AWARD NUMBER: W81XWH-18-1-0580

TITLE: Leveraging the Framingham Study to Investigate Relationships Between Traumatic Brain Injury, Military Service, Alzheimer's Disease and Related Dementias

PRINCIPAL INVESTIGATOR: Jesse Mez, Kristen Dams-O'Connor

CONTRACTING ORGANIZATION: Boston University Medical Center, Boston, MA

REPORT DATE: October 2020

TYPE OF REPORT: Annual Report

PREPARED FOR: U.S. Army Medical Research and Materiel Command
Fort Detrick, Maryland 21702-5012

REPORT DOCUMENTATION PAGE

Form Approved
OMB No. 0704-0188

1. REPORT DATE	2. REPORT TYPE	3. DATES COVERED
October 2020	Annual Report	01Sep2019-31Aug2020

4. TITLE AND SUBTITLE

Leveraging the Framingham Study to Investigate Relationships Between Traumatic Brain Injury, Military Service, Alzheimer's Disease and Related Dementias

5a. CONTRACT NUMBER
W81XWH-18-1-0580

5b. GRANT NUMBER

5c. PROGRAM ELEMENT NUMBER

6. AUTHOR(S)
Jesse Mez, MD, MS

E-Mail:jessemez@bu.edu

5d. PROJECT NUMBER

5e. TASK NUMBER

5f. WORK UNIT NUMBER

7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES)

TRUSTEES OF BOSTON UNIVERSITY
BOSTON UNIVERSITY MEDICAL
CAMPUS 85 E NEWTON ST M-921
BOSTON MA 02118-2340

8. PERFORMING ORGANIZATION REPORT NUMBER

9. SPONSORING / MONITORING AGENCY NAME(S) AND ADDRESS(ES)

U.S. Army Medical Research and Development Command
Fort Detrick, Maryland 21702-5012

10. SPONSOR/MONITOR'S ACRONYM(S)

11. SPONSOR/MONITOR'S REPORT NUMBER(S)

12. DISTRIBUTION / AVAILABILITY STATEMENT

Approved for Public Release; Distribution Unlimited

13. SUPPLEMENTARY NOTES

14. ABSTRACT

A large body of evidence suggests that people experiencing a single or repetitive TBI in civilian and military settings may have an increased risk of late-life cognitive decline or neurodegenerative disease, including Alzheimer's disease (AD) and AD-related dementias (ADRD). But the specific clinical features and neuropathological substrates of TBI-associated dementia, as well as the mechanisms underlying this apparent association, are less clear. This project leverages the extensive existing resources of the Framingham Heart Study (FHS), which includes access to a long-committed community-based study sample, as well as health, lifestyle, biomarker, genetic, cognitive, neuroimaging and neuropathological data. We are combining these existing resources with new self-report TBI and military service data. This study will comprehensively characterize the role of TBI and military service on key AD/ADRD outcomes, and identify genetic and non-genetic factors that modify these relationships.

15. SUBJECT TERMS
traumatic brain injury, Alzheimer's disease, dementia, mild cognitive impairment, Parkinson's disease, dementia with Lewy bodies, chronic traumatic encephalopathy, Framingham Heart Study

16. SECURITY CLASSIFICATION OF:			17. LIMITATION OF ABSTRACT	18. NUMBER OF PAGES	19a. NAME OF RESPONSIBLE PERSON
a. REPORT	b. ABSTRACT	c. THIS PAGE			USAMRMC
Unclassified	Unclassified	Unclassified	Unclassified	21	19b. TELEPHONE NUMBER *(include area code)*

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1. INTRODUCTION:

A large body of evidence suggests that people experiencing a single or repetitive TBI in civilian and military settings may have an increased risk of late-life cognitive decline or neurodegenerative disease, including Alzheimer's disease (AD) and AD-related dementias (ADRD). But the specific clinical features and neuropathological substrates of TBI-associated dementia, as well as the mechanisms underlying this apparent association, are less clear. This project leverages the extensive existing resources of the Framingham Heart Study (FHS), which includes access to a long-committed community-based study sample, as well as health, lifestyle, biomarker, genetic, cognitive, neuroimaging and neuropathological data. We are combining these existing resources with new self-report and chart review TBI and military service data. This study will comprehensively characterize the role of TBI and military service on key AD/ADRD outcomes, and identify genetic and non-genetic factors that modify these relationships.

2. KEYWORDS:

traumatic brain injury, Alzheimer's disease, dementia, mild cognitive impairment, Parkinson's disease, dementia with Lewy bodies, chronic traumatic encephalopathy, Framingham Heart Study, epidemiology, neuropsychology, neuroimaging, MRI, genetics, neuropathology

3. ACCOMPLISHMENTS:

What were the major goals of the project?

Aims
AIM 1: We will determine the impact of TBI and military service on clinical AD/ADRD outcomes.
AIM 2: We will determine the impact of TBI and military service on AD/ADRD outcomes as measured by structural MRI.
AIM 3: We will determine the impact of TBI and military service on neuropathological AD/ADRD outcomes.

What was accomplished under these goals?

Major Task 1: Administrative and Regulatory Tasks: Ongoing (~ 75% complete)

A. Obtain IRB approval for study protocol & FHS data use agreements: complete Y1Q4
B. Seek and obtain approval from U.S. Army Medical Research and Material Command (USAMRMC) Human Research Protection Office (HRPO): complete 10/28/19
C. Submit annual IRB reports and maintain Data Use Agreements (DUA): ongoing
D. Prepare and submit quarterly progress reports to funding agency: ongoing

We worked with the BU IRB, the IMSSM IRB and the USAMRMC HRPO to obtain approvals to conduct the proposed research. Because work on the Framingham Heart Study is longstanding and many BU IRB approvals already existed, but as parts of different BU IRB applications, appropriate documentation for the HRPO took longer than expected. Several iterative changes to the BU IRB protocols were requested by the HRPO and were subsequently made.

Major Task 2: Conduct medical record review: Ongoing (~ 10% complete)

A. Train research staff to conduct medical record review- complete Y1Q4
B. Establish and implement data tracking and quality control protocols – complete Y1Q4
C. Establish and implement TBI review protocol for questionable cases -complete Y1Q4
D. Conduct medical record review for TBI for Gen 2 & Omni Gen (n=5623) - ongoing
E. Conduct on-going data cleaning and integration into FHS database - ongoing
F. Work with FHS to prepare TBI data (Gen 2/OmniGen 1) for sharing with external collaborators -Not started

Prior to approval in Major Task 1, we conducted activities that did not require IRB approval including teaching the research staff how to conduct TBI medical record reviews. We have also implemented a data tracking and quality control protocol and a TBI review protocol for questionable cases so that more clinically experienced reviewers can resolve the questions the research assistant (RA) reviewers may have.

After we received approvals in Major Task 1, we began TBI medical record review. We have access to medical records (including from hospitals, nursing facilities, urgent care, EDs, clinic visits) from nearly all FHS participants. For each TBI, data that results from the medical record review include date of event, time of injury, mechanism of injury, setting of injury, highest level of medical care, time from injury to medical care, duration of hospitalization, clinical signs and symptoms, Glascow Coma Score, ICD codes, presence of, type of and findings from cerebral imaging and confounding variables (such as substance use or previously diagnosed mental illness). Across FHS Gen 2 and Omni cohorts, 390 charts have been reviewed. As data is collected it is cleaned and integrated into the FHS database. Chart review has been substantially delayed due covid-19 restrictions (see Problems section).

Major Task 3: Collect self-reported TBI and military data - Timeline: Months 0-36: Ongoing (~ 45% complete)

A. Train staff to oversee administration of self-report questionnaires – complete Y1Q4
B. Establish and implement data tracking and quality control protocols – complete Y1Q4
C. Develop multiple methods for questionnaire administration (RedCap, mail, telephone) – complete Y2Q2
D. Administer self-report questionnaires to living Gen 2 and Omni participants - ongoing
E. ~~Conduct TBI review protocol for questionable cases~~ - included in error, only part of chart review
F. Conduct on-going data cleaning and integration into FHS database - ongoing
G. Work with FHS to prepare TBI data for sharing with external collaborators – not started

Prior to approval in Major Task 1, we conducted activities that did not require IRB approval including teaching the research staff how to oversee the administration of the TBI self-report questionnaires. We have also implemented a data tracking and quality control protocol.

After we received approvals in Major Task 1, we began contacting participants about TBI self-report questionnaires. The questionnaire includes the OSU-TBI-ID to document occurrence of TBI during the course of life, including childhood. For each reported injury, we will document type, severity, place, date, cause and mechanisms. It also includes a comprehensive questionnaire regarding military service, contact sports, and experiences that may have resulted in head trauma exposure. Military service questions include branch, years of service, whether combat exposure occurred and TBIs occurring while in the military. Contact sport questions include sport, position, years of play, levels of play and age at first exposure to contact sports. FHS participants who agreed to complete the TBI self-report questionnaire were initially given the option to complete the questionnaire by paper mail or online. In the mail format, we initially noticed substantial missing dating and have troubleshooted to determine why. We determined that the mailer left too much flexibility for the participants to skip questions. We have transitioned to the option of online questionnaire or completion over the phone with assistance from an RA. While the data is much more complete with the phone call, it is slower and takes more RA resources. We have gone back and called many of the participants who initially completed the mail format. Both options can be completed virtually and have continued during the pandemic. To date we have 1,020 completed questionnaires. As data is collected it is cleaned and integrated into the FHS database.

AIM 1: We will determine the impact of TBI and military service on clinical AD/ADRD outcomes.

Major Task 4: Process data sets for proposed analyses on clinical outcomes Timeline: Months 0-24: Ongoing (~ 20% complete)

A. Select variables/request Gen 1 dataset from FHS data staff – completed Y2Q4
B. Merge Gen 1 variables into single dataset and prepare data dictionary – not started
C. Quality control steps for Gen 1 including confirming format of ID numbers - ongoing
D. range checks of all data elements to ensure data are within expected ranges; logic checks; consistency of data with published summaries - ongoing
E. Review data dictionaries and other study documentation for Gen 1 to ensure thorough and complete data request - ongoing
F. Select variables/request Gen 2/Omni dataset from FHS data staff - not started
G. Use data from medical record review and self-reported TBI to identify cases (those with TBI exposure) and controls (those with no evidence of TBI exposure). Characterize TBI severity using standard criteria. - not started
H. Merge Gen 2/Omni variables into single dataset and prepare data dictionary not started
I. Quality control steps for Gen 2/Omni including confirming format of ID numbers, range checks of all data elements to ensure data are within expected ranges; logic checks; consistency of data with published summaries; - not started
J. Review data dictionaries and other study documentation for Gen 2/Omni to ensure thorough and complete data request -not started

As stated in the grant application, FHS Generation 1 charts had already been reviewed for TBI previous to the grant submission using other resources. For this DOD grant, we proposed to

combine this previously collected data with newly collected data from Generation 2. When we began QC and preparation of the Generation 1 dataset, we learned that several charts had been "flagged" by RA reviewers because they had questions that required additional review from more clinically experienced reviewers. This delayed preparation of the Gen 1 dataset. Resolution of flagged Gen 1 charts was ongoing when Covid-19 delays began. Due to the delays, resolution of flagged Gen 1 charts is still ongoing. We have requested and received datasets from FHS staff that contains previously collected, non-TBI variables for Gen 1. We are in the process of reviewing data dictionaries and datasets to ensure we have all needed variables and correct ID formats, variable ranges and distributions.

Major Task 5: Statistical analyses (marginal effects – aims 1a, b) Timeline: Months 9-30: Not Started

A. For Gen 1, review/specify details of model design to test the hypotheses that TBI is ~~and military service are independently and jointly~~ associated with risk for MCI, dementia, AD, PD/DLB, decline in cognition, ADLs, mood, and motor function. Note military data is being collected prospectively for Gen 2, but is not available from Gen 1 chart review. We are not obtaining Gen 1 self-report questionnaires as most have passed away. -not started
B. For Gen 1, run statistical models to test the above hypotheses -not started
C. For Gen 1, interpret results of above statistical models -not started
D. For Gen 2/Omni, review/specify details of model design to test the hypotheses that TBI and military service are independently and jointly associated with risk for MCI, dementia, AD and PD/DLB, decline in cognition, ADLs, mood, and motor function. -not started
E. For Gen 2/Omni, run statistical models to test the above hypotheses -not started
F. For Gen 2/Omni, interpret results of above statistical models -not started

Major Task 6: Statistical analyses (genetic interactions– aim 1c) Timeline: Months 0-33: Ongoing (~ 5% complete)

A. Review literature for each outcome to identify relevant variants and genes - ongoing
B. Use bioinformatic tools that output related genes and rankings -not started
C. Extract data on variants/genes of interest from genome-wide datasets. Note that quality control, imputation and generation of principal components for population substructure has already been completed in previous efforts -not started
D. Conduct gene-based interaction tests for Gen 1 using Aim 1 clinical outcomes -not started
E. Conduct gene-based interaction tests for Gen 2/Omni using Aim 1 clinical outcomes -not started
F. Interpret results of above genetic models -not started

In preparation for the genetic interaction analyses, we comprehensively reviewed the literature and identified candidate genes and top SNPs and minor allele frequencies for the following phenotypes: poor acute and sub-acute outcomes after TBI, poor chronic outcomes after TBI, Alzheimer's disease and PSP (see appendix). We will periodically review the literature to look for updates until we can begin analyses.

Major Task 7: Statistical analyses (demographic, clinical, and lifestyle factors as moderators – aim 1d) Timeline: Months 12-36: Not Started

A. For covariates that demonstrate significant marginal effects in Aims 1a and b for Gen 1, introduce an interaction term between primary exposure and the covariate and also conduct stratified analyses by the primary exposure. -not started

B. For covariates that demonstrate significant marginal effects in Aims 1a and b for Gen 2/Omni, introduce an interaction term between primary exposure and the covariate and also conduct stratified analyses by the primary exposure. -not started
C. Interpret results of above moderation models -not started
D. Prepare Aim 1 results for presentation and publication -not started

AIM 2: We will determine the impact of TBI and military service on AD/ADRD outcomes as measured by structural MRI.

Note that as part of another effort, MRI processing to generate all imaging variables, including harmonized longitudinal data, proposed to use in this grant, is currently being updated using FreeSurfer by colleagues at Harvard. Given the delay in collection of TBI data and the substantial improvement in MRI outcomes with the updated processing, we have not made significant progress on Aim 2.

Major Task 8: Process data sets for proposed analyses on imaging outcomes Timeline: Months 18-24: Not Started

A. Select imaging variables/request dataset from FHS data staff -not started
B. Merge variables into single dataset that incorporates participants across generations with MRI data and prepare data dictionary- -not started
C. Quality control steps including confirming format of ID numbers, range checks of all data elements to ensure data are within expected ranges; logic checks; consistency of data with published summaries -not started
D. Review data dictionaries and other study documentation to ensure thorough and complete data request -not started

Major Task 9: Statistical analyses (marginal effects – aims 2a, b); Timeline: Months 24-30 Not Started

A. Review/specify details of model design to test the hypotheses that TBI and military service are independently and jointly associated with a) cross- sectionally smaller TCBV, smaller lobar volumes, smaller HV, greater WMHV, decreased FA and increased MD and b) longitudinally greater decline in TCBV and lobar volumes and greater increase in WMHV. -not started
B. Run statistical models to test the above hypotheses -not started
C. Interpret results of above statistical models -not started

Major Task 10: Statistical analyses (genetic interactions – aim 2c) Timeline: Months 0-33; Ongoing (~ 5% complete)

A. Review literature for each outcome to identify relevant variants and genes - ongoing
B. Use bioinformatic tools that output related genes and rankings - not started
C. Extract data on variants/genes of interest from genome-wide datasets. Note that quality control, imputation and generation of principal components for population substructure has already been completed in previous effort - not started
D. Conduct gene-based interaction tests using Aim 2 imaging outcomes -not started
E. Interpret results of above genetic models -not started

Progress is the same as Major Task 6.

Major Task 11: Statistical analyses (demographic, clinical, and lifestyle factors as moderators – aim 2d) Timeline: Months 27-36: Not Started

A. For covariates that demonstrate significant marginal effects in Aims 2a and b, introduce an interaction term between primary exposure and the covariate and also conduct stratified analyses by the primary exposure. -not started

B. Interpret results of above moderation models -not started
C. Prepare Aim 2 results for presentation and publication -not started

AIM 3: We will determine the impact of TBI and military service on neuropathological AD/ADRD outcomes.

Major Task 12: Perform quantitation of AP and P-tau in selected regions in FHS brain donors Timeline: Months 0-36: Ongoing (~ 20% complete)

A. Train staff to conduct quantitation—Complete Y1Q4
B. Establish and implement data tracking and quality control protocols – complete Y1Q4
C. Digitally scan slides using Aperio slide scanner - ongoing
D. Label slides with subject ID, region and stain -ongoing
E. Manually circle anatomic regions - ongoing
F. Derive quantitative counts of amyloid and tau stained pixels, amyloid plaques and neurofibrillary tangles - ongoing
G. Conduct on-going data cleaning and integration into FHS database - ongoing
H. Work with FHS to prepare quantitative neuropath data for sharing with external collaborators -not started

As part of other efforts, all brain donors undergo a comprehensive neuropathological exam, including preparation of approximately 75 fixed glass slides across multiple brain regions, using multiple stains. As part of this DOD effort, we are digitally scanning all slides using an Aperio slide scanner.

Prior to approval in Major Task 1, we conducted activities that did not require IRB approval including training staff to conduct quantitation and establishing and implementing data tracking and quality control protocols. Neuropathologists have taught RAs to differentiate gray from white matter, to differentiate subfields of the hippocampus and to identify nuclei like the locus coeruleus. They were also trained on how to use Leica software so that anatomic regions could be manually outlined so that quantitation of pathology can be performed. Values are standardized based on the area outlined and reported as a density. Our data team has built a robust digital tracking system that includes barcoding (indicates ID, region, stain) and tracks individual slides based on current location (as efforts occur at multiple locations), whether scanning has occurred, whether outlining has occurred, whether quantitation has occurred and whether results have been returned to our data team.

Since approval in Major Task 1, we have digitally scanned slides and manually outlined anatomic regions from 44 brain donors. This effort has been delayed due to covid-19 restrictions (see problems section). No slides were scanned during the 4th quarter.

Major Task 13: Process data sets for proposed analyses Timeline: Months 18-24: Ongoing Not Started

A. Select neuropathology variables/request dataset from FHS data staff -not started
B. Merge variables into single dataset that incorporates participants across generations with neuropathology data and prepare data dictionary -not started
C. Quality control steps including confirming format of ID numbers, range checks of all data elements to ensure data are within expected ranges; logic checks; consistency of data with published summaries – not started

D. Review data dictionaries and other study documentation to ensure thorough and complete data request – not started

Major Task 14: Statistical analyses (marginal effects – aims 3a, b) Timeline: Months2 4-30 Not Started

A. Review/specify details of model design to test the hypotheses that TBI and military service are independently and jointly associated with a) pathologically confirmed AD, PD/DLB and CTE and b) AD/ADRD semi-quantitative (Braak stage, CERAD score, Thal phase, Lewy bodies, TDP-43 and microinfarcts) and quantitative outcomes (average density of p-tau stained pixels and average density of aB stained pixels). -not started
B. Run statistical models to test the above hypotheses -not started
C. Interpret results of above statistical models -not started

Major Task 15: Statistical analyses (genetic interactions – aim 3c) Timeline: Months 0-36: Ongoing: (~ 5% complete)

A. Review literature for each outcome to identify relevant variants and genes - ongoing
B. Use bioinformatic tools that output related genes and rankings -not started
C. Extract data on variants/genes of interest from genome-wide datasets. Note that quality control, imputation and generation of principal components for population substructure has already been completed in previous effort - not started
D. Conduct gene-based interaction tests using Aim 3 neuropathology outcomes -not started
E. Interpret results of above genetic models -not started

Progress is the same as Major Task 6.

Major Task 16: Statistical analyses (demographic, clinical, and lifestyle factors as moderators – aim 3d) Timeline: Months 18-36: Not Started

A. For covariates that demonstrate significant marginal effects in Aims 3a and b, introduce an interaction term between primary exposure and the covariate and also conduct stratified analyses by the primary exposure. -not started
B. Interpret results of above moderation models -not started
C. Prepare Aim 3 results for presentation and publication -not started

Describe the Regulatory Protocol and Activity Status (if applicable).

Describe the Protocol and Activity Status for sections a-c, as applicable, using the format described for each section. If there is nothing significant to report during this reporting period, state "Nothing to Report."

(a) ***Human Use Regulatory Protocols***

TOTAL PROTOCOLS: *State the total number of human use protocols required to complete this project (e.g., 5 human subject research protocols will be required to complete the Statement of Work.").*

TOTAL PROTOCOLS: 3

PROTOCOL (1 of 3 total):

Protocol [HRPO Assigned Number]: E00206.1a

Title: Leveraging the Framingham Study to Investigate Relationships between Traumatic Brain Injury, Military Service, Alzheimer's Disease and Related Dementias: Prospective

Target required for clinical significance: Although we would like to include as many of the living participants in Gen 2 (2,677) and Omni Gen 1 (433) as possible, our past experience suggests that a realistic goal is to have about 2,400 (~75%) participate in the protocol.

Target approved for clinical significance: N/A

SUBMITTED TO AND APPROVED BY:

This protocol is currently approved by the Boston University School of Medicine IRB and the USAMRMC HRPO (10/28/19)

STATUS:

(i) Number of subjects recruited/original planned target: N/A
Number of subjects screened/original planned target: N/A
Number of subjects enrolled/original planned target: 1,061/2,400
Number of subjects completed/original planned target: 1,020/2,400

(ii) Report amendments submitted to the IRB and USAMRMC HRPO for review:

An amendment to this protocol that also incorporates the non-human subjects work (described in the human cadavers section below) is currently approved by the BU SOM IRB and the USAMRMC HRPO

An amendment to this protocol that changes the language of the consent form to acknowledge that the research is funded by the DOD and that DOD representatives is currently approved by the BU SOM IRB and the USAMRMC HRPO

(iii) Adverse event/unanticipated problems involving risks to subjects or others and actions or plans for mitigation:

None

PROTOCOL (2 of 3 total):

Protocol [HRPO Assigned Number]: E00206.1a

Title: Leveraging the Framingham Study to Investigate Relationships between Traumatic Brain Injury, Military Service, Alzheimer's Disease and Related Dementias: Retrospective

Target required for clinical significance: N/A – all participants are already part of the FHS (Gen 2: 5,124; Omni: 499, Gen 1: 5,209)

Target approved for clinical significance: N/A

SUBMITTED TO AND APPROVED BY:

This protocol is currently approved by the Boston University School of Medicine IRB and the USAMRMC HRPO (10/28/19)

STATUS:

(i) Number of subjects recruited/original planned target: N/A

Number of subjects screened/original planned target: N/A
Number of subjects enrolled/original planned target: N/A
Number of subjects completed/original planned target: 5,599/10,832

(ii) Report amendments submitted to the IRB and USAMRMC HRPO for review:
An amendment to this protocol that also incorporates the non-human subjects work (described in the human cadavers section below) is currently approved by the BU SOM IRB and the USAMRMC HRPO

(iii) Adverse event/unanticipated problems involving risks to subjects or others and actions or plans for mitigation:
None

PROTOCOL (3 of 3 total):

Protocol [HRPO Assigned Number]: E00206.1b

Title: Leveraging the Framingham Study to Investigate Relationships between Traumatic Brain Injury, Military Service, Alzheimer's Disease and Related Dementias

Target required for clinical significance: N/A – all participants are already part of the FHS (Gen 1 5,209; Gen 2: 5,124; Omni: 499)

Target approved for clinical significance: N/A

SUBMITTED TO AND APPROVED BY:

Note that this protocol is for non-human subjects work only

This protocol is currently approved by the Icahn School of Medicine at Mount Sinai IRB and the USAMRMC HRPO (10/28/19)

STATUS:

(i) Number of subjects recruited/original planned target: N/A
Number of subjects screened/original planned target: N/A
Number of patients enrolled/original planned target: N/A
Number of patients completed/original planned target: N/A

(ii) Report amendments submitted to the IRB and USAMRMC HRPO for review:
None

(iii) Adverse event/unanticipated problems involving risks to subjects or others and actions or plans for mitigation:
None

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

Nothing to Report

How were the results disseminated to communities of interest?

Nothing to Report

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

During the next reporting period, we will continue contacting living Gen 2 and Omni participants for self-report TBI/RHI questionnaires. Our goal is to complete this by the end of the 4th quarter. We will also continue medical record review for TBI for Gen 2 & Omni. Covid building restrictions limit record access, but we hope to make a big push over the summer with hired interns if we are allowed by the FHS Executive Committee. We will also continue to resolve chart review questions (i.e. flags) for Gen 1 for which all of the charts have already been reviewed as part of a separately funded effort. We hope to complete this process by the end of quarter 2, though this is also a function of covid restrictions. Once flag resolution is completed for Gen 1, we will create datasets for analyses of Gen 1 data. We will conduct statistical analyses in quarters 3 and 4 with Aim 1 outcomes. Flag resolution will be ongoing for Gen 2 & Omni in all 4 quarters. We will continue digital slide scanning and quantitation with the goal to complete all scanning by the end of the 4th quarter. We expect FreeSurfer MRI variables being generated via another project to be ready by the end of quarter 3. In quarter 4, we will begin imaging variable selection.

4. IMPACT:

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

We do not yet have results to report. The digital slide images and quantitation we are generating will be a valuable resource for a variety of neuropathology projects that extend beyond TBI-neurodegenerative relationships. For instance, colleagues have expressed interest in using this data to investigate resistance and resilience for AD.

What was the impact on other disciplines?

Nothing to Report

What was the impact on technology transfer?

Nothing to Report

What was the impact on society beyond science and technology?

Nothing to Report

5. CHANGES/PROBLEMS:

Changes in approach and reasons for change

Nothing to Report

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

Approval of research protocols by the BU IRB and DOD HRPO took 14 months from start of study period. This delayed data collection. This issue is now resolved with the approvals.

As stated in the grant application, FHS Generation 1 charts had already been reviewed for TBI previous to the grant submission using other resources. For this DOD grant, we proposed to combine this previously collected data with newly collected data from Generation 2. When we began QC and preparation of the Generation 1 dataset, we learned that several charts had been "flagged" by RA reviewers because they had questions that required additional review from more clinically experienced reviewers. This delayed preparation of the Gen 1 dataset. We have since identified more experienced reviewers able to assist with reviewing flagged charts. We have also created a protocol for reviewing flagged charts. Resolution of flagged charts was ongoing when Covid-19 delays began, as described in the next paragraph.

Due to the Covid-19 pandemic, the FHS office and lab space closed on March 13, 2020 and all employees were restricted from coming to work. Per FHS rules, medical charts can only be reviewed in the FHS space. For this reason, little progress occurred on chart review after the FHS space closed. The FHS space remained closed through the end of the fourth quarter. However, we continued to work remotely via teleconference and reassigned some responsibilities so that effort was dedicated to tasks that could be completed virtually. Specifically, contacting living Gen 2 and Omni participants for self-report TBI/RHI questionnaires continued. The participants tended to be at home with less to do, so this was a particularly good time to contact them and collect this data. Similarly, BU office space, where digital slide scanning occurs, closed at the same time, preventing scanning of additional cases. However, outlining anatomic regions on previously scanned slides for quantitation of pathology can be performed remotely and we shifted effort to this front.

FHS participants who agreed to complete the TBI self-report questionnaire were initially given the option to complete the questionnaire by paper mail or online. In the mail format, we initially noticed substantial missing dating and have troubleshooted to determine why. We determined that the mailer left too much flexibility for the participants to skip questions. We have transitioned to the option of online questionnaire or completion over the phone with assistance from an RA. While the data is much more complete with the phone call, it is slower and takes more RA resources.

Changes that had a significant impact on expenditures

We delayed planned expenditures in the first 14 months prior to HRPO approval because research protocol approvals had not been completed. For Covid-related delays, as noted above, we reassigned some responsibilities rather than not paying research staff. However, for chart review, we had planned a large effort over the summer with approximately 10 summer interns with several of them continuing into the fall and winter to rapidly carry out the chart review. We did not bring any of them on because of the Covid-restrictions. For this reason, our spending remains substantially under budget, but allows us to have funds available when the restrictions are relaxed.

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

Significant changes in use or care of human subjects

Nothing to report

Significant changes in use or care of vertebrate animals

N/A

Significant changes in use of biohazards and/or select agents

N/A

6. PRODUCTS:

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

Journal publications.

Nothing to Report

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

Nothing to Report

Other publications, conference papers and presentations.

Nothing to Report

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

Nothing to Report

- **Technologies or techniques**

Nothing to Report

- **Inventions, patent applications, and/or licenses**

Nothing to Report

- **Other Products**

The digital slide images and quantitation we are generating will be a valuable resource for a variety of neuropathology projects that extend beyond TBI-neurodegenerative relationships. For instance, colleagues have expressed interest in using this data to investigate resistance and resilience for AD.

7. PARTICIPANTS & OTHER COLLABORATING ORGANIZATIONS

What individuals have worked on the project?

Name: Jesse Mez
Project Role: PI
Researcher Identifier (e.g. ORCID ID): 0000-0003-1438-5442
Nearest person month worked: 2
Contribution to Project: No Change

Name: Kristen Dams-O'Connor
Project Role: PI
Researcher Identifier (e.g. ORCID ID): 0000-0002-2506-0216
Nearest person month worked: 1
Contribution to Project: No Change

Name: Nicole Saltiel
Project Role: Research Assistant
Researcher Identifier (e.g. ORCID ID): NA
Nearest person month worked: 6
Contribution to Project: No Change

Name: Corina Mangione
Project Role: Research Assistant
Researcher Identifier (e.g. ORCID ID): NA
Nearest person month worked: 3
Contribution to Project: Data quality control, chart review

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

Nothing to Report

What other organizations were involved as partners?

Nothing to Report

8. SPECIAL REPORTING REQUIREMENTS
COLLABORATIVE AWARDS:
QUAD CHARTS:

9. APPENDICES: