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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-43. and 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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TABLE OF CONTENTS	Page
Introduction	4
Keywords	4
Accomplishments	4
Impact	15
Changes/Problems	17
Products	19
Participants & Other Collaborating Organizations	21
Appendices	27

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.

<i>Major Goals/Milestones</i>	<i>Target Date (months)</i>	<i>% Complete</i>
Major Task 1: Administrative and Regulatory Tasks		
<ul style="list-style-type: none"> Project Kickoff meeting with Investigators and Advisory Committee 	month 1	100% complete
<ul style="list-style-type: none"> Advisory Committee teleconference; ongoing advising as needed 	month 1; annually	100% complete
<ul style="list-style-type: none"> Finalize human subjects protocols and submit modification for UW and KPWHRI 	month 0	100% complete
<ul style="list-style-type: none"> Seek and obtain approval from U.S. Army Medical Research and Materiel Command (USAMRMC) Human Research Protection Office (HRPO) 	months 0-3	100% complete

<ul style="list-style-type: none"> Prepare and submit quarterly progress reports to funding agency 	months 2-48	ongoing
Major Task 2: Collect enhanced TBI and Military service exposure data on ACT participants		
<ul style="list-style-type: none"> Collect Brain Injury Screening (BISQ) and Military Service questions with living eligible ACT participants 	months 1-3	100% complete (with non-DoD funds)
<ul style="list-style-type: none"> 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 	months 1-12	100% complete (with non-DoD funds)
<ul style="list-style-type: none"> Enter and check all TBI and Military service data into local KPWHRI databases 	months 1-12	100% complete
<ul style="list-style-type: none"> 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	20% complete
<ul style="list-style-type: none"> 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
<ul style="list-style-type: none"> Use data from the BISQ (n~1500) to identify cases and controls. 	months 12-36	30% complete
<ul style="list-style-type: none"> Use data from the BISQ to characterize the injury, etiology, chronicity and severity based on published criteria. 	months 12-36	Not yet started
<ul style="list-style-type: none"> Use data from the medical record abstraction to identify cases and controls in the autopsy cohort (n~660). 	months 12-36	Not yet started
<ul style="list-style-type: none"> 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

<ul style="list-style-type: none"> Use data from BISQ and ACT employment questions to identify those with and without military service. 	months 12-24	20% complete
<p>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).</p>		
<ul style="list-style-type: none"> <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	25% complete
<ul style="list-style-type: none"> Deparaffinize and rehydrate sections. Incubate sections in blocking solution. (step 3) 	months 4-48	10% complete
<ul style="list-style-type: none"> Wash slides; incubate with alkaline phosphatase-conjugated secondary antibody. (step 4) 	months 4-48	10% complete
<ul style="list-style-type: none"> Wash slides; incubate with p-nitrophenyl solution. (step 5) 	months 4-48	10% complete
<ul style="list-style-type: none"> Remove slides, wash and place in NBT/BCIP and cover slip. (step 6) 	months 4-48	10% complete
<ul style="list-style-type: none"> Trace gray and white matter area using Nikon 90 microscope and Stereo Investigator software 	months 4-48	10% complete
<ul style="list-style-type: none"> Complete data processing, data production and quality assurance 	months 6-48	10% complete
<ul style="list-style-type: none"> Calculate PNPP concentration and normalize to area of gray and white matter on slide 	months 4-48	10% complete
<ul style="list-style-type: none"> Use IgG isotype stains to address non-specific antibody staining. 	months 4-48	10% complete
<ul style="list-style-type: none"> Ensure uniform data coding and establish data transfer portal 	months 6-48	Not yet started
<p>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.</p>		
<ul style="list-style-type: none"> Complete volumetric segmentation and 	months 1-20	30% complete

analysis on existing research scans in ACT participants		
<ul style="list-style-type: none"> • Pull all scans from UW Imaging Archive 	months 1-20	100% complete (prep-to-research work only)
<ul style="list-style-type: none"> • Unpack DICOMs and extract MEMPRAGE nifti 	months 1-20	100% complete
<ul style="list-style-type: none"> • 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	Not yet started
<ul style="list-style-type: none"> • 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. 	months 1-20	Not yet started
Major Task 5: Process data sets for proposed analyses		
<ul style="list-style-type: none"> • Receive ACT data sets from KPWHRI staff 	months 1-12	75% complete
<ul style="list-style-type: none"> • Ensure uniform data documentation is in place, perform quality control procedures 	months 1-12	75% complete
<ul style="list-style-type: none"> • Review data dictionaries and other study documentation to ensure thorough and complete data request 	months 1-12	75% complete
<ul style="list-style-type: none"> • Review manifest of received data compared to data request to ensure completeness of data received 	months 1-12	75% complete
<ul style="list-style-type: none"> • Receive ACT data sets from UW Neuropathology; combine with clinical data sets 	months 6-40	Not yet started
<ul style="list-style-type: none"> • Careful review of data sets; identifying discrepancies and addressing them; confirming specific data received (e.g. 	months 6-40	Not yet started

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.		
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.		
<ul style="list-style-type: none"> Perform analyses on n=5400 cases with and without TBI and military exposure 	months 2-24	20% complete
<ul style="list-style-type: none"> Conduct primary analyses using ACT's TBI exposure data (since it is available on >99% of the cohort). 	months 2-14	50% complete
<ul style="list-style-type: none"> 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	50% complete
<ul style="list-style-type: none"> We will test the robustness of our findings to residual confounding, missing data, misclassification and selection bias using several sensitivity analyses. 	months 12-24	Not yet started
<ul style="list-style-type: none"> 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	Not yet started
<ul style="list-style-type: none"> 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

<p>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 β-amyloid, PHF-τ, τ-synuclein, and phospho-TDP-43 in multiple brain regions.</p>		
<ul style="list-style-type: none"> Perform analyses on data from autopsy cases with and without TBI and military exposure. 	months 12-48	Not yet started
<ul style="list-style-type: none"> 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	Not yet started
<ul style="list-style-type: none"> Models for TBI or military service main effects will be adjusted for non-primary exposure of interest as in Aim 1a. 	months 12-48	Not yet started
<p>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.</p>		
<ul style="list-style-type: none"> Perform analyses on n=5,400 cases with and without TBI and military exposure. 	months 19-42	Not yet started
<p>Major Task 9: We will perform gene x TBI and gene x military service analyses to identify interactions between these exposures and dementia outcomes.</p>		
<ul style="list-style-type: none"> Review literature for each outcome to identify relevant genes 	months 3-36	Not yet started
<p>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.</p>		
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. Planned work for this quarter was focused on seeking HRPO approval for the current project. 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.
 - b. The third quarterly report was submitted prior to the 7/15/18 deadline.
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' continues in accordance with the timeline delineated on this project's SOW in preparation for this project; these data are critical to the work of this project and are now available for use. Task 'b' has begun; 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' began and extensive data checking is underway to ensure accuracy of case classification.
3. Other achievements: N/A
4. Goals not met: N/A

Major activity 3: Perform Histelide assays for A β 1-42, 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 5 μ m 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. For most of the period we were limited to preparatory work, including identifying cases for evaluation and planning our approach. Once the protocol was approved we began the task of pulling blocks, cutting sections for the quantitative assays (Task 3a), and generating orders for supplies and reagents. We have begun histelide analyses with a will focus on beta amyloid histelide assays first.
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 nifti
 - 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 has begun; progress has focused on unpacking DICOMs and extracting MEMPRAGE. We are on target to complete planned work for this major activity on time 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. Dams-O'Connor and the biostatistics core focused on prep-to-research work under this activity during standing weekly data core calls as we awaited IRB and HRPO approval and data use agreements. This work includes weekly planning meetings, drafting a list of desired ACT variables to be included in shared datasets and determining how datasets will be tracked and shared across sites. Dr. Gibbons and Elizabeth Sanders (UW) and Bill Lee (KPWHRI) compiled BISQ TBI data gathered through multiple prior studies. We have begun using BISQ TBI data to characterize TBI exposure; data checks highlighted need for consensus coding a small number of ambiguously reported exposures. Dr. Dams-O'Connor and Power have mapped out an analytic plan for first planned analyses and manuscript (Aim 1a). Drs. Gibbons and Dams-O'Connor along with the data core verified coding for standard ACT TBI variables. Rod Walker (KPWHRI) has begun annotating a code book for the core study dataset which will facilitate accurate use of variables across analysts. Dr. Gibbons (UW) has been working with her team to verify and edit the code book and data dictionary. ACT datasets have now been shared along with data dictionaries, for the ACT biennial analytic data (attached to some of the KPWA clinical and enrollment data). This data also includes the standard TBI and military history variables collected as part of standard ACT questionnaire data, and some study outcomes for Aim

1 (clinical AD, all-cause dementia) and the outcomes for Aim 2 (CASI, CASI_IRT, ADLs, comorbidity scores, and CES-D). We will be adding to these datasets, as needed. Dr. Power has verified data accuracy using the draft data dictionary upon receipt of dataset. Data sent to GWU includes BISQ data and Dr. Dams-O'Connor and Power (GWU) are testing TBI ascertainment code and expanding code to delineate exposure severity. Work in the last quarter includes gathering some of the KPWA medication data to be linked to these files. With input from our Advisory Committee and pharmacy experts, we are using KPWA medical claim and medication data to define disease morbidity and polypharmacy, and refining clinical Parkinson's disease diagnosis coding based on ICD-10.

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.
2. Significant results or key outcomes: Dr. Power has developed an analytical dataset derived from the core study dataset, and has begun work on the specific objectives above. Initial efforts have focused on completing objective 'b' with the methods described in objective 'c' and we include preliminary results as part of this progress report (Appendix A). Specifically, we have developed analyses quantifying the association between TBI and military service with time to AD or dementia.
3. Other achievements: N/A
4. Goals not met: N/A

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 β -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 ϵ 4 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 has not yet been started.
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 has not yet been started under this activity.
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 12-15 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.

All HRPO approvals have now been received. Work will now proceed in accordance with the statement of work.

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.

HRPO approval took longer than anticipated per the SOW, and accordingly timelines for some tasks may require revision moving forward. In the proposal we estimated the number of MRI scans of relevant participants we would have available to evaluate for this study at n=250. As noted above, we have begun on a prep-to-research basis to identify the scans available for this aspect of the project. Currently, there are 163 scans available with new scans accumulating over the next year as a part of a separate study. All available scans will be included in planned analyses. We will still be able to perform all analyses described in the statement of work.

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.*

<p>The Adult Changes in Thought study has become increasingly recognized as a data resource for investigators from multiple disciplines across the United States</p>
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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.)

<p>Name: Project Role: Researcher Identifier (e.g. ORCID ID): Nearest person month worked: Contribution to project:</p>	<p>Kristen Dams-O’Connor, PhD. PI (ISMMS) ORCID 0000-0002-2506-0216 3 Dr. Dams-O’Connor worked with each study site to submit and revise necessary human subjects approvals and/or exceptions required to conduct the work proposed in this grant and submitted them to funding agency</p>
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	<p>for HRPO review, and participated in teleconferences to discuss documents submitted from all study sites and determine what additional documentation will be required for HRPO approval. She convened weekly teleconferences with the Data Core to specify data management and analytic workflow across all study aims, contributed to drafting and revision of Data Core Workflow plans, and worked with the Data Core to select data elements 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 verify accuracy and completeness of datasets, data coding, and data dictionary. She has worked with the data core and Dr. Lisa Spielman to curate TBI exposure data. 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.</p>
<p>Name: Project Role: Researcher Identifier (e.g. ORCID ID): Nearest person month worked: Contribution to project:</p>	<p>John Crary, MD PhD. Co-I (ISMMS) era Commons JC2892 1 Dr. Crary helped prepare requested documents related to human cadaver work related to the current project, which was approved by HRPO.</p>
<p>Name: Project Role: Researcher Identifier (e.g. ORCID ID): Nearest person month worked: Contribution to project:</p>	<p>Paul Crane, MD MPH PI (UW) ORCID 0000-0003-4278-7465 1 Dr. Crane worked with UW research team to secure necessary human subjects approvals and/or exceptions required to conduct the work proposed in this grant, and consulted to the specification of workflow plans within the Data core.</p>
<p>Name: Project Role: Researcher Identifier (e.g.</p>	<p>C. Dirk Keene, MD PhD. Co-I (UW) ORCID 0000-0002-9585-8143</p>

<p>ORCID ID): Nearest person month worked: Contribution to project:</p>	<p>1 Dr. Keene participated in teleconferences to delineate workflow in Neuropathology Core for the current project, reviewed all protocols submitted to the UW human subjects office, participated in teleconference to verify all required security and safety protections are in place, and provided documentation to demonstrate lack of overlap relating to the current award. Upon receipt of HRPO approval, Dr. Keene initiated the neuropathology core as laid out in the SOW.</p>
<p>Name: Project Role: Researcher Identifier (e.g. ORCID ID): Nearest person month worked: Contribution to project:</p>	<p>Christine Mac Donald, PhD. Co-I (UW) ORCID 0000-0003-1792-3808 1 Dr. Mac Donald has begun work on Task 3, which involves preparation for volumetric segmentation and quantitative neuroimaging analysis. She has pulled imaging datasets collected from multiple studies and stored in different locations, all of which will be used in the current study. Initial preprocessing began after HRPO approval was granted.</p>
<p>Name: Project Role: Researcher Identifier (e.g. ORCID ID): Nearest person month worked: Contribution to project:</p>	<p>Eric Larson, MD, MPH. PI (KPWHRI) ORCID: 0000-0003-1108-6164 1 Dr. Larson participated in ongoing project meetings and correspondence, attended in-person meetings with KPWHRI study staff as well as extensive email and phone conversations with Dr. Dams-O'Connor to determine how to optimally staff the current study. Dr. Larson also assisted in providing information required for any ongoing IRB and HRPO review, exploring and detailing the data request for this project, reviewing ACT data collection and Repository data-sharing procedures, and provided documentation to demonstrate lack of overlap relating to the current award.</p>
<p>Name:</p>	<p>Melinda Power, ScD</p>

<p>Project Role: Researcher Identifier (e.g. ORCID ID): Nearest person month worked: Contribution to project:</p>	<p>PI (GWU) ORCID 0000-0001-9099-7964 1 Dr. Power participated in weekly Data Core meetings to discuss what variables should be included in the core dataset and in what form. She has collaborated with the Data core to verify completeness of the dataset she received upon execution of the Data Use agreement, and worked with Dr. Dams-O'Connor to delineate analytic plans and approach for Aim 1a. She has developed an analytic dataset and has completed preliminary analyses for Aim 1a.</p>
<p>Name: Project Role: Researcher Identifier (e.g. ORCID ID): Nearest person month worked: Contribution to project:</p>	<p>Leanne Hellstern Pathology Technician (UW) 850001272 1 No change.</p>
<p>Name: Project Role: Researcher Identifier (e.g. ORCID ID): Nearest person month worked: Contribution to project:</p>	<p>Troy Marxen Pathology Technician (UW) 821002319 1 Troy Marxen has begun work on Task 3, assisting Leanne Hellstern in neuropathological processing.</p>

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.

Table 1. Descriptive Characteristics of ACT Study Participants at Baseline and Cumulative Incidence of Dementia During Follow-Up by Exposure Status at Baseline

Characteristics	Total	Served in Military as 1st or 2nd Longest Occupation			TBI with LOC Prior to Baseline ACT Visit		
		Yes	No	Missing	Yes	No	Missing
n (%)	5236 (100%)	295 (5.6%)	4926 (94.1%)	15 (0.3%)	771 (14.7%)	4394 (83.9%)	71 (1.4%)
Age in Years (mean, ± SD)*	74.8, ± 6.5	74.6 ± 5.5	74.8 ± 6.5	75.6 ± 6.4	74.2 ± 6.0	74.9 ± 6.5	72.1 ± 5.8
Sex (%)							
Female	41.7%	24.20%	60.30%	66.70%	42.00%	61.10%	69.60%
Male	58.3%	75.60%	39.70%	33.30%	58.00%	38.90%	39.40%
Race/ethnicity (%)							
Non-Hispanic White	88.8%	90.2%	88.7%	80.0%	92.1%	88.2%	87.3%
Other	11.1%	9.8%	11.1%	20.0%	7.9%	11.6%	12.7%
Missing	0.1%	0.0%	0.2%	0.0%	0.0%	0.2%	0.0%
Educational attainment (%)							
Less than high school	9.2%	10.2%	9.1%	6.7%	8.0%	9.5%	2.8%
Completed high school	20.5%	18.0%	20.7%	6.7%	17.4%	21.2%	8.5%
Some college	24.2%	25.8%	24.1%	33.3%	23.6%	24.4%	18.3%
Completed college	46.1%	46.1%	46.1%	53.3%	51.0%	44.9%	70.4%
Missing	0.02%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%
APOE e4 Allele Status (%)							
Present	22.5%	20.7%	22.6%	20.0%	21.7%	22.8%	15.5%
Absent	63.6%	68.8%	63.3%	46.7%	65.4%	63.6%	42.3%
Missing	13.9%	10.5%	14.1%	33.3%	13.0%	13.6%	42.3%
Height in Inches (mean, ± SD)*	65.3 ± 3.9	67.4 ± 3.8	65.2 ± 3.9	65.4 ± 4.0	66.4 ± 3.9	65.1 ± 3.9	66.0 ± 4.3
Dementia Diagnosis (DSM-IV) During Follow-Up (%)	22.2%	25.4%	22.0%	26.7%	22.3%	22.5%	2.8%
Alzheimer's Disease Dementia Diagnosis (NINDS/ADRD) During Follow-Up (%)	18.0%	19.7%	17.9%	26.7%	17.3%	18.4%	2.8%

*N missing of continuous variable "height"= 107.

Table 2. Association between TBI and Incidence of Dementia and Alzheimer's Disease Using Cox Regression Models Adjusted for Potential Confounders

Dementia		
	Model 1*	Model 2**
TBI		
No	1.0 (ref)	1.0 (ref)
Yes	1.07 (0.91, 1.26)	1.06 (0.89, 1.26)

Alzheimer's Disease		
	Model 1*	Model 2**
TBI		
No	1.0 (ref)	1.0 (ref)
Yes	1.02 (0.85, 1.23)	1.03 (0.84, 1.25)

* Adjusted for age.

**Adjusted for age, gender, race, height, educational attainment, military as first or second longest occupation, and APOE e4 allele status.

Table 3. Association between Military Service and Incidence of Dementia and Alzheimer's Disease Using Cox Regression Models Adjusted for Potential Confounders

Dementia		
	Model 1*	Model 2**
Military Service		
No	1.0 (ref)	1.0 (ref)
Yes	0.99 (0.79, 1.26)	1.00 (0.78, 1.30)

Alzheimer's Disease		
	Model 1*	Model 2**
Military Service		
No	1.0 (ref)	1.0 (ref)
Yes	0.95 (0.73, 1.24)	0.99 (0.74, 1.31)

* Adjusted for age.

**Adjusted for age, gender, race, height, educational attainment, baseline TBI status, and APOE e4 allele status.

Table 4. Association between Military Service and TBI with LOC combined and Incidence of Dementia and Alzheimer's Disease Using a Cox Regression Model Adjusted for Potential Confounders*

Dementia		
	Model 1*	Model 2**
Neither	1.0 (ref)	1.0 (ref)
TBI only	1.09 (0.92, 1.29)	1.08 (0.90, 1.30)
Military service only	1.03 (0.80, 1.33)	1.05 (0.80, 1.38)
TBI + Military service	0.88 (0.49, 1.60)	0.80 (0.40, 1.61)
<i>p-value for interaction</i>	0.48	0.36
Alzheimer's Disease		
	Model 1*	Model 2**
Neither	1.0 (ref)	1.0 (ref)
TBI only	1.04 (0.86, 1.26)	1.05 (0.85, 1.29)
Military service only	0.98 (0.74, 1.31)	1.04 (0.77, 1.41)
TBI + Military service	0.80 (0.40, 1.59)	0.75 (0.34, 1.69)
<i>p-value for interaction</i>	0.52	0.41

* Adjusted for age.

**Adjusted for age, gender, race, height, educational attainment, and APOE e4 allele status.