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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 refined 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 traumatic 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.

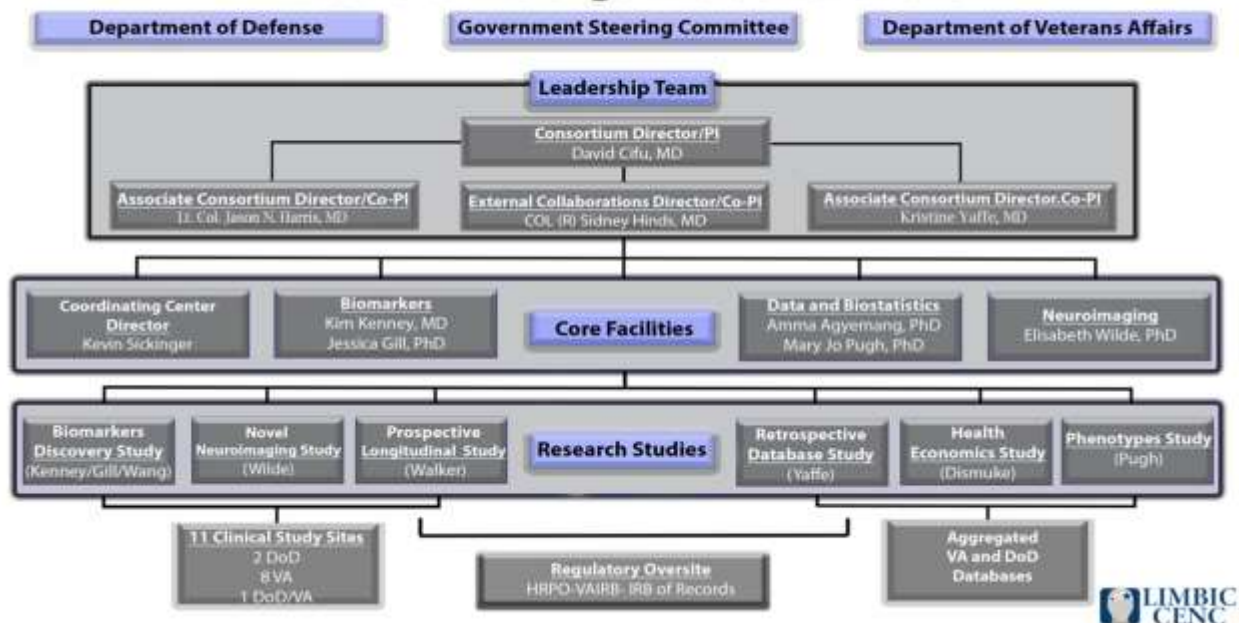
The Biomarker Core coordinates with appropriate LIMBIC-CENC personnel to submit relevant NED, APOE data to FITBIR. It conducts DNA extraction and APOE genotyping (in batches of 100-200) based on acquired consents for genetic testing. It continues to perform LIMBIC-CENC service operations-limited genotyping 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:

LIMBIC-CENC Organizational Chart



2. KEYWORDS:

chronic effects
 prognostic biomarker
 health services
 Veterans
 VA costs
 DoD costs
 Service Connected Disability Compensation
 FITBIR
 MRI
 neuroepidemiology
 phenotype
 chronic pain
 mTBI
 epidemiology
 neurodegeneration
 biospecimen biorepository
 neurotrauma
 dementia
 comorbidity
 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 traumatic brain injury (mTBI) cohort including servicemembers (SMs), veterans (Vs), and relevant populations, and through a series of scientific analyses it will fulfill all of the required LIMBIC-CENC research elements. Under LIMBIC, this includes targeted expansion of pre-911 era SMs, current SMs, and heavily blast exposed populations. Initial and longitudinal data are collected under TBI CDE guidelines using comprehensive assessments and submitted to the FITBIR. Scientific analyses investigate mTBI co-morbidities and neurologic outcomes including change over time. Though this process, the PLS will identify potential differences in outcomes between SMs & Vs with various histories of lifetime mTBI and repetitive low-level blast exposures, identify pathophysiological and biomarker signatures for chronic mTBI subgroups of recovery patterns and neurodegeneration susceptibility, and evaluate neuroimaging techniques to understand the relationships between mTBI and neurodegenerative disease and other co-morbidities.

Retrospective Database Study:

The primary objective of this project is to integrate and analyze existing VA healthcare data to study the long-term effects of traumatic brain injury (TBI) on neurodegenerative disease, mental health, and other outcomes. Our group of experts in TBI and epidemiology created a highly pragmatic national analytic database of over 2 million Veterans. In LIMBIC-CENC, we are rapidly investigating unanswered questions related to health risks associated with TBI:

Task 1: Planning and regulatory review, data updating, and variable creation (Months 1-12).

Task 2: Analysis assessing the role of mental health comorbidities on the association between mTBI and long-term outcomes such as dementia and other neurodegenerative diseases (Months 6-30).

Task 3: Analyses assessing the role of demographics and socioeconomic status to the risk of developing dementia and examining the characteristics and longitudinal course of younger veterans (<55) with cognitive impairment after mTBI (Months 24-50).

Task 4: Develop prognostic models to better determine risk of dementia and mortality and associations with risk factors in veterans with mTBI; create and validate clinical tool determining risk of poor short-term and long-term outcomes in patients with mTBI (Months 24-60).

Phenotype Study:

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

the observation period and provide data to 1) describe the population of SMs and Vs with mTBI, no TBI and TBI of other severities; 2) identify phenotypes and risk for specific phenotypes accounting for baseline characteristics, acute injury characteristics, and acute and chronic treatment patterns. The study aims to compare the prevalence of key comorbidities by TBI severity and study group, and then use deep learning models that incorporate mTBI phenotype, acute and chronic treatment approaches, and emergence of diverse comorbidities to develop risk scores for poor military outcomes, and risk for developing key comorbidities. The major goals for this study are as follows:

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

Task 2: Conduct phenotype analysis by deployment strata to examine the role of mTBI in emergence of neurodegenerative disease, psychological health status, neurosensory deficits and pain over time.

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

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

Health Economics Study:

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

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

Novel Neuroimaging Study:

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

Task 1: Assess available methods of overcoming variability introduced by differences in scanner hardware and software.

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

Task 3: Develop and test aspects of pre-processing which enhance accuracy and consistency.

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

Task 5: Incorporate elements of advanced statistical analysis (e.g., Bayesian analysis, machine learning) to utilize multi-modality imaging data in conjunction with other injury, demographic and outcome data to develop subgroups/phenotypes and identify related variables in those at highest risk for poor outcome.

Task 6: Assess merits and challenges of existing methods of “individualized” data analysis.

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

Biomarker Discovery Study:

In addition to supporting the Prospective Longitudinal Study, the Biomarkers Core will carry out projects in collaboration with the other VCU LIMBIC Cores to address the following objectives:

Task 1: Identify biologic signatures that may be predictive (prognostic biomarkers) of long-term TBI outcomes or maintenance of symptoms. Identify novel biomarkers for chronic mTBI; characterize mTBI subgroups based on recovery and neurodegeneration.

Task 2: Collaborate with Dr. Wang (Gainesville VA), as externally funded, to develop and validate a rapid throughput multiplex immunoassay of candidate chronic TBI biomarkers for commercialization.

Task 3: To collaboratively carry out GWAS within the CENC/LIMBIC cohort (N = 3,000) in collaboration with the Genetic Association in Neurotrauma (GAIN) consortium that has data from >10,000 participants.

Task 4: To expand the miRNA study and to carry out a DNA methylation study in chronic TBI patients.

What was accomplished under these goals?

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

Cores

Coordinating Center:

Major Task 1: Transition and Expand CENC to LIMBIC:

1. Submission of IRB approved master protocol.

Month(s): 1 - 3

Progress: Completed in the 1st Quarter of Year 1.

2. Delivery of expanded Consortium SOP.

Month(s): 1 - 3

Progress: Completed in the 1st Quarter of Year 1.

3. Submission of timeline for onboarding performance sites.

Month(s): 1 - 3

Progress: Completed in the 1st Quarter 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: Ongoing.

5. HRPO Approval of Master Protocol.

Month(s): 1 - 6

Progress: Completed. See **Appendix #1 (Regulatory Tracker)** for updates.

6. IRB/HRPO/JIT approvals for all performance sites and consortium cores.

Month(s): 1 - 12

Progress: All IRB and JIT submissions were submitted and approved. See above for HRPO approvals.

7. Hiring, training and certification of subaward personnel, particularly subaward clinicians and associate researchers.

Month(s): 1 - 6

Progress: Ongoing.

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

1. Onboard 3 new enrollment sites (Salisbury/San Diego/Fort Gordon).

Month(s): 1 - 6

Progress: This was completed on time, well before the end of the 2nd Quarter of Year 1.

2. Assist with hiring, training and certifying staff.

Month(s): 1 - 6

Progress: Completed the initial staffing process and now we are in the continuation of maintaining proper staff levels phase.

3. Assist with regulatory approvals to include IRB and HRPO.

Month(s): 1 - 6

Progress: All sites were gained IRB and HRPO approvals. We have now moved to the Continuing Review process. See **Regulatory Tracker Appendix #1** for specific updates.

Major Task 3: Conduct Call Center operations:

1. Assist with hiring, training and certifying staff.

Month(s): 1 - 60

Progress: Ongoing.

2. Conduct liaison between enrollment sites.

Month(s): 1 - 60

Progress: Ongoing.

3. Conduct all necessary follow-up calls to include BTACTs and Annual Telephone Assessments for Prospective Longitudinal Study.

Month(s): 1 - 60

Progress: The Call Center has attempted to conduct all necessary follow-up calls to include Annual Follow Up Assessments and BTACTs. For completion numbers, see Appendix #3.

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

1. Coordinate with CDMRP Science Officer to make tentative schedule for semi-annual GSC meetings.

Month(s): 4 - 60

Progress: We completed two GSC meetings within the reporting period (November 2021 and May 2022) 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 November and May GSC Meeting presentations.

2. Coordinate with all performance site PIs to ensure that their schedules permit attendance at meetings.

Month(s): 4 - 60

Progress: We were able to get all of the primary PIs to attend the virtual meetings in November 2021 and May 2022.

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

Month(s): 4 - 60

Progress: Continued to utilize the new timeline for meeting materials, not only ensuring that we met the turn-in suspense but also allowed for review time for our Science Officer to ensure that we turned in the best product possible.

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

1. Establish Site Metrics.

Month(s): 1 - 60

Progress: This task has been completed. We initiated the Full Site Metrics Reports during this reporting period and conducted them on a monthly basis. We put one enrollment site on probation and were able to work through their issues and they actually exceeded their enrollment goals in the 4th quarter.

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

Month(s): 1 - 60

Progress: The initial recruitment and retention plan that was adjusted during year two due to COVID is still in effect. However, we have taken a close look at site enrollments compared to published goals and are in the process of initiating small adjustments to each enrollment site's goals going forward. We are still confident that we will be the ultimate goal of 3000 participants months before the end of the current Period of Performance.

3. Monitor and report site performance.

Month(s): 1 - 60

Progress: This has been completed throughout the year to include monthly feedback to the sites.

4. Maintain and establish regular communication through meetings, teleconferences, e-mails, site visits and other methods to maintain consortium function.

Month(s): 1 - 60

Progress: We continue to communicate through our established and maintained regular teleconferences, emails and other calls as needed. We have not been able to conduct site visits due to travel restrictions and safety precautions due to COVID-19 but will resume travel once it is deemed safe.

Major Task 6: Collect required information, prepare and submit Quarterly, Annual and Final Reports.

Month(s): 1 - 60

Progress: Completed all required reports on time and to standard.

Major Task 7: Conduct Consumer Advisory Board Meetings:

1. Select Board Members and attain GSC approval of the selectees.

Month(s): 1 - 3

Progress: Completed in Year 1.

2. Publish the LIMBIC CAB Charter.

Month(s): 1 - 6

Progress: Completed in Year 1.

3. Publish the LIMBIC CAB Meeting Schedule.

Month(s): 1 - 6

Progress: Completed in Year 1.

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

Month(s): 6 – 60

Progress: Consumer Advisory Board. On April 14 2022 and September 28 2022, we solicited input from the CAB on the website and types and format of actionable information to be provided to consumers. We have obtained input on the redesign of the dissemination material subpages of the Service Member/Veterans/ Public and Clinician/Research section subject icons, developing and releasing Dementia Risk Profile Personalized Report (V2.0) including providing resource links on personalized recommendations to activate healthy lifestyle behaviors, and on a new digital video product on brain health risk factors and companion infographs series.

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

1. Ensure maximum Consortium PI involvement in scientific conferences.

Month(s): 1 - 60

Progress: We encouraged and assisted as many LIMBIC-CENC personnel to attend the MHSRS Conference this year. All members in attendance met for a casual gathering but it was the first time we were able to meet in person due to COVID.

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.

3. Monitor overall and individual site finances.

Month(s): 1 - 4

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

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

Month(s): 1 - 60

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

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

Month(s): 1 - 60

Progress: Ongoing.

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

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

Month(s): 12 - 24

Progress: These activities are ongoing for the entire consortium. However, Dr. Walker provides a detailed analysis plan within the PLS section 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: The Special Edition of *Brain Injury* was published and we also assisted in the recording of podcasts for each primary author under the title of “The Abstract Veteran”. The Director of the Coordinating Center will be a co-host for Season 2 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):

- Search Engine Optimization (SEO). We are working with SEO consultants to develop a plan and implement website changes to drive additional traffic to our website. We have a draft of “meta-tags” to attach to the LIMBIC-CENC website URL, headers and sub headers so that Google searches will more readily identify the website. The SEO consultants presented their initial findings on 10-21-22 with a final written report deliverable 11-4-22..

Broader Dissemination of LIMBIC-CENC Products and Progress:

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

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

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

Updated Prospective Longitudinal Study Data Visualization Dashboard (On-going):

- Updated “at a glance” summary scheduled for Fall 2021.

LIMBIC-CENC Searchable Journal Database:

- Publication Database. Added abstracts of at least 194 newly published articles by LIMBIC-CENC authors published through 9-16-2022 to the LIMBIC-CENC publication database..

Information Awareness Campaign (The Abstract Veteran Podcast Series):

- Podcasts. Ron Johnson, MA, VCU assistant professor, and producer of the Abstract Athlete and Abstract Doctor podcast series, was selected to produce the Abstract Veteran podcasts associated with the LIMBIC-CENC Special Issue in Brain Injury. Char Gatlin and Dr. Seel co-hosted 12 recorded 30-minute podcasts in which a lead author for each special issue article was interviewed. All podcasts were completed and posted on the Abstract Doctor website and the LIMBIC-CENC website. Season 2 of the Abstract Veteran has 12 podcasts planned, one released each month, with a focus on patient and family care partner information and resource needs. Four season 2 podcasts have been published through 9/30/2022.

Brain Injury Special Issue:

- The LIMBIC-CENC multi-center research investigator team completed the submission, revision and publication of 12 research articles on the LIMBIC-CENC prospective longitudinal study as a special issue in the journal, *Brain Injury*. The reference information on these 12 articles can be found in the Appendix. A podcast series was also created as knowledge translation products and are discussed in the ‘Other Products’ section of this report.

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: In FY2021, LIMBIC-CENC established its formal external collaborations operations plan, levels of collaborations and collaborations tracker (**see APPENDIX #4**). Since then, from 2021-2022 we have had a wide range of external collaborations, with the following highlights:

PREDICT TBI: QTR2 FY2021, LIMBIC-CENC has had 2 virtual and 2 in-person meetings, including at MHSRS 2022) with the United Kingdom, PREDICT TBI group, led by Dr. Alexandra Sinclair, to provide guidance, support, and other resources. QTR 3 FY2022, LIMBIC-CENC introduced the PREDICT-TBI researchers to the TBI Center of Excellence leadership.

Football Players Health Study (Harvard University): LIMBIC-CENC is working with the FPHS team, led by Ross Zafonte, DO, to compare data to evaluate the effects of general health and socioeconomic issues in its and LIMBIC-CENC populations. The FPHS and LIMBIC-CENC researchers are dedicated to exploring and creating practical knowledge products to address the associated medical disorders that accompany mTBI/concussion such as diabetes, obesity, chronic pain, osteoarthritis, hypertension, cardiovascular disease, and dementia. A common dataset has been created and preliminary analyses are being planned while funding is identified.

NFL/NFLPA: LIMBIC-CENC had representation at the NFL/NFLPA’s annual health and safety meetings during the NFLPA’s Health and Safety meeting at the NFL Draft, Las Vegas, Nevada, May 2022. One of the Co-PIs presented findings which included the work of LIMBIC-CENC among those of other DoD funded research studies.

NASEM: NASEM invited LIMBIC-CENC senior leadership to present and be part of the “Accelerating Progress in TBI Research and Care” open forums, TBI Forum presentations, and representation on the Forum. <https://www.nationalacademies.org/our-work/accelerating-progress-in-traumatic-brain-injury-research-and-care> NASEM was funded by JPC-6/DHA to execute the “Report” and the TBI Forum includes members of the Federal Government, Veteran Support Organizations, and concerned organizations.

Cohen Veterans Bioscience Brain Trauma Blueprint: The LIMBIC-CENC. Senior leaders were part of the planning of the Blueprint and the developing the Roadmap. Drs. Mary Jo Pugh, Elisabeth Wilde, Ms. Lee and Dr. Ramoni are planned speakers and participants for the CVB meeting in October 2022. <https://www.cohenveteransbioscience.org/2022/08/25/btb-action-summit/>

Acute Neurotrauma Consortium: LIMBIC-CENC provided guidance to Catherine Johnson, PhD, University of Missouri Science and Technology and Acute Neurotrauma Consortium researcher at Ft. Leonard Wood) and UK based researcher, Roger Sloman, PhD to help focus their work on blast-effect mitigation for warriors in vehicles in combating TBI. This resulted in a collaborative application for the “Fiscal Year 2022 (FY22) CDMRP Traumatic Brain Injury and Psychological Health Research Program (TBIPH) Focused Program Award”: using combined experience and

expertise to provide research which is poised to propel the field of TBI, forward.

TBI Center of Excellence: LIMBIC-CENC and TBI Center of Excellence have been interacting since LIMBIC-CENC's inception. In the past year, leaders from LIMBIC-CENC and TBI CoE have held meetings to discuss a strategy of collaboration and products:

Phase 1: Transition of knowledge (LIMBIC-CENC) to TBI-CoE (completed Qtr 3 FY 2022)

- Monthly written summary of LIMBIC-CENC updates to TBI-CoE
- Series of 4 research meetings among LIMBIC-CENC researchers and TBI-CoE staff

Phase 2: Translate knowledge (completion date Qtr 2 FY 2023)

- 10 LIMBIC-CENC database projects developed with TBI-CoE team and analyses ongoing.
- Work with TBI-CoE's Clinical Affairs branch to inform existing clinical recommendations or prompt the creation of new clinical recommendations.

Other organizations that LIMBIC-CENC has had external collaborations with include;

- TRACK-TBI
- NCAA Care Consortium
- InTBIR
- Veterans Against Alzheimer's
- ENIGMA
- University of Pennsylvania
- Concussion Legacy Foundation
- TBI Center of Excellence (formerly DVBIC)
- Harvard's Football Players Health Study investigators
- Million Veterans Program
- Biogen
- CONNECT-TBI
- Operation Backbone
- University of Virginia
- Perspecta
- University of Utah
- Peer-reviewed Alzheimer's Research Program (CDMRP)
- Shepherd Center (Rusty Gore)
- NICOE (CAPT Carlos Williams)
- Intrepid Spirit, Fort Campbell (Dr. Mark Zola)
- Henry Jackson Foundation (HJF)
- Wounded Warrior Project (WWP)
- Steady Mind (Seth Hickerson)
- National Academy of Science, Engineering, and Medicine, TBI Forum
- VA, National Research Advisory Council (NRAC)
- Dr. Fred Drery (clinical consultation)
- LifeScore (John Wordin) (interactive software focused on helping warriors/veterans manage their brain health)
- Operation Backbone (Mike Sformo)
- Eric Escobar (formerly with Biogen)
- Prevent Biometrics (acceleration and deceleration technology)
- Synaptex (mTBI/Concussion management system)
- BIG 10/Ivy Concussion (Keynote presentation)
- Marcus Institute for Brain Health (site visit and discussion)
- Cohen Veterans Bioscience Brain Trauma Blueprint Roadmap
- University of Michigan Concussion Center
- United States Air Force Academy concussion researchers
- National Academy of Science, Engineering, and Medicine (NASEM) TBI Report and TBI

Forum

- LIMBIC-MATARS – Poster presentations at 6th International Consensus Conference on Concussion in Sports (The Amsterdam Conference)

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

Data and Biostatistics Core:

Major Task 1: Hire and maintain DBC staff.

Month(s): 1 - 60

Progress: New Core staff (1 project manager) were hired, onboarded and trained. 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. In addition to Medidata, raw data files are being captured through the secure file transfer protocol. Developed and iteratively improving Study Portal system to capture and manage PLS participant contact information and to track Call Center call completion. Added feature in Study Portal to facilitate sites' tracking of upcoming visits. Completed training of all 11 sites in all IT systems and provide ongoing support. Conducting monthly data quality checks and feedback to sites on visit completion rates, data entry timing and quality, raw data uploads, FITBIR GUID and pseudo GUID tracking. Generate multiple monthly reports to track retention, comprehensive, annual telephone, and BTACT visit completion, and consent 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, a desktop application was created to automate data extraction for new data requests. The application underwent rigorous testing and validation and has been implemented and is in production. Using the application, the DBC is able to respond to approved data requests within two business days compared to 10 to 15 days with the previous processes. The DBC has created analytic data sets that are updated every six months. The data sets sync the data elements across three platforms: The web-based data dictionary, the CRF documents, and the Analytic data sets. The synchronization is an attempt to further enhance investigators' experiences usability of the LIMBIC data sets.

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

Month(s): 1 - 60

Progress: During year 3, the analyses of two data sets focusing on cognitive functioning are in progress by the Central Biostatistics group.

Major Task 4: Translate knowledge and disseminate knowledge products.

Month(s): 1 - 60

Progress: Continuously refining searchable, comprehensive publication database of CENC and LIMBIC-CENC publications (publicationdatabase.limbic-cenc.org), and developing a 'Recent Findings' page for

clinicians and other non-academic populations. 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 3, the DBC received 18 data requests. Of which 6 were approved and 12 are in progress with 7 that preliminary requests approved, but need requester to submit Full request (4 of these requests have been sent back asking for revisions). Another 4 are pending SRC review (deadline still ongoing), and 1 is pending additional information from requester. Accordingly, the DBC has responded to the 6 approved data requests. Three data sets were leased to investigators and three data were shared with Central Biostatistics group for analyses and manuscript preparation. All analyses by the Central Biostatistics group are in progress.

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, 2022 for the period of October 1st, 2020 thru September 30th, 2021 and on September 30th, 2022 for the period of October 1st, 2021 thru March 31st, 2022. The first submission (March 2022) included 90 (out of 94) required Forms. No data were collected for two forms during the report period. The other two were in the process of being modified. For the September 2022 submission, 91 (out of 94) required forms were submitted. One form is currently being modified, while the other two forms had no data collected (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. GOSE form was kept on hold for the first submission pending approval from FITBIR to submit the data without outcome scaled score. Approval was provided in the month of August 2022, therefore the form was submitted in the second submission without scaled score.

Major Task 7: Attendance at biannual GSC meetings.

Month(s): 4 – 60

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

Neuroimaging Core:

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

Month(s): 1 - 60

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

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

Month(s): 1 - 60

Progress: At the beginning of the project, we submitted a new IRB under LIMBIC to the University of Utah and George E. Wahlen VA and received formal determination from the IRB that activities conducted under the Neuroimaging Core were not considered human subjects research and did not require further oversight by the IRB (03 Dec 2019). We subsequently submitted a separate IRB for the Novel Neuroimaging Project, which was also determined to be non-human subjects research. Since no continuing review is necessary, this is considered complete. We will continue to undergo annual RR&D committee approval at the VA; this was last submitted October 2022 for both the Core and the Novel Neuroimaging

Project.

Major Task 3: HRPO approval and continuing review.

Month(s): 1 – 60

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

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

Month(s): 1 - 60

Progress: We have continued began site-specific training on imaging –related procedures for all sites. We review and discuss imaging quality and consistency in weekly Imaging Core Operations meetings. We have prepared feedback to each site from our semi-annual audit process (October 2022) and meet with sites to correct issues, as needed.

Quality assurance-related procedures include quarterly self-assessments performed by the sites (due January, April, July, and October) as well as semiannual assessments performed by the Core (due April and October). These assessments address adherence to established procedures and are detailed in the SOP. Phantom object (every two weeks) testing is anticipated to be ongoing through the course of the project.

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

Month(s): 6 - 60

Progress: We have completed scheduled data uploads of the raw imaging data to FITBIR (most recent was September 2022). We also assist in the data entry and review for the results of the imaging Common Data Elements based on the clinical reviews by the neuroradiologists. We meet weekly with the Data Core, and participate in other subgroup calls, as needed. We continue to provide coded summary imaging data (including specific measures and composites) and guidance to investigators within and outside the consortium with proposals that have been approved through LIMBIC. This represents an ongoing activity, but members of the Core have participated during this reporting period in planning projects and distributing data to ENIGMA and VA Center of Excellence investigators as well as projects by individual investigators.

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

Month(s): 1 - 60

Progress: Sequence parameters and phantom testing results are monitored in weekly Neuroimaging Core Operations meetings (Wilde, Welsh, Hunsaker, Hovenden, Lindsey), and detailed in reports created as part of the semi-annual review. We have not yet completed annual human phantom testing at some sites due to anticipated scanner upgrades, resolving contracting issues and other reasons, but will complete this in the coming year as these issues resolve. 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: As above, sequence parameters are monitored in weekly Neuroimaging Core Operations meetings (Wilde, Welsh, Hunsaker, Hovenden, Lindsey). In addition to examining consistency between and within sites, we perform visual (qualitative) inspection of data to assess data quality at a preliminary review level. We have also instituted quantitative QA procedures that assess metrics such as motion, signal to noise, contrast to noise, etc. These parameters are assessed in a 7-page report that is generated for each scan. This is anticipated to be an ongoing activity throughout the course of the project.

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

Month(s): 1 - 60

Progress: In addition to reports that are generated for each participant/scan, we have created a system to compile aggregate group reports which graph the data distribution in violin plots, both for each site and the data as a whole; this enables identification of outliers and provides a snapshot of the data quality overall. To date, data quality has generally been good. This is anticipated to be an ongoing activity throughout the course of the project.

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

Month(s): 1 – 60

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

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

Month(s): 1 - 60

Progress: See above description under item 9.

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

Month(s): 1 - 60

Progress: The preprocessing of imaging data maintained by the Neuroimaging Core is largely up-to-date for the standard analysis pipelines (including recent versions of FreeSurfer (v7.1) and updated ENIGMA diffusion processing); we have also completed additional longitudinal pipelines, which are in process. We are in the process of completing a newly-updated functional connectivity pipeline (HAF-PIPE) which has been optimized for large-scale use. 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 the core's GitHub repository site to maintain version control and documentation of changes. The Neuroimaging Core presents weekly reports to the Data Core regarding CDE coding completion. This is anticipated to be an ongoing activity throughout the course of the project.

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

Month(s): 1 - 60

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

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

We have continued to work with other investigators with existing analysis requests to facilitate access to data and to assist in analysis and data dissemination including, but not limited to, 1) Drs. Stone, Tustison and Avants, 2) Dr. Mary Newsome, 3) Dr. Emily Dennis, 4) Dr. David Tate, 5) Dr. Ben Wade, 6) Dr. Randy Swanson, 7) Dr. Carrie Esopenko, and 8) requests from VA Center of Excellence investigators

We have resubmitted manuscripts on 1) the relation between performance on Grooved Pegboard Test and diffusion/volumetric imaging (lead author: Benjamin Wade), 2) persistent imaging findings in chronic TBI (Lead author: David Tate), and 3) white matter hyperintensities and their association with cognitive performance and other health indicators.

During this reporting period, we also published a manuscript on advanced brain age in individuals with

deployment-related TBI based on LIMBIC data as well as participated in a manuscript on age-related white matter disruption that was a larger ENIGMA study related to diffusion findings in military personnel. We performed an analysis on a subset of LIMBIC data which included 822 participants (mean age = 40.4 years, 714 male/108 female) who underwent MRI sessions at baseline, and 201 who completed a follow-up scan between five months and four years later. Predicted brain ages were calculated using T1-weighted MRIs and then compared with chronological ages to generate an Age Deviation Score for cross-sectional analyses and an Interval Deviation Score for longitudinal analyses. In cross-sectional analyses, males with a history of deployment-related mTBI showed advanced brain age compared to those without, while this association was not significant in females. In follow-up analyses of the male participants, severity of posttraumatic stress disorder (PTSD), depression symptoms, and alcohol misuse were also associated with advanced brain age.

In collaboration with the ENIGMA Military TBI Working Group (lead by Drs. Tate, Wilde and Dennis), we examined the use of non-negative matrix factorization (NMF), which is a data-driven approach that detects covarying patterns within high-dimensional data. We applied NMF to diffusion imaging data from 1,475 Active Duty Service Members and Veterans with and without a self-reported history of TBI, and identified 12 independent components derived from fractional anisotropy (FA). Regressions were used to examine mTBI-related associations in NMF-derived components while adjusting for age, sex, posttraumatic stress disorder, depression, and site/scanner. We found significantly stronger age-dependent effects of lower FA in Veterans with vs without TBI in four components. We found NMF to be powerful and effective in detecting covarying patterns of FA associated with mTBI by applying standard parametric regression modeling. Our results highlight patterns of white matter alteration that are differentially affected by mTBI in younger as compared to older Veterans.

Members of the Imaging Core have also participated in manuscripts associated with the larger consortium (lead authors: Amanda Garcia, Ian Stewart, Eamonn Kennedy, Bill Walker, Peter Fino, Christina Devoto, Jackie Gottshall)

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

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

Month(s): 1 - 60

Progress: The Imaging Core oversees consortium member accounts to securely transfer data. Imaging data is organized for consistency and stored in DICOM format as well as BIDS format. Data is securely archived and stored with redundancy. This task will continue through the course of the project.

Major Task 15: Attendance at biannual GSC meetings.

Month(s): 6 - 60

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

Biomarkers Core:

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

Month(s): 1 - 60

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

- Continued to fund NED screening of PLS enrollees (IGF-1, testosterone, TSH) at their baseline visit through a CLIA-certified lab (currently under an active contract with Quest).
- The Biorepository (BR) received PLS biospecimens from all 11 enrollment sites. For the period Sept. 30, 2021 to the end of Sept. 2022 the BR received locally processed and frozen aliquots from 341 LIMBIC PLS participants, including 23 from follow-up PLS visits. There were specimens from 318 new subjects and 3,688 cryovials were added to inventory during this time period from the PLS study. As of 29 September 2022, the BR has collated/stored processed/aliquoted biospecimens (DNA/buffy coat, plasma, serum, saliva, RNA (PaxGene)

from 2,415 study 1 (495 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 32,500 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 3/16/2022).
- 5-way CRADA for the FBCH PLS LIMBIC site still in process as of Oct. 2022 among USUHS, Geneva, Eisenhower (EAMC), WRNMMC and FBCH, as required by WRNMMC Research Department.

Major Task 3: HRPO approval and continuing review.

Month(s): 1 - 60

Progress: HRPO second level approval 10-16-2020.

- Most recent HRPO approval 3/16/2022
- CR approved by USUHS IRB 3/10/2022.

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 in this period of performance for a total of 1,383 PLS participants with DNA extraction and APOE genotyping to date.

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

Month(s): 1 – 60

Progress:

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

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

Month(s): 1 - 60

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

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

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

A Longitudinal Investigation of altered Blood and Imaging markers of Neuroinflammation, Neurodegeneration and Microvascular Integrity and their Clinical Correlates in relation to COVID-19 Infections in Combat Veterans with varying mild TBI histories (“Long-COVID”)- (David Cifu PI, LIMBIC consortium Co-Is Kimbra Kenney) **FUNDED**

“Long Term Neurological Consequences of Traumatic Brain Injury; Association between Neuroimaging Measures of microvascular function and modifiable CV risk factors”, Randy Swanson (Phil VA) VA CDA (Randy Swanson, Cifu, Walker, Ramon, Lisa Wilde, Jessica Gill, Kimbra Kenney)- FUNDED. Working on setting up biomarker section through LIMBIC.

Longitudinal Information on Neurologic Outcomes and Knowledge Translation Study of Severe TBI: A Joint VA TBIMS and LIMBIC Collaboration - (Risa Nakase-Richardson PI, Jessica Gill & Kimbra Kenney Co-PIs Biomarker section). **Under review**

The UNRAVELLED study: Understanding Neurodegenerative Risks of Adverse childhood experiences and Violence, and Elucidation of Long-term and Lasting Effects on social Determinants of health, was submitted to NIH (Dave Cifu and Sam Walton as Co-PIs, VCU, and Jessica Gill, as Investigator). **Under Review**

Blood test for early neurodegeneration in Veterans (Jessica Gill- Investigator). Submitted to CDMRP - FY22 PRARP Accelerating Diagnostics Research Award (W81XWH-22-PRARP-ADRA). **Not yet reviewed**

APOE4 genotype related blood metabolites of cognitive and psychological health in mTBI patients, Laila Abdullah, Fiona Crawford, Roskamp Institute, Jessica Gill, Kimbra Kenney; IIRA; submitted 10/7/2022. **NOT FUNDED.**

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

Month(s): 1 - 60

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

Major Task 9: Attendance at biannual GSC meetings.

Month(s): 6 - 60

Progress: Drs. Gill and Kenney attended (virtually) and presented at both bi-annual GSC meetings during this period of performance (November 2021 and May 2022) and will present at the upcoming GSC meeting October 2022.

Studies

Prospective Longitudinal Study:

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

Month(s): 1 - 60

Progress: Previously 100% met for initial hires, with ongoing work to maintain staff. Continuing to address challenges of COVID pandemic and macroeconomic conditions on maintaining staffing levels at all PLS sites. A new P.I. was successfully onboarded at Fort Belvoir site.

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

Month(s): 1 - 60

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

In the current reporting period, we added to language to protocol and consent form and achieved IRB

approvals across sites for the following elements:

- Details of FITBIR data transfers of de-identified participant data.
- Details of de-identified data transfers to the Data and Biostatistics Core.
- Details on Biorepository Saliva samples storage; will be stored indefinitely for future research.
- Neuroimaging Core omitting listing of sites to cut down on future regulatory submissions when sites are added or removed.
- Sharing SSN with Dr. Libby Dismuke for the Health Economics study.

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.

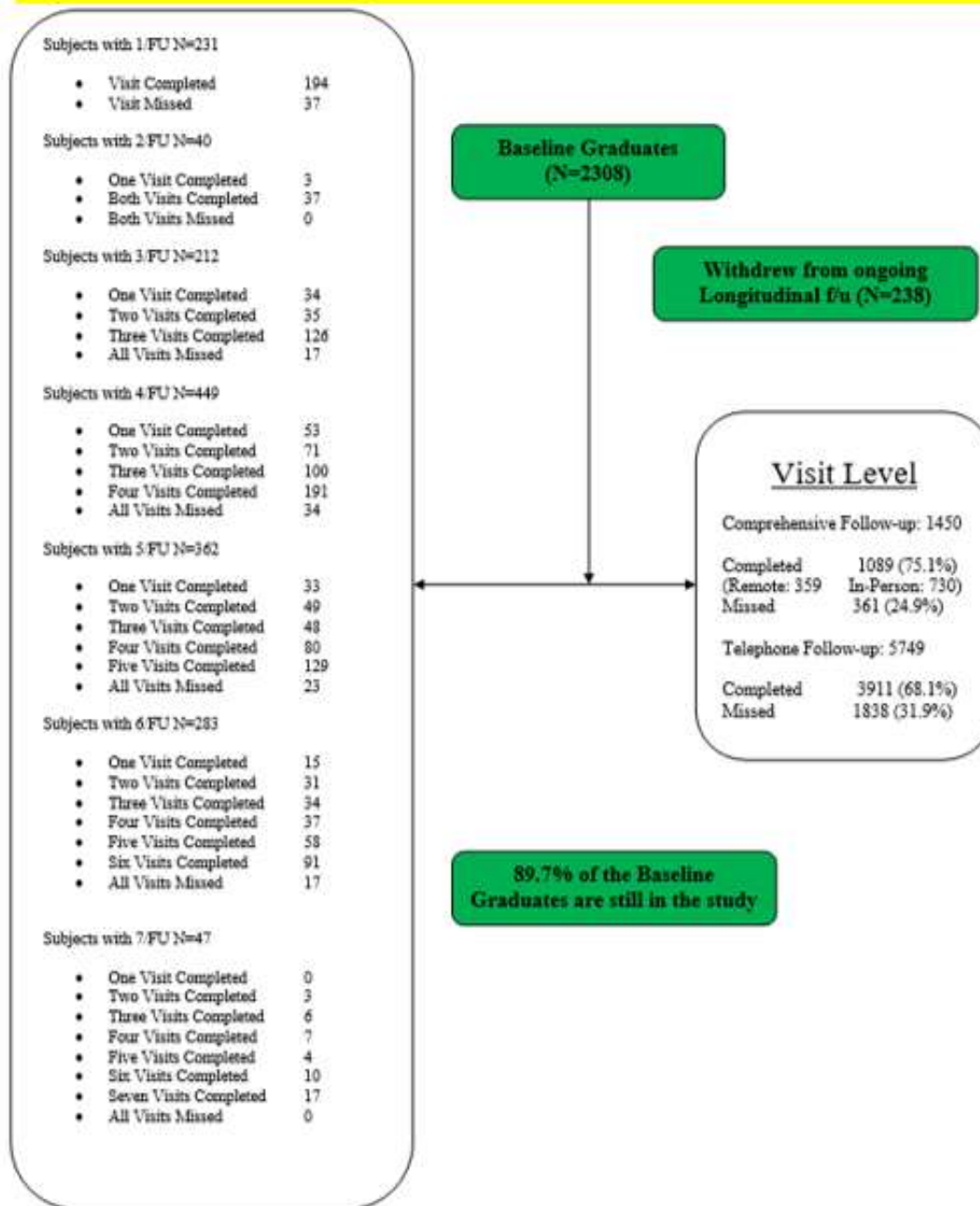
Month(s): 1 - 60

- Progress: From Oct 01, 2021 to Sep 30, 2022, a total of 1107 new follow-up assessments were completed. This consisted of 192 new comprehensive and 877 new annual phone follow-up assessments which resulted in completion rates of 60% and 68% out of those that were due. Of the new comprehensive longitudinal evaluations completed, 98 (51%) were in-person and 94 (49%) were the remote-collection version. Additionally, 147 BTACT assessments were completed during period for a completion rate of 85%.

Cumulative Totals:

- During LIMBIC (since Oct 01, 2019), a total of 3043 follow-up assessments have been completed, consisting of 612 comprehensive and 2431 annual brief phone follow-up assessments. Of the comprehensive longitudinal evaluations completed under LIMBIC, 267 (44%) were in-person and 345 (56%) were the remote-collection version. Additionally, 488 BTACT assessments have been completed.
- Since CENC inception, a total of 5000 follow-up assessments have been completed, consisting of 1089 comprehensive and 3911 annual brief phone follow-up assessments. This translates into overall completion rates of 75% for comprehensive and 71% for annual telephonic. See longitudinal Consort diagram below. Additionally, 868 BTACT assessments have been completed since CENC inception with an overall completion rate of 89%.
- Cumulative data since the inception of CENC PLS that is broken down by subject level and visit level are presented as the Longitudinal Evaluation Study Participant Flow Diagram in the figure below.

Participant Flow Diagram for Initial Evaluations



Major Task 6: Report descriptive data.

Month(s): 1 - 60

Progress: 100% met; ongoing to maintain.

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

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

Month(s): 1 - 60

Progress: Good progress with ongoing acquisition and storage of eye tracking data (see record counts below). Also progressed with developing a cross-walk across data collected with the legacy EyeLink

equipment versus the current state-of-the art and easier to use and analyze RightEye equipment. Note: scientific analyses are shown elsewhere in this report.

- Total records acquired for reporting period (10/1/21-9/30/22) was 419, consisting of 335 baseline and follow-up 84 eye-tracking tests.

Cumulative Totals:

- During LIMBIC (since Oct 01, 2019), a total of 669 records have been acquired, consisting of 526 baseline and 143 follow-up eye-tracking tests.
- Since CENC inception, a total of 1509 records have been acquired, consisting of 1176 baseline and 333 follow-up eye-tracking tests.

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

Month(s): 1 - 60

Progress: Good progress with ongoing acquisition and storage of Balance Master data (see record counts below). Note: scientific analyses are shown elsewhere in this report.

- Total records acquired for reporting period (10/1/21-9/30/22) was 400, consisting of 334 baseline and 66 follow-up Balance Master tests.

Cumulative Totals:

- During LIMBIC (since Oct 01, 2019), a total of 726 records have been acquired, consisting of 541 baseline and 185 follow-up Balance Master tests.
- Since CENC inception, a total of 1781 records have been acquired, consisting of 525 baseline and 2306 follow-up Balance Master tests.

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

Month(s): 1 – 60

Progress: Good progress with ongoing acquisition and storage of hearing test data (see record counts below). A noise meter software was deployed to all sites to improve quality control of data for scientific analyses. A larger size headband for the bone oscillator was deployed to all sites to accommodate participants with very large head circumferences. Note: analyses are shown elsewhere in this report.

- Total records acquired for reporting period (10/1/21-9/30/22) was 464, consisting of 386 baseline and 78 follow-up Hearing tests.

Cumulative Totals:

- During LIMBIC (since Oct 01, 2019), a total of 838 records have been acquired, consisting of 640__ baseline and 198 follow-up Hearing tests.
- Since CENC inception, a total of 2391 records have been acquired, consisting of 1865 baseline and 526 follow-up Hearing tests.

Major Task 10: Administer and interpret neuropsychological data.

Month(s): 1 - 60

Progress: Good progress with ongoing acquisition and interpretation of neuropsychological data (see record counts below).

- Total records acquired/interpreted for reporting period (10/1/21-9/30/22) was 650, consisting of 465 baseline and 185 follow-up Neuropsychological testing batteries.

Cumulative Totals:

- During LIMBIC (since Oct 01, 2019), a total of 1350 records have been acquired and interpreted, consisting of 757 baseline and 593 follow-up Neuropsychological testing batteries.
- Since CENC inception, a total of 3371 records have been acquired and interpreted, consisting of 2311 baseline and 1060 follow-up Neuropsychological testing batteries.

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

Month(s): 1 – 60

Progress: Good progress with ongoing acquisition and storage of biospecimen sets (see counts below). Note: analyses are shown elsewhere in this report.

- Total biospecimen sets acquired for reporting period (10/1/21-9/30/22) was 409, consisting of 349

baseline and 60 follow-up biospecimen sets.

Cumulative Totals:

- During LIMBIC (since Oct 01, 2019), a total of 669 biospecimen sets have been acquired, consisting of 527 baseline and 172 follow-up biospecimen sets.
- Since CENC inception, a total of 1825 biospecimen sets have been acquired, consisting of 1419 baseline and 406 follow-up biospecimen sets.

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

Month(s): 1 – 60

Progress: Good progress with ongoing acquisition and storage of imaging data (see imaging session counts below). Note: analyses are shown elsewhere in this report.

- Total imaging sessions of data acquired for reporting period (10/1/21-9/30/22) was 176, consisting of 150 baseline and 26 follow-up imaging sessions.

Cumulative Totals:

- During LIMBIC (since Oct 01, 2019), a total of 407 imaging sessions have been acquired, consisting of 292 baseline and 115 follow-up imaging sessions.
- Since CENC inception, a total of 1825 imaging sessions have been acquired, consisting of 1419 baseline and 406 follow-up imaging sessions.

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

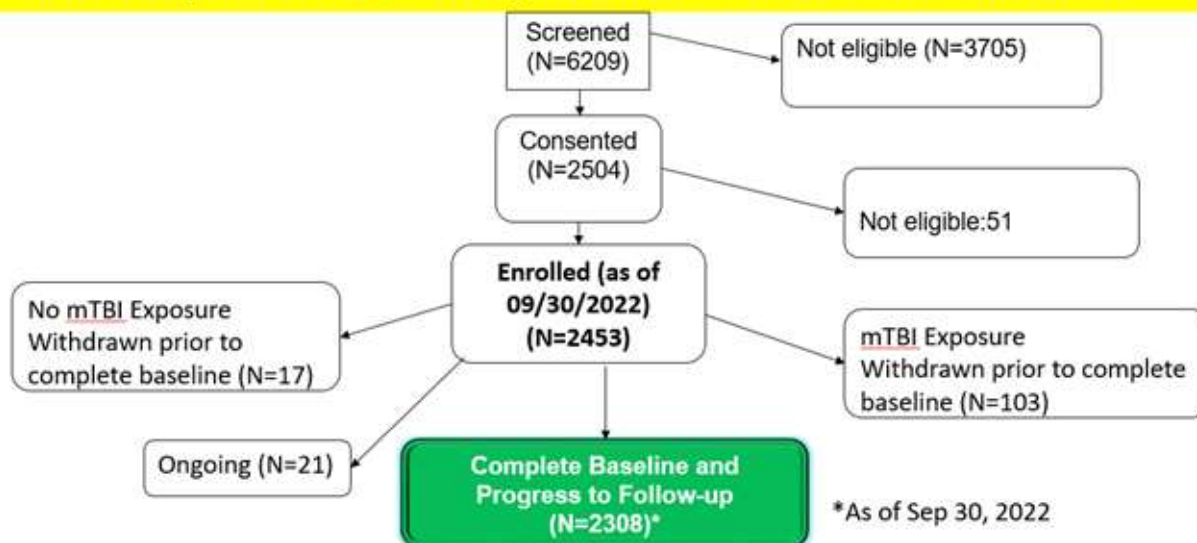
Month(s): 1 - 60

Progress: Excellent progress was made toward target enrollment despite the ongoing and evolving nature of the COVID pandemic which continues to hamper recruitment and enrollment activities. During this reporting year, the only site still prohibited by local authorities from in-person research activities (Boston site) was permitted to restart their in-person research activities. Thus, all eleven PLS sites have been and continue to actively enroll.

This reporting year (10/1/21-9/30/22), there were 501 new participants consented, 488 new participants enrolled, and 474 new baseline evaluations completed (graduated to follow-up).

Throughout the course of the study (from CENC to LIMBIC-CENC), a total of 2504 participants have been consented, 2453 participants enrolled, and 2308 baseline evaluations completed. (see initial evaluation consort diagram in figure below).

Participant Flow Diagram for Initial Evaluations



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



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

Month(s): 1 - 60

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

Major Task 15: Implement recruitment and retention plan.

Month(s): 1 – 60

Progress: Previously 100% met for implementation.

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

Month(s): 12 - 60

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

- **Analyses:** During the reporting period (10/1/21-9/30/22), __ new PLS analytic datasets were released for new projects, and __ 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 **Appendix #2**.
- **Scientific journal publications and scientific meeting presentations:** See table below for number of publications and presentations during the reporting period (10/1/21-9/30/22). For details on these as well as cumulative scientific, see Appendix #5 (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			
Electronic			
Print			
Total			

- Select key publication utilizing PLS data from this reporting period ((10/1/21-9/30/22) are highlighted below along with their key points:
- Analysis of cognitive outcomes; manuscript published
 - Walker WC, O'Neil ME, Ou Z, et al. Can mild traumatic brain injury alter cognition chronically? A LIMBIC-CENC multicenter study. *Neuropsychology*. 2022 Sep 29. doi: 10.1037/neu0000855. Online ahead of print. PMID: 36174184.
 - **Question:** Is cognitive performance altered long-term after mTBI?
 - **Findings:** Among combat-exposed SMs and Veterans, neither of the mTBI positive groups, non-repetitive or the repetitive (>3), differed from the TBI negative controls on any cognitive testing domain when adjusting for other factors.
 - **Meaning:** Cross-sectional analysis does not support an association between remote mTBI(s) alone and objective cognitive problems in the average Veteran or SM.
 - **Clinical Translation:** A holistic healthcare approach including comorbidity assessment is indicated for patients reporting chronic cognitive difficulties after mTBI(s), and strategies for addressing misattribution may be beneficial.
 - **Research Translation:** Future study is recommended to assess phenotypes (e.g. cognitive impaired) and longitudinal decline from potential neurodegeneration.
- Analysis of balance deficits; manuscript published in leading journal (Impact Factor 9.9)
 - Fino PC, Dibble LE, Wilde EA, Fino NF, Johnson P, Cortez MM, Hansen C, Van der Veen SM, Skop KM, Werner JK, Tate DF, Levin HS, Pugh MJ, Walker WC. Sensory Phenotypes for Balance Dysfunction after Mild Traumatic Brain Injury. *Neurology*, 2022 May 16;99(5):e521-35. doi: 10.1212/WNL.0000000000200602. Online ahead of print. PMID: 35577572.
 - **Question:** How can sensory phenotypes for balance explain heterogeneity in clinical

characteristics and injury mechanisms in Veterans and SMs with mTBI?

- **Findings:** In this cross-sectional analysis, heterogeneous sensory phenotypes for balance control were associated with distinct clinical characteristics, symptom severity, and physical and cognitive functioning.
- **Meaning:** Recognizing the variety of balance deficits that involve heterogeneous sensory dysfunction in Veterans and SMs after mTBI will enable rehabilitation programs more tailored to the nuances of each individual's sensory phenotype.
- Analysis of SM and Veteran characteristics by mild TBI history and PTSD status published
 - O'Neil ME, et al. Demographic, military, and health comorbidity variables by mild TBI and PTSD status in the LIMBIC-CENC cohort. *Brain Inj.* 2022 Feb 5;1-9. doi: 10.1080/02699052.2022.2033847.
Question: How do demographic, military, and health comorbidity profiles vary by mTBI history and PTSD status?
 - **Findings:** Combat-exposed SM/Vs with PTSD, irrespective of mTBI history, had high rates of obesity, sleep problems, and pain. Those with PTSD and a positive mTBI history, even if very remote, had the highest rates of depression symptoms, pain, and sleep apnea risk relative to SM/Vs without both of these conditions.
 - **Meaning:** This chronic symptom burden and comorbidities among SM/Vs with mTBI history and PTSD suggest that ongoing monitoring and intervention is critical for improving quality of life.
- Analysis of symptom profiles across mTBI history and PTSD groups
 - O'Neil ME, et al. Associations Among PTSD and Postconcussive Symptoms in the Long-Term Impact of Military-Relevant Brain Injury Consortium-Chronic Effects of Neurotrauma Consortium Prospective, Longitudinal Study Cohort. *J Head Trauma Rehabil.* 2021 Nov-Dec 01;36(6):E363-E372. doi: 10.1097/HTR.0000000000000665
 - **Question:** How do Neurobehavioral Symptom Inventory (NSI) symptom profiles vary by mTBI history and presence of PTSD symptoms?
 - **Findings:** NSI symptom severity was highly correlated with PTSD symptoms in those with or without mTBI history. Symptom clustered similarly (somatosensory, affective, cognitive, and vestibular) regardless of mTBI and PTSD status.
 - **Meaning:** 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.
- Analysis of EEG AEPs as objective markers for chronic effects of mTBI published
 - Franke LM, et al. Auditory evoked brain potentials as markers of chronic effects of mild traumatic brain injury in mid-life. *Clin Neurophysiol.* 2021;132(12):2979-2988. doi: 10.1016/j.clinph.2021.09.007.
 - **Question:** Do auditory brain potentials previously shown to change in pre-dementia exhibit similar changes in an earlier phase of life in mTBI?
 - **Findings:** The N200 potentials were reduced in those with any mTBI exposure, while P50 was enhanced and N100 and N200 reduced in repetitive mTBI. The N200 showed the largest amplitude change with injury group and was strongly associated with symptoms of depression and anxiety, as well as hearing deficits.
 - **Meaning:** Auditory evoked 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.
- Analysis of dementia cases in PLS cohort identified through VA ICD coding published.
 - Walker WC, et al. Clinical Features of dementia cases ascertained by ICD coding in LIMBIC-CENC multicenter study of mild traumatic brain injury. *Brain Inj.* 2022 Apr 16;36(5):644-651. doi: 10.1080/02699052.2022.2033849.
 - **Question:** What are the clinical features of early dementia cases identified by ICD coding among SMs and Veterans with mTBI?
 - **Findings:** Five cases of dementia were identified, all under 65 years old, with two being possible false positives. Among them, visual memory and verbal learning and memory were the

most common abnormal cognitive tests. They reported poorer functional status and QoL relative to the rest of cohort with positive mTBI histories.

- **Meaning:** 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. This will aid interpretation of future studies using these ICD codes
- Analysis of Pituitary disorder screening labs published.
 - Walker WC, et al. Relation of Mild Traumatic Brain Injury history to abnormalities on a preliminary Neuroendocrine screen; A multicenter LIMBIC-CENC analysis. *Brain Injury*. 2022 Apr 16;36(5):607-619. doi: 10.1080/02699052.2022.2068185.
 - **Question:** Are mild TBI (mTBI) history or post-concussive clinical features associated with abnormalities on a preliminary neuroendocrine disorder (NED) screen?
 - **Findings:** None of mTBI positive groups, including repetitive (> 3 mTBI) and blast-related, differed from the non-TBI controls on rates of abnormal serum sample lab screen or rates of growth hormone deficiency, hypothyroidism or male hypogonadism in treatment records. Lab screen findings were also not associated with any clinical feature (fatigue, depression, cognitive symptoms, executive function, processing speed).
 - **Meaning:** Evidence from this study does not support a link between remote mTBI(s) and these NEDs. Large case-control studies that incorporate definitive NED testing are needed to determine whether mTBI(s) alone elevate one's risk for chronic NED and how best to select patients for comprehensive testing.
- Analysis of physical activity led by a junior mentee; revised manuscript submitted
 - Wright B, Zhong C, Fisher R, et al. Relation of aerobic activity to cognition and well-being in chronic mild traumatic brain injury; A LIMBIC-CENC study. Submitted to *J Head Trauma Rehabil* in Sep 2022.
 - **Question:** Do SMs & Vs with remote mild TBI(s) who perform more aerobic physical activity have better cognition?
 - **Findings:** Combat-exposed SMs and Veterans with positive mTBI histories were classified based on level of aerobic activity. Using cross-sectional design and multivariable regression adjusting for other factors, no significant differences emerged on our prespecified tests of executive function, learning and memory across these groups. However, engaging in regular aerobic activity was associated with better life satisfaction and perceived overall health status. Exploratory analyses also suggested a positive association with working memory and verbal fluency.
 - **Meaning:** Regular aerobic exercise was associated with better subjective outcomes in this study and has proven benefit in the general population. Thus, regular aerobic exercise is recommended for SMs and Veterans with chronic mild TBI. Future longitudinal analyses should seek evidence of objective cognitive enhancement or preservation not demonstrated with this cross-sectional analysis.
- Analysis of anger control; manuscript completed and submitted for publication
 - Miles S, et al. Putting the Pieces Together to Understand Anger in Combat Veterans and Service Members: Psychological and Physical Contributors. Submitted to *J Psychiatr Res* in Sep 2022.
 - **Questions:** When examined simultaneously, what established correlates of anger (e.g., combat exposure, PTSD symptoms, TBI, pain interference, and hazardous alcohol use) predict anger in Veterans and Service Members? Are the anger predictors moderated by sleep impairments (poor sleep quality and OSA risk)?
 - **Findings:** PTSD symptoms, combat exposure, pain interference, and hazardous alcohol use were significantly associated with anger. Neither self-reported sleep quality nor OSA risk moderated their relationships.
 - **Meaning:** There is an urgent need for integrated anger treatments that target PTSD, pain, and alcohol use.

For dissemination in general, there was continued ongoing close collaboration between the leadership and coordinating center team-members of the LIMBIC-CENC PLS and the LIMBIC-CENC knowledge translation (KT) center on our website offerings and other KT products. This includes developing and cataloging Key Points (**see KeyPoint tab of the PublicationMonitor – Appendix #5**) for each and every submitted publication, which summarizes a succinct takeaway message summary.

Additionally, the PLS leadership has been actively engaged in collaborations with multiple individuals and other study groups to further advance productivity of our analysis and dissemination of the PLS dataset. This including mentorship of junior investigators and projects that may involve supplemental funding opportunities to cover additional unaccounted-for effort and/or resources. Progress in these areas are summarized below:

- During the past year, LIMBIC-CENC worked with VA RR&D to determine how we could leverage the PLS for additional study of the long-term effects of COVID-19 infections among our cohort, including the interaction effect of mild TBI and COVID-19. Funding for additional data collection has been set aside and we worked with external subject matter experts in infectious disease to develop a protocol with associated consent form that is nearly finalized for IRB submissions. We plan to invite all of our active study participants into this addendum study. The title of the protocol is: *LIMBIC-CENC PLS Long COVID Addendum Module (LCAM)*.
- Other efforts included ongoing collaborations for additional PLS data secondary analyses with multiple external groups including the TBI CoE and other individuals including young investigator mentees. See below for listing of some ongoing efforts (*denotes young investigator mentee).
- External PLS dataset collaborations with funding awarded:
 - Randall Swanson, DO, PhD*. Traumatic and Treatable Vascular Pathology in the Outcome of TBI. VA CDA grant.
 - Christina Sheerin, PhD*. Functional relations between alcohol use and mental health in the wake of the COVID-19 pandemic. NIH K01 award supplement.
- External PLS dataset collaborations with funding applied for:
 - Jasmohan Bajaj, MD. Salivary microbiota composition and function linkage with outcomes in PTSD with TBI. TMCity Foundation grant RFA, full application.
 - Christina Sheerin, PhD*. Characterizing the genetic architecture and risk for PCCS, PTSD, and AUD in a longitudinal military cohort. CDMRP Young Investigator. Full application.
 - Sarah L. Martindale, PhD. Evaluating Reductions in Hippocampal Volume Related to Blast Exposure and their Effect on Memory Function. VA Merit Review. Full application.
 - Jasmohan Bajaj, MD. Safety, Tolerability, and Dose Response of Intestinal Microbiota Transplantation for Veterans with AUD and PTSD. PASA SRPP Compound Development Planning Grant. LOI.
 - Donald D. McGeary, PhD. Contribution of Psychological Health Comorbidity to Personalized Treatment for Headache Attributable to mTBI. Pre-application submitted.
- Other collaborative PLS secondary analyses:
 - Rosemay Remigio-Baker, PhD. (TBI CoE)
 - Race/Ethnic Disparities in the Treatment of Depressive and PTSD Symptoms Among SMs with mTBI
 - Social Support and Self-efficacy As Factors That Mitigate Mental Health Symptoms and Promote Quality of Life of SMs with mTBI
 - Characteristics of mTBI History as a Function of Quality of Life and Mental Health Symptomatology
 - Jay Uomoto, PhD. (TBI CoE)
 - A Pathway Analysis of the Impact of TBI Characteristics and Healthcare Utilization on Participation Outcomes.
 - In pipeline: Additional TBICoE collaborative analyses
 - Other LIMBIC-CENC organizational collaborations – defer to Dr Hinds section of report
 - ENIGMA and other neuroimaging data collaborations – defer to imaging core section of report

- During the reporting period (Oct 01, 2021 to Sep 30, 2022), the following analytic projects were also presented on the biweekly LIMBIC-CENC PLS All-Sites audiovisual meeting/conferences:

Date	Publication	Presentation
1-Nov-21	Laura Manning	Repetitive transcranial magnetic stimulation (rTMS) after traumatic brain injury
7-Mar-22	Dr. Zezong Gu	Low-Intensity Open Field Blast Exposure
21-Mar-22	Dr. Amy Byers	TBI and Death
18-Apr-22	Dr. Hall	Identification and Reporting Asymmetry
13-Jun-22	Dr. Terri Pogoda	Veterans who Screen Positive for TBI and do not Receive a Follow-up Comprehensive TBI Evaluation are at Increased Risk for Adverse Outcomes
25-Jul-22	Bryson Hewins	Reduced plasma glial fibrillary acid protein correlates with poor sleep quality in warfighters with mild traumatic brain injury
22-Aug-22	Ian Stewart	Association between Traumatic Brain Injury and Subsequent Cardiovascular Disease Among Post-9/11 Veterans

Major Task 17: Analysis & Publication of Longitudinal Data.

Month(s): 24 - 60

Progress: During the reporting period (Oct 01, 2021 to Sep 30, 2022), our longitudinal data analysis activity continued ramping up. This was enabled by our continued high rates of retention and follow-up visit completion rates and accumulation of a critical mass of repeated measures, especially for data collected in the brief annual assessment. Work on a key scientific analysis of rate of cognitive change overtime using longitudinal annually-collected BTACT data was begun and progressed well.

- Analyses: Among the new datasets released during the reporting period or pending release, there were 3 analytic projects that included longitudinal data and study aims. This brings to a total of 9 longitudinal analysis projects. For details on these, see Excel spread sheet entitled 'PLS data request tracker' in **Appendix #2**; 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 Appendix #5**.
- 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: Completed - All required regulatory approvals have been received. The LIMBIC Epidemiology Study was approved through UCSF IRB on 25-OCT-2019, the SF VA Medical Center on 8-NOV-2019 and approved through HRPO on 31-DEC-2019.

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

Month(s): 1 - 60

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

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

Month(s): 1 – 12

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

Milestone: 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).

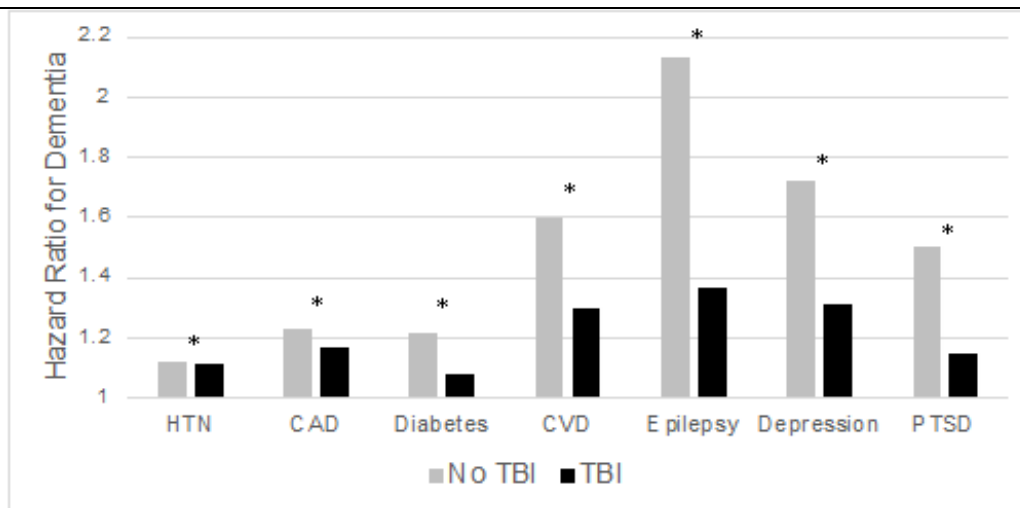
Month(s): 1 – 24

Progress: In Year 3, we submitted a manuscript examining cause-specific mortality after TBI in a group of Veterans. The study is now in press in the *Journal of Psychiatric Research*. 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.

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.

Milestone: Manuscript in press at the *Journal of Psychiatric Research*, Byers et al.

Progress: In Year 3 we completed data analysis and submitted 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. Although the magnitude of risk of dementia associated with each baseline risk factor was consistently (slightly) lower among TBI cohort vs. no TBI cohort, the population attributable fraction (PAF) of dementia due to hypertension, CVD, epilepsy, and depression were higher in Veterans with TBI due to their high prevalence in this group. These findings suggest that targeting depression, CVD, hypertension, and epilepsy may be especially important for dementia risk reduction among Veterans with TBI.



Milestone: Manuscript is under review, Gardner et al.

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

Month(s): 12 - 24

Progress: Switched timeline with Major Task 8. Will begin collaboration in Year 4 of the project.

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

Month(s): 24 – 36

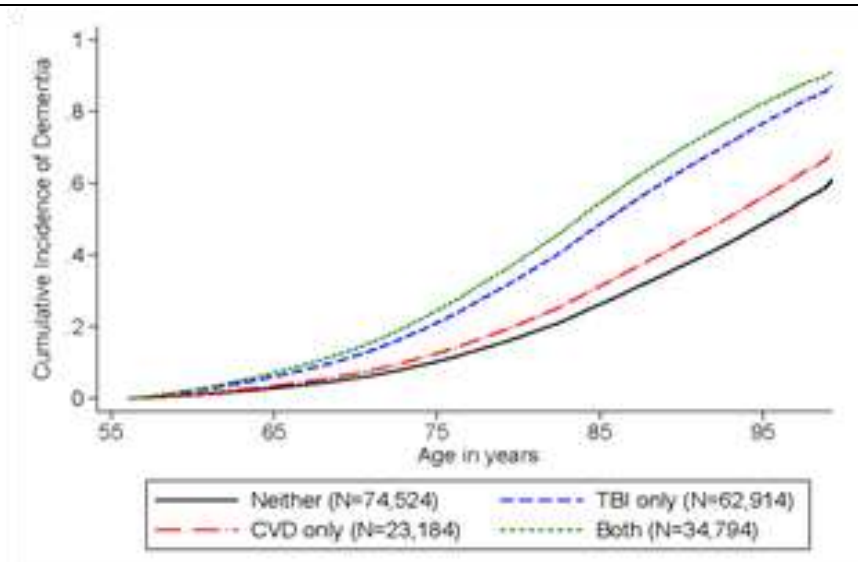
Progress: We investigate incident dementia in older veterans with TBI exposure by race and sex. Using a sample of nearly 1 million veterans with data from 2000-2015, we excluded all people with prevalent dementia. Both Male and Female veterans had more than 2X increased risk of dementia after TBI [Males HR=2.60 (2.54-2.66); Females HR=2.36 (2.08-2.69)]. There was a significant interaction effect between sex and TBI ($p=0.02$), however, the magnitude of differences was small and likely not clinically significant. Compared to those without TBI, Hispanic Veterans with TBI were almost two times more likely (HR: 1.74, 95% CI: 1.51-2.01), Black Veterans with TBI were over two times more likely (HR=2.15, 95% CI: 2.02-2.30), and White Veterans with TBI were nearly three times more likely to develop dementia (HR=2.71, 95% CI: 2.64-2.77). A significant interaction between TBI and race for developing dementia was observed ($p<0.001$). The racial differences may be due to differences in dementia risk, dementia diagnosis rates, or potentially an interaction between race, APOE, and neurotrauma.

Milestone: Manuscript published in *Neurology*, Kornblith et al., 2020.

Month(s): 24 – 36

Progress: In Year 3 our manuscript was published in *Brain Injury* examining how cardiovascular disease (CVD) and TBI affect dementia risk in a diverse, nationally representative sample. 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 increased 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: Manuscript published in *Brain Injury*; Kornblith et al.

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

Month(s): 24 - 48

Progress: Many studies on TBI and different types of outcomes are conflicting or have widely varying effect sizes. We recently published a manuscript in the *Journal of Neurotrauma* examining how different control groups might affect these findings and chose the outcome of dementia as an example. We used a 5% random sample of Veterans within the VHA who are aged 55+ and have no dementia at baseline. Veterans with TBI (defined by ICD 9/10 codes + Emergency Department visit + MRI/CT scan; n = 9,440) compared to three groups: 1) Randomly selected non-TBI Veterans, n = 119,003 (All VA); 2) Veterans who received care at a VA Emergency Department, n=111,342 (VA ED); 3) Veterans who received care at a VA ED for non-TBI trauma, n=65,710 (VA ED NTT). We then estimated the association between TBI and dementia with death as a competing risk using Fine Grey models for each comparison cohort, and then used inverse probability of treatment weighted models to adjust for differences between cohorts.

Veterans with TBI were older with greater medical and psychiatric comorbidities compared to all control groups. Before and after adjustment for demographics and comorbidities, risk of dementia associated with TBI varied widely by comparison group, with the lowest risk estimate for VA ED NTT and highest estimate for ALL VA. (see Table)

	All VA n=119,003	VA ED n=111,342	VA ED NTT n=65,710
Unadjusted	2.63 (2.51, 2.76)	2.00 (1.91, 2.10)	1.59 (1.51, 1.66)
IPTW*	1.94 (1.84, 2.04)	1.42 (1.35, 1.50)	1.12 (1.06, 1.18)

TBI was associated with elevated incidence of dementia, but the estimated effect was strongly impacted by choice of the control group. Understanding the impact of control group on estimates of the causal effect of TBI on outcomes will inform carefully considered study designs.

Milestone: Manuscript published in *Journal of Neurotrauma*; Albrecht et al., 2022.

Progress: Risk of dementia associated with traumatic brain injury (TBI) varies across studies. In Year 3 we conducted a systematic review and meta-analysis of risk of dementia after TBI and investigated effect of participant characteristics, methods, and region. We examined journal articles examining all-cause dementia after all-severity TBI (search window 1/1990-1/2019). We identified observational studies reporting age-adjusted risk for all-cause dementia after TBI among individuals with average age ≥ 40 years. Data were pooled using random-effects models; between study variability was assessed using the I² index.

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

Population attributable risk (PAR) of dementia due to TBI exposure in the U.S. population, including specifically among U.S. Veterans, men, and women, is reported in the Table below. Women had the lowest estimated PAR (9% U.S. Females; 3.8% U.S. Female Veterans) while men had the highest estimated PAR (32% U.S. Males; 29% U.S. Male Veterans). Estimated PAR of dementia due to TBI among U.S. Veterans was twice that of the general U.S. population and three times that of U.S. women. Estimated PAR of dementia due to TBI among U.S. men was 4 times that of U.S. women. Overall, we estimated that approximately 860,700 cases of dementia in the U.S. are attributable to TBI exposure. A manuscript detailing these important results is under review.

Table. Population attributable risk (PAR) of dementia due to TBI in the U.S.

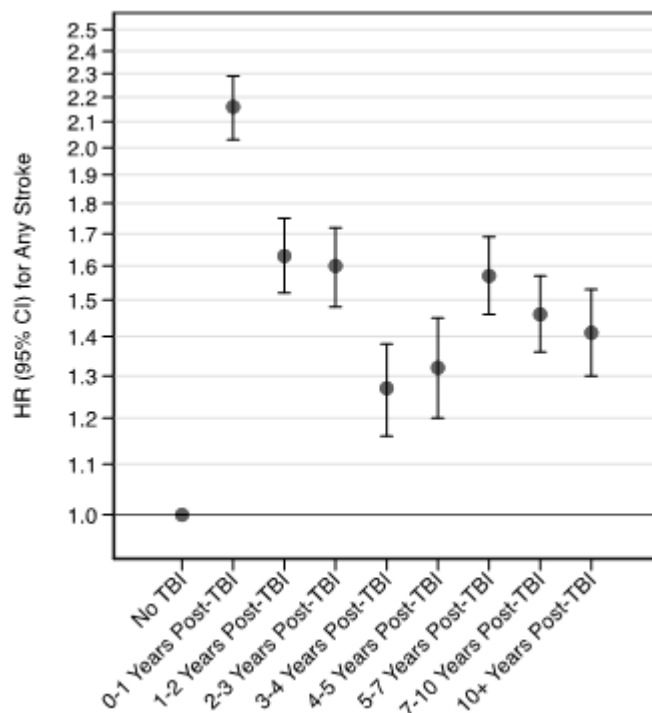
Population	Estimated RR	TBI Prevalence	PAR	Estimated total cases of dementia in U.S.	Estimated cases of dementia attributable to TBI exposure
Total U.S. population	1.52	31%	14%	6,200,000	860,696
U.S. Males	2.07	43%	32%	2,400,000	756,277
U.S. Females	1.43	22%	9%	3,800,000	328,412
U.S. Veterans	2.13	35%	28%	767,544	217,530
U.S. Male Veterans	2.13	36%	29%	738,304	213,493
U.S. Female Veterans	2.13	3.5%	3.8%	29,240	1,112

Milestone: Manuscript under review

Progress: In Year 3 we completed and analysis and submitted a manuscript examining stroke after remote TBI. TBI results in cerebrovascular injury and has been associated with short-term (i.e., < 5 years) risk of stroke. Long-term associations of TBI with stroke remain less clear, thus, we analyzed the risk of long-term stroke after TBI in Veterans. We have 613,592 veterans without stroke at baseline (306,796 with TBI matched 1:1 on age, sex, race, and TBI index date to 306,796 without TBI) from the VHA inpatient and outpatient database (NPCD) from 10/1/2002 to 9/30/2019. TBI and stroke were defined using ICD-9/10 codes.

Overall, included veterans were an average age of 50 years, 9% were female, and 75% were non-Hispanic white. Over a median of 5 years of follow-up, 36,351 stroke events (23,241 among veterans with TBI and 13,290 among veterans without TBI) occurred. TBI was associated with an increased risk of all stroke [HR: 1.69 (1.64-1.73)] in an analysis adjusted for demographics, medical comorbidities, and psychiatric comorbidities. The risk of hemorrhagic stroke after TBI [Adjusted HR: 3.73 (3.40-4.08)] was greater than risk of ischemic stroke after TBI [Adjusted HR: 1.56 (1.52-1.61)].

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



Among U.S. military veterans, TBI was associated with increased long-term risk of stroke. These novel results were presented as an Oral Presentation at the 2022 American Heart Association Epidemiology Lifestyle Conference. The manuscript was written and is currently under review.

Milestone: Manuscript under review.

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 3, a manuscript was published 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.

Milestone: Manuscript published in *Brain Injury*; Dismuke et al., 2022.

Major Task 9: Prepare manuscripts for journal publication.

Month(s): 24 - 60

Progress: We currently have one manuscript in press, two under review, and one in preparation.

Milestone: Since the beginning of the grant, we have published 5 manuscripts.

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

Month(s): 24 – 48

Progress: In the second half of Year 3 we began preliminary analysis on our prognostic model for dementia and mortality after TBI. We created a dataset with all Veterans from 2002-2019 with a TBI over age 55, who didn't have dementia at baseline, and have follow-up data (N=113,779). We will compare characteristics of Veterans with TBI who developed dementia within 5 years to those who did not, adjusting for age, sex and race. We are now in the process of examining the associations between demographic, military, healthcare, medical, and psychiatric variables and future dementia in this group. Once we complete the analysis on dementia we will also look at future mortality as an outcome.

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.

Major Task 13: Attendance at biannual GSC meetings.

Month(s): 6 - 60

Progress: We presented updates on our work at the November 2021 and May 2022 meetings. The feedback we received was informative and thoughtful.

Phenotype Study:

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

Month(s): 1 - 12

Progress: Regulatory approvals were complete as of June 2020.

- We updated DoD and VA health system data including the Theatre Data Management Store (TMDS) through FY21 in December 2021.
- 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 December 2021; we are in process of updating the NDI and Vital Status Files to the most recent data available.
- We obtained DoDTR data for individuals with indication of TBI (GSC, TBI, AIS codes) in theatre (07/21/21).
- We obtained the VA-DoD Identity Repository data 07/27/2021 and have identified most military variables including deployment status.
- We obtained refreshed data from the US VETS data source for the cohort.

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

Month(s): 1 - 36

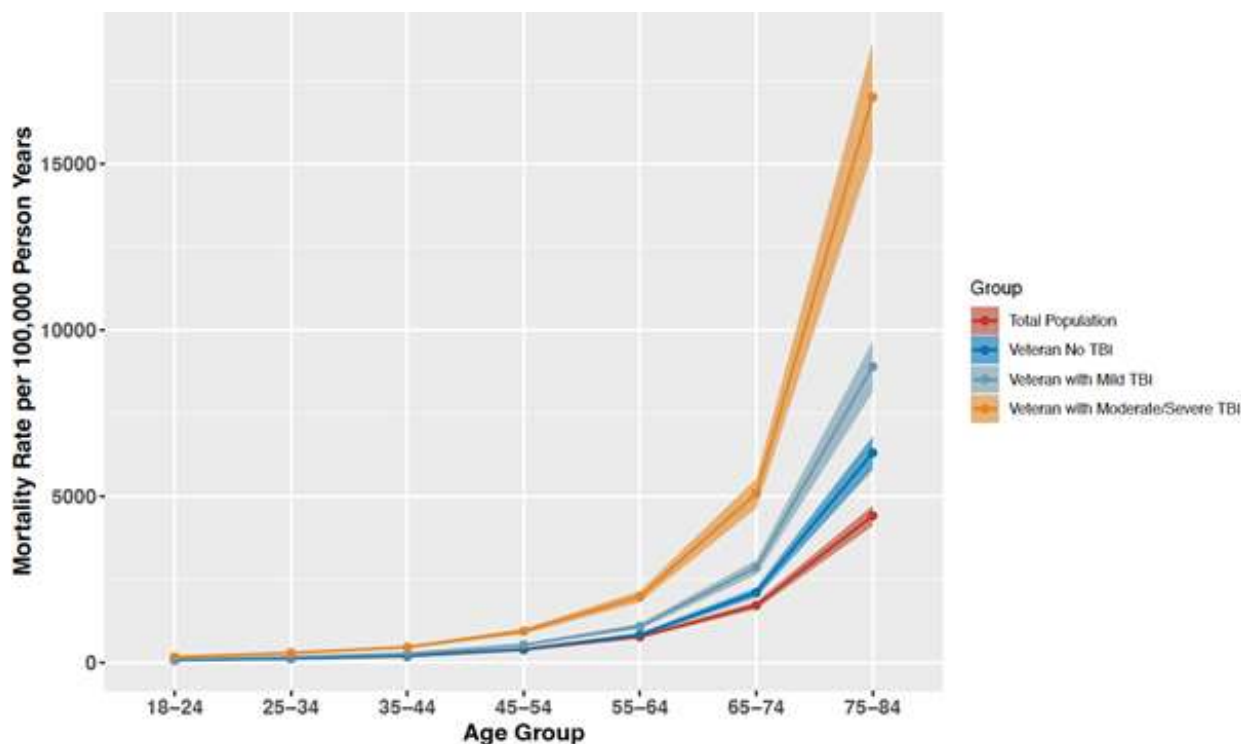
Progress: We have identified comorbidities of interest in VA and DoD data for this cohort using all data and completed analyses for cognitive dysfunction (from FY21; not included below), mortality, and cardiovascular disease. We also completed analyses adverse outcomes (substance use disorder) in distinct TBI phenotypes using health system data and data from the VA comprehensive TBI evaluation. We began analyses of the characteristics of individuals who transition to VA care in order to understand the generalizability of findings from the phenotype and economic studies, and are in the early days of analyses for substance use disorder in DoD/VA data and phenotypes of comorbidity in DoD data.

A) Mortality of Veterans with TBI (by severity) compared to Veterans without TBI and the General US Population

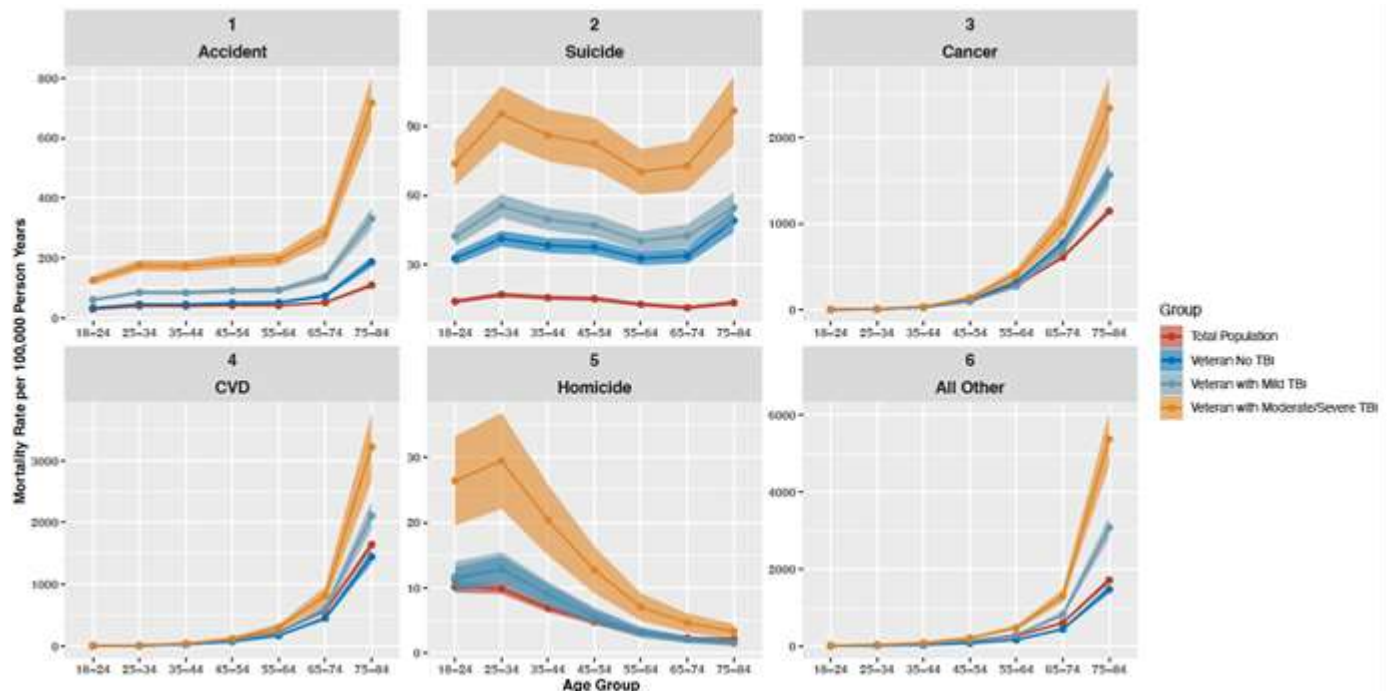
The United States (US) military recently withdrew from Afghanistan after 20 years of war. Emerging evidence suggests that harmful exposures during military service, such as traumatic brain injury (TBI), may contribute to mental health, chronic disease, and mortality risks. We sought to assess the total 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.

This study was published in JAMA Network Open

We are extending this mortality analysis to examine differences in deployed/non-deployed Veterans and specific differences by race/ethnicity. Tables below show results of models for all cause mortality, and distinct types of mortality with Incidence Rate Ratios for age, sex, race/ethnicity, deployment and TBI status.

As expected, older age was associated with higher mortality. Mortality was higher for men than women in all areas other than cancer where women had higher mortality incidence. For Blacks, mortality was significantly higher than whites only for cancer. For Hispanics and Asians, IRRs were significantly lower than for whites for all causes examined below. IRR for those who were deployed were significantly lower than for those not deployed suggesting a healthy soldier (deployer) effect. Mortality was also higher for individuals with TBI history except for cancer.

Table 1: Incidence Rate Ratio in Post-9/11 Veterans

Characteristic	All-Cause (41,391 Deaths)			Accident (10,281 Deaths)		
	IRR ¹	95% CI ¹	p-value	IRR ¹	95% CI ¹	p-value
Year	1.05	1.04, 1.06	<0.001	1.02	1.01, 1.04	<0.001
Age Group						
18-24	—	—		—	—	
25-34	1.88	1.74, 2.04	<0.001	1.86	1.66, 2.09	<0.001
35-44	3.27	3.01, 3.56	<0.001	2.07	1.82, 2.34	<0.001
45-54	5.81	5.33, 6.33	<0.001	1.79	1.55, 2.06	<0.001
55-64	10.7	9.72, 11.7	<0.001	1.71	1.43, 2.05	<0.001
65 and older	21.0	18.8, 23.5	<0.001	2.18	1.66, 2.85	<0.001

Sex						
Female	—	—		—	—	
Male	1.25	1.18, 1.32	<0.001	1.78	1.61, 1.97	<0.001
Race/Ethnicity						
White Non-Hispanic	—	—		—	—	
Asian	0.65	0.57, 0.72	<0.001	0.36	0.28, 0.46	<0.001
Black Hispanic	0.88	0.74, 1.04	0.14	0.73	0.52, 0.99	0.053
Black non-Hispanic	1.09	1.02, 1.16	0.012	0.72	0.65, 0.80	<0.001
White Hispanic	0.73	0.68, 0.79	<0.001	0.68	0.60, 0.76	<0.001
Native American	1.06	0.96, 1.18	0.3	1.03	0.87, 1.22	0.7
Pacific Islander	0.53	0.39, 0.70	<0.001	0.23	0.09, 0.48	<0.001
Unknown	1.49	1.37, 1.62	<0.001	1.50	1.32, 1.71	<0.001
Deployed						
No	—	—		—	—	
Yes	0.63	0.60, 0.67	<0.001	0.68	0.63, 0.74	<0.001
TBI Exposure						
No TBI	—	—		—	—	
TBI	1.69	1.61, 1.78	<0.001	2.42	2.24, 2.63	<0.001

	Cancer (6,444 Deaths)			Deaths of Despair ¹ (8,673 Deaths)		
Characteristic	IRR ¹	95% CI ¹	p-value	IRR ³	95% CI ¹	p-value
Year	0.99	0.98, 0.99	<0.001	1.07	1.03, 1.06	<0.001
Age Group						
18-24	—	—		—	—	
25-34	3.69	3.02, 4.57	<0.001	1.49	3.29, 5.73	<0.001
35-44	13.7	11.3, 16.9	<0.001	1.75	12.1, 20.9	<0.001
45-54	46.0	37.9, 56.6	<0.001	1.99	32.3, 55.5	<0.001
55-64	120	99.0, 148	<0.001	1.66	57.9, 101	<0.001
65 and older	244	199, 302	<0.001	1.01	114, 206	<0.001
Sex						
Female	—	—		—	—	
Male	0.58	0.54, 0.62	<0.001	1.89	1.51, 1.96	<0.001
Race/Ethnicity						
White Non-Hispanic	—	—		—	—	
Asian	0.84	0.69, 1.02	0.09	0.44	0.55, 0.94	0.02
Black Hispanic	1.29	0.86, 1.85	0.20	0.74	0.34, 1.21	0.20
Black non-Hispanic	1.14	1.07, 1.21	<0.001	0.62	1.48, 1.84	<0.001
White Hispanic	0.79	0.71, 0.88	<0.001	0.63	0.61, 0.83	<0.001
Native American	0.85	0.66, 1.06	0.20	1.04	0.81, 1.38	0.60
Pacific Islander	0.73	0.37, 1.29	0.30	0.39	0.59, 1.97	0.70
Unknown	0.96	0.82, 1.11	0.60	1.46	1.01, 1.49	0.03
Deployed						
No	—	—		—	—	
Yes	0.59	0.56, 0.62	<0.001	0.76	0.48, 0.58	<0.001
TBI Exposure						
No TBI	—	—		—	—	
TBI	1.07	1.00, 1.14	0.04	1.83	1.27, 1.55	<0.001

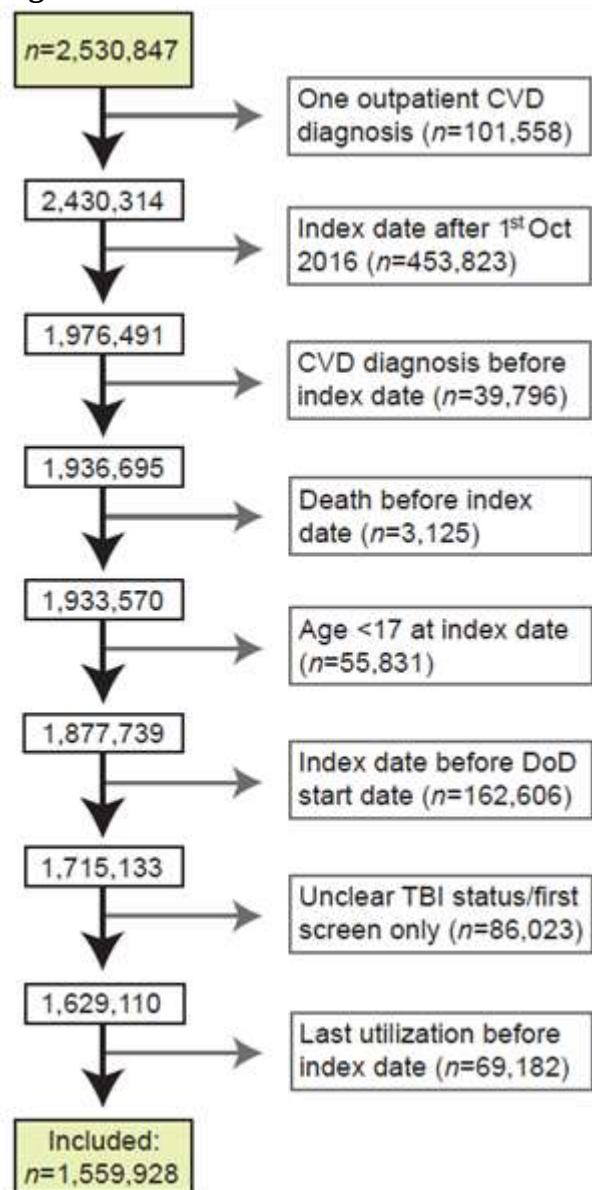
b) Cardiovascular Disease

While there is some evidence to suggest that TBI increases the risk of cardiovascular disease (CVD), prior reports were predominantly limited to cerebrovascular outcomes. The potential impact of TBI on CVD has not been comprehensively examined in Post-9/11 Veterans which is a young population that may benefit significantly from prevention efforts.

Objective: To determine the association between an episode of TBI and subsequent CVD in Post-9/11 Veterans.

Methods: Retrospective cohort of Post-9/11 Veterans with (N=301,169) and without (N=1,258,759) TBI history and index date (TBI or simulated) from 1 Oct 1999 to 30 Sep 2016. Participants were followed until 31 Dec 2018. Our exposure was history of TBI. TBI diagnosis was identified using a hierarchical approach prioritizing data from DoDTR and TMDS (Glasgow Coma Scale score, Abbreviated Injury Severity Score, ICD-9/10 codes), followed by self-reported loss of consciousness (≤ 30 minutes: mild; > 30 minutes: moderate/severe), alteration of consciousness or post-traumatic amnesia (< 24 hours mild; ≥ 24 hours moderate/severe) identified in the VA comprehensive TBI evaluation (CTBIE), followed by ICD-9/10 diagnosis codes from the 2012 Armed Forces Health Surveillance System published algorithm. The primary outcome for our analysis was CVD, a composite of CAD, stroke, PAD, and CVD death. We also examined the association of TBI with individual components of this primary outcome. Figure 1 shows exclusion criteria.

Figure 1: Inclusion and exclusion criteria for cardiovascular analysis:



Analysis: We utilized competing risks models to estimate the impact of the independent variables on subsequent CVD. For Veterans with TBI, the index date was determined as the first date of a TBI diagnosis in the medical record. If multiple TBI diagnoses were present, the most severe injury categorization was used in the analysis. For Veterans without TBI, index dates were simulated by drawing from the distribution of true index dates within each age bracket as previously described.²⁰ Veterans with an index date between 1 Oct 1999 and 30 Sep 2016 were included for analysis. The competing risk was non-cardiovascular death. Participants were censored at the date of their last healthcare system encounter or 31 Dec 2018 (whichever came first).

Results: Characteristics of the study cohort, stratified by TBI diagnosis, are shown in **Table 2**. All variables examined were significantly different between the groups, likely as a result of the large sample size. Veterans with TBI were younger and more likely to be male than those without TBI history. A larger proportion of those without TBI history had post-high school education compared to those with TBI. Slight differences in race and ethnicity were also observed. Veterans with TBI were more likely to be active duty, in the Army or Marines, and have enlisted rank. They were also more likely to have deployed and have combat exposure. With regards to diagnoses, Veterans with TBI were more likely to have a history of smoking, SUD, obesity, OSA, insomnia, PTSD, depression, and anxiety. Conversely, hyperlipidemia, kidney disease, HTN, and DM were more common in the group of Veterans without TBI.

Table 2: Descriptive Statistics by TBI History	TBI History N=301,169 N (%)	No TBI History N=1,258,759 N (%)	Standardized Mean Difference[†]
Age at index date			
17-24	105,157 (34.92)	354,645 (28.17)	0.15
25-34	123,563 (41.03)	474,689 (37.71)	0.07
35-44	48,244 (16.02)	238,370 (18.94)	-0.08
45-54	20,398 (6.77)	153,261 (12.18)	-0.19
55-64	3,455 (1.15)	34,292 (2.72)	-0.11
≥ 65	352 (0.12)	3,502 (0.28)	-0.04
Sex			
Male	265,217 (88.08)	1,012,159 (80.41)	0.21
Female	35,898 (11.92)	246,600 (19.59)	
Race and Ethnicity			
Asian/Pacific Islander	23,789 (7.9)	72,771 (5.78)	0.08
Hispanic	29,184 (9.69)	120,438 (9.57)	0.004
Hispanic Black	1,411 (0.47)	6,997 (0.56)	-0.01
Native American	6,083 (2.02)	20,669 (1.64)	0.03
Non-Hispanic Black	42,996 (14.28)	224,996 (17.87)	-0.10
Non-Hispanic White	194,841 (64.69)	789,136 (62.69)	0.04
Unknown	2,865 (0.95)	23,752 (1.89)	-0.08
Smoking History	173,318 (57.55)	497,203 (39.50)	0.37
Substance Use Disorder	47,616 (15.81)	130,755 (10.39)	0.16
Obesity	38,091 (12.65)	157,393 (12.50)	0.004
Obstructive Sleep Apnea	20,890 (6.94)	68,519 (5.44)	0.06
Insomnia	55,677 (18.49)	98,978 (7.86)	0.32
Post-Traumatic Stress Disorder	82,543 (27.41)	82,230 (6.53)	0.58
Depression	74,704 (24.80)	157,472 (12.51)	0.32

Anxiety	60,558 (20.11)	119,947 (9.47)	0.30
Hyperlipidemia	37,598 (12.48)	192,814 (15.32)	-0.08
Kidney Disease	1,047 (0.35)	5,282 (0.42)	-0.01
Hypertension	32,220 (10.70)	142,694 (11.34)	-0.02
Diabetes	4,388 (1.46)	25,481 (2.02)	-0.04

For the bivariate analyses, mild TBI (hazard ratio [HR] 1.18, 95% confidence interval [CI] 1.16-1.21; $p<0.001$), moderate/severe TBI (HR 2.11, 95% CI 2.02-2.20; $p<0.001$), and penetrating TBI (HR 3.99, 95% CI 3.73-4.28; $p<0.001$) were significantly associated with CVD compared to Veterans without TBI. **Figure 2** demonstrates this association graphically by showing the cumulative incidence functions. These findings remained significant in both multivariable models 1 and 2. In model 2, mild TBI (HR 1.69, 95% CI 1.65-1.74; $p<0.001$), moderate/severe TBI (HR 2.75, 95% CI 2.63-2.88; $p<0.001$), and penetrating TBI (HR 4.64, 95% CI 4.31-5.00; $p<0.001$) remained significantly associated with CVD compared to Veterans without TBI. The results for the models that evaluated the individual components of our primary outcome (utilizing the same covariates as in model 2) are shown in **Figure 3**. The results from the composite outcome are also included in this figure for reference. For the outcome of cardiovascular death, Veterans with mild TBI (HR 1.35, 95% CI 1.18-1.51; $p<0.001$) and moderate/severe TBI (HR 1.78, 95% CI 1.44-2.20; $p<0.001$) were at significantly higher risk compared to Veterans without TBI. Penetrating TBI did not appear to be associated with this outcome (HR 1.24, 95% CI 0.73-2.11; $p=0.423$). All categories of TBI were significantly associated with stroke, PAD, and CAD. For each of these outcomes, there was the suggestion of a dose response relationship whereby more severe TBI resulted in a higher risk of the outcome (**Figure 3**). The association with stroke was particularly prominent, with HRs ranging from 2.61 for mild TBI to 12.18 for penetrating TBI.

Figure 2: Cumulative Incidence of Cardiovascular Disease by TBI Status/Severity

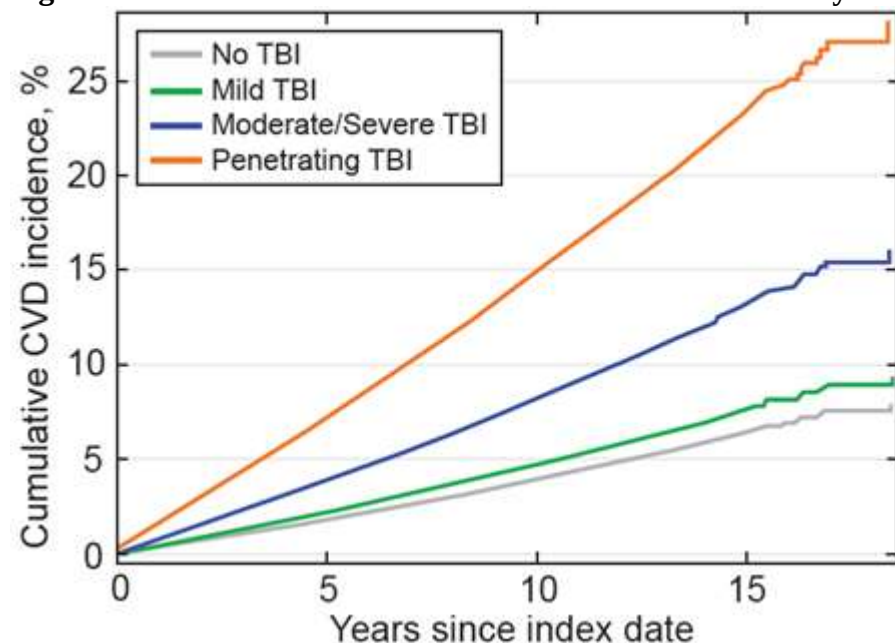
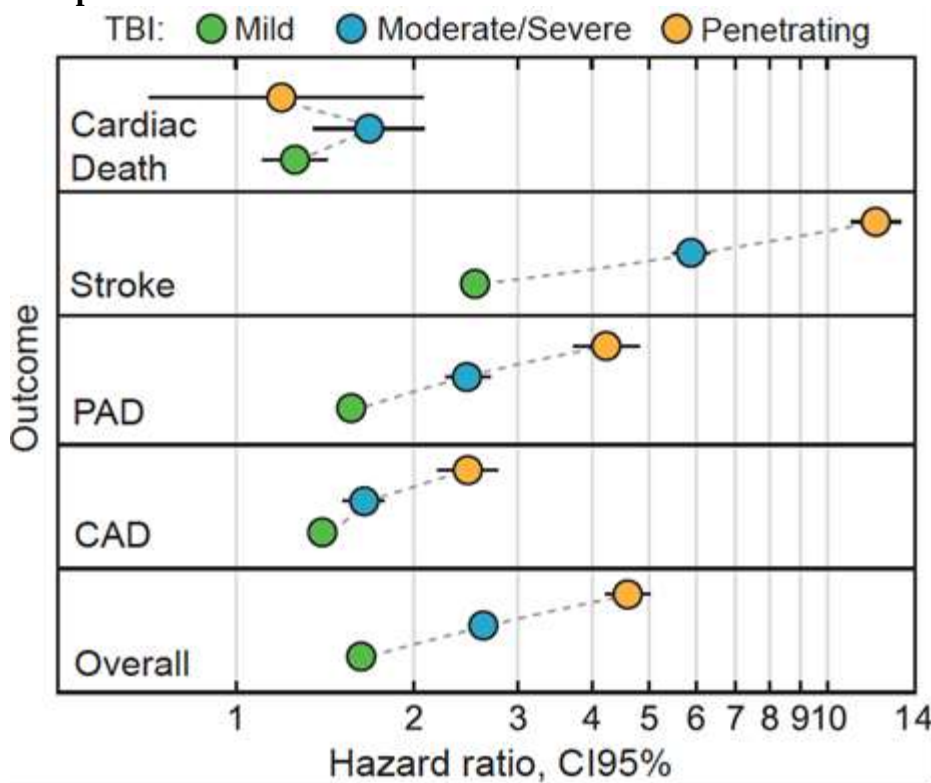


Figure 3: Hazard Ratios of Multivariable Models for Composite (Overall) and Cardiovascular Disease Components



These findings suggest that Veterans with a history of TBI were more likely to develop CVD compared to Veterans without TBI. Given the relatively young age of the cohort, our results imply that there may be an increased burden of CVD as these Veterans age and develop other CVD risk factors. Future studies are needed to determine if the increased risk associated with TBI is modifiable.

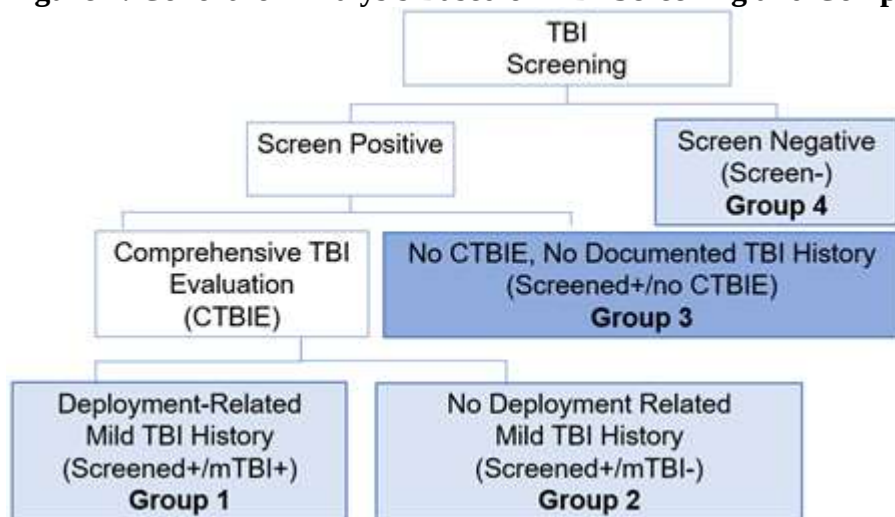
c) Substance Use Disorder in Distinct TBI Phenotypes

Question: Are Post-9/11 Veterans who screen positive for TBI, but do not receive a follow-up VA Comprehensive TBI Evaluation, at increased hazard for substance use disorder?

Background: There is significant evidence linking TBI to substance use disorder in civilian and Military/Veteran populations. Many Veterans who screen positive for TBI do not receive Comprehensive TBI Evaluations (CTBIE). It is unclear whether those who screen positive but do not receive CTBIE are at similar risk for SUD as those with diagnosed TBI. Understanding this difference has important implications for VA clinical care as about 1 in 3 who screen positive for TBI never receive a second level TBI evaluation including the possibility of providing remote CTBIE evaluations.

Among those who screened positive for TBI we identified those who screened positive/negative. For those who screened positive we classified Veterans regarding whether or not they received the CTBIE. For those who received the CTBIE we identified those who received a determination of deployment related TBI (yes/no) leading to four study groups illustrated in Figure 4.

Figure 4: Cohort for Analysis Based on TBI Screening and Comprehensive TBI Evaluation Results



Outcomes:

- Substance use disorder (SUD)
 - Alcohol use disorder (AUD)
 - Opioid use disorder (OUD)

Analysis: Fine-Gray Competing Events Models controlling for demographic, military, and clinical characteristics

Table 3 shows descriptive statistics for this cohort; Alcohol use disorder was significantly higher for Group 3 vs. Groups 2 and 4, suggesting similar outcomes for those who screened positive without follow-up to those who screened positive and had a confirmed TBI.

Table 3: Outcomes and Comorbid Conditions by Study Group

	Group 1: Screened+/ mTBI+ (n = 18,208) %	Group 2: Screened+/ mTBI- (n = 6,619) %	Group 3: Screened+/ no CTBIE (no TBI) (n = 10,163) %	Group 4: Screened- (n = 246,352) %
Any SUD	13.1	11.1	10.6	6.6
OUD	12.2	10.5	9.6	5.8
AUD	2.1	1.4	2.3	1.2
Cognitive issues	17.4	10.3	9.9	7.4
PTSD	78.7	71.3	67.1	25.6
Depression	55.8	56.4	53.1	39.9
Anxiety	42.3	43.3	41.7	32.4
Headache	47.5	38.1	29.3	25.0
Neuromuscular pain	84.4	84.8	79.7	78.2

Table 4 provides results of a competing events Fine-Gray model predicting time to substance use disorder by study group controlling for age, sex, race/ethnicity, deployment (yes/no), deployment-related injury events (TBI screener Q.1 blast/explosion, vehicular accident/crash, fragment wound, or bullet wound above the shoulders, fall), branch, component, rank, and deployment. Hazard Ratios for Group 3 were similar to Group 1 for all analyses, including the prediction of OUD where the screen positive no TBI group was not considered “at risk” of OUD.

Table 4: Hazard Ratios for time to any substance use disorder (SUD), alcohol use disorder (AUD) and opioid use disorder (OUD)

Incident Diagnosis	Group 1: Screened+/ mTBI+ (n = 18,208)	Group 2: Screened+/ mTBI- (n = 6,619)	Group 3: Screened+/ no CTBIE (no TBI) (n = 10,163)	Group 4: Screened- (n = 246,352)
	Adjusted HR (95% CI)	Adjusted HR (95% CI)	Adjusted HR (95% CI)	
SUD	1.62 (1.49-1.77)	1.42 (1.28-1.57)	1.40 (1.27-1.54)	---
AUD	1.59 (1.45-1.74)	1.40 (1.26-1.56)	1.32 (1.19-1.45)	---
ODD	1.43 (1.16-1.77)	1.05 (.80-1.39)	1.68 (1.35-2.09)	---

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

Among 1,594,869 post-9/11 veterans who separated from military service and received at least 3 years of MHS care prior to fiscal year (FY) 2017 (on or before 30 September 2016), 81.9% were male, 54.2% Active Duty; and 48.8% were 25-34 years old. 78% transitioned to VHA care. Of those, 70% had a combat deployment; 17.5% were women; and 38.5% were racialized minorities (Black, Hispanic, Asian/Pacific Islander, or Native American). Prevalent conditions included pain (55.8%), smoking history (40.8%), and headache (17.5%). Only a small proportion (6.8%) had psychiatric or substance use disorder (SUD) hospitalizations. National Guard (OR 2.23; 95% CI 2.19-2.27) and Reserve (OR 1.35; 95% CI 1.34-1.37) transitioned more than Active members. The finding that National Guard members are more likely to transition to VHA is consistent with prior research indicating that these service members experience greater distress after deployment. Non-Hispanic Black (OR 1.85; 95% CI 1.83-1.88) and Black Hispanic (OR 1.70; 95% CI 1.59-1.81) members transitioned more than White members.

Half (50.6%) transitioned FY2012-2016, over one-third (35.6%) had 2-4 years of MHS care prior to military separation. Post-9/11 veterans with physical and behavioral health comorbidities experienced successful MHS-VHA care transitions. Mental health, substance use disorder (SUD), traumatic brain injury (TBI), and pain comorbidities significantly increased odds of transitioning to VHA care. Additionally, the polytrauma clinical triad (PCT), which is the signature injury of the conflicts in Iraq and Afghanistan, significantly increased the odds of successful transition to VHA care. Suicidal ideation/attempt was not associated with transitioning to VHA care and gaps in MHS-VHA care continuity exists for post-9/11 veterans who received care for suicidal ideation/attempt 2 years before military separation.

d) DoD Characteristics in preparation for latent class analysis

Longitudinal analyses of DoD data require appropriate longitudinal data—3 years of data in the past five years before military discharge/last DoD care. **Table 5** shows demographic characteristics for Service Members meeting those criteria. Those who deployed were significantly more likely to be older when they left DoD, having served in the Army. National Guard component was more likely to have been deployed than expected by chance. Women were less likely to have deployed, and those deployed were more likely to have been married when leaving military service. **Table 6** shows mental health characteristics in DoD care. Those who deployed were significantly more likely to have received two or more outpatient (or one inpatient) diagnoses for cognitive complaints, PTSD and other substance use disorder; they were less likely than those who did not deploy to have diagnosis of suicidal ideation or attempt.

Table 5: Demographic Characteristics of DoD Latent Class Analysis Cohort by Deployment Status

	Non-Deployed 29.03 (495,022)	Deployed 70.97 (1,210,360)
Age at Last year of DoD care		
Mean Age	31.45	33.29
Branch		
Air Force	21.04 (104164)	19.77 (239337)

Army	40.56 (200757)	50.78 (614561)
Coast Guard	5.00 (24753)	0.21 (2598)
Marines	15.60 (77209)	12.26 (148395)
Navy	17.35 (85891)	16.97 (205406)
Other	0.45 (2248)	0.01 (63)
Component		
Active	66.12 (327309)	62.24 (753353)
Guard	6.78 (33549)	10.74 (130052)
Reserve	27.10 (134164)	27.01 (326955)
Rank		
Enlisted	84.73 (419390)	86.01 (1040978)
Officer	14.24 (70495)	12.49 (151196)
Warrant	1.03 (5109)	1.50 (18132)
Education		
Less Than High School	1.18 (5822)	1.25 (15185)
High School / GED	66.66 (329968)	66.22 (801454)
Some College	11.59 (57389)	14.25 (172508)
College Graduate	11.25 (55675)	11.22 (135837)
Graduate School	6.55 (32440)	6.33 (76649)
Unknown	2.77 (13728)	0.72 (8727)
Sex		
Female	28.18 (139494)	14.58 (176413)
Race/Ethnicity		
White	59.94 (296724)	62.67 (758529)
Black Hispanic	0.63 (3120)	0.55 (6605)
Black Non-Hispanic	19.27 (95401)	17.49 (211730)
Hispanic	10.08 (49896)	9.41 (113860)
Asian American and Pacific Islander	6.06 (30000)	6.77 (81942)
Native American	1.70 (8417)	1.71 (20727)
Unknown	2.32 (11464)	1.40 (16967)
Marital Status upon discharge		
Married	38.10 (188612)	45.13 (546206)

Table 6: Mental Health and Pain Characteristics in DoD care for Latent Class Analysis Cohort by Deployment Status

	Non-Deployed 29.03 (495022)	Deployed 70.97 (1210360)
Mental Health		
Alcohol Abuse	12.15 (60145)	14.04 (169995)
Anxiety	26.61 (131744)	26.77 (324009)
Attention	7.40 (36635)	7.48 (90487)
Bipolar/Schizophrenia	7.69 (38068)	6.09 (73753)

Cognitive (All)	3.33 (16467)	6.49 (78559)
Depression	26.30 (130179)	24.55 (297110)
Opioid Abuse	2.21 (10943)	2.00 (24258)
Overdose	5.57 (27590)	5.59 (67612)
PTSD	7.79 (38553)	18.09 (219005)
Other Substance Use Disorder	17.89 (88568)	20.72 (250823)
Suicide	5.91 (29244)	4.75 (57477)
Pain		
Back Pain	60.46 (299288)	61.25 (741385)
Headache	38.98 (192959)	36.01 (435830)
Neck Pain	30.70 (151954)	30.82 (373049)
Neuropathic Pain	19.61 (97050)	18.54 (224361)
Other Pain	71.21 (352524)	70.71 (855851)

Table 7: DoD Health Characteristics of DoD Latent Class Analysis Cohort by Deployment Status

	Non-Deployed 29.03 (495022)	Deployed 70.97 (1210360)
Health Characteristics		
Coronary Artery Disease	3.69 (18264)	2.63 (31875)
Cancer	3.86 (19122)	2.73 (32985)
Cardiac	18.98 (93942)	16.18 (195868)
Cholesterol	26.43 (130845)	28.47 (344590)
Chronic Fatigue	1.60 (7901)	1.29 (15673)
Diabetes	7.13 (35314)	5.63 (68114)
Dizziness	17.57 (86987)	14.96 (181031)
Hearing Loss	12.38 (61262)	16.22 (196371)
High Blood Pressure	23.82 (117898)	24.07 (291329)
Hypersomnia	11.54 (57136)	12.89 (156034)
Irritable Bowel Syndrome	3.99 (19749)	3.00 (36265)
Injury (All)	4.14 (20503)	4.06 (49170)
Insomnia	26.52 (131270)	31.01 (375305)
Kidney	2.60 (12856)	2.10 (25392)
Liver	6.57 (32507)	5.74 (69533)
Lung Disease	12.22 (60515)	10.09 (122131)
Neurological conditions (All)	5.68 (28099)	4.48 (54214)
Obesity	29.67 (146858)	30.18 (365250)
Obstructive Sleep Apnea	18.16 (89883)	23.76 (287564)
Skin Disease	30.99 (153395)	29.04 (351475)
Stroke	3.59 (17790)	2.59 (31329)
Tinnitus	7.31 (36194)	11.23 (135971)
Traumatic Brain Injury	10.38 (51389)	15.19 (183879)
Vestibular Dysfunction	5.79 (28659)	5.17 (62628)
Vision	7.54 (37337)	7.39 (89399)

Table 7 shows other health characteristics for our DoD latent class analysis cohort. Those who did not deploy had significantly higher prevalence of coronary artery disease, cancer, diabetes, dizziness, and stroke then those who deployed. Those who deployed had significantly higher prevalence of hearing loss, insomnia, obstructive sleep apnea, tinnitus and TBI compared to those who did not deploy. Our next steps will be to conduct LCA based on diagnoses of these conditions each year and compare by deployment and transition to VA status.

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

Month(s): 24 - 48

Progress: We are beginning LCA phenotypes. We planned to use machine learning approaches but do not currently have the computing power to complete these analyses on VINCI, and do not have funds to pay for cloud computing environments which will be available in the near future. .

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

Month(s): 48 - 60

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

Milestone: Compile VA data for Post-9/11 Veteran Cohort from existing data repository. **COMPLETE**

Milestone: Convene stakeholder panel of VA and DoD operational partners. **Complete for 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. **Complete data sets; working on LCA models; insufficient computing power on VINCI to conduct deep learning analyses and unable to install server behind VA firewall yet. We continue to work on this.**

Milestone: Develop DoD+VA phenotypes in: deployed VA users; nondeployed VA users; deployed no VA care; non-deployed no VA care. **Currently conducting LCA analyses for those without VA care as we have no prior information on this cohort.**

Milestone: Compare phenotypes among sub-strata (deployed/nondeployed/VA/non-VA).

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

Progress: Completed

- a. HES received IRB approval for the following protocol amendments (1) added dates, specifically, all elements of dates (e.g., birthdate, admission date), (2) added geographic subdivisions smaller than a state, and geocodes (e.g., zip, county or city codes, street addresses), (3) replaced "VCU server" with "Department of Defense and Secure Access File Exchange (DOD SAFE)" as DOD SAFE will be the method that DOD sites will send participant EDIPIN and study ID to Dr. Dismuke-Greer and her team, (4) noted that VCU can share deidentified data with anyone with whom VCU has a DUA, and (5) added VA COVID-19 Volunteer Registry as a data source.
- b. The HES worked with the VA Houston to add a LIMBIC coordinator from their site to the HES local IRB and DART so the individual could access the project folder in VINCI to upload a password protected excel spread sheet containing study ID, station ID, and real SSN from VA Houston's study cohort.
- c. We've received site data, including participant SSN by study ID and station ID from the following VA sites: Boston, Houston, Minnesota, Portland, Richmond, Salisbury, San Antonio, San Diego, and Tampa. Dr. Dismuke will request that VINCI provide the VA utilization and cost data for the SSN. She will then strip the SSN from the data and send the data to LIMBIC Data and Biostatistics Core with only the study ID.
- d. We've met with DoD sites (Ft. Belvoir and Ft. Gordon) to discuss DoD regulatory measures to receive EDIPIN; they'll follow up with our team once they are ready to transfer data.
- e. For the phenotype study, all authorizations have been obtained by Dr. Pugh's team.

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

Month(s): 1 - 24

Progress: Completed

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

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

Month(s): 1 - 24

Progress: Completed

- a. Phenotype databases SM/VA without TBI are completed

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

Completed: Year 2, Q4

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

Month(s): 24 - 36

Progress: Completed year 3, quarter 3

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

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

Month(s): 24 - 36

Progress: 50%

- a. Data has been merged in VINCI for the 1.5 million veteran phenotype subjects with Service-Connected Disability Compensation. It is in progress for DoD and VA cost data for the 1.5 million veterans and 1.1 million service members. Additional data source: Department of Labor Zip Codes for Native American Tribal Lands.
- b. Service-connected disability (SCD) compensation analysis:
We assessed the compensation and award received by veteran with service-connected disability (SCD) by TBI status. We looked for health care system disparities among demographic variables (i.e., race, gender) and service duty factors (i.e., branch of service, years on service). The aims were to (1) examine the association of social and military Veteran factors with risk of TBI SCD, (2) estimate the association of TBI SCD by VA with total SCD compensation, (3) examine the association of social and military Veteran factors with total SCD compensation. For our methods we used a retrospective observational study design, using Phenotype administrative data from EHR of VHA using veterans diagnosed with DoD/VA ICD codes for TBI in DoD or VA. Phenotype data was merged with data from Veterans Benefit Administration (VBA) (VETSNET) data to obtain total SCD, TBI SCD, and most recent 2022 monthly compensation. TBI SCD is determined by Veterans Benefits Administration (VBA) based on the following ICD codes:
 - 9304 = neurocognitive disorder due to TBI
 - 8045 = Residuals of TBI
 - Phenotype Study
 - Obtained military characteristics
 - Obtained race/ethnicity

- Obtained geographic regions (Urban, Rural, Highly Rural, US Territory)
- Given early results, we sought to identify Native American Tribal Lands which is not available in current VA databases.
 - Obtained zip codes for the Tribal Chiefs for Native American Tribal Lands from a colleague at the US Department of Labor.

The tables and graphs are finalized (see below), and we are writing the initial draft for the report and manuscript.

Table 1. Demographic Characteristics with Service-Connected Disability by TBI*

	No TBI	TBI	Total
Overall	1,225,679 (92.88)	93,911 (7.12)	1,319,590 (100)
Female	221,585 (18.08)	6,514 (6.94)	228,099 (17.29)
Age Entered VA Median (Semi IQR)	30.73 (15.43)	27.52 (9.45)	30.4 (15.21)
DoD Service Years Median (Semi IQR)	8 (10)	6 (8)	8 (10)
Number of SC Conditions Median (Semi IQR)	6 (8)	6 (6)	6 (8)
Education			
Less Than High School	16,718 (1.36)	1,588 (1.69)	18,306 (1.39)
High School/GED	842,942 (68.77)	74,707 (79.55)	917,649 (69.54)
Some College	174,465 (14.23)	9,558 (10.18)	184,023 (13.95)
College Degree	121,670 (9.93)	5,897 (6.28)	127,567 (9.67)
Graduate School	66,471 (5.42)	2,065 (2.2)	68,536 (5.19)
Unknown	3,413 (0.28)	96 (0.1)	3,509 (0.27)
Marital Status			
Not Married	557,578 (45.49)	46,937 (49.98)	604,515 (45.81)
Married	666,942 (54.41)	46,932 (49.97)	713,874 (54.1)
Unknown	1,159 (0.09)	42 (0.04)	1,201 (0.09)
Race/Ethnicity			
AAPI	79,177 (6.46)	8,386 (8.93)	87,563 (6.64)
Black Hispanic	6,753 (0.55)	387 (0.41)	7,140 (0.54)
Black Non-Hispanic	257,889 (21.04)	11,446 (12.19)	269,335 (20.41)
Hispanic	118,124 (9.64)	9,080 (9.67)	127,204 (9.64)
Native American	21,998 (1.79)	1,832 (1.95)	23,830 (1.81)
White Non-Hispanic	735,370 (60)	62,511 (66.56)	797,881 (60.46)
Unknown	6,368 (0.52)	269 (0.29)	6,637 (0.5)
Geographic Status			
Urban	851,208 (69.82)	60,791 (65.02)	911,999 (69.48)
Rural	336,175 (27.58)	29,515 (31.57)	365,690 (27.86)
Highly Rural	28,988 (2.38)	2,972 (3.18)	31,960 (2.43)
US Territory	1,767 (0.14)	129 (0.14)	1,896 (0.14)
Native American Tribe	964 (0.08)	88 (0.09)	1,052 (0.08)
Number of Dependents			
0	445,122 (36.32)	29,992 (31.94)	475,114 (36)
1	327,211 (26.7)	20,760 (22.11)	347,971 (26.37)
2	174,801 (14.26)	15,268 (16.26)	190,069 (14.4)
3	158,570 (12.94)	15,390 (16.39)	173,960 (13.18)

4	76,533 (6.24)	7,843 (8.35)	84,376 (6.39)
5--12	42,535 (3.47)	4,608 (4.91)	47,143 (3.57)
Unknown	907 (0.07)	50 (0.05)	957 (0.07)
Deployed	858,707 (70.06)	82,640 (88)	941,347 (71.34)
Branch Of Service			
Air Force	202,439 (16.52)	5,605 (5.97)	208,044 (15.77)
Army	605,988 (49.44)	60,555 (64.48)	666,543 (50.51)
Marines	189,973 (15.5)	19,267 (20.52)	209,240 (15.86)
Navy/Coast Guard	226,341 (18.47)	8,470 (9.02)	234,811 (17.79)
Other Branch	938 (0.08)	14 (0.01)	952 (0.07)
Rank			
Enlisted	1,104,415 (90.11)	88,934 (94.71)	1,193,349 (90.44)
Officer	104,354 (8.51)	4,310 (4.59)	108,664 (8.24)
Warrant	16,831 (1.37)	662 (0.7)	17,493 (1.33)
Combat Exposure	894,184 (72.95)	81,508 (86.79)	975,692 (73.94)
VA Service-Connected Disability %			
0	26,831 (2.19)	1,581 (1.68)	28,412 (2.15)
10--40	212,319 (17.32)	8,105 (8.63)	220,424 (16.7)
>=50	986,529 (80.49)	84,225 (89.69)	1,070,754 (81.14)
Gross Amount	1,818.95 (2373.62)	2,108.43 (2141.58)	1,877.43 (2311.62)

*Aside from # of SC Conditions, all other variables are significant at <0.001

Table 2. The Probability of TBI Service-Connected Disability in Veterans who have received compensation (N= 1,319,590)

	Crude	P-Value	Adjusted	P-Value
Female	0.34 (0.33, 0.35)	<0.001	0.44 (0.43, 0.46)	<0.001
Age Entered VA	0.96 (0.96, 0.96)	<0.001	0.96 (0.96, 0.96)	<0.001
DoD Service Years	0.96 (0.96, 0.96)	<0.001	0.99 (0.99, 1)	<0.001
Number of SC Conditions	1.00 (1.00, 1.00)	0.609	1.03 (1.02, 1.03)	<0.001
Education				
College Degree	Reference		Reference	
Less Than High School	1.96 (1.85, 2.08)	<0.001	1.22 (1.14, 1.29)	<0.001
High School/GED	1.83 (1.78, 1.88)	<0.001	1.21 (1.17, 1.25)	<0.001
Some College	1.13 (1.09, 1.17)	<0.001	1.05 (1.01, 1.09)	0.021
Graduate School	0.64 (0.61, 0.67)	<0.001	0.88 (0.84, 0.93)	<0.001
Unknown	0.58 (0.47, 0.71)	<0.001	1.03 (0.83, 1.28)	0.757
Marital Status				
Not Married	Reference		Reference	
Married	0.43 (0.32, 0.59)	<0.001	0.68 (0.49, 0.92)	0.014
Unknown	0.84 (0.82, 0.85)	<0.001	0.89 (0.88, 0.91)	<0.001
Race/Ethnicity				
White Non-Hispanic	Reference		Reference	
AAPI	1.25 (1.22, 1.28)	<0.001	1.19 (1.16, 1.22)	<0.001
Black Hispanic	0.67 (0.61, 0.75)	<0.001	0.81 (0.73, 0.9)	<0.001
Black Non-Hispanic	0.52 (0.51, 0.53)	<0.001	0.63 (0.61, 0.64)	<0.001
Hispanic	0.9 (0.88, 0.93)	<0.001	0.89 (0.86, 0.91)	<0.001
Native American	0.98 (0.93, 1.03)	0.406	1.12 (1.06, 1.18)	<0.001

Unknown	0.5 (0.44, 0.56)	<0.001	0.74 (0.65, 0.84)	<0.001
Geographic Status				
Urban				
Rural	1.23 (1.21, 1.25)	<0.001	1.08 (1.07, 1.1)	<0.001
Highly Rural	1.44 (1.38, 1.49)	<0.001	1.18 (1.14, 1.23)	<0.001
US Territory	1.02 (0.85, 1.22)	0.809	1.09 (0.91, 1.31)	0.361
Native American Tribe	1.28 (1.03, 1.59)	0.028	0.96 (0.76, 1.21)	0.723
Number of Dependents*				
0	Reference		Reference	
1	0.94 (0.92, 0.96)	<0.001	1.13 (1.11, 1.15)	<0.001
2	1.3 (1.27, 1.32)	<0.001	1.16 (1.14, 1.19)	<0.001
3	1.44 (1.41, 1.47)	<0.001	1.16 (1.14, 1.19)	<0.001
4	1.52 (1.48, 1.56)	<0.001	1.17 (1.14, 1.2)	<0.001
5--12	1.61 (1.56, 1.66)	<0.001	1.2 (1.16, 1.24)	<0.001
Unknown	0.82 (0.62, 1.09)	0.167	0.92 (0.69, 1.22)	0.554
Deployed	3.13 (3.07, 3.2)	<0.001	2 (1.94, 2.06)	<0.001
Branch of Service				
Army	Reference		Reference	
Air Force	0.28 (0.27, 0.28)	<0.001	0.38 (0.36, 0.39)	<0.001
Marines	1.01 (1, 1.03)	0.088	0.79 (0.78, 0.81)	<0.001
Navy/Cost Guard	0.37 (0.37, 0.38)	<0.001	0.46 (0.45, 0.47)	<0.001
Other Branch	0.15 (0.09, 0.25)	<0.001	0.95 (0.56, 1.62)	0.857
Rank				
Enlisted	Reference		Reference	
Officer	0.51 (0.5, 0.53)	<0.001	0.95 (0.91, 1)	0.037
Warrant	0.49 (0.45, 0.53)	<0.001	0.67 (0.62, 0.73)	<0.001
Combat Exposure	2.44 (2.39, 2.48)	<0.001	1.28 (1.24, 1.32)	<0.001

Table 3. Association of TBI Service-Connected Disability with Total Service-Connected Compensation

	Crude	P-Value	Partially Adjusted	P-Value	Fully Adjusted	P-Value
VBA TBI	362 (353, 370)	<0.001	310 (303, 317)	<0.001	268 (261, 275)	<0.001
Female	5 (-1, 11)	0.083	-14 (-18, -9)	<0.001	9 (4, 14)	<0.001
Age Entered VA	13 (13, 13)	<0.001	-1 (-1, -1)	<0.001	-1 (-1, 0)	<0.001
DoD Service Years	47 (47, 47)	<0.001	1 (1, 2)	<0.001	2 (2, 2)	<0.001
Number of SC Conditions	103 (103, 103)	<0.001	97 (97, 98)	<0.001	97 (97, 97)	<0.001
Education						
College Degree						
Less Than High School	-51 (-71, -32)	<0.001	230 (214, 246)	<0.001	128 (112, 145)	<0.001
High School/GED	-67 (-74, -59)	<0.001	121 (114, 127)	<0.001	67 (59, 74)	<0.001
Some College	108 (99, 117)	<0.001	84 (76, 91)	<0.001	25 (17, 33)	<0.001
Graduate School	13 (2, 25)	0.026	-136 (-146, -126)	<0.001	-58 (-68, -47)	<0.001
Unknown	-284 (-327, -242)	<0.001	-42 (-76, -7)	0.019	77 (42, 112)	<0.001
Marital Status						
Not Married						
Married	298 (293, 302)	<0.001	-111 (-115, -107)	<0.001	-112 (-116, -	<0.001

					108)	
Unknown	-297 (-368, -226)	<0.001	-330 (-389, -271)	<0.001	-274 (-333, -216)	<0.001
Race/Ethnicity						
White Non-Hispanic						
AAPI	290 (281, 299)	<0.001	217 (210, 225)	<0.001	170 (162, 177)	<0.001
Black Hispanic	252 (223, 281)	<0.001	240 (216, 264)	<0.001	255 (231, 279)	<0.001
Black Non-Hispanic	433 (428, 439)	<0.001	346 (342, 351)	<0.001	317 (312, 322)	<0.001
Hispanic	199 (191, 206)	<0.001	184 (177, 190)	<0.001	176 (170, 183)	<0.001
Native American	169 (153, 185)	<0.001	117 (103, 131)	<0.001	137 (124, 151)	<0.001
Unknown	-35 (-65, -4)	0.025	-57 (-82, -32)	<0.001	-27 (-52, -2)	0.034
Geographic Status						
Urban						
Rural	26 (22, 31)	<0.001	47 (43, 51)	<0.001	32 (28, 36)	<0.001
Highly Rural	-14 (-28, 0)	0.050	80 (69, 92)	<0.001	56 (44, 67)	<0.001
US Territory	149 (92, 206)	<0.001	132 (86, 179)	<0.001	99 (53, 145)	<0.001
Native American	-80 (-157, -4)	0.040	-7 (-71, 57)	0.825	-42 (-106, 21)	0.192
Number of Dependents						
0						
1	743 (738, 748)	<0.001	484 (479, 489)	<0.001	479 (475, 484)	<0.001
2	832 (826, 838)	<0.001	636 (630, 641)	<0.001	624 (619, 630)	<0.001
3	864 (858, 871)	<0.001	723 (717, 729)	<0.001	712 (706, 718)	<0.001
4	995 (986, 1004)	<0.001	858 (850, 866)	<0.001	844 (836, 852)	<0.001
5--12	1,234 (1222, 1245)	<0.001	1,075 (1065, 1085)	<0.001	1,056 (1046, 1066)	<0.001
Unknown	735 (659, 811)	<0.001	533 (467, 598)	<0.001	530 (465, 595)	<0.001
Deployed	209 (205, 214)	<0.001			40 (34, 47)	<0.001
Branch Of Service						
Army						
Air Force	-265 (-271, -258)	<0.001			-202 (-207, -197)	<0.001
Marines	-221 (-227, -215)	<0.001			-198 (-203, -193)	<0.001
Navy/Coast Guard	-281 (-287, -275)	<0.001			-203 (-208, -198)	<0.001
Other	-115 (-195, -35)	0.005			66 (0, 133)	0.049
Rank						
Enlisted						
Officer	-91 (-99, -84)	<0.001			-178 (-187, -169)	<0.001
Warrant	309 (291, 328)	<0.001			-86 (-102, -71)	<0.001
Combat Exposure	248 (243, 253)	<0.001			61 (55, 68)	<0.001

Figure 1: Probability of TBI Service-Connected Disability in Veterans Who Have Received Compensation (Unadjusted Odds Ratios and 95% CI)

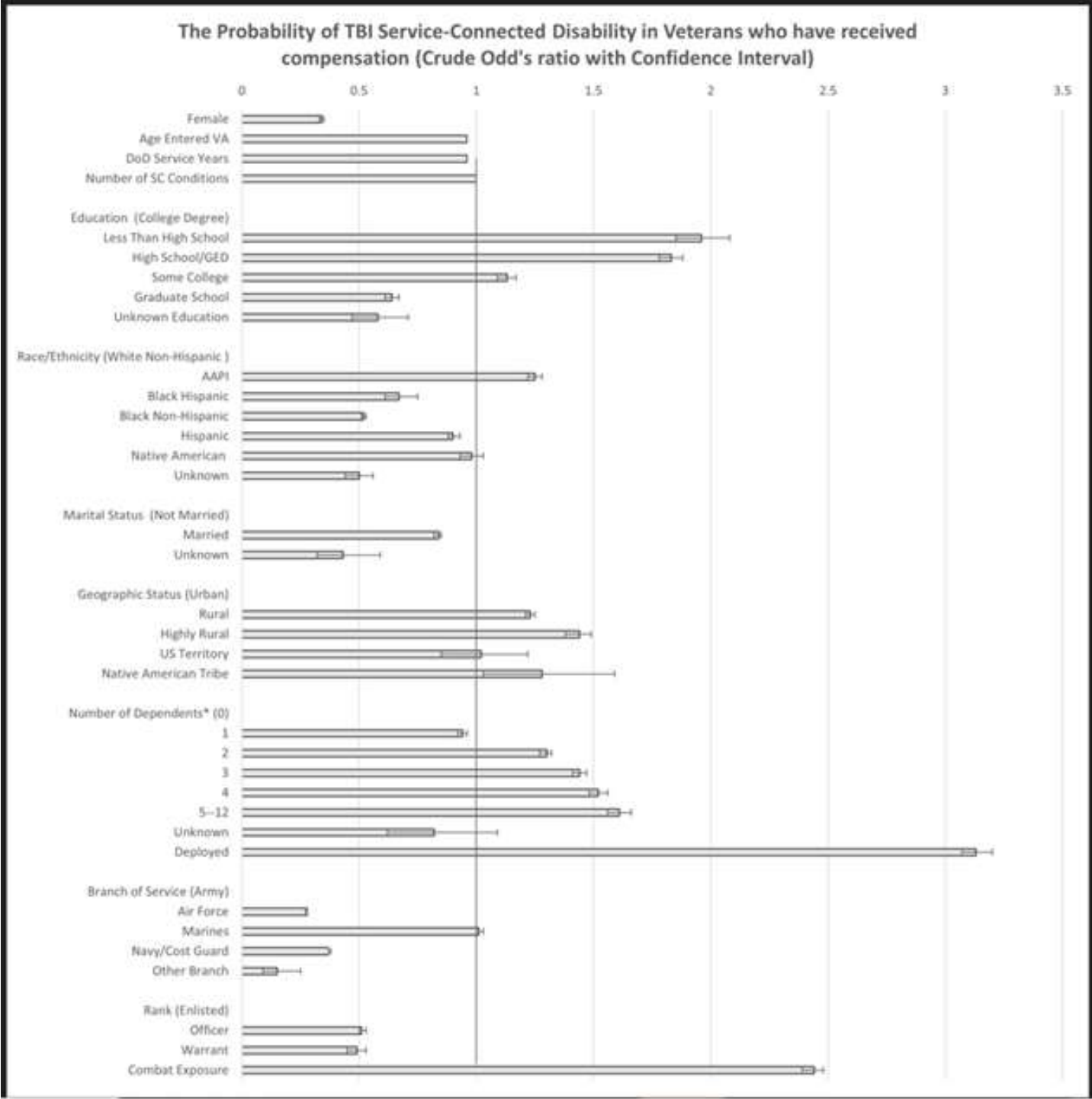


Figure 2: Probability of TBI Service-Connected Disability in Veterans Who Have Received Compensation (Fully Adjusted Odds Ratios and 95% CI)

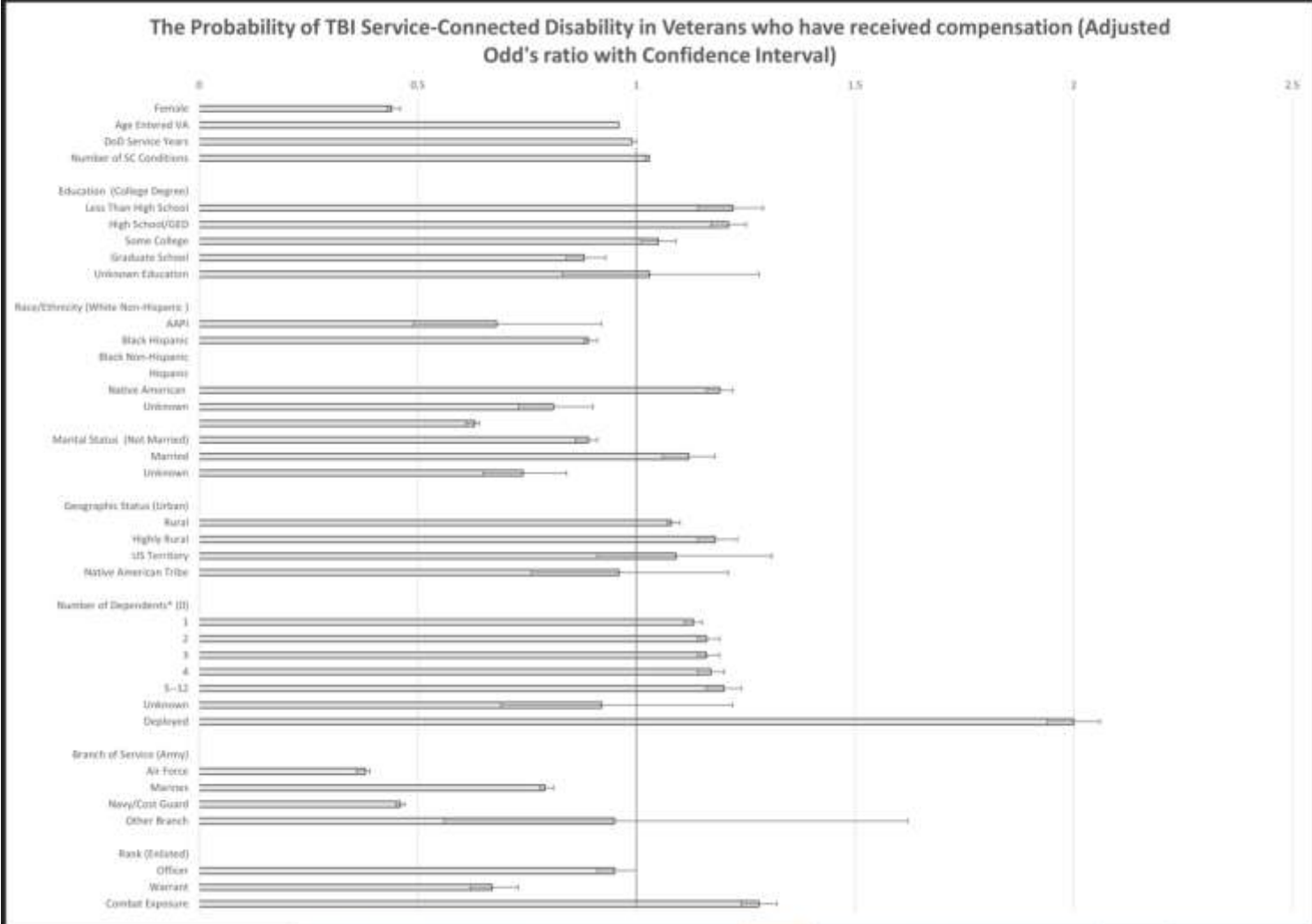


Figure 3: Unadjusted Association of TBI SCD with TBI SCD Compensation

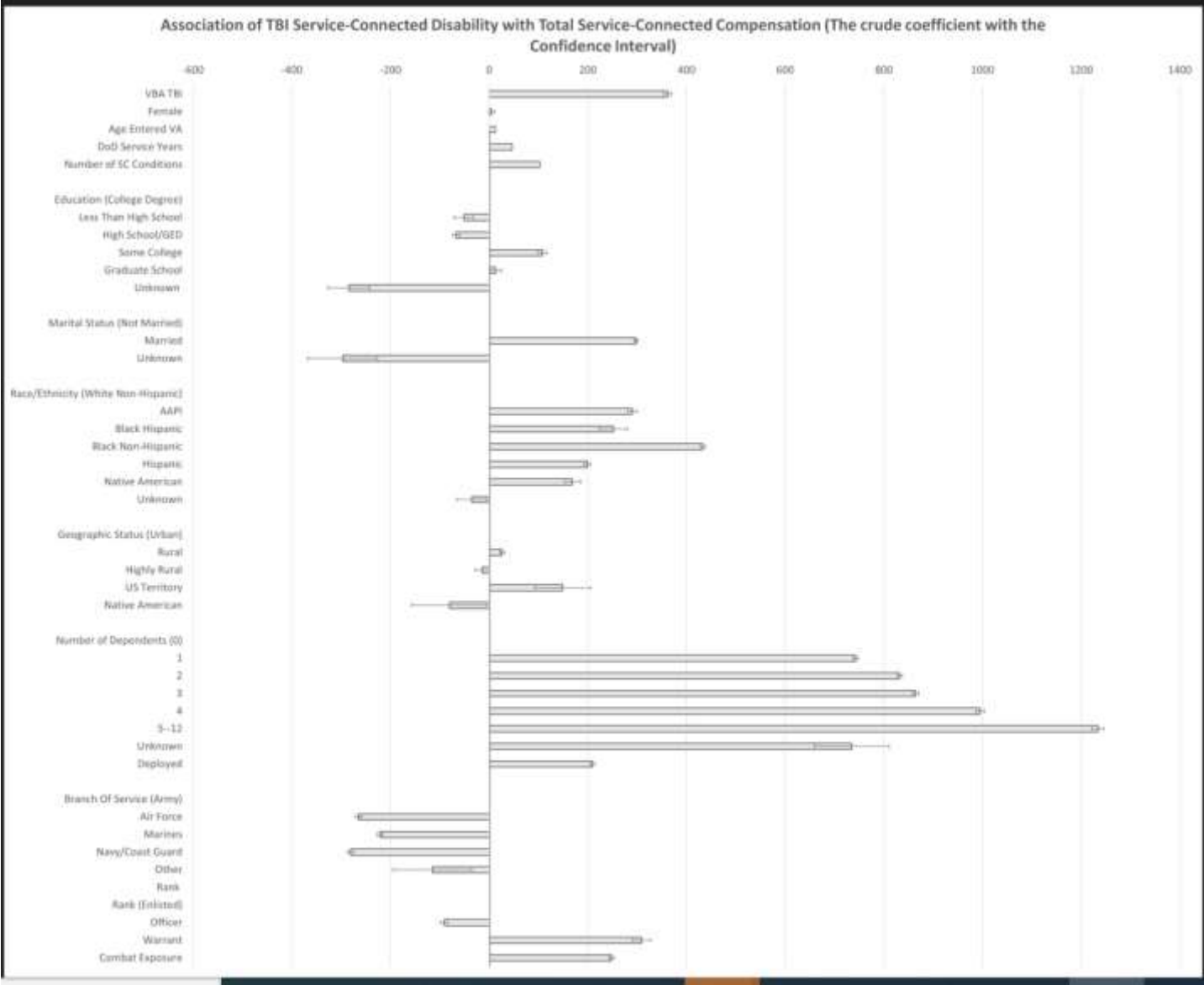


Figure 4: Partially Adjusted Association of TBI SCD with TBI SCD Compensation

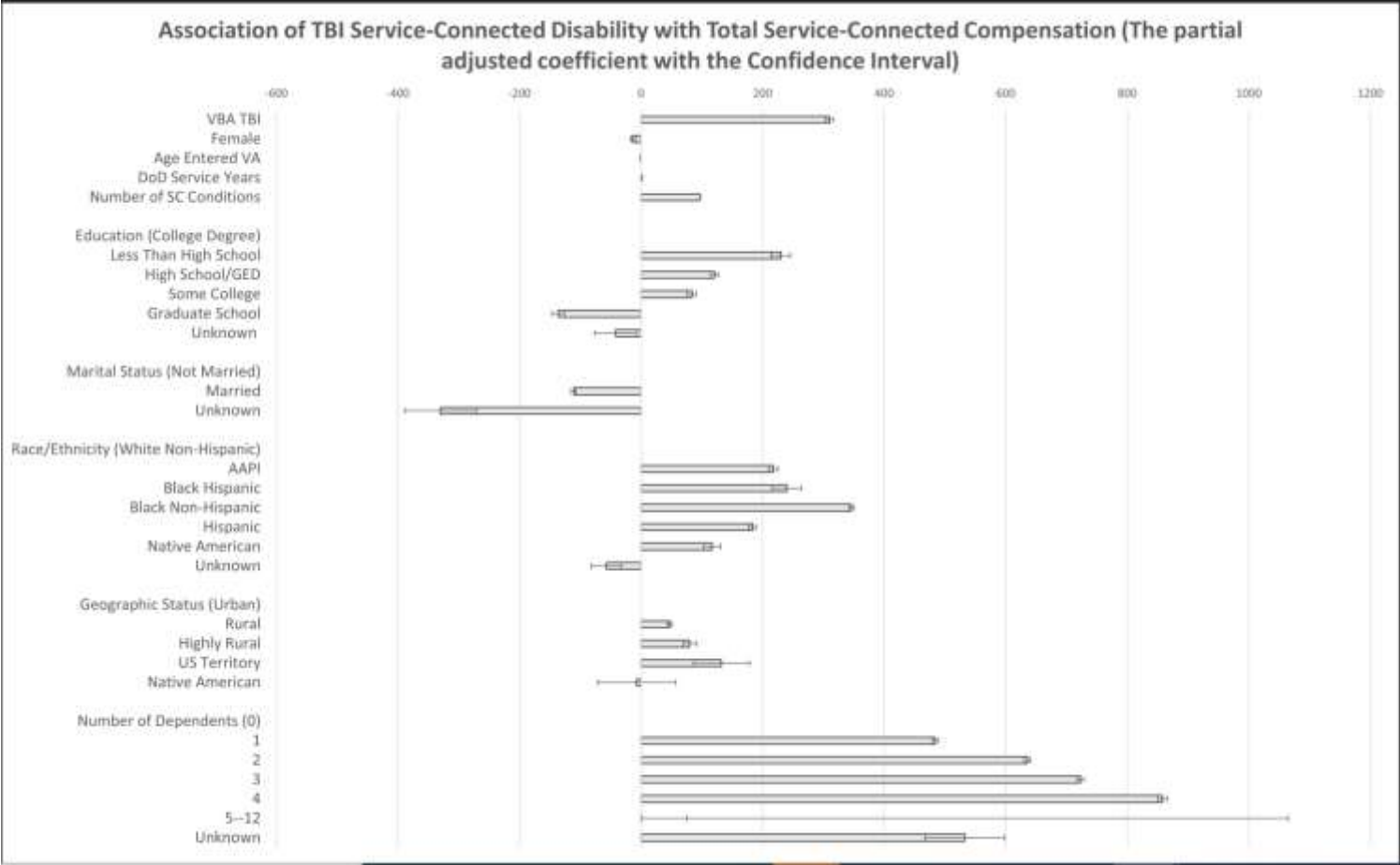
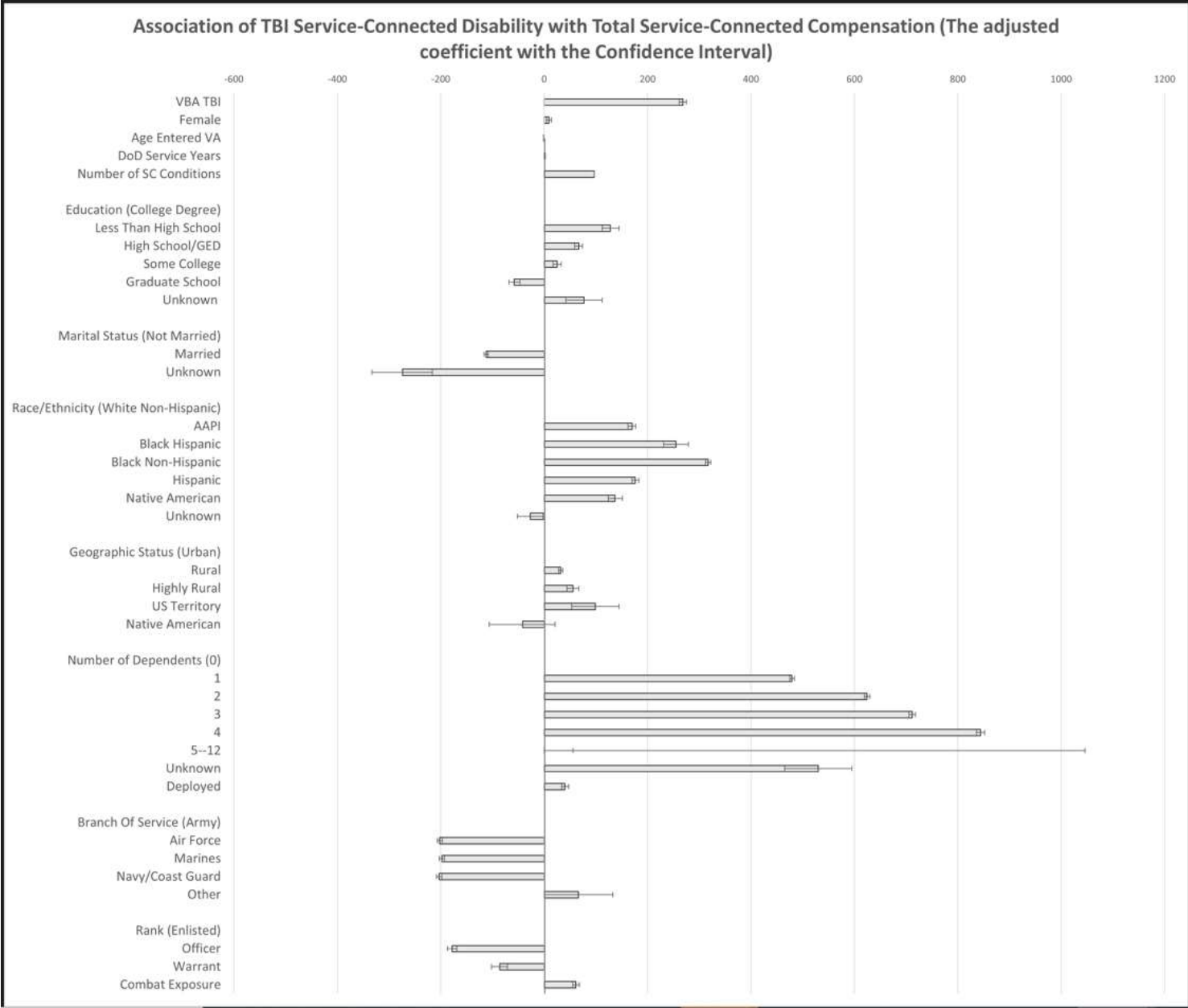


Figure 5: Fully Adjusted Association of TBI SCD with TBI SCD Compensation

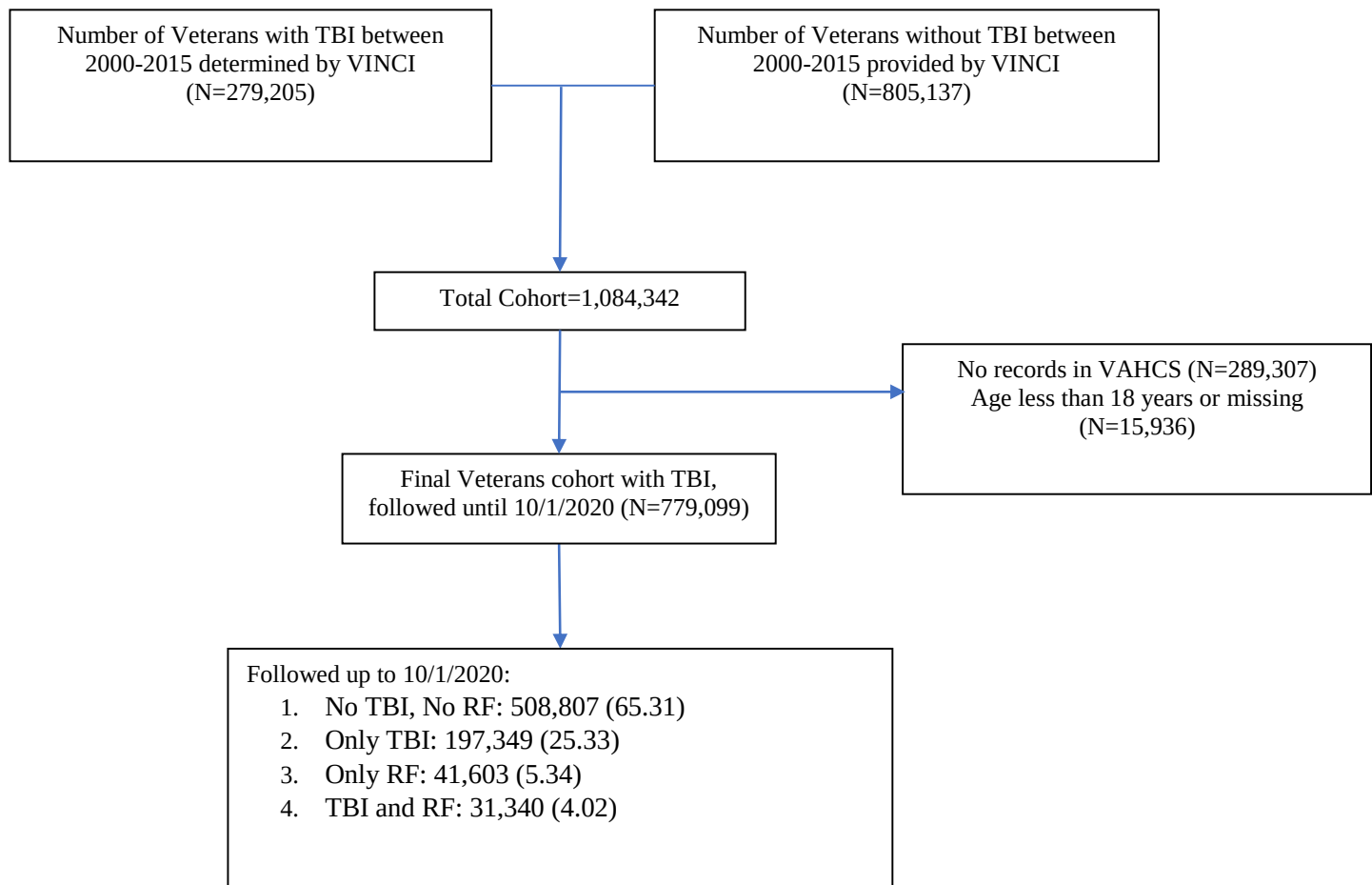


TBI and Renal Failure analysis:

We examined race/ethnicity and urban/rural/US territory residence with onset of renal failure (RF) in veterans with and without TBI. We also examined racial/ethnic and geographic disparities in Veterans Affairs (VA) TBI+RF resource cost, 2000-2020. For methods, we estimated Cox Proportional Hazards models for risk of RF, and generalized estimating equations for inpatient, outpatient, and pharmacy cost annually and time since TBI+RF diagnosis.

Racial/Ethnic and Geographic Disparities in Comorbid Traumatic Brain Injury (TBI)-Renal Failure (RF) in US Veterans and Associated Veterans Administration (VA) Resource Costs, 2000-2020 (under Review in Journal of Racial and Ethnic Health Disparities)

Figure 1- Flowchart showing participant inclusion and exclusion



Abbreviations: RF=Renal Failure, TBI= Traumatic Brain Injury, VAHCS= Veterans Affairs Health Care System, VINCI= VA Informatics and Computing Infrastructure.

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: 50% Complete

- Classification of 10,801 exposures for 1,816 PLS subjects has been completed based on advice from Dr. Agimi of Walter Reed. Linkage to DoD and VA cost data is in process.
- Operations Theater data on battle vs non-battle injuries and blast vs non-blast has been explored along with theater disposition (return to duty, quarters, evacuated). An algorithm for computing the Injury Severity Score (ISS) has been applied. This will be applied to the Phenotype data.

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-of-pocket costs incurred by individuals as well as payments to health care providers made on their behalf by Tricare.

Month(s): 36 - 60

Progress: 25% Complete

- Dr. Dismuke-Greer has been working with a team from Walter Reed led by Dr. Peter Hoover examining costs for current SMs with recent mTBIs which provides the MEPRS codes for

identifying outpatient clinic types of care. We will cite this study and use their MEPRS codes to identify the type of care. Sick days variables have been identified in the DoD outpatient data. Disposition after injury (return to duty, quarters, etc.) has been identified in Theater data. Out of pocket cost variables have been identified in the Tricare data.

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

Month(s): 36 - 60

Progress: 50% Complete

- a. Phenotype data include 1.5 million Vs and 1.1 million SMs to allow identification of transition to VA. Working with Dr. Pugh and Dr. Agimi to identify SM predictors of transition and access to VA care. Death dates have been identified in DoD and VA data.

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: 50% Complete

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

Exposure Categories

New_Cause	Freq.	Percent	Cum.
Artillery	362	3.35	3.35
Bomb	115	1.06	4.42
C4	993	9.19	13.61
Controlled Detonation	418	3.87	17.48
Fall	893	8.27	25.75
Grenade (including RPG)	561	5.19	30.94
Hit by something	846	7.83	38.77
IED	1,439	13.32	52.10
Land mine	172	1.59	53.69
Mixture of explosives	781	7.23	60.92
Mortar	854	7.91	68.83
Motor vehicle accident	1,051	9.73	78.56
Other	53	0.49	79.05
Parachute	271	2.51	81.56
Physical assault	558	5.17	86.72
Rocket (includes Missile)	402	3.72	90.45
Sports collision	945	8.75	99.19
Uncontrolled Blast	87	0.81	100.00
Total	10,801	100.00	

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: 50% Complete

Milestone: Develop statistical analyses to economic and epidemiological models. (See tasks listed above)

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. (See: Section 6 Products)

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. (Nothing to report yet)*

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. (Section 6 Products- Additionally, abstracts have been accepted for oral presentations at ACRM and VA HSR&D)*

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 are awaiting the new release of an adapted method of decentralized ComBat, for which University of Utah will be a beta testing site using the LIMBIC data to overcome site differences; we anticipate beginning to implement and test the new pipeline in the next review period.

We had previously identified another novel method of data harmonization using a technique developed by colleagues at Brigham and Women's Hospital (BWH) which is being applied in other consortia. We continue our collaboration with this group and with others in the InTBIR and ENIGMA communities to complete our implementation of this method.

Drs. Wilde, Tate and Dennis have acted as special editors for two special issues related to harmonization which are nearing completion (*Neuropsychology* and *Frontiers in Neurology*). Members of the Core participated in 3 manuscripts in the *Neuropsychology* SI, which addressed methods to harmonize PTSD scales, cultural considerations in harmonization, and general considerations in harmonization of outcome measures. Members of the Core also participated in two manuscripts for the *Frontiers* SI, which focused upon harmonization in imaging. One of these papers outlined a plan for harmonization using the phantom that was developed under CENC.

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

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

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

Month(s): 1 - 12

Progress: In addition to the standard "Core" pipelines that we have been using as part of CENC, we have identified several additional pipelines that we are continuing to investigate. We have continued our work with Drs. Stone, Tustison and Avants to utilize their SyMLR method, and are in the process of reviewing and refining those results (now with the opportunity to expand biomarker results). We are also leveraging work on a NIH R61/R33 project to build a novel pipeline for both structural and functional imaging analysis; University of Utah/SLC VA is the primary beta test site for this, and LIMBIC data will be used as test data for the new pipelines.

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 are continuing our comparison of distortion correction pipelines and tools in analysis of diffusion imaging; this work is ongoing.

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. This has largely been completed as part of our work with the SiMLR analysis team, but we are examining the data for completion and adding additional data that has been collected since we last analyzed data. Pending receipt of additional clinical and outcome data, we will perform analysis examining the relation of these variables.

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. A series of frequentist and Bayesian models were used to evaluate the relationships among imaging measures and the clinical features of mTBI. Each model included acquisition site, participant sex, age, and time since injury as covariates. After controlling for multiple comparisons, no significant main effect was noted for comparisons between participants with and without a history of mTBI. However, the mechanism of injury (blast-related) was associated with volumetric reductions of several subregions of the corpus callosum. Additionally, the mTBI characteristic of having repetitive mTBIs was associated with increases in 1) left hippocampal and hippocampal subfield volumes, 2) cortical thickness in right insula and frontal and temporal regions, and 3) mean diffusivity values throughout the brain.

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 the next review period.

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 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 samples from 871 participants (328 baseline and 462 follow-up blood draws) for a current total of 4-plex proteomic measures on 1,720 (1,206 previously tested) PLS participants (1,729 baseline with 462 longitudinal follow-up measures) Prospective Study participants.

- Published the following 12 manuscripts:

1. 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, Front. Pharmacol. 12:745348, doi: 10.3389/fphar.2021.745348.
2. Wang KK, Mondello S, Diaz-Arrastia R, Wellington C, Munoz-Pareja JC, Kenney K, et al, InTBIR Biospecimens/Biomarkers Working Group. Blood-based Traumatic Brain Injury Biomarkers – Clinical Utilities and Regulatory Pathways in the United States, Europe and Canada. **Expert Reviews Molecular Diagnostics 2021**. doi.org/10.1080/14737159.2021.2005583 Published 11-2021.
3. Wilde EA, Wanner I-B, Kenney K, Gill J, Stone J, Disner S, Schnakers C, Prager EM, Jeromin A. A Framework to Advance Biomarker Development in the Diagnosis, Outcome Prediction and Treatment of Traumatic Brain Injury. **Journal Neurotrauma** special issue, doi: 10.1089/neu.2021.0099, 12-2021. Top 10 J Neurotrauma media attention manuscript per Altmetric for 2021
4. 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**, doi: 10.3389/fphar.2021.762077, 12-2021. PMID: 35153739.
5. 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 Inj.** 2022 Apr 16;36(5):662-672. PMID: 35125044.
6. 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 Inj.** 2022 Apr 16;36(5):644-651. doi: 10.1080/02699052.2022.2033849. PMID: 35108129.
7. 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 early onset dementia in Post 9-11 Veterans. **Brain Inj.** 2022 Apr 16;36(5):620-627. doi: 10.1080/02699052.2022.2033846. PMID: 35125061.
8. 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, and post-concussive symptoms to biomarkers of neurodegeneration in TBI patients. **Brain Inj.** 2022 Apr 16;36(5):633-643. doi: 10.1080/02699052.2022.2037711. PMID: 35188022.

9. 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 Inj.** 2022 Apr 16;36(5):652-661. doi: 10.1080/02699052.2022.2042854. PMID: 35322723.
10. Walker WC, Agyemang AA, Allen CM, Werner JK, Troyanskaya M, Kenney K. Relation of Mild Traumatic Brain Injury History to Preliminary Neuroendocrine Screen Abnormalities; A Multicenter LIMBIC-CENC Analysis. **Brain Inj.** 2022 Apr 16;36(5):607-619. doi: 10.1080/02699052.2022.2068185. Epub 2022 May 4. PMID: 35507697.
11. Stewart IJ, Amuan ME, Kennedy E, Kenney K, Werner JK, Carlson K, Tate D, Wright WS, Pogoda T, Dismuke C, Wilde E, Pugh MJ. Association between Traumatic Brain Injury and Subsequent Cardiovascular Disease Among Post-9/11 Veterans. **JAMA Neurol.** 2022 Sep 6. doi: 10.1001/jamaneurol.2022.2682. Online ahead of print. PMID: 36066882.
12. Werner JK, Shahim P, Pucci JU, Lai C, Raiciulescu 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.* 2021 Jun 11;44(6):zsaa272. doi: 10.1093/sleep/zsaa272. PMID: 33280032; PMCID: PMC8343591.

• Following 10 manuscripts and under review:

1. 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**, under revision, 11-2021.
2. Tate DF. Wade BSC, Velez CS, Bigler ED, Davenport N, Dennis E, EApenn 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 11-2021.
3. Wade BSC, Tate DF, Kennedy E, Bigler ED, York GE, Taylor BA, Troyanskaya M, Hovenden ES, Goodrich-Hunsaker N, Newsome MR, Dennis EL, Abildskov T, Pugh MJ, Walker WC, Kenney K, Betts A, Shih R, Welsh RC, Wilde EA. Microstructural Organization of Disturbed White Matter Associated with Fine Motor Control in US Service Members with Mild Traumatic Brain Injury. **J Neurotrauma**, under revision, 5-2022.
4. Garcia A, Wilde EA, Tate DF, Reljic T, Kenney K, Troyanskaya M, Agyemang A, Walker WC, Nakase-Richardson R. Obstructive Sleep Apnea Risk is Associated with Number of White Matter Hyperintensities, but History of Mild TBI Exposure is NOT: A LIMBIC-CENC Study. **J of Neurology**, under review, 3-2022.
5. Wright B, Zhang C, Fisher R, Karmarker A, Bjork JM, Pugh MJ, Hodges CB, Martindale SL, Wilde EA, Kenney K, McDonald SD, Scheibel RS, Newsome MR, Cook LJ, Walker WC. Relation of aerobic activity to cognition and well-being in chronic mild traumatic brain injury; A LIMBIC-CENC study. **Arch PMR**, under review, 9-2022.
6. Dennis EL, Newsome MR, Lindsey HM..... Kenney K, Ollinger J, Werner JK... Thompson PM, Tate DF, Wilde EA. Altered Lateralization of the Cingulum in Deployment-Related Traumatic Brain Injury: An ENIGMA Military-Relevant Brain Injury Study. **HBM**, under review. 8-2022.

13 Abstracts, Posters, and Presentations:

1. Gotshall JL, Sheth P, Pucci JU, Brooks D, Watson N, Gabriel A, Mithani S, Leete JJ, Lai C, Qu X-X, Deoto C, Gill JM, Kenney K, Werner JK. Poor sleep quality is associated with elevated exosomal inflammatory cytokines in warfighters with chronic mild TBI. Abstract presented at the 74th Annual meeting of the **American Academy of Neurology**, Seattle, WA, April 2-7, 2022.
2. Guedes V, Mithani S, Gottshall J, Lai C, Devoto C, Gill J, Kenney K, Werner JK. 0320 Sex Differences in Sleep Quality and Biomarker Levels in Service Members and Veterans with Chronic Mild Traumatic Brain Injury. **Sleep** 45 (Supplement_1), A144-A144, June 2022.
3. Guedes V, Gottshall J, Mithani S, Leete J, Lai C, Gill J, Kenney K, Werner JK. 0282 Elevated levels of Extracellular Vesicle Cytokines are Associated with Poor Sleep Quality in Warfighters with Chronic Mild TBI. **Sleep** 45 (Supplement_1), A126-A128, 6/2022.
4. Newsome MR, Liu Q, Wilde EA, Steinberg JL, Scheibel RS; Levin H, Tate DF, Martindale-Supak S, Davenport N, Hodges CB, Rowland J, Kenney K, Werner JK, Mayer AR, Taylor BA, Jaramillo C, & Walker WC. Aberrant Striatal Functional Connectivity in Relation to Walking in Veterans with mTBI. Poster presented at The **Organization for Human Brain Mapping** 2022, Glasgow, Scotland, June 19-23, 2022.
5. Hewins B, Guedes V, Solano A, Gottshall J, Mithani S, Sheth P, Leete J, Lai C, Devoto C, Gill J, Kenney K, Werner JK. Reduced Plasma Glial Fibrillary Acid Protein Correlates with Poor Sleep Quality in Warfighters with Mild Traumatic Brain Injury. **J Neurotrauma** 39 (11-12), A53-A53, 6/1/2022.
6. Dennis EL, Newsome MR, Lindsey HM, Adamson MM, Austin TA, Hinds SR, Eapen BC, Esopenko C, Franz CE, Geuze C, Haswell C, Disner SG, Hodges CB, Irimia A, Kenney K, Koerte IK, Kremen WS, Morey RA, Ollinger J, Rowland JA, Scheibel RS, Shenton ME, Sullivan DR, Talbert LD, Thomopoulos SI, Troyanskaya M, Walker WC, Wang X, Ware AL, Werner JK, Williams W, Thompson PM, Tate DF, Wilde EA. Altered Lateralization of the Cingulum in Deployment-Related Traumatic Brain Injury: An ENIGMA Military-Relevant Brain Injury Study. **International Neurotrauma**, Berlin, Germany, July, 2022.
7. Newsome MR, Liu Q, Wilde EA, Steinberg JL, Scheibel RS; Levin H, Tate DF, Martindale-Supak S, Davenport N, Hodges CB, Rowland J, Kenney K, Werner JK, Mayer AR, Taylor BA, Jaramillo C, & Walker WC. Aberrant Striatal Functional Connectivity in Relation to Walking in Veterans with mTBI. Abstract oral presentation at the 15th **International Neurotrauma Symposium**, Berlin, Germany, July 17-20, 2022. **Nominated for Best Poster Presentation.**
8. Garcia A, Wilde EA, Tate DF, Reljic T, Kenney K, Troyanskaya M, Agyemang A, Walker WC, Nakase-Richardson R. Obstructive Sleep Apnea Risk is Associated with Number of White Matter Hyperintensities, But History of Mild TBI Exposure is Not: A LIMBIC-CENC Study (MHSRS-22-07663). Poster presentation at the 2022 **Military Health System Research Symposium (MHSRS)**, Kissimmee, FL, SEP, 2022.
9. Walker WC, Wright B, Zhang C, Karmarkar A, Bjork JM, Pugh MJ, Hodges CB, Martindale SL, Wilde EA, Kenney K, McDonald SD, Scheibel RS, Newsome MR, Cook LI. Relation of aerobic activity to cognition and well-being in chronic mild traumatic brain injury; A LIMBIC-CENC study. Poster presentation at the 2022 **Military Health System Research Symposium (MHSRS)**, Kissimmee, FL, SEP, 2022.
10. Stewart IJ, Amuan ME, Kennedy E, Kenney K, Werner JK, Carlson K, Tate D, Wright WS, Pogoda T, Dismuke C, Wilde E, Pugh MJ. Association Between Traumatic Brain Injury and Subsequent

Cardiovascular Disease Among Post-9/11 Veterans: A Long-term Impact of Military Relevant Brain Injury Consortium Study (MHSRS-22-05870). Plenary oral presentation at the 2022 ***Military Health System Research Symposium (MHSRS)***, Kissimee, FL, SEP, 2022.

11. Dennis EL, Wilde EA, Ashley W, Wade BSC, Abildskov TJ, HOvenden ES, Bigler ED, Betts AM, Davenport N, Duncan T, Gill J, Hinds SR, Kenney K, Newsome MR, Pugh MJ, Scheibel RS, Shahim P-P, Shih R, Taylor BA, Troyanskaya M, Walker WC, Werner JK, York GE, Cifu DX, Tate D,. Cerebellar Structural Alterations in Military-Relevant Traumatic Brain Injury and their Correlations with Psychiatric and Cognitive Measures (MHSRS-22-07664). Poster presentation at the 2022 ***Military Health System Research Symposium (MHSRS)***, Kissimee, FL, SEP, 2022.
12. 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 mTBI is Associated with Differential Expression of Exosomal microRNAs Identified in Neurodegenerative and Immunological Processes (MHSRS-22-06137). Abstract accepted as oral presentation at the 2022 ***Military Health System Research Symposium (MHSRS)***, Kissimee, FL, SEP, 2022.
13. Invited Speaker, Kimbra Kenney, June 29, 2022, National Neurotrauma Symposium, Implementing TBI Biomarkers in a Real-World Clinical Setting (InTBIR Work Group) session, “Biomarkers of Long-Term TBI Outcomes”

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

Month(s): 1 - 36

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

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

5 analyses ongoing:

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

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

Month(s): 1 - 36

Progress: Collaborating with Roskamp Institute for lipidomic analysis on Biomarker Discovery set.

We are implementing a non-hypothesized based approach to identify novel markers, and pathways, so that we can then develop or optimize assays to undertake within the entire cohort. This method has been

developed in the laboratory, and will be used in this cohort.

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

Month(s): 1 - 36

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

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

Month(s): 1 - 36

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

- Milestone: Carry out blood and saliva biomarker assays from all subjects with baseline specimens in the biorepository.
- Progress: Completed baseline samples with 4 plex. Analysis under way as described in Tasks 1 & 2 above.
- Milestone: Carry out candidate biomarker correlations with TBI status (repetitive versus mTBI with LOC versus blast versus no TBI), pre-deployment/pre-injury biomarker levels, neurobehavioral symptoms, advanced imaging, neuropsychological testing, serial biomarker levels among small cohort with incident neurodegenerative disorder (e.g. dementia).
- Progress: Completed baseline samples with 4 plex. Working with PLS and 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 collection of sufficient number of DNA samples for analysis (minimum 2,000). Carry Forward Request was submitted to VCU to carry over year 3 GWAS funds into Year 4. Will collaboratively carry out GWAS testing through the Broad Institute with GAIN and/or Minnesota VA under LIMBIC year 4 funding once 2,000 DNA samples extracted and available for GWAS testing.

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

Month(s): 12 - 60

Progress: Pending completion of Task 7.

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

Month(s): 12 - 60

Progress: Pending completion of Tasks 7 & 8.

- Milestone: Carry out and complete case-control GWAS assessment. Pending completion of Tasks 7 & 8.

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

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

Month(s): 24 - 60

Progress: To be launched during funding years 4-5. We are currently selecting a sub-cohort to examine for this task. We have worked to set up the laboratory protocol to examine this, and plan to measure methylation and acetylation of genes of interest, that are known to be related to brain injuries and psychiatric symptoms, including PTSD and depression.

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

Month(s): 24 - 60

Progress: To be launched during funding years 4-5. The laboratory protocol for these assays. Specifically, we will do extraction using our standard protocol, and then nanostring using the assay best covering the most candidates, which includes 830 microRNAs.

Milestone: Carry out DNA methylation study on extracted DNA from 200 subjects in longitudinal study and associate methylated genes with chronic TBI outcomes.

Milestone: Carry out validation microRNA analysis of miRNA biomarkers identified in the CENC biomarker discovery project (in process).

Milestone: Develop panel of miRNA biomarkers associated with chronic TBI outcomes.

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

Month(s): 6 - 60

Progress: Completed by the VCU DBC team.

What opportunities for training and professional development has the project provided?

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 junior faculty/research associates (Hannah Lindsay, Paula Johnson, and Ben Wade) who are working on the project as well as 1 graduate student (Carmen Velez), 2 post-bachelor and 2 undergraduate students. These trainees have now had specific training in and experience with numerous aspects of imaging acquisition and analysis.. 2) Drs. Wilde, Tate, Pugh, Gill, Werner, 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: Drs. Dennis and Tate presented at the MHSRS meeting in September. Dr. Wilde participated/presented at the VA NAII BRAIN Summit meeting (Sept 7-9, 2022; Arlington), and the National Academy of Sciences, Engineering and Medicine meeting on TBI (Washington DC).

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

- Kelsee Stromberg, PhD
 - Dysregulated Behavior. Analysis underway.
- Brennan Wright, MD
 - Aerobic exercise after chronic mTBI and relation to cognition and well-being. Manuscript submitted.
- David Garavito, PhD.
 - Gist and Verbatim Memory Performance in Vs Exposed to Combat and mTBI. Analysis underway.
- Samuel Walton, PhD, ATC
 - Brain structure and function in relation to physical activity. Formative stage.
 - Pituitary gland volumetric assessment: building a freely available tool to measure pituitary volume. Formative stage.
 - NIH RO1. Application submitted. Effects of TBI, adverse childhood experiences, and social determinants of health on changes in blood-based and neuroimaging biomarkers of brain health

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

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

Phenotype Study: One junior investigator (Dr. Eamonn Kennedy) led the EOD analysis and manuscript for the Brain Injury Special Issue and is leading phenotyping analyses. A Post-doc (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).

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 Appendix #5, which includes peer-reviewed journal publications and scientific meeting presentations including posters, oral paper presentations, and topical seminars.
- A wide range of dissemination activities and product development took place in collaboration with the LIMBIC KT center targeting all stakeholders including the scientific community, SMs and Veterans and their families, and the public. 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.

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

Phenotype Study: Dr. Pugh presented phenotype findings at the following: Pugh MJ. [Trajectories of Comorbidity in Chronic TBI Recovery](#). Uniformed Services University, Bethesda, MD. December 11, 2021

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. Maintain and upgrade data cube, the interactive platform for on demand review of data.
2. Continue QA/QC of data.
3. Continue development of snapshot data sets for data cubes.
4. Continue development of analytic data sets for investigator data requests.
5. Continue central biostatistics support.
6. Maintain and upgrade integration of data dictionary on the LIMBIC-CENC website as needed.
7. Continue FITBIR Ops and preparation of FITBIR data for the next submission.

Biomarkers Core: In the next year, the Biomarkers Core will accomplish the following:

1. Continue receiving and storing locally processed LIMBIC biospecimen samples into biorepository as collected.
2. Maintain inventory of LIMBIC-CENC BR samples and validate BSI database with Medidata through VCU informatics.
3. Continue to carry out NED screening at baseline visits of participants in the Prospective Study.
4. Continue to carry out DNA extraction and APOE genotyping at baseline visits of participants in the Prospective Study who give permission for genetic testing on their blood specimen.
5. Continue to make LIMBIC-CENC samples available for LIMBIC-CENC related studies as sufficient samples are obtained and as approved by the procedures outlined and approved by the USUHS IRB.
6. As approved, move the Biorepository to WRAIR.
7. Initiate epigenetic study in 200 subjects.
8. Assay additional samples for microRNA within exosomes.
9. Continue to meet with the DoD Biorepository to obtain pre-deployment samples, and then undertake assays.

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 2023.
2. Continue to monitor quality assurance, as above.
3. Continue to perform and update analysis of imaging data on standard pipelines, as above, with re-analyses as new software versions are released.
4. Continue to assist in preparation of data requests, distribution of data for approved requests, and integration of imaging data with other consortium data.
5. Ongoing coding of CDE imaging data.
6. Annual refresher training and monitoring of site compliance with SOP
7. Continue to participate in joint meetings with the PLS study team, Data Core, Biostatistics Core, and Biomarker Core.
8. Continue to assist in sequence parameter adjustment following software and hardware upgrades or changes.
9. Completion of additional manuscripts which are currently in preparation

STUDIES

Prospective Longitudinal Study: In the next year, the Prospective Longitudinal will accomplish the following:

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

Retrospective Database Study: In the next year, the Retrospective Database Study will accomplish the

following:

1. Manuscripts examining the risk and resiliency for dementia after TBI, TBI and risk of stroke, and the dementia and TBI meta-analysis will be published.
2. We will continue the development of a prognostic model for dementia and mortality after TBI and begin drafting the manuscript.
3. Initiate collaboration with Dr. Dismuke examining health utilization and comorbidities after TBI
4. We will start other new collaborations with investigators on novel projects with our database of more than 2.2 million Veterans.
5. 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 Paper focused on substance use disorder in distinct TBI phenotypes.
2. Complete LCA analyses of DoD data and DoD+VA data and submit paper on DoD LCA analyses.
3. Complete substance use disorder phenotypes and draft paper.
4. Add to dataset as data become available.
5. Continue to work on getting server behind VA firewall to facilitate machine learning analysis.
6. Examine feasibility of incorporating 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. Merge Theater type of injury (battle/non-battle), exposure (blast/non-blast) and outcome (return to duty, quarters, evacuated, etc.) with Phenotype data
2. Complete incorporation of DoD and VA utilization and cost data as well as theatre data on injuries and outcomes as well as MTF data on sick days into Phenotype data
3. Publish TBI-Renal Failure VA Cost Study
4. Submit Social Determinants of Service-Connected TBI and VA Compensation analysis
5. Finalize association of 18 categories of PLS weapons and other exposures with DoD and VA costs analysis
6. Examine associations of TBI, SM and veteran demographics and military characteristics with DoD and VA costs.

Novel Neuroimaging Study: In the next year, the Novel Neuroimaging Study will accomplish the following:

1. Continue to conduct phantom testing with the diffusion phantom to collect data for data harmonization.
2. Complete additional planned work with colleagues at Brigham and Women's Hospital and through the ENIGMA consortium who are developing additional harmonization methods.
3. Continue to critically examine the impact of different aspects of the analysis, including use of distortion correction and various aspects of pre-processing.
4. Perform additional analyses using machine learning and other advanced statistical techniques.
5. Continue to work with other consortia and military-relevant groups (e.g., ENIGMA, InTBIR, TRACK-TBI) to collaborate on data aggregation and analysis.
6. Complete additional planned expansion on the white matter hyperintensity analysis program developed under CENC and also multimodal analysis using 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 4 (of 4 total for this project), as follows:

1. Obtain pre-deployment specimens from DoD biorepository, as available and analyze pre-injury candidate biomarkers and correlate with post-injury lab measures.
2. Correlate plasma biomarker results with Neuroimaging and neurocognitive outcomes in collaboration with LIMBIC Cores and prepare results for dissemination.
3. Identify subsets of Prospective study with TBI neurodegenerative outcomes (e.g. dementia, sleep disorders, epilepsy) and analyze relevant biomarkers in these sub-cohorts
 - Complete current collaborative analyses, as follows:
 - Cohort analysis- 7 proteins & outcomes

- DTI-NfL, collaboratively with Neuroimaging
 - Volumetrics-NfL, collaboratively with Neuroimaging
 - Big Data, collaboratively with Neuroimaging and Informatics
 - rsfMRI- sleep dysfunction, collaboratively with Neuroimaging
 - Continue correlations of candidate prognostic biomarker correlations with symptoms and outcomes
- Correlations planned for Year 3 of SOW
- ***Milestone:** Carry out blood and saliva biomarker assays from all subjects with baseline specimens in the biorepository.*
 - ***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).*
 - ***Milestone:** 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: Initiate GWAS project with GAIN through the Broad Institute.
- Study 5: Initiate epigenetic study and plan for assays, and analyses

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, exosomal 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.
 8. Poor sleep that is associated with inflammation

Data and Biostatistics Core: The procedures (i.e., data request process, web data dictionary, analytic dataset development) and systems (i.e., Study Portal) developed by the DBC to support the PLS and the LIMBIC-CENC

consortium at large can be applied to other university-VA-DoD research partnerships.

Prospective Longitudinal Study: **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 of highlights from new scientific findings from manuscripts that were published or submitted for publication during the past reporting year of LIMBIC (Oct 01, 2021 to Sep 30, 2022):

Highlights from PLS:

- New evidence that cross-sectional analysis does not support an association between remote mTBI(s) alone and objective cognitive problems in the average Veteran or SM.
 - Clinical Translation: A holistic healthcare approach including comorbidity assessment is indicated for patients reporting chronic cognitive difficulties after mTBI(s), and strategies for addressing misattribution may be beneficial.
 - Research Translation: Future study is recommended to assess phenotypes (e.g. cognitive impaired) and longitudinal decline from potential neurodegeneration.
- New evidence that PTSD symptoms, combat exposure, pain interference, and hazardous alcohol use are significantly associated with anger. Neither self-reported sleep quality nor OSA risk moderated their relationships.
 - Clinical Translation: There is an urgent need for integrated anger treatments that target PTSD, pain, and alcohol use.
 - Research Translation: Future research should examine objective measures of sleep quality and OSA as potential modifiable mediators of anger and treatment targets.
- New evidence that heterogeneous sensory phenotypes for balance control are associated with distinct clinical characteristics, symptom severity, and physical and cognitive functioning.
 - Clinical Translation: By recognizing these types of balance deficits that involve heterogeneous sensory dysfunction in Veterans and SMs, rehabilitation programs can be tailored to the nuances of each individual's sensory phenotype.
- New evidence that although all combat-exposed SM/Vs with PTSD and a positive mTBI history, even if very remote, had the highest rates of chronic comorbidity symptoms including depression, pain, and sleep apnea risk.
 - Clinical Translation: It is especially critical to provide SM/Vs with PTSD and a positive mTBI history ongoing monitoring and intervention for chronic symptom and comorbidity burden in order to maximally improve their quality of life.
- New evidence that some, but not all, dementia cases identified by ICD coding among Veterans under 65 years old partially have lower functional status, QoL, and cognitive test scores
 - Research Translation: 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. This information will aid interpretation of future studies using these ICD codes.
- New evidence that EEG N200 potentials are reduced in those with any mTBI exposure, while P50 is enhanced and N100 and N200 reduced in repetitive mTBI, with the N200 showing the largest amplitude change and also strongly associated with symptoms of depression and anxiety, and hearing deficits.
 - Clinical/Research Translation: Auditory evoked 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.
- New evidence that TBI-like symptom severity on the Neurobehavioral Symptom Inventory (NSI) is highly correlated with PTSD symptoms in those with or without mTBI history. Symptom clustered similarly (somatosensory, affective, cognitive, and vestibular) regardless of mTBI and PTSD status.
 - Clinical/research translation: NSI symptom clusters are broadly valid for future research and may serve as useful clinical constructs for clinical evaluation and treatment
- New evidence that mild TBI history has no association with abnormalities on a commonly-used NED serum lab screen, and has no association with rates of growth hormone deficiency, hypothyroidism or male hypogonadism in treatment records. Lab screen findings are also unrelated to any clinical feature (fatigue, depression, cognitive symptoms, executive function, processing speed).

- **Clinical Translation:** The clinical use of this commonly-used NED screen to specifically assess for late effects of mTBI is highly questionable and not supported by this data.
- **Research Translation:** Large case-control studies that incorporate definitive NED testing are needed to determine whether mTBI(s) alone elevate one's risk for chronic NED and how best to select patients for comprehensive testing.
- New evidence that engaging in regular aerobic activity is associated with better life satisfaction and perceived overall health status among combat-exposed SMs and Veterans with positive mTBI histories. A lack of group differences for the primary cognitive performance measures may have been due to study design limitations including cross-sectional approach and self-report of exercise. Exploratory analyses did suggest a positive association with working memory and verbal fluency.
 - **Clinical Translation:** To maximize their overall well-being, SMs and Veterans with chronic mild TBI should engage in at least some level of regular aerobic exercise.
 - **Research Translation:** Future longitudinal analyses should seek evidence of objective cognitive enhancement or preservation not demonstrated with this cross-sectional analysis.

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

Phenotype Study: TBI and TBI severity were associated with all-cause mortality and specific types of mortality. There was a dose response relationship with moderate/severe TBI having a greater relationship with mortality rates over all and for specific causes of death than mTBI, which in turn had higher mortality rates than those with no TBI and the general population. We also see that there is differential mortality by TBI and deployment status. Deployment status was associated with significantly lower mortality suggesting a healthy deployer effect. We are working on analyses to examine the interaction between TBI history and deployment status. Our finding that TBI is associated with cardiovascular disease (CVD) and death is an important finding that warrants prevention/behavioral approaches to reduce risk for CVD. Our finding that individuals who screened positive for TBI but did not receive a comprehensive TBI evaluation (CTBIE) had outcomes similar to individuals with CTBIE and confirmed TBI, these individuals may benefit from a remotely delivered CTBIE where they can be connected to services based on findings of the clinical encounter.

What was the impact on other disciplines?

Biomarkers Core: Study findings show that within TBI cohorts, there are a number of biomarkers that relate to chronic symptoms, including NfL. This finding expands the possible role of NfL as a marker of neurological risk that should be examined beyond this study.

Health Economics Study: Worked with Ralph Depalma, MD and team to petition ICD 10 code for Primary Blast Injury to the Brain. The new code will be implemented in ICD-10 by the CDC in October 2022. Our findings regarding the high prevalence of TBI service connected disability in Pacific Islanders and Native Americans led us to acknowledge that VA did not yet have a special geographic designation for Native American/Tribal Lands/Reservations. We undertook research and outreach to the US Department of Labor to obtain zip codes for Tribal Elders and Leaders to incorporate into VA databases. We merged COVID-19 data from VINCI with the PLS study participants to identify a cohort of COVID-19 positive veterans that can be followed in a newly funded Long-COVID TBI study (PI Cifu). We examined COVID-19 hospitalization cost

data in VA and DoD to support the new TBI-COVID-19 study. We worked with TBI Model Systems to submit a study examining the association of Post Traumatic Amnesia with First Year VA Hospitalization Costs as lead author. We worked as co-I with TBI Model Systems to submit studies on TBI Rehabilitation needs and employment after TBI. We worked as co-I with Walter Reed to submit a study on Active Duty Military Treatment Facility Costs of TBI and Mental Health Conditions. We submitted a VA/DoD JIF project with a DoD partner from Uniformed Services University of the Health Sciences to create a DoD/VA Dashboard of Hospitalization Costs based on AHRQ criteria as well as Outpatient Costs.

Prospective Longitudinal Study: The range of KT products developed and available on the LIMBIC-CENC website are intended to reach a range of disciplines and audiences. The LIMBIC CAB provides ongoing input on how best to reach wide audience groups. Ideas from the Government Steering Committee (GSC) have also been embraced and used to shape our KT planning. The audience for the national meeting presentations (such as ACRM) and national podcasts 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. See KT section of this report for more details.

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

3. Our joint work with DoD colleagues has strengthened partnerships as well as understanding of both DoD and VA systems of care.

5. CHANGES/PROBLEMS:

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.

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

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

Biomarkers Core:

With a change in CNRM organization and leadership, CNRM conveyed to LIMBIC leadership in March 2022 that they could not renew the MOU that delineated shared space and personnel between the CNRM and LIMBIC-CENC biorepository any longer. Specifically, they clarified that they could not support the LIMBIC Biorepository DNA extractions and APOE genotyping, along with additional faculty and staffing challenges. A series of discussions were held between March and September 2022 with CNRM, LIMBIC, USU/DoD, VA and GSC personnel and a recommendation was made to GSC leadership and the DoD Program Officer to relocate the LIMBIC Biomarker Core to WRAIR. The required paperwork and regulatory materials were submitted.

As a result, no DNA extractions were performed after all LIMBIC Biorepository functions were centralized at the Rockledge USUHS off-site location (HJF and CNRM biorepository) in September 2021. Currently, DNA extraction and APOE genotyping has been carried out on 1,383 PLS participants and 490 are pending. This has not delayed the GWAS study as a minimum of 2,000 DNA samples are required for analysis. Under the Biomarker Discovery Projects, proteomic (4-plex: NfL, GFAP, tau, UCHL-1) assays were delayed due to CNRM restructuring and staffing, but all samples available for testing were completed by 30 September 2022 at the Rockledge campus.

Action/Plan to Perform all tasks under Biomarker Core SOW that were either delayed or no longer able to be carried out under a MOU with CNRM: Relocate LIMBIC Biomarker Core to WRAIR once fully approved by LIMBIC Leadership and GSC.

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

1. The biorepository protocol for storage of samples was submitted to Walter Reed Army Institute of Research (WRAIR) on 9/29/2022. This is required to initiate material transfer agreements to move samples from the Center for Neuroscience and Regenerative Medicine (CNRM) to WRAIR. Dr. Capaldi

will be the site primary investigator (PI).

2. We expect the protocol to be reviewed, and then edits to be made, to address issues, and then to have the protocol be approved by 10/30/2022.
3. Once the protocol is approved, then MTAs will be executed to send samples, within freezers from CNRM to WRAIR by 11/15/2022.
4. A cooperative research and development agreement (CRADA) is in development, which will include Drs. Gill and Kenney, as well as WRAIR, and investigators at Virginia Commonwealth University (VCU), including LIMBIC-CENC PI, Dr. Cifu. The CRADA will provide an avenue to communicate expectations, and regulations regarding operation of the LIMBIC-CENC biomarker core at WRAIR.
5. There will be 2 individuals supported by LIMBIC-CENC who will be relocated to have their work station at WRAIR.
6. Drs. Gill and Kenney will work with Dr. Cifu to communicate a change in shipping address for the biomarker core, as well as required changes to institutional review boards (IRB), at each of the blood collecting sites to communicate the change in the address and physical location of the biorepository.
7. Analyses of samples, including DNA extractions and genotyping, as well as epigenetic profiles related to long-term samples will be initiated by 01/2023.

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

Prospective Longitudinal Study:

- There have been ongoing challenges with Task 1 (maintaining research consortium staff levels) due to the COVID pandemic, current/recent macroeconomic conditions, and changing expectations of workers (e.g. increased desire for telework and flexible hours. To address this, Dr Walker, Dr Cifu and the VCU Coordinating Core have worked closely with all sites to offer and provide competitive compensation and enabling remote data collection. Another approach has been to foster more tighter bonds and interpersonal connections across sites and with the central cores. We deployed a new regular agenda item for our biweekly PLS all-sites Zoom meeting to meet and greet staff at all sites which has been very well-received. Each meeting, a different site is highlighted with brief presentations by each site investigator and staff-member on their background, interests, hobbies and other aspects of their professional or personal life they want to share. We have continued to provide resources and direct training for new staff hires. Among higher level positions, we successfully onboarded a new site PI at Fort Belvoir site (Dr. Patricia Hantsch).
- For PLS Major Task 7, eye-tracking data collection and storage, we dealt more with the challenges of cross-walking data between legacy EyeLink equipment to the currently used state-of-the art and easier to use and analyze RightEye equipment. The PLS leadership and our DBC continued to work with our SME on analysis related to cross-walk development, with a final product pending at this time.
- Our hearing testing data collection and storage (PLS Major Task 9) is going very well, but there has continued to be challenges from low frequency noise (this challenge is not unique to our study) and the on-size-fits-all bone oscillator head-band. To address these, a noise meter software was deployed to all sites to facilitate quality control, and a larger size headband for the bone oscillator was deployed to all sites to accommodate participants with very large head circumferences.
- For PLS Major Task 13 (recruit not less than 3000 subjects), excellent progress was made despite the ongoing and evolving nature of the COVID pandemic which continues to hamper recruitment and enrollment activities. We addressed this challenge by continuing our well-established practice of consent/enrollment site targets/metrics reporting with positive and negative feedback, coaching and problem solving in multiple formats including written score cards, site-specific audio-visual meetings, and featuring it prominently on every bi-weekly PLS all-sites meeting. During this reporting year, the only site still prohibited by local

authorities from in-person research activities (Boston site) was permitted to restart their in-person research activities. Thus, all eleven PLS sites have been and continue to actively enroll. Our enrollment numbers have been steadily ramping up on average on a monthly basis, and for the September of 2022, we reached our target total enrollment goal for the first time since the COVID outbreak first curtailed in-person research. Because of conservative monthly targets, we remain on track to meet our final end of funding-cycle target.

- Participant retention (PLS Major Task 14) is a continual challenge for any longitudinal clinical study. We continue to seek new opportunities for improvement with new strategies and refinements with sharing of recruitment and retention obstacles and failures across all sites of the PLS. Additionally, during the past year we launched a participant-burden reduction project. The goal was to identify any pieces of the assessment battery that are redundant or have no/trivial scientific value. This project has been a major work effort by Dr Walker and the LIMBIC DBC to conduct tertiary data quality analyses and comparisons across instruments. This work has so far led to our recommendation to eliminate one instrument (UPDRS), with additional formal recommendations pending at the time of this report.

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

Changes that had a significant impact on expenditures

Biomarkers Core:

As described above, a change in CNRM organization and leadership, CNRM conveyed to LIMBIC leadership in March 2022 that they could not renew the MOU that delineated shared space and personnel between the CNRM and LIMBIC-CENC biorepository any longer. Specifically, they clarified that they could not support the LIMBIC Biorepository DNA extractions and APOE genotyping, along with additional faculty and staffing challenges. A series of discussions were held between March and September 2022 with CNRM, LIMBIC, USU/DoD, VA and GSC personnel and a recommendation was made to GSC leadership and the DoD Program Officer to relocate the LIMBIC Biomarker Core to WRAIR. The required paperwork and regulatory materials were submitted.

As a result, no DNA extractions were performed after all LIMBIC Biorepository functions were centralized at the Rockledge USUHS off-site location (HJF and CNRM biorepository) in September 2021. Currently, DNA extraction and APOE genotyping has been carried out on 1,383 PLS participants and 490 are pending. This has not delayed the GWAS study as a minimum of 2,000 DNA samples are required for analysis. Under the Biomarker Discovery Projects, proteomic (4-plex: NfL, GFAP, tau, UCHL-1) assays were delayed due to CNRM restructuring and staffing, but all samples available for testing were completed by 30 September 2022 at the Rockledge campus.

Significant changes in use or care of human subjects

Prospective Longitudinal Study: Minor changes in informed consent language for the PLS were reported under

the PLS section for Accomplished on Major Task 2.

6. PRODUCTS:

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

Journal publications.

See attached **Appendices #5 & #6** for the Publication Tracker and Publications.

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

See attached **Appendices #5 & #6** for the Publication Tracker and Publications.

Other publications, conference papers and presentations.

See attached **Appendices #5 & #6** for the Publication Tracker and Publications.

- **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/](https://www.limbic-cenc.org/index.php/for-scientists-and-clinicians/data-cube/)). 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 data 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**

Nothing to 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 Stewart was added as a Co-PI for the Phenotype Study.
- Dr. Patricia Hanstch assumed the role of PI at the Fort Belvoir Prospective Longitudinal enrollment site upon LtCDR LaCroix' departure.

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: