

**LIMBIC-CENC Clinical Care Monograph #2**

**Overall LIMBIC-CENC 2019-2024 Performance**

from the LIMBIC-CENC Knowledge Translation Center (LIMBICTM)

April 17, 2024, Richmond, VA

Monograph ‘Impacts’ are interpretations of LIMBIC-CENC (Long-term Impact of Military-relevant Brain Injury Consortium-Chronic Effects of Neurotrauma Consortium) study findings and their integration into current research literature. All ‘Key Findings’ in this Monograph are from LIMBIC-CENC investigator-led studies and derived from Post-9/11 Service Members (SMs) and/or Veterans (Vs) data. These views are endorsed by LIMBIC-CENC leadership but may vary across individual researchers.

**All LIMBIC-CENC Service Members, Veterans, Clinician and Researcher knowledge translation products are available at:** [**https://www.limbic-cenc.org/**](https://www.limbic-cenc.org/)

1. **TBI and Neurodegeneration**

**Key Findings**

1. **TBI and Neurodegenerative Conditions.** LIMBIC-CENC research found that Veterans with mTBI, with or without loss of consciousness, had about a 2.5-fold increase in dementia risk.1 Veterans with moderate-severe TBI approached a 4-fold increase in dementia risk. 1 Veterans with TBI of any severity had a 71% increased risk of a Parkinson’s disease diagnosis but the overall rate of Parkinson’s disease following TBI remained <1%.2 All cause-dementia for Veterans with TBI occurred 1-2 years earlier than for Veterans without TBI. The estimated Veteran U.S. population risk of dementia due to TBI is twice that of the general U.S. population, and three times that of U.S. women.3 Approximately 860,700 U.S. Veteran dementia cases are attributable to TBI exposure.3
2. **Three or More Lifetime mTBIs are Associated with Increased Risk of Neurodegeneration.** Mounting, converging biologic (biomarker) and epidemiological (symptoms, pain related disability) evidence from multiple LIMBIC-CENC PLS studies supports that repetitive (>3) mTBI is associated with elevated neurodegeneration risks.4-9
3. **Early Onset Dementia (EOD).** Veterans with EOD are more likely to have TBI, cardiovascular conditions (stroke, heart disease), mental health conditions (PTSD, depression, anxiety, attention disorders), other significant neurological disorders (epilepsy, Parkinson’s disease, encephalopathy, anoxic brain injury), self-reported memory loss, and renal disease.10
4. **TBI, Dementia, and Health.** There is a high prevalence of alcohol abuse, substance abuse, depression, sleep disorders, PTSD, cardiovascular disease (CVD), and epilepsy among Veterans <65 years of age with comorbid TBI and dementia.10 In a longitudinal study by LIMBIC-CENC researchers, the prevalence of baseline health risk factors, especially depression, cardiovascular disease, PTSD and epilepsy, was higher in Veterans with TBI compared to without TBI; at 6-year follow-up, Veterans with TBI were twice as likely (14%) to develop dementia compared to those with no TBI (6%).11 TBI and cardiovascular disease independently increased the risk for dementia in older Veterans and have an additive effect.11 CVD does not appear to mediate the association between TBI and dementia.11 Preliminary evidence suggests that sleep physiology is a common pathophysiological process that underlies persistent post-concussive, depressive, post-traumatic stress, and sleep-related symptoms in mTBI.9

**Clinical Impact**

* **MTBI Clinical Practice Guideline (CPG).** LIMBIC-CENC findings on the association between TBI and higher risk of Veteran neurodegenerative disorders extend the current literature, especially for mTBI and EOD. These findings improve the specificity and the strength of evidence for number and severity of TBIs as risk factors for neurodegenerative disorders and can be applied in the next VA-DOD mTBI CPG. Findings also highlight the need for CPG recommendations that emphasize making specialty evaluation referrals when early signs of dementia are present, even if Veterans are younger than would normally be expected.
* **Support for VHA and DOD TBI Policies**. The high prevalence and magnitude of preventable behavioral health risk factors (e.g., sleep, mental health, cardiovascular) found in Veterans with TBI and dementia provide clear evidentiary support for VHA and DOD healthcare initiatives such as 1) TBI screening and comprehensive evaluation for lifetime TBI history, 2) General brain health and overall wellness initiatives, and 3) Targeted, proactive treatment and prevention approaches for modifiable, lifestyle health risk factors to prevent or delay the onset of dementia.
* **Brain Health and Wellness Tool**. LIMBIC-CENC findings on preventable behavioral health risk factors after TBI, synthesized with the current research literature, led to the development, testing, and release of the LIMBIC-CENC a brain health and wellness survey that generates personalized recommendations to support Service Members and Veterans efforts to identify and self-manage their health-related risk factors after TBI. The LIMBIC-CENC’s Brain Health and Wellness Video Series complements the survey tool and provides a series of 4-minute primers on how to identify, prevent or self-manage TBI and co-morbid risk factors that can decrease dementia risk.
* **Developing mTBI Phenotypes**. LIMBIC-CENC research using PLS data is underway to identify mTBI phenotypes for neurodegeneration susceptibility that can inform implementation of personalized, high intensity treatments.
* **Contributions to National TBI Research Registries**. LIMBIC-CENC PLS data collection on 3,000+ participants with multiple, longitudinal follow-ups downloaded into FITBIR will spur future collaborative research with lifestyle medicine researchers.
* **More Nuanced Prognostic Models**. Increasing the LIMBIC-CENC PLS cohort and its robust long-term follow-up will allow for analyses of sub-group effects and interactions between risk factors on the long-term risk of dementia. More nuanced prognostic models can then be created to identify individualized, modifiable behavioral and biomarker-based risk factors (phenotypes) and better inform personalized treatments (precision medicine) to enhance long-term outcomes.

**Primary Knowledge Translation Products**

* LIMBIC-CENC assessment tools, including PLS Study Variables and [Concussion Assessment Tools for Identifying and Diagnosing Lifetime mTBI History](https://www.limbic-cenc.org/index.php/knowledge-translation-center/limbic-cenc-concussion-assessment-tools/) are available for clinical and research use.
* LIMBIC-CENC provides a repository of information on [TBI, Aging, and Dementia Risk for SMs, Vs and Families](https://www.limbic-cenc.org/for-service-members-and-veterans-with-tbi/aging-with-tbi-dementia-risk-veterans/) and [TBI, Aging, and Dementia Risk for Clinicians](https://www.limbic-cenc.org/for-tbi-clinicians/aging-with-tbi-dementia-risk-clinicians/).
* LIMBIC-CENC’s [Brain Health and Wellness Survey and Personalized Recommendations Report](https://knowledgetranslation.limbic-cenc.org/BrainHealthWellnessTool/BrainHealthWellnessTool)  provides a yes-no survey for SMs and Vs to identify their behavioral health risk factors for dementia and receive personalized information and recommendations.
* LIMBIC-CENC’s [Brain Health and Wellness Video Series](https://www.limbic-cenc.org/for-service-members-and-veterans-with-tbi/the-brain-health-and-wellness-video-series/) includes 10 easy to understand and apply videos on how to identify, prevent or self-manage behavioral health risk factors for dementia including Depression, PTSD, Hearing Loss, Hypertension, Diabetes, Tobacco Use, Alcohol Use, Obesity-Activity-Nutrition, and Poor Sleep. The series also provides links to self-management tools and/or access to healthcare services.
* The 2024 Ralph G. DePalma Memorial TBI Clinical Strategies Seminar provides [Updates on the Relationship between TBI and Dementia](https://www.hsrd.research.va.gov/for_researchers/cyber_seminars/archives/video_archive.cfm?SessionID=6490).

**LIMBIC-CENC TBI and Neurodegeneration Primary References**

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12. **TBI, Mortality, and Suicide**

**Key Findings**

1. **TBI and Mortality**. Risk of early death is higher for Veterans with TBI than those with no TBI and varies by TBI severity and time since exposure.1 All Veteran groups have higher mortality rates than the general population, with the highest rates for Veterans with moderate-severe TBI followed by mTBI and then no TBI.1 For moderate to severe TBI, mortality risk is highest within 6 months of injury and decreases over time.1 For mild TBI, risk for mortality is elevated and remains constant over time.1 Research on mTBI comorbidity phenotypes indicates that Polytrauma and Mental Health subtypes have a >3 times risk of early mortality; the Moderately Health and Declining subtype has a 2 times greater risk of early mortality.2
2. **TBI and Mortality Causes**. Risk of death due to unintentional injury and stroke are higher in the first 6 months after moderate to severe TBI. 1 For cancer, cardiovascular disease, and other causes of death, Veterans with moderate-severe TBI have significantly higher rates than all others in older age groups (e.g., 55+).1, 3
3. **TBI and Suicide**. Veterans with mild and moderate-to-severe TBI are at increased risk of death by drug overdose and firearms; overdose risk is heightened in middle-aged and older adults.4 Research on mTBI comorbidity phenotypes indicates that the ‘Mental Health’ subtype had 2 times the risk of overdose and suicide-related behavior.2 The ‘Polytrauma’ and ‘Moderately Healthy and Declining’ subtypes have a small but significant increased risk of overdose and suicide-related behavior.2

**Clinical Impact**

* **Recommendations to Reduce Mortality following TBI**. LIMBIC-CENC findings on the association between TBI and higher risk of Veteran mortality replicate and extend the current literature in both military and civilian populations, especially for the risk of death due to unintentional injury in the first year following moderate to severe TBI.
* **Clinical Care Policies.** LIMBIC-CENC research provides evidence for DOD/V.A. healthcare policies that recommend: 1) providing full-time, direct supervision in the first year for individuals with severe TBI who have cognitive impairments and lack awareness of their deficits, 2) self-management training and/or caregiving assistance to Veterans with moderate-severe TBI who have multiple, complex, chronic health conditions, and 3) a combination of counseling, family involvement, and targeted means reduction to prevent suicide and unintended death.
* **Brain Health and Wellness Tool**. LIMBIC-CENC findings on preventable behavioral health risk factors after TBI, synthesized with the current research literature, led to the development, testing, and release of the LIMBIC-CENC a brain health and wellness survey that generates personalized recommendations to support Service Members and Veterans efforts to identify and self-manage their health-related risk factors after TBI. The LIMBIC-CENC’s Brain Health and Wellness Video Series complements the survey tool and provides a series of 4-minute primers on how to identify, prevent or self-manage TBI and co-morbid risk factors that can decrease mortality risk.

**Primary Knowledge Translation Products**

* LIMBIC-CENC provides a repository of information on [Suicide Prevention for Service Members, Veterans and Families](https://www.limbic-cenc.org/for-service-members-and-veterans-with-tbi/suicide-prevention-veterans/) and [Managing Medical Conditions for Service Members, Veterans, and Families](https://www.limbic-cenc.org/for-service-members-and-veterans-with-tbi/medical-conditions-veterans/), and [Suicide Prevention and Managing Medical Condition Information for TBI Clinicians](https://www.limbic-cenc.org/for-tbi-clinicians/).
* LIMBIC-CENC’s [Brain Health and Wellness Survey and Personalized Recommendations Report](https://knowledgetranslation.limbic-cenc.org/BrainHealthWellnessTool/BrainHealthWellnessTool)  provides a yes-no survey for SMs and Vs to identify their behavioral health risk factors and receive personalized information and recommendations.

**LIMBIC-CENC TBI, Mortality and Suicide Primary References**

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2. Stewart IJ, Amuan ME, Wang CP, et al: Association between traumatic brain injury and cardiovascular disease among post-911 veterans. JAMA Neurol 2022;79(11):1122-1129.
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4. Byers, A. L., Li, Y., Barnes, D. E., Seal, K. H., Boscardin, W. J., & Yaffe, K. (2019). A national study of TBI and risk of suicide and unintended death by overdose and firearms. Brain Injury, 34(3), 328-334. doi:10.1080/02699052.2019.1701708
5. **MTBI, Mental Health and Persistent Symptoms**

**Key Findings**

1. **MTBI and PTSD**. About 40% of Service Members and Veterans with mTBI screened positive for PTSD compared to about 25% without mTBI.1  Service Members and Veterans with both mTBI and PTSD have the highest rates of depression symptoms, pain, and sleep apnea risk relative to those without either condition.2 Service Members and Veterans with PTSD, irrespective of mTBI history, had high rates of obesity, sleep problems, depression, and pain.2 For Veterans with both TBI and PTSD who receive cognitive processing therapy for trauma, worse baseline sleep quality was associated with less improvement in PTSD and cognitive symptoms.3
2. **MTBI and Persistent Symptoms**. Service Members and Veterans with mTBI report more neurobehavioral symptoms compared to those without mTBI.1 A dose-response association was found between greater number of mTBIs (blast-related or non-blast) and increased rates and severity of self-reported neurobehavioral symptoms and pain among Service Members and Veterans.4-6 An association was also identified between PTSD symptom severity, low social support, deployment-related mild TBI, and increased risk of behavioral dyscontrol.7
3. **Neurobehavioral Symptom Inventory (NSI)**. The NSI has four symptom clusters (somatosensory, affective, cognitive, and vestibular) that have been validated in the LIMBIC-CENC PLS cohort with factor analytic techniques.1 NSI clusters show evidence of good reliability and validity.1
4. **MTBI and Cognitive Performance**. LIMBIC-CENC research did not find evidence that presence or number of mTBIs directly impacted cognitive performance including attention, working memory, executive function, and processing speed.7, 8 Sleep disorders, PTSD, and pain decreased cognitive performance.9 Evidence suggests that telehealth delivery of group cognitive rehabilitation and aerobic activity are promising interventions to improve cognition following mTBI.10, 11
5. **MTBI and Sleep Disorders**. Veterans with a mTBI history were about 40% more likely to develop a sleep disorder of any type including sleep apnea, insomnia, hypersomnia, and sleep-related movement disorders.12 The association with mTBI remained consistent over time; PTSD had little effect.12 Obstructive sleep apnea has a stronger relationship to neurocognitive function than mTBI history.9 Poor sleep is associated with sequelae of TBI including executive dysfunction and with exosomal microRNA differences previously implicated in psychiatric disorders, progressive neurodegeneration, and vascular physiology.13
6. **MTBI and Depression.** Service Members andVeterans depression symptoms were greater for those with a history of multiple mTBIs compared with those who had a single mTBI or no TBI.14 Service Members andVeterans depression symptoms were greater for those who had a single mTBI compared to no TBI.14 Combat deployment-related injuries were associated with higher depression scores than injuries occurring in non-combat or civilian settings.14 Service Members and Veterans increased rates of depression after mTBI persisted in the absence of PTSD.14

**Clinical Impact**

* **Inclusion of Service Member and Veteran Issues in Revised mTBI Case Definition.** LIMBIC-CENC findings and research leadership played a critical role in the consideration and incorporation of Service Member and Veteran-centric issues into the 2023 Revised ACRM mTBI Case Definition.15
* **Policy Recommendations for Holistic Approaches to mTBI Treatment**. LIMBIC-CENC findings have helped differentiate the effects of co-occurring mTBI, PTSD, depression, pain, behavioral dyscontrol, and sleep disturbance. These findings extend the current literature and strengthen evidence for DOD and VHA healthcare policies that emphasize: (1) early, comprehensive, assessment and personalized, (2) holistic treatment to manage symptoms and reduce chronicity, and (3) improved social support systems. When treating Service Members and Veterans with a history of mTBI and chronic cognitive performance issues, employing a holistic approach is important to assess and treat the most common causes, i.e., sleep disorders, PTSD and pain.
* **Recommendations for Early Sleep Assessment and Treatment**. Growing and converging biological (serum markers, neuroimaging) and epidemiological (prognostic) findings from LIMBIC-CENC researchers point to sleep disturbance as a potential primary root cause for Service Members and Veterans cascading post-mTBI symptoms and neurodegeneration risk. Early identification, treatment, and prevention strategies for post-TBI sleep disorders are critical but understanding the evolution of post-TBI sleep disturbance and its impact on other symptoms remains elusive. LIMBIC-CENC research protocol development is underway to identify real-time, longitudinal digital biomarkers of early sleep, depression, acute stress, and pain to better inform post-mTBI symptom evolution, prognosis, and treatment targets.
* **Brain Health and Wellness Tool**. LIMBIC-CENC findings on preventable behavioral health risk factors after TBI, synthesized with the current research literature, led to the development, testing, and release of the LIMBIC-CENC a brain health and wellness survey that generates personalized recommendations to support Service Members and Veterans efforts to identify and self-manage their health-related risk factors after TBI. The LIMBIC-CENC’s Brain Health and Wellness Video Series complements the survey tool and provides a series of 4-minute primers on how to identify, prevent or self-manage TBI and co-morbid risk factors that can decrease impact of co-morbid and secondary conditions.
* **Need for Personalized mTBI and Mental Health Treatment**. LIMBIC-CENC research is underway to further develop mTBI mental health phenotypes that identify subgroups of Service Members and Veterans with common symptoms, biomarkers and root causation in order to tailor personalized treatment algorithms for each sub-phenotype.
* **Policy Recommendations on the Need for Secondary TBI Prevention Strategies**. Our findings on the linear associations between number of mTBIs and increased symptom frequency, severity and chronicity make clear that DOD-VA policy recommendations must prioritize proactive, secondary TBI prevention strategies.

**Primary Knowledge Translation Products**

* LIMBIC-CENC provides a repository of information on [Mental Health and TBI for SMs, Vs and Families](file:///\\rams.adp.vcu.edu\SOM\Shares\PMR\LIMBIC-CENC\Knowledge%20Translation\Clinician%20KT%20Products\Monographs\Mental%20Health%20and%20TBI%20for%20SMs,%20Vs%20and%20Families), [TBI and Wellness for Service Members, Veterans, and Families](https://www.limbic-cenc.org/for-service-members-and-veterans-with-tbi/wellness-veterans/), [Mental Health and TBI for Clinicians](https://www.limbic-cenc.org/for-tbi-clinicians/mental-health-clinicians/), and [TBI and Wellness for Clinicians](https://www.limbic-cenc.org/for-tbi-clinicians/wellness-clinicians/).
* LIMBIC-CENC’s **Brain Health and Wellness Video Series** provides 4-minute, easy to read and apply primers on how to identify, self-manage or prevent [TBI and Depression](file:///\\rams.adp.vcu.edu\SOM\Shares\PMR\LIMBIC-CENC\Knowledge%20Translation\Clinician%20KT%20Products\Monographs\TBI%20and%20Depression), [TBI and PTSD](file:///\\rams.adp.vcu.edu\SOM\Shares\PMR\LIMBIC-CENC\Knowledge%20Translation\Clinician%20KT%20Products\Monographs\TBI%20and%20PTSD), [TBI and Tobacco Use](https://www.youtube.com/watch?v=SJ6Vawx4qkU), [TBI and Alcohol Use](https://www.youtube.com/watch?v=3D5y_lsjTJc&t=49s), and [TBI and Sleep](https://www.youtube.com/watch?v=ODlHArfPSJo). The series also provides links to self-management tools and/or access to healthcare services for mental health and chronic symptoms.
* The [Abstract Veterans TBI Health and Outcomes Podcasts](https://www.limbic-cenc.org/for-service-members-and-veterans-with-tbi/the-abstract-veterans-tbi-health-and-outcomes-podcasts/) provide evidence-informed and real world patient, family and clinician perspectives on assessing and self-managing TBI, mental health conditions, and symptoms.

**MTBI, Mental Health and Persistent Symptom References**

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16. **TBI, Medical Conditions, and Sensory Disorders**

**Key Findings**

1. **TBI, Stroke, and Cardiovascular Disease**. LIMBIC-CENC researchers have identified that TBI is associated with an increased risk of all stroke. 1,2 Risk of stroke is highest in the first year post-TBI and remains elevated for 10+ years.1 There is a higher risk of hemorrhagic versus ischemic stroke after TBI.1 Veterans who sustained moderate-severe TBI are twice as likely to have a stroke than those with no TBI; Veterans who sustained mTBI are about 50% more likely to have stroke.1 Prevalence of cardiovascular disease is higher in Veterans with TBI compared to no TBI.2-5
2. **TBI and Epilepsy**. TBI is associated with an increased risk of epilepsy, is strongest in Veterans with moderate-severe TBI, and is present in Veterans with mTBI.5-7
3. **TBI and Pituitary Disorders**. LIMBIC-CENC research did not find mTBI to be a risk factor for pituitary disorders, i.e., growth hormone deficiency, hypothyroidism, or male hypogonadism.8
4. **TBI, Dizziness, and Balance**. LIMBIC-CENC researchers have identified that TBI increases the risk for dizziness, vestibular dysfunction, and balance impairments.9-12 The association between all three conditions was strongest in Veterans with moderate-severe TBI, but still present for mTBI.9, 11 As many as 40% of Veterans with post-mTBI dizziness may continue to have symptoms for years; predictors of poor dizziness prognosis include PTSD or hearing loss diagnoses, abnormal vestibular function, increased age, identification as a Black Veteran, and high school education level.11 Service Members and Veterans with 3+ mTBIs had a small but important decrease in balance performance on computerized posturography.12, 13 In addition to prior mTBI, pain has a strong relationship with poorer balance performance.12 Using diagnostic approaches that disrupt sensory inputs may help unmask balance deficits in Service Members and Veterans with mTBI.12, 14
5. **MTBI and Balance Phenotypes.** There is an interaction effect between number of mTBIs sustained and impairment of vision, vestibular or proprioception systems, that is associated with lower scores on dynamic posturography tests.15 In Service Members and Veterans with mTBI, 8 heterogeneous phenotypes of balance control with varying combinations of intact or impaired visual, vestibular and proprioception were identified.15 Overall findings indicated that all mTBI-related balance dysfunction does not cleanly fall under a vestibular dysfunction umbrella.15
6. **TBI and Hearing**. LIMBIC-CENC researchers have identified that TBI increases the risk of hearing loss and tinnitus and was strongest in Veterans with moderate-severe TBI and blast-related TBI.16, 17 Veterans with tinnitus diagnoses have higher rates of mental health diagnoses, including anxiety, depression, and substance use disorders, and higher annual health care utilization than those without tinnitus.18
7. **TBI, Cannabis Use Disorder (CUD), and Cognitive Disorders.** Progression to cognitive disorder was highest among those with a history of TBI and concomitant CUD followed by those with TBI only, and then CUD only compared to those without a TBI or CUD diagnosis.19

**Clinical Impact**

* **Policy to Increase Stroke Monitoring**. The associations between all severity-TBI and increased stroke risk are concerning and provide evidentiary support for policies to heighten monitoring of Veterans with a moderate-severe TBI history for traditional stroke risk factors. Future LIMBIC-CENC research using the PLS’ longitudinal follow-up data will identify subgroups of high risk mTBI Veterans who require early monitoring and intervention for stroke.
* **Epilepsy Treatment**. Except for penetrating TBI, routine prophylaxis with antiepileptic medication for epilepsy is not warranted after TBI of any severity.
* **Pituitary Disorder Screening**. LIMBIC-CENC research suggests that presence of mTBI should not be a risk consideration for hypogonadism, hypothyroidism, and growth hormone deficiency.
* **Increased Understanding of TBI and Balance Pathophysiology**. Our LIMBIC-CENC PLS research confirms that balance performance is a delicate and complex process controlled by brain networks that integrate and process multiple afferent and efferent pathways. Pain can also disturb pathways through a number of potential central or peripheral mechanisms. There is an apparent cumulative ‘dose effect’ of repetitive mild TBI on balance performance that may impact treatment requirements and lengthen the recovery course.
* **TBI and Balance Recommendations**. Our LIMBIC-CENC PLS findings suggest that use of balance diagnostics that disrupt sensory inputs, particularly vision, may lead to more efficient and effective diagnosis and treatment of balance disorders. Clinicians treating Service Members and Veterans with a TBI history should address pain before and during vestibular rehabilitation or other balance-related interventions. The further development and validation of TBI and balance phenotypes that include sensory impairments and pain will lead to vestibular rehabilitation protocols tailored to each individual's balance phenotype.
* **TBI and Hearing Loss Recommendations**. Our LIMBIC CENC findings on the frequent co-diagnosis of tinnitus, TBI, and hearing loss and increased risk of mental health disorders extend the current clinical research literature. These findings can improve the strength of evidence and recommendations for coordinated TBI, tinnitus/hearing loss, and mental health service care for Service Members and Veterans in future VA-DOD mTBI and hearing loss CPGs.
* **Brain Health and Wellness Tool**. LIMBIC-CENC findings on preventable behavioral health risk factors after TBI, synthesized with the current research literature, led to the development, testing, and release of the LIMBIC-CENC a brain health and wellness survey that generates personalized recommendations to support Service Members and Veterans efforts to identify and self-manage their health-related risk factors after TBI. The LIMBIC-CENC’s Brain Health and Wellness Video Series complements the survey tool and provides a series of 4-minute primers on how to identify, prevent or self-manage TBI and common symptoms that can impact function and quality of life.

**Primary Knowledge Translation Products**

* LIMBIC-CENC provides a repository of information on [TBI and Medical Conditions for SMs, Vs and Families](https://www.limbic-cenc.org/for-service-members-and-veterans-with-tbi/medical-conditions-veterans/) , [Sensory Function and TBI for Service Members, Veterans and Families](https://www.limbic-cenc.org/for-service-members-and-veterans-with-tbi/sensory-function-and-tbi-veterans/), [TBI and Medical Conditions for Clinicians](https://www.limbic-cenc.org/for-tbi-clinicians/medical-conditions-clinicians/) and [Sensory Function and TBI for Clinicians](https://www.limbic-cenc.org/for-tbi-clinicians/sensory-function-clinicians/).
* The [Abstract Veterans TBI Health and Outcomes Podcasts](https://www.limbic-cenc.org/for-service-members-and-veterans-with-tbi/the-abstract-veterans-tbi-health-and-outcomes-podcasts/) provide evidence-informed and real world patient, family and clinician perspectives on self-managing TBI and related health conditions.
* LIMBIC-CENC’s **Brain Health and Wellness Video Series** provides a 4 minute primer on how to identify, prevent or self-manage TBI and [Hearing Loss](https://www.youtube.com/watch?v=s4UVUlg_XcA&t=14s), [Hypertension](https://www.youtube.com/watch?v=eMe6GDOVNHk&t=3s), [Diabetes](https://www.youtube.com/watch?v=kPgH9Nv5BWA), and [Obesity, Activity, and Nutrition](https://www.youtube.com/watch?v=X596eBpKCiA).

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20. **TBI, Pain, and Opioid Therapy**

**Key Findings**

1. **TBI, Pain and Deployment**. LIMBIC-CENC researchers have identified that deployed Service Members were more likely to have diagnoses of back pain and headache, while non-deployed personnel were more likely to have diagnoses of other musculoskeletal pain.1 The most common types of pain among Service Members and Veterans with mTBI were headaches/migraines, back pain, and arm, leg, and/or joint pain.2 Headache risk increases with more lifetime mTBIs and reaches 78% prevalence with 3 or more mTBIs.3
2. **TBI, Pain and Mediating Health Conditions**. LIMBIC-CENC researchers have identified little evidence that Service Members’ and Veterans’ mTBI history is directly related to their chronic pain; rather, PTSD, anxiety, depression, insomnia, arthritis, and extracranial injuries are more directly related to chronic pain.2 Given the linkage between TBI and development and response to mental health conditions however, TBI must still be considered. Veterans’ neuroimaging data indicate that chronic pain is associated with decreased functional connectivity in select brain networks that mediate pain. Veterans PTSD symptom severity, history of deployment TBI, and sleep quality predicted pain-related interference with day-to-day functional activities.4 TBI, PTSD and depression diagnoses were associated with Veteran chronic pain disability ratings.5
3. **MTBI and Pain Phenotypes**. Service Members’ and Veterans’ with a mTBI history who are Female sex, Black racial identity, Hispanic/Latino ethnicity, and younger age may have a higher risk of headache.3 Baseline pain scores were generally higher in Veterans with mild TBI and five preliminary pain phenotypes were identified: (a) simple low impact stable pain, (b) complex low impact stable pain, (c) complex low impact worsening pain, (d) complex moderate impact worsening pain, and (e) complex high impact stable pain.5
4. **TBI, Pain and Opioid Treatment**. Opioid prescribing patterns for pain management did not appear to differ substantially for Veterans with or without TBI.7, 8 About 80% of Service Members and Veterans with pain initially received at least one non-opioid therapy.7 About 20% of Service Members and Veterans with TBI and pain received short-term opioid therapy, while only 3% received long-term opioid therapy.7 About 90% of Veterans with TBI treated with long-term opioid therapy had moderate to extreme levels of pain, PTSD symptoms, sleep disturbance, and suicidal ideation.7 Similarly,Service Members and Veterans with mTBI in the ‘complex moderate impact pain with worsening’ and ‘complex high impact pain’ phenotypes had significantly higher probabilities for use of psychotropics, opioids, and interventional pain than those with no TBI.6

**Clinical Impact**

* **Chronic Pain as a Complex, Multidimensional Condition**. LIMBIC-CENC findings demonstrate that chronic pain has a myriad of causes and contributing factors, with the role of isolated mTBI being minimal. Mental health conditions have a stronger relationship to chronic pain than mTBI history. Given the complexity and overlap of chronic pain symptoms with other comorbid mental health conditions, and the interactions between TBI and the development and response to mental health conditions, Service Members and Veterans with mTBI will benefit most from a comprehensive assessment and holistic treatment approach that includes multimodal pain management. Modulation of brain networks through biofeedback or other means to reduce pain and improve brain function seems an appealing treatment approach, however more research is needed to formulate clinical recommendations.
* **CPGs Recommend Against Prescribing Opioids to Veterans.** Opioid prescribing patterns did not differ between Veterans with or without TBI. Only 3% of Veterans with TBI in the VHA were treated long-term with opioids, which provides evidence of strong adherence with VA-DOD Pain CPG recommendations.
* **TBI and Pain Phenotypes**. LIMBIC-CENC research will further develop and validate TBI and pain phenotypes using the PLS longitudinal data to better incorporate contributing mental health factors that can lead to the development of personalized pain rehabilitation programs that are tailored to the nuances of each Veterans pain profile.

**Primary Knowledge Translation Products**

* LIMBIC-CENC provides a repository of information on [Pain and TBI for SMs, Vs, and Families](https://www.limbic-cenc.org/for-service-members-and-veterans-with-tbi/pain-and-tbi-veterans/) and [Pain and TBI for Clinicians](https://www.limbic-cenc.org/for-tbi-clinicians/pain-and-tbi-clinicians/).
* The [Abstract Veterans TBI Health and Outcomes Podcasts](https://www.limbic-cenc.org/for-service-members-and-veterans-with-tbi/the-abstract-veterans-tbi-health-and-outcomes-podcasts/) provides evidence-informed and real world patient, family and clinician perspectives on assessing and self-managing TBI and pain.

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9. **TBI, Biomarkers, and Neuroimaging**

**Key Findings**

1. **TBI and Serum Exosomal Proteins**. Blood levels of exosomal proteins, especially neuronal proteins (i.e., Neurofilament light or NfL, p-tau, tau) and neuroinflammatory proteins (IL-6 and IL-10) have drawn interest as mTBI biomarkers of dementia risk and other suboptimal outcomes. In LIMBIC-CENC research studies: (a) NfL has been elevated in Service Members and Veterans with mTBI compared to those without TBI,1-5 with 3 or more mTBIs,1-3 chronic neurobehavioral symptoms,1, 2 cognitive impairment,2, 4, 5 and poor sleep/obstructive sleep apnea;2, 4 (b) tau has been elevated in chronic neurobehavioral symptoms1, 3  and poor sleep/obstructive sleep apnea;5 and (c) p-tau, IL-6 and IL-10 are elevated in mTBI and chronic neurobehavioral sysptoms.1
2. **TBI and Exosomal micro-RNAs (miRNAs)**. In LIMBIC-CENC research, miRNAs, which are mediators of intercellular communication, have been shown to be dysregulated in Service Members and Veterans with 3 or more mTBIs and 1-2 mTBI compared to no TBI,5 and chronic neurobehavioral symptoms;5 mTBI blast exposure group, which correlated with inflammatory, neurodegenerative, and androgen receptor pathways;6 and extracellular vesicles (EV) levels of proteins and miRNAs that correlated with PTSD symptom levels.7
3. **TBI and Imaging-based Advanced Brain Age.** Brain age, based on MRI data, was noted to be associated with history of deployment-related mTBI, depression, PTSD, and alcohol misuse.8,9 Males with a history of deployment-related mTBI showed advanced brain age compared to those without deployment mTBI, while females did not. 8 In follow-up analyses of male participants, severity of PTSD, depression symptoms, and alcohol misuse were also associated with advanced brain age.9, 10
4. **Functional Neuroimaging and EEG Research.** Functional neuroimaging suggests that there are distinct patterns of resting-state functional connectivity in the middle frontal gyrus of the frontoparietal region, in which connectivity is increased in mTBI and decreased in PTSD.11 Executive function complaints, poorer cognitive performance, and higher psychological distress.12

**Clinical Impact**

* **NfL and Tau as mTBI Dementia Biomarkers**. Five LIMBIC-CENC studies found small effect sizes that extend the current research literature on the potential value of NfL and tau as markers of neuro-axonal damage in the mTBI population. In early discovery studies, exosomal proteins emerged as potential diagnostic or prognostic biomarkers of late effects of mild TBI, especially for repetitive (≥3), mild TBI. LIMBIC-CENC research is in development to examine the potential use of biomarkers in mTBI phenotype development.
* **Potential Role of Exosomal miRNAs in Chronic mTBI**. LIMBIC-CENC researchers are among the first to examine exosomal miRNAs in remote TBI and early findings provide novel insights into the potential underlying pathobiology in chronic TBI symptom persistence. Levels of proteins and miRNAs that correlated with PTSD symptom levels may provide insights into signaling pathways linked to persistent PTSD symptoms after mTBI and the biological mechanisms underlying susceptibility to PTSD. Study results suggest a possible role for axonal degeneration and neurodegenerative changes in the development of persistent or later-in-life PTSD symptoms.
* **LIMBIC-CENC Research Reveals Novel Imaging Finding.** LIMBIC-CENC PLS research identified opposing patterns of connectivity in the lateral Prefrontal Cortexthat increased in mTBI and decreased in PTSD. These opposite patterns highlight the potential for a biomarker that could differentiate mTBI and PTSD pathophysiology and symptoms.
* **TBI, Sleep and Neurodegeneration**. LIMBIC-CENC PLS findings from a number of biomarker, neuroimaging, and medical condition studies provide strong evidentiary support for implementing validated sleep measures in both longitudinal studies investigating pathobiological mechanisms of TBI related neurodegeneration and comprehensive clinical evaluations.

**Primary Knowledge Translation Projects**

* LIMBIC-CENC provides a repository of information on [TBI and Pathophysiology for Clinicians](https://www.limbic-cenc.org/for-tbi-clinicians/pathophysiology-and-tbi-clinicians/) and [TBI and Diagnostics for Researchers](https://www.limbic-cenc.org/for-tbi-researchers/diagnostic-researchers/).
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13. **TBI and Military Service**

**Key Findings**

1. **Deployment Status and TBI Risk**. LIMBIC-CENC researchers found that deployed Service Members were 7 times more likely than non-deployed Service Members to screen positive for any level of TBI severity. Deployed Service Members were 5.5 times more likely to have a mTBI and 3 times more likely to have a moderate-severe TBI. Deployed Service Members were 3 times more likely to sustain spinal injury.1 In the long-term, Veterans who were deployed are more likely than non-deployed Veterans to use alcohol and other substances (cocaine, amphetamine, opioid, and cannabis) and have diagnoses consistent with cognitive dysfunction (memory loss, mild cognitive impairment, and dementia).1-3
2. **Deployment Status, TBI, and Mental Health Risk**. Deployed Service Members were more likely than non-deployed Service Members to have TBI, PTSD, depression, anxiety, pain interference and impaired sleep (hypersomnia, insomnia, and obstructive sleep apnea) based on self-report and ICD diagnoses.4 Deployed Service Members were also more likely than non-deployed SMs to have suicidal ideation and attempts and overdoses.4
3. **Deployment Status, TBI, and Cognitive Functioning**. Veterans who sustained deployment mTBI had small but significantly lower performance on objective tests of working memory, processing speed and trail making (A and B). Six neuropsychological profiles of deployment-related mTBI were identified based on high, moderate and low self-reported functioning levels and high or low cognitive performance.5 Service Members andVeterans with deployment-related mTBI and meeting criteria for PTSD were more likely to be grouped within poorer outcome profiles.5
4. **TBI Due to Blasts**. Multiple LIMBIC-CENC studies found little to no direct differences in outcomes between blast-related and non-blast-related mTBI, when adjusting for other factors such as PTSD, pain, depression, sleep.6-10 There was little evidence that self-reported blast-exposure history impacted cognitive functioning.4, 6 However, blast-related mTBI has a significant impact on VA health services utilization and costs relative to non-blast mTBI and no mTBI.10 Further, blast exposures in both combat and training settings are predictors of Service Connected Disability; number of controlled detonations in training may be much more impactful.9

**Clinical Impact**

* **Advancing the TBI, Deployment and Outcomes Literature**. Identifying the association between combat deployment and increased risk of TBI, traumatic injuries, mental health disorders and substance use further elucidates the magnitude of both the physical and mental health impacts of deployment and TBI. These findings provides evidentiary support for DOD and VA healthcare policies on screening for TBI and follow-up comprehensive evaluation of positive TBI screens, particularly for Veterans with a deployment history.
* **Controlled Detonations, TBI and Morbidity.** LIMBIC-CENC researchers have begun to lay an evidence base on the impact of controlled detonations on service connected disability and by extension mTBI, comorbidities and outcomes. These findings may have more immediate implications for DOD training approaches. There remains significant heterogeneity in outcomes between Service Members and Veterans with varying histories of lifetime mTBI and repetitive low-level blast exposures.
* **Untangling Evidence on the Effects of Blast and non-Blast TBI**. LIMBIC-CENC symptom research has found little to no evidence that blast-related TBI directly impacts outcomes, when adjusting for other comorbidities such as PTSD, pain, depression, and sleep. Increasing the LIMBIC-CENC PLS cohort and its robust longitudinal follow-up will allow for analyses of sub-group effects and interactions between risk factors related to both blast injuries and controlled detonations. More nuanced prognostic models can then be created to identify individualized, modifiable behavioral and biomarker-based risk factors (mTBI blast phenotypes) and better inform personalized treatments (precision medicine).

**Primary Knowledge Translation Products**

* LIMBIC-CENC provides a repository of information on [TBI and Epidemiology](https://www.limbic-cenc.org/for-tbi-researchers/epidemiology-of-military-tbi-researchers/) in the For TBI Researchers section. We also provide a repository on [TBI and Polytrauma for Service Members, Veterans, and Families](https://www.limbic-cenc.org/for-service-members-and-veterans-with-tbi/) and [TBI and Polytrauma for Clinicians](https://www.limbic-cenc.org/for-tbi-clinicians/polytrauma-and-tbi-clinicians/).
* The [Abstract Veterans TBI Health and Outcomes Podcasts](https://www.limbic-cenc.org/for-service-members-and-veterans-with-tbi/the-abstract-veterans-tbi-health-and-outcomes-podcasts/) provides evidence-informed and real world patient, family and clinician perspectives on accessing and best leveraging DOD and VA health care services and resources.

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11. **TBI, Disability and Veterans Health Services**

**Key Findings**

1. **TBI and Service-connected Disability Ratings**. Service-connected disability ratings1 and medical service use2 are highest for Veterans with blast-related mTBI, followed by blunt mTBI, and are lowest for Veterans without TBI. 1, 2 High prevalence of TBI service connected disability was found in Veterans who identified as Pacific Islanders and Native Americans.2
2. **TBI, Race, Ethnicity and Outcomes**. Dementia risk in Veterans with TBI differ by race with White Veterans having 3 times higher risk, and Black and Hispanic Veterans having 2 times higher risk compared to Veterans by racial group without TBI.3 Racial/ethnic disparities and service connected disability disparities are related to TBI mechanism of injury and differentiate those referred to a Level 1 Trauma Center.4 Veterans with TBI were twice as likely to progress faster to RF than those without TBI.5 Black Veterans and Veterans in U.S. Territories progressed faster to RF relative to non-Hispanic Whites and those in urban mainland areas.5 Black and Hispanic/Latino Veterans on average received $5,000 fewer annual total VA resources; Veterans in U.S. Territories on average received about $4,000 less.5
3. **TBI, Dementia, and Veterans Health Economics**.6 Veterans with TBI had higher annual total costs relative to Veterans without TBI or with dementia. Veterans <65 with comorbid TBI and dementia had 2 times the annual total costs of Veterans ≥65 without TBI or dementia. Veterans <65 with TBI and dementia showed a shift from V.A. to non-VA inpatient facility placements. Annual VA and non-VA facility inpatient costs are higher than for Veterans without TBI or dementia. Veterans with TBI resulting from assault or gunshot have higher long-term VA costs compared to Veterans with other TBI mechanisms of injury.6 The benefits of MRI in diagnosing and managing TBI may be cost-effective despite its per unit costs.6

**Clinical Impact**

* **Better Access of Greater Need for TBI Service Utilization**. Veterans with mTBI, especially those with blast-related mTBI, are receiving more VHA health care services than those without TBI, which may be an indicator that the VA’s TBI care mission. Prospective research is needed to better understand how clinical service type and other treatment factors contribute to disability after mTBI.
* **Novel Racial Findings in TBI, Dementia Risk and Disability Rating**. Racial differences in dementia risk are novel and may be due to differences in dementia risk, dementia diagnosis rates, or potentially an interaction between race, APOE, and neurotrauma. Our results on socio-determinants of mechanism of injury in a Level 1 Trauma Center may have implications for prevention of assault and gunshot related TBI. The high prevalence of TBI service-connected disability in Pacific Islanders and Native Americans led us to acknowledge that the VA did not yet have a special geographic designation for Native American/Tribal Lands/ Reservations. We worked with the US Department of Labor to obtain zip codes for Tribal Elders and Leaders to incorporate into VA databases.
* **TBI and Dementia Placements and Costs**. Future LIMBIC-CENC research will compare the quality of care and outcomes between VA and non-VA facilities, and the impact of shifting placements on VA costs. Our results on the cost-effectiveness of MRI may have implications for its increased use in the diagnosis and management of mTBI.
* **Brain Health and Wellness Tool**. LIMBIC-CENC findings on preventable behavioral health risk factors after TBI, synthesized with the current research literature, led to the development, testing, and release of the LIMBIC-CENC a brain health and wellness survey that generates personalized recommendations to support Service Members and Veterans efforts to identify and self-manage their health-related risk factors after TBI. The LIMBIC-CENC’s Brain Health and Wellness Video Series complements the survey tool and provides a series of 4-minute primers on how to identify, prevent or self-manage TBI and co-morbid risk factors that can decrease dementia risk.

**Primary Knowledge Translation Products**

* LIMBIC-CENC provides a repository of information on [TBI and Epidemiology](https://www.limbic-cenc.org/for-tbi-researchers/epidemiology-of-military-tbi-researchers/) in the For TBI Researchers section.
* The [Abstract Veterans TBI Health and Outcomes Podcasts](https://www.limbic-cenc.org/for-service-members-and-veterans-with-tbi/the-abstract-veterans-tbi-health-and-outcomes-podcasts/) provides evidence-informed and real world patient, family and clinician perspectives on accessing and best leveraging DOD and VA health care services and resources.

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*LIMBIC-CENC research and its KT products were supported financially by the Department of Defense, Chronic Effects of Neurotrauma Consortium (CENC) Award W81XWH-13-2-0095 and Department of Veterans Affairs CENC Award I01 CX001135. Any opinions, findings, conclusions or recommendations expressed in this publication are those of the author(s) and do not necessarily reflect the views of the U.S. Government or the U.S. Department of Veterans Affairs, and no official endorsement should be inferred.*