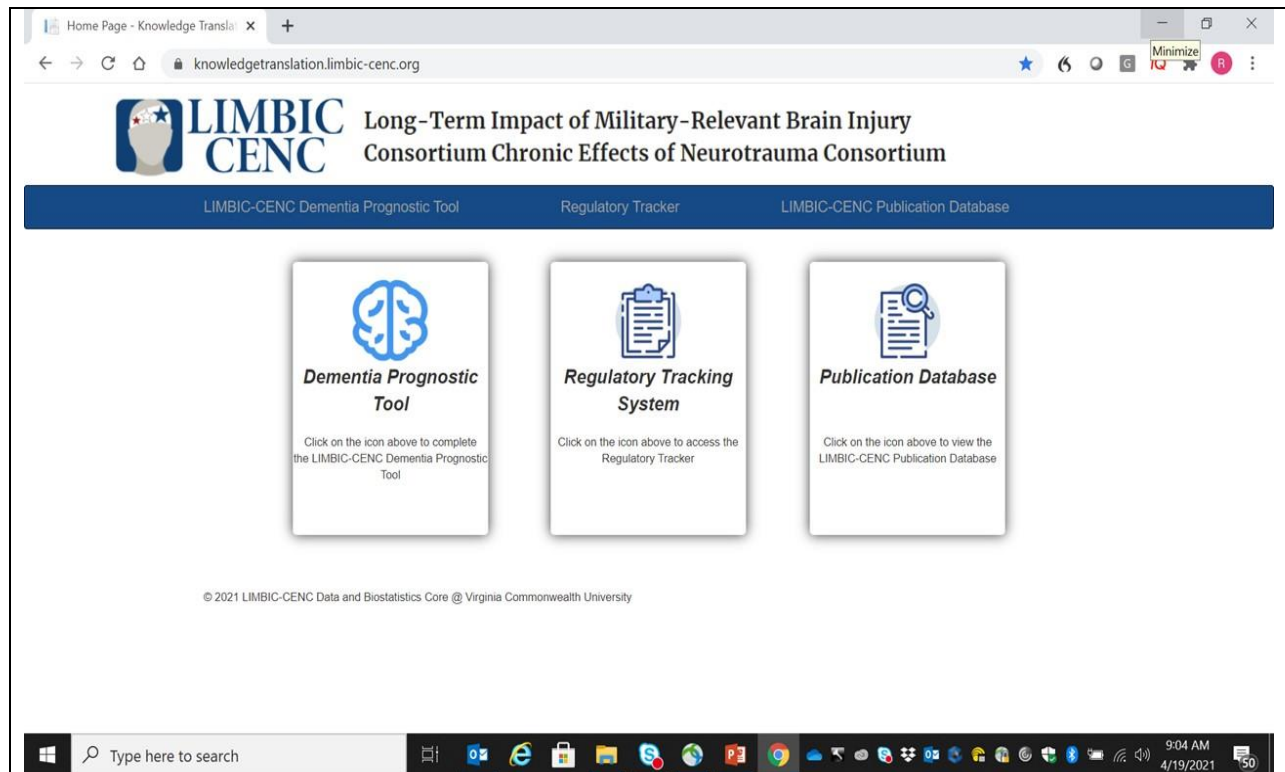
TBI + CVD : HR=2.83 (2.72-2.94)

Additive effect between TBI and CVD; no interaction



Kornblith et al., *in progress*

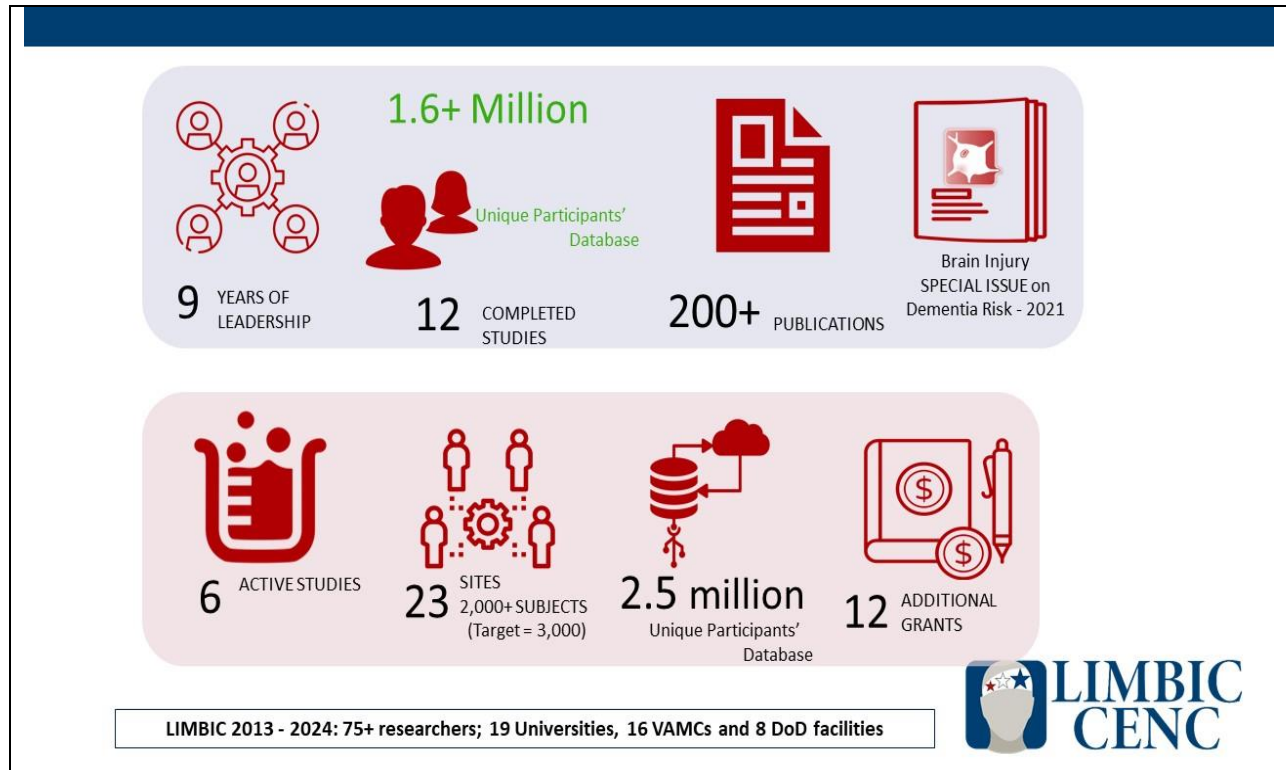




LIMBIC Key Findings 2021

- Veterans with TBI have higher rates of dementia, pain, opioid usage, mental health diagnoses, cardiovascular disease, stroke, and sleep dysfunction
- Service members and veterans with mTBI or blast do NOT have increased rates of neuroendocrine dysfunction.
- Tau and p-tau levels increased by number of blast exposures in Combat-exposed service members and veterans with mTBI.
- In service members and veterans, a greater # of mTBIs (3+) is associated with increased symptom burden and serum NFL levels
- In service members and veterans, increased “brain age” by imaging associated with increased h/o combat mTBI, # mTBI’s, depression, PTSD, poor sleep.





Brain Injury Special Edition – February 2022

- **Practical Approaches to Assessing and Mitigating the Risk of Cognitive Decline after Concussion: *Findings from the Long-term Impact of Military-relevant Brain Injury Consortium (LIMBIC)***

1. *Relationship of Advanced Neuroimaging Findings to Symptom Burden and Dementia Risk after Concussion*
2. *Relationship of Fluid Biomarker Findings to Symptom Burden and Dementia Risk after Concussion*
3. *Role of Physical Activity following Combat-related Concussion in Impacting Dementia Risk*
4. *Association of TBI History and Dementia in Veterans: A Mega-Database Analysis*
5. *Clinical Phenotypes of Post-TBI Symptoms and Risk for Dementia*
6. *Sleep disorders in TBI patients: potential new targets for reducing dementia risk*
7. *Health Economics of Concussion, TBI and Dementia*
8. *The Role of Transcranial Magnetic Stimulation in Post-Traumatic Cognitive Dysfunction*
9. *Impact of PTSD on Symptom Burden and Dementia Risk After Concussion*
10. *Long-term Cognitive Outcomes Following Military Concussion: LIMBIC 2021*

- **Supporting Resources from KTC for each topic area:** Consumer Knowledge Cards, Lay Person Abstracts, Clinical and Research Pearls, Podcast



LIMBIC Roadmap – 2013-2021

Describe the Common Effects after mTBI

Area	Contributing Studies
Neurosensory Vision Hearing Vestibular	<ul style="list-style-type: none"> Described in 5 completed CENC projects (Aiken, MacDonald, Kardon, Yaffe, Walker) Being addressed in 3 active LIMBIC studies (Walker, Yaffe, Pugh)
Neuroendocrine	<ul style="list-style-type: none"> Described in 1 completed LIMBIC study (Walker, Kenney) Being addressed in VA CSP collaborative study with LIMBIC (Walker)
Seizures	<ul style="list-style-type: none"> Described in 2 completed CENC project (Yaffe, Walker) Being addressed in VA Epilepsy CoE collaborative study with LIMBIC (Pugh)
Sleep	<ul style="list-style-type: none"> Described in 5 completed CENC project (Jak, MacDonald, Jak, Yaffe, Walker) Being addressed in TBIMS/TBICoE collaborative study with LIMBIC (Richardson, Dismuke) Being addressed in 2 LIMBIC studies (Werner, Richardson, Kenney, Wilde)
Pain	<ul style="list-style-type: none"> Described in 4 completed CENC projects (MacDonald, Taber, Yaffe, Walker) Being addressed in 3 active LIMBIC studies (Walker, Yaffe, Pugh)
Cognitive	<ul style="list-style-type: none"> Described in 5 completed CENC projects (Mufson, Crawford, MacDonald, Taber, Yaffe, Walker) Being addressed in all 6 active LIMBIC studies (Wilde, Kenney, Yaffe, Walker, Pugh, Dismuke) Fall 2021 <i>Brain Injury</i> special issue dedicated to risks for cognitive decline after TBI
Psychological	<ul style="list-style-type: none"> Described in 5 completed CENC projects (Jak, MacDonald, Taber, Yaffe, Walker) Being addressed in 4 active LIMBIC Studies (Walker, Yaffe, Pugh, Dismuke)
Neurological	<ul style="list-style-type: none"> Described in 6 completed CENC projects (Mufson, Crawford, MacDonald, Yaffe, Taber, Jak, Walker) Being addressed in 4 active LIMBIC Studies (Walker, Yaffe, Pugh, Dismuke)

Define the Association Between mTBI, Symptom Burden And Neurodegeneration

Area	Contributing Studies
Symptom Burden	<ul style="list-style-type: none"> Described in 7 completed CENC projects (Aiken, MacDonald, Yaffe, Taber, Jak, Mufson, Crawford, Walker) Being addressed in 4 active LIMBIC studies (Walker, Pugh, Yaffe, Dismuke)
Neurodegeneration	<ul style="list-style-type: none"> Described in 6 completed CENC projects (MacDonald, Yaffe, Taber, Jak, Mufson, Crawford, Walker) Being addressed in 6 active LIMBIC studies (Walker, Pugh, Yaffe, Dismuke, Wilde, Kenney) Fall 2021 <i>Brain Injury</i> special issue and knowledge translation products dedicated to risks for cognitive decline after TBI (Cifu, Hinds, Seel)



LIMBIC Roadmap – The Journey Ahead 2021-2024 (and Beyond)

Define and Disseminate Tools to Diagnosis and Prognosticate Symptom Burden and Neurodegeneration

Research Question	Contributing Studies
Symptom Burden	<ul style="list-style-type: none"> Described in 8 completed CENC projects (Wilde, MacDonald, Yaffe, Taber, Jak, Davenport, Aiken, Walker) Being addressed in 6 active LIMBIC studies (Walker, Pugh, Kenney, Wilde, Dismuke, Yaffe) Knowledge Translation Core developing suite of tools (Seel, Hinds) KTC: Risk Assessment Tool linked with Amelioration Strategies (Seel) Completed rTMS for cognitive deficits after mTBI at LIMBIC site (Manning) ** Examining sleep interventions to reduce cognitive symptoms (Werner) ** Collaborating with VA-CSP NeuroEndocrine Assessment and Intervention trial across nine LIMBIC VA sites (Walker) **
Neurodegeneration	<ul style="list-style-type: none"> Described in 8 completed CENC projects (Wilde, MacDonald, Yaffe, Taber, Jak, Davenport, Walker, Mufson, Crawford) Being addressed in 6 active LIMBIC studies (Walker, Pugh, Kenney, Wilde, Yaffe Dismuke) Knowledge Translation Core developing suite of tools (Seel, Hinds) KTC: Risk Assessment Tool linked with Amelioration Strategies (Seel) Fall 2021 <i>Brain Injury</i> special issue and knowledge translation products dedicated to risks for cognitive decline after TBI (Cifu, Hinds, Seel)

Next Steps: Interventions 2024-2029

- Continue Active Research applying interventions:
 - Multiple LIMBIC collaborators with additional grant funding to study mTBI interventions
- Partner with other investigators to leverage LIMBIC PLS site infrastructure and participants for intervention trials
- Mentor and Support next generation of TBI researchers
 - Co-Investigators on LIMBIC projects
 - Mentors on CDA/K-award grants



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Questions

