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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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1. INTRODUCTION:

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:

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.

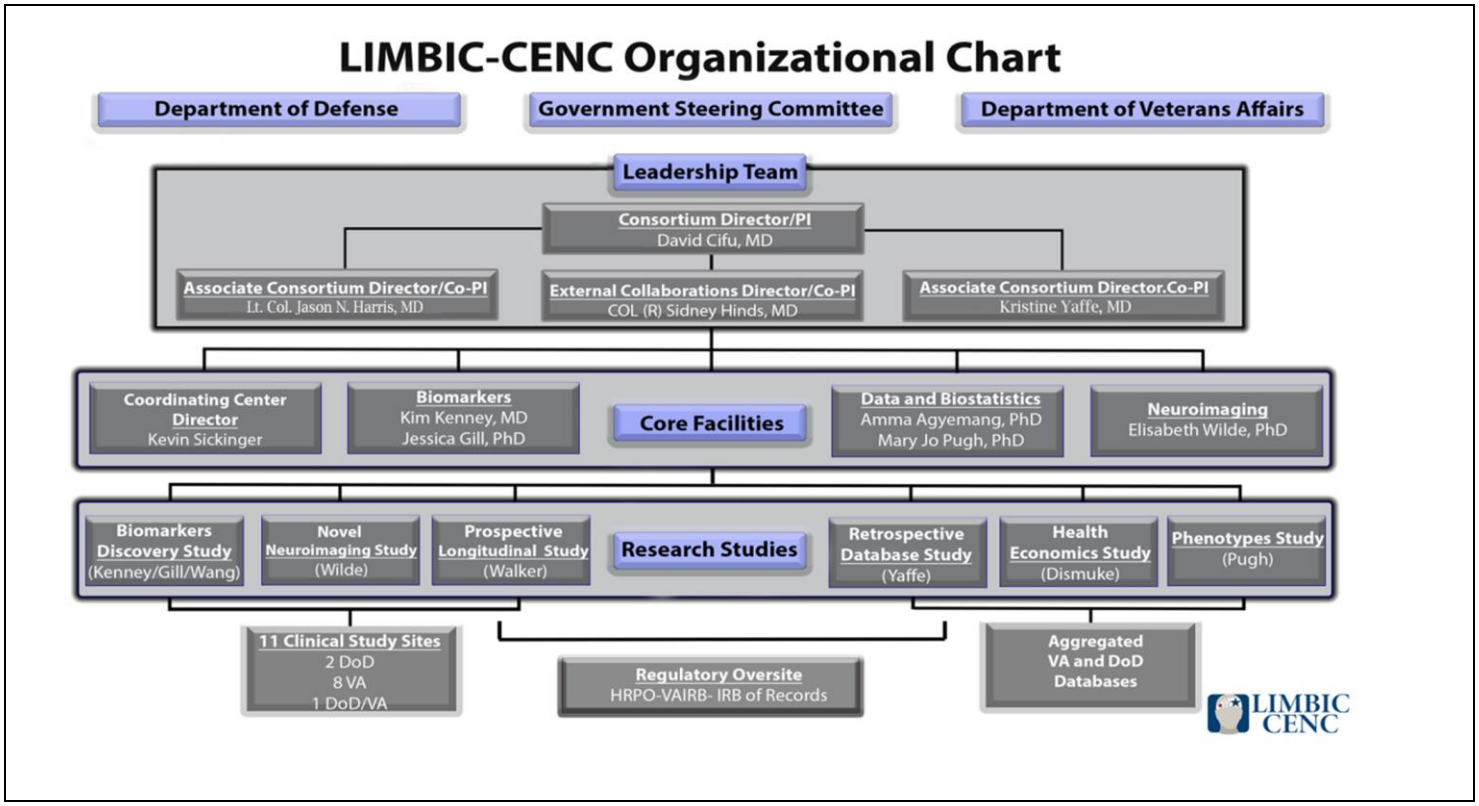
The Data and Biostatistics Core establishes procedures to receive, share, and adjudicate requests related to imaging data. It creates and implements efficient logistics for data-sharing both within and outside of the consortium. It develops and refines procedures for data collection and QA/QC, storage 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:

chronic effects
prognostic biomarker
NfL
miRNA
FITBIR
MRI
neuroepidemiology
phenotype
chronic pain
Veterans
mTBI
epidemiology
neurodegeneration
biomarkers
biospecimen biorepository
neurotrauma
dementia
comorbidity
cognition
Facilities and Services Utilization

3. ACCOMPLISHMENTS:

What were the major goals of the project?

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?

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 and briefed during our GSC Meeting in February. All performance sites have been successfully onboarded.

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: We were able to complete a DUA between Palo Alto VA and VCU so that Dr. Dismuke could share information in regards to DoD Identifiers from her Health Economics Study with the Data and Biostatistics Core. We are currently attempting to finalize the last DUA between USU and VCU in order to share DoD identifiers for one of the Biomarker Study Aims.

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: We have spent a lot of time and effort in assisting many of the enrollment sites with the training and certification of new personnel. Once the COVID restrictions lifted, there was a very high turnover rate at many sites due to personnel making life changes i.e. pursuing higher education, changing career paths or deciding to have families. Regardless of the reasons, the sites along with the Coordinating Center have been working very hard for the past four months to ensure sites are staffed at the appropriate level and they are trained and certified.

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.

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: We are continuing to have a lot of turnover in the Call Center as we did during Year 1. However, the Call Center Manager has become very proficient in the hiring, training and certification process. Despite some personnel shortages throughout the year, the Call Center was able to maintain the call schedule level as planned.

2. Conduct liaison between enrollment sites.

Month(s): 1 - 60

Progress: The Call Center Manager has continued the success that we were seeing at the end of

last year and has been doing a great job at working with the enrollment sites to ensure that we complete as many calls as possible.

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.

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 GSC meetings within the reporting period (October 2020 and April 2021) and initiated coordination for another meeting during the period and that meeting was scheduled for November 2021 in year three of the Period of Performance. See **Appendix #6a** 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 almost all of the primary PIs to attend the virtual meetings in October 2020 and April 2021.

3. Provide CDMRP Science Officer with all required meeting materials in accordance with approved schedule.

Month(s): *4 - 60*

Progress: After instituting a new timeline for meeting materials, we not only ensured meeting 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 conduct them on a monthly basis.

2. Establish recruitment and retention goals as well as the overall plan.

Month(s): *1 - 60*

Progress: This was completed during the negotiation phase of the project, however, we have adjusted the site recruitment goals based on the fact that the sites were not able to recruit during the first year and have had staggered opening throughout year 2. Fortunately, we had planned to meet our goal within year four which has now allowed us to shift the recruitment goals on the calendar to the right by a year. See table below for the new recruitment goal:

Projected Quarterly New Enrollments for Study A: Prospective Longitudinal Study

Subject enrollment will be expected at a rate of 2-5 per month for the duration of the study period

	Year 1				Year 2				Year 3				Year 4				Year 5				
Target Enrollment Study A	**Q1**	**Q2**	**Q3**	**Q4**	**Q1**	**Q2**	**Q3**	**Q4**	**Q1**	**Q2**	**Q3**	**Q4**	**Q1**	**Q2**	**Q3**	**Q4**	**Q1**	**Q2**	**Q3**	**Q4**	**Total**
(01) Hunter Holmes McGuire	0	0	0	0	9	9	9	9	9	9	9	9	9	9	8	8	4	3	3	0	116
(02) Michael E. DeBakey	0	0	0	0	9	9	9	9	6	6	6	6	6	6	6	6	4	4	2	0	94
(03) James A. Haley	0	0	0	0	9	12	12	12	12	12	12	12	8	8	8	8	4	4	2	0	135
(04) South Texas Veterans	0	0	0	0	9	9	9	9	9	9	9	9	9	9	9	9	5	5	4	4	126
(05) Fort Belvoir	0	0	0	0	9	9	9	9	9	9	9	9	9	9	9	9	6	6	6	0	126
(06) Portland Health Care	5	6	0	0	10	15	15	15	15	15	15	15	12	12	12	12	4	4	1	0	183
(07) Minneapolis VA	0	0	0	0	10	15	15	15	15	15	15	15	15	15	12	12	10	10	8	0	197
(08) Boston Healthcare System	0	0	0	0	10	12	12	12	12	12	12	12	12	12	12	12	12	12	12	6	184
(09) W.G. (Bill) Hefner VA	0	0	0	0	10	15	15	16	16	16	16	16	16	16	16	16	16	16	15	11	242
(10) Dwight D. Eisenhower	0	0	0	0	10	15	15	15	15	15	15	15	15	15	15	15	15	15	15	6	226
(11) San Diego Healthcare System	0	0	0	0	10	14	14	14	14	14	14	14	14	14	14	14	14	14	8	0	200
Target Enrollment (cumulative)	5	6	0	0	105	134	134	135	132	132	132	132	125	125	121	121	94	93	76	27	1829

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 have not had any in-person meetings since March 2020 but we have established and maintained regular communications through 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: Competed 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: We conducted two CAB meetings during this year. During one meeting, they were briefed by the Knowledge Translation Director on the Prognostic Tool Indicator and provided feedback that was used to improve the product. During our second meeting, the board members were provided all of the abstracts from the manuscripts that will be in the upcoming Special Edition of *Brain Injury*. They in turn provided us with a list of questions about the articles that we used to drive the discussions during our taping of the Podcast Series "The Abstract Veteran".

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 had several Consortium PIs who were going to attend the MHSRS meeting this summer but this conference and all others were canceled due to COVID-19. However, we have included several of the approved abstracts from the MHSRS in our Appendices.

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: CRADA with Geneva and VCU delayed, in progress with VUC, Geneva and USU to come to an agreement. Dr. Fontaine is aware of the issue but VCU has the lead in getting this fixed.

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 wells 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 and the Data Request Tracker is also included as **Appendix #2 (PLS Data Request Tracker)** to the report.

2. Assist Consortium PIs in publishing of results in both Scientific Journals and Conferences.
   Month(s): 24 - 60
   Progress: We are in the final editing process for the Special Edition of Brain Injury and we also assisted in the recording of podcasts for each primary author under the title of "The Abstract Veteran".

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):
   - Created new formatted product to translate and disseminate LIMBIC-CENC publication

findings to clinicians and clinical researchers
- Identified a large number of products, resources and resource links to put out on the website.
- Continued to make the website pages more visually appealing and remain current.

Broader Dissemination of LIMBIC-CENC Products and Progress:
- Met monthly with Linda Picon (VA Rehab R&D KT & Dissemination Lead) on distributing materials to V.A. TBI researchers and clinicians and the Dementia Risk Awareness Campaign.
- Coordinating Center contacted all LIMBIC-CENC partner sites regarding creating links to the LIMBIC-CENC website; changes are dependent on a major V.A. system-wide website update that is currently in process.
- Met with Cindy Cai, PhD, Model Systems Knowledge Translation Center Co-PI to discuss lessons learned; primary recommendation was to maximize search optimization to increase links to website

Deployed Dementia Risk Assessment Tool for Service members, Veterans and their Clinicians:
- Identifying tangible resources and how to link them to the My Dementia Risk Profile Personalized Report, which would then link to the Service Member and Veterans page on the LIMBIC-CENC website.
- Updating the personalized report for version 2.0 is dependent on resource links being set-up on a major LIMBIC-CENC website update that will be completed for the 11/9 GSC meeting.

Updated Prospective Longitudinal Study Data Visualization Dashboard (On-going):
- Updated "at a glance" summary scheduled for Fall 2021.

LIMBIC-CENC Searchable Journal Database:
- Conducted a literature search for all peer-reviewed articles published by LIMBIC-CENC investigators from 3-1-2021 thru 8-31-2021; 82 new articles identified.
- Data from abstracts have been organized/formatted for updating the master publication data base.
- Programmers have received the abstracts and will be uploaded for the 11/9 GSC meeting; the updated database will contain over 400 peer-reviewed publications.

Veterans and Service Member Dementia Awareness, Education and Prevention Campaign:
- Agreement in principle established with Biogen regarding funding the Dementia Awareness, Education and Prevention Campaign, including scope of work and primary deliverables.
- Contract is being negotiated between VCU Office of Sponsored Programs and Biogen Legal Department; estimated start date of contract is 10/15/2021.
- Safeguards put in place to avoid conflict of interest, clearly delineate products from different funding sources, and create a separate brand and website to make published material distinctions clear.

Brain Injury Special Issue:
- All Brain Injury articles are under review; target date for authors receiving journal review feedback is 10/15.
- Target date for articles and special issue going into print is January/February 2022.
- Char Gatlin and Dr. Ron Seel will serve as podcast moderators for 11 of the special issue articles; Dr. Kenney and Gill are awaiting approval to participate.
- On 9/21, we solicited questions from the LIMBIC-CENC Consumer Advisory Board for each published article and incorporated those questions into the podcast format.

- On 9/28, the first podcast was conducted with Dr. Cifu who provided an overview of the special issue
- All 10 other podcasts have been scheduled for between 10/1/2021 and 10/14/2021

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: During the second year of LIMBIC-CENC, the senior leadership continued to use the formalized process to conduct external collaborations, that was created in year one. LIMBIC-CENC created a consortium operation plan to capitalize on the innate desire of the LIMBIC-CENC cores, researchers and leaders to work with other like-minded individuals and organizations, to improve the fields of mild traumatic brain injury and the discovery of risk factors which may lead to neurodegeneration.

Recognizing that there are limitations to the consortium's time, finances, and space resources, LIMBIC-CENC created a framework to maximize and prioritize its external interactions. The LIMBIC-CENC consortium operation plan takes a tiered approach to prioritize the efforts in which it will be involved:

- The highest level of external collaboration efforts consume the most resources to cultivate and may also have the highest impact. Data sharing agreements, creation of a research proposal, or preparation for an evidence-based consensus conference represent the highest level, or tier 1, LIMBIC-CENC activities.
- Create tangible outputs/deliverables to share, advance, and create knowledge, which when accomplished will improve the overall mild traumatic brain injury and neurodegeneration practices in research and clinical care.
- Produce collaborative outputs include but are not limited to manuscripts, clinical recommendations, research proposals, clinical practice guidelines, letters of understanding, data sharing agreements, specimen sharing agreements, and knowledge and technical products.

During fiscal year 2021 LIMBIC-CENC has continued its external collaborations as the development of the consortium operation plan for external collaborations was being created. This year's external collaborations included:

- Interviewing and vetting numerous candidates for the DoD co-PI position.
- Selecting and on-boarding of the new DoD co-PI, Lt.Col. Jason Harris, who replaced Col. Kristopher Radcliffe. This involved an extensive search for a military co-PI with the highest experience and credentials in the fields of neurotrauma and neurodegeneration; an individual with military medical and combat experience; and experience with the higher echelons of military medical administration. LIMBIC-CENC leadership coordinated with Lt.Col Harris' command, over the course of numerous meetings to ensure a seamless assumption of duties. Col. Radcliffe was instrumental in this process. Lt. Col. Harris brings the additional experience as a neuro-ophthalmologist who has worked at the United States Army Institute for Surgical Research.
- LIMBIC-CENC secured non-research funding from Biogen to create a awareness campaign which will capitalize on the LIMBIC-CENC knowledge translation team.
- LIMBIC-CENC facilitated numerous collaborative proposal submissions to VA research, USAMRDC's MTEC. Projects such as neuroimaging data harmonization were selected and funded.
- Collaborations with University of Birmingham, UK have been underway to share

best practices in conducting multi-center, military and veteran TBI research.
- Participation in the virtual IBIA meeting, PINK Concussion sponsored diversity in neuroscience presentation
- Proposal and research meetings with UPMC's TEAM TBI neuroimaging/TMS team to move to the next steps in evaluating successful treatments through a multi-center trial.
-

During this year, LIMBIC-CENC continued processing and approving data and specimen sharing agreements; creation of manuscripts and presentations; hosting and participating in virtual external collaboration working meetings; and iterative meetings to create research proposals aligned with the LIMBIC-CENC mission.

LIMBIC-CENC continued interactions:

- TRACK-TBI
- NCAA Care Consortium
- InTBIR
- Veterans Against Alzheimer's Disease
- ENIGMA
- University of Pennsylvania
- Concussion Legacy Foundation/Project Enlist
- DVBIC
- DoD/USU Brain Bank
- Harvard's Football Player's Health Study investigators
- Million Veterans Program
- Biogen
- CONNECT-TBI (NIH U-54)
- Operation Backbone
- University of Virginia
- Perspecta
- University of Utah

LIMBIC-CENC began collaborative work:

- University of Birmingham, UK
- Wounded Warrior Project
- Emory University/Shepherd Center
- Naval Research Laboratory, San Diego
- UPMC
- Prevent Biometrics
- Synaptek
- Blink TBI

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 #5**.

2. Addition of other consortium members on our Advisory Boards.

Month(s): 1 - 60

Progress: We currently do not have any other consortium members on our Advisory Boards but we will continue to look into how we can make this happen.

Data and Biostatistics Core:

Major Task 1: Hire and maintain DBC staff.

Month(s): *1 - 60*

Progress: All Core staff (1 data manager, 1 project manager, 3 data scientists, 1 data analyst, 1 full stack developer, 1 research associate) were hired, onboarded and trained by the end of the 2nd quarter of LIMBIC-CENC. Due to staff turnover (transition to graduate school), the Salt Lake City team is in process of hiring another research analyst 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. We have optimized the system (implemented over 200 edit checks and custom functions in more than 50% of PLS 92 CRFs) to improve efficiency. In addition to Medidata, raw data files will be captured through new secure file transfer protocol. Developed new system (Study Portal) 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 provide ongoing support. Developed and refined system for monthly 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 report for biofluid samples. Developed and implemented REDCap survey to enable completion of self-report questionnaires remotely. Worked with Neuroimaging Core to build 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. Developed data dictionary which allows users to search and conveniently look for data element and their definitions/specifications. The dictionary is structured by CRF and data elements.. Developed 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, the SLC data core collaborated with a University of Utah IT application developer team to create a desktop application to automate data extraction for new data request. The application went under rigorous testing and validation and is ready to be implemented once LIMBIC Web data request portal is ready to go live. The SLC data core team are in the process of creating analytic data sets that will 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.

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

Month(s): *1 - 60*

Progress: **During year 2, the SLC team** developed analytic datasets, completed analyses, and worked with investigators on manuscripts for three papers focused on cognitive decline/sleep for the Brain Injury special issue; 1 additional manuscript was submitted to other another journal. The SLC team is working on analyses and manuscript development with investigators for three papers addressing cognitive outcomes. The SLC DBC team provided data to investigators for analysis for one additional paper focused on cognitive outcomes.

Major Task 4: Translate knowledge and disseminate knowledge products.

Month(s): *1 - 60*

Progress: Implemented first iteration of searchable, comprehensive publication database of CENC and LIMBIC-CENC publications (publicationdatabase.limbic-cenc.org). Developed mockup for Prognostic Tool.

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

Month(s): 1 – 60

Progress During year 2, the DBC approved and the SLC team completed 14 data requests. Five data sets were submitted to investigators and 9 were submitted to Utah Biostatistics group for analyses and manuscript preparation. The Utah Biostatistics group has completed analyses/manuscripts for 6 requests and three analyses approved in the previous fiscal year are in process of analysis and manuscript development.

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

Month(s): *6 – 60*

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. Data were submitted to FITBIR on March 31, 2021 for the period of October 1st, 2019 thru September 30th, 2020 and on September 30th, 2021 for the period of October 1st, 2019 thru March 31st, 2021. The first submission (March 2021) included 87 (out of 92) required Forms. No data were collected for the other five forms during the report period. The second submission (September 2021) included two new Forms: Blast Exposure Threshold (BETS) and Clinical Dimension Rating (CDR). For that submission, 91 (out of 94) required forms were submitted. There were not data collected for two forms (Adverse Events and Adverse Events Appendix. Data from the Eyelink form, was put on hold for later submission due to structural changes on data elements.

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 had a change in the MR physicist from Dr. Brian Taylor (left VCU in July 2020) to Dr. Robert Welsh (University of Utah), who has been actively involved in quality control, data review, physics and pulse programming assistance and data analysis since September 2020). 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). The IRB for Neuroimaging Core-related work at Baylor College of Medicine and the Michael E. DeBakey VA was also resubmitted and approved. 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 submitted October 2021.

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.

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: During this reporting period, we began additional (annual) 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 and will be meeting with sites to correct issues, as needed.

New 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) and human phantom (annual) testing has resumed and is anticipated to be ongoing through the course of the project.

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

Month(s): *6 - 60*

Progress: We have also completed scheduled data uploads of the raw imaging data to FITBIR (most recent was September 2021). 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.

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, Hovenden, Lindsey). We have not yet completed annual human phantom testing secondary to COVID, but will resume this in the coming year. This is anticipated to be an ongoing activity throughout the course of the project.

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

Month(s): *1 - 60*

Progress: Sequence parameters and phantom testing results are monitored in weekly Neuroimaging Core Operations meetings (Wilde, Welsh, Hovenden, Lindsey). We perform visual (qualitative) inspection of data to assess data quality at a preliminary review level. However, 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 and number of cases reviewed by

neuroradiologists for clinical findings are reported weekly in a joint meeting with Data Core. New cases are assigned each week. 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 ENIGMA diffusion processing which were released during this review period); we have also instituted some additional longitudinal pipelines, which are in process. Functional connectivity data has been processed in one pipeline, and we are working with Dr. Welsh to optimize the use of a second pipeline for fMRI. This 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 our 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: Drs. Wilde and Tate and Mr. Abildskov have been attending regularly scheduled teleconference meetings with the FITBIR and Data Core teams.

We are in the process of assisting in the analysis of an approved request by Kimbra Kenney related to the relation between biomarker and imaging data.

We have continued to work with other investigators with outstanding 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, 2) Dr. Mary Newsome, 3) Dr. Cooper Hodges, 4) Drs. Risa Richardson and Amanda Garcia, 5) Dr. Harvey Levin, 6) Dr. Emily Dennis, 7) Dr. David Tate, 8) Dr. Ben Wade, 9) Drs. Kenney/Werner/Gill. We are also working with Dr. Randy

We have resubmitted a manuscript on the relation between hippocampal and amygdala subfields and symptoms of PTSD and mood disorders (lead author: Benjamin Wade). We have also submitted two additional manuscripts (diffusion imaging and Brainage).

Members of the Imaging Core have also participated in manuscripts associated with the larger consortium (lead authors: Amanda Garcia, Maya O'Neill)

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. Data is securely archived and stored with redundancy. This task will continue through the course of the project.

Major Task 15: Attendance at biannual GSC meetings.

Month(s): *6 - 60*

Progress: Dr. Wilde attended and presented at the GSC meeting 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:

- Renewed Contract with CLIA-certified lab (Quest) for NED screen (IGF-1, testosterone, TSH).
- Continued to fund NED screening of PLS enrollees (IGF-1, testosterone, TSH) as requested through Quest contract.
- The Biorepository (BR) received PLS biospecimens from enrollment sites, post-COVID restrictions. For the period Sept. 1, 2020 to the end of Sept. 2021 the BR received 158 blood draws, including 50 from follow-up visits. There were specimens from 108 new subjects and 2,251 cryovials were added to inventory during this time period from Study 1. As of 30 September 2021, the BR has collated/stored processed/aliquoted biospecimens (DNA/buffy coat, plasma, serum, saliva, RNA (PaxGene) from 2,075 study 1 (473 F/U) subjects, as well as samples from 144 Study 49 subjects (1801 aliquots) & 20 Study 20 subjects (312 aliquots) for a current total of 29,420 aliquots in the biorepository available for analysis.
- The Biorepository worked with the Informatics core and 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 3/16/2021).
- New CRADA still in the works as of Oct. 2021 among USUHS, Geneva, Eisenhower (EAMC), and FBCH, requested by FBCH.

Major Task 3: HRPO approval and continuing review.

Month(s): *1 - 60*

- ***Progress:*** HRPO second level approval 10-16-2020.
- Most recent HRPO approval 7-1-2021.
- CR approved by USUHS IRB 3-16-2021.

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: APOE genotyping carried out on 111 specimens from 106 new participants for a total of 1,383 PLS participants with DNA extraction and APOE genotyping.

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

Month(s): *1 – 60*

Progress:

- Renewed Contract 6-2020 with CLIA-certified lab (Quest) for NED screen (IGF-1, testosterone, TSH).
- Continued NED screening of samples from all new enrollments in LIMBIC prospective study.
- Continued collaboration with Dr. Bill Walker for evaluation of NED screen in Longitudinal sample and manuscript submitted to Bran Injury CENC special publication, currently under review. Abstract of analysis results submitted and accepted for 8/2021 MHSRS.
- Modified Manual of Operations to state that serum samples must be submitted to analysis to Quest Lab for biochemical assays no later than 21 days from collection to insure viable samples for TSH.

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

Month(s): *1 - 60*

Progress:

- Grant submitted collaboratively with Kevin Wang, PhD at Gainesville, FL VA for VA biomarker project of sweat biomarkers in LIMBIC participants with VA prime and USUHS Biorepository as a sub-contract. This was not funded. Seeking further opportunities to collaborate with Dr. Wang.
- MSD, Chris Campbell, "Ultrasensitive Blood Tests for Investigating Pathogenesis of Chronic TBI Symptoms". Presented abstracts of preliminary results showing possible association between p-tau isoforms and blast mTBI mechanisms at Neurotrauma 2020 and accepted for MHSRS 2021, but canceled. Based on results, request submitted to Research committee and approved to expand analysis to additional 500 samples from LIMBIC PLS This collaborative analysis is under way.
- NED analysis- Submitted to Brain Injury special issue (currently under review) and Abstract accepted as oral presentation at MHSRS, CENC (Walker). Our analysis suggests that mTBI is not associated with greater risk of abnormal NED screening tests in our active duty/veteran population with remote mTBI.
- Lipidomic Discovery project in process with Dr. Fiona Crawford at Roskamp Institute is under way. They have submitted a FY21 TBI PH IIRA grant for funding to further explored the association between lipidomics and remote mTBI outcomes collaboratively with the Biomarker Core investigators.
- MTA for non-coding RNA biomarker project with Dr. Nakase-Richardson, and her team at the Tampa VA approved Oct. 7, 2020. Research project titled: ""Noncoding RNA in traumatic brain injury", and specimens for sub-analysis and 150 samples shared with the Tampa VA laboratory with analysis in process.
- During the period Sept. 2020 to the end of Sept. 2021, specimens from the BR were sent out to the following investigators:

1. Dr. Patel (James A Haley VA Hospital) : 150 serum specimens from Study 1
2. Dr. Campbell (MSD): 501 Serum specimens from Study 1
3. Dr. Gill: 140 Plasma specimens from Study 1
4. Bao-Xi Qu: 111 Buffy Coats for DNA extractions

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

Month(s): *1 - 60*

Progress:

- Specimens shared with Roskamp Institute, Fiona Crawford for lipidomic analysis
- Specimens shared with the 4 investigators listed in Major Task 7 above.
- Completed inflammation panel (IL-6, IL-10, TNF-α) and now database locked and analyses underway collaboratively with Imaging Core.
- Samples shared with Dr. Jessica Gill's lab at NIH for LIMBIC Study genetic testing.

Major Task 9: Attendance at biannual GSC meetings.

Month(s): *6 - 60*

Progress: Drs. Gill and Kenney attended (virtually) and presented at the GSC meetings during this

period of performance, Oct. 2020 and April 2021. Drs. Gill and Kenney will attend the November 2021 GSC meeting.

Studies

Prospective Longitudinal Study:

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

Month(s): *1 - 60*

Progress: 100% met; ongoing to maintain. Continuing to address challenges of COVID pandemic on maintaining staffing levels at all PLS sites.

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

Month(s): *1 - 60*

Progress: 100% met; ongoing to maintain. Added consent language required for data sharing on FITBIR.

Major Task 3:HRPO approval and continuing review.

Month(s): *1 - 60*

Progress: 100% met; ongoing to maintain.

Major Task 4: Onboard 3 new recruitment sites.

Month(s): *1 - 4*

Progress: 100% met; all three new sites are fully operational with recruitment, enrollment and testing.

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

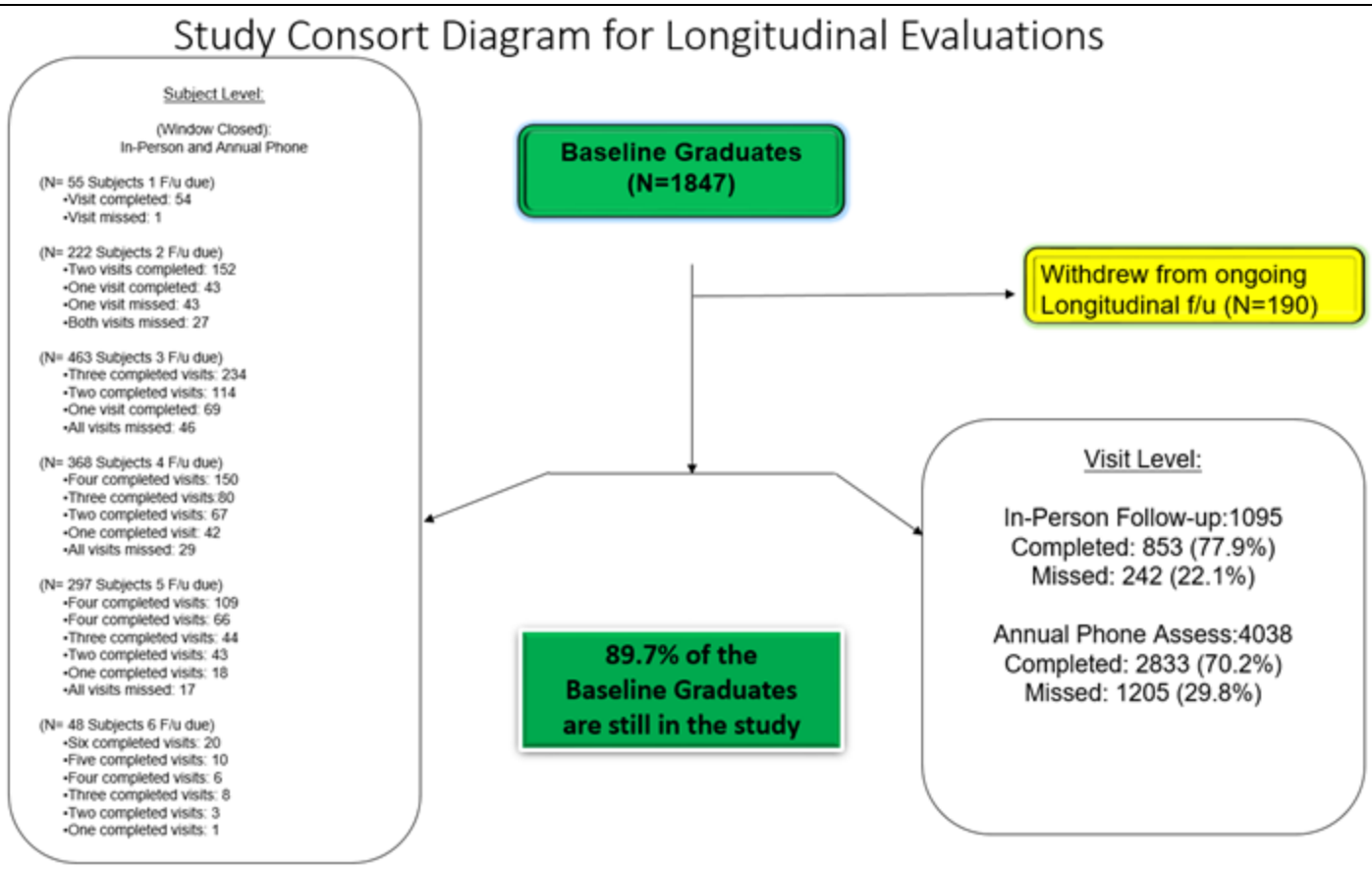
Month(s): *1 - 60*

Progress: Ongoing acquisition. In-person components remain hampered by COVID pandemic.

- From Oct 01, 2020 to Sep 30, 2021, a total of 865 new follow-up assessments were completed. This consisted of 177 new comprehensive and 688 new annual phone follow-up assessments which resulted in completion rates of 68% and 70% out of those that were due. Additionally, 381 BTACT assessments were completed during period for a completion rate of 90%.

Cumulative Totals:

- During LIMBIC (since Oct 01, 2019), a total of 1954 follow-up assessments have been completed, consisting of 421 comprehensive and 1533 annual brief phone follow-up assessments. Additionally, 580 BTACT assessments have been completed.
- Since CENC inception, a total of 3910 follow-up assessments have been completed, consisting of 898 comprehensive and 3012 annual brief phone follow-up assessments. This translates into overall completion rates of 78% for comprehensive and 71% for annual telephonic. See longitudinal Consort diagram below. Additionally, 2316 BTACT assessments have been completed since CENC inception with an overall completion rate of 88%.



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: Acquisition ongoing, but because in-person visit is required, it remains slightly hampered by COVID pandemic. Note: analyses are shown elsewhere in this report.

- Total records acquired for reporting period (10/1/20-9/30/21) was 322, consisting of 268 baseline and follow-up 54 eye-tracking tests.

Cumulative Totals:

- During LIMBIC (since Oct 01, 2019), a total of 426 records have been acquired, consisting of 355 baseline and 71 follow-up eye-tracking tests.
- Since CENC inception, a total of 1093 records have been acquired, consisting of 844 baseline and 249 follow-up eye-tracking tests.

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

Month(s): *1 - 60*

Progress: Acquisition ongoing, but because in-person visit is required, it remains slightly hampered by COVID pandemic. Note: analyses are shown elsewhere in this report.

- Total records acquired for reporting period (10/1/20-9/30/21) was 414, consisting of baseline and 343 follow-up 71 Balance Master tests.

Cumulative Totals:

- During LIMBIC (since Oct 01, 2019), a total of 665 records have been acquired, consisting of 524 baseline and 141 follow-up Balance Master tests.

- Since CENC inception, a total of 1906 records have been acquired, consisting of 1448 baseline and 458 follow-up Balance Master tests.

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

Month(s): *1 – 60*

Progress: Acquisition ongoing, but because in-person visit is required, it remains slightly hampered by COVID pandemic. Note: analyses are shown elsewhere in this report.

- Total records acquired for reporting period (10/1/20-9/30/21) was 464, consisting of 382 baseline and 82 follow-up Hearing tests.

Cumulative Totals:

- During LIMBIC (since Oct 01, 2019), a total of 731 records have been acquired, consisting of 588 baseline and 143 follow-up Hearing tests.
- Since CENC inception, a total of 1928 records have been acquired, consisting of 1480 baseline and 448 follow-up Hearing tests.

Major Task 10: Administer and interpret neuropsychological data.

Month(s): *1 - 60*

Progress: Acquisition and interpretation ongoing, but because in-person visit is required for most of data, it remains slightly hampered by COVID pandemic.

- Total records acquired/interpreted for reporting period (10/1/20-9/30/21) was 474, consisting of 280 baseline and 194 follow-up Neuropsychological testing batteries.

Cumulative Totals:

- During LIMBIC (since Oct 01, 2019), a total of 732 records have been acquired and interpreted, consisting of 293 baseline and 439 follow-up Neuropsychological testing batteries.
- Since CENC inception, a total of 2724 records have been acquired and interpreted, consisting of 1847 baseline and 877 follow-up Neuropsychological testing batteries.

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

Month(s): *1 – 60*

Progress: Acquisition ongoing, but because in-person visit is required for most of data, it remains slightly hampered by COVID pandemic. Note: analyses are shown elsewhere in this report.

- Total biospecimens acquired for reporting period (10/1/20-9/30/21) was 198, consisting of 163 baseline and 35 follow-up bio specimens.

Cumulative Totals:

- During LIMBIC (since Oct 01, 2019), a total of 288 records have been acquired, consisting of 176 baseline and 112 follow-up biospecimens.
- Since CENC inception, a total of 2125 records have been acquired, consisting of 1604 baseline and 521 follow-up biospecimens.

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

Month(s): *1 – 60*

Progress: Acquisition ongoing, but because in-person visit is required for most of data, it remains hampered by COVID pandemic. Note: analyses are shown elsewhere in this report.

- Total imaging sessions of data acquired for reporting period (10/1/20-9/30/21) was 241, consisting of 197 baseline and 44 follow-up imaging sessions.

Cumulative Totals:

- During LIMBIC (since Oct 01, 2019), a total of 526 imaging sessions have been acquired, consisting of 426 baseline and 100 follow-up imaging sessions.
- Since CENC inception, a total of 1606 records have been acquired, consisting of 1231 baseline and 375 follow-up imaging sessions.

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

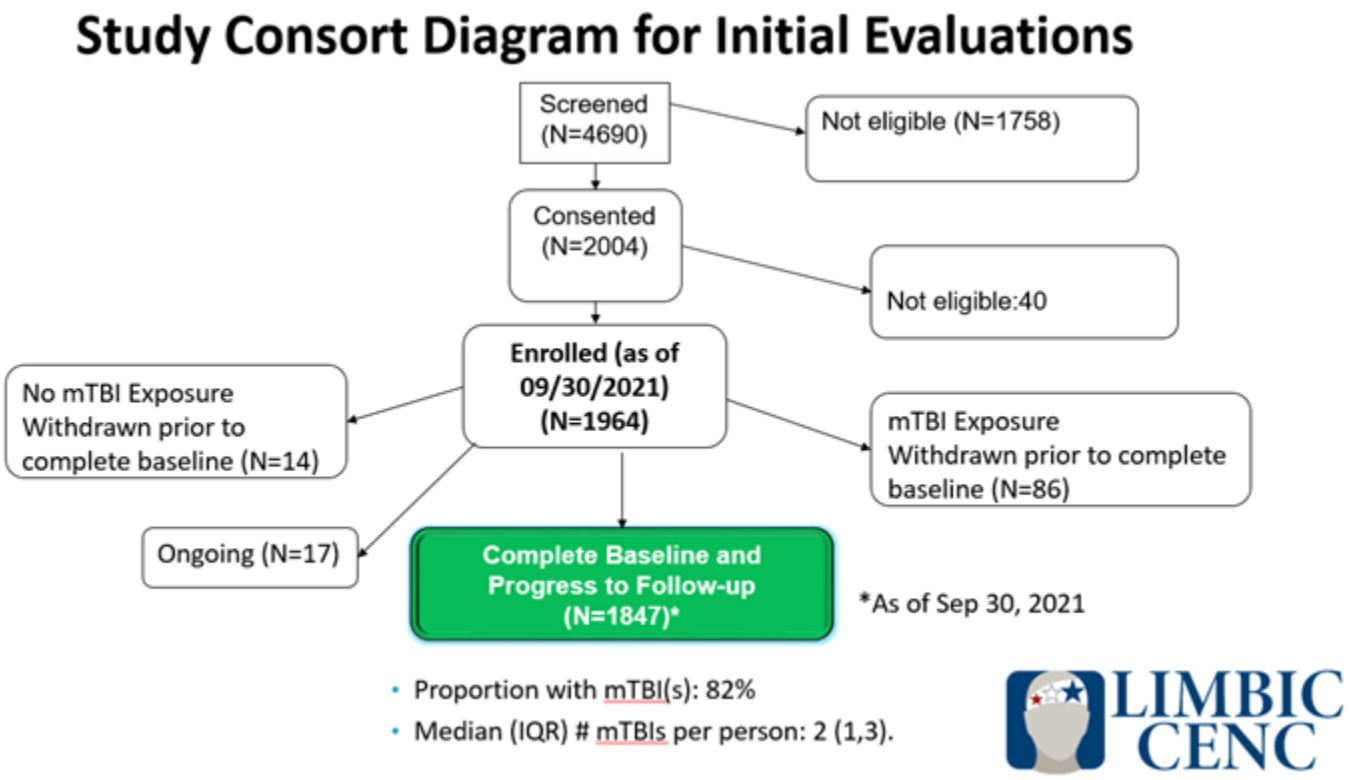
Month(s): *1 - 60*

Progress: Ongoing, but this activity has been heavily impacted by the COVID pandemic, with in-person research activities banned and or restricted at all sites during portions of this reporting period. By the end of the reporting period, all recruitment and enrollment sites did restart face-to-face recruitment and enrollment procedures, however the pandemic is still somewhat dampening recruits' ability and willingness to come on site for consenting and testing.

- However, we are still on-course to meet our projected goal of 3000 total participants prior to the end of the period of performance, just not as quickly as originally projected.

During this reporting period (10/1/20-9/30/21), there were 280 new participants consented, 280 new participants enrolled, and 278 new baseline evaluations completed.

- Throughout the course of the study (from CENC to LIMBIC-CENC), a total of 2004 participants have been consented, 1964 participants enrolled, and 1853 baseline evaluations completed. (see initial evaluation consort diagram below):



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

Month(s): *1 - 60*

Progress: 100% met; See more details about the recruitment plan and changes made due to COVID in the Coordinating Center section.

Major Task 15: Implement recruitment and retention plan.

Month(s): *1 – 60*

Progress: 100% met; however, we have initiated a thorough review of all of our End of Study participants across all of the sites and will look for any trends on why participants might be dropping out and determine whether or not there is something that we can do to either eliminate it or at least reduce it.

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: During the reporting period (10/1/20-9/30/21), 12 new PLS analytic datasets were

released for new projects, and 4 more analytic dataset requests were approved. All included some aspect of cross-sectional analysis. For details on these as well as cumulative analytic datasets released, see Excel spread sheet entitled 'PLS data request tracker 9.29.21' in the Appendix.

- Scientific journal publications and scientific meeting presentations: See table below for number of publications and presentations during the reporting period (10/1/20-9/30/21). For details on these as well as cumulative scientific, see Excel spread sheet entitled 'LIMBIC-CENC PublicationMonitor' in the Appendix (To limit to PLS data driven and Fiscal Year 2 only, go to Project Database tab, filter for only Y2 under GSC Report (Column Q), then for only PLS under Study/Core Affiliation (Column M). Further details of these projects are provided under the Publication Database tab.

Y2 (10/1/20-9/30/21)	Publication	Presentation	Total
Submission	11	4	15
Electronic	16	1	17
Print	8	3	11
Total	35	8	**43**

- Additional dissemination efforts included developing and cataloging Key Points (see KeyPoint tab of the PublicationMonitor), which summarizes a succinct takeaway message summary of each publication; these are shown in. Other efforts included national webinars and a series of podcasts on the manuscripts submitted for the LIMBIC Special Edition of the journal Brain Injury, and ongoing close collaboration with the LIMBIC-CENC knowledge translation (KT) center on the website and other KT products.
- During the reporting period (Oct 01, 2020 to Sep 30, 2021), the following analytic projects were also presented on the biweekly LIMBIC-CENC PLS All-Sites audiovisual meeting/conferences:

Date	Publication	Presentation
19-Apr-21	Shannon Miles	Sleep Apnea and Posttraumatic Stress after TBI: A VA TBIMS Study
17-May-21	Amanda Garcia	Obstructive Sleep Apnea Risk is Associated with Number of White Matter Hyperintensities, But History of Mild TBI Exposure is Not
14-Jun-21	Karen Skop	Sleep Apnea and Vestibular Dysfunction in Patients with TBI
28-Jun-21	Becky Guis	What Sociodemographic and Mental Health Challenges are Linked to Criminal Justice Involvement among Veterans and Service Members?
26-Jul-21	Bridget Cotner	Stakeholder engagement to inform obstructive sleep apnea screening and diagnostic tools during inpatient rehabilitation for traumatic brain injury
20-Sep-21	Emily Dennis	CENC-LIMBIC Brain Age analysis

Major Task 17: Analysis & Publication of Longitudinal Data.

Month(s): *24 - 60*

Progress: During the reporting period (Oct 01, 2020 to Sep 30, 2021), our longitudinal data analysis activity began ramping up. This was enabled by our continued high rates of retention and follow-up visit completion rates and starting to accumulate a critical mass of repeated measures.

- Analyses: Among the new datasets released during the reporting period or pending release, there were 5 analytic projects that included longitudinal data and study aims. This brings to a total of 7 longitudinal analysis projects. For details on these, see Excel spread sheet entitled 'PLS data request tracker 9.29.21' in the Appendix; note that column AH shows whether it included longitudinal data.
- Scientific journal publications and scientific meeting presentations: For details on these as well as cumulative scientific, see Excel spread sheet entitled 'Publications Tracker' in the Appendix.
- Scientific publications and meeting presentations: So far, only one manuscript using longitudinal PLS data analysis has been published (an ENIGMA project). However, a recently completed analysis was presented as a poster at a major scientific meeting and won an award; "ACRM is pleased to recognize the work of Becky Gius, MA, et al with the BI-ISIG Early Career Poster Award for their poster, 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 was presented at the ACRM 2021 VIRTUAL Annual Conference." https://acrm.org/acrm-

communities/brain-injury/bi-isig-awards/bi-isig-2021-poster-awards/

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: 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: 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: 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 year two, 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.

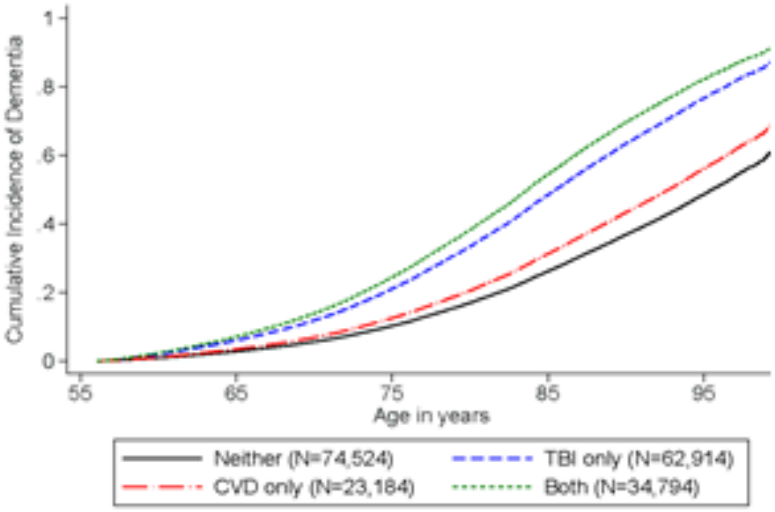
Milestone: Data repository ready for analysis: The database, consisting of 2.2 million Veterans, including 426,643 with TBI, was completed in September of 2020, and is continually updated as required.

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

Month(s): *1 – 24*

Progress: In Year 2 we analyzed data and submitted a manuscript examining how cardiovascular disease (CVD) and TBI affect dementia risk. TBI is associated with elevated rates of CVD, and both CVD and TBI are important risk factors for dementia. We investigated whether CVD moderates or underlies the association between TBI and dementia in 195,416 Veterans age 55+ diagnosed with TBI within the VHA and a demographically matched sample of Veterans without TBI.

During follow-up (mean of almost 7 years), 12.0% of Veterans with TBI only (HR: 2.17 95% CI 2.09-2.25), and 10.3% with CVD only developed dementia (HR 1.21 95% CI 1.15-1.28), compared to 6.5% with neither. There was evidence of an additive association between TBI and CVD on dementia risk (HR 2.51, 95% CI 2.41-2.61).

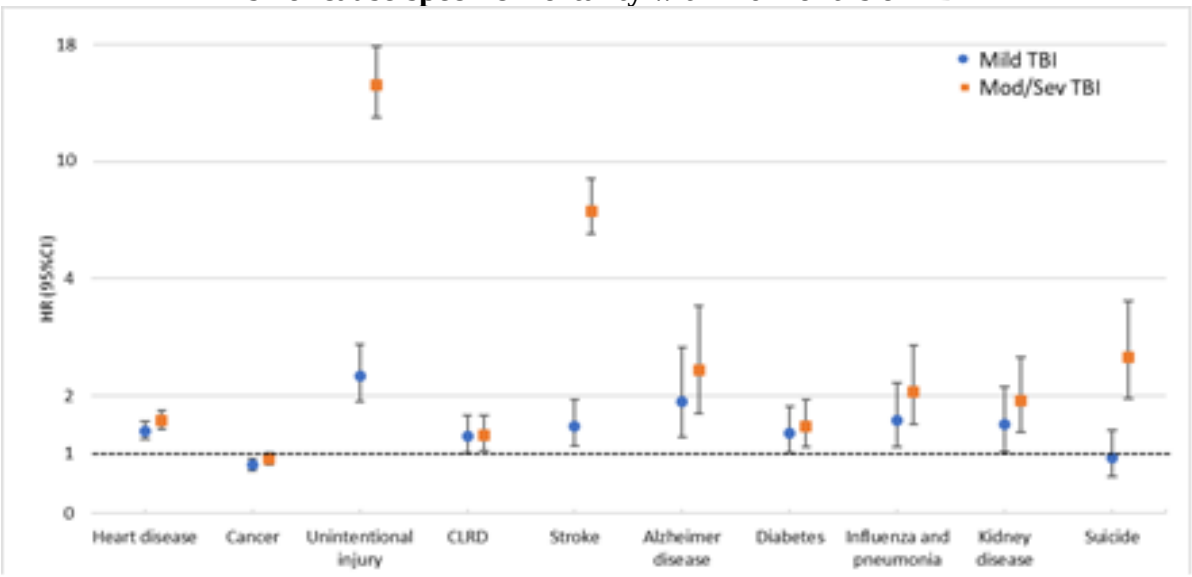


TBI and CVD independently increase risk for dementia among older US Veterans; together they had an additive effect with risk highest for Veterans who have both exposures. However, CVD did not account for much of the association between TBI and dementia, suggesting that more research is needed to understand the mechanisms for TBI-dementia and to inform clinical guidelines post-TBI. The manuscript describing these exciting results is submitted to Brain Injury for the Special Issue.

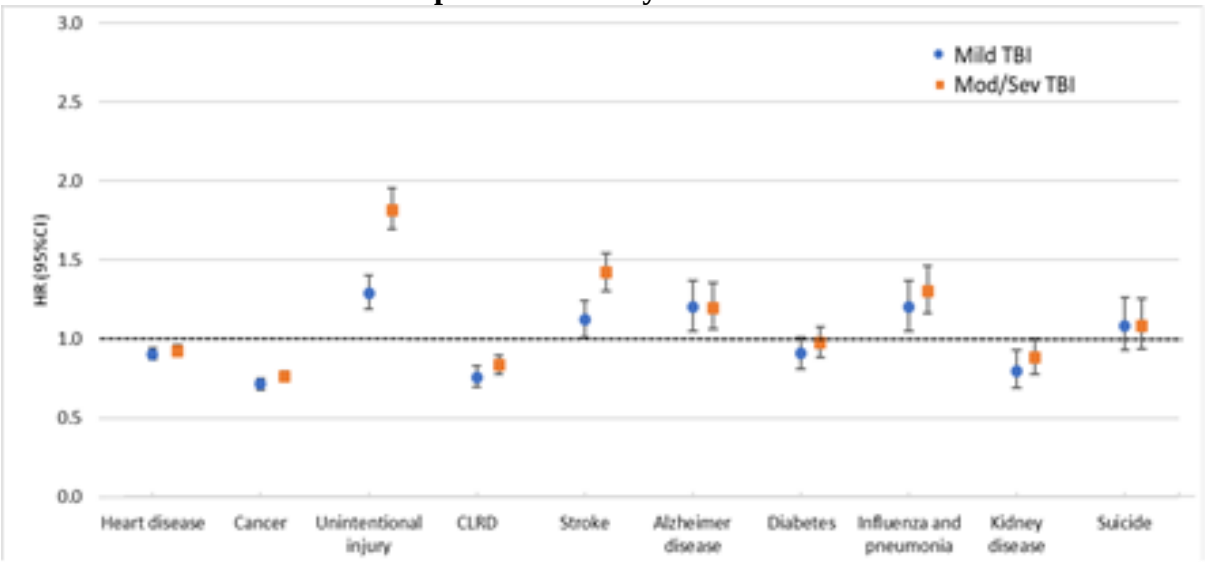
***Milestone**:* Data analysis completed and manuscript submitted for publication.

Progress: In the past year we worked on an analysis examining cause-specific mortality after TBI in a group of Veterans. Prior studies found a strong association between TBI and increased risk of death, but few studies have examined causes of death and timing of death after TBI. We examined a group of Veterans ≥18 years with TBI (N=213,290) and 1:1 propensity-matched them to Veterans without TBI (N=213,290). We then looked at short (within 6 months of TBI) and longer-term (> 6 months post-TBI) specific causes of death provided by VA's National Mortality Data Repository. Cox proportional hazards were used for all-cause mortality; Fine-Gray proportional hazards regression was used for cause-specific mortality, accounting for competing risk. We found that the risk of death varied over time and by TBI severity. For moderate/severe TBI, the risk for mortality was highest within 6 months of injury and decreased over time; for mild TBI, risk for mortality elevated but remained relatively constant over time.

Risk of cause-specific mortality within 6 months of TBI



Risk of cause-specific mortality > 6 months after TBI



Looking at causes of death, we found that cause-specific mortality depends on timing, with unintentional injury and stroke being especially critical after moderate to severe injury in first 6 months after injury. These results suggest that Veterans who have experienced mild as well as mod/sev TBI need to be monitored very closely across multiple services, practices, and programs. A paper detailing these important results is in progress.

Milestone: Data analysis completed and manuscript in preparation.

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.

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).

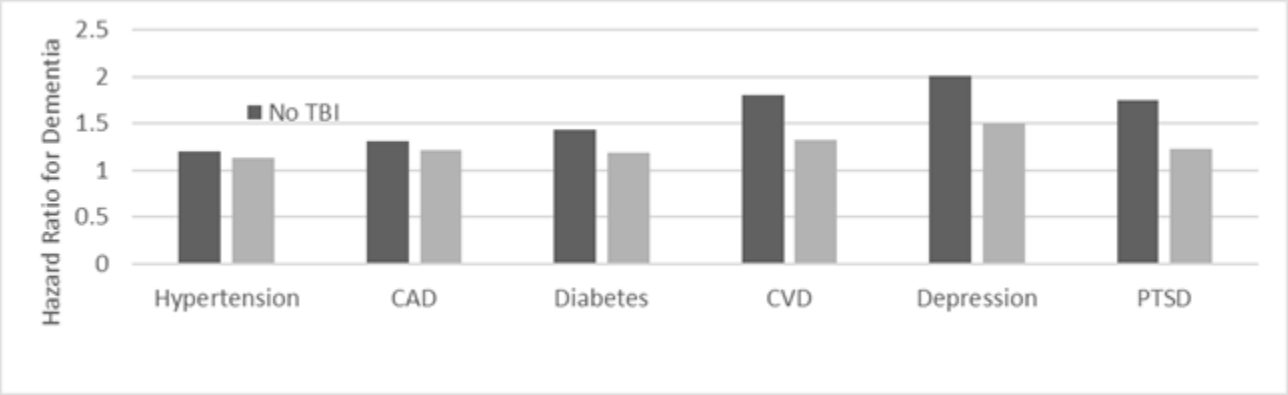
Month(s): *24 – 36*
Progress: Completed in Year 1

Milestone: Manuscript published: Kornblith et al., 2020.

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 the past year we analyzed data and are preparing a manuscript 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. Magnitude of risk of dementia associated with each baseline risk factor was consistently (slightly) lower among TBI cohort vs. no TBI cohort. These findings suggest that targeting common dementia risk factors in TBI-exposed Veterans is important given the high prevalence of risk factors, but TBI-specific prevention efforts may also be needed. A manuscript describing these interesting results is in preparation.



Milestone: Data analysis completed and manuscript in preparation.

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: In Year 2 we collaborated with Dr. Libby Dismuke examining health care costs associated with TBI dementia. Few studies have investigated the cost associated with TBI and dementia, which are both highly prevalent in Veterans. We examined the marginal impact of comorbid TBI-dementia relative to TBI only, dementia only and neither condition on VA and non-VA facility as well as pharmacy costs. We evaluated data for 523,906 Veterans without TBI or dementia, 194,596 with TBI only, 26,504 with dementia only, and 34,093 with comorbid TBI-dementia. The study found that Veterans <65 and ≥65 with TBI only had similar adjusted higher annual total costs relative to Veterans without TBI or dementia. However, Veterans with comorbid TBI-Dementia <65 had almost twice the annual total costs of Veterans ≥65, relative to Veterans without TBI or dementia. A manuscript detailing these important results is under review for the Brain Injury Special Issue.

Major Task 9: Prepare manuscripts for journal publication.

Month(s): *24 - 60*

Progress: None yet as this will occur during year 3.

Milestone: *Data analysis completed and manuscripts prepared for journal submission.*

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: None yet as this will occur during year 3.

Major Task 11: Create and validate prognostication clinical tool.

Month(s): *36 - 60*

Progress: *None yet as this will occur during year 4.*

Major Task 12: Prepare manuscripts on prognostic models.

Month(s): *48 - 60*

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

Milestone: Data analysis completed, manuscripts prepared for journal submission, and clinical modeling tool ready for use.

Major Task 13: Attendance at biannual GSC meetings.

Month(s): *6 - 60*

Progress: We presented updates on our work at the February 2020. 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.

• We obtained DoD and VA health system data through FY20 in December 2020.

• We obtained National Death Index (NDI) through 2018 in February 2020 and identified cause of death for deaths within that timeframe. Date of death has been obtained through April 2020 and will be refreshed (along with NDI data through 2019) as they become available.

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

• We obtained Theatre data management store data to identify TBI in theatre that was not among individuals in DoDTR in December 2020.

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

• We obtained US VETS data that provide information on post-military outcomes on September 27, but determined that the data pull was insufficient (only 297k of 2.5 million possible participants) and asked for another pull of those data.

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 preliminary analyses for cognitive dysfunction and mortality.

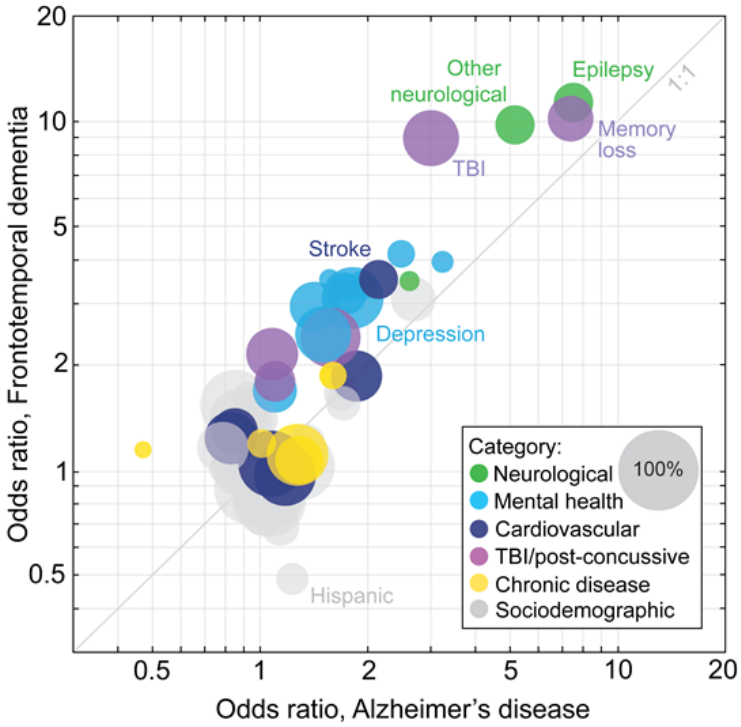
Early Onset Dementia (EOD) in Post-9/11 Veterans:

Because we did not receive DoDTR until the third quarter of FY21, we conducted our initial paper describing early onset dementia using data from our prior cohort including those who received at least 2 years of care within the VA during fiscal years (FY) 2002-2018, who also received DoD care for at least two years between FY2000-FY2019 (N=1,226,253). To develop the EOD cohort, we used algorithms to identify all Veterans within the full cohort with AD (PPV=0.88) or FTD (PPV=0.96) who were diagnosed at age <=65 (n=973). We then matched each member of the EOD group to similar controls using a nearest neighbor algorithm that paired individuals based on age, sex, race/ethnicity, service-connected disability/retirement status, and deployment status. Table 1 shows characteristics of those with EOD and matched controls. Veterans with EOD were more likely than matched controls to have TBI, stroke, cardiac conditions, PTSD, depression, attention disorders, epilepsy, other significant neurological disorders (e.g., Parkinson's disease, encephalopathy, anoxic brain injury), kidney disease, headache, and the symptom diagnosis of "memory loss."

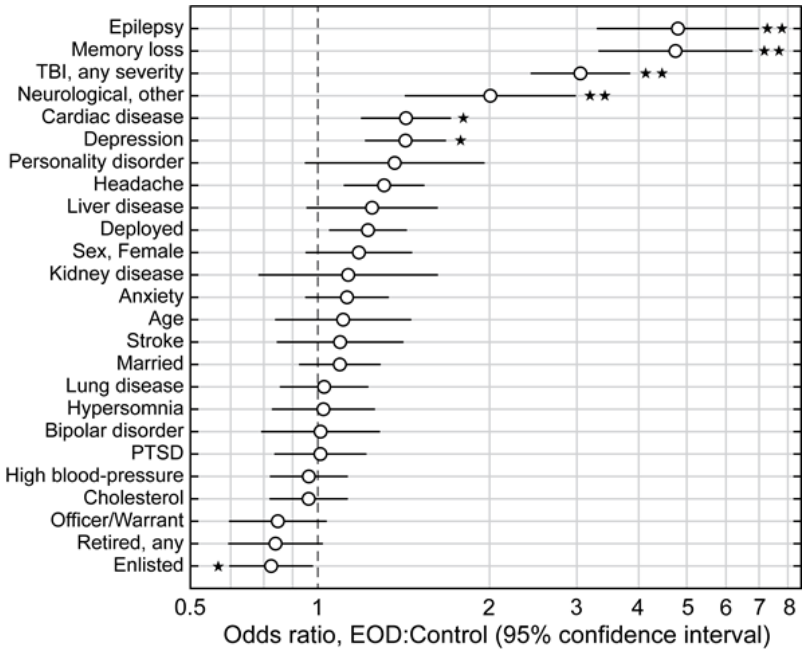
Table 1: Characteristic of Post-9/11 Veterans with EOD (Alzheimer's and Frontotemporal Dementia)

	Percentage	Full cohort N=1.22x10^6	MC n=973	EOD n=973	p value MC v. EOD
Demographics	Age, years	41.7	54.7	54.0	>0.5
	Female	17	15.6	15.6	>0.5
	Married	48.9	65.3	65.1	>0.5
	Retired	5.3	10.3	21.3	>0.5
	SVC Disability	46.5	52.2	69.4	>0.5
Race/Ethnicity	White	59.8	62.3	62.8	>0.5
	Black	18.0	18.1	18.3	>0.5
	Hispanic	10.0	9.9	10.3	>0.5
	Other	14.0	9.0	8.6	>0.5
Military	Deployed	69.9	51.5	51.6	>0.5
TBI	TBI, any	26.5	11.8	36.3	**<0.001***
Cardiovascular	Stroke	4.1	7.5	16.9	**<0.001***
	Cardiac	11.1	20.2	32.1	**<0.001***
	Smoking	47.1	43.7	48.6	0.03
	Diabetes	8.9	11.7	14.4	0.06
	Hypertension	28.9	46.2	48.8	0.24
	Cholesterol	38.5	55.0	56.5	>0.5
	Obesity	31.7	35.9	34.3	>0.5
Mental Health	Anxiety	35.3	27.0	39.2	**<0.001***
	Depression	42.6	30.8	48.6	**<0.001***
	Attention	7.7	3.9	8.1	**<0.001***
	PTSD	37.6	19.0	29.5	**<0.001***
	Subst. abuse	35.6	19.1	22.9	0.037
	Suicide attempt	4.0	1.0	2.1	0.07
Neurological	Epilepsy	2.5	1.6	11.3	**<0.001***
	Other neurological conditions	2.3	2.1	17.3	**<0.001***
Chronic Disease	Kidney disease	2.4	3.2	6.3	**<0.001***
	Liver disease	9.9	1.5	6.3	0.02
Post-concussive symptoms	Headache	30.2	31.9	45.4	**<0.001***
	"Memory loss"	3.9	3.9	24.8	**<0.001***
	Insomnia	26.2	27.3	33.5	0.004

The figure below shows unadjusted odds ratios for conditions in the table above AD on the X-axis and FTD on the Y- axis. Conditions above the diagonal more strongly predicted FTD, and those below the diagonal were stronger predictors of AD. These unadjusted odds ratios revealed that epilepsy, self-reported complaints of memory problems, other neurological conditions, and TBI strongly predicted both AD and FTD, but had stronger relationships with FTD.



Because proportional hazards assumptions were not met, we conduced logistic regression models controlling for demographic, military and clinical conditions described above to determine the association of TBI and related comorbidity/symptoms accounting for other characteristics. The figure below demonstrates that even after controlling for all demographic, military and clinical covariates, epilepsy, self-reported memory loss, TBI, other neurological conditions, cardiovascular disease and depression were significant predictors of subsequent early onset AD/FTD.



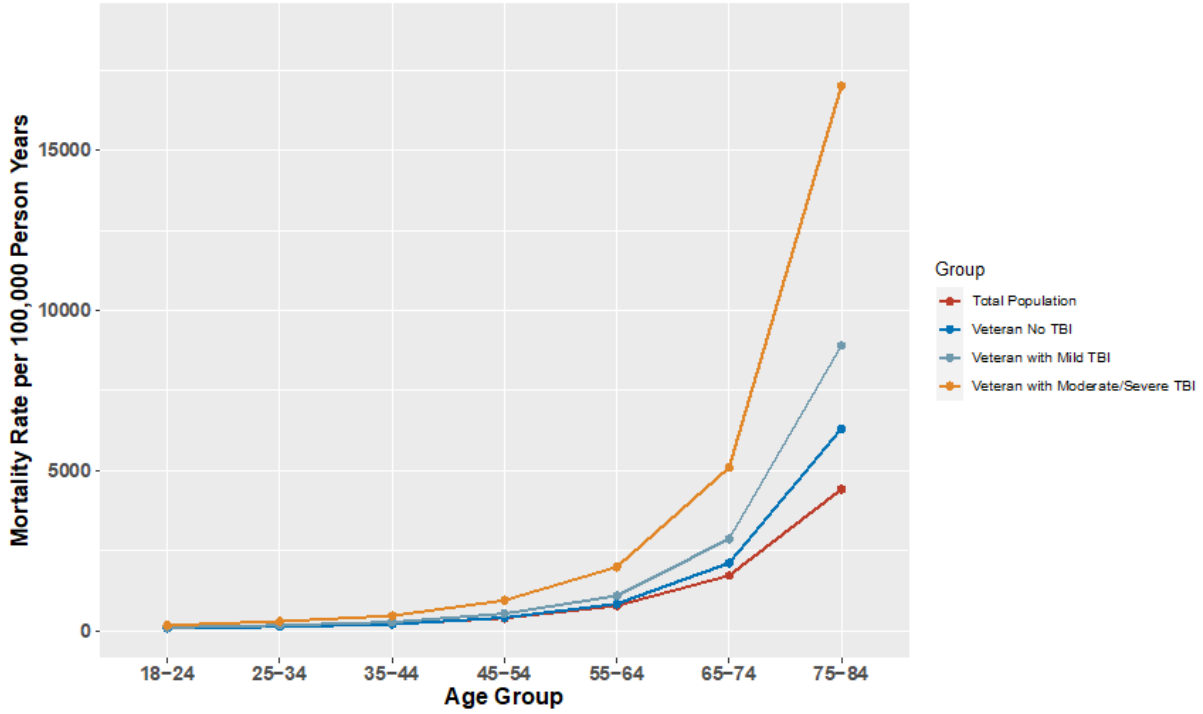
This manuscript was submitted to the Brain Injury special issue.

A second manuscript that is currently under review in JAMA.
The United States (US) military recently withdrew from Afghanistan after 20 years of war. Emerging evidence suggests that harmful exposures during military service, such as traumatic brain injury (TBI), may contribute to

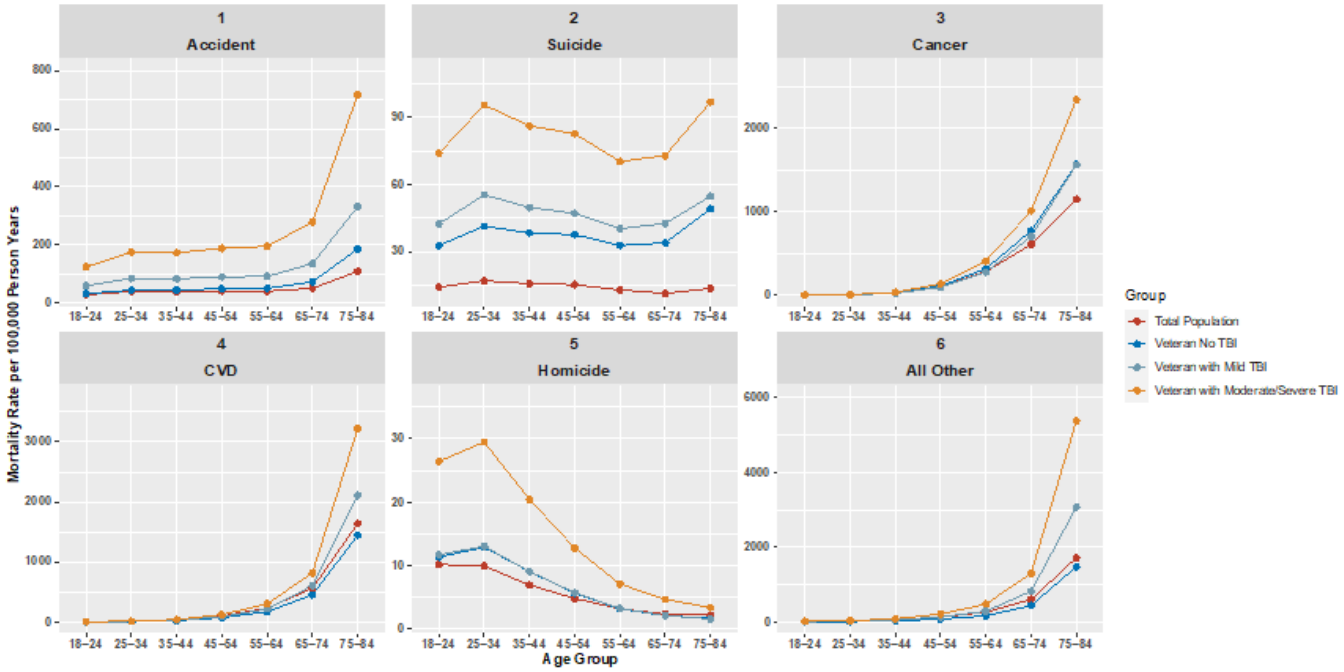
mental health, chronic disease, and mortality risks. We sought to assess the total mortality burden and estimate excess mortality among post-9/11 military veterans.

Methods: The population of post-9/11 military veterans who received three years of care from the Department of Defense were followed for mortality by matching to the National Death Index from 2002-2018. Multivariable, negative binomial regression models were used to estimate adjusted all-cause and cause-specific mortality rates for the post-9/11 military veteran population, stratified by TBI severity level, and the total US population. Differences in mortality rates between post-9/11 military veterans and the total US population were used to estimate excess deaths from each cause of death.

The figure below shows mortality rates and 95% confidence intervals by 5-year age groups for Veterans and the general population. This figure demonstrates that age adjusted mortality was significantly higher for Post-9/11 Veterans, and that mortality for Post-9/11 Veterans with TBI was higher than for those with no TBI. Moreover, moreover, mortality was significantly higher for those with moderate/severe TBI than for those with mild TBI.



We also examined variation in cause of death by the same strata and age groups. While there was little difference between younger Veterans without TBI and the general population for death by accidents, rates were significantly higher for Veterans with mTBI, and even higher for those with moderate/severe TBI.



For death by suicide, all Veteran groups had higher rates than the general population, with the highest rates for those with moderate/severe TBI followed by mTBI and no TBI. For older age groups, mTBI and no TBI were not significantly different. For cancer, cardiovascular disease and other causes of death, Veterans with moderate/severe TBI had significantly higher rates than all others in older age groups (e.g., 55+). Veterans with moderate/severe TBI also had higher rates of death by homicide than other Veterans and the general population. Future research will try to disentangle TBI and deployment effects.

Finally, we continue to finalize our manuscript on risk of cardiovascular outcomes associated with TBI. A comprehensive description of that analysis will be provided as analyses are completed in the next quarter.

A comprehensive description of our cohort by deployment status is provided below:

Table: Demographic Characteristics of LIMBIC Phenotype cohort (three or more years of DoD care [DoD+VA cohort also has two or more years of VA care]) by Deployment Status

No. (%)	**Non-Deployed**	**Deployed**
DEMOGRAPHICS		
Age (Mean [SD]) at VA entry**)**		
17-29	46.70 (175,634)	55.08 (478,991)
30-39	21.43 (80,610)	23.83 (207,193)
40-49	23.79 (89,471)	16.83 (146,322)
50 and older	8.07 (30,367)	4.26 (37,060)
Sex: Female	26.56 (99,894)	12.90 (112,155)*
Race/Ethnicity		
White	54.73 (205,814)	62.04 (539,506)

Black	21.41 (80,532)	16.77 (145,823)
Hispanic	8.22 (30,909)	10.61 (92,250)
Asian	2.44 (9,174)	2.37 (20,637)
Native American/Pacific Islander	1.69 (6,356)	1.85 (16,106)
Unknown	11.51 (43,297)	6.35 (55,244)
Marital Status upon discharge		
Married	49.22 (185,124)	48.73 (423,774)

Chi square analyses found that those who were deployed were younger, less likely to be female, and more likely to be White non-Hispanic and Hispanic ($p<.0001$).

Table 2 shows descriptive statistics for injury data by deployment status. Those deployed were significantly more likely to have TBI, including all levels of severity ($p<.0001$) and spinal injury ($p<.0001$). Those who were non-deployed were significantly more likely to have a documented burn injury ($p<.001$), however burn severity was not identified in this analysis. While those who were deployed were significantly more likely to have amputation ($p<.01$), this small difference is due to the extremely large cohort. Future descriptions are restricted to those differences that are more clinically meaningful and $p<.0001$.

Table 2: DoD Injury Characteristics of LIMBIC Phenotype Cohort by Deployment Status

	Non-Deployed N=386,082 % (n)	**Deployed N=859,566 % (n)**
TBI Severity		
Screen Positive no other Evidence (based on VA screening data)	1.08 (4,058)	7.26(63,102)
Mild	2.43 (9,122)	13.36 (11,6215)
Moderate/Severe	0.96 (3,607)	3.10 (26,980)
Penetrating	0.10 (369)	0.33 (2,897)
History of Code/Unclassified	2.04 (7,658)	3.98 (34,591)
No Evidence of TBI	93.40 (351,268)	71.96 (625,781)
Other Injury		
Burn Injury	8.20 (30,844)	7.50 (65,238)
Amputation Injury	0.69 (2,601)	0.73 (6,378)
Spinal Injury	2.41 (9,068)	7.63 (66,356)

Table 3 shows the proportion of deployed and non-deployed service members with diagnoses of neurosensory and pain-related conditions. Those who were deployed were significantly more likely to have blurred vision/photophobia, tinnitus, and hearing loss than non-deployed personnel ($p<.0001$). Regarding pain, deployed service members were more likely to have diagnoses of backpain and headache, while non-deployed personnel were more likely to have diagnoses of other musculoskeletal pain ($p<.0001$).

Table 3: DoD Diagnoses of Neurosensory and Pain Conditions in LIMBIC Phenotype Cohort by Deployment Status

	Non-Deployed	**Deployed**

	N=386,082 % (n)	N=859,566 % (n)
Neurosensory Disorders		
Blurred Vision/Photophobia	1.23 (4,632)	1.41 (12,265)
Blindness	0.74 (2,784)	0.73 (6,391)
Vestibular Dizziness	3.28 (12,342)	3.17 (27,579)
Tinnitus	5.80 (21,818)	9.79 (85,159)
Balance Problems	1.39 (5,231)	1.07 (9,339)
Hearing Loss	10.66 (40,078)	12.70 (110,398)
Pain		
Back Pain	42.44 (159,617)	45.83 (398,538)
Neck Pain	14.48 (54,438)	14.00 (121,721)
Other Musculoskeletal Pain	29.64 (111,486)	25.45 (221,286)
Headache	19.69 (74,046)	22.17 (192,806)

Table 4 shows proportions of deployed and non-deployed individuals who had diagnoses of specific mental health and substance use disorder diagnoses while in DoD care. Deployed personnel were profoundly more likely to have diagnoses of PTSD ($p<.0001$) and significantly more likely to have diagnoses of depression, anxiety, suicidal ideation/attempt, and overdose than non-deployed service members ($p<.0001$). Non-deployed personnel were significantly more likely than deployed personnel to have diagnoses of bipolar disorder and schizophrenia ($p<.0001$). Deployed service members were also more likely to have any substance use disorder and a number of different types of substance use disorders ($p<.0001$). Of particular interest are alcohol use, amphetamine, cocaine, opioid and cannabis use.

Table 4: DoD Diagnoses of Mental Health and Substance Use Disorders in LIMBIC Phenotype Cohort by Deployment Status:

	Non-Deployed N=386,082 % (n)	Deployed N=859,566 % (n)
Mental Health		
Depression	34.10 (128,257)	38.07 (331,042)
PTSD	17.24 (64,830)	43.78 (380,737)
Anxiety	26.18 (98,452)	28.54 (248,177)
Bipolar Disorder	11.19 (42,074)	9.64 (83,843)
Schizophrenia	1.56 (5,881)	0.84 (7,344)
Suicidal Ideation/Attempt	5.54 (20,818)	6.47 (56,280)
Any Overdose	3.27 (12,305)	3.72 (32,326)
Substance Use Disorders		
Any Drug/Alcohol Abuse	19.37 (72,861)	27.33 (23,7647)
Alcohol Abuse	14.46 (54,383)	22.82 (198,472)
Amphetamine Abuse	1.82 (6,830)	2.10 (18,252)
Cannabis Abuse	6.28 (23,623)	8.06 (70,093)
Cocaine Abuse	2.27 (8,544)	2.65 (23,053)
Opioid Abuse	3.27 (12,314)	3.48 (30,234)
Sedative Abuse	1.10 (4,120)	1.16 (10,051)
Hallucinogen Abuse	0.25 (925)	0.25 (2,167)
Other Drug Abuse	5.54 (20,847)	6.85 (59,528)

Table 5 shows comparisons of deployed and non-deployed personnel on sleep and central nervous system disorders. Deployed personnel had significantly higher rates of hypersomnia, insomnia, and obstructive sleep apnea. There were also more likely than non-deployed personnel to have diagnoses consistent with any cognitive dysfunction which includes diagnoses of memory loss, mild cognitive impairment and diagnoses included in VA's dementia diagnoses (p<.0001); most diagnoses were for "memory loss". Non-deployed personnel were significantly more likely to have higher prevalence of pituitary disorders, stroke, and epilepsy/seizures (p<.0001). These data also suggest certain individuals have multiple substance use disorders that require further evaluation.

Table 5: DoD Diagnoses of Sleep and Central Nervous System Disorders in LIMBIC Phenotype Cohort by Deployment Status:

	Non-Deployed N=386,082 % (n)	**Deployed N=859,566 % (n)**
Sleep		
Hypersomnia	6.53 (24,558)	6.93 (60,252)
Obstructive Sleep Apnea	18.46 (69,423)	20.06 (174,446)
Insomnia	12.49 (46,991)	18.04 (156,856)
CNS/Cognitive Conditions		
Stroke-Cerebrovascular Disease	1.01 (3,806)	0.72 (6,295)
Pituitary Disorders	0.80 (2,999)	0.64 (5,588)
Any Cognitive Dysfunction	0.92 (3,478)	1.55 (13,461)
Epilepsy/Seizures Status		
Epilepsy	3.20 (12,044)	2.16 (18,800)
Seizure, No Epilepsy	1.91 (7,175)	1.42 (12,342)

Table 6 shows differences in chronic disease in DoD by deployment status. For all chronic diseases except liver disease, the non-deployed cohort was significantly more likely to be diagnosed in DoD (p<.0001). Mortality data through February 2020 revealed those who were not deployed were also significantly more likely to be deceased.

Table 6: DoD Diagnoses of Chronic Disease in LIMBIC Phenotype Cohort by Deployment Status

	Non-Deployed N=386,082 % (n)	**Deployed N=859,566 % (n)**
Chronic Disease		
Cancer	2.58 (9,686)	1.67 (14,545)
Coronary Artery Disease	1.88 (7,088)	1.17 (10,195)
Other Cardiac Disease	7.10 (26,694)	5.05 (43,944)
Hypercholesterolemia	30.96 (116,440)	30.11 (261,865)
Chronic Lung Disease	1.14 (4,285)	0.92 (7,986)
Hypertension	25.16 (94,627)	21.33 (185,462)
Liver Disease	3.00 (11,284)	2.90 (25,204)
Kidney/Renal Failure	1.71 (6,432)	1.19 (10,343)
Obesity	24.14 (90,802)	23.36 (203,147)
Diabetes	8.92 (33,556)	6.31 (54,897)
Osteoarthritis	10.61 (39,916)	7.78 (67,636)
Mortality (As of 06 FEB 2020)	2.39 (9,006)	1.80 (15,692)

These data suggest that the non-deployed cohort experienced some injuries consistent with trauma, possibly due to motor vehicle accidents, and that they were more likely to have certain CNS related conditions, and chronic disease. Those who were deployed were significantly more likely to have TBI, traumatic injuries, mental health and substance use disorders, suggesting both physical and psychic impact of combat deployment. Further analyses will explicate the relationship of these DoD diagnoses to VA comorbidity and adverse outcomes.

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: None yet as this will occur during year 3.

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.

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 FY21***
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. ***50% Complete***
Milestone: Develop DoD+VA phenotypes in: deployed VA users; nondeployed VA users; deployed no VA care; non-deployed no VA care.
Milestone: Compare phenotypes among sub-strata (deployed/nondeployed/VA/non-VA).
Milestone: Examine association of military relevant outcomes and repetitive low-level blast occupations with phenotypes.

Health Economics Study:

Major Task 1: Obtain DoD and VA authorizations.

Month(s): *1 – 24*

a. We amended the IRB with Stanford IRB and DART adding the newly hired analyst, and received IRB approval for accessing and transferring EDIPI (Electronic Data Interchange Personal Identifier) to VCU DBC by study ID to obtain biomarkers.

b. A DUA amendment to transfer EDIPI to VCU DBC was approved and executed.

c. We've contacted San Diego and Salisbury VAs and Fort Belvoir's military treatment center to receive site data and SSN/EDIPI. The points of contact noted they'll follow up with our study team once they are ready to transfer data.

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:

a. We obtained newly available DOD Tri Care cost data for inpatient and outpatient care for all Veterans in the Longitudinal Study Cohort who use VHA. MTF cost data are now available and we are in the process of obtaining this cost data as well.

b. We have used a lookback into DoD Theater data for Veterans with a TBI diagnosis to compare return to duty from injury or disease in theatre by TBI vs other conditions and TBI severity in a preliminary analysis. We will be working with Dr. Hinds, Dr. Cifu, Dr. Pugh, and Dr. Stewert to expand and interpret these analyses.

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:

a. Tricare Cost Data. We have added DoD Tricare Cost data to our administrative data cohort.

b. Military Treatment Facility Data- Military Treatment Facility Cost data have just become available in DaVINCI so we will be requesting this data as well.

c. Merging longitudinal data with VINCI DATA. We have merged data from the longitudinal study on combat and training exposures as well as potential concussive events and TBIs for analysis of the association of combat and training exposures with 1) VA utilization and costs as well as 2) DoD utilization and Tricare costs. After we received the updated cohort dataset from VCU, we performed the following analysis 1) pulled VA inpatient, outpatient, pharmacy costs and utilization of health service in both individual collapsed and annual levels, 2) pulled non-VA inpatient, outpatient costs and utilization of health service in both individual collapsed and annual levels, 3) pulled the number of Elixhauser Comorbidity and Index, including inpatient and both inpatient and outpatient ICD codes, 4) pulled high risk conditions including dementia and PTSD, 5) merged datasets and total costs and health care utilization, and, 6) transferred and cleaned datasets to STATA. We are in the process of analysis of association of TBI type and exposures with longitudinal VA costs and then we will analyze DoD costs.

d. TBI + Dementia for Special Brain Injury Issue. Veterans with a diagnosis of TBI were age-matched with a cohort without TBI diagnosis from inpatient and outpatient patient treatment file (PTF) between January 1, 2000 and December 31, 2015. The data was pulled from VA Informatics and Computing Infrastructure (VINCI). TBI diagnosis came from the standard surveillance case definitions used by the Armed Forces Health Surveillance Branch (AFHSB) Veterans were followed for any dementia diagnosis after TBI exposure until September 30, 2020. A clinical diagnosis of dementia was based on the FY21 VHA Dementia ICD codes list) applied to the PTF files.

The VA's Vital Status Files (VSF) and Health Economics Resource Center (HERC) files were linked to PTF files using a scrambled social security number to calculate annual survival and identify VHA annual costs from FY2000-2020 (FY2020 was the last year available for annual cost by Veteran). All costs were adjusted for 2020 inflation. Demographics and co-morbidities were obtained from inpatient and outpatient PTF, mini vital, and OMOP files.
To estimate the covariate-adjusted likelihood of dementia with a TBI diagnosis, logit models were used. To estimate the covariate-adjusted association of TBI diagnosis status with dementia, a Cox Proportional Hazards Survival model (time to dementia) was used. To estimate the covariate-adjusted association of TBI/dementia diagnosis status with all-cause mortality, a Cox Proportional Hazards Survival model was used. For estimation of the inpatient, outpatient, pharmacy, and community care cost categories for different TBI and dementia statuses, a generalized linear model (GLM) with gaussian family and identity link were used. To estimate the covariate-adjusted association of TBI and dementia status with annual total VHA plus community care, a generalized estimating equations (XTGEE) was used.

For the adjusted model we tested two models:
Model 1: Adjusting for age, gender, race/ethnicity, marital status, insurance, urban/rurality,

service-connected disability, number of Elixhauser conditions, OEFOIF, and death.

Model 2: we added the PTSD, alcohol abuse, drug abuse, psychoses, depression comorbidities to the first model.

We used panel datasets for GLM and XTGEE estimation and added years to adjusted models. All costs were converted to 2020-dollar values using the US Department of Labor Consumer Price Index (CPI) Inflation calculator. All analyses were performed using STATA version 15.0 in VINCI. Statistical significance was determined at P<0.05.

e. TBI and Dementia

i. Methods: Methods: The HES team evaluated panel data for 523,906 Veterans without TBI or dementia, 194,596 with TBI only, 26,504 with dementia only, and 34,093 with TBI plus dementia using VA Informatics and Infrastructure (VINCI) inpatient and outpatient patient treatment files (PTF) database. Data from PTF was pulled between January 1, 2000 and December 31, 2015. These Veterans were longitudinally followed for ICD-9 or ICD-10 dementia codes after TBI diagnosis through September 30, 2020. HES obtained costs for annual per veteran total, inpatient (VA and non-VA facilities), outpatient (VA and non-VA facilities), and VA pharmacy during FY2000-2020. Cost data was adjusted for inflation to 2021 $ values. We examined unadjusted costs by category over time since TBI diagnosis, and stratified by age<65 and age≥65. To estimate the cost categories by TBI-dementia status, we used generalized estimating equations for panel data. Cost models were also stratified by age<65 vs age ≥65. In addition, we estimated the incremental costs associated with time since dementia for 1-5 and 5-10 years relative to the first-year post-diagnosis in veterans diagnosed with TBI.

ii. Results: Results: In fully adjusted models, Veterans<65 with TBI plus dementia ($9,759, 9031:10487) and Veterans ≥65 ($6,193, 5643:6743) higher annual VA facility inpatient costs relative to Veterans without TBI or dementia. Veterans <65 with TBI plus dementia)$19,912, 15448:21376) and Veterans ≥65 ($8,514, 5498:11529) higher annual non-VA facility inpatient costs relative to Veterans without TBI or dementia. Over time since TBI+D diagnosis, Veterans <65 with TBI plus dementia ($28,315, 19262:37368) had higher annual non-VA inpatient facility costs in years ≥10 while veterans ≥65 had no significant differences over time. Tables of results, including a figure follow..

Demographics, Clinical Characteristics, and Mortality Stratified by Traumatic Brain Injury (TBI) and Dementia

*$P < 0.001$	No TBI-Dementia	TBI Only	Dementia Only	TBI & Dementia
N	523,906	194,596	26,504	34,093
Age				
<65*	80.3%	78.2%	44.4%	35.0%
≥65	19.7%	21.7%	55.6%	65.0%
Gender*				
Male	89.1%	91.9%	96.5%	96.5%
Female	10.9%	8.1%	3.5%	3.5%
Race*				
Non-Hispanic White	54.9%	64.8%	70.0%	66.1%
Non-Hispanic Black	6.6%	14.5%	6.1%	13.5%
Hispanic	3.5%	8.3%	3.4%	9.0%
Other	35.1%	12.3%	20.6%	11.4%

Marital Status*				
Married	37.9%	41.8%	46.4%	42.9%
Single	12.4%	19.5%	6.9%	11.4%
Widowed/Separated/Divorced	20.3%	36.1%	31.8%	44.5%
Unknown	29.4%	2.6%	14.9%	1.2%
Insurance*				
VA Only	75.0%	54.4%	61.8%	49.8%
Medicare/Supp/Medicaid	18.6%	30.7%	37.3%	48.4%
Major Medical/HMO/PPO	6.4%	14.9%	1.0%	1.8%
Location*				
Urban	52.0%	68.0%	50.6%	71.3%
Rural/Highly Rural	47.6%	32.0%	49.3%	28.7%
US Territory	0.4%	0.1%	0.2%	0.0%
OEF/OIF*	8.2%	29.8%	0.3%	1.8%
Service-Connected Disability*				
<50%	26.5%	17.4%	22.9%	19.5%
>50%	28.9%	52.2%	34.8%	40.1%
No Service-Connected Disability	44.6%	30.4%	42.3%	40.4%
Death*	29.8%	28.6%	68.6%	68.4%
PTSD*	11.1%	34.2%	11.5%	14.8%
Elixhauser Comorbidities*				
Alcohol Abuse	13.7%	31.0%	22.4%	29.5%
Drug Abuse	9.2%	24.0%	12.5%	19.9%
Psychoses	19.3%	40.6%	41.5%	56.3%
Depression	28.5%	55.5%	47.4%	60.4%
Congestive Heart Failure	8.6%	13.4%	25.3%	31.4%
Valvular Disease	4.7%	7.5%	13.2%	16.6%
Pulmonary Circulation Disease	2.6%	4.7%	6.1%	8.8%
Peripheral Vascular Disease	9.2%	14.1%	24.9%	30.9%
Hypertension	47.6%	58%	78.8%	86.5%
Paralysis	2.7%	7.6%	10.4%	18.7%
Other Neurological Disorder	9.5%	28.6%	65.7%	77.2%
Chronic Pulmonary Disease	24.5%	34.5%	43.2%	50.5%
Diabetes without Chronic Complications	22.1%	26%	38.8%	43.7%
Diabetes with Chronic Complications	13.2%	16.9%	26.2%	29.7%
Hypothyroidism	6.6%	9.5%	14.4%	18.5%
Renal Failure	6.9%	11.3%	21.2%	27.5%
Liver Disease	7.1%	13.6%	10.7%	15.2%
Peptic Ulcer Disease x Bleeding	0.6%	1.2%	1.6%	2.2%
Acquired Immune Deficiency Syndrome	0.5%	0.8%	0.8%	0.9%
Lymphoma	1.2%	1.5%	1.9%	2%

Metastatic Cancer	3.1%	4%	4.5%	5.4%
Solid Tumor without metastasis	12.7%	15.5%	23.7%	27.9%
Rheumatoid Arthritis / Collagen Disease	3.7%	5%	5.7%	6.2%
Coagulopathy	4.4%	9.1%	11.9%	18.3%
Weight Loss	5.6%	11.5%	21.7%	28.9%
Fluid and Electrolyte Disorder	13.5%	28.2%	42.7%	61.5%
Chronic Blood Loss/ Anemia	1.3%	2.5%	3.8%	5.2%
Deficiency Anemia	12.9%	23.9%	37.9%	52.4%

Adjusted Marginal Impact (95% CI) of TBI-Dementia Status on Annual VHA Costs Per Veteran, 2000-2020 in 2021 $ Values[†]

	Unadjusted	**P value**	**Model 1**	**P value**	**Model 2 Age<65**	**P value**	**Model 3 Age≥65**	**P value**
VA Facility Outpatient								
No TBI & Dementia	**Reference**							
Only TBI	$2,995 (2963:3026)	<0.001	$1051 (1019:1084)	<0.001	$931 (894:967)	<0.001	$1494 (1416:1571)	<0.001
Only Dementia	$1,573 (1496:1650)	<0.001	$-701 (-783:-618)	<0.001	$-720 (-856:-584)	<0.001	$-386 (-478:-293)	<0.001
TBI & Dementia	$3,851 (3762:3940)	<0.001	$246 (152:341)	<0.001	$506 (334:678)	<0.001	$464 (346:583)	<0.001
VA Facility Inpatient								
No TBI & Dementia	**Reference**							
Only TBI	$3,705 (3624:3786)	<0.001	$793 (709:877)	<0.001	$814 (724:904)	<0.001	$460 (225:695)	<0.001
Only Dementia	$8,488 (8134:8841)	<0.001	$2007 (1661:2353)	<0.001	$2427 (1921:2933)	<0.001	$1069 (618:1520)	<0.001
TBI & Dementia	$16,974 (16531:17416)	<0.001	$8157 (7713:8601)	<0.001	$9759 (9031:10487)	<0.001	$6193 (5643:6743)	<0.001
Non-VA Facility Outpatient								
No TBI & Dementia	**Reference**							
Only TBI	-$3,249 (-3681:-2818)	<0.001	$-829 (-1196:-462)	<0.001	$-997 (-1403:-590)	<0.001	$874 (86:1663)	0.03
Only Dementia	$6,421 (4905:7936)	<0.001	$-598 (-1772:575)	0.318	$-904 (-2907:1100)	0.377	$237 (-714:1187)	0.626
TBI & Dementia	$4,485 (3436:5534)	<0.001	$-1184 (-2325:-43)	0.042	$-262 (-2428:1905)	0.813	$-102 (-1331:1128)	0.871
Non-VA Facility Inpatient								
No TBI & Dementia	**Reference**							
Only TBI	$2,383 (1656:3111)	<0.001	$2292 (1725:2860)	<0.001	$2643 (2010:3276)	<0.001	$948 (-394:2290)	0.166

Only Dementia	$27,657 (24312:31002)	<0.001	$4340 (2418:6261)	<0.001	$3189 (538:5839)	0.018	$4833 (2141:7525)	<0.001
TBI & Dementia	$32,919 (29636:36202)	<0.001	$12900 (10363:15437)	<0.001	$19912 (15448:24376)	<0.001	$8514 (5498:11529)	<0.001
Pharmacy VA								
No TBI & Dementia	**Reference**							
Only TBI	$619 (595:644)	<0.001	$-5 (-28:18)	0.663	$-35 (-60:-11)	0.005	$219 (176:263)	<0.001
Only Dementia	$869 (826:913)	<0.001	$-251 (-297:-206)	<0.001	$-266 (-340:-192)	<0.001	$-152 (-204:263)	<0.001
TBI & Dementia	$1,660 (1605:1714)	<0.001	$28 (-32:89)	0.356	$211 (94:328)	<0.001	$187 (117:257)	<0.001
Total								
No TBI & Dementia	**Reference**							
Only TBI	$6,506 (5596:7416)	<0.001	$3344 (2627:4061)	<0.001	$3379 (2582:4176)	<0.001	$4252 (2609:5895)	<0.001
Only Dementia	$45,729 (41872:49586)	<0.001	$4822 (2467:7177)	<0.001	$3708 (242:7174)	0.036	$5824 (2828:8819)	<0.001
TBI & Dementia	$60,537 (56962:64111)	<0.001	$20408 (17526:23290)	<0.001	$30376 (25262:35491)	<0.001	$15650 (12271:19028)	<0.001

† Models 2 and 3 adjusted for Year, Age, Gender, Race/Ethnicity, Marital Status, Insurance, Urban/Rural/Territory, Service-Connected Disability, All Elixhauser Comorbidities, OEFOIF, and Death. Model 1 also adjusted for age ≥65 vs age <65.

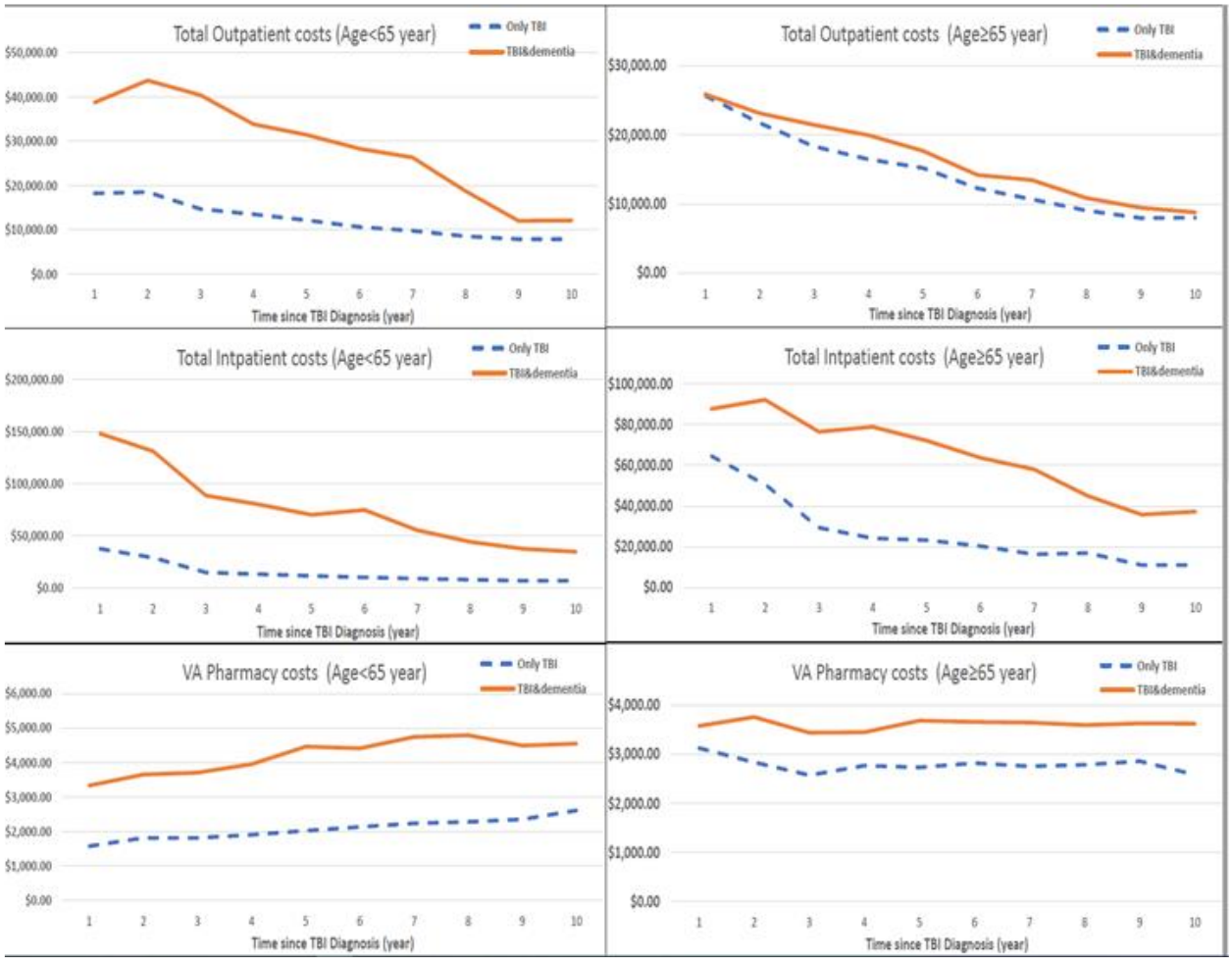
Adjusted Marginal Impact (95% CI) of Years Since Dementia Diagnosis on Annual VHA Costs Per Veteran Diagnosed with Comorbid TBI-Dementia, 2000-2020 in 2021 $ Values†

Years Since Dementia Diagnosis	**Unadjusted**	**P value**	**Model 1 All ages**	**P value**	**Model 2 Age<65**	**P value**	**Model 3 Age≥65**	**P value**
VA Facility Outpatient								
0-1	**Reference**							
1-5	$347 (-85:778)	0.115	$521 (142:899)	0.007	$863 (284:1441)	0.003	$91 (-395:577)	0.713
5-10	$-742 (-1159:-325)	<0.001	$232 (-146:610)	0.229	$755 (169:1341)	0.012	$-276 (-754:202)	0.258
≥10	$-1683 (-2101:-1264)	<0.001	$604 (178:1029)	0.005	$884 (252:1517)	0.006	$118 (-387:623)	0.647
VA Facility Inpatient								
0-1	**Reference**							
1-5	$5022 (3862:6182)	<0.001	$266 (-904:1436)	0.656	$2630 (794:4467)	0.005	$-1138 (-2546:270)	0.113
5-10	$10713 (9527:11898)	<0.001	$3211 (1904:4517)	<0.001	$5605 (3474:7735)	<0.001	$3401 (1811:4990)	<0.001
≥10	$17848 (16481:19216)	<0.001	$12420 (10881:13959)	<0.001	$9758 (7588:11929)	<0.001	$16261 (14041:18482)	<0.001
Non-VA Facility Outpatient								

0-1	**Reference**							
1-5	$-1715 (-12354:8925)	0.752	$-2686 (-13667:8295)	0.632	$-5490 (-25704:14724)	0.595	$722 (-2755:4200)	0.684
5-10	$-1327 (-11884:9231)	0.805	$-3970 (-15081:7140)	0.484	$-5681 (-26299:14937)	0.589	$-367 (-3674:2941)	0.828
≥10	$14839 (4216:25463)	0.006	$1928 (-9546:13402)	0.742	$-4049 (-25353:17254)	0.709	$7196 (3563:10828)	<0.001
Non-VA Facility Inpatient								
0-1	**Reference**							
1-5	$627 (-6456:7710)	0.862	$-5176 (-12628:2275)	0.173	$-1062 (-6990:4865)	0.725	$-9499 (-24395:5397)	0.211
5-10	$7409 (91:14728)	0.047	$-6477 (-15129:2174)	0.142	$-826 (-11383:9732)	0.878	$-11149 (-26733:4436)	0.161
≥10	$85512 (74783:96241)	<0.001	$19571 (10734:28409)	<0.001	$28315 (19262:37368)	<0.001	$12421 (-3808:28651)	0.134
Pharmacy								
0-1	**Reference**							
1-5	$223 (-84:529)	0.155	$153 (-130:435)	0.289	$346 (-32:723)	0.073	$-37 (-457:382)	0.862
5-10	$52 (-238:341)	0.727	$178 (-97:454)	0.205	$297 (-91:684)	0.133	$84 (-300:468)	0.668
≥10	$-76 (-375:222)	0.617	$912 (600:1223)	<0.001	$907 (413:1401)	<0.001	$844 (437:1252)	<0.001
Total								
0-1	**Reference**							
1-5	$4760 (-8288:17809)	0.475	$-6898 (-20204:6409)	0.31	$-2637 (-23639:18365)	0.806	$-9920 (-25518:5679)	0.213
5-10	$16675 (3551:29800)	0.013	$-6477 (-20604:7650)	0.369	$367 (-22776:23510)	0.975	$-7786 (-24016:8444)	0.347
≥10	$116855 (101487:132223)	<0.001	$36278 (21709:50847)	<0.001	$36431 (13301:59561)	0.002	$37589 (20568:54610)	<0.001

†Models 2 and 3 adjusted for Year, Age, Gender, Race/Ethnicity, Marital Status, Insurance, Urban/Rural/Territory, Service-Connected Disability, All Elixhauser Comorbidities, OEFOIF, and Death. Model 1 also adjusted for age ≥65 vs age <65.

Unadjusted Annual Costs Over Time Since TBI Diagnosis by Age Group, 2000-2020 in 2021 $ Values



f. <u>TBI and Chronic Kidney Disease (CKD)</u>
   i. Using the same method and dataset for the TBI-Dementia analysis, we evaluated the economic burden of the TBI and Chronic Kidney Disease in Veterans. Currently we are submitting this manuscript.

<u>Milestone:</u> 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.

a. We received the cohort subjects' ID and SSN (TBI subjects) from VCU for the Health Economics Study. We uploaded the cohort to the VINCI firewall area, and performed quality checks to evaluate the availability of subjects' information in CDW and our research study projects.
b. For the Health Economics Longitudinal Study, the Veterans Heath Administration (VHA) Health Economics Resource Center (HERC), Center for Innovation to Implementation (Ci2i), Veterans Affairs Palo Alto Health Care System (VAPAHCS) transferred all the health related VA/DoD information for the LIMBIC study (up to November/December of 2020) to the Data and Biostatistics Core (DBC) at Virginia Commonwealth University (VCU). We have received Social Security Numbers (SSN) and their study IDs for 1556 subjects (both TBI and non TBI)

from VCU. The Subject SSN and ID are stored within the VINCI folder in our research project study. We identified the health care related information of 1542 subjects (SCRSSN) in the CDW (14 subjects do not have health records in VA health system). Using SAS grid, we created a macro to de-identify (removing the PHI) the available/requested tables in CDW. We de-identified and created total of 189 tables in 13 folders (25.91 GB) from VA/DoD database within VINCI and transferred them to the DBC at VCU web portal (https://www.limbic- cenc.org, LIMBIC-CENC). The transmitted data included the subject ID that can be matched with the Longitudinal Study data. We removed all the de-identified tables from all VAPAHCS's and VINCI servers to comply with VA data security policies. The transferred tables stored in the VCU web portal as following:

1- BCMA (8 tables, 58.44 MB)
2- COVID (14 tables, 3.06 MB)
3- DaVINCI (33 tables, 2.56 GB)
4- Fee (7 tables, 1.11 GB)
5- HERC (7 tables, 46.56 MB + (Duplicated files in CSV=7 tables, 37.88 MB))
6- MEDSAS (8 tables, 58.44 MB)
   A- INC (12 tables, 2.25 MB)
   B- INP (16 tables, 22.5 MB)
   C- OUTPAT (2 tables, 404.19 MB)
7- NOSOS (2 tables, 24.5 MB)
8- OMOP (14 tables, 973.44 MB) +
   A- DIM_Other (23 tables, 19.1 GB)
9- OUTPAT (16 tables, 1.32 GB)
10- PATSUB (7 tables, 9.94 MB)
11- PSSG Geocoded (11 tables, 4.38 MB)
12- RXOUT (4 tables, 257.25 MB)
13- SSTAFF (3 tables, 3.94 MB)
14- VETSNET (1 table, 1.5 MB)
15- VITAL Status (1 table, 704 KB)

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

Month(s): *24 - 36*
Progress: 10%

a. Dr. Esmaeili is currently working with Utah personnel to clean and merge cost data with Phenoytype VA and DOD databases.

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

Month(s): *24 - 36*
Progress: 10%

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: 10%

a. This information will be updated to at least FY 2020 and we are already doing this for VA cost data. DoD Military Treatment Facility cost data has just become available and we are working on comparing VA facility and DoD Military Facility costs as well as a VA clinic stop code and DoD MTF MEPRS codes cross walk.

b. The HES team pulled health economic data from the VA Corporate Data Warehouse (CDW and merge it to the dataset from VCU). We requested and received exposure variables from VCU. We merged the DOD and VA cohorts. We identified appropriate exposure variables, including the symptoms and circumstance s of impact exposures in combat and training, and ran analysis on the frequency distribution.

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: 5%

a. We are working on comparing VA and DoD costs and crosswalking VA clinic stop codes and DoD MEPRS codes.

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: 10%

a. This information wil be updated to at least FY2020. We have categorized the mechanisms of injury in the Longitudinal study.

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: 10%

a. This information will be updated to at least FY2020. We have categorized the mechanisms of injury in the Longitudinal study.

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: 10%

Milestone: Develop statistical analyses to economic and epidemiological models.
Milestone: 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.
Milestone: Write reports for the Defense and Veterans Brain Injury Center (DVBIC), United States Army Medical Research and Development Command (USAMRDC), VA and CMTBIAC/VHA.
Milestone: 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.

Novel Neuroimaging Study:

Major Task 1: Assess available methods of overcoming variability introduced by differences in scanner hardware and software.
Milestone: Examine phantom-based and statistical correction for variability introduced by scanner hardware and software.

Month(s): *1 - 60*

Progress: We have performed further analyses of the CENC data to examine the ComBat method of data harmonization to overcome site differences. Our initial analysis resulted in substantial reduction of variability across sites, but we have completed additional data to examine how this affects relationships with other clinical and outcome data. We have started to draft an initial manuscript on the results obtained to date.

We have 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 have obtained funding and advanced collaboration with this group and with others in the InTBIR and ENIGMA communities.

We are also special editors for two special issues related to harmonization which will be completed in the coming year (Neuropsychology and Frontiers in Neurology)

This task remains in progress, and we will explore additional harmonization techniques over the next review period (12 months).

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 CENC, we have identified several additional pipelines for comparison of results. These data analyses are in process at the University of Utah. We have also received additional VA funding and advanced our work with Drs. Stone, Tustison and Avants to utilize their SyMLR method, and are in the process of reviewing and refining those results. We also received an NIH R61/R33 grant application to build a novel pipeline for both structural and functional imaging analysis; we have received the Notice of Award and have recently started this project. We will work, in connection with other colleagues, to develop a modified ComBat technique over the next three years.

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: We have completed some initial analysis comparing distortion correction pipelines and options, and have also completed analysis on comparison of pipeline parameters in a commonly used diffusion tractography; we are starting to draft manuscripts based on these findings.

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 (and later, to a larger dataset in conjunction with ENIGMA and NICoE using data we have now received). Pending receipt of additional clinical and outcome data, we will perform analysis examining the relation of these variables. We aim to complete this within the coming year of the grant.

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. This manuscript has been submitted.

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: Work on this task is scheduled for a later stage in the project.

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, TED, and InTBIR. 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 1,200 Prospective Study participants.
- Completed inflammation panel (IL-6, IL-10, TNF-a) and now database locked and analyses underway collaboratively with imaging.
- Published following 10 manuscripts:

1. Guedes VA, **Kenney K**, Shahim P, Qu B-X, Lai C, Devoto C, Walkder WC, Nolen T, Diaz-Arrastia R, Gill JM. Exosomal NFL, a prognostic biomarker for remote symptoms after mild traumatic brain injury? ***Neurology*** 2020 May 27: 10.1212/WNL.0000000000009577 doi: 10.1212/WNL.0000000000009577 Epub 2020 May 27. PMID: 32461282.

2. Peltz C, **Kenney K**, Gill J, Diaz-Arrastia R, Gardner RC, Yaffe K. Blood-based biomarkers of traumatic brain injury-associated cognitive impairment in older veterans. ***Neurology*** 2020 June 22: DOI: 10.1212/WNL.0000000000010087 Epub 2020 Jun 22. PMID: 32571850

3. **Kenney KL**, Guedes VA, Gill JM. Author response: Exosomal neurofilament light: A prognostic biomarker for remote symptoms after mild traumatic brain injury? ***Neurology*** 2021;96:726. doi:10.1212/WNL.0000000000011786. PMID: 32461282

4. Dennis E, Baron D, Bartnik-Olson B, Caeyenberghs K, Esopenko C, Hillary F, **Kenney K**, Koerte I, Lin A,

Mayer A, Mondello S, Olsen A, Thompson P, Tate D, Wilde E. ENIGMA Brain Injury: Framework, Challenges, and Opportunities. ***Hum Brain Mapping*** 2020 Jun 1. doi: 10.1002/hbm.25046 online ahead of print. PMID: 32476212.

5. Devoto C, Lai C, Qu B-X, Guedes V, Wilde E, Walker WC, Diaz-Arrastia R, **Kenney K**, Gill JM. Exosomal MicroRNAs in Veterans with Mild Traumatic Brain Injury: Preliminary Results from a Chronic Effects of Neurotrauma Consortium (CENC) Biomarker Discovery Project. ***J Neurotrauma*** 2020 May 27. doi: 10.1089/neu.2019.6933 online ahead of print. PMID: 32458732.

6. Koerte IK, Esopenko C, Hinds SR, Shenton ME, Bazarian J, **Kenney K**, et al. Thompson PM, Tate DF, Dennis EL, Wilde EA, Baron D. The ENIGMA Sports Injury Working Group: an International Collaboration to Further our Understanding of Sports-Related Brain Injury. ***Brain Imaging and Behav*** April, 2020. DOI: 10.31234/osf.io/7d3z9 online ahead of print. PMID: 32720179.

7. Garcia A, Reljic T, Pogoda TK, **Kenney K**, Agyemang A, Belanger HG, Troyanskaya M, Wilde EA, Walker W, Nakase-Richardson R. Obstructive Sleep Apnea Risk is Associated with Cognitive Impairment After Controlling for TBI: A Chronic Effects of Neurotrauma Consortium Study. ***J Neurotrauma*** 2020 Jul 24. doi: 10.1089/neu.2019.6916. Online ahead of print. PMID: 32709212.

8. Tate DF, Dennis EL, Adams JT, Adamson MM, Belanger HG, Bigler ED, Bouchard HC, Clark AL, Delano-Wood LM, Disner SG, Goodrich-Hunsaker NJ, Hayes JP, Hinds SR, Hodges CB, Hovenden ES, Irimia AI, **Kenney K**, Lindsey HM, Morey R, Newsom MR, Scheibel RS, Shenton ME, Sullivan DR, Troyanskaya M, Wade B, Thompson PM, Wilde EA. Coordinating Global Multi-Site Studies of Military TBI: Potential, Challenges, and Harmonization Guidelines. ***Brain Imaging and Behavior*** (Military Special Issue) 2021 Jan 7. doi: 10.1007/s11682-020-00423-2. Online ahead of print. PMID: 33409819

9. Werner JK, Shahim P, Pucci JU, Lai C, Raiculescu S, Gill JM, Nakase-Richardson R, Diaz-Arrastia R, **Kenney K**. Poor sleep correlates with biomarkers of neurodegeneration in mild traumatic brain injury patients: a CENC Study. ***Sleep*** 2020 Dec 6:zsaa272. doi: 10.1093/sleep/zsaa272. Online ahead of print. PMID: 33280032

10. Guedes VA, Chen L, Devoto C, Qu B-X, Edwards K, Martin C, Mithani S, Rush H, Wilde E, Walker WC, Diaz-Arrastia R, Gill J, **Kenney K**. Exosomal MicroRNAs and Proteins are linked to Psychiatric Symptoms of PTSD and Depression in Veterans with mild Traumatic Brain Injuries. Invited submission, ***Frontiers Pharmacology, Invited Biomarker special issue***, in print 9-6-2021.

    - Following 10 manuscripts and under review:

11. Wilde EA, Wanner I-B, **Kenney K**, Gill J, Stone J, Disner S, Schnakers C, Prager EM, Jeromin A. Biomarker Development to Advance Diagnosis and Treatment of Traumatic Brain Injury. ***Journal Neurotrauma special issue***, under review, 4-2021.

12. Wade BSC, Tate DF, Velez C, Dennis EL,…., **Kenney K**, Pugh MJ, Cifu DX, Wilde EA. Mapping Post-traumatic Stress Disorder and Depressive Symptoms to Hippocampal Subfields and Amygdala Nuclei in Service Member and Veterans with Mild Traumatic Brain Injury. ***Clin Neuroimage*** 2020, under revision, 7-2021.

13. Tate DF. Wade BSC, Velez CS, Bigler ED, Davenport N, Dennis E, EApen B, Hinds, S, Kean J, Jaramillo C, Kennedy E, **Kenney K**….Walker W, Wilde EA. Persistent Neuroimaging Findings Following Remote Traumatic Brain Injury: A Chronic Effects of Neurotrauma Consortium (CENC) Study. ***J Neurotrauma,*** under review 7-2021.

14. Walker WC, Agyemang AA, Allen CM, Werner JK, Troyanskaya M, **Kenney K**. Does Mild Traumatic Brain Injury disturb the Endocrine System long-term? A multicenter LIMBIC-CENC analysis. ***Brain Injury, LIMBIC special issue***, under review 5-2021.

15. Devoto C, Guedes VA, Lai C, Lete JJ, Mithani S, Edwards K, Vorn R, Qu B-X, Wilde EA, Walker WC, Diaz-Arrastia R, Werner JK, **Kenney K**, Gill J. Remote Blast-related Mild Traumatic Brain Injury is Associated with Differential Expression of Exosomal microRNAs Identified in Neurodegenerative and Immunological Processes. ***Brain Injury, Limbic special issue*** under review, 5-2021.

16. Dennis EL, Taylor BA, Troyanskaya M, Newsome MR, Abildskov T, Betts AM, Bigler E, Cole J, Davenport N, Duncan T, Gill J, Guedes V, Hinds SR, HOvenden ES, **Kenney K**, Pugh MJ, Scheibel RS, Shahim PP, Shih R, Walker WC, Werner JK, York GE, Cifu DX, Tate DF, Wilde EA. Advanced Brain Age in Deployment-Related Traumatic Brain Injury: A LIMBIC-CENC Neuroimaging Study. ***Brain Injury, Limbic special issue*** under review, 5-2021.

17. Walker WC, O;Rourke J, Wilde EA, Pugh MJ, **Kenney K**, Dismuke, CL, Ou Z, Presson AP, Werner JK, Kean J, Barnes D, Yaffe K, Cifu D. Clinical Features of dementia ascertained by ICD coding in LIMBIC-CENC multicenter study of mild traumatic brain injury. ***Brain Issue, Limbic special issue*** under review, 5-2021.

18. Kennedy E, Panahi S, Stewart IJ, Tate DF, Wilde EA, **Kenney K**, Werner JK, Gill J, Diaz-Arrastia R, Amuan M, VanCott A, PughMJ. Traumatic brain injury and risk of early onset dementia in Post 9-11 Veterans. ***Brain Injury, Limbic special issue*** under review, 5-2021.

19. Gottshall JL, Agyemang AA, O'Neil M, Wei G, Presson A, Hewins B, Fisher D, Mithani S, Shahim P, Pugh MJ, Wilde EA, Devoto C, Yaffe K, Gill J, **Kenney K**, Werner JK. Sleep quality: A common thread linking depression, post-traumatic stress, andpost-concussive symptoms to biomarkers of neurodegeneration in TBI patients. ***Brain Injury, Limbic special issue*** under review, 5-2021.

20. Gottshall JL, Pucci JU, Brooks D, Watson N, Sheth P, Gabriel A, Mithani S, Leete JJ, Lai C, Qu B-X, Devoto C, Gill JM, Kenney K, Werner K. Poor sleep quality is associated with elevated exosomal inflammatory cytokines in warfighters with chronic mild TBI. ***Frontiers Pharmacology, Invited Biomarker special issue***, under review 9-2021.

- Produced 1 podcast of Neurology NfL manuscript with AAN.
- Gave 1 invited talk to the VA TBI seminars May 14, 2021, " Poor sleep correlates with biomarkers of neurodegeneration in mild traumatic brain injury patients: a CENC study with a second sleep-TBI talk by LCDR Kent Werner scheduled
- Presented 14 abstracts at national/international conferences, as follows: (3 accepted as oral presentations):

-3 presented at European Sleep Research Society (9/2020)
-2 presented at ANA (10/2020),
-2 presented at the SfN global connectome (1/2021)
-2 presented to Sleep (6/2021)
-1 presented at Neurotrauma (7/2021)
-4 accepted at MHSRS, 2 as oral, but canceled (8/2021)

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.
MSD p-tau species- Abstract presentation accepted at 2021 MHSRS, 8-2021, but canceled DTI-NfL- Poster presentation at virtual 2021 Neurotrauma, 7-2021.

6 analyses ongoing:

1. Cohort analysis – 7 proteins & outcomes, as above
2. Brain aging, a collaboration with Imaging Core
3. DTI-NfL, collaboratively with Neuroimaging
4. Volumetrics-NfL, collaboratively with Neuroimaging
5. Big Data, collaboratively with Neuroimaging
6. rsfMRI – sleep dysfunction, collaboratively with Neuroimaging

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. Sent plasma samples to Roskamp and running assays on protein biomarkers of chronic TBI and working with Dr. Wang to submit additional proposals for collaborative biomarker projects.

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: As above, working with PLS enrollment sites and Informatics to obtain 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 1,200 Prospective Study participants. Currently, have collected follow-up samples on 470 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 and 3 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 and 3 plex. Working with PLS and informatics 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 sufficient number of DNA samples for analysis and availability of Broad to analyze samples. Carry Forward Request was submitted to and approved by VCU to carry over year 2 funds GWAS into Year 3. Will collaboratively carry out GWAS testing through the Broad Institute with GAIN under LIMBIC year 3 funding.

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 years 3-5.

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 years 3-5.

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?

Prospective Longitudinal Study: Dr Walker and Dr Cifu along with other senior investigators mentored multiple LIMBIC junior investigators on analytic, publication, and dissemination work across including Dr. Becky Gius, Dr. Randel Swanson, Dr. Jacob Resch, Dr. Christina Sheerin, Dr. Justin O'Rourke, Amanda Garcia, Dr. Amma Agyemang, Jonathan Yee, Dr. Susan Van der Veen and Dr. Bilal Khokhar. (see Attached LIMBIC-CENC PLS analysis and dissemination tracker for details). Dr Walker also continue to mentor two PM&R physician residents in training on an analytic project using PLS data. Multiple trainees and junior investigators received mentoring by senior LIMBIC investigators and worked with LIMBIC on separately

funded research projects to further their scientific career including Dr. C. Hodges.

Neuroimaging Core: 1) Personnel in our own laboratory at the University of Utah have been exposed to significant training opportunities as a result of their work on this project. We currently have 3 post-doctoral fellows (Hannah Lindsay, Paula Johnson, and Ben Wade) who are working on the project as well as 1 graduate student (Carmen Velez) and 2 undergraduate students (Josephine Dimanche and Elizabeth Hovenden). These trainees have now had specific training in and experience with numerous aspects of imaging acquisition and analysis. Until his transfer to VCU for post-doctoral work (also LIMBIC-related), another graduate student (Cooper Hodges) utilized LIMBIC data for a doctoral dissertation. 2) Drs. Wilde, Tate, Pugh, Gill and Kenney hold regular analysis meetings which involve trainees and junior faculty at different levels. 3) Drs. Wilde and Tate have also contributed to mentorship of other local trainees and junior faculty (e.g., Peter Fino, Melisa Cortez) and assisted in formulating analysis plans and requests using LIMBIC-CENC data. 4) Drs. Tate and Wilde co-lead the Enhancing Neuroimaging and Genetics through Meta-analysis (ENIGMA) Military Working Group, which facilitates data sharing, mega- and meta-analysis, with a particular focus on assisting younger investigators and trainees. Participation in professional development activities include the following: We note that Dr. Wilde and Tate were scheduled to attend and present at multiple conferences and workshops that were canceled due to COVID restrictions.

Retrospective Database Study: Two junior investigators, Erica Kornblith, PhD, and Yue Leng, PhD, have worked with the study team and completed projects resulting in two published manuscripts and one under review. We recently brought on two new junior investigators, Andrea Schneider, MD, PhD, and Jennifer Albrecht, PhD., and their project analyses are underway. 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) led the EOD analysis and manuscript for the Brain Injury Special Issue and is leading phenotyping analyses. A graduate student (Samin Panahi) was also instrumental in completing that analysis. These two junior investigators/students will also be working with our new DoD Epilepsy research program study (W81XWH-21-1-0327) funded September 30, 2021 that includes health system data, survey data, ecological momentary assessment data, neuroimaging/neuropsychological testing and biomarker analysis (collaboration with Drs. Tate, Wilde, Kenney and Gill). We are recruiting a post-doctoral fellow for the upcoming fiscal year.

How were the results disseminated to communities of interest?

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 LIMBIC-CENC Publication Monitor Excel spreadsheet, which includes peer-reviewed journal publications and scientific meeting presentations including posters, oral paper presentations, and topical seminars.
- National podcasts were recorded that interviewed several LIMBIC investigators on manuscripts submitted to the LIMBIC Special Edition of Brain Injury journal that focused on findings from the PLS.
- 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. Details are provided in the KTC section of this report and the Publication

Monitor. These can be further supplemented by visiting the Website.

- 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.

Phenotype Study: Dr. Pugh presented phenotype findings at the following:

- Pugh M. February 2021. Phenotypes of Comorbidity in Mild TBI: Development, Meaning and Utility for Use in Clinical Practice. National VA Traumatic Brain Injury Cyberseminar. 115 Clinicians, researchers, staff.
- Pugh M. December 11, 2021. ***Trajectories of Comorbidity in Chronic TBI Recovery.*** Visiting Professor to Uniformed Services University Medicine Seminar.
- Pugh M. Plenary Speaker at the Utah Brain Injury Conference, October 2, 2020.

Health Economics Study: The PI presented 2 VA Cyberseminars, published 2 manuscripts and a book chapter and had a poster presented at Academy Health.

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What do you plan to do during the next reporting period to accomplish the goals?

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 as we attempt to get our recruiting numbers to the projected levels.
3. Continue working with the CAB in order to garner feedback and forward recommendations to Consortium Leadership.
4. Once VCU lifts travel restrictions, schedule trips to all 11 PLS sites.
5. Continue the Site Metrics.
6. Continue working with the DBC in order to overcome all FITBIR obstacles.
7. Continue working towards CRADA finalization and approval.

Data and Biostatistics Core: In the next year, the DBC will accomplish the following:
1. Continue development of the interactive platform for on demand review of data.
2. Continue QA/QC of data.
3. Continue development of analytic data sets for investigator data requests.
4. Continue central biostatistics support.
5. Work on development of integration of data dictionary on the LIMBIC-CENC website.
6. Continue FITBIR Ops and preparation of FITBIR data for the next submission.

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 vists 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.

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 2022.
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. Portland will be undergoing an upgrade to their system, and before the scanner is decommissioned, we will work with the site to collect pre- and post-upgrade data as well as to create a new protocol for the Vida scanner.
9. Completion of 4 or more additional manuscripts which are currently in preparation
10. Complete reconciliation of all outstanding CDE coding data.

STUDIES

Prospective Longitudinal Study: In the next year, the Prospective Longitudinal will accomplish the following:
1. Ramp up in-person research activities across the LIMBIC-CENC PLS to achieve or surpass target rates of study enrollments across all sites. This may be constrained by the course of the COVID pandemic as we anticipate continued COVID-19 related headwinds including not only safety concerns for the in-person aspect but also economic factors and lifestyle factors that will lead to decreased participant interest, willingness, and availability.
2. Continue the retention and longitudinal reassessment study activities with high completion rates.
3. Continue efforts and success with scientific analysis and dissemination activities.

Retrospective Database Study: In the next year, the Retrospective Database Study will accomplish the following:
1. The TBI and CVD manuscript and the paper in collaboration with Libby Dismuke will be published.
2. We will submit manuscripts for the TBI and cause-specific mortality analysis as well as the risk and resiliency for dementia after TBI analysis.
3. We will begin an exciting new analysis examining risk of stroke after TBI. We will start other new collaborations with investigators on novel projects with our database of more than 2.2 million Veterans.
4. 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 Cardiovascular impact of TBI paper led by LTC Stewart.
2. Conduct Delphi process with LIMBIC investigators to identify conditions to include in phenotype/deep learning models.
3. Complete TBI screening outcomes paper led by Dr. Pogoda.
4. Add to dataset as data become available.
5. Complete development of datasets for deep learning analysis.
6. Complete process to connect computer servers to VA network to facilitate machine learning capacity.
7. Incorporate NLP processes from other DoD funded projects to extend cohort with cognitive dysfunction.

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 and non-VA facility utilization and costs 2) DoD Military Treatment Facility and Tricare utilization and costs.
2. We will work on exposures and costs data

- We have classified individuals into type and frequency of exposures to examine annual VA facility and non-VA facility inpatient and outpatient as well as pharmacy costs from entry into VA until FY 2020.
- We have classified exposures into different classification systems for the individual cost models. E.g. any rocket exposure, number of rocket exposures, number of types of exposures (rocket + IED + controlled detonation), total frequency of exposures.
- We will report annualized costs adjusted for inflation to 2021 dollar values.

3. We will model VA users and non-VA users for differences in demographics.
4. We have received the MTF cost data for the Phenotype study to complete the cost data acquisition to begin analyses of costs and utilization by Phenotypes identified by the Phenotype team.
5. We will begin work on acquiring VA disability costs for veterans with TBI.
6. We will work on improving our cost comparison dashboard across VA, DoD and community care private sector data based on VA facility, non-VA facility, DOD MTF, and Tricare costs.

Novel Neuroimaging Study: In the next year, the Novel Neuroimaging Study will accomplish the following:
1. If allowed given the COVID travel and infection control restrictions, 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, and complete harmonization manuscript.
3. Within the ENIGMA pipeline, 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 additional machine learning techniques following receipt of feedback from collaborators.
5. Continue to work with other consortia and military-relevant groups (e.g., ENIGMA, InTBIR, TED, TRACK-TBI) to collaborate on data aggregation and analysis.
6. Complete additional planned work on the white matter hyperintensity analysis program developed under CENC and also multimodal analysis using SyMLR in conjunction with colleagues at University of Virginia.

Biomarker Discovery Study: In the next year, the Biomarker Discovery Study will accomplish the following:
Project 1: Continue SOW into year 3 (of 3 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
-rsfMRI- sleep dysfunction, collaboratively with Neuroimaging

- Continue correlations of candidate prognostic biomarker correlations with symptoms and outcomes Correlations planned for Year 3 of SOW
    - *<u>Milestone:</u> Carry out blood and saliva biomarker assays from all subjects with baseline specimens in the biorepository.*
    - *<u>Milestone:</u> 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).*
    - *<u>Milestone:</u> Develop panel of prognostic biomarkers for each phenotype of chronic neurotrauma (e.g. dementia, headache, PTSD, sleep disorder)*

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

Project 2: Prepare and submit a GWAS project to the research committee and initiate GWAS project with GAIN through the Broad Institute.

4. **IMPACT:**

What was the impact on the development of the principal discipline(s) of the project?

Biomarkers Core: Significant discoveries that may translate into diagnostics: The goal is to discover biomarkers that could be used to detect mild TBI and someday be able to make judgements about prognosis for injury outcome.
1. First to examine exosomal microRNA in remote TBI; 4 miRNA significant in rTBI and 1-2 mTBI vs TBI neg analyses; associations with chronic symptoms and outcomes.
2. Remote, repetitive mTBI is associated with higher levels of exosomal p-tau, exosomal and plasma t-tau, NFL, IL-6, exoxomal IL-10.
3. Higher exosomal levels of all 5 candidate biomarkers are variably associated with chronic neurobehavioral symptom burdens.
4. With GLM, higher levels of exosomal tau, p-tau, NFL, IL-6 and plasma NFL are associated with higher scores on PCL, PHQ-9 and NSI.
5. NFL levels, markers of axonal damage, and miRNAs linked to neurogenerative and inflammatory processes, and glucocorticoid receptor signaling pathways, are associated with symptom severity of PTSD in participants with a history of mTBI. These findings point to potential pathways for the development of chronic and susceptibility of PTSD after TBI.
6. Poor sleep correlates with biomarkers of neurodegeneration in patients with mTBI.
7. Post-acute mild TBI history is not an independent risk factor for acquired adult-onset male hypogonadism, hypothyroidism, or GHD.

Prospective Longitudinal Study: Almost 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 for products derived or disseminated during the second year of LIMBIC:

Highlights:

- Ongoing evidence that prior mTBIs primarily a risk factor for symptom burden.
    - New evidence: patients with mTBI history, especially if blast-related, also receive more care in VHA.
- Minimal evidence for direct association between mTBI history and objective findings.
    - Negative: Pituitary disorder markers.
    - Minimal signal: Auditory ERPs, computerized posturography, MRI brain age.
- Additional evidence of the importance of comorbidities on variety of outcomes including arrest/incarceration, Auditory ERPs, MRI brain age, cognition, biomarkers:
    - Comorbidities implicated: Sleep apnea, Sleep quality, Pain, PTSD, Depression, Alcohol.
    - Outcomes affected include: arrest/incarceration, Auditory ERPs, balance, MRI brain age, cognition, biomarkers.
- New insight into measurements:
    - NSI symptom clusters, ICD dementia codes, Auditory ERPs, LIMBIC vs DVBIC study cohorts, MRI, biomarkers.
- Other new insights with treatment implications for patient with mTBI history:

- Balance-control phenotypes for personalized vestibular rehabilitation.
- Those engaging in Aerobic exercise have better perceived health and cognitive functioning.

More detail is provided in the bullets below and Key Points Table further below:

- Veterans with with mTBI, especially those with blast-related mTBI, are receiving more VHA health care services than those without mTBI indicating that the TBI patient care mission is making some impact.
- The complexity and overlap of chronic pain symptoms with other comorbid symptoms suggest that SMs and Veterans with lingering effects of mTBI may require a more comprehensive approach during treatment to include multimodal pain management.
- The four NSI symptom clusters (somatosensory, affective, cognitive, and vestibular) are broadly valid for future research and may serve as useful clinical constructs for evaluation and treatment.
- Clinicians should suspect, screen, and diagnose male hypogonadism, hypothyroidism, and GHD based on clinical presentation alone without regard to mTBI history based on this study's negative findings.
- First-hand open-ended narratives of injury events from current and former SMs offer a richness in description and intensity that may add to understanding of acute and long-term after-effects.
- Correlates of criminal arrest and incarceration for SMs and Vs with mTBI span demographic and psychological dimensions. Addressing the modifiable factors, which include PTSD symptoms and alcohol use, may lower the risk of future criminal justice involvement.
- Remote mTBI(s) was not supported as a risk factor for markers of GHD, hypothyroidism, or male hypogonadism. Clinicians should assess for these pituitary disorders based on other clinical factors.
- Features of five participants positive for early dementia ICD codes in the VHA were described. The codes have specificity concerns, but appear to have some utility in signifying lower cognitive performance and function.
- Auditory brain potentials are a promising target for the study of longitudinal brain changes after mTBI, and may be sensitive to both neural injury (early auditory processing) and psychopathological effects (higher order task relevant processing) after mTBI.
- Demographics and NIH TBI CDEs were compared between the LIMBIC-CENC and DVBIC-TBICoE studies. Unique difference between cohorts adds perspective and interpretability for assimilating past and future findings.
- Balance deficits in SMs and Vs with mTBI histories may be unmasked when sensory inputs are perturbed (swaying of visual surround or base of support or the occlusion of vision). These findings provide a basis for assessment, prevention and treatment of chronic balance difficulties after mTBI.
- Heterogeneous phenotypes of balance control having unique clinical features were identified in SMs and Vs with mTBI histories. This may enable developing vestibular rehabilitation programs more tailored to the nuances of each individual's sensory phenotype.
- Advanced brain age based on MRI data is associated with history of deployment-related mTBI and common comorbidities, including depression, PTSD, and alcohol misuse. Neuroimaging data may be a useful biomarker for tracking health and treating these comorbidities may help decelerate brain aging.
- Poor sleep was associated with exosomal microRNA differences previously implicated in psychiatric disorders, progressive neurodegeneration, and vascular physiology, as well as sequelae of TBI. This underscores the importance of identifying and treating sleep problems.
- Study results suggest a possible role for axonal degeneration and neurodegenerative changes in the development of persistent or later-in-life PTSD symptoms.
- Among SMs and Vs with mTBI histories, there was a link between poor sleep, cognition, and elevated

plasma Neurofilament light (NfL) chain, a biomarker of neurodegeneration. Findings support further research and have potential therapeutic implications.

- Extracellular vesicles (EV) levels of proteins and miRNAs correlated with PTSD symptom levels. Findings provide insights into signaling pathways linked to persistent PTSD symptoms after TBI and biological mechanisms underlying susceptibility to PTSD.

Key Points Table:

Question	Findings	Meaning
Are Veterans' long-term comorbidities and/or VA health services utilization/costs related to their mild TBI (mTBI) history?	Covariate adjusted regression analysis showed that co-morbidities, health services use and costs were all highest for blast-related mTBI, followed by non-blast mTBI , and lowest with negative TBI histories.	Veterans with mTBI, especially those with blast-related mTBI, are receiving additional health care services by VHA. The nature of the relationship between mTBI history, comorbidities and health care utilization/costs needs further study.
What are the associations between pain interference and other comorbidities in OIF/OEF/OND service members and veterans with mTBI?	Those with post-traumatic stress disorder, anxiety, depression, and repetitive TBI were at highest risk for pain-related functional limitations. Over 76% reported moderate to high pain interference, which was consistent in other OEF/OIF/OND populations.	These findings highlight the complexity and overlap of comorbid symptoms. Service members and veterans with lingering effects of mTBI may require a more comprehensive approach during treatment.
How do mTBI history and PTSD symptoms relate to symptom clusters on the Neurobehavioral Symptom Inventory (NSI), a measure of mTBI-related symptoms used in clinical and research settings.	Symptoms measured by the NSI were highly correlated with PTSD symptoms in those with or without mTBI history. There were similar clusters of symptoms (somatosensory, affective, cognitive, and vestibular) regardless of mTBI and PTSD status.	These findings suggest that the NSI symptom clusters are broadly valid for future research and may serve as useful clinical constructs for evaluation and treatment.
Are there links between exosomal proteins and microRNAs measured in the peripheral blood and persistent PTSD symptoms in a military cohort with remote mTBI(s)?	We observed higher levels of exosomal NfL ($p = 0.0082$), a marker of axonal degeneration, in individuals with more severe PTSD symptoms. microRNAs that have been previously associated with neurodegenerative diseases were also linked to PTSD symptom severity.	Our results suggest a possible role for axonal degeneration and neurodegenerative changes in the development of persistent or later-in-life PTSD symptoms.
Do poor sleepers with mild TBI (mTBI) have worse cognition and/or elevated biomarkers of neurodegeneration?	Poor sleepers with mTBI had elevated plasma Neurofilament light (NfL) chain and lower executive function scores by verbal fluency and stop-go tests compared to good sleepers with TBI. These findings were not observed in controls.	These findings suggest a link exists between poor sleep, cognition, and biomarkers of neurodegeneration in the military mTBI population, supporting further research with potential for therapeutic implications.
What are some of the ways that current and former Post-9/11 combat-deployed U.S. military Service Members experienced potential concussive events?	50.9% identified blast exposure as their worst event, which included: driving over improvised explosive devices, being knocked off their feet and hitting their heads on another object or surface due to the physical force of the blast, and experiencing headache or disorientation even in the absence of physical impact to the head.	First-hand accounts of injury events reported by current and former U.S. Service Members offer a richness in description and intensity not often captured in quantitatively-oriented head injury research, and these narratives highlight the importance of continued documentation of these experiences to understand how they may relate to any acute and long-term after-effects.
Are there changes in exosomal microRNA (exomiRs) expression levels in a military cohort of poor sleepers with traumatic brain injury compared to good sleepers?	We observed a total of 8 significantly different exomiRs and found 4 exomiRs that significantly positively correlated with PSQI global score hsa-miR-1250-5p ($r=0.229$, $p=0.017$), hsa-miR-139-5p ($r=0.236$, $p=0.014$), hsa-miR-211-3p ($r=0.206$, $p=0.033$), and hsa-miR-4516 ($r=0.212$, $p=0.028$) within the TBI groups.	The significantly different exomiRs have been reported to play a role in psychiatric disorders, progressive neurodegeneration, and vascular physiology, which have been previously linked to the sequelae of TBI.
What sociodemographic and psychological factors factors are associated with prior arrests and felony incarceration among combat-exposed Veterans and Service Members (Vs/SMs)?	In the LIMBIC-CENC PLS, 35% of Vs/SMs had prior arrest and 3% had prior felony incarceration. The incarcerated group was younger, less educated, and had less social support, greater PTSD symptoms and had higher proportions of men, never being married, and hazardous alcohol use. The same pattern of differences was observed for the arrest-only group compared to the no arrest group. Non-correlates included mTBI history.	Among combat-exposed Vs/SMs, the correlates of legal involvement span demographic and psychological dimensions. Some are modifiable, including social support, PTSD symptoms, and alcohol use. Addressing these risk factors may lower the risk of future criminal justice involvement.
Is history of mild traumatic brain injury (mTBI) associated with advanced and/or accelerated brain aging among US military Service Members and Veterans?	Brain age was estimated from MRI data. Males with a history of deployment-related mTBI show advanced brain aging. Several common comorbidities, including depression, post-traumatic stress disorder, and alcohol misuse were also associated with advanced brain age.	Deployment-related mTBI has a long-term impact on the brain health of US military Service Members and Veterans. Brain age estimated from neuroimaging data may be a useful biomarker for tracking health.
What are the clinical features of early dementia cases identified by International Classification of Diseases (ICD) coding among servicemembers and Veterans with mild traumatic brain injury (mTBI)?	Five cases of dementia were identified, all under 65 years old, with two being possible false positives. The most common abnormal domains in the dementia group were visual memory and verbal learning and memory. Compared to the non-dementia group, the dementia group also reported poorer functional status and quality of life, and was more likely to have PTSD, greater blast exposures, and historical blast-related mTBI.	ICD codes for early dementia in the VA system have specificity concerns, but appear to have some utility in signifying cognitive performance and self-reported cognitive function. Further research is needed to better determine links to blast exposure, blast-related mTBI, and PTSD to early dementia in the military population.
Do auditory brain potentials previously shown to change in pre-dementia exhibit similar changes in an earlier phase of life in	The N200 potentials were reduced in a group with any mTBI exposure, while P50 was enhanced and N100 and N200 reduced in a subgroup with repetitive mTBI (3 or	Auditory brain potentials are a promising target for the study of longitudinal brain changes after mTBI, and may be sensitive to both neural injury (early

mild traumatic brain injury?	more exposures). The N200 showed the largest amplitude change with injury group, however this change was strongly associated with symptoms of depression and anxiety, as well as hearing deficits.	auditory processing) and psychopathological effects (higher order task relevant processing) after mTBI.
Are pituitary disorders a potential late effect of mild traumatic brain injury (mTBI)?	Rates of markers of growth hormone deficiency (GHD), hypothyroidism, and male hypogonadism did not differ across any mTBI groups including TBI negative controls, repetitive mTBI and blast-etiology mTBI. Positive lab screens also failed to meaningfully differentiate any of the putative clinical effects of these disorders in the mTBI population (fatigue, depression, cognitive symptoms, or poorer executive function or processing speed).	These results do not support that remote mTBI(s) is a risk factor for these pituitary disorders. Clinicians should assess for these pituitary disorders based on other clinical factors. Large longitudinal design studies that include provocative lab testing may provide further insights.
Is repetitive transcranial magnetic stimulation of the right prefrontal cortex beneficial for cognition after mild to moderate traumatic brain injury and does it affect delta frequency EEG activity?	In this randomized sham-controlled clinical trial of 5 days of stimulation, rTMS was not beneficial for cognition, but was beneficial for neurobehavioral and executive function symptoms. Prefrontal delta frequency EEG waves increased in the 1-2 weeks after active stimulation.	rTMS was not shown to be effective for objective cognition, however may improve subjective functioning and cognitive difficulties, and can induce changes in slow frequency cortical communication.
There are two consortiums conducting large, longitudinal, federally funded TBI studies of Service members and veterans, LIMBIC-CENC and the Defense and Veterans Brain Injury Center – TBI Center of Excellence (DVBIC-TBICoE). How do their mild TBI and injury control participants compare in clinical features?	LIMBIC-CENC participants have higher enrollment age, education level, proportion of Black race, and time from injury as well as less combat deployments and are less likely to be married than in DIVBIC-TBICoE. The distribution of military service branches also differed. Most differences on symptom scales and cognitive tests had small effect sizes. Reaching medium effect sizes, LIMBIC-CENC participants endorsed higher PTSD symptoms while DVBIC-TBICoE study IC participants endorsed higher somatosensory and vestibular symptoms.	The heavy use of NIH common data elements in both studies and collaboration with the DVBIC-TBICoE study team on development of the LIMBIC-CENC assessment battery enabled this comparative analysis. Results highlight unique differences in study cohorts, and adds perspective and interpretability for assimilating past and future findings.
What are the relationships amongst balance, gait and sensory measures amongst combat-exposed current and former SMs with and without histories of mTBI?	Participants with mTBI maintained postural balance and ambulate as well as their non-TBI counterparts. However, when any of the sensory systems (vision, vestibular or proprioception) are compromised (swaying of visual surround or base of support or the occlusion of vision), the number of TBI's sustained was associated with lower scores on the balance assessment.	TBI patients seem to adapt to their impairments in sensory input from vision, proprioception, or vestibular systems. However, balance deficits may be unmasked when adjustments in weighting of sensory inputs are required by perturbations. This provides a basis for evaluation and treatment of chronic vestibular symptoms after mTBI.
What are relationships between PTSD symptoms and extracellular vesicles (EV) levels of proteins and miRNAs in service members and Veterans with and without remote mild TBIs (mTBIs)?	EV levels of neurofilament light chain (NfL) were elevated in participants with more severe PTSD symptoms and positive mTBI history, when compared to TBI negative controls and mTBI participants with less severe PTSD symptoms. Levels of EV NfL, plasma NfL, and hsa-miR-139-5p were linked to PCL-5 scores in regression models.	Our findings provide insights into signaling pathways linked to the development of persistent PTSD symptoms after TBI and biological mechanisms underlying susceptibility to PTSD.
How can sensory phenotypes for balance explain heterogeneity in clinical characteristics, symptomatic clusters, functional measures, and injury mechanisms in Veterans and Service Members with mTBI?	In this cross-sectional analysis of observational data from the Long-Term Impact of Military-Relevant Brain Injury Consortium - Chronic Effects of Neurotrauma Consortium, heterogeneous sensory phenotypes for balance control were associated with distinct clinical characteristics, symptom severity, and physical and cognitive functioning.	Recognizing the variety of balance deficits that involve heterogeneous sensory dysfunction in Veterans and Service Members after mTBI may enable more tailored rehabilitation programs to the nuances of each individual's sensory phenotype.

Health Economics Study: We published a study on the association of blast vs non-blast exposure and TBI with VA outpatient utilization and costs and found that in general blast exposure was associated with higher VA utilization and costs. This study was highlighted on the BIRCO website. It is important to provide this feedback to DoD as well as VA for possible prevention and long-term planning.

We have submitted 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: Our analyses found that TBI and TBI severity were strong predictors of early onset dementia (AD/FTD). However, other conditions such as epilepsy, stroke, cardiovascular disease, may have direct effects on EOD or indirect effects that result from TBI. Analyses that incorporate causal inference will be used to further disentangle these relationships.

TBI and TBI severity were also 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.

What was the 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.

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 will 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.

What was the impact on technology transfer?

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?

Health Economics Study:
1. Our results on the importance of controlled detonations on service connected disability may have implications for DoD training.
2. Our results on socio-determinants of mechanism of injury in a Level 1 Trauma Center may have implications for prevention of assault and gunshot related TBI.

3. Our results on the cost-effectiveness of MRI may have implications for its use in the diagnosis and management of TBI, especially mild TBI.

5. CHANGES/PROBLEMS:

Changes in approach and reasons for change

Prospective Longitudinal Study: The COVID-19 pandemic necessitated a change in approach during the past reporting year as described below in the Problems / Delays /Plans to Resolve section. All changes were within the initially approved scope of work.

Actual or anticipated problems or delays and actions or plans to resolve them

Biomarkers Core: In March of 2020, COVID-19 restrictions were instituted and the site labs closed and enrollment of new participants was halted for several months. Sites/labs began working on limited basis for biospecimen analysis in August 2020 in the LIMBIC Biorepository laboratories at USUHS and NIH. Sites reopened in Sept./Oct. 2020 for some face-to-face clinical research and sample shipping resumed.
1. The halting of new enrollments and shipments imposed unexpected delays in workflow.
2. Budget considerations: The study continued paying personnel salaries and overhead during the shutdown period at sites. A carry forward request was submitted to carry over funds that were not spent last year to give the study more time to enroll.
3. Anticipated long-term impact: Since the study is behind schedule due to a year of COVID restrictions, nevertheless, the study budget provided staff salaries. Because of the lack of enrollment of new participants in LIMBIC Prospective study, the GWAS sub-study may be delayed until sufficient LIMBIC participants have been enrolled for our power analysis.
There are currently 1,383 extracted DNA samples from participants currently available for GWAS analysis with a few more than 100 new enrollments with DNA extractions in process and carrying out APOE genotyping; We need 2,000 minimum samples for GWAS. Carry Forward Request was approved by VCU in order to allow us to use the portion of GWAS funds unexpended in year 2 so that we will have sufficient funds in the Biomarker core to carry out GWAS when sufficient samples have been collected and are available for GWAS project. The pandemic is a waxing and waning situation and the lab activities may stop and start more than once.

Neuroimaging Core: The initial trainings related to neuroimaging data collection were initially delayed due to regulatory issues and COVID-19 restrictions, so these were completed by web-conferencing. We have been unable to collect human phantom data, but will plan to do this once travel restrictions are lifted. We are still awaiting some CDE codings from some of the neuroradiologist central readers who have had periods of difficulty due to COVID-19 and fires.

Prospective Longitudinal Study: The main operational challenge was the ongoing COVID-19 pandemic. After the national vaccine rollout, we did successfully reopen all sites to in-person research activities including face-to-face recruitment, new enrollments, and in-person testing. Nevertheless, the broad effects of the ongoing pandemic are still affecting operations and we anticipate PLS activities will continue to be hindered for an unknown period due to residual pandemic effects on behaviors. These broad effects have led to staffing shortages at several PLS and barriers to study participation due to health concerns and logistical challenges among our participants and recruits such as more home responsibilities due to caring for children who were

previously in day cares or physical schooling. To mitigate these effects, participants can now complete all questionnaires and some neuropsychological testing by secure web-based method from home to reduce the amount of time needed to be spent in the testing facility.

Changes that had a significant impact on expenditures

Neuroimaging Core and novel Neuroimaging Project: We were able to continue most activities (except in person training and human phantom data collection). However, our expenditures were essentially unchanged.

Biomarkers Core: The delays in collecting and shipping samples for almost 6 months delays reaching the enrollment goals while personnel are receiving salary. This may have some impact on the funding for the project.

Significant changes in use or care of human subjects

Nothing to report.

6. PRODUCTS:

- **Publications, conference papers, and presentations**

Journal publications.

See attached **Appendix #6** for the Publication Tracker and **Appendix #6a** for Publications.

1. **Dismuke-Greer CE**, Hirsch S, Carlson KF, Pogoda TK, Nakase-Richardson R, Bhatnagar S, Eapen BC, Troyanskaya M, Miles SR, Nolen T, Walker WC. Health services utilization, healthcare costs, and diagnoses by mild traumatic brain injury exposure: A 14-year longitudinal chronic effects of neurotrauma consortium study. *Arch Phys Med Rehabil*. 2020. Also featured in Monthly Newsletter and Website at the Department of Defense Blast Injury Research Coordinating Office (BIRCO).

2. Haarbauer-Krupa J, **Pugh MJ**, Prager EM, Harmon N, Wolfe J, Yaffe K (2021). Epidemiology of Chronic Effects of Traumatic Brain Injury.(Epub ahead of print) *J Neurotrauma*.

3. **Pugh MJ**, Kennedy E, Gugger J, Mayo J, Tate DF, Swan A, Kean J, Altalib HH, Gowda S, Towne A, Hinds SR, Van Cott A, Lopez MR, Jaramillo C, Eapen BC, McCafferty R, Salinsky M, Cramer J, McMillan KK, Kalvesmaki A, Diaz-Arrastia R (2021). The Military Injuries-Understanding post-Traumatic Epilepsy Study: Understanding Relationships Among Lifetime TBI History, Epilepsy, and Quality of Life.(Epub ahead of print) *J Neurotrauma*.

4. Swan AA, Akin FW, Amuan ME, Riska KM, Hall CD, Kalvesmaki A, Padilla S, Crowsey E, **Pugh MJ** (2021). Disruptive Dizziness Among Post-9/11 Veterans With Deployment-Related Traumatic Brain Injury.(Epub ahead of print) *J Head Trauma Rehabil*.

5. **Pugh MJ**, Kennedy E, Prager EM, Humpherys J, Dams-O'Connor K, Hack D, McCafferty MK, Wolfe J, Yaffe K, McCrea M, Ferguson AR, Lancashire L, Ghajar J, Lumba-Brown A (2021). Phenotyping the Spectrum of Traumatic Brain Injury: A Review and Pathway to Standardization.(Epub ahead of print) *J Neurotrauma*.

6. Valera EM, Joseph AC, Snedaker K, Breiding MJ, Robertson CL, Colantonio A, Levin H, **Pugh MJ**, Yurgelun-Todd D, Mannix R, Bazarian JJ, Turtzo LC, Turkstra LS, Begg L, Cummings DM, Bellgowan PSF (2021). Understanding Traumatic Brain Injury in Females: A State-of-the-Art Summary and Future Directions. *J Head Trauma Rehabil*, *36*(1), E1-E17.

7. Kornblith E, Peltz CB, Xia F, Plassman B, Novakovic-Apopain T, **Yaffe K**. Sex, Race, and Risk of Dementia Diagnosis after Traumatic Brain Injury among Older Veterans. Neurology, 2020, 95(13).

8. Leng Y, Byers AL, Barnes DE, Peltz CB, Li Y, and **Yaffe K**. Traumatic brain injury and incidence risk of sleep disorders in nearly 200,000 US veterans. Neurology, 2021, 96(13).

9. Kornblith E, Bahorik A, Li Y, Peltz CB, Barnes DE, **Yaffe K**. Traumatic Brain Injury, Cardiovascular Disease, and Risk of Dementia among Older US Veterans. Under review.

10. Dismuke-Greer CE, Esmaeli A, Pugh MJ, Garcia C, **Yaffe K**. Economic Impact of Comorbid TBI-Dementia on VA Facility and non-VA Facility costs, 2000-2020. Under review.

11. Dennis EL, Taylor BA, Newsome MR, Troyanskaya M, Abildskov TJ, Betts AM, Bigler ED, Cole J, Davenport N, Duncan T, Gill J, Guedes V, Hinds II SR, Hovenden ES, Kenney K, Pugh MJ, Scheibel RS, Shahim PP, Shih R, Walker WC, Werner K, York GE, Cifu DX, Tate DF, **Wilde EA** (2021). Advanced Brain Age in Deployment-Related Traumatic Brain Injury: A LIMBIC-CENC Neuroimaging Study. Brain Injury, Under Review.

12. Guedes VA, **Kenney K**, Shahim P, Qu B-X, Lai C, Devoto C, Walkder WC, Nolen T, Diaz-Arrastia R, Gill JM. Exosomal NFL, a prognostic biomarker for remote symptoms after mild traumatic brain injury? ***Neurology*** 2020 May 27: 10.1212/WNL.0000000000009577 doi: 10.1212/WNL.0000000000009577 Epub 2020 May 27. PMID: 32461282.

13. Peltz C, **Kenney K**, Gill J, Diaz-Arrastia R, Gardner RC, Yaffe K. Blood-based biomarkers of traumatic brain injury-associated cognitive impairment in older veterans. ***Neurology*** 2020 June 22: DOI: 10.1212/WNL.0000000000010087 Epub 2020 Jun 22. PMID: 32571850

14. **Kenney KL**, Guedes VA, Gill JM. Author response: Exosomal neurofilament light: A prognostic biomarker for remote symptoms after mild traumatic brain injury? ***Neurology*** 2021;96:726. doi:10.1212/WNL.0000000000011786. PMID: 32461282

15. Dennis E, Baron D, Bartnik-Olson B, Caeyenberghs K, Esopenko C, Hillary F, **Kenney K**, Koerte I, Lin A, Mayer A, Mondello S, Olsen A, Thompson P, Tate D, Wilde E. ENIGMA Brain Injury: Framework, Challenges, and Opportunities. ***Hum Brain Mapping*** 2020 Jun 1. doi: 10.1002/hbm.25046 online ahead of print. PMID: 32476212.

16. Devoto C, Lai C, Qu B-X, Guedes V, Wilde E, Walker WC, Diaz-Arrastia R, **Kenney K**, Gill JM. Exosomal MicroRNAs in Veterans with Mild Traumatic Brain Injury: Preliminary Results from a Chronic Effects of Neurotrauma Consortium (CENC) Biomarker Discovery Project. ***J Neurotrauma*** 2020 May 27. doi: 10.1089/neu.2019.6933 online ahead of print. PMID: 32458732.

17. Koerte IK, Esopenko C, Hinds SR, Shenton ME, Bazarian J, **Kenney K**, et al. Thompson PM, Tate DF, Dennis EL, Wilde EA, Baron D. The ENIGMA Sports Injury Working Group: an International Collaboration to Further our Understanding of Sports-Related Brain Injury. ***Brain Imaging and Behav*** April, 2020. DOI: 10.31234/osf.io/7d3z9 online ahead of print. PMID: 32720179.

18. Garcia A, Reljic T, Pogoda TK, **Kenney K**, Agyemang A, Belanger HG, Troyanskaya M, Wilde EA, Walker W, Nakase-Richardson R. Obstructive Sleep Apnea Risk is Associated with Cognitive Impairment After Controlling for TBI: A Chronic Effects of Neurotrauma Consortium Study. ***J Neurotrauma*** 2020 Jul 24. doi: 10.1089/neu.2019.6916. Online ahead of print. PMID: 32709212.

19. Tate DF, Dennis EL, Adams JT, Adamson MM, Belanger HG, Bigler ED, Bouchard HC, Clark AL, Delano-Wood LM, Disner SG, Goodrich-Hunsaker NJ, Hayes JP, Hinds SR, Hodges CB, Hovenden ES, Irimia AI, **Kenney K**, Lindsey HM, Morey R, Newsom MR, Scheibel RS, Shenton ME, Sullivan DR, Troyanskaya M, Wade B, Thompson PM, Wilde EA. Coordinating Global Multi-Site Studies of Military TBI: Potential, Challenges, and Harmonization Guidelines. ***Brain Imaging and Behavior*** (Military Special Issue) 2021 Jan 7. doi: 10.1007/s11682-020-00423-2. Online ahead of print. PMID: 33409819

20. Werner JK, Shahim P, Pucci JU, Lai C, Raiculescu S, Gill JM, Nakase-Richardson R, Diaz-Arrastia R, **Kenney K**. Poor sleep correlates with biomarkers of neurodegeneration in mild traumatic brain injury patients: a CENC Study. ***Sleep*** 2020 Dec 6:zsaa272. doi: 10.1093/sleep/zsaa272. Online ahead of print. PMID: 33280032

21. Guedes VA, Chen L, Devoto C, Qu B-X, Edwards K, Martin C, Mithani S, Rush H, Wilde E, Walker WC, Diaz-Arrastia R, Gill J, **Kenney K**. Exosomal MicroRNAs and Proteins are linked to Psychiatric Symptoms of PTSD and Depression in Veterans with mild Traumatic Brain Injuries. Invited submission, ***Frontiers Pharmacology, Invited Biomarker special issue***, in print 9-6-2021.

Books or other non-periodical, one-time publications.

Other publications, conference papers and presentations.

22. **Dismuke-Greer CE**, Hirsch S, Carlson KF, Pogoda TK, Nakase-Richardson R, Bhatnagar S, Eapen BC, Troyanskaya M, Miles SR, Nolen T, Walker WC. Health services utilization, healthcare costs, and diagnoses by mild traumatic brain injury exposure: A 14-year longitudinal chronic effects of neurotrauma consortium study. *Arch Phys Med Rehabil*. 2020. Also featured in Monthly Newsletter and Website at the Department of Defense Blast Injury Research Coordinating Office (BIRCO).

23. **Dismuke-Greer CE.** Traumatic Brain Injury (TBI) and Chronic Kidney Disease (CKD) in Veterans: Risk, Survival and Costs. Presented at the American Congress of Rehabilitation of Medicine Annual Conference, Virtual Conference, September 26-29, 2021.

24. **Dismuke-Greer CE.** Economics of Traumatic Brain Injury (TBI) Biomarkers. Presented at the American Congress of Rehabilitation of Medicine Annual Conference, Virtual Conference, September 26-29, 2021.

25. **Dismuke-Greer, CE,** Gujral K, Garcia CC, Egede LE. Traumatic Brain Injury in Veterans: Risk, Survival, and Costs. Poster presentation, Academy Health Annual Research Meeting, June 14-17, 2021.

26. **Dismuke-Greer, CE,** Ozieh, MN, Gujral, K., Garcia, CC, Egede, LE. Traumatic Brain Injury and Chronic Kidney Disease in Veterans: Risk, Survival, and Costs. Poster presentation, Academy Health Annual Research Meeting, June 14-17, 2021.

27. **Dismuke-Greer, CE.** Overview of DaVINCI/DoD Data VA Data Bootcamp, Health Economics Resource Center Data Bootcamp, Palo Alto VA Health Care System, October 19, 2020.

28. Pugh MJ and Wilde EA. Updates from the Long-term Impact of Military-relevant Brain Injury Consortium. Presented at VA Salt Lake City Healthcare System Research Week (5/20/21).

29. Wilde EA. Recent Advances in Neuroimaging in Military-relevant TBI. Presented at Brigham and Women's Hospital (4/26/21).

30. Brinck V, Ferguson A, Harris M, Nathan D, Wilde EA. Best Data Management Practices. Presented at the 3rd Stakeholders Meeting for the Federal Interagency Traumatic Brain Injury Research Informatics System (7/19/21).

31. Hillary FG, Dennis ED, Tate DF. Collaborative Approaches to Advance Neuroimaging in Traumatic Brain Injury. Traumatic Brain Injury Conference, Oct 2021. Virtual.

32. **Title:** Poor sleep is associated with increased inflammation in warfighters with mild traumatic brain injury.**Authors**: Pucci JU, Mithani SM, Leete J, Nakase-Richardson R, Lai C, Kenney K, Gill JM, Werner JK. **Meeting:** Poster presentation at the 145th annual meeting of the American Neurological Association 2020 virtual meeting, OCT 4-9, 2020.

33. **Title:** Sleep Quality Affects Plasma Exosomal MicroRNA Expression Profiles in Military

Personnel with Traumatic Brain Injury. **Authors:** Mithani SM, Leete J, Pucci JU, Guedes V, Kenney K, Werner JK, Gill JM. Meeting: Poster presentation at the 145th annual meeting of the American Neurological Association 2020 virtual meeting, OCT 4-9, 2020.

34. **Title:** Exosomal microRNAs and proteins as biomarkers of posttraumatic stress disorder symptoms in veterans with history of mild traumatic brain injury. **Authors**: Guedes VA, Lai C, Devoto C, Edwards K, Qu B-X, Mithani S, Wilde EA, Walker WC, Diaz-Arrastia RD, Gill JM, Kenney K. **Meeting:** 2021 SfN Global Connectome Virtual Event, January 11-13, 2021.

35. **Title:** Exosomal MicroRNA is Associated with Sleep Quality in Military Personnel with Traumatic Brain Injury. **Authors**: Mithani SM, Leete J, Pucci JU, Guedes V, Kenney K, Werner JK, Gill JM. **Meeting:** 2021 SfN Global Connectome Virtual Event, January 11-13, 2021.

36. **Title**: Exosomes may serve as an inflammatory biomarker in service members with sleep disturbances following concussion. **Authors:** Pucci JU, MIthani S, Leete J, Lai C, Kenney K, Gill JM, Werner JK. **Meeting:** 2021 Sleep annual meeting, June 12-16, 2021.

37. **Title**: OSA Risk is Associated with Number of White Matter Hyperintensities, But History of Mild TBI is Not: A LIMBIC-CENC Study. **Authors:** Garcia A, Wilde EA, Tate D, Reljic T, Kenney K, Troyanskaya M, Agyemang A, Pogoda T, Walker WC, Richardson. **Meeting:** 2021 Sleep annual meeting, June 12-16, 2021.

38. **Title:** Sleep Quality Affects Plasma Exosomal MicroRNA Expression Profiles in Military Personnel with Traumatic Brain Injury. **Authors:** Mithani SM, Leete J, Pucci JU, Guedes V, Kenney K, Werner JK, Gill JM. **Meeting:** Abstract presented as poster presentation at the 35th Annual Meeting of the Associated Professionals Sleep Societies, Virtual Conference, June 10-13, 2021

39. **Title:** Poor sleep quality in traumatic brain injury patients is associated with elevated inflammatory biomarkers. **Authors:** Pucci JU, Mithani S, Leete J, Lai C, Kenney K, Gill JM, Werner JK. **Meeting:** Abstract presented as poster presentation at the 35th Annual Meeting of the Associated Professionals Sleep Societies, Virtual Conference, June 10-13, 2021

40. **Title:** Obstructive Sleep Apnea Risk is Associated with Number of White Matter Hyperintensities, But Mild TBI Exposure is Not: A CENC-LIMBIC Study. **Authors:** Garcia A, Wilde EA, Tate D, Reljic T, Kenney K, Troyanskaya M, Agyemang A, POgoda T, Walker W, Richardson R. **Meeting**: Abstract presented as oral presentation at the 35th Annual Meeting of the Associated Professionals Sleep Societies, Virtual Conference, June 10-13, 2021

41. **Title**: Does Mild Traumatic Brain Injury lead to Chronic Pituitary Disorders? A multicenter LIMBIC-CENC analysis. **Authors:** Walker WC, Kenney K, Agyemang AA, Allen CM, Werner JK. **Meeting:** Abstract accepted and in prep as Platform presentation at MHSRS for AUG, 2021.

42. **Title:** Ultrasensitive Blood Test for Hyperphosphorylated Tau is Associated with Blast Exposures in Military Veterans with Chronic Traumatic Brain Injury. **Authors:** Edwards KA, Campbell C, Kendrick N, Kenney K, Diaz-Arrastia R, Davenport N, Gill JM, Debad J. **Meeting:** Abstract accepted and in prep as poster presentation at MHSRS, for AUG, 2021.

43. **Title:** Exosomal MicroRNA is Associated with Sleep Quality in Military Personnel with Traumatic Brain Injury. **Authors:** Mithani SM, Leete J, Pucci JU, Guedes V, Kenney K, Werner JK, Gill JM. **Meeting**: Abstract accepted and in prep as Platform presentation at

MHSRS for AUG, 2021.

44. **Title:** Extracellular Vesicle Proteins and MicroRNAs as Biomarkers of Persistent PTSD Symptoms in Veterans with History of Mild TBI. **Authors:** Guedes VA, Lai C, Devoto C, Edwards K, Qu B-X, MIthani S, Walker WC, Wilde EA, Diaz-Arrastia R, Werner JK, Gill JM, Kenney K. **Meeting:** Abstract accepted and in prep as poster presentation at 2021 MHSRS for AUG, 2021.

45. **Title:** Extracellular Vesicle Proteins and MicroRNAs as Biomarkers of Persistent PTSD Symptoms in Veterans with History of Mild TBI. **Authors:** Vivian A. Guedes, Chen Lai, Christina Devoto, Katie Edwards, Bao-Xi Qu, Sara Mithani, William C. Walker, Elisabeth A. Wilde, Ramon Diaz-Arrastia, J Kent Werner Jr, Jessica M. Gill, Kimbra Kenney. **Meeting:** 15th Annual Amygdala, Stress, and PTSD Conference: STRESS AND THE MIND, Virtual Conference, April 20, 2021 – Poster presentation, outstanding poster award.

- **Website(s) or other Internet site(s)**

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

- **Technologies or techniques**

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**

Nothing to report.

- **Other Products**

- Dismuke-Greer stripped real SSN and other patient identifiers from all Veterans in the longitudinal VINCI data for the following files: INP_PB, INP_PM, INPEXC_SM, INPEXC_XB, INPNVA_NB, INPNVA_NM, INPPCE, OUTP_SE. These files represent all inpatient stays inside and outside VA including long term care and bed stays. They also include all outpatient care within VA and provider claims associated with inpatient care inside and outside the VA. These files were uploaded to VCU servers for statisticians involved in the Dementia Study to search for dementia related diagnosis codes.

- The LIMBIC-CENC PLS database, PLS Data Cube, PLS Dashboard of descriptive data, and LIMBIC-CENC Knowledge Translation Center all represent outcomes in this area and are all described earlier in this report.

7. PARTICIPANTS & OTHER COLLABORATING ORGANIZATIONS

What individuals have worked on the project?

See Appendix #7 (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?

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

- LTC Harris assumed the role of Consortium Co-Director upon the retirement of COL Kristoffer Radcliffe.
- LtCdr Christina La Croix assumed the role of PI at the Fort Belvoir Prospective Longitudinal enrollment site upon Dr. Hee Chin Chae's departure.
- Dr. Melissa Guerra assumed the role of PI at the San Antonio Prospective Longitudinal enrollment up the departure of Dr. Carlos Jaramillo.

What other organizations were involved as partners?

Nothing to report.

8. SPECIAL REPORTING REQUIREMENTS

COLLABORATIVE AWARDS:

QUAD CHARTS: See Appendix #8 (Quad Charts)

9. APPENDICES: