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

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Fort Detrick, Maryland 21702-5012

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

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The goal of this project is to compare the differences in risk and resiliency factors for cognitive impairment and dementia among older male and female Veterans. Our overall hypothesis is that male and female Veterans will each have a unique set of risk factors for these adverse health outcomes and that there will be an additive increase in risk related to military service factors including post-traumatic stress disorder and traumatic brain injury. In the first year of the project we received all IRB approvals (local and HRPO) and assembled a dataset of all women veterans aged 55 and older who received care in the VHA between 2005 and 2015. We finalized an analysis examining the relationship between TBI, PTSD, and depression on dementia risk in veteran women. We found that both depression and PTSD alone increased the risk of dementia (depression hazard ratio (HR)=1.76 fully adjusted (95% confidence interval (CI): 1.65, 1.88); PTSD HR= 1.71 fully adjusted (95%CI: 1.36, 2.16)). The co-occurrence of depression and PTSD also increased the risk of dementia (HR=1.63 fully adjusted (95%CI: 1.38, 2.16)). The TBI plus depression and/or PTSD group had the highest risk of dementia (HR=2.36 fully adjusted (95%CI: 1.56, 3.57)). These results were presented at the 2017 Alzheimer’s Association International Conference. We plan to publish these results in the next few months. Identification of gender differences in key risk and resiliency factors for dementia will help target appropriate care and treatment for Veteran patients.
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1. **INTRODUCTION:** Narrative that briefly (one paragraph) describes the subject, purpose and scope of the research.

Cognitive impairment and dementia are major contributors to declines in functional independence, however, existing studies have primarily focused on male Veterans, even though the number of female Veterans is increasing with an expected concomitant rise in the population of older female Veterans at risk for dementia. Our goal is to compare the differences in risk and resiliency factors for cognitive impairment and dementia among older male and female Veterans. Our overall hypothesis is that male and female Veterans will each have a unique set of risk factors for these adverse health outcomes and that there will be an additive increase in risk related to military service factors including post-traumatic stress disorder and traumatic brain injury. We plan to capitalize on our prior experience working with the Veterans Health Administration National Patient Care Database. We will use data from this well-defined, existing cohort of Veterans age 55 years and older to gain key insights into the factors that are associated with health and military-related risk factors for cognitive impairment and dementia in older male and female Veterans.

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

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

3. **ACCOMPLISHMENTS:** The PI is reminded that the recipient organization is required to obtain prior written approval from the awarding agency Grants Officer whenever there are significant changes in the project or its direction.

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

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

1. Planning and regulatory approval: Months 1-5
   - Study IRB protocols were approved by local UCSF IRB and by HRPO in the first quarter of the project. We also submitted and received approval to receive data from the Veterans Health Administration (VHA) National Patient Care Database (NPCD)
2. Obtain data from the Veterans Health Administration (VHA) National Patient Care Database (NPCD): Months 6-12
   - In the second quarter, we submitted and received approval to receive data from the VHA NPCD
   - In the third quarter, we cleaned and prepared the data for analysis
3. Specific Aim 1: Months 12-19
   - We have completed one analysis and are currently writing it up for publication.
4. Specific Aim 2: Months 20-26
   - Nothing to report
5. Specific Aim 3: Months 27-33
   - Nothing to report

**What was accomplished under these goals?**

For this reporting period describe: 1) major activities; 2) specific objectives; 3) significant results or key outcomes, including major findings, developments, or conclusions (both positive
and negative); and/or 4) other achievements. Include a discussion of stated goals not met. Description shall include pertinent data and graphs in sufficient detail to explain any significant results achieved. A succinct description of the methodology used shall be provided. As the project progresses to completion, the emphasis in reporting in this section should shift from reporting activities to reporting accomplishments.

In the first quarter of the project, we obtained first level UCSF IRB, VA ACOS/R&D, and second level HRPO approval for our study protocol. In the second quarter of the project, we received the data approvals to receive data from the Veterans Health Administration (VHA) National Patient Care Database (NPCD) for this project. We requested data on all women aged 55+. In the third quarter of the project, we began compiling the datasets from the Veterans Health Administration (VHA) National Patient Care Database (NPCD) we requested for this project. We received data on all women aged 55+ in the VHANPCD, approximately 300,000 individuals. We cleaned the data and created the variables needed for our first analyses.

In the fourth quarter of the project we ran and completed an analysis examining the relationship between TBI, PTSD, and depression on dementia risk in veteran women. We found that both depression and PTSD alone increased the risk of dementia [depression hazard ratio (HR)=1.76 fully adjusted (95% confidence interval (CI): 1.65, 1.88); PTSD HR= 1.71 fully adjusted (95%CI: 1.36, 2.16)]. The co-occurrence of depression and PTSD also increased the risk of dementia (HR=1.63 fully adjusted (95%CI: 1.38, 2.16)). The TBI plus depression and/or PTSD group had the highest risk of dementia (HR=2.36 fully adjusted (95%CI: 1.56, 3.57)). Cumulative incidence of dementia in the six groups (None, depression only, PTSD only, TBI only, depression plus PTSD, and TBI plus depression and/or PTSD) is shown below. These results were written up into an abstract and presented as an oral presentation at the 2017 Alzheimer’s Association International Conference.

Cumulative Incidence of Dementia Among Older Women Veterans by TBI and Depression and PTSD
**What opportunities for training and professional development has the project provided?**

If the project was not intended to provide training and professional development opportunities or there is nothing significant to report during this reporting period, state “Nothing to Report.”

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

Nothing to report

**How were the results disseminated to communities of interest?**

If there is nothing significant to report during this reporting period, state “Nothing to Report.”

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

Nothing to report

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

If this is the final report, state “Nothing to Report.”

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

In the next year, we will write up the results of the depression, PTSD, and TBI and dementia analysis and submit for publication. We will further use the dataset we created of all older women veterans to examine risk factors for dementia. We continue to hold regular study meetings with all study investigators and personnel to plan analyses and discuss progress.

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

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

If there is nothing significant to report during this reporting period, state “Nothing to Report.”

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

Nothing to report

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

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

Nothing to report

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

Describe ways in which the project made an impact, or is likely to make an impact, on commercial technology or public use, including:

- transfer of results to entities in government or industry;
- instances where the research has led to the initiation of a start-up company; or
- adoption of new practices.

Nothing to report

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

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

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

Nothing to report

5. CHANGES/PROBLEMS: The Project Director/Principal Investigator (PD/PI) is reminded that the recipient organization is required to obtain prior written approval from the awarding agency Grants Officer whenever there are significant changes in the project or its direction. If not
Changes in approach and reasons for change
Describe any changes in approach during the reporting period and reasons for these changes. Remember that significant changes in objectives and scope require prior approval of the agency.

Nothing to report

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

Nothing to report

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

Although, we were awarded the grant on 15-AUG-2016, due to delays from first level UCSF IRB, VA ACOS/R&D, and second level HRPO approval, we were delayed in initiating spending. Per our institutional rules, we are required to have approvals in place before we can begin to spend. In the second quarter, two investigators were added to the project; however, they are unable to take their level of effort detailed in the budget until the 4th quarter due to unforeseen prior commitments. We added all staff and investigators in the 4th quarter as detailed in the budget.

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

Significant changes in use or care of human subjects

Nothing to report

Significant changes in use or care of vertebrate animals

Nothing to report
Significant changes in use of biohazards and/or select agent

Nothing to report

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

- **Publications, conference papers, and presentations**
  Report only the major publication(s) resulting from the work under this award.

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

  Nothing to report

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

  Nothing to report

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

  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.

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

  Nothing to report
• Technologies or techniques
Identify technologies or techniques that resulted from the research activities. In addition to a description of the technologies or techniques, describe how they will be shared.

Nothing to report

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

Nothing to report

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

We created a database containing demographic, psychiatric, medical information, etc., for all women age 55 and over who received healthcare in the VA from 2005-2015.

7. PARTICIPANTS & OTHER COLLABORATING ORGANIZATIONS

What individuals have worked on the project?
Provide the following information for: (1) PDs/PIs; and (2) each person who has worked at least one person month per year on the project during the reporting period, regardless of the source of compensation (a person month equals approximately 160 hours of effort). If information is unchanged from a previous submission, provide the name only and indicate “no change.”
<table>
<thead>
<tr>
<th>Name</th>
<th>Kristine Yaffe</th>
</tr>
</thead>
<tbody>
<tr>
<td>Project Role</td>
<td>Principal Investigator</td>
</tr>
<tr>
<td>Researcher Identifier (e.g. ORCID ID)</td>
<td>KYAFFE</td>
</tr>
<tr>
<td>Nearest person month worked:</td>
<td>1</td>
</tr>
<tr>
<td>Contribution to Project:</td>
<td>Dr. Yaffe provides leadership and oversees research activities.</td>
</tr>
<tr>
<td>Funding Support:</td>
<td>n/a</td>
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<table>
<thead>
<tr>
<th>Name</th>
<th>Deborah Barnes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Project Role</td>
<td>Co-Investigator</td>
</tr>
<tr>
<td>Researcher Identifier (e.g. ORCID ID)</td>
<td>BARNESD</td>
</tr>
<tr>
<td>Nearest person month worked:</td>
<td>1</td>
</tr>
<tr>
<td>Contribution to Project:</td>
<td>Dr. Barnes provides expertise on dataset creation, data analysis, and is involved in manuscript publication.</td>
</tr>
<tr>
<td>Funding Support:</td>
<td>n/a</td>
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<table>
<thead>
<tr>
<th>Name</th>
<th>Shira Maguen</th>
</tr>
</thead>
<tbody>
<tr>
<td>Project Role</td>
<td>Co-Investigator</td>
</tr>
<tr>
<td>Researcher Identifier (e.g. ORCID ID)</td>
<td>SMAGUEN</td>
</tr>
<tr>
<td>Nearest person month worked:</td>
<td>1</td>
</tr>
<tr>
<td>Contribution to Project:</td>
<td>Dr. Maguen provides expertise in women’s mental health and is involved in manuscript publication.</td>
</tr>
<tr>
<td>Funding Support:</td>
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<table>
<thead>
<tr>
<th>Name</th>
<th>Carrie Pelz</th>
</tr>
</thead>
<tbody>
<tr>
<td>Project Role</td>
<td>Project Coordinator</td>
</tr>
<tr>
<td>Researcher Identifier (e.g. ORCID ID)</td>
<td>n/a</td>
</tr>
</tbody>
</table>
Dr. Yaffe:

Summary: Dr. Yaffe had one grant end and one grant begin in the past year.

Title: Healthy Heart, Healthy Brain? A Pooled Life-course Cohort for Dementia Risk Assessment (Yaffe: co-PI)
Time Commitment: 1.35 calendar months
Supporting Agency: NIA
Performance Period: 05/01/17-04/30/21
Level of Funding: $1,384,845 TDC

Title: Frontotemporal Dementia: Genes, Images, and Emotions: Data Management and Biostatistics Core (Yaffe: co-PI)
Time Commitment: 0.12 calendar months
Supporting Agency: NIA
Performance Period: 09/01/12-08/31/17
Level of Funding: $663,642 TDC
**Dr. Barnes:**

Dr. Barnes had no changes to her support in the past year.

**Dr. Maguen:**

Summary: Dr. Maguen had three grants begin and one end in the past year.

<table>
<thead>
<tr>
<th>Title</th>
<th>Time Commitment</th>
<th>Supporting Agency</th>
<th>Performance Period</th>
<th>Level of Funding</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pilot Test of Telephone-Delivered Cognitive Behavioral Therapy for Insomnia for Veterans with Gulf War Illness (PI: Chao, Co-Investigator: Maguen)</td>
<td>1.2 calendar months</td>
<td>VA SCR&amp;D Merit</td>
<td>07/01/16-08/31/19</td>
<td>$236,795</td>
</tr>
<tr>
<td>Improving Care for Veterans with PTSD: Comparing Effectiveness of Medications to Augment First-line Pharmacotherapy (PI: Cohen, Co-Investigator: Maguen)</td>
<td>1.2 calendar months</td>
<td>VA SCR&amp;D Merit</td>
<td>07/01/16-08/31/19</td>
<td>$315,351</td>
</tr>
<tr>
<td>Improving Frontal Emotion Regulation in PTSD by Targeting Sleep (PI: Neylan, Co-Investigator: Maguen)</td>
<td>0.6 calendar months</td>
<td>NIH</td>
<td>10/01/16-09/30/17</td>
<td>$499,643</td>
</tr>
<tr>
<td>Women, Trauma and Eating (PI: Maguen)</td>
<td>1.2 calendar months</td>
<td>Northern California Institute for Research and Education</td>
<td>10/01/12-09/30/16</td>
<td>$38,235</td>
</tr>
</tbody>
</table>

What other organizations were involved as partners?

*If there is nothing significant to report during this reporting period, state “Nothing to Report.”*

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

Provide the following information for each partnership:

- **Organization Name:**
- **Location of Organization:** (if foreign location list country)
- **Partner’s contribution to the project** (identify one or more)
  - Financial support;
  - In-kind support (e.g., partner makes software, computers, equipment, etc., available to project staff);
  - Facilities (e.g., project staff use the partner’s facilities for project activities);
• Collaboration (e.g., partner’s staff work with project staff on the project);
• Personnel exchanges (e.g., project staff and/or partner’s staff use each other’s facilities, work at each other’s site); and
• Other.

Nothing to report

8. SPECIAL REPORTING REQUIREMENTS

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

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

9. APPENDICES: Attach all appendices that contain information that supplements, clarifies or supports the text. Examples include original copies of journal articles, reprints of manuscripts and abstracts, a curriculum vitae, patent applications, study questionnaires, and surveys, etc.
Risk and Resiliency for Dementia: Comparison of Male and Female Veterans
(#AZ150046)
W81XWH-16-1-0507

PI: Dr. Kristine Yaffe  Org: Northern California Institute of Research and Education  Award Amount: $642,152 (Directs + F&A)

**Study/Product Aim(s)**

- **Aim 1.** Compare prevalence of mild cognitive impairment and dementia among male and female veterans receiving VHA healthcare and identify key health-related risk factors for developing cognitive impairment
- **Aim 2.** Examine the associations between key military related factors and diagnoses of mild cognitive impairment and dementia among older female and male veterans
- **Aim 3.** Determine whether the risk of nursing home placement and mortality differs between older female and male veterans with a documented diagnosis of dementia, and examine whether there are gender specific associations between military and health-related factors and nursing home placement and mortality

**Approach**

We propose a series of specific aims that capitalize on existing national databases to further our understanding of the association between dementia, gender, and risk factors for cognitive impairment.

**Goals/Milestones**

**Year 1 Goal**
- Obtain all necessary regulatory approvals
- Clean and prepare data

**Year 2 Goals**
- Conduct Analyses for Aims 1-3

**Year 3 Goal**
- Write Manuscripts
- Dissemination and Publication

**Comments/Challenges/Issues/Concerns**
- We have received IRB and HRPO approval, as well as approval and access to VHA databases
- We encountered budgetary delays due to a slower start-up than anticipated and plan to use the unspent funds for the same purpose as proposed and awarded

**Year 1 Budget Expenditure**
- Projected Expenditure: $127,160
- Actual Expenditure: $15,684

**Timeline and Cost**

<table>
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<tr>
<th>Activities</th>
<th>Year 1</th>
<th>Year 2</th>
<th>Year 3</th>
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<tr>
<td>Planning and regulatory approval</td>
<td></td>
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<tr>
<td>Conduct Analyses</td>
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<tr>
<td>Manuscript Prep &amp; Submission</td>
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<td></td>
<td></td>
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<tr>
<td>Dissemination</td>
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</tr>
<tr>
<td>Estimated Budget ($K)</td>
<td>$127</td>
<td>$164</td>
<td>$127</td>
</tr>
</tbody>
</table>

**Updated:** (9/14/2017)

Accomplishments: Created a dataset with all women aged 55 and older in the VHA database.