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TITLE: Late-Life Consequences of TBI and Military Service: A Population-Based Study

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13. SUPPLEMENTARY NOTES

14. ABSTRACT (Enter a brief (approximately 200 words) summary of the most significant finding during the research period).

The goal of this interdisciplinary project is to comprehensively examine the chronic health consequences of TBI and military service by leveraging extensive existing data resources from a well-defined large-scale population-based longitudinal cohort study of veterans and civilians, the Adult Changes in Thought (ACT) study. In preparation for this proposal, we implemented an expanded TBI and military service questionnaire to characterize lifetime history of TBI and other head trauma exposures, duration and branch(es) of military service, rank, and combat exposure. We have not been able to use these new data on military service or TBI history in any prior analyses. ACT is a phenomenal resource for studying the associations of military service and TBI on a wide array of health outcomes. Our proposal addresses the overarching hypothesis that TBI and military service have independent and joint effects on AD/ADRD, late-life cognition, medical health, functional independence, and mood. We will explore this hypothesis through the following Specific Aims: We will determine the impact of TBI and military service on clinical & pathological AD/ADRD outcomes. a. We will test the hypothesis that TBI and military service are independently and jointly associated with risk for clinical AD, dementia, and Parkinson's disease. b. We will use autopsy data to determine associations of TBI and military service with pathologically confirmed AD (Braak stage and CERAD score), other pathological indices of ADRD and chronic traumatic encephalopathy (CTE) using quantitative assessments of beta-amyloid, paired-helical filament tau, alpha-synuclein, and phospho-TDP-43and additional endpoints including Thal phase, microinfarcts, amyloid angiopathy, and atrophy.

15. SUBJECT TERMS (Key words or phrases identifying major concepts in the report)
Traumatic brain injury; head injury; Alzheimer's disease; dementia; military; veteran; neuropathology; cognition; health; mood; epidemiology

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a. REPORT	**b. ABSTRACT**	**c. THIS PAGE**	Unclassified	30	**19b. TELEPHONE NUMBER** *(include area code)*
Unclassified	Unclassified	Unclassified			

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

The overall objective of this research is to comprehensively examine the chronic health consequences of TBI and military service. To that end, this study seeks to evaluate the impact of TBI and military service on clinical and pathological AD/ADRD outcomes; to evaluate the associations between TBI and military service on late life cognitive, physical, and emotional health; and to characterize clinical dementia phenotypes among individuals with and without TBI and military service who are diagnosed with dementia during life. We use existing data resources from a population-based cohort study of veterans and civilians to address the overarching hypothesis that TBI and military service have independent and joint associations with clinical and pathological signatures of AD/ADRD, late-life cognition, medical health, functional independence, and mood.

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

Traumatic brain injury; head injury; Alzheimer's disease; dementia; military; veteran; neuropathology; cognition; health; mood; epidemiology

3. **ACCOMPLISHMENTS:**

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

Major Goals/Milestones	***Target Date (months)***	***% Complete***
Major Task 1: Administrative and Regulatory Tasks		
• Project Kickoff meeting with Investigators and Advisory Committee	month 1	100% complete
• Advisory Committee teleconference; ongoing advising as needed	month 1; annually	100% complete
• Finalize human subjects protocols and submit modification for UW and KPWHRI	month 0	100% complete
• Seek and obtain approval from U.S. Army Medical Research and Materiel Command (USAMRMC) Human Research Protection Office (HRPO)	months 0-3	100% complete
• Prepare and submit quarterly progress reports to funding	months	ongoing

agency	2-48	
Major Task 2: Collect enhanced TBI and Military service exposure data on ACT participants		
• Collect Brain Injury Screening (BISQ) and Military Service questions with living eligible ACT participants	months 1-3	100% complete (with non-DoD funds)
• Complete Brain Injury Screening Questionnaire and Military Service questions with proxies of ACT participants who come to autopsy prior to completing exposure questionnaires at an ACT study visit (estimated n=50).	months 1-12	100% complete (with non-DoD funds)
• Enter and check all TBI and Military service data into local KPWHRI databases	months 1-12	100% complete
• Use data from BISQ, standard ACT TBI screen, and medical records to identify cases (with TBI exposure) and controls (no evidence of TBI exposure). Characterize TBI severity using standard criteria.	months 3-36	60% complete
• Use data from standard ACT TBI screen to identify cases (TBI with LOC, characterized by duration of LOC) and controls (no TBI with LOC).	months 3-12	100% complete
• Use data from the BISQ (n~1500) to identify cases and controls.	months 12-36	100% complete
• Use data from the BISQ to characterize the injury, etiology, chronicity and severity based on published criteria.	months 12-36	20% complete
• Use data from the medical record abstraction to identify cases and controls in the autopsy cohort (n~660).	months 12-36	70% complete
• Use combined data from standard ACT TBI screen, BISQ and medical record to refine the subsample of controls (no TBI exposure) to include only individuals with no evidence of TBI based on any data sources.	months 3-36	10% complete
• Use data from BISQ and ACT employment questions to identify those with and without military service.	months 12-24	100% complete
Major Task 3: Perform Histelide assays for Aβ1-42, PHF-tau, α-synuclein, and phospho-TDP-43 in selected regions for ACT autopsy cohort (n=660 have died and provided consent for brain autopsy).		
• <u>Complete Histelide assays:</u> Cut sections at 5μm thick on a microtome from a FFPE block (steps 1-2) and place onto a charged microscope slide	months 1-48	35% complete

• Deparaffinize and rehydrate sections. Incubate sections in blocking solution. (step 3)	months 4-48	30% complete
• Wash slides; incubate with alkaline phosphatase-conjugated secondary antibody. (step 4)	months 4-48	30% complete
• Wash slides; incubate with p-nitrophenyl solution. (step 5)	months 4-48	30% complete
• Remove slides, wash and place in NBT/BCIP and cover slip. (step 6)	months 4-48	30% complete
• Trace gray and white matter area using Nikon 90 microscope and Stereo Investigator software	months 4-48	30% complete
• Complete data processing, data production and quality assurance	Months 6-48	10% complete
• Calculate PNPP concentration and normalize to area of gray and white matter on slide	months 4-48	10% complete
• Use IgG isotype stains to address non-specific antibody staining.	months 4-48	10% complete
• Ensure uniform data coding and establish data transfer portal	months 6-48	Not yet started
Major Task 4: Perform quantitative neuroimaging analysis on existing high resolution MRI scans conducted in ACT Participants (n=250) through other study protocols which were limited to ACT participants who had provided consent to brain autopsy and had no contraindications to MRI.		
• Complete volumetric segmentation and analysis on existing research scans in ACT participants	months 1-20	100% complete
• Pull all scans from UW Imaging Archive	months 1-20	100% complete
• Unpack DICOMs and extract MEMPRAGE nifti	months 1-20	100% complete
• Complete Freesurfer post-processing analysis for each extracted MEMPRAGE (including automated segmentation of the sub-cortical anatomy and parcellated regions of cortex. 198 regions are segmented in total and volume data from these regions is extracted for each case for use in analysis planned under Aim 3.)	months 1-20	100% complete
• Complete quality assurance of the post-processing which includes review of QA/QC measures including noise values, null values, fit measures, etc. and complete visual	months 1-20	100% complete

inspection in each orthogonal plane of the segmentation and apply control points where needed to assure correct alignment of the automated Freesurfer program.		
Major Task 5: Process data sets for proposed analyses		
• Receive ACT data sets from KPWHRI staff	months 1-12	95% complete
• Ensure uniform data documentation is in place, perform quality control procedures	months 1-12	95% complete
• Review data dictionaries and other study documentation to ensure thorough and complete data request	months 1-12	95% complete
• Review manifest of received data compared to data request to ensure completeness of data received	months 1-12	95% complete
• Receive ACT data sets from UW Neuropathology; combine with clinical data sets	months 6-40	30% complete
• Careful review of data sets; identifying discrepancies and addressing them; confirming specific data received (e.g. documenting which antibodies are which brain regions for Histelide data); development of notes fields and annotation of data sets; generating reports on data completeness and reviewing with Neuropathology staff; reconciliation of discrepancies between expected and received data.	Months 6-40	30% complete
Major Task 6: Determine the impact of TBI and military service on clinical AD/ADRD outcomes. We will test the hypothesis that TBI and military service are independently and jointly associated with risk for clinical AD, all-cause dementia, and PD.		
• Perform analyses on n=5400 cases with and without TBI and military exposure	months 2-24	80% complete
• Conduct primary analyses using ACT's TBI exposure data (since it is available on >99% of the cohort).	months 2-14	90% complete
• We will use Cox proportional hazards models with age as the time scale to quantify associations between TBI and/or military service with incident all cause dementia, AD, and PD. Each model will be adjusted for baseline age, sex, education, and the presence of any APOE ε4 alleles. We will consider effect modification by age at baseline, and by APOE 4 allele status, to understand whether our findings differ by these characteristics.	months 2-14	90% complete
• We will test the robustness of our findings to residual confounding, missing data, misclassification and selection	months 12-24	90% complete

bias using several sensitivity analyses.		
• Conduct secondary analyses using the more sensitive BISQ (should improve the classification accuracy of exposed vs. unexposed, may not be available for all ACT participants).	months 12-24	10% complete
• Secondary analyses will use Cox proportional hazards models with age as the time scale to quantify associations between TBI and/or military service with incident all cause dementia, AD, and PD.	months 12-24	Not yet started
Major Task 7: Specific Aim 1b. We will use autopsy data to test the hypothesis that TBI and military service are independently and jointly associated with risk for postmortem AD based on NIA-AA Guidelines. We will determine associations of TBI and military service with pathological indices of ADRD including ß-amyloid, PHF-τ, α-synuclein, and phospho-TDP-43 in multiple brain regions.		
• Perform analyses on data from autopsy cases with and without TBI and military exposure.	months 12-48	20% complete
• Primary analyses for Aim 1b will use separate regression models to estimate the association between TBI and/or military service and each of our neuropathology outcomes. We will control for age at death, age at enrollment, sex, education and the presence of APOE ε4 alleles.	months 12-48	20% complete
• Models for TBI or military service main effects will be adjusted for non-primary exposure of interest as in Aim 1a.	months 12-48	20% complete
Major Task 8: Specific Aim 2. We will evaluate the associations between TBI and military service on late life cognitive, physical and emotional health. We will test the hypothesis that TBI and military service are associated with accelerated cognitive decline, greater functional impairment, greater depression, and greater chronic disease comorbidity.		
• Perform analyses on n=5,400 cases with and without TBI and military exposure.	months 19-42	15% complete
• We will use modern psychometric approaches to operationalize cognitive functioning (overall and domain-specific) in ACT participants using item-level CASI data gathered at each longitudinal study visit.	months 19-24	100% complete
• We will use linear mixed models adjusted for baseline age,	months 24-40	20% complete

sex, education and APOE e4 alleles, with time in study as the time scale, to estimate the effect of TBI and/or military service on cognitive trajectories.		
• We will define physical functioning using data on ADL difficulty (including walking, bathing, dressing, transferring, feeding and toileting).	months 20-28	100% complete
• We will operationalize depressive symptoms using data from the CESD.	months 20-28	50% complete
• We will define medical co-morbidity based on medications (the RxRisk index) and separately based on ICD-9/10 codes (the Klabunde comorbidity index).	months 20-30	30% complete
• We will use regression models to evaluate the relation between TBI and/or military service with the presence and severity of co-morbidities, physical outcomes, and CESD scores at baseline using linear, logistic or Poisson regression models. We will then exclude all persons with significant co-morbidities, physical disability, or depression at baseline to assess the relationship between prior TBI and incidence of these outcomes using Cox proportional hazards models or parametric survival models.	months 28-40	60% complete
• We will conduct sensitivity analyses to address (a) residual confounding by sex, (b) missing data, (c) misclassification due to use of proxy respondents for the BISQ, (d) selection bias, and (e) differential sensitivity of different methods to identify TBI exposure, as described above (Aim 1a). This will include analysis of associations of TBI and military service as defined by the BISQ on Aim 2 outcomes.	months 30-42	10% complete
• Prepare results for presentation and publication.	months 36-48	10% complete
Major Task 9: We will perform gene x TBI and gene x military service analyses to identify interactions between these exposures and dementia outcomes.		

• Review literature for each outcome to identify relevant genes	months 3-36	Ongoing
Major Task 10: Specific Aim 3. We will test the hypothesis that post-TBI neurodegeneration has features that are distinguishable from AD/ADRD by comparing extensive neurobehavioral and quantitative neuroimaging data collected on individuals with and without TBI and military service history.		
• Perform analyses on n=1,598 cases who underwent a comprehensive dementia diagnostic evaluation.	months 19-44	Not yet started

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.

Major activity 1: Administrative and Regulatory Tasks

1. Specific objectives:
    a. Seek and obtain approval from U.S. Army Medical Research and Material Command (USAMRMC) Human Research Protection Office (HRPO)
    b. Prepare and submit quarterly progress reports to funding agency
2. Significant results or key outcomes: All objectives were completed within the estimated timeframe.
    a. HRPO approvals were obtained for all sites: ISMMS approved on 5/18/18, UW approved on 6/14/18, KPWHRI approved on 5/21/18, GWU approved on 1/18/18, UW cadaver activity approved on 6/14/18, and ISMMS cadaver activity approved on 5/18/18. Each study site is responsible for sending updated human subjects research approvals to the funding agency.
    b. On 10/17/2019, UW received continuing approval from local IRB.
3. Other achievements: N/A
4. Goals not met: N/A

Major activity 2: Collect enhanced TBI and Military service exposure data on ACT participants

1. Specific objectives:
    a. Enter and check all TBI and Military service data into local KPWHRI databases.

b. Use data from BISQ, standard ACT TBI screen, and medical records to identify cases (with TBI exposure) and controls (no evidence of TBI exposure). Characterize TBI severity using standard criteria.
c. Use data from standard ACT TBI screen to identify cases (TBI with LOC, characterized by duration of LOC) and controls (no TBI with LOC).
d. Use combined data from standard ACT TBI screen, BISQ and medical record abstraction to refine the subsample of controls (no TBI exposure) to include only individuals with no evidence of TBI based on any data sources.

2. Significant results or key outcomes: Progress on task 'a' is complete and these data are now available for use. Task 'b' is nearly complete; the Data Core is writing code to define exposure and exposure severity based on widely used TBI definitions using all available data. Task 'c' is complete; we have constructed the variables from the standard ACT TBI screen to identify cases/controls (defined by TBI and duration of LOC). Task 'd' is well underway and extensive data checking is in progress to ensure accuracy of case classification. We are considering the utility of supplementing medical record information with data about sport or military participation gathered through obituary search.
3. Other achievements: N/A
4. Goals not met: N/A

Major activity 3: Perform Histelide assays for Aβ1-42, PHF-tau, α-synuclein, and phospho-TDP-43 in selected regions for ACT autopsy cohort (n=660 have died and provided consent for brain autopsy).

1. Specific objectives:
    a. Complete Histelide assays: Cut sections at 5μm thick on a microtome from a FFPE block (steps 1-2) and place onto a charged microscope slide.
    b. Complete data processing, data production and quality assurance.
2. Significant results or key outcomes: In previous quarters, we had already begun organizing cases and pulling blocks as preparatory work, optimized extraction and detection protocols, and began multiplexed Histelide analysis on frontal cortex samples. In the current reporting period, after a 3rd party incident that resulted in the closure of the research building and delay of 2 months for relocation (during which all billing was ceased), our efficient protocols have ensured that progress remains on track. We continue to process the tissue and slides in our workflow, as indicated in the progress report. The progress report reflects completeness for all brain regions.
3. Other achievements: N/A
4. Goals not met: N/A

Major activity 4: Perform quantitative neuroimaging analysis on existing high resolution MRI scans conducted in ACT Participants (n=250) through other study protocols which were limited to ACT participants who had provided consent to brain autopsy and had no contraindications to MRI.

1. Specific objectives:
    a. Complete volumetric segmentation and analysis on existing research scans in ACT participants
        i. Pull all scans from UW Imaging Archive
        ii. Unpack DICOMs and extract MEMPRAGE nifty
        iii. Complete Freesurfer post-processing analysis for each extracted MEMPRAGE

b. Complete quality assurance of the post-processing which includes review of QA/QC measures including noise values, null values, fit measures, etc. and complete visual inspection in each orthogonal plane of the segmentation and apply control points where needed to assure correct alignment of the automated Freesurfer program.

2. Significant results or key outcomes: The Imaging Core has located and pulled imaging datasets from multiple storage locations that will be used for analysis. Volumetric segmentation is complete; all DICOMs are unpacked and extraction of MEMPRAGE is complete. Post processing is complete. Planned work for this major activity was completed early per the SOW.
3. Other achievements: N/A
4. Goals not met: N/A

Major activity 5: Process data sets for proposed analyses

1. Specific objectives:
    a. Receive ACT data sets from KPWHRI staff
        i. Ensure uniform data documentation is in place, perform quality control procedures
        ii. Review data dictionaries and other study documentation to ensure thorough and complete data request
    b. Review manifest of received data compared to data request to ensure completeness of data received
    c. Receive ACT data sets from UW Neuropathology; combine with clinical data sets.
2. Significant results or key outcomes: Dr. Kristen Dams-O'Connor and the biostatistics core continue making progress, which is shared with the group during standing weekly data core calls. Drs. Laura Gibbons (UW) and Elizabeth Sanders (UW) and William Lee (KPWHRI) refined TBI exposure datasets based on standard ACT TBI screen and available BISQ TBI data. Drs. Dams-O'Connor and Power (GWU) have implemented the analytic plan for first planned analyses and manuscript and are now focusing on conducting the sensitivity analyses outlined in the SOW (Aim 1a). Drs. Dams-O'Connor and Power tested TBI ascertainment code and expanded code to implement sensitivity analyses around exposure severity and data source. Dr. Power developed operational definitions for variables around childhood SES and era of military service for use in multiple analyses. Drs. Rod Walker (KPWHRI) and Dams-O'Connor continue refining the codebook for the core study dataset, which will facilitate accurate use of variables across analysts. Dr. Gibbons has begun analyses for Aim 1b after having completed extensive data checking in collaboration with Dr. Keene's team. Drs. Dams-O'connor, Kumar and Walker have made excellent progress on Aim 2 (CASI, CASI_IRT, ADLs, comorbidity scores, and CES-D). During the current quarter, we sought input from a neurologist with expertise in movement disorders to refine a claims- and medication-based definition of clinical Parkinson's disease for use in Aim 1a analyses. Further, calculation and refinement of updated disease comorbidity indices, which will reflect both ICD-9 and ICD-10 codes, is underway.
3. Other achievements: N/A
4. Goals not met: N/A

Major activity 6: Determine the impact of TBI and military service on clinical AD/ADRD outcomes. We will test the hypothesis that TBI and military service are independently and jointly associated with risk for clinical AD, all-cause dementia, and PD.

1. Specific objectives:
    a. Perform analyses on n=5400 cases with and without TBI and military exposure.
    b. Conduct primary analyses using ACT's TBI exposure data (since it is available on >99% of the cohort).
    c. We will use Cox proportional hazards models with age as the time scale to quantify associations between TBI and/or military service with incident all-cause dementia, AD, and PD. Each model will be adjusted for baseline age, sex, education, and the presence of any APOE ε4 alleles. We will consider effect modification by age at baseline, and by APOE 4 allele status, to understand whether our findings differ by these characteristics.
    d. We will test the robustness of our findings to residual confounding, missing data, misclassification and selection bias using several sensitivity analyses.

2. Significant results or key outcomes: Dr. Power has developed an analytical dataset derived from the core study dataset, and has undertaken work, including primary analyses and sensitivity analyses, in order to evaluate the robustness of the initial findings. Drs. Dams-O'Connor and Power have investigated a range of potential confounders that warrant inclusion in these analyses, and have developed an operational measure of a key confounder, early childhood advantage. Including this variable in our models represents an important advancement relative to existing literature. Dr. Power has also made data-informed recommendations on how to operationalize era of military service when using the primary ACT military service variable, which will be useful in future analyses. Dr. Power has now completed primary analyses for the AD and total dementia outcomes, including assessment of effect modification. We have completed robustness checks assessing model fit, proportional hazards assumption, residual confounding, and selection bias. Dr. Power has completed a first draft of the manuscript including findings on the question of the association between military service and both AD/ADRD and cognitive change.
3. Other achievements: N/A
4. Goals not met: We have not yet assessed associations with the PD outcome given continued work to develop this outcome (see progress in Major Activity 5 which now permits completion of this analysis). All other Major Activity #6 goals are complete.

Major activity 7: Specific Aim 1b. We will use autopsy data to test the hypothesis that TBI and military service are independently and jointly associated with risk for postmortem AD based on NIA-AA Guidelines. We will determine associations of TBI and military service with pathological indices of ADRD including ß-amyloid, PHF-tau, alpha-synuclein, and phospho-TDP-43 in multiple brain regions.

1. Specific objectives:
    a. Perform analyses on data from autopsy cases with and without TBI and military exposure.
        i. Primary analyses for Aim 1b will use separate regression models to estimate the association between TBI and/or military service and each of our neuropathology outcomes. We will control for age at death, age at enrollment, sex, education and the presence of APOE ε4 allele.

ii. Models for TBI or military service main effects will be adjusted for non-primary exposure of interest as in Aim 1a.

2. Significant results or key outcomes: Work is well underway; additional preliminary models have been run for existing neuropathological endpoints using standard ACT TBI and military service data. Military service is likely under-represented in these analyses as the standard ACT item querying this information queries longest occupations.
3. Other achievements: N/A
4. Goals not met: N/A

Major Task 8: Specific Aim 2. We will evaluate the associations between TBI and military service on late life cognitive, physical and emotional health. We will test the hypothesis that TBI and military service are associated with accelerated cognitive decline, greater functional impairment, greater depression, and greater chronic disease comorbidity.

1. Specific objectives:
   a. Perform analyses on n=5,400 cases with and without TBI and military exposure.
   b. We will use modern psychometric methods to create indices of cognition (IRT CASI), depression (IRT CES-D) and other outcomes as indicted.
   c. We will define medical co-morbidity based on medications (the RxRisk index) and separately based on ICD-9/10 codes (the Klabunde comorbidity index).
   d. We will use regression models, linear mixed models and/or cox models as appropriate, adjusted for baseline age, sex, education and APOE e4 alleles, with time on study as the time scale, to estimate the effect of TBI and/or military service on Aim 2 outcomes.
   e. We will conduct sensitivity analyses to address (a) residual confounding by sex, (b) missing data, (c) misclassification due to use of proxy respondents for the BISQ, (d) selection bias, and (e) differential sensitivity of different methods to identify TBI exposure, as described above (Aim 1a). This will include analysis of associations of TBI and military service as defined by the BISQ on Aim 2 outcomes.
   f. Prepare results for presentation and publication.
2. Significant results or key outcomes: Work under this activity is well underway. Analyses of associations of TBI and military service on ADL impairment and depression are nearly complete and manuscripts are in development. Dr. Power has completed analyses quantifying the impact of ACT TBI and military service measures with overall cognitive change using the IRT-CASI measure. We have begun to update an index of medical comorbidity and gathering input from project investigators and Advisory Committee members as needed to ensure appropriate use of available data.
3. Other achievements: N/A
4. Goals not met: N/A

Major activity 9: We will perform gene x TBI and gene x military service analyses to identify interactions between these exposures and dementia outcomes.

1. Specific objectives:
   a. Review literature for each outcome to identify relevant genes
2. Significant results or key outcomes: Work under this activity has now begun; preliminary analyses of associations of TBI with existing standard neuropath outcomes

have been conducted. Literature search is underway to identify additional potential genetic risk factors that warrant inclusion in these models.
3. Other achievements: N/A
4. Goals not met: N/A

Major activity 10: We will compare neurobehavioral and quantitative neuroimaging data collected on individuals with and without TBI and military service history among individuals who have come to dementia evaluation.

1. Specific objectives:
   a. Review literature for each outcome to identify relevant genes
2. Significant results or key outcomes: Work under this activity has not yet begun.
3. Other achievements: N/A
4. Goals not met: N/A

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

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

Nothing to report.

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

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

Nothing to report.

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

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

During the next reporting period, we plan to begin activities that we proposed in the Statement of Work that span the 24-36 month timeframe.

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

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

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

Nothing to report.

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

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

Nothing to report.

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

Describe ways in which the project made an impact, or is likely to make an impact, on commercial technology or public use, including:
- *transfer of results to entities in government or industry;*
- *instances where the research has led to the initiation of a start-up company; or*
- *adoption of new practices.*

Nothing to report.

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

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

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

Nothing to report.

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

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

Nothing to report.

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

During the reporting period, there was a backorder on the kit required to process the deparrafinized tissue. The Keene lab has continued work on tissue processing while waiting for the kits to arrive and as such will be able to catch up quickly once the materials are in hand.

Changes that had a significant impact on expenditures

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

During the time prior to HRPO approval the study team focused on prep-to-research work, thereby preventing the delay from impacting project expenditures.

Significant changes in use or care of human subjects, vertebrate animals, biohazards, and/or select agents

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

Significant changes in use or care of human subjects

Nothing to report.

Significant changes in use or care of vertebrate animals

No animal use research was performed to complete the Statement of Work.

Significant changes in use of biohazards and/or select agents

Nothing to report.

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

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

     Report only the major publication(s) resulting from the work under this award.

Nothing to report.

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

Nothing to report.

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

Nothing to report.

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

Nothing to report.

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

Nothing to report.

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

Nothing to report.

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

Nothing to report.

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

The Adult Changes in Thought study has become increasingly recognized as a data resource for investigators from multiple disciplines across the United States and beyond. In preparation for the current project, collection of detailed data on TBI exposure and military service was initiated. Those data have not previously been used in any prior analyses, and an early accomplishment of the current study team is to curate those data for use in the current project. The availability of detailed TBI and military exposure data in the ACT data repository will make possible new avenues of inquiry for future investigators interested in studying TBI and/or military service.

7. PARTICIPANTS & OTHER COLLABORATING ORGANIZATIONS

What individuals have worked on the project?

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

Example:

Name: Mary Smith
Project Role: Graduate Student
Researcher Identifier (e.g. ORCID ID): 1234567
Nearest person month worked: 5
Contribution to Project: Ms. Smith has performed work in the area of combined error-control and constrained coding.
Funding Support: The Ford Foundation (Complete only if the funding support is provided from other than this award.)

Name:	Kristen Dams-O'Connor, PhD.
Project Role:	PI (ISMMS)
Researcher Identifier (e.g. ORCID ID):	ORCID 0000-0002-2506-0216
Nearest person month worked:	3
Contribution to project:	Dr. Dams-O'Connor provided overall study oversight by leading in teleconferences with site PIs to ensure local and HRPO regulatory documentation is in place and to monitor progress across sites in accordance with the SOW. She convened weekly teleconferences with the Data Core to specify data management and analytic workflow across all study aims, contributed to drafting and documentation of Data Core Workflow plans, and worked with the Data Core to finalize data elements and annotated documentation for the core dataset to be used for the current study. She has overseen the delineation of analytic workflow plans and works closely with each Data Core analyst to implement analyses for aims 1a, 1b, and 2 and review preliminary results. Her team has led initial analyses for Aim 2 depression outcome, conducting group-based trajectory modeling to this research question. She has invited Advisory Committee members and other experts to attend project calls as needed to optimize data use and clinical accuracy of planned analyses. In this quarter, she held individual meetings with the Data Core members to review progress to date and to complete model refinement. She also began drafting manuscripts to report Aim 2 results to date.
Name:	John Crary, MD PhD.
Project Role:	Co-I (ISMMS)
Researcher Identifier (e.g. ORCID ID):	era Commons JC2892
Nearest person month worked:	1

Contribution to project:	Dr. Crary has coordinated with Dr. Keene to facilitate sharing of ACT autopsy information, and advised on optimization of tissue assays. Regular conference calls are now scheduled, as neuropathological work is well underway.
Name: ***Project Role:*** ***Researcher Identifier (e.g. ORCID ID):*** ***Nearest person month worked:*** ***Contribution to project:***	Paul Crane, MD MPH PI (UW) ORCID 0000-0003-4278-7465 1 Dr. Crane provided oversight to the UW research team to ensure progress across study milestones. He continues to consult on the specification of workflow plans and analytic strategy for Aims 1-2 within the Data core. He provided necessary input into plans for using KPW medication data for Aims 1-2 and oversaw IRB continuation.
Name: ***Project Role:*** ***Researcher Identifier (e.g. ORCID ID):*** ***Nearest person month worked:*** ***Contribution to project:***	C. Dirk Keene, MD PhD. Co-I (UW) ORCID 0000-0002-9585-8143 1 Dr. Keene provided oversight to the Neuropathology core and participated in teleconferences to delineate workflow in Neuropathology Core for the current project. He regularly reviews all protocols submitted to the UW human subjects' office and ensures regulatory compliance. He verified that all required security and safety protections are in place. Upon receipt of HRPO approval, Dr. Keene initiated the neuropathology core work as laid out in the SOW and as described above. Effort last quarter was invested in tissue analysis using the optimized protocols and re-establishing the workflow and timeline due to a forced relocation of the laboratory.
Name: ***Project Role:*** ***Researcher Identifier (e.g. ORCID ID):*** ***Nearest person month worked:*** ***Contribution to project:***	Christine Mac Donald, PhD. Co-I (UW) ORCID 0000-0003-1792-3808 1 Dr. Mac Donald has completed work on Task 3, which involves volumetric segmentation and quantitative neuroimaging analysis. She pulled imaging datasets collected from multiple studies and stored in different locations, all of which will be used in the current study. Preprocessing is now complete and post-processing is now complete. Dr. Mac Donald will contribute to analyses using these data.
Name:	Eric Larson, MD, MPH.

Project Role:	PI (KPWHRI)
Researcher Identifier (e.g. ORCID ID):	ORCID: 0000-0003-1108-6164
Nearest person month worked:	1
Contribution to project:	Dr. Larson participated in ongoing project meetings and correspondence, attended in-person meetings with KPWHRI study staff as well as ongoing email and phone conversations with Dr. Dams-O'Connor to oversee progress per SOW timelines for the current study. Dr. Larson also assisted in ensuring data management resources are allocated to permit timely implementation of analyses as specified in the SOW.
Name:	Melinda Power, ScD
Project Role:	PI (GWU)
Researcher Identifier (e.g. ORCID ID):	ORCID 0000-0001-9099-7964
Nearest person month worked:	1
Contribution to project:	Dr. Power participated in weekly Data Core meetings. She has collaborated with the Data core to verify completeness of each updated dataset she has received since execution of the Data Use agreement. Dr. Power has worked with Dr. Dams-O'Connor to delineate analytic plans and approach for Aim 1a. She has developed an analytic dataset, conducted exploratory data visualization to understand the data, has coded and interpreted models for the primary analyses for Aim 1a, as well as multiple sensitivity analyses for Aim 1a using standard ACT TBI and military service exposure data. Dr. Power has also consulted on the development of analyses linking the ACT TBI exposure data to a variety of other endpoints of interest in Aim 1a. She has developed and executed the analytical plan for analyses testing the association between the ACT TBI and military service exposure data to longitudinal cognitive change (Aim 2). She has developed an initial draft of the manuscript summarizing the associations observed for military service and both AD/ADRD and cognitive change Throughout the proposal period, Dr. Power also regularly identifies and reads relevant articles and other sources that inform decisions related to each of the steps above and has reviewed and contributed recommendations on analyses led by others during the study period.
Name:	Jeanelle Ariza-Torres
Project Role:	Pathology Technician (UW)
Researcher Identifier (e.g. ORCID ID):	819005408
Nearest person month worked:	1

Contribution to project:	Developed optimized extraction and detection protocol for increased efficiency and sensitivity. In the current reporting period, Ms. Ariza-Torres is implementing the tissue analysis protocol in accordance with SOW timelines in the new laboratory location.
Name: ***Project Role:*** ***Researcher Identifier (e.g. ORCID ID):*** ***Nearest person month worked:*** ***Contribution to project:***	Trevor Sytsma Pathology Technician (UW) 849003772 1 Mr. Sytsma works with Ms. Ariza-Torres under the supervision of Dr. Keene to conduct neuropathological examination of existing tissue samples per optimized protocols.

Has there been a change in the active other support of the PD/PI(s) or senior/key personnel since the last reporting period?
If there is nothing significant to report during this reporting period, state "Nothing to Report."

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

Nothing to report.

What other organizations were involved as partners?
If there is nothing significant to report during this reporting period, state "Nothing to Report."

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

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

- *Financial support;*
- *In-kind support (e.g., partner makes software, computers, equipment, etc.,*
- *available to project staff);*
- *Facilities (e.g., project staff use the partner's facilities for project activities);*

- *Collaboration (e.g., partner's staff work with project staff on the project);*
- *Personnel exchanges (e.g., project staff and/or partner's staff use each other's facilities, work at each other's site); and*
- *Other.*

Nothing to report.

8. SPECIAL REPORTING REQUIREMENTS

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

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

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