**AWARD NUMBER:** W81XWH-20-1-0128

**TITLE:** Sex Differences in Stress-Related Cardiometabolic Risk in PTSD

**PRINCIPAL INVESTIGATOR:** Sabra Inslicht, Ph.D.

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

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

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**6. AUTHOR(S)**

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San Francisco, CA 94121-1563

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U.S. Army Medical Research and Development Command
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**14. ABSTRACT**

Post-traumatic stress (PTS) has been associated with biological changes in the hormonal stress response, arteries, and immune system that may increase risk for cardiovascular disease. PTS increases risk for cardiovascular disease, particularly for women compared to men. Little research has examined biological mechanisms of cardiovascular disease risk that result from PTS in women, particularly in relation to reproductive hormones that fluctuate as a result of changes in the natural menstrual cycle in younger women. However, studying pre-menopausal women may provide insight into how certain reproductive hormones and their products could either decrease or exacerbate the stress-related cardiovascular risks associated with PTS. The goal of this project is to identify biological mechanisms that may explain the relationship between PTS and cardiovascular risk in men and women with PTSD by examining biological changes in PTS that affects risk for cardiovascular disease in women. This study will use a recently developed laboratory technique called "metabolomics" that can identify circulating small molecules that affect cell and physiological function. This approach is broad and allows for a comprehensive examination of multiple physiological pathways at the same time that may be missed with traditional, more targeted approaches. A metabolomic analysis examining lipids and reproductive hormones will be performed on stored blood samples that were obtained from premenopausal women and men of similar ages with and without PTS in order to address two specific aims: Aim 1. To examine lipid metabolites that associate with CVD risk and PTS in women (across the menstrual cycle) relative to men. Aim 2. To examine which sex steroids modulate the relationship between CVD risk, PTS and lipid metabolism in women relative to men.

**15. SUBJECT TERMS**
Sex Differences; Posttraumatic Stress; Cardiovascular Diseases; Metabolomics; Hormones; Lipids

| **16. SECURITY CLASSIFICATION OF:** | | | **17. LIMITATION OF ABSTRACT** | **18. NUMBER OF PAGES** | **19a. NAME OF RESPONSIBLE PERSON** |
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| Unclassified | Unclassified | Unclassified | Unclassified | 19 | **19b. TELEPHONE NUMBER** *(include area code)* |

**Standard Form 298 (Rev. 8-98)**
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## 1. INTRODUCTION:

Post-traumatic stress (PTS) has been associated with biological changes in the hormonal stress response, arteries, and immune system that may increase risk for cardiovascular disease. PTS increases risk for cardiovascular disease, particularly for women compared to men. Little research has examined biological mechanisms of cardiovascular disease risk that result from PTS in women, particularly in relation to reproductive hormones that fluctuate as a result of changes in the natural menstrual cycle in younger women. However, studying pre-menopausal women may provide insight into how certain reproductive hormones and their products could either decrease or exacerbate the stress-related cardiovascular risks associated with PTS. The goal of this project is to identify biological mechanisms that may explain the relationship between PTS and cardiovascular risk in men and women with PTSD by examining biological changes in PTS that affects risk for cardiovascular disease in women. This study will use a recently developed laboratory technique called "metabolomics" that can identify circulating small molecules that affect cell and physiological function. This approach is broad and allows for a comprehensive examination of multiple physiological pathways at the same time that may be missed with traditional, more targeted approaches. A metabolomic analysis examining lipids and reproductive hormones will be performed on stored blood samples that were obtained from premenopausal women and men of similar ages with and without PTS in order to address two specific aims: Aim 1. To examine lipid metabolites that associate with CVD risk and PTS in women (across the menstrual cycle) relative to men. Aim 2. To examine which sex steroids modulate the relationship between CVD risk, PTS and lipid metabolism in women relative to men.

## 2. KEYWORDS:

Sex Differences; Posttraumatic Stress; Cardiovascular Diseases; Metabolomics; Hormones; Lipids

## 3. ACCOMPLISHMENTS:

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

| Major Study Goals | Timeline (months) | Percentage Complete |
|---|---|---|
| **1. Study Start Up and Approvals** | 1-3 | 100% |
| **2. Coordinate Study Staff for Sample Analysis** | 1-9 | 100% |
| **3. Assay Biological Samples** | 13-46 | 90% |
| **4. Process Physiological Data** | 13-46 | 90% |
| **5. Data Analysis** | 24-48 | 10% |
| **6. Finalize Study Requirements and Prepare for Future Funding** | 46-48 | 0% |

**What was accomplished under these goals?**

| **Major Task 1: Study Start Up and Approvals** | **Timeline** |
|---|---|
| Subtask 1: Prepare regulatory documents and submit for IRB approval | Completed |
| Develop IRB application and other regulatory documents | Completed |
| Submit IRB application to UCSF IRB and obtain full committee review | Completed |
| Review by SFVAHCS regulatory personnel | Completed |
| Review by HRPO | Completed |
| Prepare IRB reports for continuing review approvals | Annually |
| *Milestone Achieved: IRB approval from UCSF, VA, and HRPO* | *Completed* |
| **Major Task 2: Coordinate Study Staff for Sample Analysis** | **Timeline** |
| Subtask 1: Hiring and Training of Study Staff | |
| Coordinate with NCIRE to prepare job description and advertisement | Completed |
| Interview research staff candidates | Completed |
| Coordinate with SFVAHCS for candidate approval and required trainings | Completed |
| Training of research staff on study procedures and biospecimen storage, shipping, and receiving | Completed |
| *Milestone Achieved: Research staff hired and trained* | *Completed* |
| Subtask 2: Coordinate with laboratory personnel for sample shipments | |
| Contact staff at receiving laboratories (UC Davis) | Completed |
| Develop procedures manual for sample shipping and receiving | Completed |
| Develop sample tracking system | Completed |
| Schedule batched shipments | Completed |
| *Milestone Achieved: Sample shipment protocol established* | *Completed* |
| Subtask 3: Build database for incoming data | |
| Establish data extraction protocol and build database | Completed |
| Establish logistical plan for data quality check | Completed |
| *Milestone Achieved: Database built* | *Completed* |
| **Major Task 3: Assay Biological Samples** | **Timeline** |
| Subtask 1: Ship stored samples to the receiving laboratory and acquire data | |
| Package and ship stored samples to UC Davis | Completed |
| Samples received by UC Davis | Completed |
| Samples inventoried by UC Davis | Completed |
| *Milestone Achieved: Samples shipped for assay* | *Completed* |
| **Major Task 4: Process Psychophysiological Data** | **Timeline** |
| Subtask 1: Coordinate with data analyst for psychophysiological data processing | |
| Contact data analyst and discuss data processing procedure | Completed |
| Label relevant time points in data for data analyst | Completed |
| Send psychophysiological data to data analyst | Completed |
| *Milestone Achieved: Psychophysiological data sent for processing* | *Completed* |

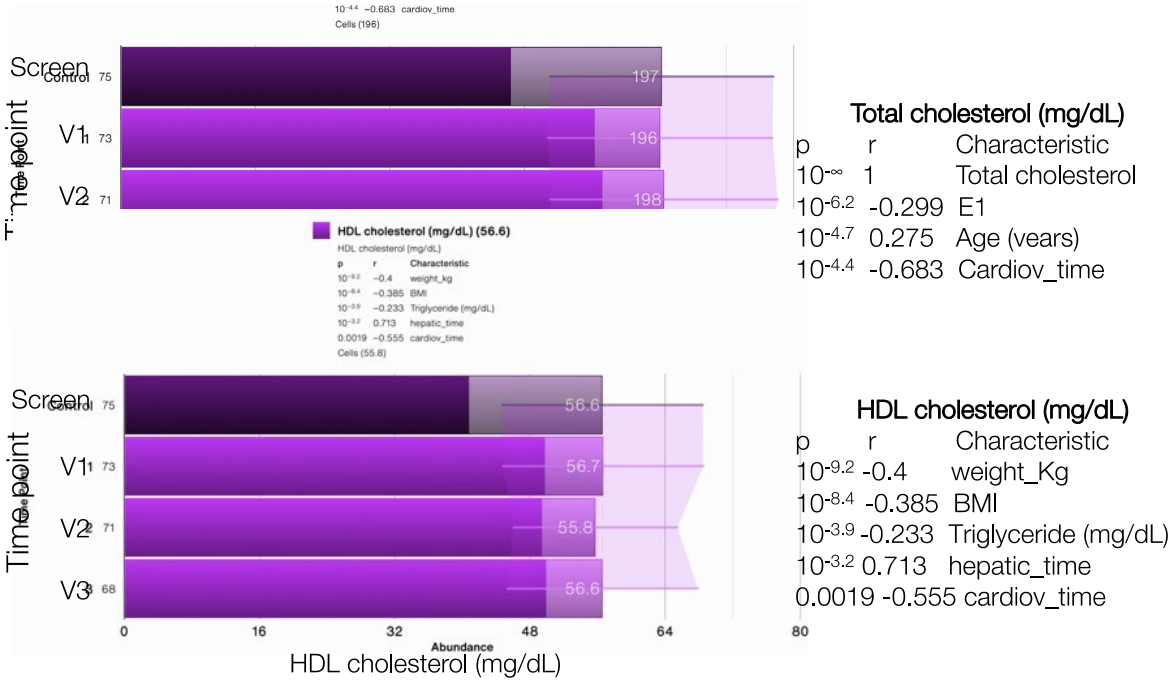
Major activities:

1) **Study Start Up and Approvals**
    a. Obtained local IRB and HRPO approval for protocols
2) **Coordinate Study Staff for Sample Analysis**
    a. Hired, trained, and coordinated study staff
    b. Staff at the receiving laboratory at UC Davis were contacted
    c. A procedures manual for sample shipping and receiving was created
    d. A sample tracking database was completed
    e. Plasma samples for steroid and lipidomic assays were organized and inventoried.
    f. Developed Study Database to include the following measures:
        i. Biochemical Assays:
            1. Metabolomic Panels.
                a) Lipidomics: >2390 compounds, including fatty acids, sphingolipids, short-chain fatty acid metabolites
                b) Steroid metabolites: 34 compounds, including progesterone, 5alpha-DHP, allopregnanolone, DHEA, Androstenedione, Testosterone, 3alpha-diol and Estradiol
        ii. Cardiovascular Health Measures:
            1. Total cholesterol
            2. HDL cholesterol
            3. insulin
            4. leptin
            5. glucose
        iii. Interview measures
            1. Clinician Administered PTSD Scale for DSM-IV (CAPS-IV).
            2. Body Mass Index (BMI). Weight in kilograms/(Height in meters)$^2$.
            3. Health Behavior. Self-report scale assessing alcohol, drug, and nicotine use, diet, exercise, and sleep quantity.
        iv. Stress Challenge Tasks. Stress tasks occurred on 3 study visits coinciding with menstrual cycle days 1-3, 5-8, and 11-14.
            1. Fear Conditioning: protocol involving visual stimuli that were either paired or unpaired with a 500 ms shock.
            2. ECG, respiration, electrodermal activity (EDA), and corrugator electromyogram (EMG) recordings during fear conditioning task.
            3. HRV, high frequency power (HF), root Mean Square of the Successive RR interval Differences (rMSSD) and low frequency to high frequency ratio (LF/HF) derived from ECG during the baseline periods and during fear conditioning task.
        v. Threat-Enhanced Acoustic Startle: protocol involving exposure to a series of 106-dB(A), 40-msec white noise bursts under low, medium, and high threat of shock.
            1. ECG, respiration, EDA, and orbicularis EMG (startle eyeblink) were recorded throughout threat enhanced startle task
            2. HRV, high frequency power (HF), root Mean Square of the Successive RR interval Differences (rMSSD) and low frequency to high frequency ratio (LF/HF) derived from ECG during the baseline periods and during threat enhanced startle task.

3) **Assay Biological Samples**
    a. Samples were shipped in batches
    b. Samples were assayed for lipid metabolites (>2390 compounds, including fatty acids, sphingolipids, short-chain fatty acid metabolites)
    c. Samples were assayed for steroid metabolites (34 compounds, including progesterone, 5alpha-DHP, allopregnanolone, DHEA, Androstenedione, Testosterone, 3alpha-diol and Estradiol) using different forms of mass spectrometry
    d. Samples assayed for total cholesterol, HDL cholesterol, insulin, leptin, and glucose
    e. Quality checks on incoming data is currently in process. Procedures involve screening data for outliers and anomalies outside of the biological range to determine whether any samples need to be reprocessed
4) **Process Physiological Data**
    a. Multiple meetings have been held with the psychophysiology data analysts to develop and finalize the data processing procedures
    b. Psychophysiological data was segmented, reviewed, and have been sent to a data analyst. All fear conditioning data has been pre-processed. Processing of startle data is currently underway.
5) **Data Analysis**
    a. Enter data and maintain database
        i. Quality checks on incoming data are in process
        ii. Available data has been entered into databases
        iii. Database merging and maintenance is in process
    b. Aim 1. To examine lipid metabolites that associate with CVD risk and PTS in women (across the menstrual cycle) relative to men.
        i. The examination, cleaning and processing incoming data in preparation for analysis is in process. We present graphs of the initial CVD risk measures and lipid metabolite data below in figures 1, 2, 3, and 4 in men and women. Next steps will include analysis of PTSD differences in these outcome variables.
    c. Aim 2. To examine which sex steroids modulate the relationship between CVD risk, PTS and lipid metabolism in women. We have examined and cleaned the sex steroid data in preparation for analysis is in process. We present graphs of sex steroid data in figure 5.

| | MEN N = 48 | WOMEN ON OC N = 13 | WOMEN OFF OC N = 20 | CONTRASTS | |
|---|---|---|---|---|---|
| | | N (%) or M (SD) | | *F or* $X^2$ | P |
| **AGE** | 38.2 (8.9) | 31.3 (7.0) | 36.4 (9.4) | 2.8 | 0.07 |
| **EDUCATION** | | | | 23.03 | 0.06 |
| **SOME HS/HS** | 8 (16.6%) | 2 (15.4%) | 3 (15%) | | |
| **GRAD/GED** | 9 (18.8%) | 0 (0%) | 4 (20%) | | |
| **SOME COLLEGE** | 26 (54.1%) | 4 (30.8%) | 10 (50%) | | |
| **AA/BA/BS** | 5 (10.4%) | 7 (53.8%) | 3 (15%) | | |
| **POST GRADUATE EDUC.** | | | | | |
| **ETHNICITY/RACE** | | | | 9.64 | 0.65 |
| **CAUCASIAN** | 26 (54.2%) | 5 (38.5%) | 7 (30%) | | |
| **BLACK/AFRICAN AMERICAN** | 5 (10.4%) | 0 (0%) | 2 (15%) | | |
| **ASIAN** | 9 (18.8%) | 5 (38.5%) | 5 (25%) | | |
| **HISPANIC** | 3 (6.3%) | 2 (15.3%) | 3 (15%) | | |
| **MULTI-RACIAL** | 3 (6.3%) | 1 (7.7%) | 1 (5%) | | |
| **AMERICAN INDIAN/ALASKAN NATIVE** | 2 (4.2%) | 0 (0%) | 2 (10%) | | |
| **CAPS TOTAL SCORE** | 27.7 (27.2) | 29.3 (24.4) | 26.6 (22.8) | 0.04 | 0.96 |

Table 1. Demographics of sample. Data is presented for men and women. Oral contraceptive (OC) use will be examined as a potential confound, since our recent research has indicated an effect of oral contraceptive use on physiological outcome data.




Numbers of side= in how many patients it was measured and top shows 4 strongest correlations with measures in your dataset

Figure 1. Data screening for traditional lipid CVD risk measures, including total cholesterol and HDL cholesterol. Data is shown across the fasting screening visit and subsequent 3 study time points, corresponding to menstrual cycle phases in women (Cycle Day 2, Day 5, and Day 10). Total cholesterol was associated with estradiol, age, and timepoints. HDL cholesterol was associated with BMI, triglycerides, and timepoints.

men and women at each visit

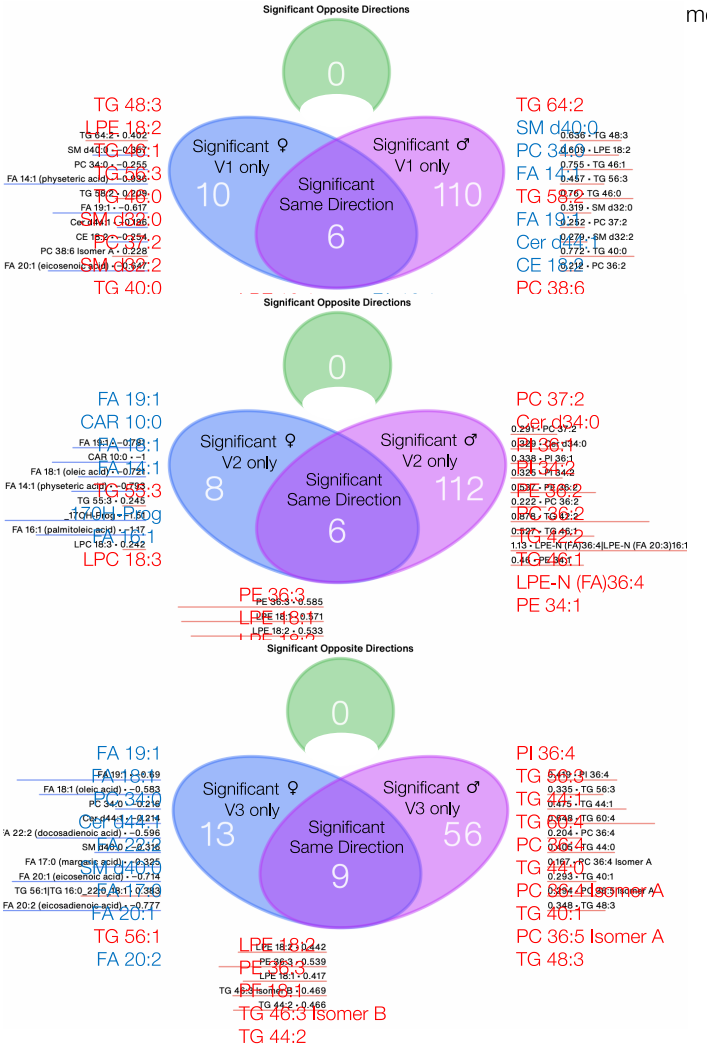
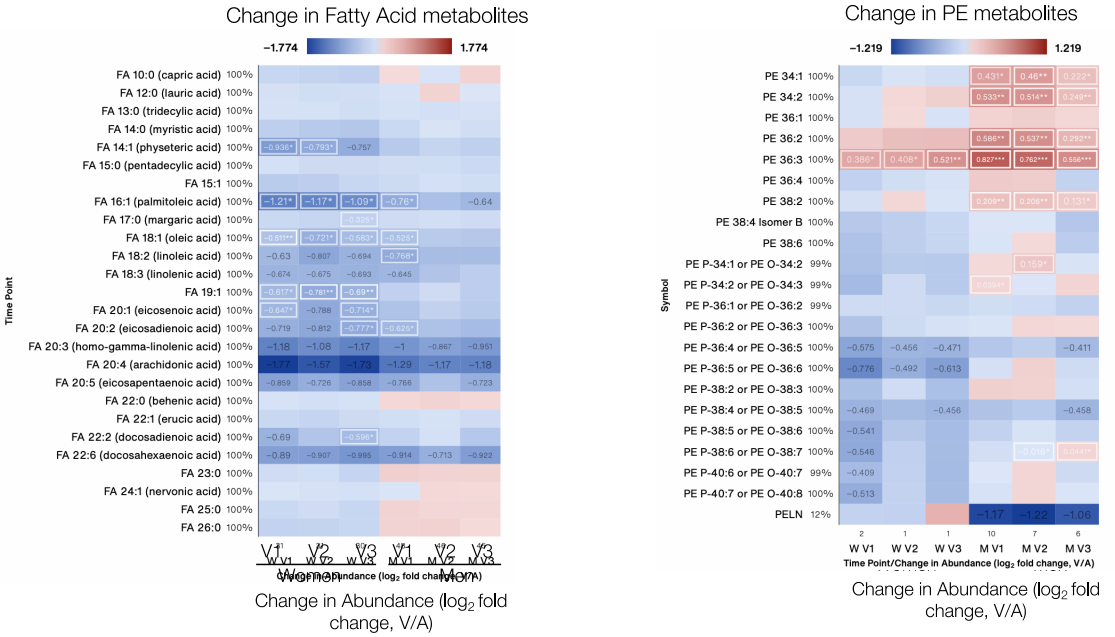
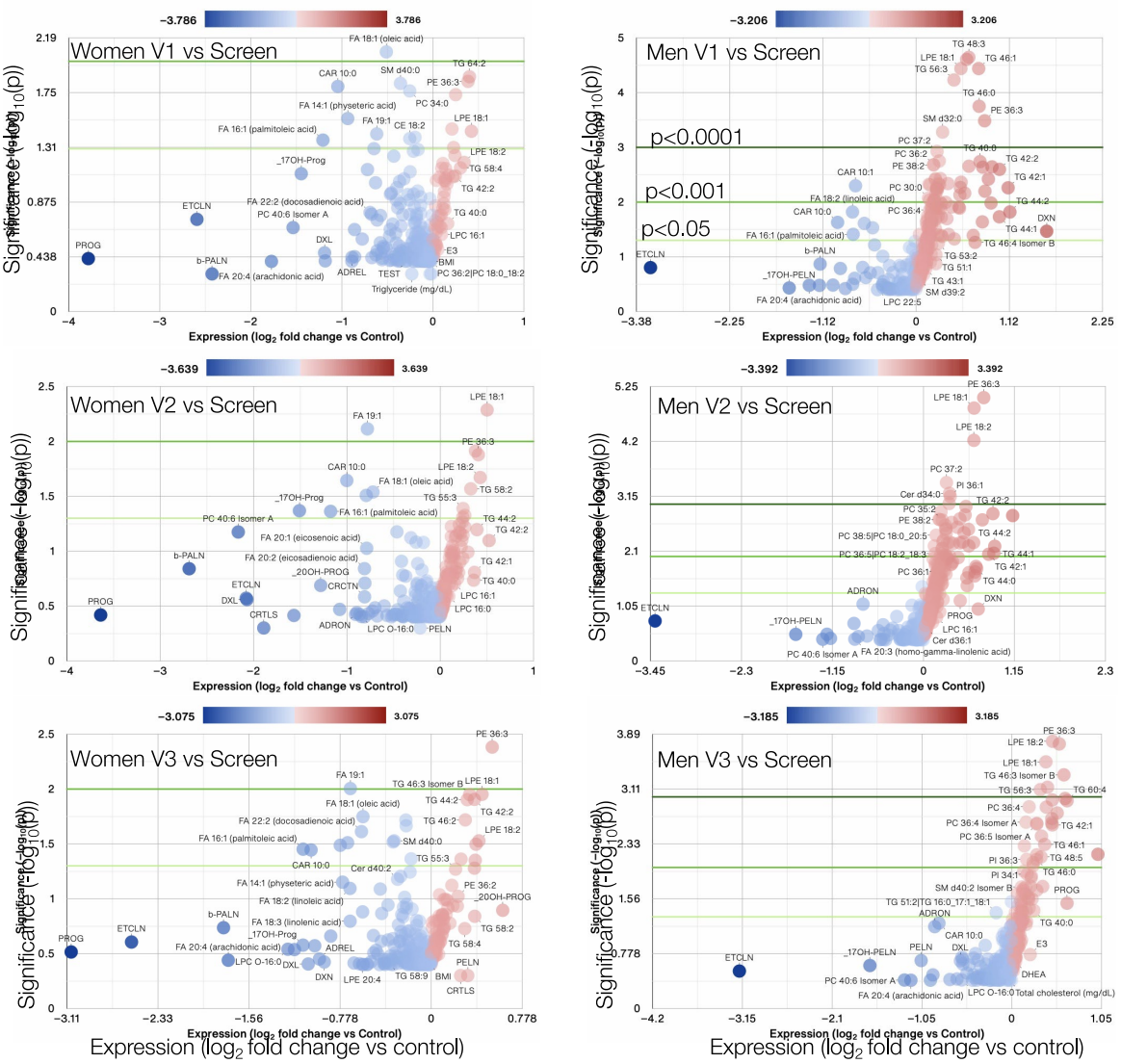



Figure 2. Ven Diagrams of lipid metabolite data across 3 study time points in men vs. women. These diagrams indicate the presence of distinct lipid metabolites that differ by sex. Our next steps will be to examine whether there are PTSD differences in lipid metabolites, in men vs. women.




Figures 3a and 3b. Heatmaps of lipid metabolites across 3 study time points in men vs. women. These diagrams indicate the presence of distinct lipid metabolites that differ by sex.




Figures 4. Lipid metabolites at the 3 study time points in men vs. women. These diagrams indicate the significant lipid metabolite alterations at each study visit compared to baseline. Our next steps are to examine PTSD effects and to determine lipid metabolites that associate with CVD risk and PTS in women (across the menstrual cycle) relative to men, addressing Aim 1.

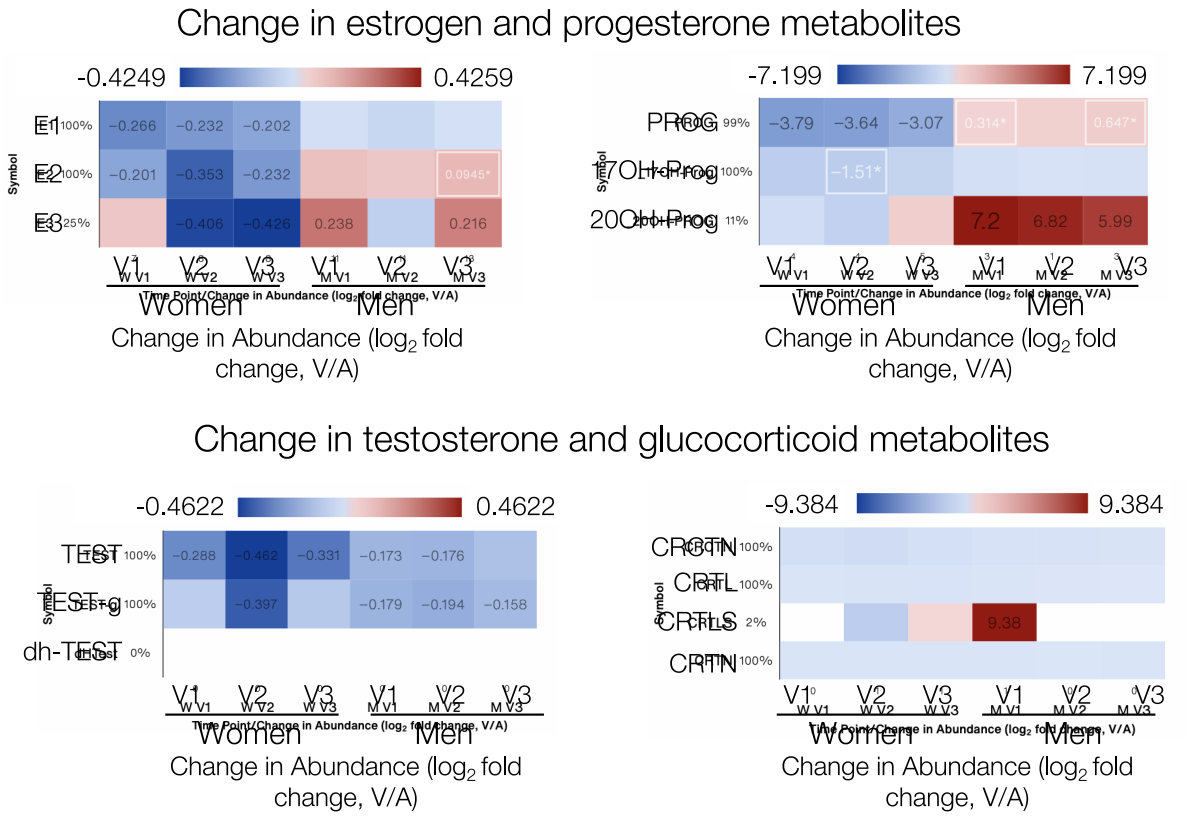



Figure 5. Changes in steroid metabolites across 3 study time points in men and women. Our next steps are to examine which sex steroids modulate the relationship between CVD risk, PTS and lipid metabolism in women to address Aim 2.

**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?**

Plans until next reporting period:

1. While the majority of biological samples have been processed (Task 3), we are currently reviewing outliers and anomolies to determine whether any samples need to be re-assayed.
2. Psychophysiological data (Task 4) for the fear conditioning task has been completed; however, the startle psychophysiological data remains to be processed. We will continue to enter incoming startle data into the database and clean data as we receive it (Task 5).
3. Finalize data analysis tasks: We are currently working with Dr. Bhargava and Dr. Fiehn to graph the incoming data across each time point (as shown in figures above). We will conduct chemRich analyses on significant metabolites and conduct correlational analyses with health outcomes (Task 5). Our next data analytic plans are to examine PTSD x sex analyses to complete Aim 1 (To examine lipid metabolites that associate with CVD risk and PTS in women (across the menstrual cycle) relative to men and Aim 2 (To examine which sex steroids modulate the relationship between CVD risk, PTS and lipid metabolism in women).
4. Disseminate study findings and finalize study closeout requirements (Task 5).
5. Apply for additional future funding (Task 6).

| **Major Task 3: Assay Biological Samples** | **Timeline** |
|---|---|
| Subtask 2: Assay biological samples | |
| Perform metabolomics analysis | In progress |
| Receive data from laboratory | 14-46 |
| *Milestone Achieved: Samples shipped and data acquired* | *13-46* |
| *Milestone Achieved: Assays complete* | *46* |
| **Major Task 4: Process Psychophysiological Data** | **Timeline** |
| Subtask 2: Process psychophysiological data | |
| Psychophysiological data cleaned by data analyst | In progress |
| Psychophysiological data processed by data analyst | In progress |
| Receive processed data from data analyst | 24-46 |
| *Milestone Achieved: Data acquired* | *15-46* |
| *Milestone Achieved: Data processing complete* | *46* |
| **Major Task 5: Data Analysis** | **Timeline** |
| Subtask 1: Enter data and maintain database | |
| Perform quality checks on incoming data | In progress |
| Enter all data and maintain database | In progress |
| Subtask 2: Aim 1. To examine lipid metabolites that associate with CVD risk and PTS in women (across the menstrual cycle) relative to men. | |
| Clean and process incoming data and prepare for analysis | 14-46 |
| Coordinate with Data Management for monitoring data entry and quality | Complete |
| Work with Biostatistician to conduct analyses | 24-46 |
| *Milestone Achieved: Aim 1 addressed* | *46* |
| Subtask 3: Aim 2. To examine which sex steroids modulate the relationship between CVD risk, PTS and lipid metabolism in women. | |
| Clean and process incoming data and prepare for analysis | In progress |
| Coordinate with Data Management for monitoring data entry and quality | In progress |

| | |
|---|---|
| Work with Biostatistician to conduct analyses | 24-46 |
| *Milestone Achieved: Aim 2 addressed* | *46* |
| *Milestone Achieved: Data analysis complete* | *46* |
| Subtask 4: Share output and findings with co-investigators and with the greater community | |
| Dissemination of findings (abstracts, presentation, publications, DOD) | 22-48 |
| *Milestone Achieved: Report results from data analyses* | *22-48* |
| **Major Task 6: Finalize Study Requirements and Prepare for Future Funding** | **Timeline** |
| Subtask 1: Prepare grant application for DOD or VA Merit Award funding for a clinical trial based on study findings | |
| *Milestone Achieved: Submit grant proposal for future funding* | *46-48* |

4. **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

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**

Due to COVID-19, we experienced laboratory closures at the San Francisco VA Health Care System laboratory and at UC Davis West Coast Metabolomics Center (WCMC). We were therefore delayed in organizing and shipping the blood samples to be assayed for lipids and steroids. However the majority of the steroid and lipidomics assays have been completed, aside from reprocessing any outliers or anomalies.

Over the course of the study, there have been several changes in personnel. The primary statistician at UC Davis has left the group. However, Dr. Bhargava has developed new statistical software using machine learning methods that will facilitate data analysis. As such, Dr. Inslicht has been trained in these methods and is working with Dr. Bhargava, Dr. Fiehn, and Mr. Metzler to analyze this data using this platform. As Dr. Inslicht will complete the analysis instead of the outside service, West Coast Metabolomics, Dr. Inslicht will conduct the data processing of the remaining assay results, as well as linking together and analyzing the multiple metabolomics panels, psychophysiological data and clinical health data.

**Changes that had a significant impact on expenditures**

Nothing to report

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

Nothing to report

## 6. PRODUCTS:

**Publications, conference papers, and presentations**

**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**

| |
|---|
| Nothing to Report |

## 7. PARTICIPANTS & OTHER COLLABORATING ORGANIZATIONS

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

| **Name:** | **Sabra Inslicht** |
|---|---|
| Project Role: | Principal Investigator |
| Researcher Identifier: | ORCID ID: 0000-0002-2456-1625 |
| Nearest person month worked: | 2.4 person months |
| Contribution to Project: | Dr. Inslicht has experience conducting clinical trials in Veterans with PTSD and mechanistic studies of human fear conditioning and stress related interactions with complex steroid pathways, reproductive hormones, immune function, metabolic responses, sleep, and health behavior. Dr. Inslicht will assume overall scientific and administrative responsibility for this project, ensuring that research goals are met in a timely manner with scientific integrity. She will design and implement each phase of the research plan and work with the study coordinator to oversee human subjects regulatory documentation and compliance, coordination of personnel involved in this protocol, the coordination of assay completion, as well as the development of a data tracking system to manage participant information, biological samples, and assay data. Over the next reporting period, additional effort will be placed on assisting with sample sorting, for which laboratory access was limited in the prior due to COVID-19 restrictions. Dr. Inslicht will also work with the statistician to conduct data analyses and will prepare manuscripts and disseminate findings. |

| **Name:** | **Thomas Neylan** |
|---|---|
| Project Role: | Co-Investigator |
| Researcher Identifier: | ORCID ID: 0000-0002-1572-2626 |
| Nearest person month worked: | 1 person month |
| Contribution to Project: | Dr. Neylan has extensive expertise in the biology of PTSD, sleep, metabolic function, clinical trials, and laboratory-based psychophysiological research. He provides onsite support to Dr. Inslicht on the design, conduction of the proposed |

| | |
|---|---|
| | project, data analysis and manuscript preparation. As the Director of the Stress and Health Research Program, Dr. Neylan leads a weekly study management meeting in which he addresses scientific, administrative, and data issues. |

| **Name:** | **Aditi Bhargava** |
|---|---|
| Project Role: | Co-Investigator |
| Researcher Identifier: | ORCID ID: 0000-0003-1334-0517 |
| Nearest person month worked: | 1 person month |
| Contribution to Project: | Dr. Bhargava is molecular biologist with extensive research experience in the area of metabolomics and neuroendocrinology, including pain, stress, and inflammation. Dr. Bhargava will contribute to study design, execution, data analysis, interpretation of the metabolomics data, and manuscript preparation. |

| **Name:** | **Joyce Gurdock** |
|---|---|
| Project Role: | Staff Research Associate |
| Nearest person month worked: | 2 person months |
| Contribution to Project: | Ms. Gurdock assists with study responsibilities including sample organization and preparation, data entry, coding, data cleaning, literature reviews, and editorial support. |

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

Since Dr. Inslicht will assume the statistical analysis of the data following the departure of the UC Davis statistician, her effort will be 2.4 CM on the project to allow her sufficient time to perform the required analyses. A rebudget request is currently pending sponsor approval to cover the increase in effort.

**What other organizations were involved as partners?**

Nothing to report

**8. SPECIAL REPORTING REQUIREMENTS:**

**Collaborative Awards:**

| |
|---|
| N/A |

**Quad Charts:**

| |
|---|
| See attachment |

**9. APPENDICES:**

| |
|---|
| N/A |