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TITLE: Genetic, comorbidities, and ethnicity: Effects of TBI on dementia

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CONTRACTING ORGANIZATION: Northern California Institute for Research and Education
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14. ABSTRACT

Up to 20% of young veterans have had a traumatic brain injury (TBI), with many older veterans having TBI as well. Some epidemiological studies have reported a link between TBI and increased risk of dementia even after years of active life post injury, however, few have examined what factors may increase or decrease the risk of dementia after TBI. In recent decades, as the country has become more racially and ethnically diverse, so has the U.S. military. However, no studies have examined how race and ethnicity may influence the TBI outcomes and risk of developing dementia. Findings have linked TBI with negative socioeconomic, medical and psychiatric consequences. Yet, these factors also have been identified independently as risk factors for cognitive impairment. This new and unique research collaboration will leverage two established epidemiological datasets to investigate factors associated with adverse cognitive outcomes among veterans with head injuries. Our overall hypothesis is that veterans who are non-white, have lower socioeconomic status and education, and those with greater psychiatric and medical comorbidities will have a higher risk of dementia after TBI. Further, we hypothesize that these differences will still be present after accounting for early life exposures and genetics by studying a large cohort of 3000 twin pairs. Finally, we will determine the population attributable risk (PAR) or proportion of dementia attributable to TBI, both among Veterans and non-veterans. This estimate will allow us to compare TBI to other important risk factors in order to design better prevention and intervention strategies and help highlight the public health significance of TBI.

15. SUBJECT TERMS

Dementia, aging, cognitive impairment (CI), Alzheimer's disease (AD), traumatic brain injury (TBI)

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- **INTRODUCTION:** Up to 20% of young veterans have had a traumatic brain injury (TBI), with many older veterans having TBI as well. Some epidemiological studies have reported a link between TBI and increased risk of dementia even after years of active life post injury, however, few have examined what factors may increase or decrease the risk of dementia after TBI. In recent decades, as the country has become more racially and ethnically diverse, so has the U.S. military. However, no studies have examined how race and ethnicity may influence the TBI outcomes and risk of developing dementia. Findings have linked TBI with negative socioeconomic, medical and psychiatric consequences. Yet, these factors also have been identified independently as risk factors for cognitive impairment. This new and unique research collaboration will leverage two established epidemiological datasets to investigate factors associated with adverse cognitive outcomes among veterans with head injuries. Our overall hypothesis is that veterans who are non-white, have lower socioeconomic status and education, and those with greater psychiatric and medical comorbidities will have a higher risk of dementia after TBI. Further, we hypothesize that these differences will still be present after accounting for early life exposures and genetics by studying a large cohort of 3000 twin pairs. Finally, we will determine the population attributable risk (PAR) or proportion of dementia attributable to TBI, both among Veterans and non-veterans. This estimate will allow us to compare TBI to other important risk factors in order to design better prevention and intervention strategies and help highlight the public health significance of TBI.

- **KEYWORDS:** Dementia, aging, cognitive impairment (CI), Alzheimer's disease (AD), traumatic brain injury (TBI)

- **ACCOMPLISHMENTS:**

  - **What were the major goals of the project?**

    - Task 1: Planning and Regulatory Review (Months 1-5)
    - Task 2: Aim 1 - To determine the contribution of sociodemographic factors such as race, ethnicity, education, and socioeconomic status (SES) to the association between TBI and dementia in the VA TBI Cohort. (Months 5-15)
    - Task 3: Aim 2 - Determine the contribution of medical and psychiatric conditions to the association between TBI and dementia in the VA TBI Cohort. (Months 8-24)
    - Task 4: Aim 3 - Capitalizing on the twin design, determine the contribution of sociodemographic factors such as SES and education to the association between TBI and risk of cognitive decline and dementia in the Twin Registry. (Months 6-15)
    - Task 5: Aim 4 - Using the Twin Registry, to determine the contribution of medical and psychiatric conditions to the association between TBI and cognitive decline/dementia. (Months 9-24)
    - Task 6: Aim 5 - Estimate the attributable risk of TBI on dementia among veterans and the portion of that risk attributable to each of the mediating or moderating variables including medical and psychiatric comorbidities. (Months 22-36)

  - **What was accomplished under these goals?**

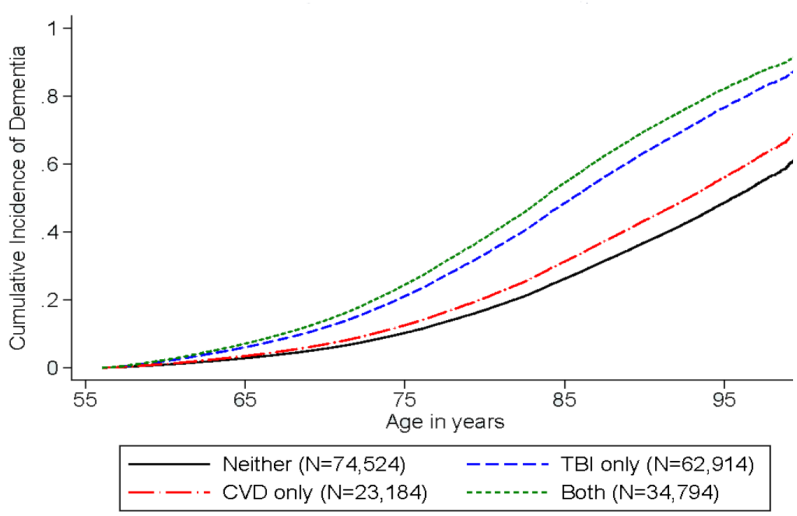
    - In the third year of this project we continue to make excellent progress, continuing the partnership between the UCSF and Duke groups. We have two manuscripts under review and two others in progress. We also submitted and received all continuing IRB reviews at Duke, UCSF, and HRPO.

      Aim 1: Using the VA TBI cohort, the team examined whether sex and race differences exist in dementia risk associated with TBI among older Veterans. In this large, nation-wide cohort of older Veterans, all race groups with TBI had increased risk of dementia, but there was an interaction effect such that White Veterans were at greatest risk for dementia following TBI. We wrote these exciting results into a manuscript, which was published in Neurology in September 2020. The manuscript generated multiple press releases as well as an interesting and favorable editorial by two prominent researchers in the field.

      Aim 2: Using the VA TBI cohort, and in conjunction with the LIMBIC project, we investigated whether cardiovascular disease (CVD) moderates or underlies the association between TBI

and dementia in 195,416 Veterans age 55+ diagnosed with TBI within the VHA and a demographically matched sample of Veterans without TBI.

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



TBI and CVD independently increase risk for dementia among older US Veterans; together they had an additive effect with risk highest for Veterans who have both exposures. The manuscript describing these exciting results is under review.

Aims 3 and 4: In the second year of this project, with the Twin Registry data, we conducted analyses using a clean and finalized dataset for over 15,000 twins which includes demographics, cognitive screening scores, dementia diagnoses and detailed history of traumatic brain injuries.

For Aim 3, a manuscript titled Traumatic Brain Injury and Dementia Risk in Male Veteran Older Twins - Controlling for Genetic and Early Life Non-Genetic Factors has been revised and resubmitted to the journal. For this manuscript, we conducted proportional hazard regression models to estimate the risk of dementia overall, the risk of Alzheimer's disease (AD) and the risk of Non-AD dementias.

Twin hazard models estimated the risk of outcome within the twin pair, adjusting for correlation in risk within the twin pair. The censoring event was onset of dementia, death or one year after last contact. We then ran the triad of models separately for MZ and DZ complete twin pairs. Main results are presented in Table 1.

Table 1. Hazard ratios of TBI and risk of dementia in full sample

	All Dementia Hazard Ratio (95% CI), p-value	Alzheimer's Disease Hazard Ratio (95% CI), p-value	Non-Alzheimer's Disease Dementia Hazard Ratio (95% CI), p-value
Model 1:			
TBI = yes*	1.44 (0.97-2.14), p=0.07	1.23 (0.76-2.00), p=0.39	2.00 (0.97-4.12), p=0.06
Model 2:			
TBI = yes*	1.31 (0.81-2.12), p= 0.28	1.20 (0.68-2.12), p= 0.54	1.60 (0.65-3.95), p= 0.31
Age of TBI < 25 years old	1.23 (0.68-2.22), p=0.49	1.07 (0.52-2.01), p=0.86	1.53 (0.53-4.36), p=0.43
Model 3:			
Monozygotic Twins, n=1618 pairs	1.71 (1.00-2.94), p=0.05	1.85 (0.94-3.63), p=0.08	1.50 (0.61-3.67), p=0.37
Dizygotic Twins, n=1592 pairs	1.15 (0.63-2.09), p=0.21	0.77 (0.37-1.57), p=0.47	3.33 (0.92-12.11), p=0.07
Model 4:			
TBI = yes*	1.40(0.73-2.68), p=0.31	1.40 (0.65-3.02), p=0.39	1.52 (0.45-5.15), p=0.50
Time since TBI (per 10 years)	1.07 (0.88-1.15), p=0.92	0.97 (0.82-1.14), p=0.68)	1.07 (0.85-1.34), p=0.59
Model 5:			
TBI = yes*	2.31 (0.98-5.46), p=0.06	2.48 (0.76-8.10), p=0.13	2.20 (0.62-7.85), p=0.22
TBI with LOC	0.55 (0.23-1.32), p=0.18	0.40 (0.12-1.32), p=0.13	1.00 (0.25-3.95), p=1.00
Model 6:			
TBI = yes*	1.39 (0.91-2.14), p=0.14	1.18 (0.70-1.97), p=0.54	2.03 (0.92-4.50), p=0.08
Number of TBIs ≥1 TBI	1.07 (0.77-1.49), p=0.68	1.12 (0.74-1.69), p=0.61	0.98 (0.57-1.67), p=0.93

TBI= traumatic brain injury; LOC= loss of consciousness; CI = confidence interval.
The number of monozygotic twins and dizygotic twins includes only pairs in which both members of the twin pair participated in the study.

In addition, we conducted co-twin control analyses estimating risk of dementia associated with TBI within twin pairs who were discordant for both TBI exposure and dementia. These analyses have the additional benefit of controlling more completely for many unidentified genetic and early life environmental exposures that are shared within twin pairs. Combined, our results consistently supported an increased risk for non-AD dementia associated with TBI. However, the analyses limited only to monozygotic twin pairs and thus fully controlling for genetic factors, showed an increased risk of AD with TBI compared to the analyses with both monozygotic and dizygotic pairs.

For Aim 4 of the project, we are currently working on an analysis addressing the association between TBI, medical and psychiatric comorbidities, and cognitive decline using linear fixed effects twin pair strata models. These analyses estimate cognitive trajectories based on at least three scores from the modified version of the Telephone Interview for Cognitive Status. Using separate models, we are currently examining if TBI plus covariates of interest (i.e. zygosity, severity of the TBI, age at time of first TBI, number of TBIs, cardiovascular and psychiatric conditions) increase the rate of cognitive decline. We plan to finish this analysis, write up the manuscript, and submit for publication during the No-Cost Extension period.

Aim 5: We conducted a systematic review and preliminary meta-analysis of risk of post-TBI dementia with the aim of specifically investigating contributors to heterogeneity including age, sex, and veteran status. We examined journal articles examining all-cause dementia after all-severity TBI (search window 1/1990-1/2019). We identified observational studies reporting age-adjusted risk for all-cause dementia after TBI among individuals with average age ≥40 years. Data were pooled using random-effects models; between study variability was assessed using the I2 index.

A total of 32 studies, reporting a total of 39 risk estimates, ultimately met all inclusion criteria, were included in the meta-analysis. The overall pooled relative risk (RR) for dementia associated with TBI from these 39 risk estimates, representing 7,634,844 individuals was 1.66 (95% CI 1.42-1.93) indicating that TBI is significantly associated with a 66% increased risk of dementia. As expected, there was substantial heterogeneity (I2 = 98.7%, Q test p<0.001).

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

Population attributable risk (PAR) of dementia due to TBI exposure in the U.S. population, including specifically among U.S. Veterans, men, and women, is reported in the Table below. Of note, women have the lowest estimated PAR while Veterans have the highest estimated PAR. Estimated PAR of dementia due to TBI among U.S. Veterans is twice that of the general U.S. population. Overall, we estimate that approximately 860,700 cases of dementia in the U.S. are attributable to TBI exposure. A manuscript detailing these important results is in process and will submitted for publication soon.

Population	Estimated RR	TBI Prevalence	PAR	Estimated total cases of dementia in U.S.	Estimated cases of dementia attributable to TBI exposure
Total U.S. population	1.52	31%	14%	6,200,000	860,696
U.S. Veterans	2.13	35%	28%	767,544	217,530
U.S. Men	2.07	43%	32%	2,400,000	756,277
U.S. Women	1.43	22%	9%	3,800,000	328,412

Throughout Year 3 of the project, all team members have participated in weekly individual core meetings, monthly project-specific team meetings to review analyses and monitor progress, and we schedule quarterly interdisciplinary team meetings.

- **What opportunities for training and professional development has the project provided?**
  - On this project, Dr. Marianne Chanti-Ketterl, a junior investigator at Duke, has been conducting the analyses examining lifetime history of TBI and cognitive change over time. In the coming year, she will draft the manuscript reporting these analyses. She has also published a manuscript in a well-respected journal and has two other manuscripts under review examining risk factors for cognitive decline in later life. Her work on this project in the area of risk factors for late life cognitive impairment has led to her appointment as a RCMAR scientist for the USC-AD cohort 2021-2022. She also continues to work with the senior statistician on the project, Dr. Carl Pieper, to expand her knowledge of analyses using twin pairs. Dr. Erica Kornblith, a junior investigator at UCSF and the SFVAMC, published a manuscript in a well-respected journal and has another under review. During this project she collaborated with this group's experienced team of researchers, gaining knowledge about traumatic brain injury, Veteran's health, and working with large administrative datasets.
- **How were the results disseminated to communities of interest?**
  - For this project we have selected national and international meetings to disseminate our work through poster and oral presentations in which a broad range of multidisciplinary researchers and clinicians invested in reducing the effects of traumatic brain injury on cognitive aging and improving Veterans' health would be present. We submit our manuscripts to journals that also target multidisciplinary researchers and clinicians who are invested in improving TBI outcomes and Veterans' health.

- **What do you plan to do during the next reporting period to accomplish the goals?**
    - During the no-cost extension period Dr. Yaffe and Dr. Plassman will continue to work together and meet or exceed the goals for this project. For Aim 2, the paper on CVD, TBI, and dementia risk will be published. We are also planning an analysis to look at the bidirectional relationship between TBI and psychiatric comorbidities. The exciting manuscript describing the co-twin control analyses estimating risk of dementia associated with TBI within twin pairs will be published for Aim 3. We will continue to work on the Twin Registry analyses and submit a manuscript on the association between TBI, medical and psychiatric comorbidities, and cognitive decline to address Aim 4 of the grant. For Aim 5, we will finalize the meta-analysis and PAR manuscript and submit for publication. We will continue to hold regular conference calls to facilitate collaboration between the sites.

- **IMPACT:**
    - **What was the impact on the development of the principal discipline(s) of the project?**
        - Nothing to report
    - **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

- **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**
        - Due to the Covid-19 pandemic, both sites experienced some delays. Conducting complex statistical analyses remotely through a secure server, requires a reliable and fast internet connection. Given the vast numbers of employees working remotely, the VPN connection to the campus and VA servers was often unstable or extremely slow. Thus, working remotely due to COVID-19 impacted the efficiency and speed of our work. This same issue had some impact on the compilation of the large datasets of medical and psychiatric conditions, which is a laborious task and also requires a sustained and reliable internet connection. Our productivity was impacted as we settled into a routine working remotely, and we experienced some slight delays in producing manuscripts.
    - **Changes that had a significant impact on expenditures**
        - We estimate that we incurred a 4-6 month delay due to the pandemic and shelter-in-place orders and we requested no-cost extension to complete the project as proposed.
    - **Significant changes in use or care of human subjects, vertebrate animals, biohazards, and/or select agents**
        - N/A

- **PRODUCTS:**
  - **Publications, conference papers, and presentations**
    - **Journal publications.**

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

      Plassman, BL., Chanti-Ketterl, M., Pieper, CF, Yaffe, K. Traumatic Brain Injury and Dementia Risk in Twins - Controlling for Genetic and Early Life Non-Genetic Factors. Under review.

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

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

      Nothing to report

    - **Other publications, conference papers, and presentations.**

      Gardner RC, Bahorik AL, Mangal P, Allen IE, Yaffe K. Novel insights into risk of dementia after traumatic brain injury: a systematic review, meta-analysis, and heterogeneity analysis. Alzheimer's & Dementia: The Journal of the Alzheimer's Association, 16 (S110). 2020 Alzheimer's Association International Conference.

      Chanti-Ketterl, M., Pieper, CF, Yaffe, K, Plassman, BL. (2020) TBI and Increased Risk of Non-Alzheimer's disease dementia in older male twins. Alzheimer's & Dementia: The Journal of the Alzheimer's Association, 16 (S110). 2020 Alzheimer's Association International Conference.

    - **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**

    - Duke compiled approximately 20 years of longitudinal data collection for analyses for this project. The researchers have cleaned and finalized data containing information on demographics, cognitive screening scores traumatic brain injuries, and diagnoses of dementia for over 15,000 twins. UCSF utilized a database containing demographic, psychiatric, medical information, etc., for nearly 2 million veterans who received healthcare in the VA from 2005-2015. The project researchers have used this database for analyses, selected subsamples, and created variables as appropriate for each project.

- **PARTICIPANTS & OTHER COLLABORATING ORGANIZATIONS**

  - **What individuals have worked on the project?**

Name:	Kristine Yaffe
Project Role:	Principal Investigator
Researcher Identifier (e.g. ORCID ID):	KYAFFE
Nearest person month worked:	1
Contribution to Project:	Dr. Yaffe, in coordination with Dr. Plassman, provides scientific leadership and input on the analyses and interpretation of results
Funding Support:	n/a

Name:	Carrie Peltz
Project Role:	Project Coordinator
Researcher Identifier (e.g. ORCID ID):	n/a
Nearest person month worked:	2
Contribution to Project:	Dr. Peltz coordinates the project and assists with data analysis and publication
Funding Support:	n/a

Name:	Feng Xia
Project Role:	Programmer
Researcher Identifier (e.g. ORCID ID):	n/a
Nearest person month worked:	1
Contribution to Project:	Ms. Xia performs statistical analyses for this project.
Funding Support:	n/a

Name:	Maggie Bruck
Project Role:	Research Associate
Researcher Identifier (e.g. ORCID ID):	n/a
Nearest person month worked:	1
Contribution to Project:	Ms. Bruck assists with project coordination, scheduling meetings, assisting with reporting requirements, etc.
Funding Support:	n/a

Name:	Brenda L. Plassman
Project Role:	Co-Principal Investigator
Researcher Identifier (e.g. ORCID ID):	000-0003-2867-7198
Nearest person month worked:	2
Contribution to Project:	Dr. Plassman, in coordination with Dr. Yaffe, provides scientific leadership and input on the analyses and interpretation of results
Funding Support:	n/a

Name:	Marianne Chanti-Ketterl
Project Role:	Co-Investigator
Researcher Identifier (e.g. ORCID ID):	000-002-0438-676X
Nearest person month worked:	5
Contribution to Project:	Dr. Chanti-Ketterl performs statistical analyses for the project
Funding Support:	n/a

Name:	Heather McDonald
Project Role:	Data Manager
Researcher Identifier (e.g. ORCID ID):	n/a
Nearest person month worked:	2
Contribution to Project:	Ms. McDonald is involved in the creation and documentation of datasets
Funding Support:	n/a

Name:	Carl Pieper
Project Role:	Senior Statistician
Researcher Identifier (e.g. ORCID ID):	0000-0003-4809-1725
Nearest person month worked:	1
Contribution to Project:	Dr. Pieper provide directions on statistical analyses and assists with writing manuscripts
Funding Support:	n/a

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

  Summary: Dr. Yaffe had three grants end and two grants begin in the past year.

  Title: Sleep Health Profiles Predicting Impaired Cognition and Depressive Symptoms in Older Adults: Extending Novel Statistical Models in Multi-Cohort Applications
  Time Commitment: 1% (0.12 calendar months)
  Supporting Agency: NIH-NIA
  Performance period: 04/2021 – 03/2024
  Level of funding:

  Title: Doris Duke Fund to Retain Clinical Scientists
  Time Commitment: 1% (0.12 calendar months)
  Supporting Agency: Doris Duke Charitable Foundation
  Performance Period: 01/2021 – 12/2023
  Level of funding:

  Title: Risk and Resiliency for Dementia Comparison of Male and Female Veterans (WAVE)
  (Yaffe: PI)
  Time Commitment: 1% (0.12 calendar months)
  Supporting Agency: DoD
  Performance period: 08/16 – 08/21NCE
  Level of funding:

  Title: Predictors of Cognitive Aging across the Lifecourse
  (Yaffe: PI)
  Time Commitment: 3.0 person months
  Supporting agency: NIH/NIA
  Performance period: 06/2013 – 06/2021 NCE
  Level of funding:

  Title: The ARIC study of midlife sleep and late-life brain amyloid
  Supporting Agency: NIH-NIA
  Performance period: 06/2016 – 3/2021

  Summary: Dr. Plassman had seven grants end and three grants begin in the past year.

  Title: Cognitive Training to Reduce Cognitive Impairment: The PACT Trial
  Supporting agency: NIH/NIA
  Performance period: 02/01/21-1/31/26
  Role: Subcontract PI

  Title: Duke/UNC Alzheimer's Disease Research Center, ORE Core
  Supporting agency: NIH/NIA
  Performance period: 09/01/21-08/31/26
  Role: Co-Investigator

  Title: Preventing Cognitive Decline by Reducing BP Target Trial (PCOT)
  Supporting agency: NIH/NIA
  Performance period: 09/01/21-08/31/25
  Role: Subcontract PI

  Title: National Health and Aging Trends Study
  Time commitments: 0.60 calendar months
  Supporting agency: Johns Hopkins University/NIH

Performance period: 06/01/19-03/31/21
Level of funding:

Title: Pesticides, Olfaction, and Prodromal Neurodegeneration among US Farmers
Time commitments: 2.40 calendar months
Supporting agency: Michigan State University/NIH
Performance period: 02/01/19-01/31/21
Level of funding:

Title: Alzheimer's Disease, Genes, and Pesticide Use in the Agricultural Health Study (plus Administrative Supplement)
Time commitments: 0.78 calendar months (plus additional 0.48 cm for supplement)
Supporting agency: NIH
Performance period: 08/13/14-04/30/21
Level of funding: (Supplement =)

Title: Decision Making for Cardiovascular Therapy in Adults with Mild Cognitive Impairment
Time commitments: 0.60 calendar months
Supporting agency: Regents of the University of Michigan/NIH
Performance period: 09/15/16-05/31/21
Level of funding:

Title: Life Course Process of Alzheimer's Disease: Sex Difference and Biosocial Mechanisms
Time commitments: 1.2 calendar months
Supporting agency: University of North Carolina – Chapel Hill/NIH
Performance period: 09/15/17-08/31/21
Level of funding:

Title: Validation of a Performance Based Measure of Functioning in MCI and Early AD (VRFCAT) (plus Administrative Supplement)
Time commitments: 0.36 calendar months
Supporting agency: VeraSci/NIH
Performance period: 03/15/18-02/28/21
Level of funding: (Supplement =)

Title: Caregivers' Reactions and Experience: Imaging Dementia - Evidence for Amyloid Scanning - CARE IDEAS
Time commitments: 0.72 calendar months
Supporting agency: Brown University/NIH
Performance period: 09/15/17-05/31/21
Level of funding:

- **What other organizations were involved as partners?**
  - Nothing to report

- **SPECIAL REPORTING REQUIREMENTS**
  - Not Applicable

- **APPENDICES:** Nothing to report