

AWARD NUMBER: W81XWH-16-1-0507

TITLE: Risk and Resiliency for Dementia: Comparison of Male and Female Veterans

PRINCIPAL INVESTIGATOR: Kristine Yaffe, MD

CONTRACTING ORGANIZATION: Northern California Institute for Research and Education  
San Francisco, CA

REPORT DATE: December 2021

TYPE OF REPORT: Final

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

DISTRIBUTION STATEMENT: Approved for Public Release;  
Distribution Unlimited

The views, opinions and/or findings contained in this report are those of the author(s) and should not be construed as an official Department of the Army position, policy or decision unless so designated by other documentation.

# REPORT DOCUMENTATION PAGE

Form Approved  
OMB No. 0704-0188

Public reporting burden for this collection of information is estimated to average 1 hour per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing this collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to Department of Defense, Washington Headquarters Services, Directorate for Information Operations and Reports (0704-0188), 1215 Jefferson Davis Highway, Suite 1204, Arlington, VA 22202-4302. Respondents should be aware that notwithstanding any other provision of law, no person shall be subject to any penalty for failing to comply with a collection of information if it does not display a currently valid OMB control number. **PLEASE DO NOT RETURN YOUR FORM TO THE ABOVE ADDRESS.**

<b>1. REPORT DATE</b> December 2021		<b>2. REPORT TYPE</b> Final		<b>3. DATES COVERED</b> 15AUG2016 - 14AUG2021	
<b>4. TITLE AND SUBTITLE</b>  Risk and Resiliency for Dementia: Comparison of Male and Female Veterans				<b>5a. CONTRACT NUMBER</b> W81XWH-16-1-0507	
				<b>5b. GRANT NUMBER</b> 13267015	
				<b>5c. PROGRAM ELEMENT NUMBER</b>	
<b>6. AUTHOR(S)</b>  Kristine Yaffe, MD				<b>5d. PROJECT NUMBER</b>	
				<b>5e. TASK NUMBER</b>	
				<b>5f. WORK UNIT NUMBER</b>	
<b>7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES)</b> Northern California Institute for Research and Education 4150 Clement Street (151 NC) San Francisco, CA 94121-1563				<b>8. PERFORMING ORGANIZATION REPORT NUMBER</b>	
<b>9. SPONSORING / MONITORING AGENCY NAME(S) AND ADDRESS(ES)</b> U.S. Army Medical Research and Development Command Fort Detrick, Maryland 21702-5012				<b>10. SPONSOR/MONITOR'S ACRONYM(S)</b>	
				<b>11. SPONSOR/MONITOR'S REPORT NUMBER(S)</b>	
<b>12. DISTRIBUTION / AVAILABILITY STATEMENT</b> Approved for Public Release; Distribution Unlimited					
<b>13. SUPPLEMENTARY NOTES</b>					
<b>14. ABSTRACT</b> The goal of this project is to identify key factors linked with risk and resiliency for cognitive impairment and dementia in older female veterans. Our overall hypothesis is that older female veterans will have a unique set of risks for cognitive impairment and dementia, with additive increases in risk for factors related to military service, such as post-traumatic stress disorder (PTSD) and traumatic brain injury (TBI). We created a database by extracting Veteran's Health Administration data from all older veteran women and studied these factors to increase our understanding of risk and resiliency in veterans. In a study of older female veterans, we found 10-year prevalence of cognitive impairment diagnoses (including dementia) was 10% and showed important medical and psychiatric risk factors for these diagnoses are also very prevalent, which emphasizes a unique population with specific healthcare burdens. In another study of veteran women, we found military-related risk factors, i.e., PTSD, TBI, and depression increased dementia risk by 50-80% when occurring alone, and 2-fold when occurring together. We also found a history of military sexual trauma is common in veteran women and is associated with several medical and psychiatric diagnoses affecting health and functioning. We found veteran women with alcohol use disorder (AUD) had a 3-fold increase in dementia risk. In a veteran study of sex differences in dementia risk, we found that dementia risk was slightly higher in women than men. These results have been written into five manuscripts: four are published and one is under review. This project contributes key insights into risk factors linked with risk and resiliency for cognitive impairment and dementia in older women veterans, and identify who may benefit from interventions and treatment for dementia and its prevention.					
<b>15. SUBJECT TERMS</b> Dementia, Women, aging, cognitive impairment (CI), Alzheimer's Disease (AD), Traumatic brain injury (TBI), Post-Traumatic Stress Disorder (PTSD)					
<b>16. SECURITY CLASSIFICATION OF:</b>			<b>17. LIMITATION OF ABSTRACT</b>	<b>18. NUMBER OF PAGES</b>	<b>19a. NAME OF RESPONSIBLE PERSON</b>
<b>a. REPORT</b> Unclassified	<b>b. ABSTRACT</b> Unclassified	<b>c. THIS PAGE</b> Unclassified			<b>19b. TELEPHONE NUMBER</b> (include area code)
			Unclassified	15	

## Table of Contents

	<u>Page</u>
Introduction -----	4
Key Words -----	4
Accomplishments -----	4-11
Impact -----	12
Changes/Problems -----	12-13
Products -----	13-14
Participants & Other Collaborating Organizations -----	14-15
Special Reporting Requirements -----	15

## Introduction

Cognitive impairment and dementia are major contributors to declines in day-to-day functioning. Veterans are at high risk for cognitive impairment and dementia due to elevated risk factors and exposure to military risk factors, but most studies have focused on men. Almost no studies have examined dementia risk factors in female veterans, despite their growing numbers and expanding roles in military service. Our goal is to identify key risk factors associated with risk and resiliency for cognitive impairment and dementia among older veterans. Our overall hypothesis is that older female veterans will have unique dementia risks, with an additive increase in risk factors linked to military service. Specifically, we hypothesize: 1) prevalence of cognitive impairment and dementia will be higher for female vs male veterans, and 2) male and female veterans will have unique risk and protective factor profiles for cognitive impairment and dementia, and 3) military risk factors will be linked to increased dementia risk and 4) dementia will increase risk of nursing home placement and mortality, and 5) there will be an additive increase of nursing home placement and mortality in military risk factors with dementia. This project will contribute key insights into the risk factors that are associated with risk and resiliency for cognitive impairment and dementia in veterans and identify who may benefit from interventions and treatment for dementia and its prevention.

## Key Words

Dementia, Women, aging, cognitive impairment (CI), Alzheimer's Disease (AD), Traumatic brain injury (TBI), Post-Traumatic Stress Disorder (PTSD)

## Accomplishments

- **What were the major goals of the project?**
  - Planning and regulatory approvals
    - In the first quarter, the study protocol was approved. We also received approval to obtain data from the Veterans Health Administration (VHA) electronic databases.
  - Obtain and extract data from all veteran women age  $\geq 55$  years old in the VHA health care system
    - Data extraction is complete. We created a database of  $\sim 300,000$  veteran women.
  - Identify prevalence of cognitive impairment and dementia in older veterans and determine key risk factors linked to cognitive impairment and dementia in this population
    - AIM 1 is complete. We completed a study on prevalence of cognitive impairment diagnoses (including dementia), finished a study on sex-differences in dementia risk, and completed another study on alcohol use disorder (AUD) and dementia risk in female veterans. The results have been written into three manuscripts: two published and one under review.
  - Determine military risk factors for cognitive impairment and dementia in older veterans
    - AIM 2 is complete. We finished a study of military risk factors (i.e., post-traumatic stress disorder [PTSD], traumatic brain injury [TBI] and depression) and dementia risk in female veterans, and completed another study on military sexual trauma and comorbidities. We wrote up these results into two manuscripts; both are published.
  - Identify nursing home placement and mortality risk in older veterans according to sex
    - AIM 3: due to unforeseen limitations with the VA nursing home databases, we were not able to address nursing home placement for AIM 3 (p. 12-13 "**Changes/ Problems**").

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

We submitted the study protocol and received full regulatory approval in the first quarter of the project. The study protocol: “Risk and Resiliency for Dementia: Comparison of Male and Female Veterans” received University of California, San Francisco (UCSF) committee on Human Research (CHR) approval on August 26, 2016. The VA Associate Chief of Staff Research and Development Committee (VA ACOS/R&D) committee reviewed and approved this protocol on September 1, 2016. This protocol was approved by the US Army Medical Research and Materiel Command (USAMRMC), Office of Research Protection (ORP), and Human Research Protection Office (HRPO), and received final approval on November 1, 2016. Continuing renewal approval was submitted and received on an annual basis from both UCSF and USAMRMC HRPO (Table 1).

**Table 1. Continuing review approval dates**

UCSF	USAMRMC HRPO
July 13, 2017	August 22, 2017
May 30, 2018	June 22, 2018
March 3, 2019	May 24, 2019
February 7 2020	March 3, 2020
January 1, 2021	January 25, 2021

*UCSF, University of California San Francisco; USAMRMC HRPO, US Army Medical Research and Materiel Command and Human Research Protection Office*

We received approval to obtain data from the VHA National Patient Care Database on November 30, 2016. Once we received the data approvals, investigators and study personnel held monthly project meetings to initiate database development.

Data extraction for the database of all veteran women age  $\geq 55$  years old in the VHA from October 2004 to September 2015 was completed in Year 1. We included approximately 300,000 older veteran women in the VHA from 2004-2015 in our database. Once we developed the database, our monthly project meetings focused on identifying variables to characterize the cohort, and on cleaning and preparing data for analysis. Variables included in our database were sourced from 2 VHA system databases (Table 2).

**Table 2. Summary of variables and data sources assessed**

Category	Variables	Data Source
<i>Demographics</i>	age, race, sex, education, income	NPCD
<i>Health-related risk factors</i>		NPCD
Medical	diabetes, hypertension, MI, TIA/ stroke	NPCD
Psychiatric	current smoking, AUD, SUD	NPCD
<i>Military risk factors</i>	TBI, PTSD, Depression, military sexual trauma	NPCD
<i>Mortality</i>	date of death	Vital Status File Database

NPCD, National Patient Care Database; MI, myocardial infarction; TIA, transient ischemic attack; AUD, alcohol use disorder; SUD, substance use disorder; TBI, traumatic brain injury; PTSD, post-traumatic stress disorder

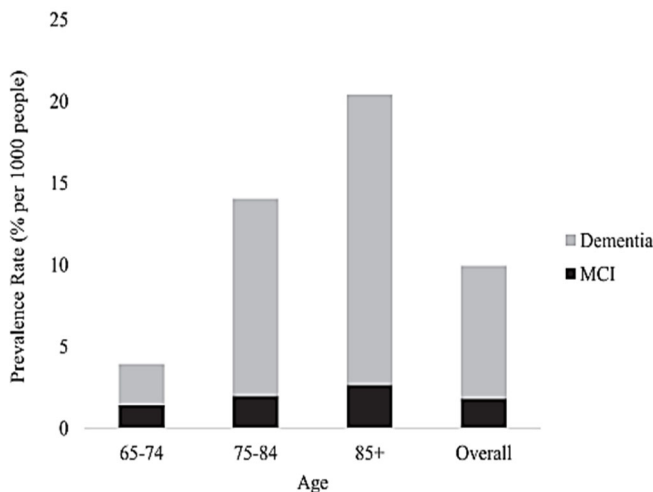
We have used this database of older veteran women for all of our analyses, and have selected subsamples, and created new variables as appropriate for each project. In the past year, we expanded and updated our original database of older female veterans who were receiving care in the VHA health care system between 2004 and 2015, and included all health care visits from 2005 to 2019, and we also included this information on male veterans. We have had four manuscripts accepted for publication based the original database (2004-2015), and one manuscript is under review using the updated database (2004-2019).

In our first analysis (AIM 1), we extracted data from VHA medical records for 168, 111 female veterans aged 65 and older and characterized 10-year prevalence of cognitive impairment diagnoses (i.e., mild cognitive impairment [MCI] and dementia) and associated medical and psychiatric conditions. We defined cognitive impairment diagnoses and medical and psychiatric conditions using International Classification of Diseases, Ninth Revision (ICD-9) codes or dementia diagnoses with medication prescriptions. We computed cognitive impairment prevalence and used generalized linear models to estimate differences in prevalence between women with and without cognitive impairment. The preliminary results were presented at the Alzheimer’s Association International Conference (AAIC) in July of 2018. We also finalized a manuscript, which was published in *The Journal of Geriatric Psychiatry*.

Of the 168, 111 female veterans, 10-year prevalence was 1.8% (3,075) for mild cognitive impairment (MCI) diagnoses and 8.1% (13,653) for dementia. Most female veterans with cognitive impairment were white (MCI: 90%; dementia: 90.9%) and living in ZIP codes with a higher education (MCI: 54.8%; dementia 54.4%). Distribution of income was fairly even across 3 tertiles (low, \$59,539; MCI: 37.8%; dementia: 36.4%; middle, \$43,918 – \$59,539; MCI: 33.1%; dementia: 32.8%; high, >\$59,539; MCI: 37.8%; dementia: 36.4%).

Figure 1 shows prevalence for mild cognitive impairment diagnoses increased with age (MCI age 65: 1.4%; age 85+: 2.7%; dementia age 65: 2.5%; age 85+ 17.7% during the 10-year period); 37.3% had dementia subtype diagnoses, with Alzheimer’s disease being the most prevalent (72.7%).

**FIGURE 1. Ten-year prevalence of cognitive impairment among female veterans stratified by**



LEGEND: Figure 1

MCI, mild cognitive impairment

The figure illustrates the 10-year prevalence of cognitive impairment for female veterans aged 65 years and older stratified by age: 65-74, 75-84, 85+

Table 3 shows female veterans with cognitive impairment had higher prevalence of all medical conditions examined than those without cognitive impairment. Table 4 shows that female veterans with cognitive impairment also had higher prevalence of psychiatric conditions vs those without cognitive impairment.

Overall, our study found 10% of female veterans had cognitive impairment diagnoses (including dementia) and showed important medical and psychiatric risk factors for cognitive impairment are also very prevalent, indicating a unique population with specific health care burdens.

**Table 3. 10-year Prevalence of Medical Comorbidities in Female Veterans with and without Cognitive Impairment**

	no cognitive impairment (N=151,383)	cognitive impairment (N=16,728)	P	Adj p <sup>a</sup>
<b>One or more medical comorbidity</b>	35,648 (23.6)	7,984 (47.7)	<0.001	
<b>Avg. number of medical conditions</b>	1.57 (0.91)	1.76 (0.97)	<0.001	
Cardiometabolic Diseases				
Diabetes	5,656 (3.7)	1,290 (7.7)	<0.001	<0.001
Hypertension	12,872 (8.5)	3,565 (21.3)	<0.001	<0.001
Obesity	3,147 (2.1)	695 (4.2)	<0.001	<0.001
Myocardial Infarction	945 (0.6)	179 (1.1)	<0.001	<0.001
Transient Ischemic Attack/Stroke	3,521 (2.3)	1,086 (6.5)	<0.001	<0.001
Congestive Heart Failure	2,849 (1.9)	495 (3.0)	<0.001	<0.001
Sleep Apnea/Insomnia	1,223 (0.8)	303 (1.8)	<0.001	0.01
Traumatic Brain Injury	843 (0.6)	130 (0.8)	<0.001	0.01
Renal Disease	2,965 (2.0)	422 (2.5)	<0.001	0.01
Chronic Obstructive Pulmonary Disease	6,148 (4.1)	1,109 (6.6)	<0.001	<0.001
Musculoskeletal Pain/Arthritis	14,430 (9.5)	3,349 (20.0)	<0.001	<0.001

Cognitive impairment = diagnoses of dementia or mild cognitive impairment. <sup>a</sup>adjusted for age, race, education, and income.

**Table 4. 10-Year Prevalence of Psychiatric Conditions in Female Veterans with and without Cognitive Impairment**

	no cognitive impairment (N=151,383)	cognitive impairment (N=16,728)	P	Adj p <sup>a</sup>
<b>One or more psychiatric conditions</b>	11,288 (7.5)	3,770 (22.5)	<0.001	
<b>Avg. number of psychiatric conditions</b>	1.19 (0.48)	1.23 (0.51)	<0.001	
PTSD	775 (0.5)	235 (1.4)	<0.001	<0.001
Other Anxiety	3,495 (2.3)	1,119 (6.7)	<0.001	<0.001
Depression	4,495 (3.0)	1,992 (11.9)	<0.001	<0.001
Schizophrenia or Psychoses	905 (0.6)	829 (5.0)	<0.001	<0.001
Tobacco use	2,250 (1.5)	505 (3.0)	<0.001	<0.001
Alcohol Dependence/Abuse	487 (0.3)	160 (1.0)	<0.001	0.01
Drug Dependence/Abuse	438 (0.3)	54 (0.3)	0.23	0.70

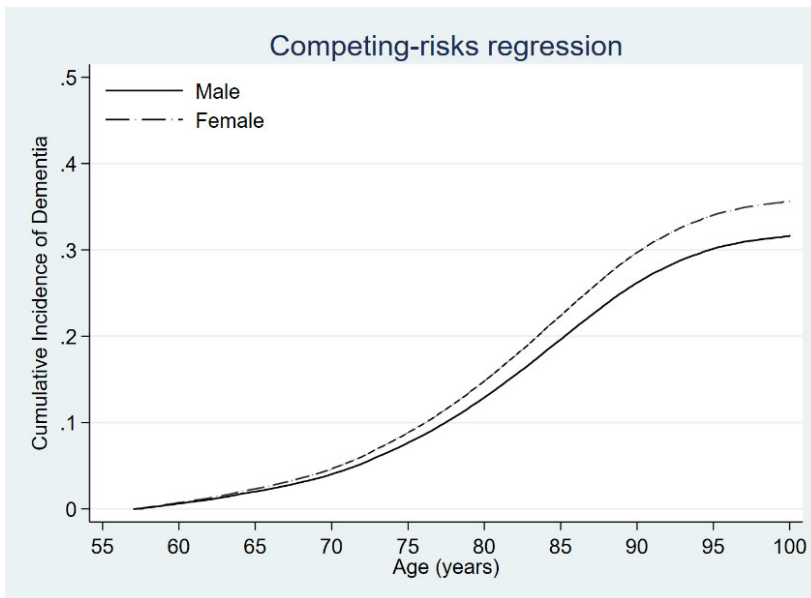
Cognitive impairment = dementia or mild cognitive impairment. <sup>a</sup>adjusted for age, race, education, and income.

In a more recent study for AIM 1, we used data from 947,797 veterans (n=944,814 men, n=29,895 women) obtaining VHA care age ≥ 55 years from October 1999 to September 2019, and investigated sex specific differences in dementia incidence and risk. We estimated age-adjusted dementia incidence by sex and Fine-Gray models were used to estimate time to diagnosis with age as time scale, accounting for the competing risk of death. The results of this study are currently under review.

Veterans were, on average, 70 years old. Age-adjusted rates of incident dementia were similar for male and female veterans. The unadjusted hazard of dementia with age as time scale and accounting for the competing risk of death was slightly higher among females compared to males (HR=1.15 95% CI 1.10-1.20). After adjusting for race/ ethnicity, the adjusted hazard ratio was 1.16 (95% CI 1.11-1.21). Figure 2 shows a higher cumulative incidence of dementia based on age at diagnosis for veteran women vs veteran men and indicates that the curves for the sex groups begin to diverge around age 70.

Overall, the results demonstrated a slightly higher risk of dementia for female veterans compared to male veterans and further emphasize the need to identify the reasons for sex differences in dementia incidence and risk as the aging female veteran population continues to grow.

**FIGURE 2. Age at dementia diagnosis according to sex accounting for mortality**



LEGEND: Figure 2

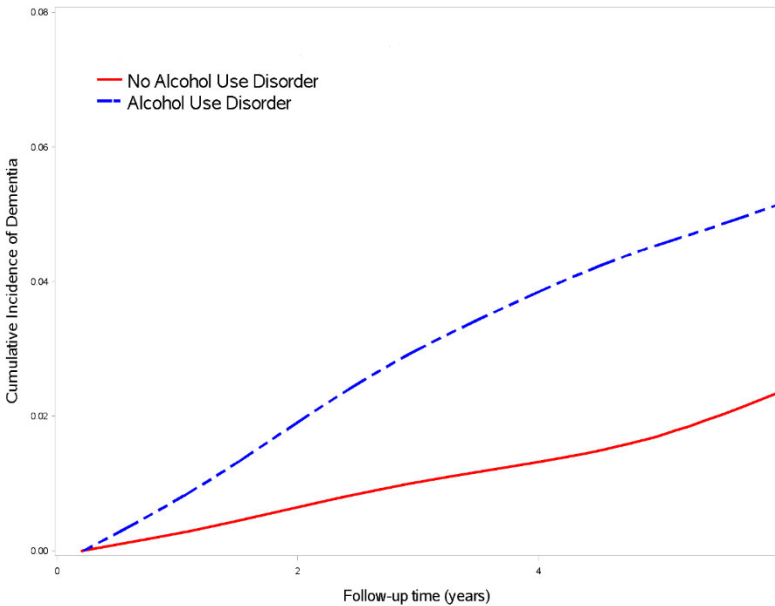
The cumulative incidence of dementia is shown for male (solid line) and female (dashed line) veterans, accounting for the competing risk of death and adjusting for race/ethnicity. Age is used as the timescale to indicate age at dementia diagnosis.

In another study focused on AIM 1, we studied the role of alcohol as a risk factor for dementia. Data were extracted from veteran women aged  $\geq 55$  years old with AUD (n=2207) receiving care at the VHA between October 2004 and September 2015 and an age-matched sample of veteran women without AUD (n = 2207). Cox proportional hazards models were used to determine the association between AUD and dementia risk. The preliminary results were presented at the 2019 AAIC International Conference. A manuscript based on the results of this study was published in *Addiction*.

During approximately 6-years of follow-up, 106 women were diagnosed with dementia (82 with AUD vs 24 without AUD). After adjusting for demographics and comorbidities and accounting for Veterans Integrated Service Network (VISN), the adjusted hazard ratio [aHR] for dementia was 3.12 (95% CI = 1.90-5.12). Figure 3 shows the adjusted cumulative incidence of dementia in women with vs without AUD. Sensitivity analyses yielded similar results, such that the association was similar to our main findings when excluding women with SUD (aHR= 3.35, 95% CI=2.13-5.85) and current smoking (aHR=3.80, 95% CI=2.11-6.84).

Our findings provide an important contribution to the evidence on risks factors associated with dementia. Given that AUD was associated with >3-fold increase of dementia, our results highlight the role of AUD as a potential important modifiable risk factor for dementia and also signal a need for enhancing screening and interventions for older women as part of dementia risk factor management strategies.

**FIGURE 3. Age at dementia diagnosis according to alcohol use disorder diagnosis among female veterans**



*LEGEND: Figure 3*

*The figure shows the cumulative incidence of dementia for female veterans with alcohol use disorder (AUD) (dashed blue line) and female veterans without AUD (solid red line), accounting for Veteran's Integrated Service Network (VISN) and adjusting for medical and psychiatric comorbidities. Age is used as the timescale to indicate age at dementia diagnosis.*

In our first analysis that centered on AIM 2, we included 109,140 female veterans  $\geq$  age 55 years receiving VHA care from October 2004 to September 2015 and studied military-risk factors (TBI, PTSD, depression) and risk of dementia. We used Fine-Gray models to determine the association between military risk factors and dementia, accounting for the competing risk of death. The preliminary results were presented at the AAIC International Conference in July of 2017. We then finalized a manuscript based on the results, which was published in *Neurology*.

We found that veteran women with depression were more likely to be white, while women with TBI and depression lived in areas with a lower education level, and women with TBI lived in less wealthy ZIP codes. Women with PTSD or depression were younger than women with no diagnoses or those with TBI. Women with TBI, depression or PTSD were also more likely to have medical comorbidities (all  $p < 0.05$ ).

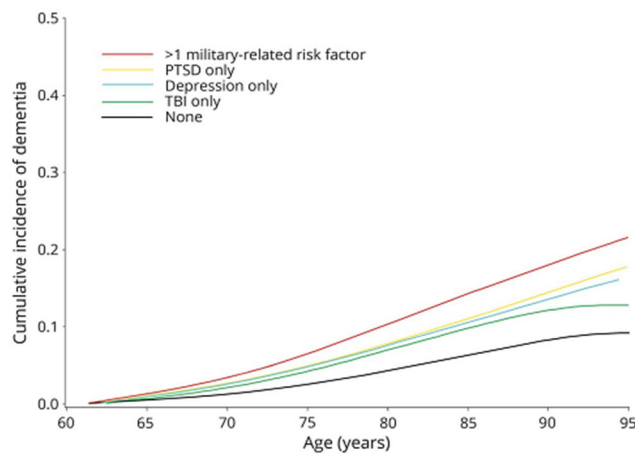
Women with TBI, depression, or PTSD had higher rates of incident dementia compared to women with no military risk factors. Table 5 shows TBI, depression, and PTSD alone increased risk of dementia in models adjusted for demographics and comorbid conditions (TBI-adjusted HR 1.49, 95% CI 1.01-2.20; depression-adjusted HR 1.67, 95% CI 1.55-1.80; PTSD-adjusted HR 1.78, 95% CI 1.34-2.36). Women with >1 military risk factor had the highest risk of dementia (adjusted HR 2.15, 95% CI 1.84-2.51). Cumulative incidence of dementia adjusted for demographics and comorbid conditions in the five groups is shown in Figure 4.

**Table 5. The association between TBI, depression, and PTSD and risk of dementia in female veterans**

Military risk factor	No.	Dementia n (%)	HR (95%CI)		
			Unadjusted	Model 1	Model 2
None	81,135	2,792 (3.4)	<i>ref</i>	<i>ref</i>	<i>ref</i>
TBI only	488	28 (5.7)	1.64 (1.12-2.39)	1.58 (1.07-2.32)	1.49 (1.01-2.20)
Depression only	20,410	1,055 (5.2)	1.78 (1.66-1.91)	1.75 (1.63-1.88)	1.67 (1.55-1.80)
PTSD only	1,363	53 (3.9)	1.81 (1.37-2.39)	1.84 (1.39-2.43)	1.78 (1.34-2.36)
>1 Risk Factor	5,044	197 (3.9)	2.41 (2.07-2.80)	2.32 (1.99-2.71)	2.15 (1.84-2.51)

Model 1: adjusted for demographics (age, race, education, income) Model 2: Model 1 + adjusted for comorbidities (diabetes, hypertension, myocardial infarction, transient ischemic attack/stroke, alcohol abuse, tobacco use)

**FIGURE 4. Cumulative incidence of dementia in veteran women accounting for mortality**



LEGEND: Figure 4

Dementia risk associated with the 5 groups of military risk factors is illustrated by showing the cumulative incidence of dementia with age as the time scale for veteran women with >1 risk factor (red), post-traumatic stress disorder (PTSD) only (yellow), depression only (blue), traumatic brain injury (TBI) only, or none (black). The model was adjusted for demographics, and comorbid conditions and accounted for the competing risk of death.

Our study of female veterans showed that military risk factors increased dementia risk by 50% to 80% when occurring independently and 2-fold when occurring together. These results emphasize the need for more comprehensive studies of dementia risk among female veterans, and highlight the role of military-related risk factor screening and treatment to reduce dementia risk.

In another study (AIM 2), we included 70,864 veteran women aged  $\geq 55$  (mean age 65.8 y) in VHA care from 2005 to 2015 and described military sexual trauma (MST), including prevalence, and common comorbidities. We categorized MST based on responses to a VA MST screening questionnaire. We used logistic regression models to examine the association between MST, psychiatric and medical conditions. We presented preliminary results at the 2018 Society for Traumatic Stress Studies International Conference. We then conducted a few additional analyses and wrote up a manuscript, which was published in the *Journal of General Internal Medicine*.

Overall, a positive MST screen was documented for 13% of women. Women with a positive MST screen were younger (mean age 60.7 vs 66.6,  $p < 0.001$ ) and more likely to be divorced/separated (41% vs 20%, overall  $p < 0.001$ ). Education and income were not associated with MST screen response. Hypertension (66%), hyperlipidemia (60%) and diabetes (25%) were the most common medical diagnoses. The most common psychiatric diagnoses were depression (34%), anxiety (21%), and PTSD (10%).

Table 6 shows in multivariable analyses adjusted for age, race/ethnicity, and marital status, a positive MST screen was associated with greater odds for obesity, chronic pain, back pain, insomnia, sleep apnea, and most mental health diagnoses. Table 7 shows that a positive MST screen was associated with >7 times the odds (95% CI 6.84-7.68) of PTSD and over 2-fold odds of depression and suicidal ideation, and greater odds of anxiety, AUD, SUD, and opioid use disorder.

**Table 6. Medical diagnoses by MST screening status**

Characteristic	Positive MST Screen (n=9,514, 13.4%)	Negative MST Screen (n=61,350, 86.6%)	Adjusted Odds Ratio (95% CI)
<b>Cardiometabolic Disease</b>			
Diabetes	2,493 (26.2)	15,297 (24.9)	1.03 (0.98, 1.09)
Hypertension	5,719 (60.1)	41,083 (67.0)	0.88 (0.84, 0.92)
Hyperlipidemia	5,793 (60.9)	36,930 (60.2)	0.98 (0.94, 1.03)
Myocardial Infarction	245 (2.6)	1,763 (2.9)	1.03 (0.90, 1.19)
Cerebrovascular disease	988 (10.4)	6,984 (11.4)	1.12 (1.04, 1.21)*
Congestive heart failure	537 (5.6)	4,337 (7.1)	1.14 (1.03, 1.25) <sup>†</sup>
Obesity	3,623 (38.1)	17,462 (28.5)	1.15 (1.10, 1.21) <sup>‡</sup>
<b>Pain</b>			
Chronic pain conditions	2,231 (23.5)	8,043 (13.1)	1.58 (1.50, 1.67) <sup>‡</sup>
Back pain	4,446 (46.7)	21,310 (34.7)	1.40 (1.34, 1.47) <sup>‡</sup>
Dementia	310 (3.3)	4,854 (7.9)	0.99 (0.88, 1.13)
<b>Sleep disorders</b>			
Insomnia	394 (4.1)	1,335 (2.2)	1.61 (1.43, 1.82) <sup>‡</sup>
Sleep apnea	891 (9.4)	3,156 (5.1)	1.48 (1.37, 1.61) <sup>‡</sup>
Menopause symptoms	2,250 (23.7)	11,286 (18.4)	1.03 (0.97, 1.08)

All models adjusted for age, race/ethnicity, and marital status. \*p<.01, <sup>†</sup>p=.01, <sup>‡</sup>p<.001

**Table 7. Medical diagnoses by MST screening status**

Characteristic	Positive MST Screen (n=9,514, 13.4%)	Negative MST Screen (n=61,350, 86.6%)	Adjusted Odds Ratio (95% CI)
Anxiety	3371 (35.4)	11,222 (18.3)	1.99 (1.89, 2.09)*
Depression	5393 (56.7)	18,754 (30.6)	2.39 (2.28, 2.50)*
PTSD	3362 (35.3)	3420 (5.6)	7.25 (6.84, 7.68)*
Tobacco use	2421 (25.5)	12,240 (20.0)	1.00 (0.95, 1.05)
Alcohol use disorder	859 (9.0)	2430 (4.0)	1.71 (1.57, 1.86)*
Substance use disorder	510 (5.4)	1204 (2.0)	1.88 (1.69, 2.10)*
Opioid use disorder	136 (1.4)	346 (0.6)	1.77 (1.44, 2.17)*
Suicidal ideation	276 (2.9)	534 (0.9)	2.42 (2.08, 2.82)*

All models adjusted for age, race/ethnicity, and marital status.

\*p<.001

Our findings indicate that positive MST screens are prevalent and associated with numerous medical and mental health conditions in veteran women. Our findings also suggest a need for additional research and highlight the importance of trauma-informed care approaches for women across the lifespan.

- **What opportunities for training/professional development has the project provided?** Nothing to report
- **How were the results disseminated to communities of interest?**
  - Preliminary results were presented at national and international meetings for researchers and clinicians invested reducing effects of cognitive aging and improving veteran’s health. The final results have been published or are under review in peer-reviewed journals.
- **What do you plan to do during the next reporting period to accomplish the goals?** Nothing to report

### Impact

- **What was the impact on the development of the principal discipline(s) of the project?**
  - We were one of the first research groups to leverage administrative VHA data for all female veterans aged  $\geq 55$  years old and examine key factors linked with cognitive impairment and dementia in this population. We were also one of the first research groups to report 10-year prevalence of cognitive impairment (including dementia) and related medical and psychiatric conditions in female veterans. Our results highlighted very important medical and psychiatric conditions that are very prevalent in female veterans, which emphasize a unique population with specific health care burdens. In another study of female veterans, we found that military-related risk factors, such as PTSD, TBI, and depression increase dementia risk by 50% to 80% when occurring alone and 2-fold when occurring together. We also were one of the first research groups to show that a history of MST is common and associated with several medical and psychiatric diagnoses in female veterans, affecting health and functioning. In another study, our results showed that older female veterans with AUD had a 3-fold risk of developing dementia compared to women without AUD, which emphasize the need for increased screening for both AUD and dementia in this population. In a study of sex-differences in dementia risk, we found that women veterans had a slightly increased risk for developing dementia compared to veteran men. Together, the implications from these studies emphasize that more comprehensive investigations are needed into prevention, treatment, and care of dementia for female veterans. Future studies building on these findings and examining the long-term health and cognitive consequences of veterans may help determine the critical role of risk factor screening to reduce dementia risk and assist in determination of more comprehensive treatment planning and dementia care.
- **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**
  - As mentioned in previous reports, we experienced minor delays in data processing and analyses for manuscripts in progress due to shelter-in-place orders from the COVID-19 pandemic. The VA servers that we use for our projects were running slowly as a result of more people working for home and accessing the servers from home. Due to these unexpected delays, we requested and received a 1-year NCE (Year 5) to finish the project as proposed and awarded. Furthermore, we regret that we were not able to directly address nursing home placement as we intended as

part of AIM 3. Once we got into the data, we realized that there were too much data missing to produce meaningful results. The datafiles we had access to only had data available for veteran women who were placed in veteran nursing homes, and the total number available for analysis was modest. Furthermore, we were certain that we would be missing veteran women who had been placed in non-VA nursing homes. Because of these issues, we determined that we would not be able to deliver meaningful results for AIM 3.

- **Changes that had a significant impact on expenditures**
  - We were awarded the grant on August 15, 2016, but initial spending was delayed due to delays in obtaining 1st level approval from the UCSF institutional review board and 2nd level approval from HRPO. Per institutional regulations, we are required to have regulatory approvals in place before we can begin to spend. In Year 1 Quarter 2, we added two investigators to the project, but they were unable to take their level of effort as detailed in the budget until Year 1 Quarter 4 due to unforeseen commitments. We added all project staff and investigators during Year 1 Quarter 4 as detailed in the budget. Because of these delays in work and in initial spending, we received and completed a 1-year NCE (Year 4). As described above, due to delays related to the COVID-19 pandemic, we received and completed a 1-year NCE to finish the project as proposed and awarded (Year 5).
- **Significant changes in use or care of human subjects, vertebrate animals, biohazards, and/or select agents.** Nothing to report

## Products

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

Publications:

    1. Lwi SJ, Barnes DE, Xia F, Peltz C, Hoang T, Yaffe K. 10-Year Prevalence of Cognitive Impairment Diagnoses and Associated Medical and Psychiatric Conditions in a National Cohort of Older Female Veterans. *The American Journal of Geriatric Psychiatry*. 2019; 27(4): 417-425
    2. Yaffe K, Lwi SJ, Hoang TD, Xia F, Barnes DE, Maguen S, Peltz CB. Military-related risk factors in female veterans and risk of dementia. *Neurology*. 2019; 92(3):e205-e211
    3. Gibson CJ, Maguen S, Xia F, Barnes DE, Peltz CB, Yaffe K. Military Sexual Trauma in Older Women Veterans: Prevalence and Comorbidities. *Journal of General Internal Medicine*. 2019; 35(1): 207-13
    4. Bahorik A, Bobrow K, Hoang T, Yaffe K. Increased risk of dementia in older female US veterans with alcohol use disorder. *Addiction*. 2021; 116:209-2055
    5. Eastman J, Bahorik A, Kornblith E, Xia F, Yaffe K. Sex Differences in the Risk of Dementia in Older Veterans. *Under Review*.
  - **Books or other non-periodical, one-time publications.** Nothing to report
  - **Other publications, conference papers, and presentations.**

1. Peltz C, Byers A, Barnes D, Xia F, Yaffe K. Common Psychiatric Conditions in Female Military Veterans and Risk of Dementia. Abstract presented as a platform presentation at the *2017 Alzheimer’s Association International Conference, London, UK.*
2. Barnes D, Hoang T, Lwi S, Peltz C, Xia F, Yaffe K. Prevalence of Dementia and Associated Conditions in a National Cohort of Older Female Veterans. Abstract presented as a poster presentation at the *2018 Alzheimer’s Association International Conference, Chicago IL.*
3. Gibson CJ, Maguen S, Barnes D, Peltz C, Yaffe K. Military Sexual Trauma and Chronic Pain among Older Women Veterans. Abstract presented as a poster at the *2018 International Society for Traumatic Stress Studies Annual Meeting, Washington, DC.*
4. Baborik AL, Barnes DE, Xia F, Hoang TD, Tangog E, Yaffe K. Alcohol use disorders in female veterans and the impact on dementia risk. *Abstract presented as a poster at the 2019 Alzheimer’s Association International Conference, Los Angeles, CA.*
5. Kornblith E, Peltz C, Xia F, Barnes D, Byers A, Yaffe K. Race but not sex differences in incidence of dementia diagnosis among older veterans. *Abstract presented as a poster at the 2020 Alzheimer’s Association International Conference, Amsterdam, Netherlands.*

- **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

**Participants and other collaborating organizations**

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

Name:	Kristine Yaffe – no change
Name:	Carrie Peltz –no change
Name:	Feng Xia –no change
Name:	Willa Brenowitz – no change

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

**Dr. Yaffe:**

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

End

Title: The ARIC study of midlife sleep and late-life brain amyloid

Name of PD/PI: Adam Spira

Status of support: completed

Supporting Agency: NIH/NIA

Primary place of performance: Johns Hopkins University

Performance Period: 06/16 – 03/21

Title: Leveraging New Data on Cognitive Aging & Dementia from Around the World  
 Name of PD/PI: Kristine Yaffe/ Rose Anne Kenney  
 Status of support: completed  
 Supporting Agency: Global Brain Health Institute  
 Primary place of performance: University of California, San Francisco  
 Performance Period: 06/18 – 12-20

Begin

Title: UCSF Population Based Research for Alzheimer’s Innovation (POP BRAIN)  
 Name of PD/PI: Kristine Yaffe  
 Supporting Agency: NIH/NIA  
 Primary Place of Performance: University of California San Francisco  
 Performance Period: 07/21 – 06-26  
 Total Award Amount (including indirect costs):  
 Person Months per budget period:

Year	Person Months
7/21-6/22	6.0
7/22-6/23	6.0
7/23-6/24	6.0
7/24-6/25	6.0
7/25-6/26	6.0

Title Sleep Health Profiles Predicting Impaired Cognition and Depressive Symptoms in Older Adults:  
 Extending Novel Statistical Models in Multi-Cohort Applications  
 Name of PD/PI: Meredith Wallace  
 Supporting Agency: NIA  
 Primary Place of Performance: University of Pittsburgh  
 Performance Period: 04/21 – 03/24  
 Total Award Amount (including indirect costs):  
 Person Months per budget period:

Year	Person Months
4/21-3/22	0.12
4/22-3/23	0.12
4/23-3/24	0.12

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

**Special Reporting Requirements**  
 Nothing to Report