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TITLE: Long-Term Impact of Military-Relevant Brain Injury Consortium (LIMBIC) Award

PRINCIPAL INVESTIGATOR: Dr. David X. Cifu

CONTRACTING ORGANIZATION: Virginia Commonwealth University, Richmond, VA

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David X. Cifu, MD

E-Mail: david.cifu@vcuhealth.org

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Virginia Commonwealth University
1223 East Marshall Street,
P.O. Box 980677,
Richmond, Virginia 23298-0677

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14. ABSTRACT

The Long-Term Impact of Military-Relevant Brain Injury Consortium (LIMBIC) is a coordinated, multicenter, nationwide translational research collaboration that is studying the effects of mild, combat-related TBIs, whether single or repeated, on chronic disabling symptoms, recovery from combat and trauma-related comorbidities, and long-term brain function. This Consortium builds upon the accrued experience of the previous Chronic Effects of Neurotrauma Consortium (CENC) funding cycle (2013-2019), where an Executive Leadership team, a Study Coordinating Center, centralized research Cores (Database and Biostatistics, Imaging, Biomarker), Scientific and Community Advisory Boards, a large, nationwide, multi-level, Prospective Longitudinal Study (PLS) and a multi-site, Retrospective Database Study (RDS) were all established and implemented. These essential elements of CENC have been carried over to LIMBIC and key enhancements of the PLS and RDS have been implemented. The LIMBIC team has completed all regulatory activities, personnel hiring, technical upgrades and documentation adjustments needed for the PLS to initiate follow-up evaluations on all extant participants and also recommence new recruitment of participants, with the easing of COVID-19 research restrictions. The LIMBIC PLS will specifically; 1) expand the current, well-characterized participant cohort with a history of deployment and combat exposure from 1,500 individuals exclusively from the OEF-OIF conflicts to 3,000 participants from all combat-eras to allow for greater statistical opportunities and flexibility in evaluating outcomes in both cross-sectional and longitudinal studies, 2) expand recruitment and testing of active duty and Veteran service members from 2 military/7 Veteran sites to 8 military/9 Veteran sites to increase recruitment of active duty service members, 3) refine existing and add new outcome measures to better evaluate the long-term effects of the number and types of blasts exposures, 4) add a well-utilized and accepted dementia measure that incorporates both participant and informant feedback to gain a better understanding of how TBI effects the development of dementia and which individuals may be more susceptible, 5) continue to refine and validate the standardized potential concussive event and concussion diagnostic interview formats, thereby allowing the field to use a common approach for evaluating concussive history which will enable better harmonization across study efforts, and 6) seek to identify specific neuroimaging and fluid biomarkers that are associated with combat-concussion and risk for poor outcome. The LIMBIC RDS has augmented and refine the CENC mega-database from 1.6 million military Veterans to more than 2.2M unique participants, with all data through 2019, of all TBI diagnoses (using ICD-10) and a random sample of non-TBI, all-era Veterans and identified subgroups with respect to risk/resilience, to 1) examine the complex association between comorbidities and TBI, 2) develop prognostic models for co-morbidity and poor outcomes, 3) identify TBI phenotypes that incorporate acute injury, mechanism of injury and blast exposure, 4) compare differences in health services utilization and costs for individuals with and without Traumatic Brain Injury (TBI) and within distinct TBI phenotypes accounting for comorbidities, 5) compare differences in service-connected disability costs for individuals by TBI status, and 6) extrapolate DoD and VA health services and disability cost estimates to provide DoD and VA annual budgetary impact of TBI accounting for comorbidities and within subpopulations of interest.

15. SUBJECT TERMS

None listed.

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Unclassified	Unclassified	Unclassified			

TABLE OF CONTENTS

1. **INTRODUCTION:** *Narrative that briefly (one paragraph) describes the subject, purpose and scope of the research.*

Background: The Long-Term Impact of Military-Relevant Brain Injury - Chronic Effects of Neurotrauma (LIMBIC-CENC) Consortium is a coordinated, multicenter, nationwide collaboration linking and utilizing basic science, translational, and clinical neuroscience researchers from the VA, military, and academia to effectively address the diagnostic and therapeutic ramifications of traumatic brain injury (TBI) and its long-term psychological, health and cognitive impacts on our active duty service members and military veterans. This Consortium builds upon the accrued experience of the previous CENC 5-year funding cycle and expands its reach and value. LIMBIC-CENC continues to be distinctively positioned because of 1) a coordinated and centralized organization directed by senior academic TBI leaders of the VA and DOD and effectively supported by an highly experienced, professional Coordinating Center; 2) close linkages between twelve major VA TBI/Polytrauma Centers with eight DoD Centers, and fourteen University research centers 3) proven ability to access large military and Veteran- relevant research subject populations and to work effectively with command personnel at those sites 4) an extensive, long term track record of collaborative TBI research 5) the ability and motivation to coordinate with other large scale TBI projects (currently over a dozen) throughout the country and collaborate to leverage resources and to achieve significant results faster 6) the establishment of a fully functioning Knowledge Translation (KT) Center that synthesizes and disseminates LIMBIC-CENC findings to all stakeholders (investigators, collaborators, community scientists, and participants) in varied formats and levels of depth allowing for easy comprehension 7) the maintenance and functional expansion of three study cores (data and biostatistics, biomarkers and neuroimaging) that support LIMBIC-CENC efforts in achieving its goals.

Objectives: The effects from TBIs, whether single or repeated, on chronic disabling symptoms, on recovery from combat and trauma-related comorbidities, and on long-term brain function in veterans and service members are not fully understood. The overarching goals of LIMBIC-CENC are to examine the critical issues related to the identification and characterization of the anatomic, molecular and physiological mechanisms of chronic brain injury and potential neurodegeneration, particularly chronic traumatic encephalopathy and dementia. The specific research studies have been designed to directly address the proposed consortium objectives and focus areas, to build on and leverage existing TBI research activities across the network, to provide meaningful answers to the current questions facing individuals and organizations affected by neurotrauma, and to identify and lead a way ahead.

Research Plan: Six current studies are underway:

STUDIES:

The Prospective Longitudinal Study (PLS) The CENC Prospective Longitudinal Study (PLS) established an active multicenter cohort of 1550 Service Members and Veterans who have all undergone comprehensive evaluation. The overall goal of the LIMBIC-CENC PLS is to maintain, expand and serially assess this multicenter cohort to anchor the solicited single Consortium of a large, longitudinal study, supporting sub-studies to analyze a large mild tramatic brain injury (mTBI) cohort including servicemembers (SMs), veterans (Vs), and relevant populations, and through a series of scientific analyses it will fulfill all of the required LIMBIC-CENC research elements. Under LIMBIC, this includes targeted expansion of pre-911 era SMs, current SMs, and heavily blast exposed populations. Initial and longitudinal data are collected under TBI CDE guidelines using comprehensive assessments and submitted to the FITBIR. Scientific analyses investigate mTBI co-morbidities and neurologic outcomes including change over time. Though this process, the PLS will identify potential differences in outcomes between SMs & Vs with various histories of lifetime mTBI and repetitive low-level blast exposures, identify pathophysiological and biomarker signatures for chronic mTBI subgroups of recovery patterns and neurodegeneration susceptibility, and evaluate neuroimaging techniques to understand the relationships between mTBI and neurodegenerative disease and other co-morbidities.

The Retrospective Database Study (RDS) continues to maintain, augment, and refine a growing database

(2.2M Veterans) of all TBI diagnoses (including converting ICD-9 diagnoses to ICD-10) and a random sample of non-TBI, all-era Veterans and identified subgroups with respect to risk/resilience. The study examines the complex association between comorbidities and TBI and will develop prognostic models from the data.

The Novel Neuroimaging Study aims to utilize neuroimaging to understand the relation between and variability in neurodegenerative dx and/or comorbidities in those with TBI by assessing available methods for overcoming variability and by harmonization across sites to incorporate elements of advanced statistical analysis and multimodal imaging in conjunction with other injury, demographic and outcome data and to 2) actively investigate new and established tools, share methodology and compare results using different approaches by critically examining and comparing strengths and limitations of analysis methods, by evolving existing analytic pipelines and creating novel analytic approaches where gaps exist.

The Biomarker Discovery Project seeks to identify biospecimen markers that are predictive of the long-term impact from concussive forces and which biomarkers may signal resilience despite experiencing TBI. Specifically, the study collects blood and saliva biomarker assays from all subjects with baseline specimens in the biorepository.
Biomarker correlations with TBI status (repetitive versus mTBI with LOC versus blast versus no TBI), pre-deployment/pre-injury biomarker levels, neurobehavioral symptoms, advanced imaging, neuropsychological testing, serial biomarker levels among small cohort with incident neurodegenerative disorder (e.g., dementia) are evaluated.
Intent is to develop panel of prognostic biomarkers for each phenotype of chronic neurotrauma (e.g. dementia, headache, PTSD, sleep disorder).

The Phenotypes Study extends the existing CENC Warfighter Cohort with respect to scope, duration of observation, and types of data included from both deployed and non-deployed participants. New types of data (e.g., radiology results, behavioral health screening, VA/DoD Suicide Data Repository, VA Homelessness Registry, text notes, vital signs, cost of care, etc.) have been added to the outcome measures to extend the validity of the phenotype attempt. The TBI severity algorithm has been extended to identify TBI phenotypes that incorporate acute injury, mechanism of injury and blast exposure. The study aims to compare the prevalence of key comorbidities by TBI severity and study group, and then use deep learning models that incorporate mTBI phenotype, acute and chronic treatment approaches, and emergence of diverse comorbidities to develop risk scores for poor military outcomes, and risk for developing key comorbidities.

The Health Economics Study (HES) seeks to compare differences in health services utilization and costs for individuals with and without Traumatic Brain Injury (TBI) and within distinct TBI phenotypes accounting for comorbidities. Further it aims to compare differences in service-connected disability costs for individuals by TBI status. Finally, it will extrapolate DoD and VA health services and disability cost estimates to provide DoD and VA annual budgetary impact of TBI accounting for comorbidities and within subpopulations of interest.

CORES:
The Coordinating Center, comprised by the key operations personnel at VCU, will work under the guidance and supervision of the VCU LIMBIC leadership team. This Coordinating Center will be responsible for most day-to-day VCU LIMBIC organizational and management issues. Principal among these functions will be establishing and maintaining the necessary infrastructure, personnel and procedures to successfully implement and complete the primary VCU LIMBIC objectives. The Coordinating Center shall be responsible for maintaining all SOPs and MOPs necessary for the operation of all studies. The Coordinating Center will ensure that all regulatory paperwork is submitted in a timely fashion and updated as required. The Coordinating Center will further ensure that study personnel are properly trained and certified in appropriate regulatory, ethical and legal research procedures, and that all personnel are credentialed by internal subject matter experts in the administration of tests and study procedures. Further, the Coordinating Center will implement tracking procedures to confirm that sites meet enrollment goals as

well as monitor follow-up evaluation sessions of already enrolled participants. This information will be obtained through biweekly site telephone conferences, regular email exchanges, dashboard metrics and site visits as required.

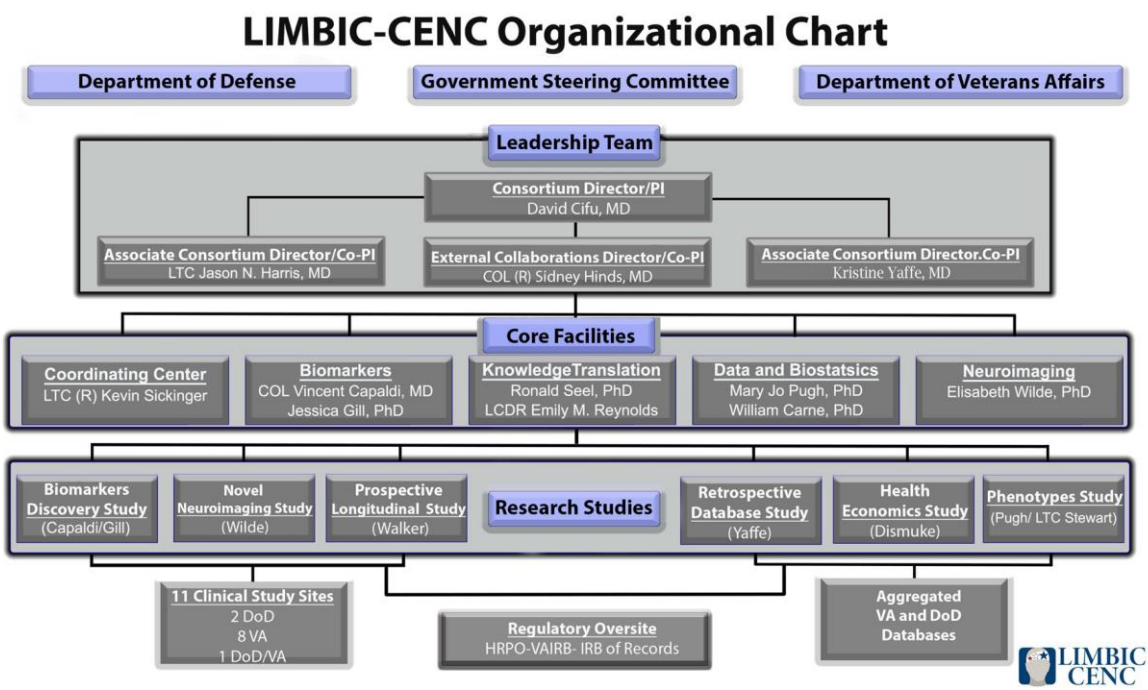
The Data and Biostatistics Core establishes procedures to receive, share, and adjudicate requests related to imaging data. It creates and implements efficient logistics for data-sharing both within and outside of the consortium. It develops and refines procedures for data collection and QA/QC, storage and management, and dissemination, while managing data capture (primarily through Medidata), and efficiently and securely storing all clinical data, and biospecimen and neuroimaging data for the Prospective Longitudinal Study. It performs QA and QC processing for all clinical data and works with Neuroimaging and Biorepository Cores to QA neuroimaging and biospecimen data. It disseminates requested data to investigators, provides analytical support for manuscripts, presentations, and other dissemination products, and submits data to FITBIR.

The Neuroimaging Core maintains an organized and well-characterized imaging dataset using standardized techniques of analysis and creates and manages the premiere database for military-relevant brain injury imaging data to identify indicators of neurodegeneration. Further, the core oversees and coordinates image procurement and promotes high-quality, accurate and consistent data collection. The core also establishes procedures to receive, share, and adjudicate requests related to imaging data. It actively creates and implements efficient logistics for data-sharing both within and outside of the consortium.

The Biomarker Core coordinates with appropriate LIMBIC-CENC personnel to submit relevant NED, APOE data to FITBIR. It conducts DNA extraction and APOE genotyping (in batches of 100-200) based on acquired consents for genetic testing. It continues to perform LIMBIC-CENC service operations-limited genotyping and NED screens through CLIA-certified lab (including complete set up for NED testing at 3 new LIMBIC sites). The Core provide samples for approved research specimen requests (LIMBIC and external investigators) once full regulatory documents are in place. Blood and saliva biomarker assays from all subjects with baseline specimens in the biorepository are performed. The core regularly carries out candidate biomarker correlations with TBI status (repetitive versus mTBI with LOC versus blast versus no TBI), pre-deployment and pre-injury biomarker levels, neurobehavioral symptoms, advanced imaging, neuropsychological testing, serial biomarker levels among small cohort with incident neurodegenerative disorder (e.g. dementia). The core is developing a panel of prognostic biomarkers for each phenotype of chronic neurotrauma (e.g., dementia, headache, PTSD, sleep disorder).

Military/VA Benefit:
LIMBIC-CENC is specifically designed to demonstrate the linkages between TBI, direct effects (cognitive, general health, behavioral) and chronic neurodegeneration. This knowledge will aid in providing clinical care that guides the development of novel interventions that prevent or mitigate cognitive and behavioral decline and contributes to long-term planning for service member and veterans.

See LIMBIC-CENC Organizational Chart Below:



2. **KEYWORDS:** *Provide a brief list of keywords (limit to 20 words).*

chronic effects
prognostic biomarker
health services
Veterans
VA costs
DoD costs
Service Connected Disability Compensation
FITBIR
MRI
neuroepidemiology
phenotype
chronic pain
mTBI
epidemiology
neurodegeneration
biospecimen biorepository
neurotrauma
dementia
comorbidity
Search Engine Optimization

3. **ACCOMPLISHMENTS:** *The PI is reminded that the recipient organization is required to obtain prior written approval from the awarding agency grants official whenever there are significant changes in the project or its direction.*

What were the major goals of the project?

List the major goals of the project as stated in the approved SOW. If the application listed milestones/target dates for important activities or phases of the project, identify these dates and show actual completion dates or the percentage of completion.

Cores

Coordinating Center:

This Coordinating Center is responsible for most day-to-day VCU LIMBIC organizational and management issues. Principal among these functions will be establishing and maintaining the necessary infrastructure, personnel and procedures to successfully implement and complete the primary VCU LIMBIC objectives. The Coordinating Center shall be responsible for maintaining all SOPs and MOPs necessary for the operation of all studies. The Coordinating Center will ensure that all regulatory paperwork is submitted in a timely fashion and updated as required. The Coordinating Center will further ensure that study personnel are properly trained and certified in appropriate regulatory, ethical and legal research procedures, and that all personnel are credentialed by internal subject matter experts in the administration of tests and study procedures. Further, the Coordinating Center will implement tracking procedures to confirm that sites meet enrollment goals as well as monitor follow-up evaluation sessions of already enrolled participants. This information will be obtained through biweekly site telephone conferences, regular email exchanges, dashboard metrics and site visits as required.

Data and Biostatistics Core:

The Data and Biostatistics Core is a collaborative effort of two sites with expertise working at HHMVANMC/VCU and VASLCHCS/UU. The Richmond group will manage data collection for the clinical studies via Medidata Rave, NIH toolbox and other mechanisms (i.e., Otogram, EEG/ERP), This Core will also collaborate with the Coordinating Center and Clinical Studies Core to conduct data checks, queries, auditing, and other data quality assurance activities. This Core Facility allows for both a centralized repository for all VCU LIMBIC data and efficient access to the data for accelerated knowledge translation and readily deployable research products.as well as ensure data quality and timely submission of data to FITBIR. The Salt Lake City team provides analytic leadership, biostatistics and informatics expertise, and facilitate data distribution and manuscript development for the clinical studies, in addition to facilitating manuscript development by consortium members from the other five Research Studies. The Salt Lake City team is also responsible for ensuring data quality (QC) and a timely submission of data to FITBIR.

Neuroimaging Core:

The Neuroimaging Core, at the VA Salt Lake City Health Care System (VASLCHCS) and the University of Utah, will facilitate acquisition, review, transfer, collation, tracking, analysis, integration, reporting, storage, and interpretation of all CENC and VCU LIMBIC neuroimaging data. Neuroimaging Core Specific Aims are to:

Task 1: Maintain the established CENC/LIMBIC neuroimaging database using the standardized techniques of image procurement, standardization and quality assurance.

Task 2: Oversee and coordinate the image procurement at each clinical study site.

Task 3: Establish procedures in collaboration with the Research Committee to receive and adjudicate requests for studies utilizing imaging data specimens.

Task 4: Establish priorities, policies and procedures to make imaging data accessible to VCU LIMBIC and associated researchers.

Biomarkers Core:

The Biomarkers Core, located within CNRM at USUHS, will manage the storage and processing of blood and saliva samples collected through the Prospective Longitudinal Study as well as other CENC-LIMBIC studies. Blood samples are locally processed and separated into plasma, serum, and packed red and white blood cells (which is further processed at the Biorepository to extract DNA and carry out limited genotyping, e.g. APOE). These biological fluids will be cataloged and tracked and stored at -80°C in a dedicated Biorepository Facility maintained within the Center for Neuroscience and Regenerative Medicine (CNRM). The work will involve

faculty and staff processing lab work on thousands of samples. Finally, the Core will administer requests for use of these biological samples from investigators inside or outside LIMBIC, according to the data and sample sharing policies of the Consortium. Biomarkers Core Specific Aims are to:
Task 1: Maintain the established Biospecimen Biorepository with standardized methods of collection, local processing, and shipment of blood and saliva from LIMBIC study sites to a centralized Biorepository where samples are collected, stored and curated.
Task 2: Screen all clinical study participants at baseline for neuroendocrine dysfunction (NED) through a CLIA-certified Laboratory.
Task 3: Carry out Deoxyribonucleic Acid (DNA) extractions and Apolipoprotein genotyping on study participants who consented to genetic testing.
Task 4: Establish procedures in collaboration with the Research Committee to receive and adjudicate requests for studies utilizing Biorepository specimens.
Task 5: Establish priorities, policies and procedures to make Biorepository specimens accessible to VCU LIMBIC and associated researchers.
Task 6: Retrieve and ship requested samples to approved projects for study.

Studies

Prospective Longitudinal Study:
The CENC Prospective Longitudinal Study (PLS) established an active multicenter cohort of 1550 Service Members and Veterans who have all undergone comprehensive evaluation. The overall goal of the LIMBIC-CENC PLS is to maintain, expand and serially assess this multicenter cohort to anchor the solicited single Consortium of a large, longitudinal study, supporting sub-studies to analyze a large mild tramatic brain injury (mTBI) cohort including servicemembers (SMs), veterans (Vs), and relevant populations, and through a series of scientific analyses it will fulfill all of the required LIMBIC-CENC research elements. Under LIMBIC, this includes targeted expansion of pre-911 era SMs, current SMs, and heavily blast exposed populations. Initial and longitudinal data are collected under TBI CDE guidelines using comprehensive assessments and submitted to the FITBIR. Scientific analyses investigate mTBI co-morbidities and neurologic outcomes including change over time. Though this process, the PLS will identify potential differences in outcomes between SMs & Vs with various histories of lifetime mTBI and repetitive low-level blast exposures, identify pathophysiological and biomarker signatures for chronic mTBI subgroups of recovery patterns and neurodegeneration susceptibility, and evaluate neuroimaging techniques to understand the relationships between mTBI and neurodegenerative disease and other co-morbidities.

Retrospective Database Study:
The primary objective of this project is to integrate and analyze existing VA healthcare data to study the long-term effects of traumatic brain injury (TBI) on neurodegenerative disease, mental health, and other outcomes. Our group of experts in TBI and epidemiology created a highly pragmatic national analytic database of over 2 million Veterans. In LIMBIC-CENC, we are rapidly investigating unanswered questions related to health risks associated with TBI:
Task 1: Planning and regulatory review, data updating, and variable creation (Months 1-12).
Task 2: Analysis assessing the role of mental health comorbidities on the association between mTBI and long-term outcomes such as dementia and other neurodegenerative diseases (Months 6-30).
Task 3: Analyses assessing the role of demographics and socioeconomic status to the risk of developing dementia and examining the characteristics and longitudinal course of younger veterans (<55) with cognitive impairment after mTBI (Months 24-50).
Task 4: Develop prognostic models to better determine risk of dementia and mortality and associations with risk factors in veterans with mTBI; create and validate clinical tool determining risk of poor short-term and long-term outcomes in patients with mTBI (Months 24-60).

Phenotype Study:
Study staff and investigators will compile the DoD-VA data to expand the CENC Warfighter cohort, extend

the observation period and provide data to 1) describe the population of SMs and Vs with mTBI, no TBI and TBI of other severities; 2) identify phenotypes and risk for specific phenotypes accounting for baseline characteristics, acute injury characteristics, and acute and chronic treatment patterns. The study aims to compare the prevalence of key comorbidities by TBI severity and study group, and then use deep learning models that incorporate mTBI phenotype, acute and chronic treatment approaches, and emergence of diverse comorbidities to develop risk scores for poor military outcomes, and risk for developing key comorbidities. The major goals for this study are as follows:
Task 1: Update data repository annually with latest VA data and merge with relevant DOD datasets and add additional DoD data to enhance acute TBI identification. Once assembled, perform quality checks and continue maintenance throughout study.
Task 2: Conduct phenotype analysis by deployment strata to examine the role of mTBI in emergence of neurodegenerative disease, psychological health status, neurosensory deficits and pain over time.
Task 3: Use phenotypes and mTBI to develop risk scores for military outcomes, neurosensory/neurodegenerative disease, and adverse outcomes by deployment.
Task 4: Examine association of phenotypes with TBI and risk for repetitive low-level blast by deployment strata.

Health Economics Study:
Study staff and investigators will compile the DoD-VA data to expand the CENC Warfighter cohort, extend the observation period and provide data to 1) describe the population of SMs and Vs with mTBI, no TBI and TBI of other severities; 2) identify phenotypes and risk for specific phenotypes accounting for baseline characteristics, acute injury characteristics, and acute and chronic treatment patterns; 3) economic impact of phenotypes from the perspective of the DoD, the VA, and society. Along with the phenotypes study, the Health Economics Studies will develop a merged DoD and VA cohort that includes individuals who were on active duty after September 11, 2001 through the end of FY19 via DaVINCI, a portal that allows sharing of VA and DoD data for all SMs and Vs (including deployed National Guard/ Reserve members), as we have done for several previous studies. Based on MHS data included in the Mental Health Data Cube compiled by Kennel Associates, we will identify individuals who were deployed to combat theatre and those who were not deployed. We will then merge the DoD data with data from the Veterans Health Administration and Veterans Benefits Administration to identify individuals who have connected with the VA for Health and/or Benefits in order to assess the long-term disability and health status impact and classify the cohort into our study groups stratified by deployment and VA health care use status: Deployed+VA, Deployed-No VA, Non-deployed+VA, Non-deployed-No VA. We will identify our cohort through FY19, and with follow-up observation through FY23.

For the Longitudinal prospective cohort, the major goals are: 1): Merge up to 4000 records from the Prospective Study, veterans and service members, with VA health service connected disability, VA diagnoses, VA health services utilization and VA cost data as data are provided from the Prospective Study PI. 2): Examine the association of self-reported combat and training mechanism of injuries with VA service connected disability ratings and costs by TBI status and severity. 3): Examine the association of self-reported combat and training mechanism of injuries with VA health services utilization and costs by TBI status and severity. 4): Examine the association of self-reported combat and training mechanism of injuries with VA diagnoses by TBI status and severity.

Novel Neuroimaging Study:
In addition to supporting Prospective Longitudinal Study, the Neuroimaging Core will utilize neuroimaging to understand the relationship between and variability in neurodegenerative disease and/or comorbidities in those with mTBI. The Novel Neuroimaging Study will actively investigate new and established tools, share methodology, and compare results using different approaches; this will enable us to evolve analytic pipelines based on these investigations, and create novel analytic approaches where gaps exist. Novel Neuroimaging Study Major Tasks are as follows:
Task 1: Assess available methods of overcoming variability introduced by differences in scanner hardware and software.

Task 2: Critically examine and compare strengths and limitations of commonly used imaging analysis pipelines.
Task 3: Develop and test aspects of pre-processing which enhance accuracy and consistency.
Task 4: Create and refine novel, automated pipelines to address aspects of imaging analysis which are currently absent or incomplete.
Task 5: Incorporate elements of advanced statistical analysis (e.g., Bayesian analysis, machine learning) to utilize multi-modality imaging data in conjunction with other injury, demographic and outcome data to develop subgroups/phenotypes and identify related variables in those at highest risk for poor outcome.
Task 6: Assess merits and challenges of existing methods of "individualized" data analysis.
Task 7: Share data with external investigators; Biannual submission to FITBIR (March and September)

Biomarker Discovery Study:
In addition to supporting the Prospective Longitudinal Study, the Biomarkers Core will carry out projects in collaboration with the other VCU LIMBIC Cores to address the following objectives:
Task 1: Identify biologic signatures that may be predictive (prognostic biomarkers) of long-term TBI outcomes or maintenance of symptoms. Identify novel biomarkers for chronic mTBI; characterize mTBI subgroups based on recovery and neurodegeneration.
Task 2: Collaborate with Dr. Wang (Gainesville VA), as externally funded, to develop and validate a rapid throughput multiplex immunoassay of candidate chronic TBI biomarkers for commercialization.
Task 3: To collaboratively carry out GWAS within the CENC/LIMBIC cohort (N = 3,000) in collaboration with the Genetic Association in Neurotrauma (GAIN) consortium that has data from >10,000 participants.
Task 4: To expand the miRNA study and to carry out a DNA methylation study in chronic TBI patients.

What was accomplished under these goals?
For this reporting period describe: 1) major activities; 2) specific objectives; 3) significant results or key outcomes, including major findings, developments, or conclusions (both positive and negative); and/or 4) other achievements. Include a discussion of stated goals not met. Description shall include pertinent data and graphs in sufficient detail to explain any significant results achieved. A succinct description of the methodology used shall be provided. As the project progresses to completion, the emphasis in reporting in this section should shift from reporting activities to reporting accomplishments.

Cores

Coordinating Center:
Major Task 1: Transition and Expand CENC to LIMBIC:

1. Submission of IRB approved master protocol.
   Month(s): 1 - 3
   Progress: Completed in the 1st Quarter of Year 1.

2. Delivery of expanded Consortium SOP.
   Month(s): 1 - 3
   Progress: Completed in the 1st Quarter of Year 1.

3. Submission of timeline for onboarding performance sites.
   Month(s): 1 - 3
   Progress: Completed in the 1st Quarter.

4. Establishment of Data Sharing Agreement with DHA for access and use of MHS data at VCU CC and appropriate sites.
   Month(s): 1 - 4
   Progress: Ongoing.

5. HRPO Approval of Master Protocol.
   Month(s): 1 - 6
   Progress: ***Completed.*** See **Appendix #1 (Regulatory Tracker)** for updates.

6. IRB/HRPO/JIT approvals for all performance sites and consortium cores.
   Month(s): 1 - 12
   Progress: ***All IRB and JIT submissions were submitted and approved***. See above for HRPO approvals.

7. Hiring, training and certification of subaward personnel, particularly subaward clinicians and associate researchers.
   Month(s): 1 - 6
   Progress: Ongoing.

Major Task 2: Add three new additional Prospective Study Enrollment Sites:

1. Onboard 3 new enrollment sites (Salisbury/San Diego/Fort Gordon).
   Month(s): 1 - 6
   Progress: ***This was completed on time, well before the end of the 2nd Quarter of Year 1***.

2. Assist with hiring, training and certifying staff.
   Month(s): 1 - 6
   Progress: Completed the initial staffing process and now we are in the continuation of maintaining proper staff levels phase. We have had tremendous turnover at several sites this past year and the process of hiring, training and certifying is an ongoing event.

3. Assist with regulatory approvals to include IRB and HRPO.
   Month(s): 1 - 6
   Progress: ***All sites were gained IRB and HRPO approvals***. We have now moved to the Continuing Review process. See **Regulatory Tracker Appendix #**1 for specific updates.

Major Task 3: Conduct Call Center operations:

1. Assist with hiring, training and certifying staff.
   Month(s): 1 - 60
   Progress: Ongoing.

2. Conduct liaison between enrollment sites.
   Month(s): 1 - 60
   Progress: Ongoing.

3. Conduct all necessary follow-up calls to include BTACTs and Annual Telephone Assessments for Prospective Longitudinal Study.
   Month(s): 1 - 60
   Progress: The Call Center has attempted to conduct all necessary follow-up calls to include Annual Follow Up Assessments and BTACTs. For completion numbers, see **Appendix #3**.

Major Task 4: Attend Semi-Annual GSC meetings with DoD and VA sponsors:

1. Coordinate with CDMRP Science Officer to make tentative schedule for semi-annual GSC meetings.
   Month(s): *4 - 60*
   Progress: We completed two to include our first in-person GSC meetings within the reporting period (October 2022 and April 2023) and initiated coordination for another meeting during the period and that meeting was scheduled for October 2023 in year four of the Period of Performance. See **Appendix #2b** for the October and April GSC Meeting presentations.

2. Coordinate with all performance site PIs to ensure that their schedules permit attendance at meetings.
   Month(s): *4 - 60*
   Progress: We were able to get all of the primary PIs to attend the virtual meeting in October 2022 and the first in-person meeting in April 2023.

3. Provide CDMRP Science Officer with all required meeting materials in accordance with approved schedule.
   Month(s): *4 - 60*
   Progress: Continued to utilize the new timeline for meeting materials, not only ensuring that we met the turn-in suspense but also allowed for review time for our Science Officer to ensure that we turned in the best product possible.

Major Task 5: Set and publish all Performance Site Metrics to include (recruiting/retention/reporting/data collecting/FITBIR reporting):

1. Establish Site Metrics.
   Month(s): *1 - 60*
   Progress: This task has been completed. We initiated the Full Site Metrics Reports during this reporting period and conducted them on a monthly basis. We put one enrollment site (Fort Belvoir) on probation. They have since made operational corrections and are no longer on probation.

2. Establish recruitment and retention goals as well as the overall plan.
   Month(s): *1 - 60*
   Progress: The initial recruitment and retention plan that was adjusted during year two due to COVID is still in effect. We are currently on the path to reach our goal of 3000 participants well ahead of schedule. Several of the sites (Houston/Tampa/Portland) will reach their site goals and will start to only conduct follow-up visits in early 2024.

3. Monitor and report site performance.
   Month(s): *1 - 60*
   Progress: This has been completed throughout the year to include monthly feedback to the sites.

4. Maintain and establish regular communication through meetings, teleconferences, e-mails, site visits and other methods to maintain consortium function.
   Month(s): *1 - 60*
   Progress: We continue to communicate through our established and maintained regular teleconferences, emails and other calls as needed. We have not been able to conduct site visits due to travel restrictions and safety precautions due to COVID-19 but will resume travel once it is deemed safe.

Major Task 6: Collect required information, prepare and submit Quarterly, Annual and Final Reports.
   Month(s): *1 - 60*
   Progress: Completed all required reports on time and to standard.

Major Task 7: Conduct Consumer Advisory Board Meetings:

1. Select Board Members and attain GSC approval of the selectees.
   Month(s): 1 - 3
   Progress: Completed in Year 1.

2. Publish the LIMBIC CAB Charter.
   Month(s): 1 - 6
   Progress: Completed in Year 1.

3. Publish the LIMBIC CAB Meeting Schedule.
   Month(s): 1 - 6

Progress: Completed in Year 1.

4. Conduct the meetings, provide appropriate feedback to Consortium Leadership and implement approved feedback.

Month(s): 6 – 60

Progress: **Consumer Advisory Board**. On March 1st 2023 and August 23rd 2023, we solicited input from the CAB several items to include website improvements as well as critiques on several Knowledge Translation products. The participation level and feedback that we receive from the CAB continues to be excellent.

Major Task 8: Ensure maximum Consortium PI involvement in scientific conferences:

1. Ensure maximum Consortium PI involvement in scientific conferences.

Month(s): 1 - 60

Progress: We encouraged and assisted as many LIMBIC-CENC personnel to attend the MHSRS Conference this year. All members in attendance also met for a casual gathering.

Major Task 9: Management of Fiscal Resources:

1. Establish appropriate approved sub contractual arrangements.

Month(s): 1 - 3

Progress: Completed in the 1st Quarter.

2. Establish CRADA and other agreements as required, provide copies to the GOR, and update as necessary.

Month(s): 1 - 3

Progress: We have finally made excellent progress with the CRADA which is currently in the process of being signed by all involved parties and will be in force soon after end of FY23.

3. Monitor overall and individual site finances.

Month(s): 1 - 4

Progress: We have closely monitored individual site finances to include expenditures and personnel effort.

4. Develop strong working relationship with both the DoD and VA Contract Personnel to ensure 100% financial regulatory compliance.

Month(s): 1 - 60

Progress: We continue to strengthen our relationship with the VA Contract Personnel as well as a working relationship with our DoD counterpart.

5. Provide Quarterly and Annual Financial Reports to be included in the Consortium's Quarterly and Annual Reports.

Month(s): 1 - 60

Progress: Ongoing.

Major Task 10: Publication of methodology, preliminary, and final study results and methodology:

1. Develop plan for analysis of study data, and reporting.

Month(s): 12 - 24

Progress: These activities are ongoing for the entire consortium. However, Dr. Walker provides a detailed analysis plan within the PLS section.

2. Assist Consortium PIs in publishing of results in both Scientific Journals and Conferences.

Month(s): 24 - 60

Progress: Ongoing. See **Appendices #2 and #2a** for results.

3. Conduct Knowledge Translation in order to transform the findings from research to practice.

Month(s): 36 – 60

Progress:

Updated Website with Core Online Products (On-going):

- Implementation of Search Engine Optimization (SEO) Plan Completed. We contracted SEO consultants to assess all aspects of the LIMBIC-CENC website from a user perspective. A primary goal of this project was to develop and implement website changes to drive additional traffic to our website. We received a final written SEO report on 11-4-22 that provided an assessment of the website and recommendations to improve the site's searchability, traffic, content, format, speed and overall usability. Our internal LIMBIC-CENC SEO group developed an implementation plan in December 2022 and met weekly to develop new naming conventions, review proposed website changes, resolve challenges, and track progress. Primary achievements included a full site directory restructure (including re-organized content, meta-titles, meta-tags, renamed all website links and online headers); a crawl robots text file upload; and revised Favicon. Website performance improvements included migration to GA4 and web structured data conversion.
- Updated High Level Website Structure. Given the differing knowledge translation needs of clinicians and researchers, we created separate website sections 'For Clinicians' and 'For Researchers'. Service Members/Veterans/Public and Clinician Website Sections. Based on Consumer Advisory board (CAB) September 2022 recommendations, we re-organized dissemination materials under each health topic icon using product type icons, e.g., practice guidelines, key point summaries, podcasts, tools/resources, etc. This reduced the amount of content and scrolling required on a single page. We re-organized and expanded content in the SM/Veterans, Clinician, and Researcher sidebars.

Development of Metrics for Evaluating Success of implementing SEO plan:

- We began planning to use analytics data to assess improvements to the LIMBIC-CENC website including increased traffic and website speed. We presented a plan to use Reach (number of people who view content such as a page/product/topic) and Engagement (percent of people who interact with content such as time spent/'likes'/ downloads/subscribes) to assess product content.

Broader Dissemination of LIMBIC-CENC Products and Progress:

- Education and Resources. Added over 125 unique products to the website with over 400 links in the Service Members/Veterans/Caregivers and Clinicians/Researchers website sections. Expanded material content includes resource links, fact sheets, updated published clinical practice guidelines, and key point summaries with particular attention focused on cognition, sensory and balance, and return to community. Incorporated access to TBICoE, Wounded Warrior Project, and Brainline resources and materials. Edited all introductory text content across website to ensure ≤10.5 grade level.

Deployed Dementia Risk Assessment Tool for Service members, Veterans and their Clinicians:

- Deploy Dementia Risk Assessment Tool for Service members, Veterans and Clinicians. We are working on version 2.0 of the My Dementia Risk Profile and Personalized Report, which will provide Service Members and Veterans with links to more actionable recommendations and resources for leading healthy lifestyles that reduce risk. We will rebrand this tool as a Brain Health and Wellness Assessment Tool. Version 2.0. We are awaiting website content and format recommendations from the SEO consultation prior to finalizing program implementation decisions. Update will be completed by 3-31-2023..

Consumer Advisory Board (CAB).

- On March 1 2023 and August 28 2023, we solicited input from the CAB on the website and types and format of actionable information to be provided to consumers. In the March meeting, we obtained and incorporated feedback on Brain Health and Wellness Video Series. The CAB remained highly pleased with the focus on brain health and wellness and the

concepts, risk factors, and general content. The CAB reviewed four video scripts during the meeting and provided specific change requests based on SM/Veteran values with an emphasis on de-emphasizing medication use and highlighting healthy lifestyle changes. The CAB also suggested adding a video on sleep functioning, which we incorporated as a 10th video in the series. In the August meeting, we obtained and incorporated feedback on the newly developed Brain Health and Wellness Personalized Recommendations Report. The CAB reviewed Report was highly pleased with Brain Health Report concept, format and content. Feedback included keeping formatting standard and simple, removing bullets, keeping text for videos brief, and collapsing four sections into three on the untreated conditions page.

Education and Resources:

- Added over 150 unique products to the website Service Members/Veterans, Clinicians and Researchers website sections. Expanded material content includes resource links, fact sheets, updated published clinical practice guidelines, and key point summaries with particular attention focused on cognition, sensory and balance, and return to community. The LIMBIC-CENC website now supports well over 500 dissemination materials including clinician-targeted key point research summaries, consumer postcards and education modules, and links to healthy lifestyle resources, clinical practice guidelines, and self-management tools.

Major Task 11: Interface with other researchers, entities, and consortiums as directed by the Government Steering Committee and Program officer.

Maximum participation in conferences, with a minimum attendance at 1 scientific conference per year and at 2 military conferences (DoD or VA-sponsored) over 5 years.

Month(s): 1 - 60

Progress: Ongoing: LIMBIC-CENC will continue to foster external collaborations which will provide the most impactful achievements, and which will propel the expansive knowledge in the fields of neuroscience, neurotrauma, neurodegeneration and rehabilitation forward. For more details on External Collaborations, please see our Collaboration Tracker located at **Appendix #4**.

Data and Biostatistics Core:

Major Task 1: Hire and maintain DBC staff.

Month(s): *1 - 60*

Progress: New Core staff (1 full-stack developer) position is currently in process of being hired at VCU to expand DBC capabilities. Due to staff turnover (transition to graduate school), the Salt Lake City team recently hired another research analyst (Abigail White, Graduate Research Assistant) to assist the biostatistics team.

Major Task 2: Collect data using Medidata RAVE and supplementary platforms; clean and check data quality; share data with internal investigators as requested.

Month(s): 1 - 60

Progress: Transitioned from CENC data capture system in Medidata to LIMBIC-CENC system also in Medidata, including transferring all previously collected data from six years of CENC. In addition to Medidata, raw data files are being captured through the secure file transfer protocol. Developed and iteratively improved the Study Portal system to capture and manage PLS participant contact information and to track Call Center call completion. Added feature in Study Portal to facilitate sites' tracking of upcoming visits. Completed training of all 11 sites in all IT systems and provided ongoing support. Conducting monthly data quality checks and feedback to sites on visit completion rates, data entry timing and quality, raw data uploads, FITBIR GUID, and pseudo-GUID tracking. Generate multiple monthly reports to track retention, comprehensive, annual telephone, and BTACT visit completion, and consent reports for biofluid samples. Developed and implemented REDCap survey to enable the completion of self-report questionnaires remotely. Worked with Neuroimaging Core to build a system for capture of data from common data element coding of MRIs and QA/QC of data. Refined internal data request process

based on feedback from investigators. Expanded data dictionary which allows users to search and conveniently look for data elements and their definitions/specifications. The dictionary is structured by CRF and data elements. Developed a system to release data snapshots and analytic data sets 2x/year in conjunction with FITBIR submissions. To expedite the turnaround time of data submission to investigators, a desktop application was created to automate data extraction for new data requests. The application underwent rigorous testing and validation and has been implemented and is in production. Using the application, the DBC is able to respond to approved data requests within two business days compared to 10 to 15 days with the previous processes. The DBC has created analytic data sets that are updated every six months. The data sets sync the data elements across three platforms: The web-based data dictionary, the CRF documents, and the Analytic data sets. The synchronization is an attempt to further enhance investigators' experiences usability of the LIMBIC data sets. Added IT ticketing/operational support system to LIMBIC-CENC website to decrease turnaround time to fix data/technical issues.

Major Task 3: Analyze data to evaluate cognitive decline and related late effects.

Month(s): *1 - 60*

Progress: During year 4, the analyses of two data sets focusing on cognitive functioning are in progress by the Central Biostatistics group.

Major Task 4: Translate knowledge and disseminate knowledge products.

Month(s): *1 - 60*

Progress: Underwent SEO audit and updated LIMBIC-CENC website and KT products in accordance with the independent firm's recommendations. Continuously refining searchable, comprehensive publication database of CENC and LIMBIC-CENC publications (publicationdatabase.limbic-cenc.org). Developed Dementia Prognostic Tool. Continuously adding more relevant Brain Health-related tools for public and clinicians.

Major Task 5: Provide advanced biostatistical support to develop analysis plans, conduct analyses, and support manuscripts.

Month(s): 1 – 60

Progress: During year 4, the SLC data core released 18 PLS/VINCI data sets. 11 curated data sets, out of the 18 data requests, were submitted to investigators to perform their own analyses and the remaining 7, were shared with the Central Biostatistics analysts to help investigators with statistical analyses and preparing manuscripts and papers. Due to the extended scope, aims, and analyses of the two projects, several individual requests were split into separate requests, and each was led by different investigators. As a result of the split, the Biostatistics analysts are currently analyzing 9 data projects. During this reporting period, the analysts have completed 3 projects and the rest of the 6 analyses are in progress. Three projects included additional data sets from VINCI core data sets enabling investigators and analysts for more in-depth analytics of PLS & VINCI data sets linkage. See Appendix X for a list of year 4 data requests, lead investigators, the status, and a short title.

Major Task 6: Share data with external investigators; Biannual submission to FITBIR (March and September).

Month(s): *6 – 60*

Progress: Progress: Attended biweekly meetings with FITBIR Ops. Set up FITBIR account access for LIMBIC-CENC Data and Biostatistics Core personnel for data submission and all Prospective Longitudinal Study site personnel for GUID creation as new staff entered study team. During this reporting period, the SLC data core team submitted more than 90+ separate data sets to FITBIR. Below are the FITBIR submission details:

March 2023 Submission Status			September 2023 Submission Status		
Submission Status:	Form Count		Submission Status:	Form Count	
Submitted	93		Submitted	93	
Exclude Right Eye	1		Excluded Right Eye	1	
Grand Total	94		Grand Total	94	

Cumulative data were submitted to FITBIR on March 31, 2023, for the period of October 1st, 2019 through September 30th, 2022, and on September 30th, 2023 for the period of October 1st, 2019 through March 31st, 2023. Both periods included 93 (out of 94) successful submissions; Right eye was excluded and waiting for the form structure to be created in FITBIR.

Major Task 6a: LIMBIC/CENC Not Applicable & Missing Data Project (continues):

Updates: The DBC team has accomplished a significant milestone by thoroughly reviewing and identifying the extensive skip logic instances involving "Not Applicable" (NA) in over 90 PLS instruments. Presently, the SLC data core team is actively engaged in programming and integrating these NA values into the Analytics data sets. This implementation will enable investigators and Biostat analysts to easily differentiate between missing values and cases where the NA designation is appropriate. By doing so, the team aims to enhance the accuracy and clarity of the data sets, facilitating more precise analyses and interpretations.

Major Task 6b: Data Dictionary Development.

Update: The data dictionary for PLS data sets is consistently being updated to accurately reflect the inclusion of "Not Applicable" (NA) values wherever applicable.

We are currently expanding our data dictionary offerings by including the VINCI dataset. This addition aims to provide investigators with enhanced visibility and valuable insights into the available variables.

Major Task 7: Attendance at biannual GSC meetings.

Month(s): *4 – 60*

Progress: Attended and presented progress to GSC at both scheduled meetings.

Neuroimaging Core:

Major Task 1: Hire and maintain all research consortium staff.

Month(s): *1 - 60*

Progress: We have generally maintained existing research staff. All staff members have WOC appointments at the VA, and are current on all required CITI training for University of Utah, SLC VA, and Office of the Undersecretary of the Department of Defense. While some staff training is anticipated to continue throughout the project (as staff assume additional responsibilities or duties evolve), we have an effective and well-integrated team.

Major Task 2: IRB protocol development, submission, and continuing review. (Locally and in conjunction with Coordinating Center at VCU).

Month(s): *1 - 60*

Progress: At the beginning of the project, we submitted a new IRB under LIMBIC to the University of Utah and George E. Wahlen VA and received formal determination from the IRB that activities conducted under the Neuroimaging Core were not considered human subjects research and did not require further oversight by the IRB (03 Dec 2019). We subsequently submitted a separate IRB for the Novel Neuroimaging Project, which was also determined to be non-human subjects research. Since no continuing review is necessary, this is considered complete. We will continue to undergo annual RR&D committee approval at the VA; this was last approved October 2023 for both the Novel Neuroimaging Project, and we will be submitting the continuing review for the Core in the coming weeks (due in November 2023).

Major Task 3: HRPO approval and continuing review.

Month(s): *1 – 60*

Progress: Neuroimaging Core activities were also determined by HRPO to not constitute human subjects research. Therefore, no further review or oversight is necessary, and this is considered complete.

Major Task 4: Oversee image acquisition for accuracy and consistency across sites through standardized protocols, MR and human phantom testing.

Month(s): *1 - 60*

Progress: We have continued began site-specific training on imaging –related procedures for all sites. We review and discuss imaging quality and consistency in weekly Imaging Core Operations meetings. We have prepared feedback to each site from our semi-annual audit process (April 2023) and meet with sites to correct issues, as needed. The next semi-annual audit will occur at the end of October 2023.

Quality assurance-related procedures include quarterly self-assessments performed by the sites (due January, April, July, and October) as well as semiannual assessments performed by the Core (due April and October). These assessments address adherence to established procedures and are detailed in the SOP. Phantom object (every two weeks) testing is anticipated to be ongoing through the course of the project. The most recent human phantom data collection was performed in September in Boston and in October in Houston, and Dr. Wilde met with the MR technologists to review basic procedures.

Major Task 5: Share data with external investigators; Biannual submission to FITBIR (March and September).

Month(s): *6 - 60*

Progress: We have completed scheduled data uploads of the raw imaging data to FITBIR (most recent was September 2023). We also assist in the data entry and review for the results of the imaging Common Data Elements based on the clinical reviews by the neuroradiologists. We meet weekly with the Data Core, and participate in other subgroup calls, as needed. We continue to provide coded summary imaging data (including specific measures and composites) and guidance to investigators within and outside the consortium with proposals that have been approved through LIMBIC. This represents an ongoing activity, but members of the Core have participated during this reporting period in planning projects and distributing data to ENIGMA,VA Center of Excellence investigators as well as projects by individual investigators both within and outside the consortium. We continue our collaboration with other groups that have been specifically recruited to address specific methods of harmonization (e.g., Brigham and Women's Hospital) and multi-modal analyses (e.g., University of Virginia)

Major Task 6: Review MRI sequence parameters adherence and bi-monthly testing with research phantoms. Annual and pre-/postupgrade human phantom testing.

Month(s): *1 - 60*

Progress: Sequence parameters and phantom testing results are monitored in weekly Neuroimaging Core Operations meetings (Wilde, Welsh, Hunsaker, Hovenden, Lindsey), and detailed in reports created as part of the semi-annual review. Human phantom testing is anticipated to be an ongoing activity throughout the course of the project. Additionally, we are able to address some issues related to scanner upgrades remotely through local testing and export of sequence parameters for scanner models and software that exist in Salt Lake City (e.g., upgrade to XA platforms on Siemens Prisma, Vida, or Skyra models).

Major Task 7: Perform qualitative and quantitative QA review of imaging data.

Month(s): *1 – 60*

Progress: As above, sequence parameters are monitored in weekly Neuroimaging Core Operations meetings (Wilde, Welsh, Hunsaker, Hovenden, Lindsey). In addition to examining consistency between and within sites, we perform visual (qualitative) inspection of data to assess data quality at a preliminary review level. We have also instituted quantitative QA procedures that assess metrics such as motion, signal to noise, contrast to noise, etc. These parameters are assessed in a 7-page report that is generated for each scan. This is anticipated to be an ongoing activity throughout the course of the project.

Major Task 8: Review quantitative testing for T1-weighted, diffusion, and functional connectivity QA, and qualitative data.

Month(s): *1 - 60*

Progress: In addition to reports that are generated for each participant/scan, we have created a system to compile aggregate group reports which graph the data distribution in violin plots, both for each site and the data as a whole; this enables identification of outliers and provides a snapshot of the data quality overall.

To date, data quality has generally been good. This is anticipated to be an ongoing activity throughout the course of the project.

Major Task 9: Review imaging data for clinical and incidental findings, and code imaging data according to the Inter-agency CDE for Imaging.

Month(s): *1 – 60*

Progress: The number of new cases received from collection sites, the number of cases reviewed by neuroradiologists for clinical findings, and the number of scans with reported abnormalities are reported weekly in a joint meeting with Data Core. New cases are assigned for review by the project neuroradiologists each week. Project staff review data entry in Medidata for completion and consistency. This is anticipated to be an ongoing activity throughout the course of the project.

Major Task 10: Ongoing review and CDE coding of newly acquired conventional sequence data by neuroradiologists.

Month(s): *1 - 60*

Progress: See above description under item 9.

Major Task 11: Pre-process and analyze volumetric, diffusion, perfusion, and functional connectivity data, using pipelines for longitudinal analysis.

Month(s): *1 - 60*

Progress: The preprocessing of imaging data maintained by the Neuroimaging Core is largely up-to-date for the standard analysis pipelines (including recent versions of FreeSurfer (v7.1) and updated ENIGMA diffusion processing); we have also completed additional longitudinal pipelines, which are in process. We have also completed a newly-updated functional connectivity pipeline (HALF-PIPE) which has been optimized for large-scale use. Additional analyses are ongoing for established ANTS pipelines, which represent an update during the current reporting period. We have also utilized ACAPULCO and BrainAgeR pipelines during this year. Continued analysis is anticipated to be an ongoing activity throughout the course of the project.

Major Task 12: Quarterly update of analyzed, summary imaging data provided to Data Core.

Month(s): *3 - 60*

Progress: The analyzed summary data are available on the core's GitHub repository site to maintain version control and documentation of changes. The Neuroimaging Core presents weekly reports to the Data Core regarding CDE coding completion. This is anticipated to be an ongoing activity throughout the course of the project.

Major Task 13: With other Prospective Longitudinal Study investigators, examine imaging data in relation to demographic, injury, and biomarker data.

Month(s): *1 - 60*

Progress: Progress: Dr. Wilde and Mr. Abildskov have been attending regularly scheduled teleconference meetings with the FITBIR and Data Core teams.

We are continuing to assist in the analysis of approved requests by Kimbra Kenney, Kent Werner and Laila Abdullah related to the relation between biomarker, lipidomics, clinical and imaging data.

We have continued to work with other investigators with existing analysis requests to facilitate access to data and to assist in analysis and data dissemination including, but not limited to, 1) Drs. Stone, Tustison and Avants (additional data provided during the current reporting period), 2) Dr. Mary Newsome, 3) Dr. Emily Dennis, 4) Dr. David Tate, 5) Dr. Ben Wade, 6) Dr. Randy Swanson, 7) Dr. Carrie Esopenko, 8) Dr. Sam Walton, 9) Dr. Shannon Miles, 10) Dr. Sarah Gimble, and 11) requests from VA Center of Excellence investigators. We have also been working with individuals at University of Colorado and University of New Mexico to develop requests. Finally, in collaboration with investigators from the Translational Research Center for TBI and Stress Disorders (TRACTS) and Denver VA, we were awarded additional grant funding from the VA to combine and harmonize imaging and biomarker data between the two consortia (Total Brain Diagnostics).

Manuscripts previously submitted on 1) the relation between performance on Grooved Pegboard Test and diffusion/volumetric imaging (lead author: Benjamin Wade, Journal of Neurotrauma), 2) persistent imaging findings in chronic TBI (Lead author: David Tate) were accepted during this reporting period (see Appendix) and a manuscript on white matter hyperintensities and their association with cognitive performance and other health indicators has been resubmittedAn additional manuscript related to altered lateralization of diffusion imaging metrics in TBI sustained during deployment was published in Human Brain Mapping during this reporting period (see Appendix).

During this reporting period, we also submitted amanuscript on the relation between gait functioning and resting state imaging by Dr. Newsome; this manuscript has been accepted and will appear in the LIMBIC-CENC Special Issue in Frontiers of Neurology.

We have completed analysis and are currently drafting a manuscript on findings using tensor- based morphometry which demonstrate regions of enhanced vulnerability to deep white matter tissue volume in individuals with blst-related injury. This work has been led by Dr. Emily Dennis.

Members of the Imaging Core have also participated in manuscripts associated with the larger consortium as reflected in the list of manuscripts for the consortium (lead authors include two manuscripts by Kennedy et al., two by van der Veen et al., two by Walker et al., and by Esopenko, de Souza and Stewart

Members of the Imaging Core regularly participate in several working groups and have or are currently contributing to multiple manuscripts and joint investigations.

Major Task 14: Organize, transfer, archive, and securely store neuroimaging data.

Month(s): *1 - 60*

Progress: The Imaging Core oversees consortium member accounts to securely transfer data. Imaging data is organized for consistency and stored in DICOM format as well as BIDS format. Data is securely archived and stored with redundancy. This task will continue through the course of the project. We have expanded our electronic storage and processing capacity during the last reporting period and remain well-equipped to continue to store the data.

Major Task 15: Attendance at biannual GSC meetings.

Month(s): *6 - 60*

Progress: Dr. Wilde attended and presented at the two GSC meetings scheduled during this review period.

Biomarkers Core:

Major Task 1: Maintain consistent infrastructure, management, and centralized resources for longitudinal collection and curation of bio specimen.

Month(s): *1 - 60*

Progress: The Biorepository director and staff continued the management, collection and distribution of LIMBIC samples as previously described during the past year, as itemized below:

- Continued to fund NED screening of PLS enrollees (IGF-1, testosterone, TSH) at their baseline visit through a CLIA-certified lab (currently under an active contract with Quest).
- The Biorepository (BR) received PLS biospecimens from all 11 enrollment sites. For the period Sept. 30, 2022 to the end of Sept.30, 2023 the BR received locally processed and frozen aliquots from 273 LIMBIC PLS participants, including 63 from follow-up PLS visits. There were specimens from 210 new subjects and 2,274 cryovials were added to inventory during this time period from the PLS study. As of 30 September 2023, the BR has collated/stored processed/aliquoted biospecimens (DNA/buffy coat, plasma, serum, saliva, RNA (PaxGene) from a total of 2,828 study 1 blood samples; these include 2247 baseline samples and 581 follow-up samples. as well as samples from 144 Study 49 subjects (1801 aliquots) & 20 Study 20 subjects (312 aliquots) for a current total of 34,616 aliquots in the biorepository available for analysis. A total of 5,186 aliquots have been shipped to other investigators to date.
- The Biorepository worked with the Coordinating Center and the Data and Biostatistics Core

along with PLS enrollment sites to request and receive pre-injury serum samples from DoD serum biorepository. This is still in process.

Major Task 2: IRB protocol development, submission, and continuing review. (Locally and in conjunction with Coordinating Center at VCU).

Month(s): *1 - 60*

Progress: Local regulatory approvals complete:

- USUHS IRB has approved all continuing review submissions (most current CR approved on 3/10/2023).
- There is a 5-way CRADA being executed for the FBCH PLS LIMBIC site USUHS, Geneva, Eisenhower (EAMC), WRNMMC and FBCH, as required by WRNMMC Research Department. As of 8-31-23, The CRADA is under final evaluation by Dr. Victor E. Buckwold, Walter Reed Med Ctr, Chief of the Department of Research Programs Business Office.

Major Task 3: HRPO approval and continuing review.

Month(s): *1 - 60*

Progress: Initial HRPO/OHRO second level approval under LIMBIC 10/16/2020:

- Most recent OHRO approval 4/21/2023
- CR approved by USUHS IRB 3/10/2023

Major Task 4: Share data with external investigators; Biannual submission to FITBIR (March and September).

Month(s): *6 - 60*

Progress: NED and APOE data entered into FITBIR in March and September by the LIMBIC Data and Biostatistics Core.

Major Task 5: Carry out genotyping assays of common genetic variants associated with the chronic effects of neurotrauma.

Month(s): *1 - 60*

Progress: No APOE genotyping carried out on specimens from new participants in this period of performance. There has been a total of 1,383 PLS participants with DNA extraction and APOE genotyping to date. Waiting for a sufficient number to run the analysis.

Major Task 6: Carry out service operations (limited genotyping and neuroendocrine screen through CLIA-certified lab).

Month(s): *1 – 60*

Progress: Continued NED screening of samples from all new enrollments in LIMBIC prospective study. Published manuscript of NED screen in Longitudinal sample in Brain Injury LIMBIC special publication.

Major Task 7: Manage biospecimen sharing with CENC and external investigators.

Month(s): *1 - 60*

Progress: Continued collaborative analyses on following 5 Research Committee Projects that received samples from the LIMBIC Biorepository:

- Roskamp- in process- Meet regularly with biomarker-imaging groups and discussed results. Analysis of lipidomics, imaging, and mTBI on cognitive outcomes underway.
- Tampa (Dr. Patel and Dr. Richardson): Analysis in process by Tampa VA group.
- Study 49/MSD: Manuscript in prep of novel p-tau isotope analyses and PRARP follow on grant submitted.
- Post-Traumatic Epilepsy: Regulatory documents in place and human subjects research launched at the Utah VA. Initial enrollments at Utah scheduled for 11 and 12/2022.
- Swanson data request: Ongoing planning meetings to support his grant.

The following collaborative grants were submitted during this period of performance:

- A Longitudinal Investigation of altered Blood and Imaging markers of Neuroinflammation, Neurodegeneration and Microvascular Integrity and their Clinical Correlates in relation to COVID-19 Infections in Combat Veterans with varying mild TBI histories ("Long-COVID")- (David Cifu PI, LIMBIC consortium Co-Is Kimbra Kenney) **FUNDED**
- "Long Term Neurological Consequences of Traumatic Brain Injury; Association between Neuroimaging Measures of microvascular function and modifiable CV risk factors", Randy Swanson (Phil VA) VA CDA (Randy Swanson, Cifu, Walker, Ramon, Lisa Wilde, Jessica Gill, Kimbra Kenney)- **FUNDED**. Working on setting up biomarker section through LIMBIC.
- Longitudinal Information on Neurologic Outcomes and Knowledge Translation Study of Severe TBI: A Joint VA TBIMS and LIMBIC Collaboration - (Risa Nakase-Richardson PI, Jessica Gill & Kimbra Kenney Co-PIs Biomarker section). Under review.
- Parkinson's-disorder Risks for Onset and Genetics for Non-motor Outcomes and Stress and TBI Indicators of Causality; The PROGNOSTIC Study, Under Review.
- Military Hypertension and PTSC Study (MHAPS), Under Review.
- Identifying Mental health Predictors Evolving from Deployment and TBI Endophenotypes (IMPEDE) TBI Biomarker Study, Under Review.
- Trauma Related Impacts and Biomarkers Underlying Trajectories Evaluation (TRIBUTE) Study, Under Review,

Major Task 8: Provide biospecimens for approved LIMBIC biomarker projects.

Month(s): *1 - 60*

Progress: No new Research Committee projects using Biorepository specimens were approved this past year and no specimens were shared**.**

Major Task 9: Attendance at biannual GSC meetings.

Month(s): *6 - 60*

Progress: Drs. Gill and Capaldi attended and presented at both bi-annual GSC meetings during this period of performance October and April, and Dr. Gill will present at the upcoming GSC meeting October 2023.

Studies

Prospective Longitudinal Study:

Major Task 1: Hire and maintain all research consortium staff.

Month(s): *1 - 60*

Progress: Previously 100% met for initial hires, with ongoing work to maintain staff. Continuing to address challenges of COVID pandemic and macroeconomic conditions on maintaining staffing levels at all PLS sites. A new P.I. was successfully onboarded at Fort Belvoir site (Mellanie P. Medina, FNP, APRN) and a Co-PI at the San Antonio site (Alicia A. Swan, Ph.D).

Major Task 2: IRB protocol development, submission, and continuing review.

Month(s): *1 - 60*

Progress: 100% met to date with ongoing need to maintain continuing review approvals.
In the current reporting period, we added to language to protocol and consent form and achieved IRB approvals across sites for the following elements:

- Approval of Long-COVID Addendum Module (LCAM), an add-on study leveraging PLS participants and data, at 4/7 eligible VA sites.
- Reduction of PLS Battery including the revision of one research measure and removal of two other measures in order to reduce participant burden during in-person visits.
- Addition of informed consent language for participants to opt-in to text message reminders for LIMBIC Call Center visits.
- Details on Biorepository samples storage procedures; specimens will be maintained indefinitely for future

research in the event additional study funding is not received.

- Details on saliva samples testing procedure; samples will be tested for body chemicals not just cortisol.

Major Task 3: HRPO approval and continuing review.

Month(s): *1 - 60*

Progress: 100% met to date with ongoing need to maintain continuing review approval.

Major Task 4: Onboard 3 new recruitment sites.

Month(s): *1 - 4*

Progress: 100% met during FY1.

Major Task 5: Conduct follow-up Assessments to include phone assessments.

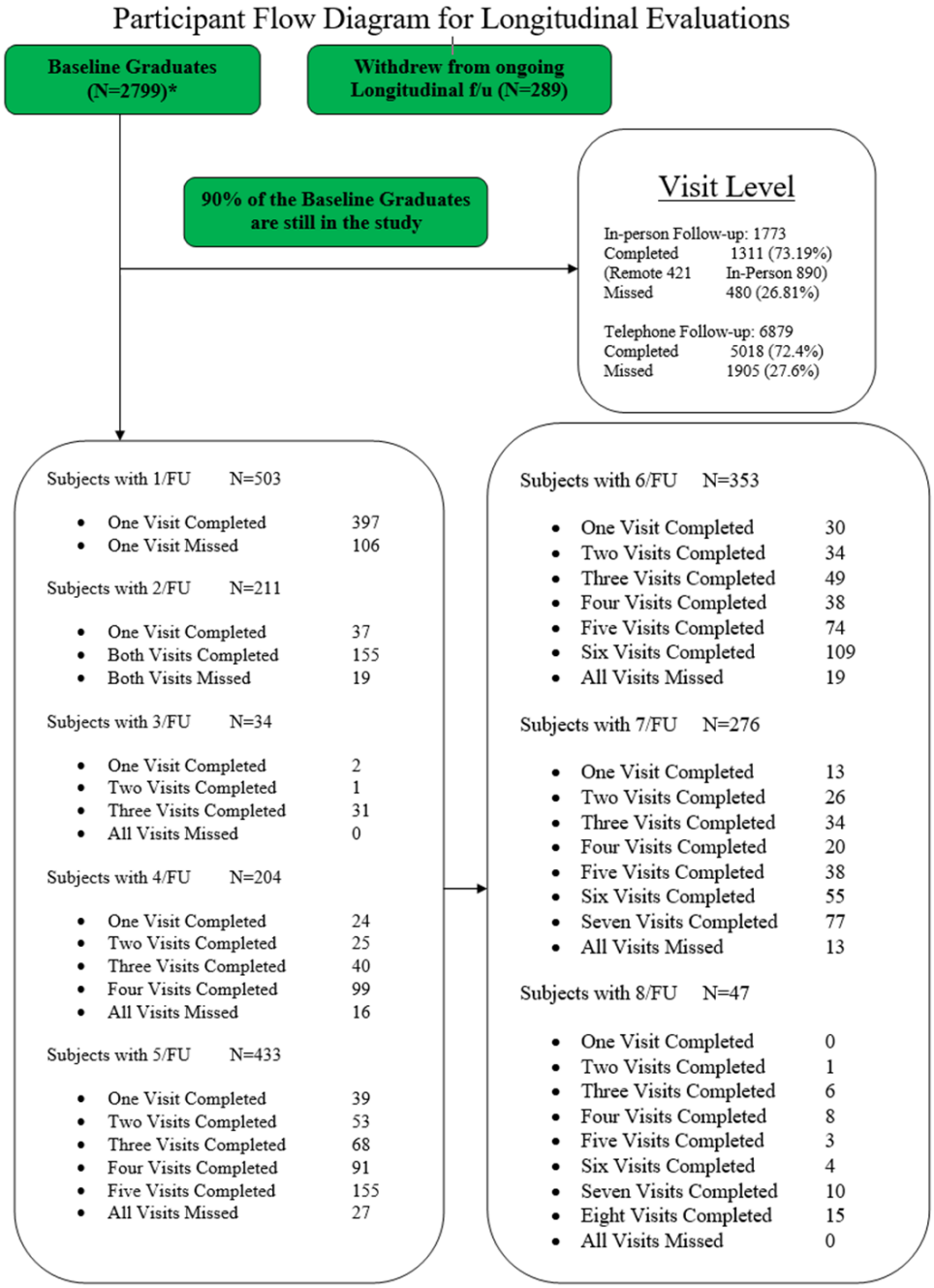
Month(s): *1 - 60*

Progress: Ongoing acquisition. In-person follow-up visit completions have improved through the course of the COVID pandemic.

- From Oct 01, 2022 to Sep 30, 2023, a total of 1300 new follow-up assessments were completed. This consisted of 222 new comprehensive and 1078 new annual phone follow-up assessments which resulted in completion rates of 56% and 58% out of those that were due. Of the new comprehensive longitudinal evaluations completed, 156 (70%) were in-person and 66 (30%) were the remote-collection version. Additionally, 183 BTACT assessments were completed during period for a completion rate of 91%.

Cumulative Totals:

- During LIMBIC (since Oct 01, 2019), a total of 4378 follow-up assessments have been completed, consisting of 834 comprehensive and 3544 annual brief phone follow-up assessments. Of the comprehensive longitudinal evaluations completed under LIMBIC, 427 (51%) were in-person and 407 (49%) were the remote-collection version. Additionally, 673 BTACT assessments have been completed.
- Since CENC inception, a total of 6329 follow-up assessments have been completed, consisting of 1311 comprehensive and 5018 annual brief phone follow-up assessments. This translates into overall completion rates of 73% for comprehensive and 72% for annual telephonic. See longitudinal Consort diagram below. Additionally, 1060 BTACT assessments have been completed since CENC inception with an overall completion rate of 83.3%.
- Cumulative data since the inception of CENC PLS that is broken down by subject level and visit level are presented as the Longitudinal Evaluation Study Participant Flow Diagram in the figure below.



Major Task 6: Report descriptive data.

Month(s): *1 - 60*

Progress: 100% met; ongoing to maintain.

- See our internet site for the latest updates
- https://www.limbic-cenc.org/index.php/knowledge-translation-center/data-at-a-glance/
- https://www.limbic-cenc.org/index.php/for-scientists-and-clinicians/data-cube/

Major Task 7: Acquire, safely store and analyze eye tracking data.

Month(s): *1 - 60*

Progress: Good progress with ongoing acquisition and storage of eye tracking data (see record counts below). Also progressed with developing a cross-walk across data collected with the legacy EyeLink equipment versus the current state-of-the art and easier to use and analyze RightEye equipment. Note: scientific analyses are shown elsewhere in this report.

• Total records acquired for reporting period (Oct 01, 2022 to Sep 30, 2023) was 467, consisting of __358_

baseline and follow-up 109 eye-tracking tests.
Cumulative Totals:
• During LIMBIC (since Oct 01, 2019), a total of 1149 records have been acquired, consisting of 896 baseline and 253 follow-up eye-tracking tests.
• Since CENC inception, a total of 1990 records have been acquired, consisting of 1547 baseline and 443 follow-up eye-tracking tests.

Major Task 8: Acquire, safely store and analyze Balance Master data.

Month(s): *1 - 60*

Progress: Good progress with ongoing acquisition and storage of Balance Master data (see record counts below). Note: scientific analyses are shown elsewhere in this report.
• Total records acquired for reporting period (Oct 01, 2022 to Sep 30, 2023) was 419, consisting of 332 baseline and 87 follow-up Balance Master tests.
Cumulative Totals:
• During LIMBIC (since Oct 01, 2019), a total of 1159 records have been acquired, consisting of 888 baseline and 271 follow-up Balance Master tests.
• Since CENC inception, a total of 2740 records have been acquired, consisting of 2129 baseline and 611 follow-up Balance Master tests.

Major Task 9: Acquire, safely store and analyze hearing test data.

Month(s): *1 – 60*

Progress: Good progress with ongoing acquisition and storage of hearing test data (see record counts below). A noise meter software was deployed to all sites to improve quality control of data for scientific analyses. A larger size headband for the bone oscillator was deployed to all sites to accommodate participants with very large head circumferences. Note: analyses are shown elsewhere in this report.
• Total records acquired for reporting period (Oct 01, 2022 to Sep 30, 2023) was 484, consisting of 375 baseline and 109 follow-up Hearing tests.
Cumulative Totals:
• During LIMBIC (since Oct 01, 2019), a total of 1336 records have been acquired, consisting of 1029 baseline and 307 follow-up Hearing tests.
• Since CENC inception, a total of 2890 records have been acquired, consisting of 2255 baseline and 635 follow-up Hearing tests.

Major Task 10: Administer and interpret neuropsychological data.

Month(s): *1 - 60*

Progress: Good progress with ongoing acquisition and interpretation of neuropsychological data (see record counts below).
• Total records acquired/interpreted for reporting period (Oct 01, 2022 to Sep 30, 2023) was _685__, consisting of 474 baseline and 211 follow-up Neuropsychological testing batteries.
Cumulative Totals:
• During LIMBIC (since Oct 01, 2019), a total of 2050 records have been acquired and interpreted, consisting of 1245 baseline and 805 follow-up Neuropsychological testing batteries.
• Since CENC inception, a total of 4070 records have been acquired and interpreted, consisting of 2798 baseline and 1272 follow-up Neuropsychological testing batteries.

Major Task 11: Acquire, safely store and analyze biospecimens.

Month(s): *1 – 60*

Progress: Good progress with ongoing acquisition and storage of biospecimen sets (see counts below). Note: analyses are shown elsewhere in this report.
• Total biospecimen sets acquired for reporting period (Oct 01, 2022 to Sep 30, 2023) was 439, consisting of 330 baseline and 109 follow-up biospecimen sets.
Cumulative Totals:
• During LIMBIC (since Oct 01, 2019), a total of 1147 biospecimen sets have been acquired, consisting of

866 baseline and 281 follow-up biospecimen sets.
• Since CENC inception, a total of 2984 biospecimen sets have been acquired, consisting of 2294 baseline and 690 follow-up biospecimen sets.

Major Task 12: Acquire, safely store and analyze imaging data.

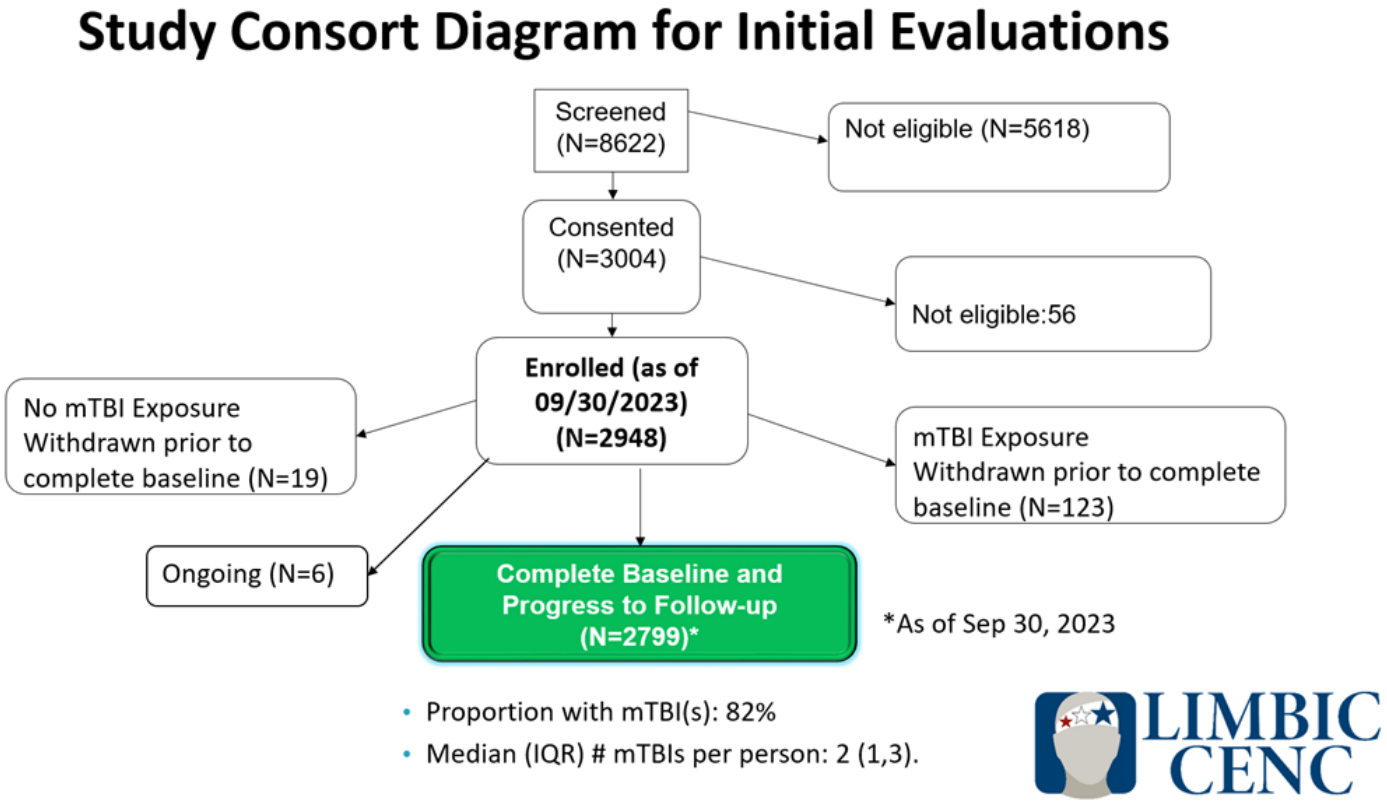
Month(s): *1 – 60*

Progress: Good progress with ongoing acquisition and storage of imaging data (see imaging session counts below). Note: analyses are shown elsewhere in this report.
• Total imaging sessions of data acquired for reporting period (Oct 01, 2022 to Sep 30, 2023) was _263__, consisting of 196 baseline and 67 follow-up imaging sessions.
Cumulative Totals:
• During LIMBIC (since Oct 01, 2019), a total of 704 imaging sessions have been acquired, consisting of 517 baseline and 187 follow-up imaging sessions.
• Since CENC inception, a total of 2122 imaging sessions have been acquired, consisting of 1644 baseline and 478 follow-up imaging sessions.

Major Task 13: Recruit study total of not less than 3000 subjects.

Month(s): *1 - 60*

Progress: Excellent progress was made toward target enrollment despite the ongoing and evolving nature of the COVID pandemic which continues to hamper recruitment and enrollment activities. During this reporting year, the only site still prohibited by local authorities from in-person research activities (Boston site) was permitted to restart their in-person research activities. Thus, all eleven PLS sites have been and continue to actively enroll.
This reporting year (Oct 01, 2022 to Sep 30, 2023), there were 492 new participants consented, 482 new participants enrolled, and 474 new baseline evaluations completed (graduated to follow-up).
Throughout the course of the study (since CENC inception through LIMBIC), a total of 3004 participants have been consented, 2948 participants enrolled, and 2799 baseline evaluations completed. (see initial evaluation consort diagram in figure below).



Major Task 14: Develop site-wide recruitment and retention plan.

Month(s): *1 - 60*

Progress: Previously 100% met for development. We continue to seek new opportunities for improvement with new strategies and refinements with sharing of recruitment and retention obstacles and failures across all sites of the PLS.

• During the reporting period (Oct 01, 2022 to Sep 30, 2023), the following presentations were given on the biweekly LIMBIC-CENC PLS All-Sites audiovisual meeting/conferences that addressed recruitment, retention, and/or quality and completeness of assessment data collection:

Date	Presenter	Topic
6-Mar-23	Joe Montanari	Participant Travel
20-Mar-23	San Diego	Visit Checklists and SOPs
3-Apr-23	Yasmonia Mack	Subject Portal Reports
17-Apr-23	Houston	Harvey Levin Tribute
1-May-23	Tampa	Rapport Building with the Subjects
15-May-23	Minneapolis	Data Management
12-Jun-23	DBC	Submitting a Data Request
26-Jun-23	Fort Gordon	Recruiting
10-Jul-23	Joe Montanari	Retention
24-Jul-23	Portland	Efficiency in Recruitment
7-Aug-23	Richmond	Recruitment Events
21-Aug-23	Fort Belvoir	Transition to MHS Genesis
18-Sep-23	Boston	Audiology Troubleshooting

Major Task 15: Implement recruitment and retention plan.

Month(s): *1 – 60*

Progress: Previously 100% met for implementation.

Major Task 16: Analysis & Publication of Cross-sectional Data.

Month(s): *12 - 60*

Progress: Ongoing. We continued to work on analyses and publications utilizing the LIMBIC-CENC PLS dataset both within LIMBIC and with external investigative groups and consortia.

• Analyses: Progress During year 4, the SLC data core released 18 PLS/VINCI data sets. 11 curated data sets, out of the 18 data requests, were submitted to investigators to perform their own analyses and the remaining 7, were shared with the Central Biostatistics analysts to help investigators with statistical analyses and preparing manuscripts and papers. [*Please see SLC DBC report section for more details and information*]. All included some aspect of cross-sectional analysis.

• Scientific journal publications and scientific meeting presentations: See tables below for new publications and presentations during the reporting period (10/1/22-9/30/23) that utilized LIMBIC-CENC PLS data. [* Indicates trainee or early career investigator.]

New Publications utilizing PLS data: During the reporting period (Oct 01, 2022 to Sep 30, 2023), the following manuscripts utilizing PLS data were newly published.

Walker WC, O'Neil ME, Ou Z, Pogoda TK, Belanger HG, Scheibel RS, Presson AP, Miles SR, Wilde EA, Tate DF, Troyanskaya M, Pugh MJ, Jak A, Cifu DX. Can mild traumatic brain injury alter cognition chronically? A LIMBIC-CENC multicenter study. *Neuropsychology*. 2023 Jan;37(1):1-19. doi: 10.1037/neu0000855. Epub 2022 Sep 29. PMID: 36174184.
Dennis E, Newsome M, Lindsey H, Adamson MM, Austin TA, Disner SG, Eapen BC, Esopenko C, Franz C, Geuze E, Haswell C, Hinds SR, Hodges CB, Irimia A, Kenney K, Koerte I, Kremen W, Levin H, Morey R, Ollinger J, Rowland J, Scheibel R, Shenton M, Sullivan DR, Talbert LD,

Thomopolous Sophia, Troyanskaya M, Walker WC, Wang X, Ware A, Werner JK, Williams M, Thompson P, Tate D, Wilde E. Altered Lateralization of the Cingulum in Deployment-Related Traumatic Brain Injury: An ENIGMA Military-Relevant Brain Injury Study. *Hum Brain Mapp.* 2023;44(5):1825-2121. doi: 10.1002/hbm.26179. PMID: 36583562.

Pickett TC, Walker WC, Lippa SM, Lange RT, Brickell TA, Dittmer TA, Smith JM, Cifu DX, French LM. Cross-walk comparison of the DVBIC-TBICoE and LIMBIC-CENC combat-related concussion prospective longitudinal study datasets. *Arch Phys Med Rehabil.* 2023 Jul;104(7):1072-1080. doi: 10.1016/j.apmr.2023.02.003. Epub 2023 Feb 25. PMID: 36842617.

Miles SR, Martindale SL, Flanagan JC, Troyanskaya M, Reljic T, Gilmore AK, Wyant H, Nakase-Richardson R.. Putting the Pieces Together to Understand Anger in Combat Veterans and Service Members: Psychological and Physical Contributors. Accepted at *J Psychiatr Res.* 2023 Mar;159:57-65. doi: 10.1016/j.jpsychires.2023.01.013. Epub 2023 Jan 11. PMID: 36657315.

*van der Veen SM, Perera RA, Manning-Franke L, Agyemang AA, Skop K, Sponheim SR, Wilde EA, Stamenkovic A, Thomas JS, Walker WC. Executive function and relation to static balance metrics in chronic mild TBI: A LIMBIC-CENC secondary analysis. Front Neurol. 2023 Jan 11;13:906661. doi: 10.3389/fneur.2022.906661. eCollection 2022. PMID: 36712459

Franke LM, Perera RA, Sponheim SR. Long-term resting EEG correlates of repetitive mild traumatic brain injury and loss of consciousness: alterations in alpha-beta power. *Front Neurol*. 2023 Aug 29;14:1241481. doi: 10.3389/fneur.2023.1241481. eCollection 2023. PMID: 37706009.

Wade BSC, Tate DF, Kennedy E, Bigler ED, York GE, Taylor BA, Troyanskaya M, Hovenden ES, Goodrich-Hunsaker N, Newsome MR, Dennis EL, Abildskov T, Pugh MJ, Walker WC, Kenney K, Betts A, Shih R, Welsh RC, Wilde EA. Microstructural Organization of Distributed White Matter Associated with Fine Motor Control in US Service Members with Mild Traumatic Brain Injury. *J Neurotrauma* 2023 Sep 11. doi: 10.1089/neu.2022.0094. Online ahead of print. PMID: 37694678

Miles SR, Martindale SL, Flanagan JC, Troyanskaya M, Reljic T, Gilmore AK, Wyant H, Nakase-Richardson R. Putting the Pieces Together to Understand Anger in Combat Veterans and Service Members: Psychological and Physical Contributors. *J Psychiatr Res.* 2023 Mar:159:57-65. doi: 10.1016/j.jpsychires.2023.01.013. Epub 2023 Jan 11.

*Gius BK, Fournier LF, Reljic T, Pogoda TK, Corrigan JD, Garcia A, Troyanskaya M, Hodges CB, Miles SR. Association Between Sociodemographic, Mental Health, and Mild TBI Characteristics with Lifetime History of Criminal Justice Involvement in Combat Veterans and Service Members. Mil Med. 2023 Aug 29;188(9-10):e3143-e3151. doi: 10.1093/milmed/usac257.

Additional publications by LIMBIC-CENC PLS investigators not reported by other cores/studies

*Lewis CJ, **Franke LM**, Lee JV, Mittal N, Gitchel GT, Perera RA, Holloway K, **Walker WC**, Peterson CL, Hadimani RL. The Relationship of Neuroanatomy on Resting Motor Threshold and Induced Electric Field Strength on Treatment Outcomes in Mild to Moderate Traumatic Brain Injury Patients During Transcranial Magnetic Stimulation. AIP Advances 2023;13(2), 025260 (on-line only); doi: 10.1063/9.0000567

Silverberg ND, Iverson GL; ACRM Brain Injury Special Interest Group Mild TBI Task Force and the ACRM Mild TBI Definition Expert Consensus Group, ACRM Brain Injury Special Interest Group Mild TBI Task Force members; Cogan A, Dams-O'Connor K, Delmonico R, Graf MJP, Iaccarino MA, Kajankova M, Kamins J, McCulloch KL, McKinney G, Nagele D, Panenka WJ, Rabinowitz AR, Reed N, Wethe JV, Whitehair V; ACRM Mild TBI Diagnostic Criteria Expert Consensus Group; Anderson V, Arciniegas DB, Bayley MT, Bazarian JJ, Bell KR, Broglio SP, **Cifu D**, Davis GA, Dvorak J, Echemendia RJ, Gioia GA, Giza CC**, Hinds SR** 2nd, Katz DI, Kurowski BG, Leddy JJ, Sage NL, Lumba-Brown A, Maas AIR, Manley GT, McCrea M, Menon DK, Ponsford J, Putukian M, Suskauer SJ, van der Naalt J, **Walker WC**, Yeates KO, Zafonte R, Zasler ND, Zemek R. The American Congress of Rehabilitation Medicine Diagnostic Criteria for

Mild Traumatic Brain Injury. Arch Phys Med Rehabil 2023 Aug;104(8):1343-1355. doi: 10.1016/j.apmr.2023.03.036. Epub 2023 May 19. PMID: 37211140.

Silva MA, **Miles SR**, O'Neil-Pirozzi TM, Arciniegas DB, Klocksieben F, **Dismuke-Greer CE**, **Walker WC**, **Nakase-Richardson**, R. Alternative Structure Models of the Traumatic Brain Injury Rehabilitation Needs Survey: A Veterans Affairs TBI Model Systems Study. Arch Phys Med Rehabil. 2023 Jul;104(7):1062-1071. doi: 10.1016/j.apmr.2023.01.004. Epub 2023 Feb 2. PMID: 36736804.

Kumar RG, **Klyce D, Nakase-Richardson R**, **Pugh MJ, Walker WC**, Dams-O'Connor K. Associations of military service history and health outcomes in the first five years after traumatic brain injury. J Neurotrauma. 2023 Jun;40(11-12):1173-1186. doi: 10.1089/neu.2022.0340. Epub 2022 Dec 28. PMID: 36401499.

Novack TA, Zhang Y, Kennedy R, Rapport LJ, Bombardier C, Bergquist T, Watanabe TK, Tefertiller C, Goldin Y, Marwitz J, Dreer LE, **Walker W**, Brunner R. Crash Risk Following Return to Driving After Moderate-to-Severe TBI: A TBI Model System Study. J Head Trauma Rehabil. 38(3):268-276, May/June 2023. doi: 10.1097/HTR.0000000000000788. Epub 2022 May 26. PMID: 35617669.

Lercher K, Kumar RG, Hammond FM, Hoffman JM, Verduzco-Gutierrez M, **Walker WC**, Zafonte RD, Dams-O'Connor K. Distal and Proximal Predictors of Rehospitalization Over 10 Years Among Survivors of TBI: A National Institute on Disability, Independent Living, and Rehabilitation Research Traumatic Brain Injury Model Systems Study. J Head Trauma Rehabil. 38(3):203-213, May/June 2023. Epub 2022 Sep 5. doi: 10.1097/HTR.0000000000000812. PMID: 36102607.

Sanders G, Rapport LJ, Marwitz JH, Novack TA, **Walker W**, Tefertiller C, Watanabe TK, Kennedy R, Goldin Y, Bergquist T, Dreer LE, Bombardier CH, Zhang Y. Barriers to Driving and Psychosocial Outcomes after Traumatic Brain Injury. Brain Inj. 2023;37(5):412-421. doi: 10.1080/02699052.2023.2172611. Epub 2023 Jan 30. PMID: 36717959.

Martin AM, Pinto SM, Tang X, Hoffman J, Wittine L, **Walker WC**, Schwartz DJ, Kane G, Takagishi C, PhD, Nakase-Richardson R. Associations between early sleep-disordered breathing following moderate-to-severe traumatic brain injury (TBI) and long-term chronic pain status: A TBI Model Systems study. J Clin Sleep Med. 2023 Jan 1;19(1):135-143. doi: 10.5664/jcsm.10278. PMID: 36591795

Vos L, Ngan E, Novelo LL, Williams M, Hammond F, **Walker WC**, Clark A, Lopez AO, Juengst S, Sherer M. Predictors of Missed Follow-up Visits in the National Traumatic Brain Injury Model Systems Cohort Study. Arch Phys Med Rehabil. 2022 Dec;103(12):2325-2337. doi: 10.1016/j.apmr.2022.05.003. Epub 2022 Jun 13. PMID: 35709982.

New Acceptances for Publication (in-Press) utilizing PLS data: During the reporting period (Oct 01, 2022 to Sep 30, 2023), the following manuscripts utilizing PLS data were newly accepted for publication.

*Wright B, Zhong C, Fisher R, Karmarkar A, Bjork JM, Pugh MJ, Hodges CB, Martindale SL, Wilde EA, Kenney K, McDonald SD, Scheibel RS, Newsome MR, Cook LJ, **Walker WC**. Relation of aerobic activity to cognition and well-being in chronic mild traumatic brain injury; A LIMBIC-CENC study. In-Press. Accepted at *Mil Med* in Jan 2023.

Newsome MR, Martindale SL, Davenport N, Dennis EL, Diaz M, Esopenko C, Hodges C, Jackson GR, Liu Q, Kenney K, Mayer AR, Rowland JA, Scheibel RS, Steinberg JL, Taylor BA, Tate DF, Werner JK, **Walker WC**, Wilde EA. Subcortical functional connectivity and its association with walking performance following deployment related mild TBI. In-Press; Accepted at *Front Neurol* in Sep 2023.

New Publication Submissions utilizing PLS data. During the reporting period (Oct 01, 2022 to Sep 30, 2023), the following manuscripts utilizing PLS data were newly submitted for publication in peer reviewed journals:

Tate DF, … Walker WC… "Persistent Neuroimaging Findings Unique to Blast and Repetitive Mild TBI: Analysis of the CENC/LIMBIC Cohort Injury Characteristics" submitted to *Mil Med* in Jan 2023.
Andreas Jansen, Fabrizio Piras, Veena Kumari, … William Walker, … Bridging Big Data: Procedures for Combining Non-equivalent Cognitive Measures from the ENIGMA Consortium. Submitted to *Sci Adv* in Apr 2023.
Kennedy E, Vadlamani S, Lindsey HM,…. Walker WC,…Dennis EL. Linking Symptom Inventories using Semantic Textual Similarity. Submitted to *npj Digital Medicine* in Sep 2023.
*Stromberg KM, Martindale SL, Walker WC, Ou Z, Pogoda TK, Miles SR, Dismuke-Greer CE, Carlson KF, Rowland JA, O'Neil ME, Pugh MJ. Mild traumatic brain injury, PTSD symptom severity, and behavioral dyscontrol: A LIMBIC-CENC study. Submitted to *Front Neurol* in Sep 2023.
*de Souza NL, Lindsey HM, Dorman K, *Dennis EL, Kennedy E, Menefee DS, Parrott JS, Jia Y, Pugh MJ, Walker WC, Tate DF, Cifu DX, Bailie J, Martindale S, O'Neil M, Rowland J, Scheibel R, Sponheim S, Troyanskaya M, Wilde EA, Esopenko C. Neuropsychological profiles of deployment-related traumatic brain injury. Submitted to *Neurol* in Sep 2023.
Eamonn Kennedy, Mustafa Ozmen, Erin Bouldin, Samin Panahi, Helal Mobasher, Maya Troyanskaya, Shannon R. Miles, Sarah L. Martindale, Victoria Merritt, Maya O'Neil, Rosemay A. Remigio-Baker, Angela Presson, Alicia Swan, J. Kent Werner, Tom Green, Elizabeth Wilde, David Tate, William Walker, & Mary Jo Pugh. Phenotyping Depression after Mild Traumatic Brain Injury: Evaluating the Impact of Multiple Injury, Gender, and Injury Context. Submitted to *J Neurotrauma* in Aug 2023.
O'Neil ME, Krushnic D, Walker WC, Cameron D, Robinson WB, Hannon S, Clauss K, Cheney TP, Cook L, Niederhausen M, Kaplan J, Pappas M, Martin AM. Increased Risk for Clinically Significant Sleep Disturbances in Mild TBI: An Approach to Leveraging the FITBIR Database. Submitted to *J Neurotrauma* in July 2023.
Eamonn Kennedy, Ajay Manhapra, Shannon R. Miles, Sarah Martindale, Jared Rowland, Helal Mobasher, Madeleine Myers, Samin Panahi, William Walker, & Mary Jo Pugh. People with pain have a lot more than pain: Phenotyping Pain Interference among US Service Members and Veterans. Submitted to *Pain* in Apr 2023.

New Presentations at National/International Scientific Meetings utilizing PLS data. During the reporting period (Oct 01, 2022 to Sep 30, 2023), the following projects utilizing PLS data were presented at scientific meetings.

*Connor Lewis, Laura M. Franke, George T. Gitchel, Robert A. Perera, Kathryn L. Holloway, William C. Walker, Ravi L. Hadimani. *Relationship Between Resting Motor Threshold and Neuroanatomy in Mild to Moderate Traumatic Brain Injury Patients during Transcranial Magnetic Stimulation*. Poster presentation at 67th Annual Conference on Magnetism and Magnetic Materials (MMM 2022), Oct 31 – Nov 04, 2022, Minn., MN. [Note: this did not involve PLS data, but did involve LIMBIC investigators and is not reported elsewhere in report]
Walker WC, O'Neil ME, Ou Z, Pogoda TK, Belanger HG, Scheibel RS, Presson AP, Miles SR, Wilde EA, Tate DF, Troyanskaya M, Pugh MJ, Jak A, Cifu DX. *Can mild traumatic brain injury alter cognition chronically? A LIMBIC-CENC multicenter study*. Oral presentation at the International Brain Injury Association (IBIA) 14th World Congress on Brain Injury, March 31, 2023, Dublin, Ireland.
Walker WC, *Wright B, Zhang C, Karmarkar A, Bjork JM, Pugh MJ, Hodges CB, Martindale SL, Wilde EA, Kenney K, McDonald SD, Scheibel RS, Newsome MR, Cook LJ. *Relation of aerobic activity to cognition and well-being in chronic mild traumatic brain injury; A LIMBIC-CENC study*. Oral presentation at the International Brain Injury Association (IBIA) 14th World Congress on Brain Injury, April 1, 2023, Dublin, Ireland.
*Dennis EL, Newsome MR, Hunsaker NJ, Ware A, Wade BSC, Abildskov TJ, Hovenden ES, Bigler

ED, Betts AM, Davenport N, Duncan T, Gill J, Hinds SR, Kenney K, Pugh MJ, Scheibel RS, Shahim P, Shih R, Taylor BA, Troyanskaya M, **Walker WC**, Werner K, York GE, Cifu DX, Tate DF, Wilde EA. *Hyperconnectivity of the Aversion Network with Greater Psychiatric Symptoms in U.S. Service Members and Veterans*. Accepted for poster presentation at Military Health System Research Symposium (MHSRS) 2023, Aug, 2023, Kissimmee, Fl.
*Gius, B. K., Fournier, L. F., Relijc, T., Pogoda, T., Corrigan, J. D., Troyanskaya, M., Hodges, C., Miles, S. R, & Garcia, A. *Associations Between Mild Traumatic Brain Injury, Executive Function, and Criminal Justice Involvement among Veterans and Service Members: a LIMBIC-CENC study*. Poster presentation at the 51st Annual Meeting of the International Neuropsychological Society (INS), San Diego, CA., Feb 1-4, 2023.
*Walton SR, *Dennis EL, Ettenhofer ML, Wilde EA, Tate DF, Jurick SM, *Armistead-Jehle P, *Oldham JR, Hall MJ, *Swanson RL, Fraser JJ, MacGregor AJ, Agyemang AA, Cifu DX, **Walker WC**. *Exploring the Associations of Physical Activity and Combat-Related Mild Traumatic Brain Injury with Subcortical Brain Volumes among Active Duty and Veteran Service Members: a LIMBIC-CENC Study*. Accepted for poster presentation at Military Health System Research Symposium (MHSRS) 2023, Aug, 2023, Kissimmee, Fl.

Biweekly LIMBIC-CENC PLS All-Sites audiovisual meeting/conference: During the reporting period (Oct 01, 2022 to Sep 30, 2023), the following analytic projects were also presented on the biweekly LIMBIC-CENC PLS All-Sites audiovisual meeting/conferences:

Date	Presenter	Title
31 Oct 2022	Carina Martin	Remote Blast-related Mild Traumatic Brain Injury is Associated with Differential Expression of Exosomal microRNAs Identified in Neurodegenerative and Immunological Processes
06 Feb 2023	William Walker	Relation of aerobic activity to cognition and well-being in chronic mild TBI

For dissemination in general, there was continued ongoing close collaboration between the PLS leadership and coordinating center team-members of the LIMBIC-CENC PLS and the LIMBIC-CENC knowledge translation (KT) center on our website offerings and other KT products. This includes developing and cataloging Key Points for each and every submitted publication, which summarizes a succinct takeaway message summary (see section 4; Impact further below).

Additionally, the PLS leadership is actively engaged in collaborations with multiple individuals and other study groups to further advance productivity of our analysis and dissemination of the PLS dataset, both cross-sectional (Task 16) and longitudinal (Task 17 below). This including mentorship of junior investigators and projects that may involve supplemental funding opportunities to cover additional unaccounted-for effort and/or resources. Progress in these areas are summarized (*denotes early career investigator mentee).

- **External PLS dataset collaborations with funding awarded to early career investigator**:
    - Randall Swanson, DO, PhD*. Traumatic and Treatable Vascular Pathology in the Outcome of TBI. VA CDA grant.
    - Christina Sheerin, PhD*. Functional relations between alcohol use and mental health in the wake of the COVID-19 pandemic. NIH K01 award supplement.
- **LIMBIC-CENC investigator PLS dataset collaborations with external funding awarded**
    - Sarah L. Martindale, PhD. Evaluating Reductions in Hippocampal Volume Related to Blast Exposure and their Effect on Memory Function. Successfully awarded a VA Merit Review.
- **STRONG STAR**, UT Health San Antonio, STVHCS (Walker Project #3 Co-PI)
    - PI: Donald D. McGeary, PhD. Title: Contribution of Psychological Health Comorbidity to Personalized Treatment for Headache Attributable to mTBI. Grant Mechanism: Dept. of Defense Health Program, Fiscal Year 22 Congressionally Directed Medical Research Programs Traumatic

Brain Injury (TBI) and Psychological Health Research Program Clinical Trial Award. FY22 TBIPH Focused Program Award. Project Number: W81XWH-22-S-TBIPH2.

- **VA TRACTS,** Boston and Houston VAMC (William Milberg, PI, Cate Fortier, co-PI)
    - Four separate grants designed to create unified, prospective longitudinal dataset from LIMBIC (n=3,000) and TRACTS (n=1,000) to allow for enhanced power and generalizability by 2025.
    - Total Brain Diagnosis: Creating a Unified Prospective, Longitudinal Dataset with LIMBIC and TRACTS data. VA RR&D. FOA [RX23-005] - Total Brain Diagnostics (TBD) Proof-of-Concept (PoC) Merit Awards (I01) Award Document Number: IRX004908A. Project Period 10/01/2023 - 09/30/2025.
    - Cifu, Wilde, O'Neill and Brenner PI's of new grants with Milberg and Fortier co-PI)
- **TBI CoE**
    - Multiple collaborative PLS secondary analyses underway and progressing including:
    - Rosemay Remigio-Baker, PhD. (TBI CoE)
        - Race/Ethnic Disparities in the Treatment of Depressive and PTSD Symptoms Among SMs with mTBI
        - Social Support and Self-efficacy As Factors That Mitigate Mental Health Symptoms and Promote Quality of Life of SMs with mTBI
        - Characteristics of mTBI History as a Function of Quality of Life and Mental Health Symptomatology
    - Jay Uomoto, PhD. (TBI CoE)
        - A Pathway Analysis of the Impact of TBI Characteristics and Healthcare Utilization on Participation Outcomes.
- **VA RR&D**
    - LIMBIC-CENC was awarded a small plus-up grant by VA RR&D to leverage the PLS for additional study of the long-term effects of COVID-19 infections among our cohort, including the interaction effect of mild TBI and COVID-19. Over the past year, this supplemental study protocol entitled "LIMBIC-CENC PLS Long COVID Addendum Module (LCAM)" was finalized and enrollment began.
- **NIDILRR TBI-Model Systems**
    - Supplemental NIDDILRR grant to study Chronic Pain after TBI in the national TBI-MS cohort; Dr Walker lead author on one and co-author on 6 other papers invited and submitted for JHTR Special Edition.
    - de Souza NL, Bogner J, Corrigan JD, Rabinowitz AR, Walker WC, Kumar RG, Dams-O'Connor K. The effects of repetitive head impact exposure on functional outcomes following traumatic brain injury. Submitted to *J Head Trauma Rehabil* in Aug 2023.
- **ENIGMA**
    - Andreas Jansen, Fabrizio Piras, Veena Kumari, et al. Bridging Big Data: Procedures for Combining Non-equivalent Cognitive Measures from the ENIGMA Consortium. Submitted to *Sci Adv* in Apr 2023.
    - Dennis E, Newsome M, Lindsey H, et al. Altered Lateralization of the Cingulum in Deployment-Related Traumatic Brain Injury: An ENIGMA Military-Relevant Brain Injury Study. *Hum Brain Mapp.* 2023;44(5):1825-2121. doi: 10.1002/hbm.26179. PMID: 36583562.
- **Mental Illness Research, Education, and Clinical Center (MIRECC)**
    - VA Portland Health Care System and Oregon Health & Science Univ. Grant on FITBIRR data-mining that includes LIMBIC-PLS data
    - O'Neil ME, Krushnic D, Walker WC, et al. Increased Risk for Clinically Significant Sleep Disturbances in Mild TBI: An Approach to Leveraging the FITBIR Database. Submitted to *J Neurotrauma* in July 2023.
- **VCU Biomedical Engineering**
    - Lewis CJ, Franke LM, Lee JV, et al. The Relationship of Neuroanatomy on Resting Motor Threshold and Induced Electric Field Strength on Treatment Outcomes in Mild to Moderate Traumatic Brain Injury Patients During Transcranial Magnetic Stimulation. AIP Advances 2023;13(2), 025260 (on-line only); doi: 10.1063/9.0000567.

Major Task 17: Analysis & Publication of Longitudinal Data.

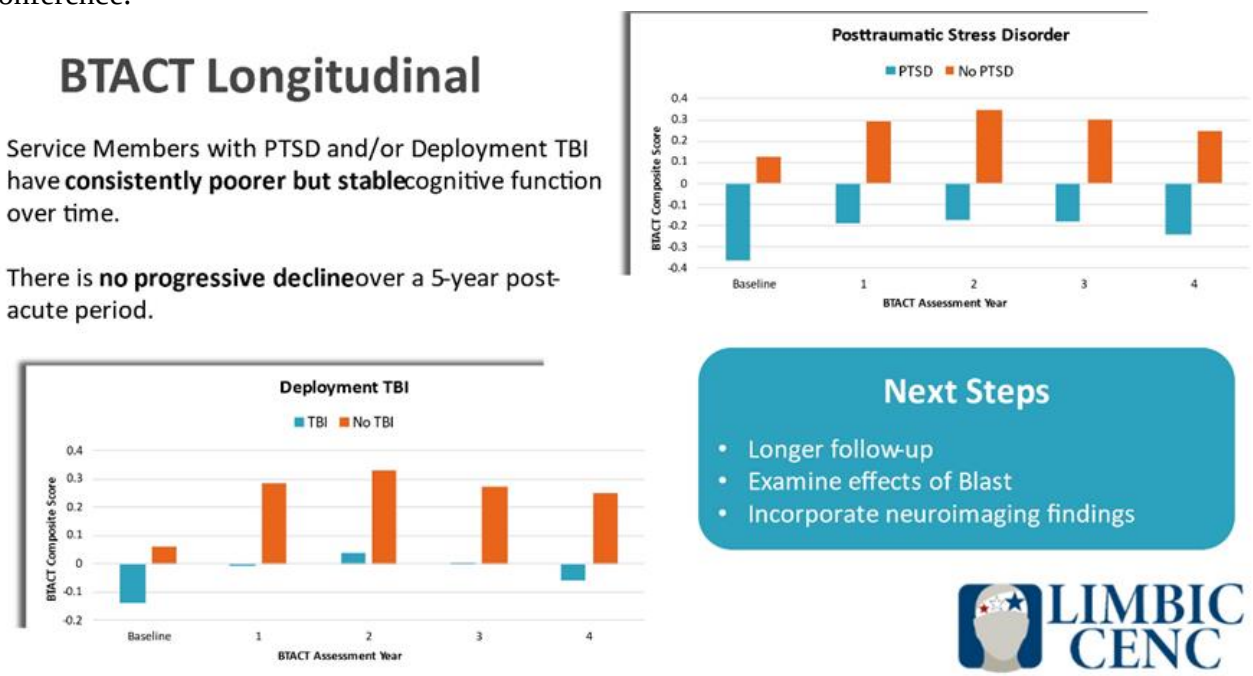
Month(s): *24 - 60*

Progress: During the reporting period (Oct 01, 2022 to Sep 30, 2023), our longitudinal data analysis activity continued. This was enabled by our continued high rates of retention and follow-up visit completion rates and accumulation of a critical mass of repeated measures, especially for data collected in the brief annual assessment.

- Significant progress was made on a key scientific analysis of rate of cognitive change overtime using longitudinal annually-collected BTACT data. A short synopsis of the preliminary results and the implications is shown further below.
- New Analyses: During the reporting period (Oct 01, 2022 to Sep 30, 2023), the SLC DBC released 7 new longitudinal data sets. Below is a list of the investigators, and a short title for the 7 projects:

Lead Investigator	**Short Title**
Jasmohan Bajaj	Salivary microbiota composition and function linkage with outcomes in PTSD with TBI
Eamonn Kennedy	Phenotyping Depression after Mild Traumatic Brain Injury: Evaluating the Impact of Multiple Injury and Injury Context.
Christina Sheerin	Functional relations between alcohol use and mental health in the wake of the COVID-19 pandemic
Eamonn Kennedy	Chronic Pain - Data Sets update (See Notes)
George Vega Yon	Phenotype Transition Pattern using binary modeling
Sam Walton	Exploring Demographic and Social Determinants of Cognitive Brain Health Among Military Service Members and Veterans with and without a History of Mild Traumatic Brain Injury
Rosemay Remigio-Baker	Examination of Race and Ethnic Group and Gender Disparities in the Symptom and Treatment of Depressive and PTSD Symptoms Among Service Members with Mild Traumatic Brain Injury: LIMBIC-CENC Study

- Scientific publications and meeting presentations: So far, only one manuscript with ture longitudinal design from PLS dataset has been published (an ENIGMA project) and one presentation has occurred "What Psychological and Sociodemographic Challenges are Linked to Criminal Justice Involvement among Veterans and Service Members with and without TBI? A LIMBIC-CENC Study". This poster won an award (BI-ISIG Early Career Poster Award) at the ACRM 2021 VIRTUAL Annual Conference.



Retrospective Database Study:

Major Task 1: Investigators already have access to databases to be accessed. They will annually renew IRB/VA data access approvals.

Month(s): *1 - 60*

Progress: Completed **-** All required regulatory approvals have been received. The LIMBIC Epidemiology Study was approved through UCSF IRB on 25-OCT-2019, the SF VA Medical Center on 8-NOV-2019 and approved through HRPO on 31-DEC-2019.

Major Task 2: Annually update database; merge with DOD data; perform quality checks and continue maintenance throughout study.

Month(s): *1 - 60*

Progress: Completed **-** In the first year, we updated our database through 2019, which was a monumental task. In the second year of the study we continued to request, download, and clean data as needed for new projects using our dataset of 2.2 million Veterans.

Major Task 3: Create, define, and refine variables (i.e, TBI).

Month(s): *1 – 12*

Progress: Completed **-** In year one, we updated all previously used diagnosis codes with ICD-10 codes (TBI, dementia, comorbidities, etc.) in addition to ICD-9 codes. In years two and three, we continued to create, define, and refine variable definitions in our dataset for new analyses. For all new variables, ICD-9 and ICD-10 codes must be used, and it is a time-consuming and complicated process to complete.

Milestone for Tasks 1-3: Data repository ready for analysis: The database, consisting of 2.2 million Veterans, including 426,643 with TBI, was completed in September of 2020, and is continually updated as required.

Major Task 4: Analyze data assessing mental health comorbidities in association between TBI and late effects (i.e., dementia).

Month(s): *1 – 24*

Milestone: Published manuscript in *Journal of Psychiatric Research*, Byers et al., 2022.

Month(s): *24-48*

Progress: In Year 4 we published a manuscript in *The Journal of the Prevention of Alzheimer's Disease* on risk and resiliency factors for dementia after TBI. Among US Veterans, TBI – including mild TBI – is a risk factor for dementia. However, it is not known whether TBI modifies the effect of other well-established risk factors for dementia, such as hypertension, diabetes, post-traumatic stress disorder (PTSD) or depression. In this study, our aim is to comprehensively compare medical and psychiatric risk factors for dementia in Veterans with a history of TBI compared to Veterans without a history of TBI. Our sample includes Veterans aged 55 and older without dementia at baseline, using a 1:2 matching (age-, sex-, and index date-matched) TBI (n=95,139) to no TBI (n=190,278). During follow-up (average of 6 years), 6% of Veterans without TBI developed dementia compared to 14% of Veterans with dementia. We assessed baseline dementia risk factors, then the relative risk of dementia associated with each risk factor was calculated using Fine-Gray competing risk of death and age-adjustment. Prevalence of all baseline risk factors was higher in TBI cohort vs. no TBI cohort, especially cardiovascular disease, epilepsy, depression, and PTSD. Although the magnitude of risk of dementia associated with each baseline risk factor was consistently (slightly) lower among TBI cohort vs. no TBI cohort, the population attributable fraction (PAF) of dementia due to hypertension, CVD, epilepsy, and depression were higher in Veterans with TBI due to their high prevalence in this group. These findings suggest that targeting depression, CVD, hypertension, and epilepsy may be especially important for dementia risk reduction among Veterans with TBI.

Milestone: Manuscript published in *The Journal of the Prevention of Alzheimer's Disease,* Gardner et al. 2023.

Progress: In collaboration with Carolyn Gibson at the San Francisco VA, we examined the relationships between intimate partner violence (IPV) [with and without Traumatic Brain Injury (TBI)] and aging-related health outcomes among men and women Veterans across the lifespan. A growing body of evidence, largely from reproductive-aged women, suggests adverse health outcomes related to intimate partner violence (IPV), including traumatic brain injury (TBI). We wanted to examine this relationship in a sample of men and women Veterans.

We completed a cross-sectional analysis of Department of Veterans Affairs (VA) administrative data from fiscal years 2000-2019. Descriptive statistics and chi-square analyses were used to compare key comorbidities in matched samples of Veterans with and without IPV (gender-stratified and matched 1:3 on demographics, index date). Participants were Veterans from our sample aged 18+ with and without documented IPV in VA electronic health records (n=4108 men, 2,824 women). ICD codes were used to identify IPV, TBI, and aging-related medical (sleep disorder, hypertension, diabetes, dementia) and common psychiatric (depression, posttraumatic stress disorder, alcohol use disorder, and substance use disorder) diagnoses.

Demographic characteristics were reflective of VA-enrolled Veterans (men: mean age 66, SD 16; 72% non-Hispanic White; women: mean age 47, SD 13; 64% non-Hispanic White). Relative to Veterans without IPV, both men and women with IPV had higher rates of all examined medical (e.g., sleep disorders, men: 33% vs. 52%; women: 45% vs. 63%) and psychiatric diagnoses (e.g., depression, men 32% vs. 74%; women 59% vs. 91%; all ps<.001.), with evidence of an additive effect of TBI on some psychiatric outcomes.

Figure 1a. Medical and psychiatric comorbidities of men Veterans with or without IPV (n=4,108)

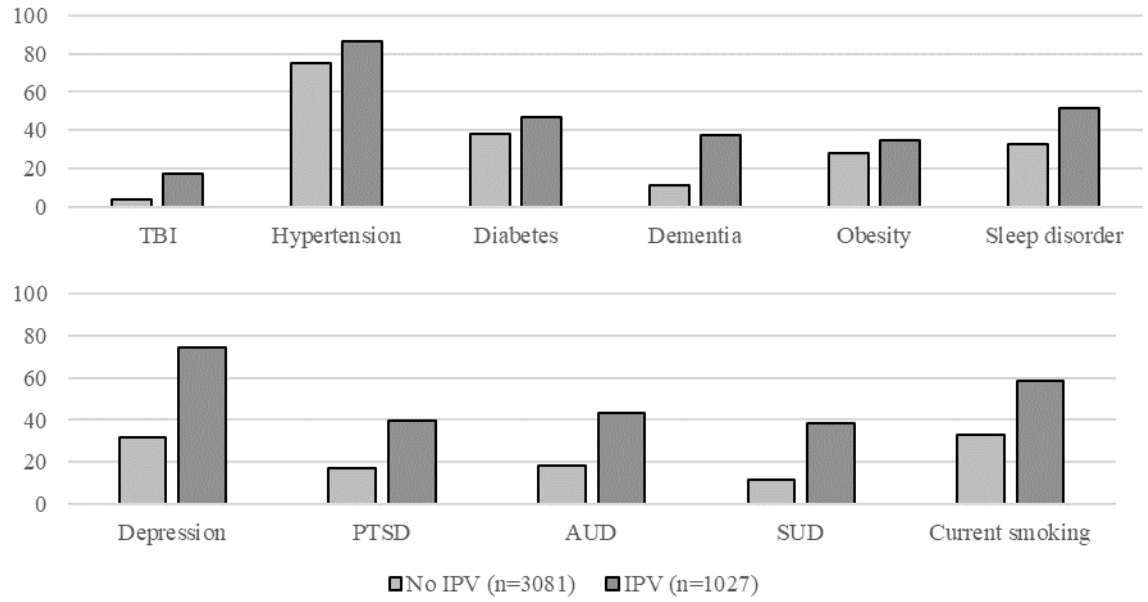
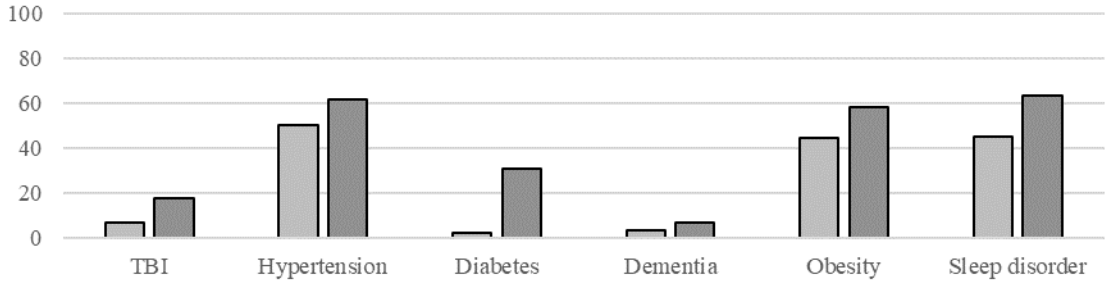


Figure 1b. Medical and psychiatric comorbidities of women Veterans with or without IPV (n=2,824)



Abbreviations: IPV=intimate partner violence, TBI=traumatic brain injury, PTSD=posttraumatic stress disorder, AUD=alcohol use disorder, SUD=substance use disorder
p<.001 for all comparisons shown (chi-square)

Overall, we found that IPV is broadly associated with aging-related and mental health among men and women across the lifespan, and comorbid TBI may further contribute to psychiatric outcomes. A manuscript detailing these findings is currently in press.

Milestone: Manuscript in press in *Journal of General Internal Medicine,* Gibson et al.

Major Task 5: Collaborate with Dr. Dismuke on analyses to examine health care utilization and costs of mental and physical health comorbidities after mTBI.

Month(s): *12 - 24*
Progress: Switched timeline with Major Task 8. Will begin collaboration in Year 5 of the project.

Major Task 6: Analyze data assessing the role of race/ethnicity, gender, and socioeconomic status on the association between mTBI and risk of neurodegeneration (i.e., dementia).

Month(s): *24 – 36*
Progress: Completed Year 2
Milestone: Manuscript published in *Neurology,* Kornblith et al., 2020.

Month(s): *24 – 36*
Progress: Completed Year 3
Milestone*:* Manuscript published in *Brain Injury;* Kornblith et al.

Major Task 7: Analyze data on the characteristics and longitudinal course of veterans with early-onset dementia after mTBI.

Month(s): *24 - 48*
Progress: In Year 4 we published a manuscript in the Journal of Neurotrauma; a systematic review and meta-analysis of risk of dementia after TBI and investigated effect of participant characteristics, methods, and region. We examined journal articles examining all-cause dementia after all-severity TBI (search window 1/1990-1/2019). We identified observational studies reporting age-adjusted risk for all-cause dementia after TBI among individuals with average age ≥40 years. Data were pooled using random-effects models; between study variability was assessed using the I2 index.

Overall, age, sex, region, TBI exposure ascertainment method, and dementia outcome ascertainment method all contributed to heterogeneity with at least borderline significance (p<0.07). Specifically, risk was highest in individuals under age 65 compared to those over 65, risk was higher for studies using ICD codes vs. those using a brief screen to identify TBI exposure, risk was higher for studies using ICD codes vs. those using other methods for dementia diagnosis, risk was highest in Asia and lowest in North America, and risk was highest in studies with <50% females vs. those with >50% females.

Population attributable risk (PAR) of dementia due to TBI exposure in the U.S. population, including specifically among U.S. Veterans, men, and women, is reported in the Table below. Women had the

lowest estimated PAR (9% U.S. Females; 3.8% U.S. Female Veterans) while men had the highest estimated PAR (32% U.S. Males; 29% U.S. Male Veterans). Estimated PAR of dementia due to TBI among U.S. Veterans was twice that of the general U.S. population and three times that of U.S. women. Estimated PAR of dementia due to TBI among U.S. men was 4 times that of U.S. women. Overall, we estimated that approximately 860,700 cases of dementia in the U.S. are attributable to TBI exposure. A manuscript detailing these important results is under review.
Milestone: Manuscript published in *Journal of Neurotrauma*, Gardner et al., 2023.

Progress: In Year 4 we published a manuscript examining the risk of long-term stroke after TBI in Veterans. TBI results in cerebrovascular injury and has been associated with short-term (i.e., <5 years) risk of stroke. Long-term associations of TBI with stroke remain less clear, thus, we analyzed the risk of long-term stroke after TBI in Veterans. In 613,592 older veterans without stroke at baseline, half with history of TBI, we found that TBI was associated with an increased risk of all stroke [HR: 1.69 (1.64-1.73)] in an analysis adjusted for demographics, medical comorbidities, and psychiatric comorbidities. The risk of hemorrhagic stroke after TBI [Adjusted HR: 3.73 (3.40-4.08)] was greater than risk of ischemic stroke after TBI [Adjusted HR: 1.56 (1.52-1.61)].

Looking at timing of stroke after TBI diagnosis, the risk of stroke is highest in the first year post-TBI but remains elevated for 10+ years. TBI severity is also associated with stroke risk, with moderate/severe TBI having a higher increased risk [Adjusted HR: 2.02 (1.96-2.09)]. than mild TBI [Adjusted HR: 1.47 (1.43-1.52)]

Overall, we found that Veterans with prior TBI are at increased long-term risk for stroke, suggesting they may be an important population to target for primary stroke prevention measures.

Milestone: Manuscript published in *Stroke*; Schneider et al., 2023.

Major Task 8: Examine (with Dr. Dismuke) health care utilization and costs of TBI-associated dementia vs all-cause dementia.

Month(s): *36 - 60*
Progress: Completed in Year 3
Milestone: Manuscript published in *Brain Injury;* Dismuke et al., 2022.

Major Task 9: Prepare manuscripts for journal publication.

Month(s): *24 - 60*
Progress: We currently have one manuscript in press and one in preparation.
Milestone: Since the beginning of the grant, we have published 9 manuscripts.

Major Task 10: Develop prognostic models to better determine risk of dementia and mortality and associations with potential risk factors in veterans with mTBI.

Month(s): *24 – 48*
Progress: In Year 4 we finalized the analysis for our prognostic model for dementia and mortality after TBI. We created a dataset with all Veterans from 2002-2019 with a TBI over age 55, without dementia at baseline, and have follow-up data (N=113,779). We are comparing characteristics of Veterans with TBI who developed dementia or died within 5 years to those who did not, adjusting for age, sex, and race. We performed multinomial logistic regression with Lasso to identify key predictors, assessing accuracy and calibration. We then performed a sensitivity analysis to assess for differences based on TBI date, demographics, and veteran status.

	Dementia	Death
C-statistic (95% CI)	0.756 (0.751, 0.761)	0.783 (0.779, 0.786)

The main prognostic model consisted of demographic variables, medical comorbidities, psychiatric

conditions, and healthcare utilization. The C-Statistics were good for dementia and death (see table).

C-statistics were good in all subgroups, including: TBI date, race/ethnicity, combat veteran status, socioeconomic status, and service connection.

Using EHR data we identified key characteristics (demographics, healthcare utilization, medical comorbidities, and psychiatric conditions) that predict dementia and death within 5 years with high accuracy in Veterans with a history of TBI. The predictive value of the model was similar in subgroups. A prognostic model based on data from EHR data could be built into EHR systems to help clinicians identify patients at high risk for dementia or death. In the Year 5 we begin working on drafting the manuscript, then submit to a peer-reviewed journal.

	Dementia	Death
TBI Severity		
Mild TBI	0.78 (0.77-0.78)	0.81 (0.80-0.81)
Moderate/Severe TBI	0.74 (0.74-0.75)	0.76 (0.75-0.76)
TBI Date		
2000 – 2015	0.76 (0.76-0.77)	0.78 (0.78-0.79)
2016 – 2019	0.72 (0.70-0.73)	0.75 (0.74-0.76)
Race/Ethnicity		
Non-Hispanic White	0.75 (0.75-0.76)	0.79 (0.78-0.79)
Non-Hispanic Black	0.77 (0.75-0.78)	0.78 (0.77-0.79)
Hispanic	0.76 (0.74-0.79)	0.77 (0.74-0.79)
Combat Veteran		
Yes	0.78 (0.77-0.79)	0.81 (0.80-0.81)
No	0.75 (0.75-0.76)	0.78 (0.77-0.78)

Milestone: Manuscript in process.

Major Task 11: Create and validate prognostication clinical tool.

Month(s): *36 - 60*

Progress: None yet as this will occur during year 5.

Major Task 12: Prepare manuscripts on prognostic models.

Month(s): *48 - 60*

Progress: None yet as this will occur during year 5.

Major Task 13: Attendance at biannual GSC meetings.

Month(s): *6 - 60*

Progress: We presented updates on our work at the October 2022 and April 2023 meetings. The feedback we received was informative and thoughtful.

Phenotype Study:

Major Task 1: Update data repository annually with latest VA data and merge with relevant DOD datasets and add additional DoD data to enhance acute TBI identification. Once assembled, perform quality checks and continue maintenance throughout study.

Month(s): *1 - 12*

Progress: Regulatory approvals were complete as of June 2020 – Ongoing Updates

• We updated DoD and VA health system data including the Theatre Data Management Store (TMDS) through FY22 in December 2022.

• We obtained National Death Index (NDI) through August 2020 in December 2022 and identified cause of death for deaths within that timeframe. Date of death has been obtained through September 30, 2023; we are in process of updating the NDI and Vital Status Files to the most recent data available which will likely

be in December 2023.

• We obtained DoDTR data for individuals with indication of TBI (GSC, TBI, AIS codes) in theatre (07/21/21).

• We obtained the VA-DoD Identity Repository data 07/27/2021 and have identified military variables including deployment status.

• We obtained refreshed data from the US VETS data source for the cohort.

Major Task 2: Using merged DoD-VA datasets, conduct phenotype analysis by deployment strata to examine the role of mTBI in emergence of neurodegenerative disease, psychological health status, neurosensory deficits and pain over time.

Month(s): *1 - 36*

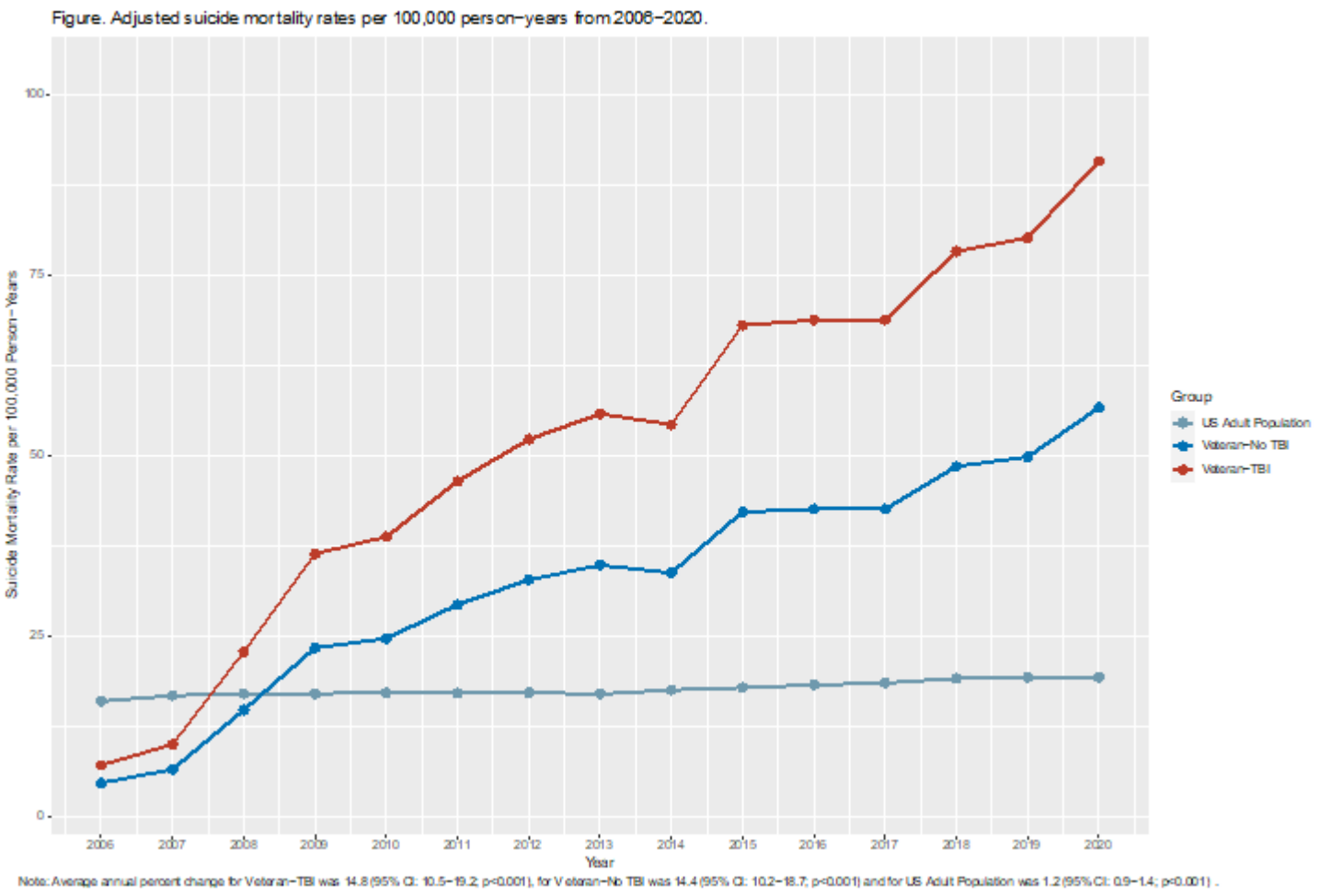
Progress: We have identified comorbidities of interest in VA and DoD data for this cohort using all data and completed analyses for cognitive dysfunction (from FY21; not included below), mortality, and cardiovascular disease (from FY22; not included below). We completed a publication examining the temporal trends in mortality for Veterans with/without TBI compared to the general population (adjusted for age/gender/race-ethnicity); completed analyses for all cause, cardiovascular disease and mortality to examine potential variation by race/ethnicity; finalized analyses of headache and cost of headache care in VA. We also finalized analyses of the characteristics of individuals who transition to VA care in order to understand the generalizability of findings from the phenotype and economic studies, submitted a publication examining the association of TBI severity and brain cancer, completed analyses for substance use disorder in DoD/VA data and association of TBI with emergence of multiple sclerosis and young onset parkinson's disease and are finalizing phenotypes of comorbidity in DoD data.

A) Temporal trends in mortality by suicide, cardiovascular disease and cancer of Veterans with TBI compared to Veterans without TBI and the General US Population:

In 2020, the suicide rate among all US veterans was 31.7 per 100,000, 57.3% greater than non-veterans, and suicide was the second leading cause of death for veterans under age 45.[1] Between 2000-2020, over 460,000 US servicemembers were diagnosed with traumatic brain injuries (TBI).[2] Veterans serving after September 11, 2001 (9/11) have higher suicide rates compared to the US population, which is exacerbated by TBI exposure.[3] Less is known about how suicide rates among post-9/11 veterans have changed over time. This study examined trends in suicide rates (2006-2020) for veterans with and without TBI compared to the US adult population.

Methods: A retrospective cohort study of suicide rates among 2,516,189 military veterans who served active duty in the US military after 9/11 and received care in the Military Health System (MHS) with/without care in the Veteran's Health Administration (VHA) were matched with mortality data from the National Death Index from 2006-2020.[3] Mortality data from the Centers for Disease Control and Prevention WONDER database for 2006-2020 were analyzed for the US adult population. The study was approved by the University of Utah institutional review board, conducted in accordance with applicable Federal regulations, and followed the STROBE reporting guidelines.

The figure below shows death by suicide rates and 95% confidence intervals by year for Veterans with (red) and without (blue) TBI and the general population (grey). This figure demonstrates that adjusted mortality was significantly lower for Post-9/11 Veterans prior to 2008, and that death by suicide for Post-9/11 Veterans increased significantly through August 2020 with rates significantly higher for those with TBI than for those with no TBI. These data were published as a research letter in JAMA Neurology.



B) Traumatic Brain Injury Exposure and Racial and Ethnic Mortality Disparities in US Military Veterans and the Total US Population:

We extended this mortality analysis to examine differences in deployed/non-deployed Veterans and specific differences by race/ethnicity. Cardiovascular disease (CVD) and cancer are the number one and two causes of death in the United States (US).[1] In 2021, 695,547 people died of CVD and 605,213 died of cancer, together accounting for 37.6% of all deaths in the USRacial/ethnic disparities in CVD and cancer are a significant public health concern and have been well documented in US civilian population. Specifically, CVD and cancer mortality rates have been persistently higher for non-Hispanic Black Americans than for non-Hispanic White Americans. Similar disparities have been reported among US military Veterans, although in some cases reduced disparities have been reported among Veterans. However, little is known about how disparities may differ among important subgroups of Veterans, including those with exposure to combat and combat injuries. Previous work by our research team has identified the presence of racial/ethnic disparities within the military health system, in which risk of hypertension was significantly higher for non-Hispanic Blacks compared to non-Hispanic Whites within a combat-injured cohort. Yet, questions remain about whether or not such disparities persist into the Veterans Health Administration (VHA) health system, and whether or not any such disparities translate into mortality disparities.

One explanation for the disparities in CVD and cancer mortality in the US population is the disproportionate lack of access to healthcare among racial/ethnic minorities, which has persisted despite implementation of the Affordable Care Act. In 2022, there were an estimated 27.6. million Americans without healthcare insurance, and the percentages were higher for Hispanic (27.6%) and non-Hispanic Black (13.3%) Americans compared with non-Hispanic Whites (7.4%). In contrast, Veterans have, at least in theory, equal access to healthcare through the Veterans Health Administration (VHA). In addition, Veterans who were exposed to combat-related and non-combat injury are likely to have a heightened need for healthcare, compared to uninjured Veterans. One might expect that if racial/ethnic health disparities are associated with differential access to care, that such disparities within the Veteran

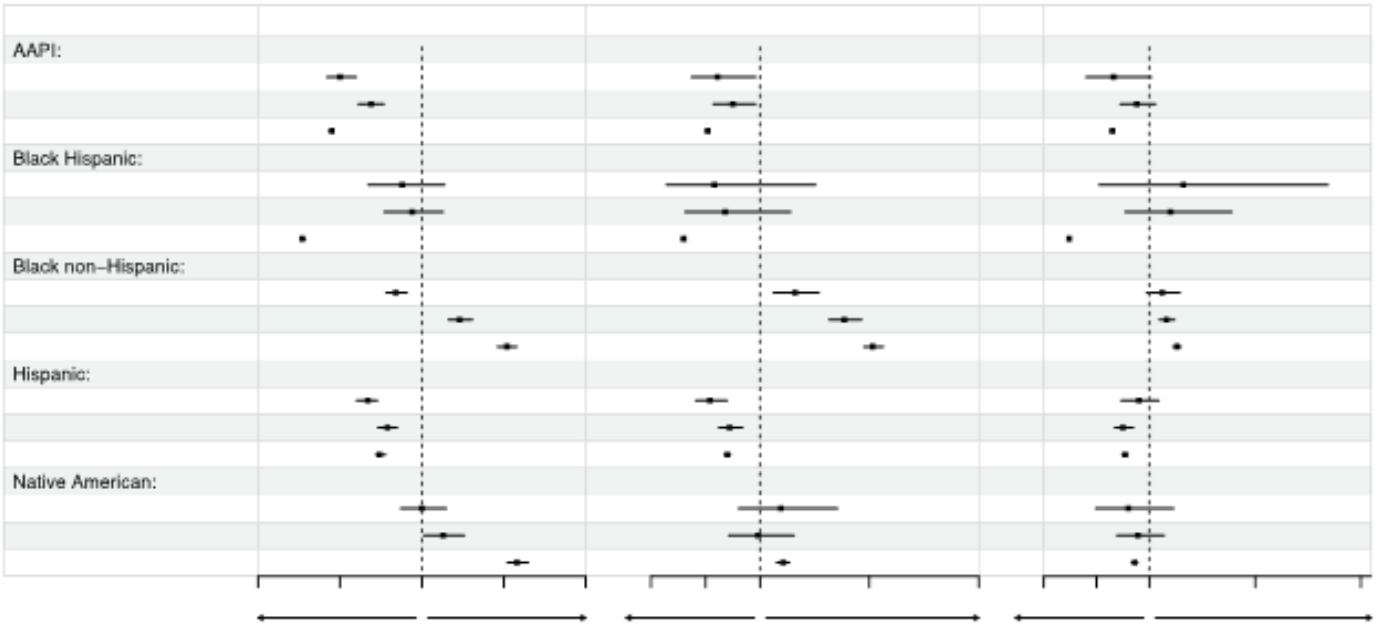
population may be diminished in comparison to the general population. Additionally, racial/ethnic disparities may be further diminished in Veterans with injury exposure and greater need for care. This concept could be referred to as an equalization hypothesis. We sought to test this equalization hypothesis in a large cohort of US military Veterans by comparing adjusted all-cause, cardiovascular and cancer mortality rates between Veterans with and without traumatic brain injury (TBI) exposure and to the total adult US population.

Participants: US military Veterans who served active duty after September 11, 2001 with 3 or more years of care in the Military Health System (MHS); or had 3 or more years of care in the MHS and 2 or more years of care in the Veterans Health Administration.
Exposure: Traumatic brain injury.
Main Outcomes and Measures: Multivariable, negative binomial regression models were used to analyze adjusted all-cause and cause-specific mortality rates for the post-9/11 military Veteran cohort, stratified by TBI exposure, and the US adult population. Mortality rate ratios (MRR) for racial/ethnic minority groups compared to white, non-Hispanic Veterans were used to measure disparity in all-cause, cardiovascular (CVD) and cancer mortality.
Results: The cohort consists of 2,530,847 Veterans out of a population of 2,983,971 post-9/11 military Veterans who had at least 3 years of care in the MHS. An additional 28,694 were excluded from this analysis due to missing or unknown racial-ethnic data and 52 were excluded due to invalid social security numbers. This study included 18,932,083 person-years of observation for 2,502,101 individuals from 2002-2020. The mean observation time was 7.6 years. Most of the person-years in the cohort were from males (86.4%) and two-thirds (67.3%) were 34 years of age or younger. Cohort person-years were also predominantly White Non-Hispanic (68.6%) race/ethnicity, while 16.2% were Black Non-Hispanic, 10.5% were Hispanic, 2.2% were Asian/Pacific Islander, 1.9% were Native American and 0.6% were Black Hispanic.

Veterans with TBI exposure accounted for 4,602,198 person-years and Veterans without TBI accounted for 14,329,885 person-years. The total number of deaths from all causes was 40,621 (214.6 per 100,000 person-years), 13,276 with TBI (288.5 per 100,000 person-years) and 27,345 (190.8 per 100,000 person-years) without TBI. Crude mortality rates for CVD were 29.4 per 100,000 person-years for Veterans with TBI and 26.5 per 100,000 person-years for Veterans without TBI. Crude mortality rates for Cancer were 28.9 per 100,000 person-years for Veterans with TBI and 38.4 per 100,000 person-years for Veterans without TBI.

In our cohort, mortality disparities were evident only among Black Non-Hispanics. Mortality rates for Black Non-Hispanic Veterans were higher for all-cause (MRR=1.21;95%CI: 1.13-1.29;$p<0.001$), CVD (MRR=1.78;95%CI: 1.62-1.96;$p<0.001$) and cancer (MRR=1.17; 95%CI: 1.10-1.25;$p<0.001$) than in White Non-Hispanic Veterans. Among Veterans with TBI, only Black Non-Hispanics had higher mortality than White Non-Hispanics and only for CVD (MRR=1.32;95%CI: 1.12-1.54;$p<0.001$), while CVD mortality was significantly higher among Veterans without TBI (MRR=1.77;95%CI: 1.63-1.93;$p<0.001$). Mortality rates for Black Non-Hispanics in the total US population, were consistently higher than those in the Veteran population for all-cause (MRR=1.52; 95%CI: 1.46-1.58;$p<0.001$), CVD (MRR=2.03;95%CI: 1.95-2.13;$p<0.001$) and cancer (MRR=1.26; 95%CI: 1.22-1.30;$p<0.001$).

Figure 2. Multivariable adjusted mortality rate ratios for racial/ethnic groups compared to non-Hispanic White (dashed reference line), for US military Veterans, with and without TBI exposure, and total US population.



Conclusions and Relevance: Consistent with an equalization hypothesis, this Veteran cohort experienced less racial/ethnic disparity in mortality than the total US population, especially among Veterans with TBI. This may suggest more intense care for those Veterans who receive interdisciplinary rehabilitation care in the polytrauma system of care.

This manuscript is under review in JAMA Network Open.

C) Understanding who is more/less likely to transition to VA care:

US Department of Defense and Veterans Affairs policies determine access to healthcare for members of the US Armed Forces. Military service component (Active, National Guard, Reserves) members have similar and contrasting military and deployment experiences influencing health status and access to care. This retrospective cohort study from the Long-Term Impact of Military-Relevant Brain Injury Consortium-Chronic Effects of Neurotrauma Consortium Phenotype Study (*N*=1,594,869) identified service component differences in factors associated with successful Military Health System (MHS) to the Veterans Health Administration (VHA) care transitions among post-9/11 veterans. Population data were extracted from US Department of Defense MHS and US Department of Veterans Affairs administrative data from fiscal years (FY) 2000-2020. Eligible participants received at least three years of MHS care and separated from military service before FY2017 (October 1, 2016). The primary outcome was transition from MHS to VHA care after military separation. Covariates included demographic, military, and deployment characteristics at military separation; physical, mental, and substance use diagnoses and comorbidities two years before military separation date.

Among 1,594,869 post-9/11 veterans who separated from military service and received at least 3 years of MHS care prior to fiscal year (FY) 2017 (on or before 30 September 2016), 81.9% were male, 54.2% Active Duty; and 48.8% were 25-34 years old. 78% transitioned to VHA care. Of those, 70% had a combat deployment; 17.5% were women; and 38.5% were racialized minorities (Black, Hispanic, Asian/Pacific Islander, or Native American). Prevalent conditions included pain (55.8%), smoking history (40.8%), and headache (17.5%). National Guard (OR 2.23; 95% CI 2.19-2.27) and Reserve (OR 1.35; 95% CI 1.34-1.37) were more likely to transition than Active members. Non-Hispanic Black (OR 1.85; 95% CI 1.83-1.88) and Black Hispanic (OR 1.70; 95% CI 1.59-1.81) members were more likely to transition to VA than White members.

Half (50.6%) transitioned FY2012-2016, over one-third (35.6%) had 2-4 years of MHS care prior to military separation. Post-9/11 veterans with physical and behavioral health comorbidities experienced successful MHS-VHA

care transitions. Mental health, substance use disorder (SUD), traumatic brain injury (TBI), and pain comorbidities significantly increased odds of transitioning to VHA care. Additionally, the polytrauma clinical triad (PCT), which is the signature injury of the conflicts in Iraq and Afghanistan, significantly increased the odds of successful transition to VHA care. Suicidal ideation/attempt was not associated with transitioning to VHA care and gaps in MHS-VHA care continuity exists for post-9/11 veterans who received care for suicidal ideation/attempt 2 years before military separation. This suggests a need for greater assistance in the military transition for service members who experience suicidal ideation/attempt while on active duty.

D) Traumatic Brain Injury Increases the Subsequent Risk of Brain Cancer:

While malignant brain cancer is rare, it has a very poor prognosis and few established risk factors. To date, epidemiologic work examining the potential impact of traumatic brain injury (TBI) on the subsequent risk of brain cancer is conflicting. We sought to examine the association between an episode of TBI and subsequent malignant brain cancer in a large cohort of post-9/11 era Veterans.

Methods: This was a retrospective study of 1,919,740 Veterans from the Long-Term Impact of Military-Relevant Brain Injury Consortium-Chronic Effects of Neurotrauma Consortium. The study combined multiple Department of Veterans Affairs (VA) and Department of Defense (DoD) data sources with data available from 2005 to 2019. The main variable of interest was TBI stratified by severity (mild, moderate/severe, and penetrating). The outcome of interest was the development of malignant brain cancer based on International Classification of Diseases diagnostic codes in either the DoD/VA medical records or from the National Death Index. Fine and Gray models were used to calculate subdistribution hazard ratios (HR) and 95% confidence intervals (CI) to determine the association of TBI with subsequent brain cancer accounting for the competing risk of non-brain cancer related death.

Results: The cohort included 1,469,860 subjects without TBI and 449,880 subjects with TBI (mild N=385,848, moderate/severe N=46,859, penetrating N=17,173). Those with penetrating TBI were significantly older, more likely to be Active Duty, and less likely to be non-Hispanic Black and enlisted.

Table 1. Characteristics of the study cohort

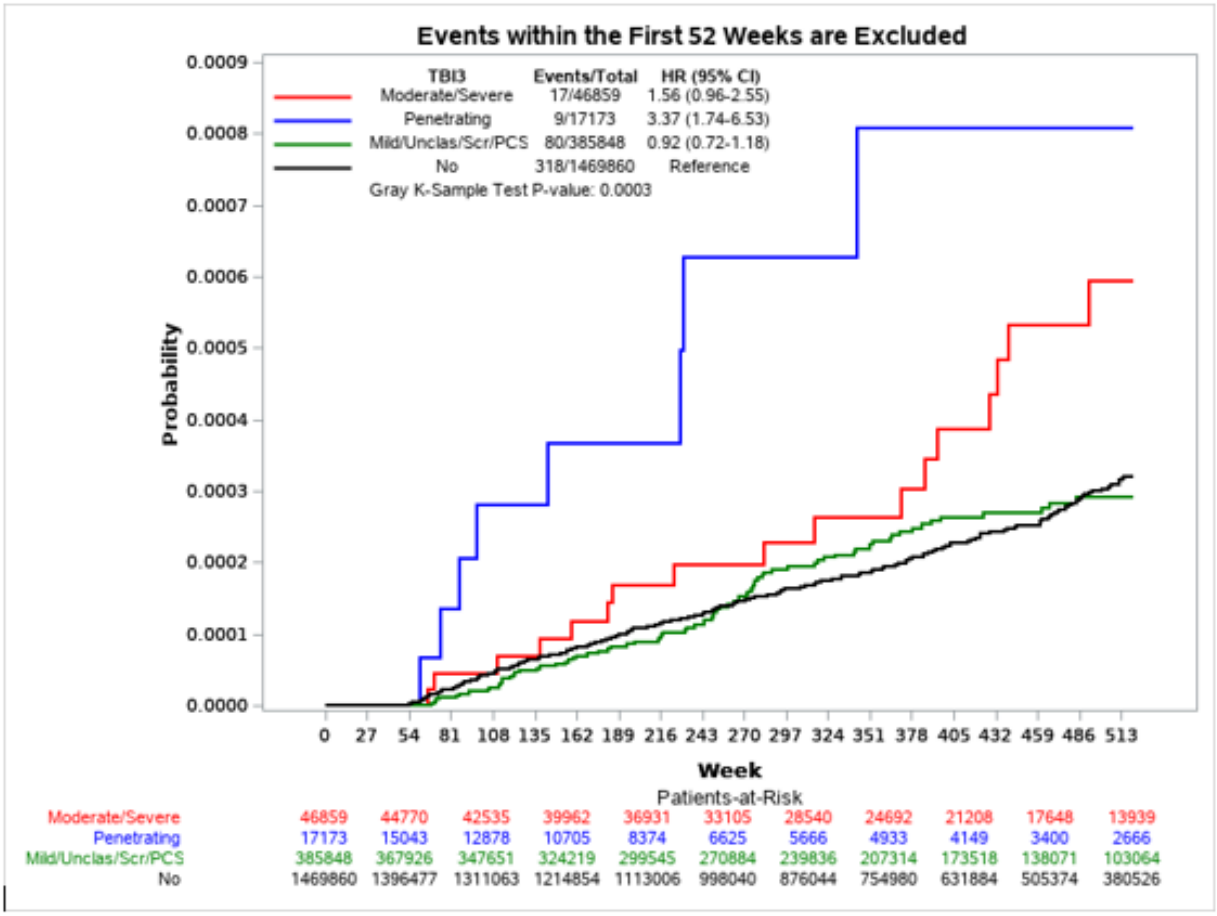
	No TBI N= 1,469,860	**Mild TBI** N= 385,848	**Moderate/Severe TBI** N= 46,859	**Penetrating TBI** N= 17,173	**P value**
Age, years median (IQR)	31 (24-43)	30 (25-40)	30 (25-39)	33 (26-43)	<0.001
Sex, N (%)					<0.001
Male	1,149,988 (78.24)	334,418 (86.67)	41,032 (87.56)	15,185 (88.42)	
Female	319,872 (21.76)	51,430 (13.33)	5,827 (12.44)	1,988 (11.58)	
Race and Ethnicity, N (%)					<0.001
White, non-Hispanic	926,620 (63.04)	243,389 (63.08)	30,456 (64.99)	11,066 (64.44)	
Black, non-Hispanic	266,045 (18.10)	64,633 (16.75)	6,941 (14.81)	2,563 (14.92)	
Hispanic	133,944 (9.11)	35,858 (9.29)	4,247 (9.06)	1,662 (9.68)	
Asian and Pacific Islander	81,994 (5.58)	28,919 (7.49)	3,711 (7.92)	1,263 (7.35)	
Unknown	31,234 (2.12)	3,632 (0.94)	394 (0.84)	231 (1.35)	
Native American	21,899 (1.49)	7,463 (1.93)	899 (1.92)	311 (1.81)	
Black, Hispanic	8,124 (0.55)	1,954 (0.51)	211 (0.45)	77 (0.45)	
Service Branch, N (%)					<0.001
Army	625,299 (42.54)	234,924 (60.89)	27,980 (59.71)	9,873 (57.49)	
Air Force	353,372 (24.04)	43,522 (11.28)	5,273 (11.25)	2,180 (12.69)	
Navy/Coast Guard	304,254 (20.70)	47,946 (12.43)	5,782 (12.34)	2,287 (13.32)	
Marines	184,715 (12.57)	59,236 (15.35)	7,794 (16.63)	2,810 (16.36)	
Other	2,220 (0.15)	220 (0.06)	30 (0.06)	23 (0.13)	
Rank, N (%)					<0.001
Enlisted	1,219,508 (82.97)	351,248 (91.03)	42,833 (91.41)	14,937 (86.98)	
Officer	229,228 (15.60)	29,929 (7.76)	3,497 (7.46)	1,871 (10.90)	
Warrant Officer	21,124 (1.44)	4,671 (1.21)	529 (1.13)	365 (2.13)	
Component, N (%)					<0.001
Active Duty	818,905 (55.71)	218,201 (56.55)	28,265 (60.32)	12,276 (71.48)	

Reserve National Guard	495,519 (33.71) 155,436 (10.57)	116,138 (30.10) 51,509 (13.35)	12,684 (27.07) 5,910 (12.61)	3,235 (18.84) 1,662 (9.68)	
Marital Status, N (%) Not married Married Unknown	 801,579 (54.53) 626,782 (42.64) 41,499 (2.82)	 195,447 (50.65) 185,899 (48.18) 4,502 (1.17)	 23,465 (50.08) 22,983 (49.05) 411 (0.88)	 8,847 (51.52) 8,077 (47.03) 249 (1.45)	<0.001
Follow up time from index date, weeks median (IQR)	373 (213-526)	387 (228-532)	384 (236-554)	204 (104-406)	<0.001
Malignant brain cancer diagnosis, N (%)	318 (0.02)	80 (0.02)	17 (0.04)	9 (0.05)	0.008

TBI: Traumatic brain injury IQR: interquartile range

Malignant brain cancer occurred in 318 subjects without TBI (0.02%), 80 subjects with mild TBI (0.02%), 17 subjects with moderate/severe TBI (0.04%), and 9 subjects with penetrating TBI (0.05%). Figure 3 shows the cumulative incident function for emergence of brain cancer stratified by TBI severity.

Figure 3. Cumulative incidence functions for the outcome of brain cancer stratified by TBI severity.



After adjustment, moderate/severe TBI (HR 1.90, 95% CI 1.16-3.12) and penetrating TBI (HR 3.35, 95% CI 1.72-6.52), but not mild TBI (HR 1.14, 95% CI 0.88-1.47), were associated with the subsequent development of malignant brain cancer.

Conclusion: Moderate/severe TBI and penetrating TBI, but not mild TBI, were associated with the subsequent development of malignant brain cancer in this large cohort of post-9/11 era Veterans.

E) Headaches after traumatic brain injury:

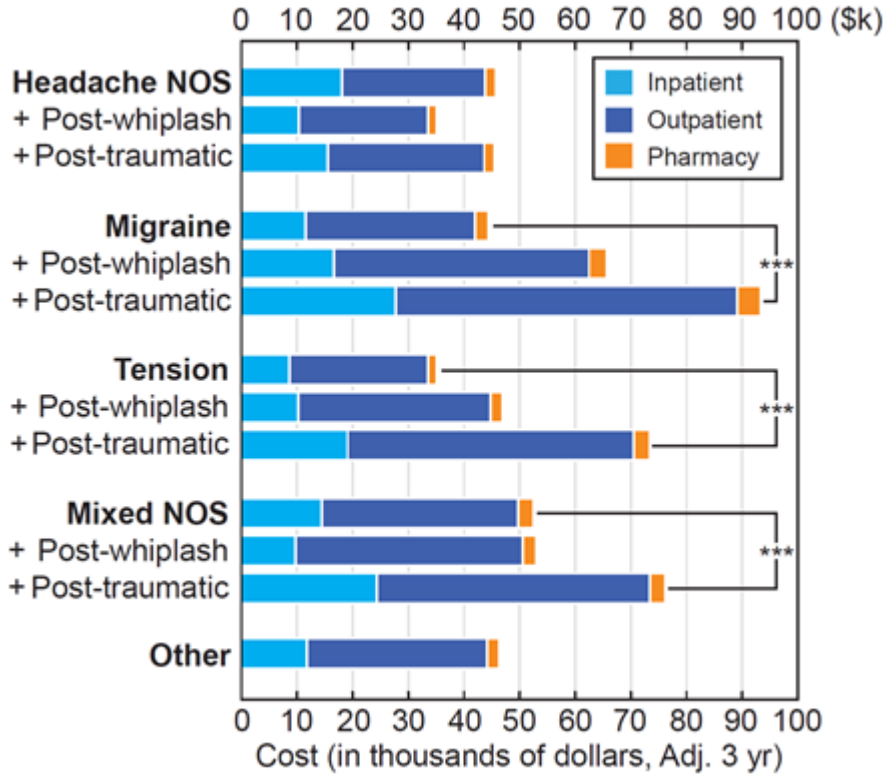
Headaches following traumatic brain injury (TBI) are a common disabling disorder whose diverse diagnostic characteristics and care needs remain poorly defined. Our objective was to examine diagnostic patterns and cost among military Veterans with comorbid chronic headache and TBI.

We identified 141,125 Post-9/11 era Veterans with military service between October 1, 2001 and September 30, 2019, and a headache disorder diagnosed after TBI. We first identified patterns of Complex Headache Combinations (CHC) and compared the patterns of healthcare costs in 2022-dollar values between the headache diagnostic groups in the three years following TBI diagnosis.

The cohort included 141,125 Post-9/11 era Veterans with an ICHD-3 headache disorder diagnosed within 3 years after TBI. The sample was predominantly male (91%), white (58%), with at least a high school diploma/GED (79%), and under 30 years of age at the time of first headache diagnosis (53%). The most common individual headache diagnoses were headache NOS (43%), migraine (18%), and post-whiplash headache (15%). Most common complex headache combinations (CHCs) were migraine + post-traumatic (5%) and migraine + post-whiplash diagnoses (3%). In bivariate analyses, men were less likely to be in the Migraine or Migraine+Post-whiplash groups. Active-duty service members were more likely to be in a post-traumatic headache (PTH) or Post-whiplash combination group of any kind (e.g., Tension+PTH) while those most recently in the Reserves had greater than expected numbers in the Headache NOS and Migraine groups.

Most of the sample had a history of mTBI (63%). In bivariate analyses, Post-whiplash CHCs were more common among those with a history of mild or moderate/severe TBI. Among individuals who screened positively for TBI without additional indicators of TBI, Headache NOS or Migraine were more common. In general, moderate to severe TBI and penetrating trauma were more prevalent among those with CHCs than individual headache categories. The majority of the cohort had persistent headache (headache diagnosed in at least two of the first three years after TBI; 60%), and had prescriptions of preventative (74%) and/or abortive (75%) headache medications.

Post-whiplash and Post-traumatic CHCs were common and consistently associated with higher costs after TBI than those with other types of headache and CHCs. Post-Traumatic Migraine had the highest unadjusted mean inpatient ($27,698), outpatient ($61,417), and pharmacy ($4,231) costs, which persisted even after adjustment for possible confounders.



The present study is one of the first to estimate costs of complex posttraumatic headache and confirmed that these headaches are common and costly for military veterans, due (at least in part) to lack of clarity in treatment guidelines and high likelihood of treatment failures. Future studies should assess treatment response as a contributor

to high costs and cost mitigation associated with new treatments and practice guidelines.

F) Association between TBI exposure and Parkinson's disease among Veterans deployed in post-9/11 U.S. conflicts: A unique opportunity to understand young onset Parkinson's disease:

Traumatic brain injury (TBI), a common injury among post-9/11 Service Members (SMs) and Veterans, is one of the risk factors for Parkinson's disease (PD) among older adults in civilian and Veteran populations. Little is known about the trajectory and elevated risk of PD among younger SMs/Veterans with TBI.

We identified Post-9/11 Era Veterans with PD cohort was identified using ICD-9/10 codes from the DoD and VA health system data as of August 1, 2021. Individuals who had care documented in the Military Health System Data Repository for at least 3 years from FY2000-2019 were also included in the final cohort. Individuals with a PD diagnosis prior to TBI were excluded from the analysis. TBI severity was identified using data from the DoD Trauma Registry (Glasgow Coma Scale and Abbreviated Injury Severity Scores and ICD-9/10 codes), ICD-9/10 codes in the Theater Medical Data Store, self-reported loss/alteration of consciousness or post-traumatic amnesia from the VA comprehensive TBI evaluation, and ICD-9/10 codes from VA and DoD health system data. Fine and Gray time-to-event models were conducted to examine the association of TBI severity with PD and to compare characteristics of individuals with young onset PD (YO-PD; 50 years or younger) vs older onset PD (OO-PD; >50 years of age). Models were adjusted for sociodemographic, clinical, and military characteristics such as age at TBI diagnosis, preexisting comorbidities, and branch of service.

Of the 1,862,458 SMs/Veterans who met inclusion criteria, 1522 were diagnosed with PD; 553 were categorized as YO-PD (36.3%) and 969 were OO-PD. 18.6% of those without PD had a history of TBI, and 32.3% of those with PD had TBI exposure documented in DoD or VA medical records. Those with YO-PD were more likely to have TBI in all severity groups compared to OO-PD: Mild TBI=28.8% (vs 17.8% OO-PD); moderate/severe=8.7% (vs 4.9% OO-PD); and penetrating=5.4% (vs 3.6% OO-PD). The mean age of YO-PD diagnosis was 39.4 years old (standard deviation [SD]=40), while the mean age of OO-PD diagnosis was 61.4 years old (SD=61).

Those with TBI had elevated hazard ratios (HR) for PD: Penetrating (HR=4.5; 95% Confidence Interval [CI]=3.4-6.0), moderate/severe (HR=2.3; 95% CI=1.8-2.9), and mild (HR=1.6; 95% CI=1.4-1.9). Among those with PD, any TBI was associated with a higher likelihood of YO-PD (e.g., mTBI OR 1.6; 95% CI=1.1-2.3; moderate TBI OR 2.0; 95% CI=1.1-3.7). Lower odds of YO-PD were found for those who were deployed (OR 0.6; 95% CI=0.4-0.8) while odds of YO-PD were markedly higher for those who served on Active Duty (OR 3.3; 95% CI=2.4-4.5) and those with schizophrenia (OR 7.1; 95% CI=1.7-29.2).

To our knowledge, this is the first study to examine the association between TBI and PD exclusively in Post-9/11 era SMs/Veterans, and examine differences between those with YO-PD vs OO-PD. Consistent with prior research regarding older Veterans, PD risk was associated with an increasing dose-response effect of TBI severity in our study. For those with a YO-PD diagnosis, a 7.1-fold risk was observed for those who were diagnosed with schizophrenia compared to older counterparts. Further investigation into this association may help inform mental health screening and interventions for Post-9/11 SMs/Veterans.

G) MS in Post-9/11 Era Veterans:

Multiple Sclerosis (MS) prevalence has nearly doubled in the US since the 1990's. A history of multiple concussions in adolescence as well as hospitalization for TBI have been linked to the development of MS. The development of MS has been linked to environmental factors such as history of smoking, and Epstein-Barr Virus infection. However, there is currently limited evidence suggesting an association between TBI and development of MS. The purpose of this study is to examine the association of TBI and MS in post 9/11 era Veterans.

The primary outcome was defined as an MS diagnosis based on ICD 9 (340) or ICD 10 codes (G35) in the LIMBIC Phenotype study cohort. Those who received either one inpatient diagnosis or two outpatient diagnoses (at least 7 days apart) indicating MS comprised the MS cohort.

The independent variable, TBI diagnosis, was identified using a hierarchical approach prioritizing data from DoD Trauma Registry and the Theater Medical Data Store (Glasgow Coma Scale score, Abbreviated Injury Severity Score, ICD-9/10 codes), followed by self-reported loss of consciousness (<30 minutes: mild; >30 minutes: moderate/severe), alteration of consciousness or post-traumatic amnesia (<24 hours mild; > 24 hours moderate/severe) in the VA comprehensive TBI evaluation (CTBIE), followed by ICD-9/10 diagnosis from the 2012 Armed Forces Health Surveillance System published algorithm. TBI was classified as no TBI, mild TBI, moderate/severe TBI, and penetrating TBI. If multiple TBI diagnoses were present, the most severe injury was used in the analysis.

Index dates were created as the first date of a TBI diagnosis in the medical record for those with TBI. For Veterans without TBI, index dates were simulated by drawing from the distribution of true index dates within age brackets. To ensure adequate follow-up, those with an index date after 1 Oct 2016 were excluded.

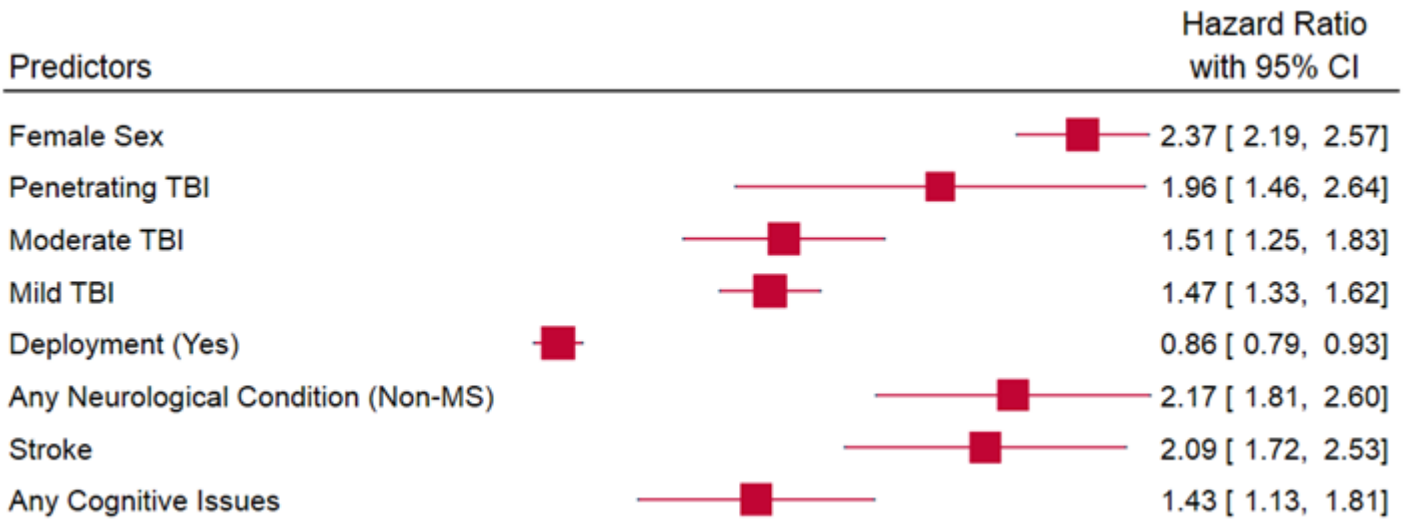
We included other covariates that have been previously associated with MS or death, including: age at index date, sex, race and ethnicity, education at the last military separation, military characteristics (branch of service, component, rank [enlisted, office, warrant officer] deployment status [yes/no], health behaviors prior to index date (smoking, substance use disorders, overdose, and obesity) and comorbid health conditions prior to index date (e.g., depression, anxiety, hypertension, hypercholesterolemia, chronic lung disease, stroke).

We conducted Fine and Gray time to event models examining the association of TBI severity and MS diagnosis.

Results

Of the 2,130,377 Veterans who met inclusion criteria (mean age=33; SD=11), 82% were male and 18% were female. Approximately two-thirds (68%) of the cohort had deployed and just over half of the cohort (52%) served in the active component. Education level was relatively high with 67% having completed either high school or a GED and 30% completed some college or more. A large majority (82%) had no evidence of TBI documented in the DoD or VA medical records. TBI was significantly more common among those with MS (any TBI: MS=27.0%; No MS=17.6%). Prevalence of TBI severity in those with MS and no MS was respectively: mild TBI: 21.4% vs. 14.1%; moderate/severe TBI: 4.1% vs. 2.6%; penetrating TBI: 1.5% vs. 0.9%. Bivariate statistics also suggested higher likelihood of MS for women than men (37.9% of those with MS were women compared to 18.1% women with no MS).

Fine and Gray models found significantly higher hazard ratios (HR) for those with TBI compared to those without TBI: penetrating [HR 1.96; 95%CI 1.5-2.6]; moderate/severe [HR 1.5; 95%CI 1.2-1.8]; mild [HR 1.5; 95%CI 1.3-1.6]. Time to MS from the index date was fastest for women (HR 2.3; 95%CI 2.1-2.5) compared to men, and the following clinical characteristics diagnosed before index date: stroke (HR 2.1; 95%CI 1.7-2.5), other neurological conditions (HR 2.2; 95%CI 1.8-2.6; [as defined by the Elixhauser Comorbidity Index excluding MS, e.g., epilepsy, anoxic brain injury, Parkinson's disease]).



Military characteristics associated with MS had lower HR than clinical characteristics, however those who served in the active component had significantly higher HR for MS than National Guard/Reserve (HR 1.3; 95% CI 1.2-1.4). Those in the Air Force had higher HR for MS than those in the Army and those who were deployed had a lower HR for MS than those not deployed (HR 0.9; 95% CI 0.8-0.9).

Conclusions:
Multiple sclerosis (MS) is an immunological disease that causes acute inflammatory lesions and chronic inflammation in the central nervous system (CNS), leading to tissue damage and disability. Neuroinflammation, a protective physiological response after TBI, may also be associated with emergence of MS—both TBI and MS are associated with inflammatory activation of microglia and astrocytes. Additionally, both TBI and MS are associated with disruption of the blood brain barrier, which may lead to the entry of peripheral immune system into privileged CNS space. This is a possible pathomechanism for the association of increased development of MS after TBI. To our knowledge, this is the first study to examine associations among TBI and MS in the Post-9/11 Veteran population where it is possible to identify initial MS diagnosis and prior military exposures in the age group where MS is commonly diagnosed (ages 20-50). Our study suggests that individuals with penetrating TBI and those with a history of stroke, are at the highest risk (HR>2) of a subsequent diagnosis of MS. This may be accounted for by increased duration/extent of inflammation in those with penetrating injuries. However, individuals with mild TBI and moderate/severe TBI both had significantly elevated risk of MS. Consistent with prior literature in civilian populations, women were significantly more likely to experience MS. Further evaluation should explore the interaction of sex and TBI to determine if women with TBI are at elevated risk compared to women without TBI history. Furthermore, our finding that the HR for those deployed is significantly lower than non-deployed demonstrates the healthy deployer effect (service members may be diagnosed with MS making them undeployable). This association warrants further evaluation of the timing of MS diagnosis during active study status.

Major Task 3: Use phenotypes and mTBI to develop risk scores for military outcomes, neurosensory/neurodegenerative disease, and adverse outcomes by deployment.

Month(s): *24 - 48*
Progress: We are working to get the servers for machine learning analyses behind the VA firewall to allow development of risk scores. We are completing LCA phenotypes during DoD care to compare to prior VA Phenotype analyses conducted during CENC.

Major Task 4: Examine association of phenotypes with TBI and risk for repetitive low-level blast by deployment strata.

Month(s): *48 - 60*
Progress: None yet as this will occur during year 5. We are currently identifying MOS that have high likelihood of repetitive low-level blast exposure in preparation for this analysis.

Milestone: Compile VA data for Post-9/11 Veteran Cohort from existing data repository. ***COMPLETE***
Milestone: Convene stakeholder panel of VA and DoD operational partners. ***Complete for FY23***
Milestone: Obtain DoD Data for Post-9/11 Veterans via DoDTR and DaVINCI. ***Complete***
Milestone: Analytic data sets for latent class/deep learning models developed. ***Complete data sets; working on LCA models; insufficient computing power on VINCI to conduct deep learning. We have permissions to add the server to the VA environment and are currently working with VINCI team to complete the installation.***
Milestone: Develop DoD+VA phenotypes in: deployed VA users; nondeployed VA users; deployed no VA care; non-deployed no VA care. ***Currently conducting LCA analyses for those without VA care as we have no prior information on this cohort.***
Milestone: Compare phenotypes among sub-strata (deployed/nondeployed/VA/non-VA). ***In progress.***
Milestone: Examine association of military relevant outcomes and repetitive low-level blast occupations with phenotypes. ***Identification of MOS associated with low-level blast occupations in process with Millenium Cohort collaborators***

Health Economics Study:

Major Task 1: Obtain DoD and VA authorizations.

Month(s): *1 – 24*

Progress: Completed – No changes

a. HES received IRB approval for the following protocol amendments (1) added dates, specifically, all elements of dates (e.g., birthdate, admission date), (2) added geographic subdivisions smaller than a state, and geocodes (e.g., zip, county or city codes, street addresses), (3) replaced "VCU server" with "Department of Defense and Secure Access File Exchange (DOD SAFE)" as DOD SAFE will be the method that DOD sites will send participant EDIPIN and study ID to Dr. Dismuke-Greer and her team, (4) noted that VCU can share deidentified data with anyone with whom VCU has a DUA, and (5) added VA COVID-19 Volunteer Registry as a data source.

b. For the phenotype study, all authorizations have been obtained by Dr. Pugh's team.

Major Task 2: Create a joint VA/DoD database within VINCI, matching on real SSN, for all Vs using VA and diagnosed with TBI either in DoD, VA or both since 2004. Once assembled, perform quality checks and continue maintenance throughout study.

Month(s): *1 - 24*

Progress: Completed – No changes

a. Phenotype SM/V with TBI databases are completed.

Major Task 3: Assemble a matching cohort on age of Vs without TBI. Once assembled, perform quality checks and continue maintenance throughout study.

Month(s): *1 - 24*

Progress: Completed – No changes

a. Phenotype databases SM/VA without TBI are completed

Milestone: Create a joint VA/DoD database within VINCI, matching on real SSN, for all veterans using VA and diagnosed with TBI either in DoD, VA or both since 2004 (matching cohort on age of veterans TBI(-) for comparisons) to include demographics, military characteristics, military exposures identified in MHS to potential concussive event mechanisms, TBI severity when diagnosed by DoD, trauma and non-trauma comorbidities identified by DoD, MHS health services utilization and costs, military readiness, disability, days of work duty limitations and time in service, date of military separation, first date of VA eligibility, VA service connected disability rating and payments, VA comorbidities, VA health services utilization and survival.
Completed: Year 2, Q4

Major Task 4: Collaborate with Drs. Pugh and Yaffe on the corrected identification of TBI severity and

comorbidities.

Month(s): *24 - 36*

Progress: Completed year 3, quarter 3 – No Changes

a. Dr. Pugh's team has determined TBI severity and comorbidities.

Major Task 5: Request, clean and merge data within the VINCI environment.

Month(s): *24 - 36*

Progress: Completed Year 4

a. Data has been merged in VINCI for the 1.5 million veteran phenotype subjects with Service-Connected Disability Compensation. It is in progress for DoD and VA cost data for the 1.5 million veterans and 1.1 million service members. Additional data source: Department of Labor Zip Codes for Native American Tribal Lands.

Major Task 6: Examine the impact of TBI along with mechanisms of injury (controlled detonations, uncontrolled blast exposures, impact exposures in combat and training), and its comorbidities with DoD health services utilization, cost and disability (days of military released with work duty limitations, sick at home/quarters, and failed to meet medical standards), 2004-2018.

Month(s): *36 - 60*

Progress: Completed Year 4

a. Classification of 10,801 exposures for 1816 PLS subjects has completed. Linkage to DoD and VA cost data completed. Operations theater data on battle vs non-battle injuries and blast vs non-blast injury explored along with theater disposition (return to duty, quarters, evacuated). In the process of incorporating TBI comorbidities based on a new study (by Dr. Agimi).

Major Task 7: Examine the impact of MHS neurology, imaging, polytrauma/TBI clinic, other rehabilitation, pain clinic and mental health services on time in military service, military readiness, sick days and DoD costs. MHS costs will include out-ofpocket costs incurred by individuals as well as payments to health care providers made on their behalf by Tricare.

Month(s): *36 - 60*

Progress: 50% Complete

a) Dr. Dismuke-Greer working with Walter Reed team led by Dr. Hoover examining costs for current SMs with recent mTBIs providing MEPRS codes to identify outpatient clinic types of care. Sick days variables have been identified in DoD outpatient data. Out of pocket cost variables identified in Tricare data. Disposition after injury has been identified in theater data. Status: Study with Dr. Hoover published in Journal of Head Trauma Rehabilitation; other analyses in progress.

Major Task 8: Examine the impact of TBI and its mechanisms of injury, along with MHS health services on VA access/transition after DoD separation, survival and VA service connected disability compensation and pension benefits, 2004-2018.

Month(s): *36 - 60*

Progress: 50% Complete

a. Phenotype data (1.5 million Vs 1.1 million SMs) to identify transition to VA. Working with Drs. Pugh and Agimi to identify SM predictors of transition and access to VA care. Death dates identified in DoD and VA data. Status: Working with Dr. Agimi to overcome regulatory hurdles to share data.Phenotype data include 1.5 million Vs and 1.1 million SMs to allow identification of transition to VA. Working with Dr. Pugh and Dr. Agimi to identify SM predictors of transition and access to VA care. Death dates have been identified in DoD and VA data.

TBI and Service-Connected Disability (SCD)

The Health Economics team was the first to obtain federal Tribal Land zip codes (longitudinal/latitudinal) for Tribal Chiefs from Seven Payson, PhD, Labor Economist, U.S. Department of Labor that has been merged with LIMBIC CENC data. David Shane Lowery, PhD, a cultural anthropologist with a focus on Native American studies currently at Brandeis University has agreed to be a collaborator and co-author on the TBI-SCD studies. Dr. Dismuke-Greer

has also initiated discussions with Christie Prairie Chicken, PhD, Director, Office of Tribal Health.

We worked on annual estimate of SCD for veterans with TBI vs no TBI. Results from the analysis follow:

- The mean SCD compensation for a large sample of (1.3 million) veterans was approximately $23,574 in 2022.
- For veterans with a TBI SCD, the mean compensation was $27,380, while the mean compensation was $23,281 for veterans without a TBI SCD.
- Army had the highest mean compensation for TBI SCD veterans ($28,054) and non-TBI SCD veterans ($24,713).
- Warrant Officer had the highest mean compensation for TBI SCD veterans ($31,934) and non-TBI SCD veterans ($26,991).
- 15-19 years of service compensation was higher in TBI SCD veterans ($33,322) than in the non-TBI veterans ($27,081).

Table 1. Distribution of Annual Compensation For Veterans with Any SCD and Stratified by TBI SCD

	N	Mean ($)	SD	SE (mean)	P25 ($)	P50 ($)	P75($)	IQR ($)
Overall	1,350,764	23,574.57	15,408.21	13.26	11,501.28	21,827.40	39,984.72	28,483.44
Branch Of Service								
Air Force	212,562	21,987.55	14,912.86	32.35	9,499.32	20,159.40	29,866.20	20,366.88
Army	683,459	25,018.67	15,552.77	18.81	12,921.24	23,117.16	42,214.08	29,292.84
Marines	212,918	22,592.03	15,182.09	32.90	10,047.36	21,341.16	33,042.24	22,994.88
Navy/Coast Guard	240,836	21,746.75	15,223.40	31.02	8,967.36	19,919.40	29,866.20	20,898.84
Other Branch	989	23,341.04	15,400.41	489.70	11,501.28	21,341.16	39,984.72	28,483.44
Rank								
Enlisted	1,221,881	23,610.62	15,403.76	13.94	11,501.28	21,827.40	39,984.72	28,483.44
Officer	110,870	22,590.63	15,334.25	46.05	9,615.36	21,339.36	39,984.72	30,369.36
Warrant	17,929	27,178.75	15,545.81	116.10	15,900.36	25,402.20	42,214.08	26,313.72
Missing	84	28,610.31	15,355.06	1,675.37	15,900.36	27,229.68	43,634.04	27,733.68
DoD Service Years								
< 10 years	740,381	21,121.15	14,772.90	17.17	8,667.36	19,391.40	28,446.24	19,778.88
10 – 14 years	382,843	26,381.98	15,637.53	25.27	14,568.36	24,425.16	42,214.08	27,645.72
15 – 19 years	208,942	27,318.71	15,522.35	33.96	15,900.36	25,314.24	42,214.08	26,313.72
Missing	18,598	21,389.52	15,824.72	116.04	7,336.68	18,359.40	39,984.72	32,648.04
TBI SCD								

No	1,254,162	23,281.42	15,336.45	13.69	10,479.36	21,341.16	39,984.72	29,505.36
Yes	96,602	27,380.46	15,825.82	50.92	15,900.36	24,425.16	42,214.08	26,313.72
No TBI SCD (Branch of Service)								
Air Force	206,799	21,880.59	14,860.16	32.68	9,099.36	19,919.40	29,442.24	20,342.88
Army	621,112	24,713.90	15,508.08	19.68	12,605.28	23,117.16	41,475.60	28,870.32
Marines	193,205	22,184.67	15,079.50	34.31	9,615.36	21,059.40	29,866.20	20,250.84
Navy/Coast Guard	232,073	21,608.59	15,143.03	31.43	8,967.36	19,919.40	29,442.24	20,474.88
Other	973	23,366.08	15,448.40	495.25	11,501.28	21,341.16	39,984.72	28,483.44
TBI SCD (Branch of Service)								
Air Force	5,763	25,825.78	16,235.91	213.87	14,525.28	23,405.16	42,214.08	27,688.80
Army	62,347	28,054.79	15,671.01	62.76	16,884.36	25,301.16	42,895.56	26,011.20
Marines	19,713	26,584.51	15,600.34	111.11	15,456.36	23,982.24	42,214.08	26,757.72
Navy/Coast Guard	8,763	25,405.84	16,808.29	179.55	13,421.28	23,117.16	41,475.60	28,054.32
Other	16	21,818.27	12,431.74	3,107.93	17,129.88	22,229.16	25,261.68	8,131.80
No TBI SCD (Rank)								
Enlisted	1,130,362	23,307.93	15,333.37	14.42	10,911.36	21,341.16	39,984.72	29,073.36
Officer	106,470	22,395.29	15,238.20	46.70	9,499.32	21,059.40	39,984.72	30,485.40
Warrant	17,251	26,991.85	15,530.58	118.24	15,900.36	25,402.20	42,214.08	26,313.72
Missing	79	28,065.60	15,511.73	1,745.21	15,900.36	26,177.16	43,634.04	27,733.68
TBI SCD (Rank)								
Enlisted	91,519	27,349.21	15,776.39	52.15	15,900.36	24,425.16	42,214.08	26,313.72
Officer	4,400	27,317.57	16,822.40	253.61	14,568.36	25,301.16	42,214.08	27,645.72
Warrant	678	31,934.28	15,184.06	583.14	21,827.40	39,984.72	43,634.04	21,806.64
Missing								

	5	37,216.61	10,098.29	4,516.10	28,870.20	42,214.08	44,954.40	16,084.20
No TBI SCD (DoD Service Years)								
< 10 years	678,192	20,765.55	14,695.95	17.85	8,079.36	18,359.40	27,597.12	19,517.76
10 – 14 years	357,597	26,027.49	15,534.73	25.98	14,568.36	24,425.16	42,214.08	27,645.72
15 – 19 years	200,991	27,081.20	15,439.58	34.44	15,900.36	25,301.16	42,214.08	26,313.72
TBI SCD (DoD Service Years)								
< 10 years	62,189	24,999.13	15,051.71	60.36	14,568.36	22,595.40	39,984.72	25,416.36
10 – 14 years	25,246	31,403.07	16,215.52	102.06	21,059.40	28,870.20	44,755.68	23,696.28
15 – 19 years	7,951	33,322.76	16,379.43	183.69	22,347.36	41,404.68	44,798.76	22,451.40

The Health Economics continued to work on annual estimate of service-connected disability (SCD) and VA compensation for veterans with TBI vs no TBI, including exploring military factors and TBI severity. Study information and analyses follow:

Aims:

1. Examine the association of military factors with a service-connected disability (SCD) designation for traumatic brain injury (TBI).
2. Estimate the annual VA SCD compensation for veterans with and without TBI SCD.
3. Analyze the association of military factors with monthly SCD compensation in Veterans with and without TBI SCD.

Methods: This is a retrospective, observational study. Data came from the DoD/VA Long-term Impact of Military-Relevant Brain Injury Consortium–Chronic Effects of Neurotrauma Consortium administrative data. Participants had a receipt of health care for ≥3 years in the DoD and for those who entered the VA, ≥2 years of VA care. Veterans with TBI index date between October 1998 and December 2020 were included. Participants were eligible for the cohort if they were veterans with any SCD designation. The primary outcome was SCD designation for TBI based on diagnostic codes:

- Residuals of TBI (8045)
- Neurocognitive disorder due to TBI (9304)

The secondary outcome was monthly compensation for each Veteran determined from VETSNET as of February 1, 2022.

TBI severity is measured in several ways:

- DoD ICD-9 or ICD-10 diagnosis code
- VA ICD-9 or ICD-10 diagnosis code
- Confirmation of TBI diagnosis based on CTBIE in VA after a positive TBI Screen in VA.

Results: Unadjusted median annual 2022 SCD compensation was $3,084 higher for Veterans with a TBI SCD ($24,425) than for Veterans without a TBI SCD ($21,341). Increasing TBI severity was associated with increasing odds ratios for TBI SCD. Increasing TBI severity was associated with increasing odds ratios for TBI SCD.
A TBI SCD was associated with $362 in monthly compensation in an unadjusted model and $45 in a fully adjusted model. After number of dependents, TBI severity was the most important predictor of SCD compensation. Despite having a lower odd of TBI SCD, females had higher monthly compensation than males ($47). Age at VA entry and

number of service years was associated with $1 and $0 additional monthly compensation.
In fully adjusted models, Army and Officer veterans were more likely to have a TBI SCD designation and deployment and combat exposure was associated with higher odds of TBI SCD. Despite having higher odds of TBI SCD, Officer veterans received significantly lower ($170) monthly compensation, relative to enlisted. Despite having the highest odds of TBI SCD after TBI severity (1.42), deployment was not significantly different from non-deployment for monthly compensation ($5). Combat exposure had the highest odds ratio after deployment (1.11) and was associated with about $46 higher monthly compensation.
Limitations: Limited to one year and used binary measure of TBI SCD. Additionally, we accounted for the number but not the type of other SCD conditions. TBI clinical severity were based on VHA and DoD ICD codes. We only have compensation information and not additional information on other benefits such as GI Bill.
Implications for VA Policy: VBA SCD TBI determinations for benefits are independent of VHA clinical TBI determinations for health care services. Veterans may not always understand why they may have a VHA clinical TBI and not a VBA SCD TBI. Compensation appears to align with TBI severity but not other military factors. If compensation is meant to compensate for civilian income, the median with or without TBI is well below the median civilian income for the US of $56,368.

Major Task 9: Examine the impact of TBI, its mechanisms of injury, and its comorbidities on VA health services utilization and cost, 2004-2018.

Month(s): *36 - 60*

Progress: Completed Year 4

a. Exposures have been categorized in the PLS data and are being merged with DoD and VA costs.

Exposures and VA Costs and Utilization:
BLUF: Almost half (47.51%) of the LIMBIC Veteran Cohort was exposed to IEDs. After IEDs with the highest mean number of exposures (0.810), the second highest mean number of exposures per Veteran was C4 (0.61). However, the highest adjusted TBI diagnosis exposure was airborne (OR 4.97), followed by fall (OR 4.45). Highest annual VA total and inpatient costs exposure, including VA facility and community care, was also airborne, followed by controlled detonation. However, highest annual VA outpatient costs exposure was bomb, followed by military vehicle collision. Interestingly in all cost categories, sports injuries were associated with significantly negative VA costs. This finding may reflect sports injuries occurring in generally healthier individuals.

We examined 8071 potential concussive event exposures self-reported for 1368 Veterans in the LIMBIC cohort and linked these exposures to LIMBIC TBI Diagnosis and VINCI cost data.
We examined type of exposure as well as the number of exposures as shown in Table 1.
We estimated a logit model of the association of types of exposure to a TBI diagnosis by LIMBIC clinical scientists as shown in Table 2. We adjusted for age, sex, race/ethnicity, education, marital status, military rank, and military branch.

We estimated a Generalized Estimating Equations of the association of types of exposure with VA annual costs of care since the Veteran entered the VA system of care, 2000-2022. All costs were adjusted for inflation to 2022 dollars. We adjusted for age, sex, race/ethnicity, education, marital status, military rank, military branch and LIMBIC TBI diagnosis determination.

Table 1: Number of Potential Concussive Event Exposures Per Veteran

Potential Concussive Event Exposure	Percent Exposed	Number of Veterans Exposed N (%)	# of exposures N	Mean Exposures per Veteran	Standard Deviation	(min, max)	Number of Veterans with TBI and Exposed N (%)
Artillery	14.11%	193 (14.1)	265	0.19	0.56	(0, 5)	158 (14.04)
Bomb	5.63%	77(5.6)	88	0.06	0.28	(0, 3)	66 (5.87)
C4	30.63%	419 (30.6)	839	0.61	1.09	(0, 6)	369 (32.8)

Controlled Detonation	13.74%	188	299	0.22	0.68	(0,10)	162 (14.4)
Fall	35.67%	488	663	0.48	0.77	(0, 5)	453 (40.27)
Grenade Including RPG	23.76%	325	425	0.31	0.63	(0, 4)	278 (24.71)
Hit By Something	33.99%	465	627	0.46	0.72	(0, 4)	421 (37.42)
IED	47.51%	650	1105	0.81	1.12	(0, 7)	573 (50.93)
Land Mine	6.87%	94	137	0.10	0.47	(0,10)	77 (6.84)
Mixture of Explosives	26.46%	362	576	0.42	0.84	(0, 9)	304 (27.02)
Mortar	34.43%	471	676	0.49	0.84	(0, 8)	393 (34.93)
Military Vehicle	40.5%	554	756	0.55	0.82	(0, 9)	502 (44.62)
Airborne/ Air Assault Including Parachute	8.33%	114	168	0.12	0.47	(0, 5)	109 (9.69)
Physical Assault	22.59%	309	407	0.30	0.64	(0, 5)	290 (25.78)
Rocket Including Missile	15.86%	217	277	0.20	0.52	(0, 4)	181 (16.09)
Sports	33.85%	463	655	0.48	0.79	(0, 5)	424 (37.69)
Uncontrolled Blast	4.46%	61	72	0.05	0.28	(0, 5)	51 (4.53)
Not Classified Above	2.49%	34	37	0.03	0.18	(0, 2)	28 (2.49)
All Exposures	100%	1368	8072	5.9	3.34	(1,24)	1125 (100)

Table 2: Adjusted Association of PCE Exposures With CENC-LIMBIC TBI

	Raw model			Adjusted Model		
Potential Concussive Event Exposure	**Odds Ratio**	**95% CI**	**P-Value**	**Odds Ratio**	**95% CI**	**P-Value**
Artillery	0.97	0.65, 1.44	0.884	0.92	0.61, 1.39	0.695
Bomb	1.31	0.68, 2.53	0.413	1.33	0.68, 2.61	0.403
C4	1.88	1.35, 2.63	0	**1.68**	**1.18, 2.39**	**0.004**
Controlled Detonation	1.4	0.9, 2.18	0.13	1.16	0.74, 1.83	0.514
Fall	4.01	2.75, 5.84	0	**4.45**	**3.02, 6.57**	**0.000**
Grenade Including RPG	1.37	0.97, 1.93	0.075	1.38	0.97, 1.98	0.077
Hit By Something	2.7	1.91, 3.83	0	**2.61**	**1.82, 3.74**	**0.000**
IED	2.24	1.67, 3	0	**2.14**	**1.56, 2.94**	**0.000**
Land Mine	0.98	0.57, 1.68	0.933	0.9	0.51, 1.58	0.704
Other Uncontrolled Blast	1.11	0.55, 2.21	0.775	1.2	0.59, 2.44	0.618
Mixture of Explosives	1.18	0.86, 1.63	0.313	1.22	0.87, 1.71	0.256
Mortar	1.14	0.84, 1.53	0.399	1.14	0.84, 1.55	0.396
Military Vehicle	2.96	2.13, 4.11	0	**3.26**	**2.31, 4.6**	**0.000**
Airborne Including Parachute	5.11	2.06, 12.65	0	**4.97**	**1.95, 12.68**	**0.001**
Physical Assault	4.09	2.52, 6.66	0	**4.14**	**2.52, 6.81**	**0.000**
Rocket Including Missile	1.1	0.75, 1.63	0.622	1.09	0.72, 1.64	0.690
Sports	3.16	2.2, 4.55	0	**3.06**	**2.1, 4.48**	**0.000**
Not Classified Above	1.01	0.41, 2.46	0.986	1.00	0.4, 2.51	0.997

Significant at P<=0.05 are in bold. Adjusted for age, sex, race/ethnicity, marital status, education, branch of service, service rank.

Table 3: Adjusted Association of PCE Exposures With Annual Costs, 2000-2022

	Raw Model	Adjusted Model

Potential Concussive Event Exposure	**Total**	**Outpatient**	**Inpatient**	**Total**	**Outpatient**	**Inpatient**
Artillery	1460 (-1385, 4305)	537 (-1271, 2346)	742 (-685, 2169)	$1502 (-1423,4427)	$575 (-917,2068)	$771 (-1061,2603)
Bomb	4132 (-900, 9164)	3436 (-127, 7000)	653 (-1381, 2688)	$4151 (-870,9171)	$609 (-1529,2747)	**$3536 (96,6975)**
C4	1945 (-147, 4038)	670 (-687, 2027)	1195 (77, 2314)	**$2448 (209,4686)**	**$1251 (37,2464)**	$1055 (-425,2536)
Controlled Detonation	4410 (658, 8163)	865 (-1116, 2846)	3208 (923, 5493)	**$4139 (439,7838)**	**$3053 (759,5346)**	$827 (-1033,2686)
Fall	1230 (-799, 3260)	247 (-1113, 1607)	857 (-133, 1848)	$1008 (-975,2991)	$889 (-88,1865)	$55 (-1263,1373)
Grenade Including RPG	2249 (-93, 4591)	937 (-672, 2545)	1222 (12, 2432)	$1975 (-372,4322)	**$1232 (13,2451)**	$637 (-983,2256)
Hit By Something	10 (-1995, 2016)	79 (-1288, 1446)	-68 (-1021, 885)	-$249 (-2235,1737)	-$78 (-1034,879)	-$127 (-1471,1216)
IED	1178 (-705, 3061)	349 (-970, 1667)	757 (-108, 1621)	**$2126 (60,4193)**	**$973 (-19,1965)**	$912 (-513,2336)
Land Mine	3364 (-2529, 9258)	3065 (-2348, 8479)	-35 (-1400, 1330)	$3243 (-2612,9098)	-$265 (-1659,1129)	$3112 (-2223,8447)
Mixture of Explosives	371 (-2109, 2850)	153 (-1802, 2109)	225 (-796, 1246)	$324 (-2109,2850)	$97 (-963,1156)	$289 (-1839,2418)
Mortar	304 (-1807, 2415)	1069 (-596, 2733)	-630 (-1485, 225)	$265 (-1794,2324)	-$656 (-1562,249)	$1032 (-519,2583)
Military Vehicle	3256 (1010, 5502)	2112 (365, 3859)	769 (-160, 1698)	**$2938 (726,5151)**	$791 (-142,1724)	**$1086 (108,3503)**
Airborne Including Parachute	7445 (2788, 12102)	1767 (-480, 4013)	5052 (1665, 8439)	**$7266 (2655,11878**)	**$5058 (1714,8402)**	$1763 (-456,3981)
Physical Assault	3259 (496, 6022)	571 (-1062, 2203)	2364 (860, 3868)	**$3474 (726,6222)**	**$2453 (925,3982)**	$657 (-923,2238)
Rocket Including Missile	817 (-1790, 3424)	366 (-1417, 2149)	545 (-646, 1735)	$790 (-1849,3428)	$526 (-686,1739)	$421 (-1379,2221)
Sports	-4541 (-6351, -2731)	-3311 (-4563, -2058)	-1175 (-2044, -307)	**-$3997 (-5848,-2145)**	**-$1309 (-2235,-383)**	**-$2644 (-3884,-1404)**
Uncontrolled Blast	2314 (-2995, 7623)	-216 (-2821, 2389)	1494 (-1742, 4729)	$2367 (-2927,7662)	$1397 (-1893,4688)	-$31 (-2551,2490)
Not Classified Above	1561 (-6462, 9584)	939 (-4003, 5882)	711 (-3267, 4689)	$2191 (-5692,10075)	$902 (-3187,4992)	$1338 (-3095,5771)

Note: 95% CI are included in parentheses. Significant at P<=0.05 are in bold. Adjusted for age, sex, race/ethnicity, marital status, education, branch of service, service rank, TBI diagnosis.

TBI, Cannabis Use Disorder, and Dementia

Aryan Esmaeili, MD, PhD (Dr. Dismuke-Greer's mentee) received a VA-ORD grant supplement to the VA-DoD LIMBIC: Health Economics Study to examine cannabis use disorder (CUD) and dementia in the LIMBIC TBI dataset. Dr. Esmaeili is submitting 2 articles to the journal: *Frontiers in Neurology*, Special Topic Issue:

Neurological and Neuropsychiatric Disorders Affecting Military Personnel and Veterans.

Information and analyses regarding Dr. Esmaeili's 2 manuscripts follow:

1. Is Cannabis Use Disorder a Contributor to Emergence of Cognitive Disorders in Veterans Diagnosed with TBI? (drafting manuscript)

Background: Cannabis is frequently used long-term to address chronic pain, sleep disturbances, and other persistent symptoms that commonly occur following traumatic brain injury (TBI). While evidence supports the link between TBI and cognitive disorders or dementia in Veterans, currently there is insufficient information on the impact of cannabis use on cognitive disorders. This study aimed to examine the incidence of cognitive disorders in Veterans with TBI and cannabis use disorder (CUD) and to evaluate the effects of both conditions on diagnoses suggesting cognitive disorders.

Methods: This retrospective cohort study used administrative data from the US Department of Veterans Affairs and the Department of Defense from the Long-term Impact of Military-Relevant Brain Injury Consortium-Chronic Effects of Neurotrauma Consortium Phenotype study. Diagnoses suggesting cognitive disorders were identified using inpatient and outpatient data in Veterans Affairs and Department of Defense. The incident cognitive disorders were identified as the diagnosis after the TBI index date and the patients were followed till September 11, 2022. We compared the differential cognitive disorders incidence in Veterans who had the following: 1) no CUD or TBI (control group), 2) CUD only, 3) TBI only, and 4) comorbid CUD and TBI (CUD & TBI). Kaplan-Meier analyses were used to estimate the overall cognitive disorders incidence in the above study groups. A Cox proportional hazards model was used to estimate crude and adjusted hazard ratios (HRs) for cognitive disorders controlling for demographics [e.g., sex, age, race/ethnicity, military characteristics] and comorbid health conditions [e.g., substance use disorder, headache, chronic pain, psychological/psychiatric disorders].

Results: A total of 1,560,556 Veterans (82.32% male, median [IQR] age at the time of TBI, 32 [16] years, and 61.35% white) were followed between 2003 and 2022. The cognitive disorder incidence rates were estimated as 0.68 (95% CI, 0.62, 0.75) for CUD only and 1.03 (95% CI, 1, 1.06) for TBI only per 10,000 person-months of observations, with the highest estimated cognitive disorder incidence observed in participants with both TBI and CUD (1.83 (95% CI, 1.72, 1.95)). Controlling for demographic and selected clinical conditions and relative to the control group, the highest hazard of progression to cognitive disorders was observed in Veterans with CUD-TBI (hazard ratio [HR], 3.32; 95% CI, 2.97, 3.72), followed by those with TBI only (2.35; 95 CI%, 2.16, 2.57) and with CUD (1.78; 95 CI%, 1.6, 1.99)

Discussion: The results of this analysis suggest that individuals with TBI or CUD may be at increased risk for cognitive disorders. Despite the highest cognitive disorders rates observed in the Veterans with TBI and CUD, the time to progression of cognitive disorders was less than expected, suggesting that TBI in combination with CUD may offer protective effects. A further study examining this relationship is warranted.

Table 1. Cognitive Disorder Incidence Rate (Overall and by TBI and CUD status), and Hazard Ratio of Dementia for CUD, TBI and Modifying Effect between TBI and CUD.

		Failures (Documented cognitive disorder)	IR (95% CI) per 10000 MO	Crude	Adjusted Model*
	Person-time			HR (95% CI)	HR (95% CI)
All types of cognitive disorder					
overall	190800000	9844	0.52 (0.51, 0.53)		
Control	136600000	4053	0.3 (0.29, 0.31)	Ref	Ref
TBI only	42558896	4381	1.03 (1, 1.06)	3.47 (3.33, 3.62)	2.35 (2.16, 2.57)
CUD only	6213722.8	423	0.68 (0.62, 0.75)	2.31 (2.09, 2.55)	1.78 (1.6, 1.99)
CUD-TBI	5386415.6	987	1.83 (1.72, 1.95)	6.21 (5.79, 6.65)	3.32 (2.97, 3.72)
EOD with disease					
overall	191300000	1053	0.06 (0.05, 0.06)		
Control	136800000	646	0.05 (0.04, 0.05)	Ref	Ref

TBI only	42866265	354	0.08 (0.07, 0.09)	1.75 (1.54, 1.99)	1.82 (1.35, 2.45)
CUD only	6237732.1	20	0.03 (0.02, 0.05)	0.68 (0.44, 1.07)	1.47 (0.92, 2.37)
CUD-TBI	5458252.4	33	0.06 (0.04, 0.09)	1.29 (0.91, 1.83)	2.82 (1.75, 4.54)
All other cognitive disorder (No EOD)					
overall	191100000	4307	0.23 (0.22, 0.23)		
Control	136700000	1529	0.11 (0.11, 0.12)	Ref	Ref
TBI only	42696148	2195	0.51 (0.49, 0.54)	4.61 (4.32, 4.92)	3.09 (2.73, 3.51)
CUD only	6228235.2	157	0.25 (0.22, 0.29)	2.27 (1.93, 2.68)	1.84 (1.54, 2.2)
CUD-TBI	5426337.5	426	0.79 (0.71, 0.86)	7.08 (6.36, 7.88)	4.03 (3.4, 4.77)

Abbreviations: HR= Hazard Ratio, IR= Incidence Rate, CI= Confidence Interval, EOD=Early Onset Dementia, TBI= Traumatic Brain Injury, CUD= Cannabis Use Disorder, MO=Months of Observations, Ref=References.
Note: The covariates included in the adjusted model: CUD, TBI, gender, age at the time of TBI, TBI severity, race, education, marital status, branch, rank, Rurality, service connected disabilities (percent), District, Headache, Chronic Pain, MAT (recent), Oncology, SMI, Depression, PTSD, Personality Disorder, Alcohol Use Disorder, Opioid Use Disorder, Other SUD, Nicotine Use disorder, anxiety, insomnia, CHF, Perivascular disease, Cardiac disease, Stroke, DM, DM with complications, convulsions disorders, Neurologic disorder (No Convulsions disorders), Liver Disease, and CKD.

2. The Economic Impact of Cannabis Use Disorder and Dementia Diagnosis in Veterans Diagnosed with Traumatic Brain Injury

Background: Studies have demonstrated that individuals diagnosed with traumatic brain injury (TBI) frequently use medical and recreational cannabis to treat persistent symptoms of TBI, such as chronic pain and sleep disturbances, that can lead to cannabis use disorder (CUD). Given the increased dementia risk associated with TBI alone and more recent findings that individuals with both TBI and CUD are at an even higher risk for dementia diagnosis, we sought to determine the Veterans Health Administration (VHA) healthcare utilization and costs associated with CUD and dementia diagnosis in veterans with TBI.

Methods: This observational study used administrative datasets from the population of Post-9/11 Veterans from the Long-term Impact of Military-Relevant Brain Injury Consortium-Chronic Effects of Neurotrauma Consortium. Veteran demographic and clinical characteristics, including CUD and dementia diagnosis, and associated healthcare service costs were identified using VA Informatics and Computing Infrastructure Corporate Data Warehouse and Health Economics Resource Center databases. We compared the differential VHA costs among the following cohort of veterans: 1) No CUD and No dementia diagnosis group, 2) Dementia diagnosis only, 3) CUD only, and 4) comorbid CUD and dementia diagnosis (Dementia & CUD). The association of Dementia and CUD status with VHA total costs (VA and non-VA facilities) from 2003-2021 were examined. Generalized estimating equations and negative binomial regression models were used to estimate total annual costs (inflation-adjusted) and incidence rate of healthcare utilization, respectively, by dementia diagnosis and CUD status.

Results: Data from 387,770 veterans with TBI (88.3% male; median [IQR] age at the time of TBI: 30 [14] years; 63.5% White) were followed from 2000 to 2020. Overall, we observed a trend of gradually increasing healthcare costs 5 years after TBI onset. Interestingly, in this cohort of veterans within 5 years of TBI, we observed substantial healthcare costs in the Dementia only group (peak= $46,808) that was not seen in the Dementia & CUD group. After controlling for sociodemographic/military characteristics and clinical conditions, relative to those without either condition, the annual total VHA costs were $3,367 higher in the CUD only group, while no significant differences were observed in the Dementia only and Dementia & CUD groups.

Discussion: Among this cohort of veterans with TBI, the findings suggest that those in the Dementia only group may be getting their healthcare needs met more quickly and within 5 years of TBI diagnosis, whereas veterans in the Dementia & CUD group are not receiving early care, resulting in higher long-term healthcare costs. Given increasing limitations on resources in all healthcare systems, it is important to identify effective clinical management approaches to optimize cost-efficient strategies for veterans with TBI who are at risk for dementia, including those with CUD. Further investigations should examine what impact the timing of dementia and CUD diagnoses have on specific categories of inpatient and outpatient care in VA and community care facilities.

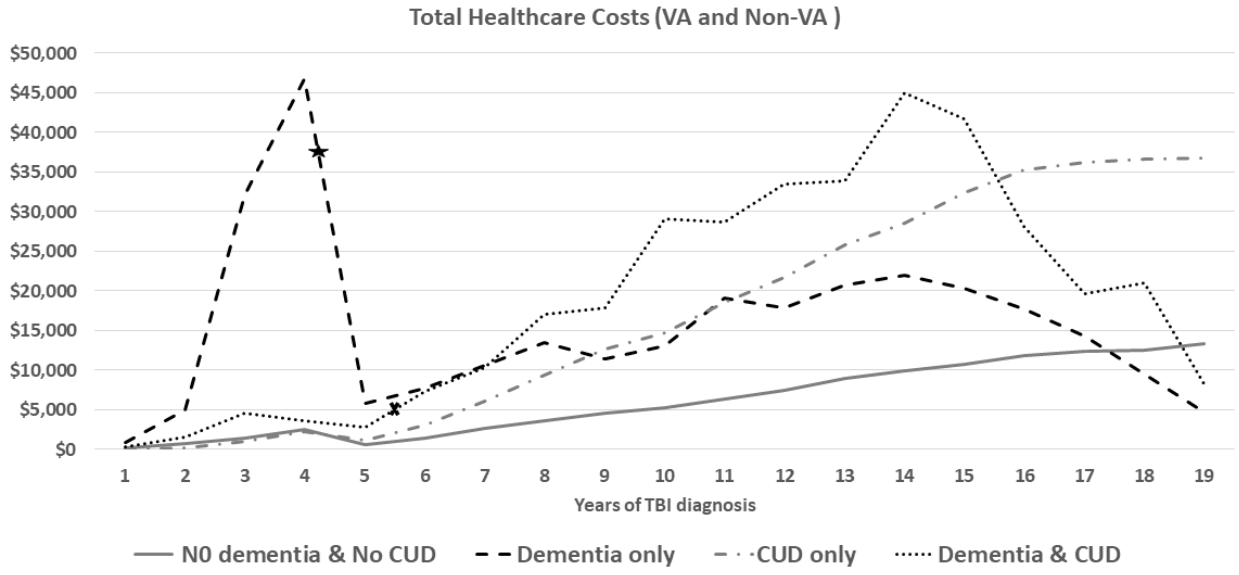
Table 1. The association between healthcare costs or utilization and CUD and dementia diagnosis status in Veterans with a history of TBI.

	Crude regression (Model 1)		Adjusted model (Model 2)		Confirmed dementia Adjusted model (Model 3)	
	Coefficient/IRR (CI%95)	p	Coefficient/IRR (CI%95)	p	Coefficient/IRR (CI%95)	p
Total healthcare costs, compared with No Dementia & No CUD group (Coefficient)						
No Dementia & No CUD	Reference		Reference		Reference	
Dementia Only	9,294 (4,747, 13,841)	<0.001	1,069 (-3,207, 5,344)	0.624	-347 (-3,025, 2,332)	0.8
CUD Only	10,840 (10,597, 11,084)	<0.001	3,367 (3,090, 3,645)	<0.001	3273 (3,000, 3,545)	<0.001
Dementia & CUD	12,515 (10,753, 14,278)	<0.001	-1,668 (-3,457, 120)	0.068	-115 (-3,108, 2,878)	0.94
Total healthcare utilizations, compared with No Dementia & No CUD group (IRR)						
No Dementia & No CUD	Reference		Reference		Reference	
Dementia Only	0.36 (0.35, 0.37)	<0.001	0.25 (0.24, 0.25)	<0.001	0.24 (0.24, 0.25)	<0.001
CUD Only	1.12 (1.12, 1.13)	<0.001	0.99 (0.98, 0.99)	<0.001	0.98 (0.98, 0.99)	<0.001
Dementia & CUD	0.38 (0.37, 0.39)	<0.001	0.25 (0.24, 0.26)	<0.001	0.26 (0.25, 0.27)	<0.001

Abbreviations: CUD= Cannabis Use Disorder, SCD=Service Connected Disability, TBI= Traumatic Brain Injury, MAT= Medication-assisted treatment, CHF= Congestive Heart Failure, CKD= Chronic Kidney Disease, PTSD= Post Traumatic Stress Disorder, SMI= Severe Mental Illness, DM= Diabetes Mellitus, IRR= Incidence Rate Ratio.

Note: We used the Generalized Estimating Equations model to estimate the healthcare costs by dementia diagnosis or CUD status. We used the Negative binomial regression model to estimate the incidence rate ratio of healthcare utilizations by dementia diagnosis or CUD status. The covariates included in the adjusted model: Year with TBI, gender, age at the time of TBI, TBI severity, race, education, marital status, branch, rank, Rurality, service connected disabilities (percent), District, Headache, Chronic Pain, MAT (recent), Oncology, SMI, Depression, PTSD, Personality Disorder, Alcohol Use Disorder, OUD, Other SUD, Nicotine Use disorder, anxiety, insomnia, CHF, Perivascular disease, Cardiac disease, Stroke, DM, DM with complications, Epilepsy, Neurologic disorder (No Epilepsy), Liver Disease, CKD, and death.

Figure 1. The average of annual total health care costs (VA and Non-VA) after TBI injury (time zero). The average time from TBI event to dementia diagnosis was 4.36 years for dementia-only (star) and 5.31 years for veterans with Dementia & CUD (x).



Major Task 10: Examine the impact of VA health services on survival and VA costs. VA costs will include inpatient, outpatient, pharmacy, and fee-basis payments to non-VA providers; Potential gender, racial/ethnic, and geographic inequities in MHS and VA health services utilization, SMs' military readiness and V's service connected disability and survival will be investigated.

Month(s): *36 - 60*

Progress: Completed Year 4

a. The racial/ethnic variables including important geographic residence in Native American Tribal

Lands has been identified and incorporated into Dr. Pugh's Phenotype databases. These databases already include death dates, and VA Service-Connected Disability Ratings. DoD and VA health services utilization and costs are in the process of being merged into the Phenotype databases.

DoD vs VA: LOS, ICU & Hospital Costs

This is the first study comparing rates of LOS, ICU, and hospitalization costs associated with TBI between military treatment factors (MTFs) and VAMCs during the same year (2020). It combines identical variables from both systems during the same timeframe and matching on TBI ICD diagnosis codes and TBI MS-DRGs enabled the ability to measure system differences in treatment and costs of TBI between MTFs and VAMCs.
Unadjusted death rates, LOS, ICU, and costs were compared with civilian hospitalizations for TBI based on Health Care Utilization Project data for 2020. Costs were adjusted for inflation to 2023 $.Adjusted models were used to estimate LOS, ICU, total cost, and cost per day.

DoD vs VA: Demographics, TBI Diagnoses, and MS-DRGs

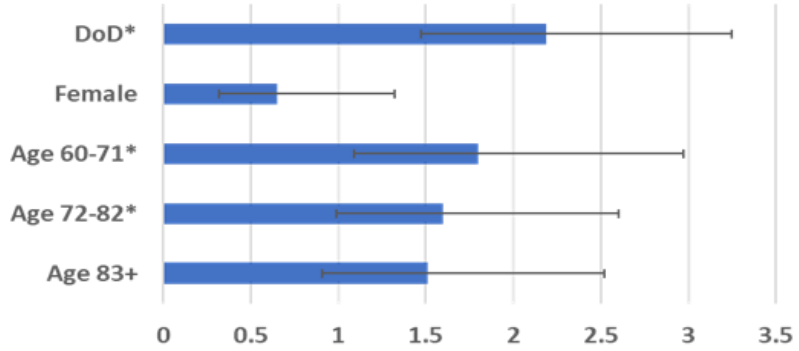
Individuals hospitalized with TBI in MTFs were much younger (44 yrs vs 73 yrs) and more likely to be female (10.7% vs 3.5%) than those hospitalized in VAMCs. Most frequent TBI diagnoses differed:

- *MTFs:* S06.5X9A-Traumatic subdural hemorrhage w/LOC, unspecified duration; S06.6X9A-Traumatic subarachnoid hemorrhage w/LOC, unspecified duration
- *VAMCs:* S06.5X0A-Traumatic subdural hemorrhage w/o LOC; S06.6X0A-Traumatic subdural hemorrhage w/LOC, unspecified duration
- Subdural hematomas common in both groups

Most frequent MS-DRGs differed:

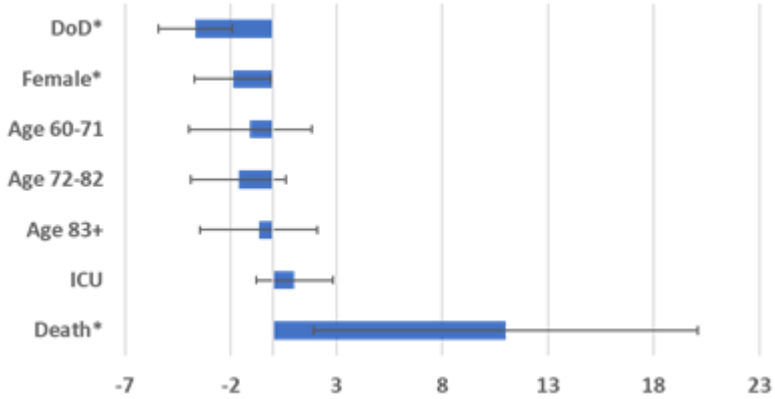
- *MTFs:* 90-Concussion w/o CC/MCC; 87-Traumatic Stupor and Coma <1 Hour w/MCC
- *VAMCs:* 86-Traumatic Stupor and Coma <1 Hour w/CC; 85-Traumatic Stupor and Coma <1 Hour w/MCC

Odds of ICU utilization (2.19 Odds Ratio) higher at MTFs



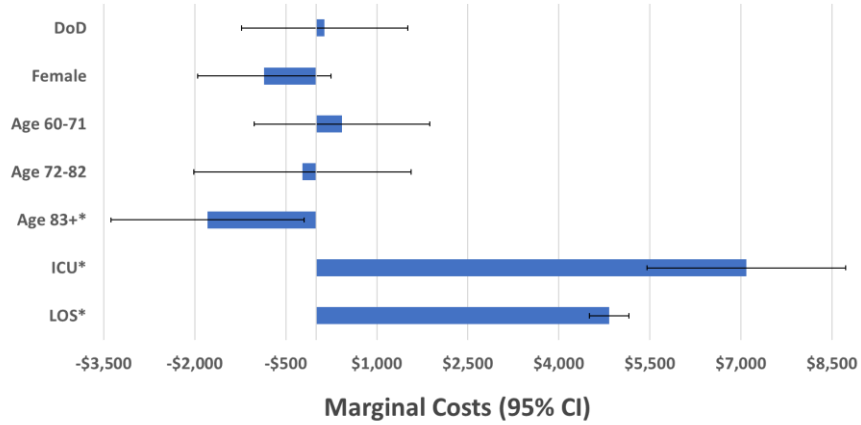
Intensive Care Unit Odds Ratio (95% CI)
*$P < 0.05$

Adjusted LOS (-3.67 days) lower at MTFs



Marginal LOS (95% CI)
*$P < 0.05$

No significant differences in adjusted DoD and VA costs



*$P < 0.05$

Comparison with Civilian TBI Hospitalizations
The unadjusted LOS for both MTFs (3 days) and VAMCs (4 days) were lower than for civilian TBI hospitalizations (6.7 days). The unadjusted hospitalization costs for MTFs ($13,548) and VAMCs ($23,084) were both lower than estimated hospitalization costs ($30,640) and actual charges ($137,622) for costs of TBI in civilian hospitals. The unadjusted civilian TBI in-hospital death (8.92%) was higher than in VAMCs (5.71%) and in MTFs (2.88%).

DoD has higher ICU and lower LOS than VA for TBI hospitalizations with no significant differences in in-hospital death or adjusted costs. Both DoD and VA have lower rates of LOS, costs, and in-hospital death than civilian hospitals. Results may suggest that DoD treats TBI more intensively and rapidly.

BeHEALTHY NIDILRR subgrant
For the BeHEALTHY NIDILRR subgrant, we've analyzed primary care, TBI, and polytrauma, including, comparing primary care between TBI vs no TBI and the mean, median utilization of TBI/Polytrauma for the TBI only group. Results from the analysis follow:

Table 1. Outpatient Visits by TBI Severity Based on the TBI Screen 2000-2021

Total Visits by patients's TBI status (LIMBIC cohort) between 2000-2021				
FINAL_TBI_SEVERITY	**Frequency**	**Percent**	**Cumulative Frequency**	**Cumulative Percent**
INITIAL SCREEN-HISTORICAL RESOLVED TBI	171930	0.47	171930	0.47
INITIAL SCREEN=POSITIVE WITH NO OTHER EVIDENCE OF TBI	1822678	5.02	1994608	5.49
MILD	5447574	15.00	7442182	20.49
MODERATE/SEVERE	1136916	3.13	8579098	23.62
PENETRATING	305162	0.84	8884260	24.46
POST-CONCUSSIVE SYNDROME	143528	0.40	9027788	24.85
UNCLASSIFIED	1497760	4.12	10525548	28.97
zNO EVIDENCE OF TBI	25801292	71.03	36326840	100.00
Total Visits by TBI status				

TBIcat2	Frequency	Percent	Cumulative Frequency	Cumulative Percent
0	27795900	76.52	27795900	76.52
1	8530940	23.48	36326840	100.00

Table 2. Frequency of Primary Care and Outpatient TBI/Polytrauma Visits in 2020 and 2021 by TBI Status

Primary care Polytrauma/TBI, Utilization in 2020 using stop codes					
Variable	**N**	**Mean**	**Std Dev**	**Minimum**	**Maximum**
AllVisit_freq	1651220	22.7931596	46.7640467	0	3228
primarycare_freq	1651220	4.6218136	6.9403431	0	1062
PolytraumaTBI_freq	1651220	0.1204128	5.242424	0	2804
Primary care Polytrauma/TBI, Utilization in 2020 using stop codes (TBI group)					
Variable	**N**	**Mean**	**Std Dev**	**Minimum**	**Maximum**
AllVisit_freq	387770	31.9451866	61.6220149	0	3228.00
primarycare_freq	387770	5.4914898	7.8634228	0	1062.00
PolytraumaTBI_freq	387770	0.4572969	10.1649506	0	2804.00
Primarycare Polytrauma/TBI, Utilization in 2021 using stop codes.					
Variable	**N**	**Mean**	**Std Dev**	**Minimum**	**Maximum**
AllVisit_freq	1651220	25.5513862	49.4442872	0	4666
primarycare_freq	1651220	5.5887998	7.7915596	0	1028
PolytraumaTBI_freq	1651220	0.1036458	3.5460429	0	1252
Primarycare Polytrauma/TBI, Utilization in 2021 using stop codes (TBI group)					
Variable	**N**	**Mean**	**Std Dev**	**Minimum**	**Maximum**
AllVisit_freq	387770	33.7928102	63.1617994	0	4666.00
primarycare_freq	387770	6.3717358	8.6185567	0	1028.00
PolytraumaTBI_freq	387770	0.3241458	5.9798478	0	1252.00

<u>Milestone:</u> Develop statistical analyses to economic and epidemiological models. (See tasks listed above)
<u>Milestone:</u> Submit manuscripts to be reported in a series of peer-review manuscripts in journals such as Brain Injury, Journal of Neurotrauma, Military Medicine, Health Equity, and Health Services Research. (See: Section 6 Products)
<u>Milestone:</u> Write reports for the Defense and Veterans Brain Injury Center (DVBIC), United States Army Medical Research and Development Command (USAMRDC), VA and CMTBIAC/VHA. (Nothing to report yet)
<u>Milestone:</u> Submit/Present results at DoD, VA, national and international TBI and neurotrauma meetings as well as rehabilitation meetings such as the ACRM, DVBIC, USAMRDC, VA, CMTBIAC/VHA. (Section 6 Products- Additionally, abstracts have been accepted for oral presentations at ACRM and VA HSR&D)

Novel Neuroimaging Study:
<u>Major Task 1: Assess available methods of overcoming variability introduced by differences in scanner hardware and software.</u>
<u>Milestone:</u> Examine phantom-based and statistical correction for variability introduced by scanner hardware and software.

Month(s): *1 - 60*
Progress: We have implemented an adapted method of decentralized ComBat, for which University of Utah has been be a beta testing site using the LIMBIC data to overcome site differences; we have begun to

implement and the new pipeline..

We had previously identified another novel method of data harmonization using a technique developed by colleagues at Brigham and Women's Hospital (BWH) which is being applied in other consortia. We continue our collaboration with this group and with others in the InTBIR and ENIGMA communities to complete our implementation of this method. This has been somewhat delayed due to a prolonged family illness of one of the key investigators, but we have resumed our work on this.

Drs. Wilde, Tate and Dennis have acted as special editors for two special issues related to harmonization which were complete during this performance period (*Neuropsychology* and *Frontiers in Neurology*). Members of the Core participated in 3 manuscripts in the *Neuropsychology* SI, which addressed methods to harmonize PTSD scales, cultural considerations in harmonization, and general considerations in harmonization of outcome measures. Members of the Core also participated in two manuscripts for the *Frontiers* SI, which focused upon harmonization in imaging.

This task remains in progress, and we will explore additional harmonization techniques over the next review period.

Major Task 2: Critically examine and compare strengths and limitations of commonly used imaging analysis pipelines.

Milestone: Using data collected as part of CENC, results of comparisons of data analysis pipelines will be submitted as one or more manuscripts for publication.

Month(s): *1 - 12*

Progress: In addition to the standard "Core" pipelines that we have been using as part of LIMBIC-CENC, we have identified several additional pipelines that we are continuing to investigate. We have continued our work with Drs. Stone, Tustison and Avants to utilize their SyMLR method, and are in the process of reviewing and refining those results (now with the opportunity to expand biomarker results). During the performance period, we performed analysis on an additional 750+ scans form LIMBIC-CENC which had been more recently acquired. We are also leveraging work on a NIH R61/R33 project to build a novel pipeline for both structural and functional imaging analysis; University of Utah/SLC VA is the primary beta test site for this, and LIMBIC data has acted u as test data for the new standardized pipeline (HALFPIPE). We have complete analysis of LIMBIC-CENC data and created a resource for internal (and external) investigators wanting to use the output.

Major Task 3: Develop and test aspects of pre-processing which enhance accuracy and consistency.
Milestone: Extend efforts to critically examine pre-processing approaches which may enhance accuracy and consistency (i.e. attenuate distortion artifacts in diffusion imaging).

Month(s): *1 - 60*

Progress: Progress: We are continuing our comparison of distortion correction pipelines and tools in analysis of diffusion imaging; this work is ongoing, but we have identified what we believe to be the optimal solution and are preparing a manuscript based on this work.

Major Task 4: Create and refine novel, automated pipelines to address aspects of imaging analysis which are currently absent or incomplete.

Milestone: Further refine CENC pipelines including an automated analysis pipeline for detection and analysis of white matter hyper-intensities as well as pipelines for volumetric, diffusion and functional connectivity, separately as well as in combination.

Month(s): *1 - 24*

Progress: The WMH pipeline has been updated and we are in the process of applying this to a larger set of data collected under LIMBIC-CENC (recently updated analysis to include additional participants). This has largely been completed as part of our work with the SiMLR analysis team, but we are examining the data for completion and adding additional data that has been collected since we last analyzed data. Pending receipt of additional biomarker data, we will perform analysis examining the relation of these findings to clinical injury and outcome data.

Major Task 5: Incorporate elements of advanced statistical analysis (e.g., Bayesian analysis, machine learning) to

utilize multi-modality imaging data in conjunction with other injury, demographic and outcome data to develop subgroups/phenotypes and identify related variables in those at highest risk for poor outcome.
Milestone: Initial analysis of existing CENC Study 1 data; interim and final analysis of imaging data utilizing sophisticated Bayesian and machine learning models to identify phenotypes and the most salient imaging-derived components that may predict high risk for future outcome.

Month(s): *1 - 60*

Progress: We have performed additional analyses examining the use of advanced statistical analysis in existing LIMBIC-CENC data, particularly with regard to diffusion imaging findings. We have initiated a collaboration with Dr. Amanda Meija at Indiana University to incorporate additional Bayesian modeling.

Major Task 6: Assess merits and challenges of existing methods of "individualized" data analysis.
Milestone: Perform a critical review and testing of existing methods which target "individual" analysis to determine their clinical utility for diagnosis, treatment planning and evaluation of treatment response.

Month(s): *36 - 60*

Progress: The aforementioned collaboration with Dr. Meija will also address this goal as her methods reflect an individualized approach to data. Furthermore, we are working on individualized analysis methods that are available for resting state data using the HALFPIPE software. We are convening additional team meetings to review other methods of analysis that have been used in imaging to address this issue.

Major Task 7: Share data with external investigators; Biannual submission to FITBIR (March and September).

Month(s): *6 – 60*

Progress: We prepared and submitted the imaging data for the scheduled March and September submissions. Please see the Neuroimaging Core report for additional information.

We are working with members of the LIMBIC Data and Biostatistics Core as well as the Biomarkers Core to propose and design additional analyses. Neuroimaging Core members are involved in a number of data request submissions.

Neuroimaging Core investigators lead and support the ENIGMA Military Working Group; we are also involved in communication with TRACK-TBI, InTBIR and the NIH-sponsored classification of TBI initiative. Please see the Neuroimaging Core report for additional information.

Biomarker Discovery Study:

Major Task 1: Obtain pre-deployment biospecimens from the DoD biorepository to assess pre-injury levels of candidate biomarkers in the CENC longitudinal cohort.

Month(s): *1 - 36*

Progress: Still in the process of obtaining pre-injury serum samples from DoD serum biorepository. We are working with the Coordinating Center and the DBC to complete this project.

Major Task 2: Carry out biomarker discovery project (N = 2000) of Prospective Longitudinal Study participants, expanding initial project CENC study 1 initial participants.

Month(s): *1 - 36*

- ***Progress:*** Completed assays of 4 proteins (t-tau, NfL, GFAP & UCH-L1) on samples from 871 participants (328 baseline and 462 follow-up blood draws) for a current total of 4-plex proteomic measures on 1,720 (1,206 previously tested) PLS participants (1,729 baseline with 462 longitudinal follow-up measures) Prospective Study participants.

Major Task 3: Examine candidate protein biomarkers in plasma/serum, centrally-derived exosomes, saliva that were tested initially from both prospectively collected chronic TBI and pre-deployment (pre-injury) samples of Prospective Longitudinal Study cohort.

Month(s): *1 - 36*

Progress: Preparing/submitted the following manuscripts/abstracts by analysis

Analysis of baseline biomarkers of full cohort under way and anticipate 3 manuscripts based on baseline

proteomic biomarker analysis (NfL, tau, GFAP, p-tau, IL-6, IL-10 & TNF-α) in the next year. Currently, finalizing results of candidate biomarker associations with PTSD symptoms and sex as well as 2-3 manuscripts lead by LCDR Kent Werner on proteomic biomarkers of mTBI and poor sleep. These analyses are completed and manuscripts are being reviewed for submission.

5 analyses ongoing:

- Cohort analysis: 4 proteins (4-plex) & outcomes; working with imaging and informatics for multimodal proteomic and imaging analyses on full cohort; just completed 4-plex measures on 1,720 baseline and 460 follow-up PLS participants to include in analyses. Laboratory data has been cleaned for quality, and is now being integrated into databases to be used for analyses
- DTI-NfL- previously based on 660 from sites using GE MRI. Waiting for clinical data to correlate with NfL measures on 1,720 baseline and 460 follow-up PLS participants that was recently completed.
- Volumtrics-NfL- analysis in prep of smaller discovery set (195 samples). See associations between volume loss and increased NfL.
- rsfMRI- sleep dysfunction- selected tracts of interest and launching analysis of up to 1,720 baseline PLS participants.
- Analysis of Sleep measures, cardiovascular and longitudinal MRI features (PVS, WML, DTI, fMRI)- Analysis under design.

Major Task 4: Test additional candidate protein biomarkers of chronic TBI as they are identified (e.g.orexin, c-reactive protein, among others).

Month(s): *1 - 36*

Progress: Collaborating with Roskamp Institute for lipidomic analysis on Biomarker Discovery set. We are implementing a non-hypothesized based approach to identify novel markers, and pathways, so that we can then develop or optimize assays to undertake within the entire cohort. This method has been developed in the laboratory, and will be used in this cohort.

Major Task 5: Correlate candidate biomarker levels from pre-deployment and post- TBI specimens, as well as with outcome measures (neurobehavioral, imaging, neurocognitive testing).

Month(s): *1 - 36*

Progress: We have worked with the phenotyping core, and leadership to make required changes to consents, to obtain the data required to pull samples from the DoD Biorepository. Now that this is in place, we are engaged with the DoD Biorepository to identify samples, and to have these pulled and sent to the Biomarker Core to undertake planned assays in pre-deployment/pre-injury samples for longitudinal analysis (pre and post injury).

Major Task 6: Correlate serial candidate biomarkers (in pre-deployment and serial samples) with neurodegeneration as symptoms/signs develop among Prospective Longitudinal Study cohort to identify unique prognostic biomarkers of chronic neurotrauma outcomes.

Month(s): *1 - 36*

Progress: Correlations of candidate prognostic biomarker correlations with symptoms and outcomes underway. *Completed assays of 4 proteins (t-tau, NfL, GFAP & UCH-L1) on 1,720 Prospective Study participants and serial measures on 462 PLS participants. Working with PLS PIs to identify informative PLS participants for longitudinal assessments (e.g. interval documentation of cognitive decline since enrollment in LIMBIC study)

- *Milestone: Carry out blood and saliva biomarker assays from all subjects with baseline specimens in the biorepository.*
- *Progress:* Completed baseline samples with 4 plex. Analysis under way as described in Tasks 1 & 2 above.
- *Milestone: Carry out candidate biomarker correlations with TBI status (repetitive versus mTBI with LOC versus blast versus no TBI), pre-deployment/pre-injury biomarker levels, neurobehavioral symptoms, advanced imaging, neuropsychological testing, serial biomarker levels among small cohort with incident*

neurodegenerative disorder (e.g. dementia).

- *Progress*: Completed baseline samples with 4 plex. Working with PLS and Data and Biostatistics Core to identify participants for informative serial candidate biomarker testing.
- *Milestone: Develop panel of prognostic biomarkers for each phenotype of chronic neurotrauma (e.g. dementia, headache, PTSD, sleep disorder).*
- *Progress:* This task is dependent on completion of Tasks 1-7

Major Task 7: Carry out GWAS using case-control assessment in discovery set using multi-chip array among subset of CENC Prospective Longitudinal Study subjects and large DoD or VA GWAS databases for each chronic TBI phenotype (e.g. dementia, PTSD, etc).

Month(s): *12 - 60*

Progress: Waiting for collection of sufficient number of DNA samples for analysis (minimum 2,000). Carry Forward Request was submitted to VCU to carry over year 3 GWAS funds into Year 4. Will collaboratively carry out GWAS testing through the Broad Institute with GAIN and/or Minnesota VA under LIMBIC year 4 funding once 2,000 DNA samples extracted and available for GWAS testing.

Major Task 8: Validate GWAS results in independent validation cohort of Prospective Longitudinal Study subjects for each chronic TBI phenotype studied.

Month(s): *12 - 60*

Progress: Pending completion of Task 7.

Major Task 9: Calculate risk ratios and Manhattan plot, controlling for multiple comparisons.

Month(s): *12 - 60*

Progress: Pending completion of Tasks 7 & 8.

- *Milestone: Carry out and complete case-control GWAS assessment.* Pending completion of Tasks 7 & 8.
- *Milestone: Correlate GWAS results with individual chronic Neurotrauma outcome (e.g. dementia, headache, PTSD).* Pending completion of Tasks 7 & 8.
- *Milestone: Develop polygenic risk scores (PRS) of genetic risk factors for chronic neurotrauma outcomes.* Pending completion of Tasks 7 & 8.

Major Task 10: Carry out DNA methylation studies on 200 CENC samples, to examine genetic influences of unique neurobehavioral TBI outcomes (e.g. dementia, sleep disorder, PTSD).

Month(s): *24 - 60*

Progress: To be launched during funding year 5. We are currently selecting a sub-cohort to examine for this task. We have worked to set up the laboratory protocol to examine this, and plan to measure methylation and acetylation of genes of interest, that are known to be related to brain injuries and psychiatric symptoms, including PTSD and depression.

Major Task 11: Carry out and extend exosomal microRNA analysis of CENC Prospective Longitudinal Study cohort based on preliminary results from CENC biomarker discovery project.

Month(s): *24 - 60*

Progress: To be launched during funding year 5. The laboratory protocol for these assays. Specifically, we will do extraction using our standard protocol, and then nanostring using the assay best covering the most candidates, which includes 830 microRNAs.

Milestone: Carry out DNA methylation study on extracted DNA from 200 subjects in longitudinal study and associate methylated genes with chronic TBI outcomes.
Milestone: Carry out validation microRNA analysis of miRNA biomarkers identified in the CENC biomarker discovery project (in process).
Milestone: Develop panel of miRNA biomarkers associated with chronic TBI outcomes.

Major Task 12: Share data with external investigators; Biannual submission to FITBIR (March and September).

Month(s): *6 - 60*
Progress: Completed by the VCU DBC team.

What opportunities for training and professional development has the project provided?
If the project was not intended to provide training and professional development opportunities or there is nothing significant to report during this reporting period, state "Nothing to Report."

Describe opportunities for training and professional development provided to anyone who worked on the project or anyone who was involved in the activities supported by the project. "Training" activities are those in which individuals with advanced professional skills and experience assist others in attaining greater proficiency. Training activities may include, for example, courses or one-on-one work with a mentor. "Professional development" activities result in increased knowledge or skill in one's area of expertise and may include workshops, conferences, seminars, study groups, and individual study. Include participation in conferences, workshops, and seminars not listed under major activities.

Prospective Longitudinal Study: Dr Walker and Dr Cifu along with other senior investigators continued to mentor multiple LIMBIC junior investigators on PLS dataset analytic, publication, and dissemination work. Over this reporting period, these mentees included Dr. Becky Gius, Dr. Randel Swanson, Dr. Christina Sheerin, Dr. Susan Van der Veen. Several efforts are highlighted below:

- Kelsee Stromberg, PhD
    - Dysregulated Behavior. Analyses completed; manuscript submission pending.
- Randall Swanson, DO, PhD
    - Traumatic and Treatable Vascular Pathology in the Outcome of TBI. VA CDA grant leveraging LIMBIC-CENC PLS data. Work progressing
- Christina Sheerin, PhD.
    - Functional relations between alcohol use and mental health in the wake of the COVID-19 pandemic. NIH K01 award supplement leveraging LIMBIC-CENC PLS data. Work progressing.
- Brennan Wright, MD
    - Aerobic exercise after chronic mTBI and relation to cognition and well-being. Manuscript accepted; in press.
- David Garavito, PhD.
    - Gist and Verbatim Memory Performance in Vs Exposed to Combat and mTBI. Analysis nearing completion.
- Sarah W. Clarke, PhD
    - 2nd author on newly published manuscript "Headache among combat-exposed veterans and service members and its relation to mild traumatic brain injury history and other factors: a LIMBIC-CENC study".
- Andrew Hwang
    - Lead investigator on: Use of Real-Time Ambient Noise Monitoring in Conjunction with Automated Method for Testing Auditory Sensitivity (AMTAS)
- Jillian Ory
    - Lead investigator on: Relationship Between Self-Reported Demographics and Healthcare Use in Combat Deployed Veterans with Mild Traumatic Brain Injury
- Austin Miller, BS (medical student at Alabama College of Osteopathic Medicine)
    - mentored his work on literature review and manuscript writing for a soon to be submitted review paper that he is lead author on: "Blast-related mild TBI: LIMBIC-CENC focused review with implications commentary"
- Samuel Walton, PhD, ATC
    - Lead investigator for: Exploring Demographic and Social Determinants of Cognitive Brain Health Among Military Service Members and Veterans with and without a History of Mild Traumatic Brain

Injury.
- Lead investigator for: Associations Among Exercise, Mild Traumatic Brain Injury, and Imaging Biomarkers of Brain Health in Military Service Members and Veterans.
- Coauthor on multiple LIMBIC-CENC PLS manuscript submissions and publications

Health Economics Study: Grant: Staff member Dr. Aryan Esmaeili received a 2-year VA ORD research supplement to promote diversity ($191,180 at 75% effort), "Supplement to: VA-DoD Long-Term Impact of Military-Relevant Brain Injury Consortium (LIMBIC): Health Economics Study" (I01HX003155-01). A summary of the proposed work follows: After the legalization process, the availability of Cannabis and cannabinoids have increased, but their efficacy and safety profile in individuals with Traumatic Brain Injury (TBI) is uncertain. Substance use is also a common long-term issue in patients with TBI. Previous neuroimaging studies showed both patients with TBI and chronic use of Cannabis have similar structural changes indicating dementia. By conducting this study, we intend to address the role of Cannabis Use Disorder (CUD) in the progression to dementia in Veterans diagnosed with TBI, along with the economic burden of comorbid TBI-CUD-dementia.

Retrospective Database Study: Two junior investigators, Erica Kornblith, PhD, and Yue Leng, PhD, have worked with the study team and completed projects resulting in three published manuscripts. In Year 3 we brought on two new junior investigators, Andrea Schneider, MD, PhD, and Jennifer Albrecht, PhD., and their project analyses are now published. In Year 4 we collaborated with another junior investigator, Carolyn Gibson, PhD. All are collaborating with our experienced team of researchers, gaining knowledge about traumatic brain injury, Veteran's health, and working with large administrative datasets.

Phenotype Study: One junior investigator (Dr. Eamonn Kennedy) is leading phenotyping analyses on the Phenotype study and parallel studies using PLS data. A Post-doc (Samin Panahi PhD) was also instrumental in completing those analyses. A doctoral student (Kelsee Stromberg) led a paper that is currently under review for the Frontiers special issue. A junior investigator (Krista Ocier PhD) is leading the PD paper and a doctoral student (Ace Adamson) is leading the MS Paper.

How were the results disseminated to communities of interest?
If there is nothing significant to report during this reporting period, state "Nothing to Report."

Describe how the results were disseminated to communities of interest. Include any outreach activities that were undertaken to reach members of communities who are not usually aware of these project activities, for the purpose of enhancing public understanding and increasing interest in learning and careers in science, technology, and the humanities.

Data and Biostatistics Core: Knowledge translation products and other updates/information shared on LIMBIC-CENC website.

Prospective Longitudinal Study:

- Conventional scientific community dissemination activities are listed in the preceding sections, which includes peer-reviewed journal publications and scientific meeting presentations including posters, oral paper presentations, and topical seminars.
- A wide range of dissemination activities and product development took place in collaboration with the LIMBIC KT center targeting all stakeholders including the scientific community, SMs and Veterans and their families, and the public. This includes an ongoing podcast series that has included data and findings from the LIMBIC-CENC PLS. Details are provided in the KTC section of this report which can be further supplemented by visiting the LIMBIC-CENC Website.
- In addition, Dr Walker presented the following Cyberseminar: William C. Walker. National presentation (Cyberseminar) for Veterans Affairs (VA) Health Services Research & Development Service (HSR&D) entitled "Cognition and mild TBI history: Recent findings from the LIMBIC-CENC prospective study

along with clinical translation". Dec 06, 2022.
- The LIMBIC Consumer Advisory Board (CAB) participated by giving feedback on the development of the KT products and website design. Details on the LIMBIC CAB is provided elsewhere in this report..

Health Economics Study: The PI has published one TBI study as lead author in Brain Injury and two TBI studies as co-I. She has 2 studies on TBI as lead author under review. She has 3 studies on TBI as co-I under review. She presented one poster on TBI as co-I at MHSRS. She has presented DoD Data Bootcamp including an example from DoD TBI cost data. She has submitted a VA/DoD JIF proposal for a cost dashboard with a DoD co-I including TBI cost. She will be presenting an oral presentation on TBI cost as a lead author at ACRM in November and has 3 TBI cost abstracts accepted for the HSR&D conference in 2023.

Phenotype Study: Dr. Pugh presented phenotype findings at the Brain Trauma Blueprint Action Summit (Panel Discussion; Dr. Pugh) October 18-19, 2022.

What do you plan to do during the next reporting period to accomplish the goals?
If this is the final report, state "Nothing to Report."

Describe briefly what you plan to do during the next reporting period to accomplish the goals and objectives.

CORES

Coordinating Center: In the next year, the Coordinating Center will accomplish the following:
1. Continue working on HRPO and IRB continuing reviews.
2. Continue working with PLS sites on recruiting methods as we get closer to the goal of 3000 participants.
3. Continue working with the CAB in order to garner feedback and forward recommendations to Consortium Leadership.
4. Now that VCU has lifted travel restrictions, schedule trips to all 11 PLS sites.
5. Continue the Site Metrics.
6. Continue working towards CRADA finalization and approval.
7. Complete the process of requesting a No Cost Extension.
8. Plan and conduct a "State of the Science" event, either virtual or in-person during the next year.

Data and Biostatistics Core: In the next year, the DBC will accomplish the following:
1. Continue SEO optimization of LIMBIC-CENC website and other KT products
2. Continue QA/QC of data.
3. Continue development of snapshot data sets for data cubes.
4. Continue development of analytic data sets for investigator data requests.
5. Continue central biostatistics support.
6. Maintain and upgrade integration of data dictionary on the LIMBIC-CENC website as needed.
7. Continue FITBIR Ops and preparation of FITBIR data for the next submission.
8. Continue development and preparation of the core VINCI data sets linkage with LIMBIC data sets for comprehensive research and data analyses by investigators
9. Continue to expand operational support via website applications (i.e., Study Portal)

Biomarkers Core: In the next year, the Biomarkers Core will accomplish the following:
1. Continue receiving and storing locally processed LIMBIC biospecimen samples into biorepository as collected.
2. Maintain inventory of LIMBIC-CENC BR samples and validate BSI database with Medidata through VCU informatics.
3. Continue to carry out NED screening at baseline visits of participants in the Prospective Study
4. Continue to carry out DNA extraction and APOE genotyping at baseline visits of participants in the

Prospective Study who give permission for genetic testing on their blood specimen.
5. Continue to make LIMBIC-CENC samples available for LIMBIC-CENC related studies as sufficient samples are obtained and as approved by the procedures outlined and approved by the USUHS IRB.
6. As approved, move the Biorepository to WRAIR
7. Provide samples for an epigenetic study in 200 subjects.
8. Perform the genotyping, including exploring additional samples for microRNA within exosomes at WRAIR under Discovery rather than at the Biorepository.
9. Continue to meet with the DoD Biorepository to obtain pre-deployment samples.

Neuroimaging Core: In the next year, the Neuroimaging Core will accomplish the following:
1. Upload of the next installment of FITBIR data, planned for March and September 2024.
2. Continue to monitor quality assurance, as above.
3. Continue to perform and update analysis of imaging data on standard pipelines, as above, with re-analyses as new software versions are released.
4. Continue to assist in preparation of data requests, distribution of data for approved requests, and integration of imaging data with other consortium data.
5. Ongoing coding of CDE imaging data.
6. Annual refresher training and monitoring of site compliance with SOP
7. Continue to participate in joint meetings with the PLS study team, Data Core, Biostatistics Core, and Biomarker Core.
8. Continue to assist in sequence parameter adjustment following software and hardware upgrades or changes.
9. Completion of additional manuscripts which are currently in preparation.

STUDIES

Prospective Longitudinal Study: In the next year, the Prospective Longitudinal will accomplish the following:
1. Continue to excel in recruitment, enrollment, retention, and study visit completions to achieve or surpass target rates of study enrollments and maintain high follow-up visit completion rates across all sites.
2. Continue to monitor metrics for #1, provide feedback, and take corrective actions as needed.
3. Continue to discuss and share and deploy across consortium best practices for recruitment and retention.
4. Continue efforts and success with scientific analysis and dissemination activities. This includes a goal of submitting for publication our first major scientific analysis of longitudinal data (rate of change of cognition using annual BTACT data).

Retrospective Database Study: In the next year, the Retrospective Database Study will accomplish the following:
1. Publish manuscript on Intimate Partner Violence and TBI in Veteran men and women.
2. Draft and submit manuscript with prognostic model for dementia and mortality after TBI.
3. Initiate collaboration with Dr. Dismuke examining health utilization and comorbidities after TBI
4. Begin project on psychiatric and medical comorbidities in older Veterans with TBI.
5. We will start other new collaborations, particularly with junior investigators on novel projects with our database of more than 2.2 million Veterans.
6. We will continue regular group meetings between investigators and regular reporting on LIMBIC consortium calls, the DoD report, and at the Government Steering Committee meetings.

Phenotype Study: In the next year, the Phenotype Study will accomplish the following:
1. Complete LCA analyses of DoD data and DoD+VA data and submit paper on DoD LCA analyses.
2. Complete substance use disorder phenotypes and draft paper.
3. Add to dataset as data become available.
4. Work with VINCI to place server behind VA firewall to facilitate machine learning analysis.
5. Conduct machine learning analyses
6. Continue work with Millennium Cohort collaborators on subconcussive blast related MOS papers Complete

Paper focused on substance use disorder in distinct TBI phenotypes.

Health Economics Study: In the next year, the Health Economics Study will accomplish the following:
1. The Health Economics team will continue to conduct analyses of combat and training exposures with service-connected disability, health services utilization and costs using the merged Longitudinal Study and VA data. Teams will be created for manuscripts to create models, estimate models, and report results for 1) VA utilization and costs 2) DoD utilization and Tricare costs.
2. The Health Economics team will draft manuscripts on VA costs for veterans with TB, including 1) SCD and exposure to TBI, 2) return to duty analysis and exposure to TBI, 3) TBI + SCD compensation and race and ethnicity, and 4) TBI + SCD compensation and military factors.
3. The Health Economics team will submit 2 manuscripts on cannabis use disorder and TBI to the Journal of Neurology.
4. Continue working to improve our cost comparison dashboard across VA, DoD, and private sector.
5. Continue collaboration with Dr. Pugh's Phenotype study at SLC with plan to pull VA costs (economic cost and encounter for cohort and pull-out VA inpatient, outpatient, pharmacy cost, then non-VA facilities costs like DOD), DOD costs, and benefits data (data source is USVETS database).
6. In process of comparing DOD ICD TBI with PLS VCU TBI determination
7. Merge theater-type of injury (battle/non-battle), exposure (blast/non-blast) and outcome (return to duty, quarters, evacuated, etc.) with Phenotype data.
8. Complete incorporation of DoD and VA utilization and cost data, theatre data on injuries and outcomes, and MTF data on sick days into Phenotype data.
9. Merge and analyze DoD cost data with PLS weapons and other exposures.
10. Examine associations of TBI, SM and Veteran demographics, and military characteristics with DoD and VA costs
11. Continue to work with VA (Houston, Salisbury, San Diego, Portland, Boston, Richmond, Tampa, Portland, Minnesota, San Antonio) and DOD sites (Fort Gordon and Fort Belvoir's military treatment centers) to receive site data and SSN and EDIPIN, respectively.
12. Collect LIMBIC-CENC participants names from the VA Volunteer COVID-19 Registry and send subject contact information to the VA CENC sites who have already sent their subjects' real SSNs. Will send contact information to the VA sites using encrypted email.
13. Submit operations study plan to the VA Office of Tribal Health (OTH) with VA partners, including John Brown, a Boston CHOIR administrative officer, American Indian and Alaska Native Special Emphasis Program (SEP) Manager, and with David Lowry, an anthropologist and author in Native American Studies at Brandies University.
14. Submit VA HSRD proposal on TBI and polytrauma system of care data analysis using Dr. Pugh's dataset and cross-referencing with LIMBIC CENC database, exposure data, and VA & DoD admin data. Outcomes would include cost and utilization, clinical (e.g., SUD, overdose, SBR), and social factors (e.g., homelessness). Partnering with Dr. Patrick Richards at DoD, Dr. William Walker at VCU, Dr. Thomas DeGraba at NICoE, and with Dr. Terri Pogoda at the Boston VA.

Novel Neuroimaging Study: In the next year, the Novel Neuroimaging Study will accomplish the following:
1. Continue to conduct phantom testing with the diffusion phantom to collect data for data harmonization.
2. Complete additional planned work with colleagues at Brigham and Women's Hospital and through the ENIGMA consortium who are developing additional harmonization methods.
3. Continue to critically examine the impact of different aspects of the analysis, including use of distortion correction and various aspects of pre-processing.
4. Perform additional analyses using machine learning and other advanced statistical techniques.
5. Continue to work with other consortia and military-relevant groups (e.g., ENIGMA, InTBIR, TRACK-TBI, TRACTS) to collaborate on data aggregation and analysis.
6. Complete additional planned expansion on the white matter hyperintensity analysis program developed under CENC and also multimodal analysis using SiMLR in conjunction with colleagues at University of Virginia.
7. This coming year, we will have a particular focus on methodologies that can be utilized to advance individualized analysis and/or applied in clinical practice.

Biomarker Discovery Study: In the next year, the Biomarker Discovery Study will accomplish the following:
Project 1: Continue SOW into year 4 (of 4 total for this project), as follows:

1. Obtain pre-deployment specimens from DoD biorepository, as available and analyze pre-injury candidate biomarkers and correlate with post-injury lab measures.
2. Correlate plasma biomarker results with Neuroimaging and neurocognitive outcomes in collaboration with LIMBIC Cores and prepare results for dissemination.
3. Identify subsets of Prospective study with TBI neurodegenerative outcomes (e.g. dementia, sleep disorders, epilepsy) and analyze relevant biomarkers in these sub-cohorts

- Complete current collaborative analyses, as follows:

-Cohort analysis- 7 proteins & outcomes
-DTI-NfL, collaboratively with Neuroimaging
-Volumtrics-NfL, collaboratively with Neuroimaging
-Big Data, collaboratively with Neuroimaging and Informatics
-rsfMRI- sleep dysfunction, collaboratively with Neuroimaging

- Continue correlations of candidate prognostic biomarker correlations with symptoms and outcomes.

4. Prepare manuscript of biomarker studies as individual analyses complete.

- Project 2: Initiate GWAS project with GAIN through the Broad Institute.
- Study 5: Initiate epigenetic study and plan for assays, and analyses

4. **IMPACT:** D*escribe distinctive contributions, major accomplishments, innovations, successes, or any change in practice or behavior that has come about as a result of the project relative to:*

What was the impact on the development of the principal discipline(s) of the project?
If there is nothing significant to report during this reporting period, state "Nothing to Report."

Describe how findings, results, techniques that were developed or extended, or other products from the project made an impact or are likely to make an impact on the base of knowledge, theory, and research in the principal disciplinary field(s) of the project. Summarize using language that an intelligent lay audience can understand (Scientific American style).

Data and Biostatistics Core: The procedures (i.e., data request process, web data dictionary, analytic dataset development) and systems (i.e., Study Portal) developed by the DBC to support the PLS and the LIMBIC-CENC consortium at large can be applied to other university-VA-DoD research partnerships.

Prospective Longitudinal Study: All scientific products utilizing LIMBIC-CENC PLS data had an impact on the base of knowledge, theory, and/or research surrounding late effects of military relevant TBI. Below is a synopsis of highlights from new scientific findings from manuscripts that were published during the past reporting year of LIMBIC (Oct 01, 2022 to Sep 30, 2023):

Key Points from recent publications from this reporting period ((10/1/22-9/30/23):

Gius BK, Fournier LF, Reljic T, Pogoda TK, Corrigan JD, Garcia A, Troyanskaya M, Hodges CB, Miles SR.

Association Between Sociodemographic, Mental Health, and Mild TBI Characteristics with Lifetime History of Criminal Justice Involvement in Combat Veterans and Service Members

Mil Med. 2023 Aug 29;188(9-10):e3143-e3151. doi: 10.1093/milmed/usac257.

Question: Which factors are associated with criminal justice involvement among Veterans/Service Members (V/SM) that could inform prevention and treatment efforts?

Findings: Ordinal regression analyses revealed that hazardous alcohol consumption (but not race, number of mTBI, employment status, or PTSD symptoms) was positively associated with increased criminal justice involvement after adjusting for all other variables. Being married or partnered was negatively associated with decreased criminal justice involvement.

Meaning: Alcohol use should be a top treatment target for V/SM at risk for arrest and those with history of criminal justice involvement.

Pickett TC, Walker WC, Lippa SM, Lange RT, Brickell TA, Dittmer TA, Smith JM, Cifu DX, French LM.

Cross-walk comparison of the DVBIC-TBICoE and LIMBIC-CENC combat-related concussion prospective longitudinal study datasets

Arch Phys Med Rehabil. 2023 Feb 24;S0003-9993(23)00102-8. doi: 10.1016/j.apmr.2023.02.003. PMID: 36842617

Question: In large, longitudinal, federally-funded TBI studies of Service members and veterans, how do the mild TBI and injury control participants compare in clinical features?

Findings:

Demographics: Compared to DVBIC-TBICoE, LIMBIC-CENC participants have:

- Higher: enrollment age, education level, % Black race, % Army branch, and time from injury
- Lower: % married, % Non-Army branches (AF, Navy, Marines), and # combat deployments

Symptom measures: Mostly similar or small effect sizes, except reaching medium effect sizes were:

- LIMBIC-CENC participants, both mTBI and controls, endorsed higher PTSD symptom levels
- DVBIC-TBICoE study control participants higher somatosensory and vestibular symptoms

Meaning: Development-stage collaboration and use of NIH TBI CDEs are key for comparing and leveraging findings across large TBI clinical research databases. Results highlight unique differences in study cohorts and adds perspective and interpretability for assimilating past and future findings.

Walker WC, O'Neil ME, Ou Z, Pogoda TK, Belanger HG, Scheibel RS, Presson AP, Miles SR, Wilde EA, Tate DF, Troyanskaya M, Pugh MJ, Jak A, Cifu DX.

Can mild traumatic brain injury alter cognition chronically? A LIMBIC-CENC multicenter study

Neuropsychology. 2023 Jan;37(1):1-19. doi: 10.1037/neu0000855. PMID: 36174184.

Question: Is cognitive performance altered long-term after mTBI among combat-exposed SM and Veterans?

Findings: Neither of the mTBI positive groups, non-repetitive or the repetitive (>3), differed from the TBI negative controls on any cognitive testing domain when adjusting for other factors such as comorbidities and education.

Meaning: Remote mTBI(s) alone is not associated with objective cognitive problems in the average Veteran or SM. Thus, a holistic healthcare approach including comorbidity assessment is indicated for patients reporting chronic cognitive difficulties after mTBI(s), and strategies for addressing misattribution may be beneficia. Future research should assess phenotypes (e.g., cognitive impaired) and for longitudinal decline from potential neurodegeneration.

Miles SR, Martindale SL, Flanagan JC, Troyanskaya M, Reljic T, Gilmore AK, Wyant H, Nakase-Richardson R..

Putting the Pieces Together to Understand Anger in Combat Veterans and Service Members: Psychological and Physical Contributors.

J Psychiatr Res. 2023 Mar;159:57-65. doi: 10.1016/j.jpsychires.2023.01.013. Epub 2023 Jan 11.

Question: When examined simultaneously, what established correlates of anger (e.g., combat exposure, PTSD symptoms, TBI, pain interference, and hazardous alcohol use) predict anger in Veterans and Service Members? Are sleep impairments (poor sleep quality and obstructive sleep apnea (OSA) risk moderators of the established predictors and anger?

Findings: PTSD symptoms, pain interference, hazardous alcohol use, and OSA were significantly associated with anger. OSA risk moderated the relationships between combat-related conditions of interest and anger, but sleep quality did not.
Meaning: Treating OSA may help Veterans and Service Members reduce their anger.

Wright B, Zhong C, Fisher R, Karmarkar A, Bjork JM, Pugh MJ, Hodges CB, Martindale SL, Wilde EA, Kenney K, McDonald SD, Scheibel RS, Newsome MR, Cook LJ, Walker WC.
Relation of aerobic activity to cognition and well-being in chronic mild traumatic brain injury (TBI): A LIMBIC-CENC study
In-Press. Accepted at Mil Med in Jan 2023.
Question: Do Servicemembers and Veterans with remote mild TBI(s) who perform more aerobic physical activity have better cognition?
Findings: Prespecified primary outcome (cognitive performance tests of overall executive function, learning and memory) did not differ across aerobic level groups. For secondary outcomes, regular aerobic activity was associated with better life satisfaction and better perceived overall health status. For exploratory outcomes, regular aerobic activity was associated with better working memory and verbal fluency.
Meaning: Regular aerobic exercise is recommended for SMs and Veterans with chronic mild TBI. Future longitudinal analyses will examine evidence of objective cognitive enhancement or preservation not demonstrated with this cross-sectional analysis.

Walker WC, Clark SW, Eppich K, Wilde EA, Martin AM, Allen CM, Cortez MM, Pugh MJ, Walton SR, Kenney K.
Headache among combat-exposed veterans and service members and its relation to mild TBI history and other factors: A LIMBIC-CENC study
Front Neurol 2023 Sep 20:14:1242871. doi: 10.3389/fneur.2023.1242871. eCollection 2023. PMID: 37808506.
Question: What are the risk factors for headache symptom prevalence and impact among previously combat-exposed military personnel and do they include lifetime mild TBI (mTBI) history?
Findings: Headache symptoms were very common and having more past mTBIs increases the likelihood, regardless of how long ago they occurred. This was shown in both bivariate analyses and multivariable regression adjusting for numerous sociodemographic, health, and symptom measures – including PTSD. In adjusted analysis, blast-related mild TBIs had the highest odds ratio at 1.81 per additional TBI (95% confidence interval: 1.48, 2.23). Blast-related mild TBIs were also uniquely associated with a higher degree of headache impact on daily life. Other risk factors we identified included demographic features (female sex, Black racial identity, Hispanic/Latino ethnicity, and younger age) and modifiable treatment targets (PTSD, depression, and sleep quality).
Meaning: These findings highlight the ramifications of lifetime mTBI history on headache conditions in the military population. Individuals with blast-related mTBI(s) are at highest risk for headaches and are uniquely vulnerable to headache impacting their daily life. Clinical screening to provide early or targeted intervention for headache should incorporate the demographic risk factors we identified, and headache treatment programs should be holistic to incorporate treatment of comorbidities including PTSD, depression and sleep difficulties.

Franke LM, Perera RA, Sponheim SR.
Long-term resting EEG correlates of repetitive mild traumatic brain injury, post-traumatic amnesia and loss of consciousness: alterations in alpha-beta power.
J Psychiatr Res. 2023 Mar;159:57-65. doi: 10.1016/j.jpsychires.2023.01.013. Epub 2023 Jan 11.
Question: How do long-term changes to EEG spectra after mild traumatic brain injury (mTBI, i.e. concussion) relate to injury characteristics and subjective or objective cognitive difficulties?
Findings: Executive function complaints, lower premorbid IQ, poorer cognitive performance, and higher psychological distress symptoms were associated with greater power of delta frequencies. PTA+LOC, poor cognitive performance, and cognitive complaints were associated with reduced power

in beta frequencies, and repetitive mTBI with higher power in alpha and beta frequencies. Neither dichotomous classification of the presence and absence of mTBI history nor blast exposures showed a relationship with EEG power variables.
Meaning: Long-term alterations in resting EEG spectra measures of brain function do not appear to reflect any lasting effect of a history of mTBI or blast exposures. Changes to alpha-beta frequency oscillations may be useful biomarkers for chronic effects of more severe/higher exposures, and for biological bases of cognitive complaints where recovery is poor.

van der Veen SM, et al.
Executive function and relation to static balance metrics in chronic mild TBI: A LIMBIC-CENC secondary analysis.
Front Neurol. 2023 Jan 11;13:906661. doi: 10.3389/fneur.2022.906661. eCollection 2022. PMID: 36712459
Question: Is mild TBI history or executive function measured by the Trail-making test (TMT) or EEG event-related potential (ERP) predictive of balance ability among combat Veterans/SMs?
Findings: Hierarchical regression accounted for 15.5% to 23.3% of the variability in balance and gait measures. More lifetime mild TBIs was associated with lower score on the sensory organization test (SOT) condition #2 (eyes occluded). Slower TMT part B was associated with worse unchallenged standing balance (SOT 1). ERP Distractor N200 latency FZ was associated with poorer balance on SOT 2 and SOT 3 (moving visual surround).
Meaning: SMs and Veterans with more lifetime mTBIs are at greater risk for balance problems. There is a connection between executive function and maintaining balance when vision is not a reliable input. These findings can inform clinical care needs, assessments and treatment strategies.

van der Veen SM, et al.
Sensory functions and their relation to balance metrics: A secondary analysis of the LIMBIC-CENC multicentre cohort
Front Neurol 2023 Sep 14:14:1241545. doi: 10.3389/fneur.2023.1241545. eCollection 2023. PMID: 37780699
Question: What is the influence of mild TBI history on the relation between balance, gait and sensory function among Veterans and Servicemembers (SMs) with combat exposure?
Findings: Overall, SMs and Veterans with TBI maintained postural balance and ambulate as well as their counterparts without mTBI. However, when any of the sensory systems (vision, vestibular or proprioception) are compromised, the number of TBI's sustained was associated with lower scores on the balance assessment (Computerized Dynamic Posturography Sensory Organization Test conditions 2-6 and composite).
Meaning: Processing of sensory information from the vision, proprioception, or vestibular systems is affected long-term after mild TBI which in turn affects balance negatively. Patients seem to adapt to these impairments; however, balance deficits may be unmasked when adjustments in weighting of theses sensory inputs are required due to various perturbations such as swaying of visual surround or base of support or the occlusion of vision. This suggests a higher fall risk and potential need for clinical evaluation and treatment.

Wade BSC, Tate DF, Kennedy E, et al.
Microstructural Organization of Distributed White Matter Associated with Fine Motor Control in US Service Members with Mild Traumatic Brain Injury.
J Neurotrauma 2023 Sep 11. doi: 10.1089/neu.2022.0094. Online ahead of print. PMID: 37694678.
See Neuroimaging Core section for key points.

Newsome MR, Martindale SL, Davenport N, et al.
Subcortical functional connectivity and its association with walking performance following deployment related mild TBI.
In-Press; Accepted for Front Neurol in Sep 2023.
See Neuroimaging Core section for key points.

Health Economics Study: Health Economics Study: We published a study on the impact of TBI and long-term dementia on VA facility and non-VA facility costs. We also did a podcast on the results. Our results showed a long-term shift to non-VA facility inpatient care for veterans<65 with TBI and dementia. This is important as we do not yet know how quality of care in Non-VA facilities compare with VA facilities as well as impact on VA budget. We also noted the high prevalence of alcohol and other substance abuse among individuals with comorbid TBI-dementia <65.

Phenotype Study: TBI and TBI severity were associated with all-cause mortality and specific types of mortality. There was a dose response relationship with moderate/severe TBI having a greater relationship with mortality rates over all and for specific causes of death than mTBI, which in turn had higher mortality rates than those with no TBI and the general population. We also see that there is differential mortality by TBI and deployment status. Deployment status was associated with significantly lower mortality suggesting a healthy deployer effect. We are working on analyses to examine the interaction between TBI history and deployment status. Our finding that temporal trends in death by suicide in Veterans that is continuing increase over time suggests that existing approaches to mitigate this problem are not sufficient. We will enhance our collaboration with Lisa Brenner and the VISN 19 Mental Illness Research Education and Clinical Center for suicide prevention to identify approaches that we may assist with to address this issue more effectively.

What was the impact on other disciplines?
If there is nothing significant to report during this reporting period, state "Nothing to Report."

Describe how the findings, results, or techniques that were developed or improved, or other products from the project made an impact or are likely to make an impact on other disciplines.

Health Economics Study: Worked with Ralph Depalma, MD and team to petition ICD 10 code for Primary Blast Injury to the Brain. The new code will be implemented in ICD-10 by the CDC in October 2022. Our findings regarding the high prevalence of TBI service connected disability in Pacific Islanders and Native Americans led us to acknowledge that VA did not yet have a special geographic designation for Native American/Tribal Lands/Reservations. We undertook research and outreach to the US Department of Labor to obtain zip codes for Tribal Elders and Leaders to incorporate into VA databases. We merged COVID-19 data from VINCI with the PLS study participants to identify a cohort of COVID-19 positive veterans that can be followed in a newly funded Long-COVID TBI study (PI Cifu). We examined COVID-19 hospitalization cost data in VA and DoD to support the new TBI-COVID-19 study.We worked with TBI Model Systems to submit a study examining the association of Post Traumatic Amnesia with First Year VA Hospitalization Costs as lead author. We worked as co-I with TBI Model Systems to submit studies on TBI Rehabilitation needs and employment after TBI. We worked as co-I with Walter Reed to submit a study on Active Duty Military Treatment Facility Costs of TBI and Mental Health Conditions. We submitted a VA/DoD JIF project with a DoD partner from Uniformed Services University of the Health Sciences to create a DoD/VA Dashboard of Hospitalization Costs based on AHRQ criteria as well as Outpatient Costs.

Prospective Longitudinal Study: The range of KT products developed and available on the LIMBIC-CENC website are intended to reach a range of disciplines and audiences. The LIMBIC CAB provides ongoing input on how best to reach wide audience groups. Ideas from the Government Steering Committee (GSC) have also been embraced and used to shape our KT planning. The audience for the national meeting presentations (such as ACRM) and national podcasts include a range of disciplines including physicians, physician extenders, nurses, physical, occupational and speech therapists, psychologists, neuropsychologists, health-care administrators, and basic science and clinical researchers. See KT section of this report for more details.

What was the impact on technology transfer?
If there is nothing significant to report during this reporting period, state "Nothing to Report."

Describe ways in which the project made an impact, or is likely to make an impact, on commercial technology or public use, including:

- *transfer of results to entities in government or industry;*
- *instances where the research has led to the initiation of a start-up company; or*
- *adoption of new practices.*

Data and Biostatistics Core and the Neuroimaging Core: Data is submitted to FITBIR for use by the wider scientific community.

Prospective Longitudinal Study: The main impact of the PLS on technology transfer has been the ongoing upload of all data into FITBIR informatics system for sharing of LIMBIC-CENC PLS data to other investigators and interested parties. Additionally, we have a system of formalizing collaborations to share directly share datasets from our Data and Biostatistics Center (DBC) and biofluid specimens from our Biomarker Core.

What was the impact on society beyond science and technology?
If there is nothing significant to report during this reporting period, state "Nothing to Report."

Describe how results from the project made an impact, or are likely to make an impact, beyond the bounds of science, engineering, and the academic world on areas such as:

- *improving public knowledge, attitudes, skills, and abilities;*
- *changing behavior, practices, decision making, policies (including regulatory policies), or social actions; or*
- *improving social, economic, civic, or environmental conditions.*

Health Economics Study:
1. Our results on long-term costs associated with TBI and Dementia highlight the concern of shifting VA financial resources from VA facilities to community care facilities as well as the important effects of alcohol and other substance abuse.
2.Our findings regarding the high prevalence of TBI service connected disability in Pacific Islanders and Native Americans led us to acknowledge that VA did not yet have a special geographic designation for Native American/Tribal Lands/Reservations. We undertook research and outreach to the US Department of Labor to obtain zip codes for Tribal Elders and Leaders to incorporate into VA databases.
3. Our joint work with DoD colleagues has strengthened partnerships as well as understanding of both DoD and VA systems of care.

5. CHANGES/PROBLEMS: *The PD/PI is reminded that the recipient organization is required to obtain prior written approval from the awarding agency grants official whenever there are significant changes in the project or its direction. If not previously reported in writing, provide the following additional information or state, "Nothing to Report," if applicable:*

Changes in approach and reasons for change
Describe any changes in approach during the reporting period and reasons for these changes. Remember that significant changes in objectives and scope require prior approval of the agency.

Phenotype Study: We have worked through VA requirements to add our server behind the VA firewall but have not had any movement in the past 6 months. We have worked through our ACOS for research to address this roadblock to no avail. Thus, we are proceeding with latent class analyses that are less computationally intense to begin our phenotyping on DoD data while we continue to work this problem. We will likely need to go beyond the local VA level to address this issue.

Actual or anticipated problems or delays and actions or plans to resolve them
Describe problems or delays encountered during the reporting period and actions or plans to resolve them.

Biomarkers Core:
No DNA extractions were performed this year. Currently, DNA extraction and APOE genotyping has been carried out on 1,383 PLS participants and 490 are pending. This has not delayed the GWAS study as a minimum of 2,000 DNA samples are required for analysis.
.
Action/Plan to Perform all tasks under Biomarker Core SOW Relocated LIMCBIC /CENC Biorepository to Dr. Capaldi's lab at USUHS and Discovery Study to WRAIR. Moves were approved by LIMBIC Leadership and GSC. The move to Dr. Capaldi's lab took several months which required a temporary halt in shipments from sites. Shipments have resumed and the BR is performing as before the move.

The following steps are required/in process to complete this action:

1. The biorepository protocol for storage of samples was submitted to Walter Reed Army Institute of Research (WRAIR) on 9/29/2022. Dr. Capaldi became the site primary investigator (PI). WRAIR recommended moving the Biorepository to Dr. Capaldi's lab space at USUHS and the Discovery Study to WRAIR. The GSC asked that the BR remain at USUHS. Dr. Capaldi offered his lab space at USUHS.

2. The Biorepository establishment at USUHS was approved by the USUHS IRB on 3/10/2023. The Discovery Study is currently under review by the WRAIR IRB.

3. MTA to send samples from USUHS BR to WRAIR for the Discovery Study is under review at HJF Tech Transfer Office and waiting for the Discovery Study approval from WRAIR IRB, and is pending approval of the discovery protocol at WRAIR.

4. A cooperative research and development agreement (CRADA) is in development, which will include Drs. Gill and Capaldi, as well as WRAIR, and investigators at Virginia Commonwealth University (VCU), including LIMBIC-CENC PI, Dr. Cifu. The CRADA will provide an avenue to communicate expectations, and regulations regarding operation of the LIMBIC Discovery Study at WRAIR.

5. There was one individual supported by LIMBIC-CENC who relocated to have their work station at USUHS as BR manager in Dr. Capaldi's lab.

6. The Manual of Operations has been revised to communicate a change in shipping address for the Biorepository, as well as required changes to institutional review boards (IRB), at each of the blood collecting sites to communicate the change in the address and physical location of the biorepository.

7. Analyses of samples, including DNA extractions and genotyping, as well as epigenetic profiles related to long-term samples have not been initiated, waiting for a sufficient number of samples.

Clinic Restructuring:

- One of the 11 sites was restructuring during the last Annual Report and not able to collect samples for a period of time, but is now collecting and shipping samples again.
- After a discussion among WRAIR and USU IRB representatives and the BR leadership, near the end of September 2023, the BR submitted to and received approval from the USUHS IRB to remove all references to analyses being done at the BR. The analyses will be done under the Discovery Study at WRAIR and results submitted to LIMBIC/CENC.

Neuroimaging Core: We are working with the LIMBIC DBC and investigators at each site to identify and remediate preventable obstacles to obtaining imaging data; we have now incorporated this data into weekly meetings with the DBC and monthly site-specific meetings.

Prospective Longitudinal Study:

- There have been ongoing challenges with Task 1 (maintaining research consortium staff levels) due to current/recent macroeconomic conditions, and changing expectations of workers (e.g. increased desire for telework and flexible hours) as well as Veterans Affairs human resource system changes that have resulted in job posting and onboarding delays. To address this, Dr Walker, Dr Cifu and the VCU Coordinating Core continue to work closely with all sites to offer and provide competitive compensation and other solutions. Another approach has been to continue to foster more tighter bonds and interpersonal connections across sites and with the central cores. A regular agenda item for our biweekly PLS all-sites Zoom meeting is to meet and greet staff at all sites which is very well-received. Each meeting, a different site is highlighted with brief presentations by each site investigator and staff-member on their background, interests, hobbies and other aspects of their professional or personal life they want to share. We have continued to provide resources and direct training for new staff hires.
- For PLS Major Task 9, hearing test data collection and storage, we spent much effort in cross-walking data between legacy Otogram equipment to the currently used state-of-the art Audiostar which is does not require sound booth or sound-proofing. We deployed a ambient noise meter and are able to flag invalid data points from excess ambient noise. We have successfully developed an algorithm that automatically filters valid data from both legacy and current systems.
- For PLS Major Task 13 (recruit not less than 3000 subjects), excellent progress was made despite the evolving expectations of current and potential participants regarding availability and time to participate, especially for in-person components. We continue to address this challenge with our well-established practice of consent/enrollment site targets/metrics reporting with positive and negative feedback, coaching and problem solving in multiple formats including written score cards, site-specific audio-visual meetings, and featuring it prominently on every bi-weekly PLS all-sites meeting. During this reporting year, the only site still prohibited by local authorities from in-person research activities (Boston site) was permitted to restart their in-person research activities. Thus, all eleven PLS sites have been and continue to actively enroll. Our enrollment numbers have been meeting goals on average on a monthly basis. We remain on track to meet our final end of funding-cycle target.
- Participant retention (PLS Major Task 14) is a continual challenge for any longitudinal clinical study. We continue to seek new opportunities for improvement with new strategies and refinements with sharing of recruitment and retention obstacles and failures across all sites of the PLS. We completed our participant-burden reduction project which led to the elimination of several assessments or portions of assessments that were redundant or had no/trivial scientific value. We eliminated, the MINI-PTSD, the UPDRS, military head jolt and training questionnaire (select items), and the BTACT stop-go test and cross-walks with ongoing data collection elements were developed where appropriate. We will continue to monitor this moving forward for potential additional deletions as well as opportunities to improve efficiency.
- First major PLS longitudinal data analysis. This project utilizes the annual BTACT data because we have now acquired enough retest data over a five-year period for large enough sample size. At least three data points are required for longitudinal analysis, and our comprehensive data is only done once every five years, so is still pending for adequate sample size. We had a setback in our timeline to complete the BTACT change analyses due to the lead investigator's resignation (Dr. Amma Agyemang). However, we have successfully transition to two co-PI's (Dr. Sarah Martindale and Dr. Jared Rowland), and we expect to have the analyses completed and manuscript submitted within the next two quarters of this coming FY.

Phenotype Study: Lack of computing capacity is delaying our progress. We are proceeding and will be able to address our aims, with less computationally intensive approaches, but we would prefer to use the most powerful approaches and have been working on obtaining the computational capacity.

Changes that had a significant impact on expenditures

Describe changes during the reporting period that may have had a significant impact on expenditures, for example, delays in hiring staff or favorable developments that enable meeting objectives at less cost than anticipated.

Biomarkers Core: Since the MOU was not renewed with CNRM last year, the BR physically moved and is now established at Dr. Capaldi's lab at USUHS and accepting sample shipments. Currently, DNA extraction and APOE genotyping has been carried out on 1,383 PLS participants and 490 are pending. Under the Biomarker Discovery Projects, proteomic (4-plex: NfL, GFAP, tau, UCHL-1) assays are delayed due to the move to WRAIR and waiting on their IRB to approve the protocol.

Significant changes in use or care of human subjects
Describe significant deviations, unexpected outcomes, or changes in approved protocols for the use or care of human subjects, vertebrate animals, biohazards, and/or select agents during the reporting period. If required, were these changes approved by the applicable institution committee (or equivalent) and reported to the agency? Also specify the applicable Institutional Review Board/Institutional Animal Care and Use Committee approval dates.

Prospective Longitudinal Study: For this reporting time period, (Oct 01, 2022 to Sep 30, 2023), minor changes in informed consent language for the PLS were made as reported under the PLS section for Accomplished on Major Task 2.

6. **PRODUCTS:** *List any products resulting from the project during the reporting period. If there is nothing to report under a particular item, state "Nothing to Report."*

- **Publications, conference papers, and presentations**
  Report only the major publication(s) resulting from the work under this award.

  Journal publications. *List peer-reviewed articles or papers appearing in scientific, technical, or professional journals. Identify for each publication: Author(s); title; journal; volume: year; page numbers; status of publication (published; accepted, awaiting publication; submitted, under review; other); acknowledgement of federal support (yes/no).*

See attached **Appendices #2, #2a and #2b** for the Publication Tracker and Publications.

Books or other non-periodical, one-time publications. *Report any book, monograph, dissertation, abstract, or the like published as or in a separate publication, rather than a periodical or series. Include any significant publication in the proceedings of a one-time conference or in the report of a one-time study, commission, or the like. Identify for each one-time publication: author(s); title; editor; title of collection, if applicable; bibliographic information; year; type of publication (e.g., book, thesis or dissertation); status of publication (published; accepted, awaiting publication; submitted, under review; other); acknowledgement of federal support (yes/no).*

See attached **Appendices #2, #2a and #2b** for the Publication Tracker and Publications.

Other publications, conference papers and presentations. *Identify any other publications, conference papers and/or presentations not reported above. Specify the status of the publication as noted above. List presentations made during the last year (international, national, local societies, military meetings, etc.). Use an asterisk (*) if presentation produced a manuscript.*

See attached **Appendices #2, #2a and #2b** for the Publication Tracker and Publications.

- **Website(s) or other Internet site(s)**
  List the URL for any Internet site(s) that disseminates the results of the research activities. A short description of each site should be provided. It is not necessary to include the publications already specified above in this section.

https://www.limbic-cenc.org https://www.limbic-cenc.org/index.php/knowledge-translation-center/

- **Technologies or techniques**
  Identify technologies or techniques that resulted from the research activities. Describe the technologies or techniques were shared.

LIMBIC-CENC Assessment tools, including PLS Variables and Concussion Assessment Tool for identifying and diagnosing lifetime mTBI history for clinical or research use remain available and kept updated on the website (https://www.limbic-cenc.org/index.php/knowledge-translation-center/limbic-cenc-concussion-assessment-tools/). Additionally, the DBC added to the website a PLS Data Cube that helps scientists and clinicians learn the depth and breadth of measures available the master dataset and estimate sample sizes. The PLS Data Cube is especially useful determining feasibility of potential dtata analysis projects and fine tuning the analytic specific aims and methods. See: https://www.limbic-cenc.org/index.php/for-scientists-and-clinicians/data-cube/

- **Inventions, patent applications, and/or licenses**
  Identify inventions, patent applications with date, and/or licenses that have resulted from the research. Submission of this information as part of an interim research performance progress report is not a substitute for any other invention reporting required under the terms and conditions of an award.

Nothing to report.

- **Other Products**
  Identify any other reportable outcomes that were developed under this project. Reportable outcomes are defined as a research result that is or relates to a product, scientific advance, or research tool that makes a meaningful contribution toward the understanding, prevention, diagnosis, prognosis, treatment and /or rehabilitation of a disease, injury or condition, or to improve the quality of life. Examples include:
  - *data or databases;*
  - *physical collections;*
  - *audio or video products;*
  - *software;*
  - *models;*
  - *educational aids or curricula;*
  - *instruments or equipment;*
  - *research material (e.g., Germplasm; cell lines, DNA probes, animal models);*
  - *clinical interventions;*
  - *new business creation; and*
  - *other.*

Developed and Implemented the Brain Health and Wellness Survey and Personalized

Recommendations Report (V2.0). We completed the revised format of the Dementia Risk Tool, which is re-branded as the Brain Health and Wellness Survey and Brain Health and Wellness Personalized Recommendations Report. This revised tool has a new format with recommendations aimed at activating user engagement and improved access to resources. Based on user response, the personalized report separate brain health factors into three sections: Strengths, Managed Health Conditions, and Untreated Health Conditions. The report provides key points and habits related to brain health for each health condition. The report also provides 'To learn more' links to the Brain Health Video Series described above. Lastly, the report provides 1st step links to key self-help resources or a tool to identify medical assessment/treatment resources close to their home.

Completed and posted ten videos for the Brain Health and Wellness Video Series. Ten brain health videos were completed and published on YouTube including: Series Overview, Depression, PTSD, Hearing Loss, Hypertension, Diabetes, Tobacco Use, Alcohol Use, Obesity-Activity-Nutrition, and Sleep.

Completed and posted final podcasts for Abstract Veteran Season 2. Hosted by CAB Chair CPT (R) Charles "Char" Gatlin, PhD, MPH, and retired LtC Kevin Sickinger, MS, Season 2 of the *Abstract Veteran* had 11 podcasts, one released per month, with a focus on patient and family care partner information and resource needs. All podcasts were completed and posted on the Abstract Doctor website and the LIMBIC-CENC website. Abstract Veteran Podcast Series Seasons 1 and 2 are also posted on Apple and Spotify. Season 3 podcasts are underway.

Created LIMBIC-CENC Monthly Release of New Publications. Implemented a new section on the website with a monthly release highlighting new LIMBIC-CENCE publications (as available).

Developed and Released Interactive Map for LIMBIC-CENC Sites and Investigators. Converted busy, static map of LIMBIC-CENC participating organizations to an interactive map. Users can click on the location of the coordinating center, research cores, research study sites, recruiting sites, and legacy sites on a U.S. map, which will reveal site information as well as biographies for investigators from that site.

Updated LIMBIC-CENC Research Publication Database. Added abstracts of 111 new LIMBIC-CENC authored published articles to the LIMBIC-CENC publication database. Abstracts include both the PLS studies described above as well as other mTBI-related published articles. There are now 621 abstracts through 8-15-2023 in the LIMBIC-CENC publication database.

7. PARTICIPANTS & OTHER COLLABORATING ORGANIZATIONS

What individuals have worked on the project?

Provide the following information for: (1) PDs/PIs; and (2) each person who has worked at least one person month per year on the project during the reporting period, regardless of the source of compensation (a person month equals approximately 160 hours of effort). If information is unchanged from a previous submission, provide the name only and indicate "no change".

Example:

Name: *Mary Smith*
Project Role: *Graduate Student*
Researcher Identifier (e.g. ORCID ID): *1234567*
Nearest person month worked: *5*

Contribution to Project: *Ms. Smith has performed work in the area of combined error-control and constrained coding.*

Funding Support: *The Ford Foundation (Complete only if the funding support is provided from other than this award.)*

See Appendix #6 (LIMBIC Financials and Effort Level)

Has there been a change in the active other support of the PD/PI(s) or senior/key personnel since the last reporting period?

If there is nothing significant to report during this reporting period, state "Nothing to Report."

If the active support has changed for the PD/PI(s) or senior/key personnel, then describe what the change has been. Changes may occur, for example, if a previously active grant has closed and/or if a previously pending grant is now active. Annotate this information so it is clear what has changed from the previous submission. Submission of other support information is not necessary for pending changes or for changes in the level of effort for active support reported previously. The awarding agency may require prior written approval if a change in active other support significantly impacts the effort on the project that is the subject of the project report.

We had the following PI changes during this period of performance:

- COL Vincent Capladi was added as a PI for the Biomarkers Core.
- Mellanie Medina assumed the role of PI at the Fort Belvoir Prospective Longitudinal enrollment site upon Dr. Hantsch's departure.
- Dr. William Carne was added as a co-PI for the Data and Bio Statistics Core upon Dr. Amma Agyemang's departure.
- Dr. Alicia Swan was added as a co-PI for the San Antonio PLS enrollment site.

What other organizations were involved as partners?

If there is nothing significant to report during this reporting period, state "Nothing to Report."

Describe partner organizations – academic institutions, other nonprofits, industrial or commercial firms, state or local governments, schools or school systems, or other organizations (foreign or domestic) – that were involved with the project. Partner organizations may have provided financial or in-kind support, supplied facilities or equipment, collaborated in the research, exchanged personnel, or otherwise contributed.

Provide the following information for each partnership:
Organization Name:
Location of Organization: (if foreign location list country)
Partner's contribution to the project (identify one or more)

- *Financial support;*
- *In-kind support (e.g., partner makes software, computers, equipment, etc., available to project staff);*
- *Facilities (e.g., project staff use the partner's facilities for project activities);*
- *Collaboration (e.g., partner's staff work with project staff on the project);*
- *Personnel exchanges (e.g., project staff and/or partner's staff use each other's facilities, work at each other's site); and*

- *Other.*

Nothing to report.

8. SPECIAL REPORTING REQUIREMENTS

COLLABORATIVE AWARDS: *For collaborative awards, independent reports are required from BOTH the Initiating Principal Investigator (PI) and the Collaborating/Partnering PI. A duplicative report is acceptable; however, tasks shall be clearly marked with the responsible PI and research site. A report shall be submitted to* ***https://ers.amedd.army.mil*** *for each unique award.*

QUAD CHARTS: *If applicable, the Quad Chart (available on https://www.usamraa.army.mil) should be updated and submitted with attachments.* **See Appendix #8 (Quad Charts)**

9. APPENDICES: *Attach all appendices that contain information that supplements, clarifies or supports the text. Examples include original copies of journal articles, reprints of manuscripts and abstracts, a curriculum vitae, patent applications, study questionnaires, and surveys, etc.*