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PRINCIPAL INVESTIGATOR: Laura Kubzansky

CONTRACTING ORGANIZATION: President and Fellows of Harvard College
Boston, MA 02115-6028

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6. AUTHOR(S)

Dr. Laura Kubzansky

E-Mail:lkubzans@hsph.harvard.edu

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President and Fellows of
Harvard College
677 Huntington Avenue
Boston, MA 02115-6028

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14. ABSTRACT

We engaged in a number of major activities to achieve our goals. First, we obtained IRB approval and began building relevant data sets. Second, we began conducting statistical analyses and writing up the findings for three pre-specified hypotheses using existing data testing whether PTSD is associated with 1) higher risk of ovarian cancer development, 2) diet low in flavonoid and poor in quality, and 3) HT use. Third, we identified and selected samples on which to obtain novel biomarker assays, and sent these samples to the laboratory to be assayed. Fourth, we began cleaning the data and identifying and analyzing information on existing biomarkers. Details on these major activities are summarized in the annual progress report.

15. SUBJECT TERMS

Ovarian cancer, PTSD, epidemiology, trauma, stress, survival, telomere, immune dysregulation, inflammation, health-related behaviors, physical activity, diet quality, flavonoid, hormone therapy

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1.0 INTRODUCTION:

We have previously identified several stress-related factors (e.g., depression, anxiety) that are associated with increased risk for incident ovarian cancer (OvCa); these findings are consistent with work conducted in animal models of ovarian carcinogenesis in which animals subjected to stress and injected with ovarian cancer cells developed larger and more invasive tumors compared to control animals. Building on this work, we proposed that post-traumatic stress disorder (PTSD), the sentinel stress-related mental disorder, may be a risk factor for ovarian cancer. PTSD occurs in some women in response to trauma. PTSD is highly prevalent among military women, and due to its significant biologic impact it may be a particularly potent risk factor for ovarian cancer. Only one study has systematically examined PTSD with incident ovarian cancer, and findings were suggestive. The goal of the current project is to examine whether PTSD is associated with increased risk of developing ovarian cancer (OvCa), and if so, by what mechanisms.

We will test a number of key hypotheses, comparing women who are not trauma exposed or who are trauma exposed but did not develop PTSD to women with PTSD: 1) Women with PTSD will have greater risk of developing ovarian cancer; 2) Of women with ovarian cancer, those with PTSD will have shorter survival; 3) Women with PTSD will have more inflammation and immune dysregulation, and shorter telomere length; 4) Women with PTSD will be more likely to have a diet low in flavonoids and poor in quality, and to use hormone therapy (HT); 5) Adverse health-related behaviors including obesity, physical inactivity, poor diet, and post-menopausal hormone use will mediate the elevated risk of ovarian cancer observed in women with PTSD. To achieve these goals, we are using data from the Nurses' Health Study 2 (NHS2), an ongoing prospective cohort study of US registered female nurses, who have completed a PTSD screener (and a subset of whom participated in a diagnostic interview), and who have also provided extensive information on a range of sociodemographic, medical, behavioral, and biological factors over time. Existing data includes information on a range of inflammatory biomarkers (e.g., C-reactive protein [CRP], tumor necrosis factor receptor 2 [TNFR2], and interleukin-6 [IL-6]) and telomere length. We will also use existing blood samples collected among women who participated in trauma and PTSD screening surveys, to obtain novel biomarkers such as interleukin-8 (IL-8), interleukin-10 (IL-10), B-cell activating factor (BAFF), CXCL13, soluble interleukin-2 receptor alpha (sIL-2R), soluble interleukin-6 receptor (sIL-6R). With these known and novel biomarkers as well as extensive behavioral assessments, we can conduct analyses to identify associations between PTSD, a range of biobehavioral pathways, and risk of ovarian cancer.

2.0 KEYWORDS:

Ovarian cancer, PTSD, epidemiology, trauma, stress, survival, telomere, immune dysregulation, inflammation, health-related behaviors, physical activity, diet quality, flavonoid, hormone therapy

3.0 ACCOMPLISHMENTS:

3.1 What were the major goals of the project?

The project has four major goals: (a) obtaining IRB approval and building relevant datasets (overall project); (b) determining if PTSD is associated with increased risk of developing OvCa or decreased survival (Specific Aim 1); (c) identifying if PTSD influences biological and behavior-related processes that are also linked to increased OvCa risk (Specific Aim 2); and (d) evaluating if behavior pathways mediate PTSD-OvCa association (Specific Aim 3).

Overall project tasks include 2 major tasks proposed for completion within 2-8 months from project initiation. Subtasks included submitting IRB for approval and identifying women with appropriate data for testing the various proposed hypotheses and creating relevant datasets.

Specific Aim 1 included 3 subtasks proposed for completion within 22 months of project initiation, as follows (1) testing whether women with versus without PTSD would have higher risk of OvCa onset; (2) among women with OvCa, identifying whether women with chronic PTSD have shorter survival; (3) exploring whether women with PTSD and co-occurring distress would have highest risk of OvCa. Stated milestones were to complete analyses, draft the findings, and submit the manuscripts to peer-review journals.

Specific Aim 2 included two major tasks. The first major task was comprised of 2 data analysis subtasks to test the following hypotheses: (1) women with PTSD will have more inflammation, immune dysregulation, and shorter telomere length; (2) women with PTSD are less likely to have a diet rich in flavonoids and high in quality, and more likely to use HRT. The proposed completion date for major task 1 (i.e., completing analyses, drafting and submitting the manuscript to peer-review journals) was 32 months from project initiation.

The second major task for Specific Aim 2 was to obtain novel biomarker assays, with 2 subtasks proposed for completion by 32 months from project initiation. Subtasks included (1) selecting participants on which to obtain blood and tumor tissue samples for novel biomarkers assays; and (2) sending samples out for assays, and conducting analyses once the assays are completed and the data are available.

Specific Aim 3 included 1 major task which was to evaluate if behavioral pathways mediate the PTSD-OvCa association. This task was proposed for completion (including completing the analyses, drafting the manuscript and submitting it to peer-review journals) by 35 months since project initiation.

3.2 What was accomplished under these goals?

We engaged in a number of major activities to achieve our goals. First, we obtained IRB approval and began building relevant data sets. Second, we began conducting statistical analyses and writing up the findings for three pre-specified hypotheses using existing data testing whether PTSD is associated with 1) higher risk of ovarian cancer development, 2) diet low in flavonoid and poor in quality, and 3) HT use. Third, we identified and selected samples on which to obtain novel biomarker assays, and sent these samples to the laboratory to be assayed. Fourth, we began cleaning the data and identifying and analyzing information on existing biomarkers. Details on these major activities are summarized below.

We successfully accomplished Major Task 1 for the overall project, and obtained IRB approval for the protocol entitled, "Understanding ovarian cancer risk and survival in the Nurses' Health Studies" (Protocol No. 1999P011118/PHS) on November 22, 2017.

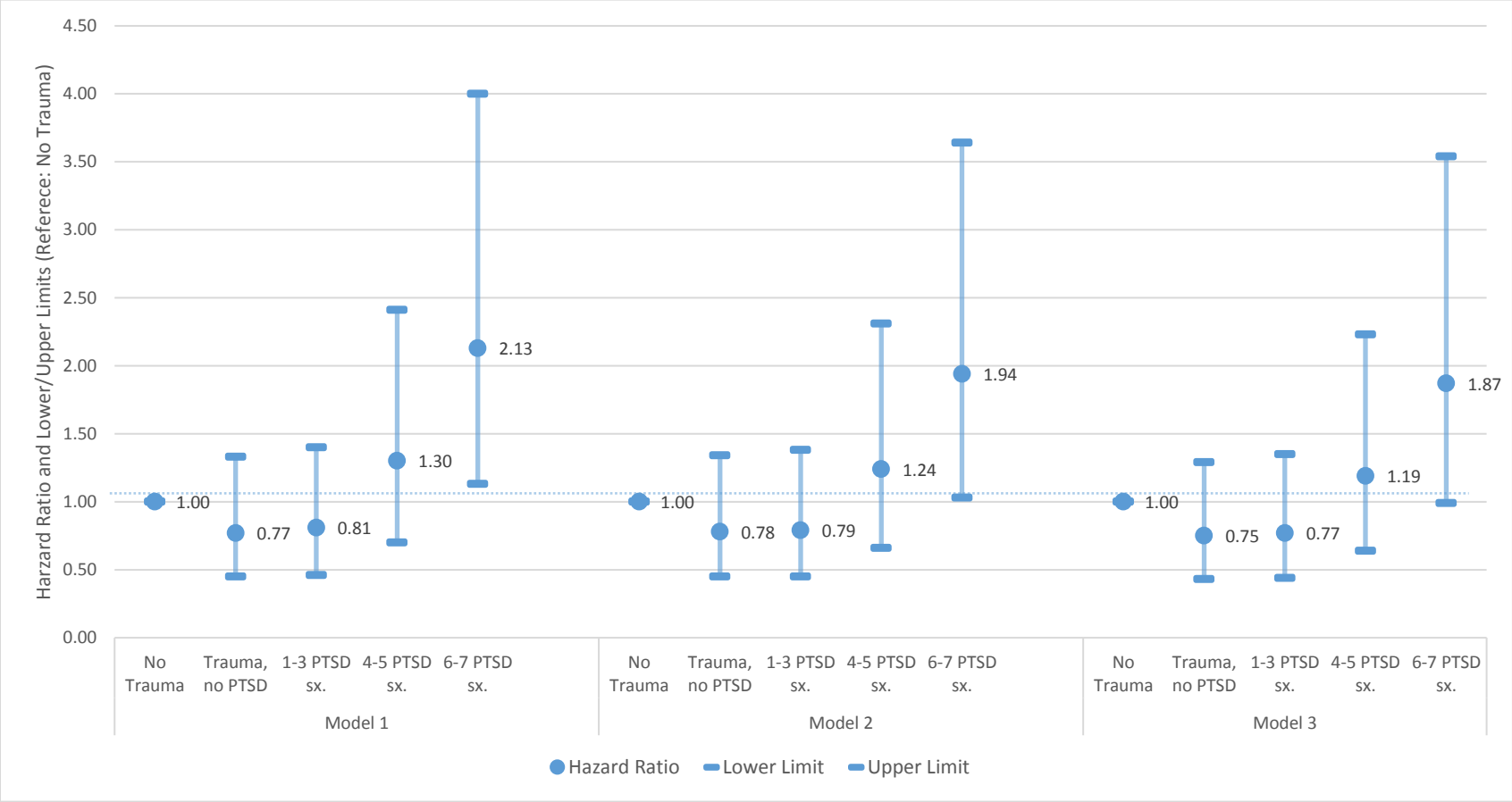
Major Task 2 for the overall project was to manage and clean data for the proposed analyses, and we have successfully accomplished this task. Thus, we identified women with appropriate data and prepared the datasets for the relevant analyses, by accomplishing the following 4 specific subtasks: (1) identifying women with confirmed OvCa who are in PTSD substudy; (2) identifying women from PTSD substudy with existing relevant assays; (3) identifying women from PTSD substudy with relevant biobehavioral measures; (4) based on the prior 3 subtasks, preparing datasets for the planned analyses. Data required for testing hypotheses regarding the association of PTSD with OvCa incidence and survival, or with behaviors including diet, physical activity, obesity, and HRT are ready for use. Information on existing biomarkers such as CRP, IL-6, TNFR2, and telomere length, was also identified and combined with information about PTSD and relevant covariates; this dataset is currently ready for use.

Tasks for Specific Aim 1 are 60% completed. We have completed analyses and drafted a manuscript reporting the findings regarding whether women with PTSD are at higher risk of developing OvCa or have poorer survival. The manuscript is currently circulating among co-authors and will be submitted to a peer-review journal by October 2018.

Specific objectives were to determine if women with PTSD were more likely to develop ovarian cancer (OvCa) than women with no trauma exposure. Trauma exposure and PTSD symptoms in relation to the worst trauma were assessed with validated trauma and PTSD screening scales. Information on ovarian cancer diagnosis was self-reported on every biennial follow-up survey and validated with medical record review, in which pathology reports and relevant medical records for all ovarian cancer cases were further obtained for our analysis. We performed Cox proportional hazard regression models using SAS 9.4 (SAS Institute, Cary, NC). We found that women with high PTSD symptoms had more than 2-fold greater risk for the development of ovarian cancer than women who were unexposed to traumatic events over 26 years among nearly 50,000 women. As presented in Figure 1, compared with women without trauma exposure, women with clinically relevant PTSD symptoms were at greater risk of being diagnosed with ovarian cancer by 2.13 times (95% confidence interval [CI] 1.13-4.00) after adjusting for age. After accounting for known cancer-risk factors and health-risk factors the association was somewhat attenuated but remained statistically significant (hazard ratio [HR] = 1.94; 95% CI = 1.03-3.67) and remained marginally statistically significant (HR = 1.87, 95% CI = 0.99-3.54) after further accounting for health-related behavioral risk that may lie on the pathway. Women with moderate PTSD symptoms were also at elevated risk of ovarian cancer, but this did not reach statistical significance. Because PTSD was retrospectively reported (including date of onset) in 2008, we also conducted more conservative analyses, considering only cases of ovarian cancer developing after PTSD was assessed. In this subset of the sample with relatively fewer cases, findings were remarkably consistent with those using the larger sample (see Table 1). In addition, as shown in Table 2, risk of ovarian cancer was somewhat lower among women whose PTSD symptoms had remitted compared to women with active symptoms.

Analyses examining shorter survival among women with ovarian cancer who had PTSD (vs. those with ovarian cancer who did not have PTSD) has not been done due to limited number of deaths among those with ovarian cancer who participated in trauma and PTSD survey.

Figure 1. The association between trauma/PTSD status (versus no trauma) and ovarian cancer diagnosis among 49443 women in Nurses' Health Study II during 1989-2015.



Model 1 adjusted for age.
Model 2 further adjusted for known ovarian cancer risk factors (family history of ovarian and breast cancer, tubal ligation, parity, post-menopausal hormone use, and oral contraceptive use).
Model 3 further adjusted for health-related behavioral risk factors (smoking, change in BMI since age 18, and physical activity).

Table 1: Risk of incident ovarian cancer during 2009-2015 by trauma exposure and PTSD symptoms status in 2008, prospective follow-up in Nurses' Health Study II

Trauma and PTSD status	Cases/ person-years	Hazard ratio (95% confidence interval)		
		Model 1	Model 2	Model 3
No trauma	11/48,525	1.0 [Reference]	1.0 [Reference]	1.0 [Reference]
Trauma, no PTSD	11/66,597	0.72 (0.32, 1.69)	0.70 (0.30, 1.63)	0.68 (0.29, 1.59)
1-3 PTSD symptoms	14/69,280	0.87 (0.39, 1.92)	0.82 (0.37, 1.82)	0.83 (0.37, 1.86)
4-5 PTSD symptoms	5/30,175	0.74 (0.26, 2.14)	0.69 (0.24, 2.02)	0.70 (0.24, 2.04)
6-7 PTSD symptoms	9/17,007	2.38 (0.98, 5.76)	2.15 (0.88, 5.26)	2.20 (0.89, 5.41)
Test of trend		p=0.16	p=0.23	p=0.20

Model 1 adjusted for age.
Model 2 further adjusted for known ovarian cancer risk factors (family history of ovarian and breast cancer, tubal ligation, parity, post-menopausal hormone use, and oral contraceptive use).
Model 3 further adjusted for health-related behavioral risk factors (smoking, change in BMI since age 18, and physical activity).

Table 2: Risk of incident ovarian cancer by trauma exposure and PTSD symptoms, remitted versus active symptoms in Nurses' Health Study II, 1989-2015 (N=49,443)

	All follow-up, 1989-2015	
	Cases/ person-years	Risk of ovarian cancer, adjusted for age
		Hazard ratio (95% CI)
Trauma and PTSD		
No trauma	25/285,053	1.0 [Reference]
Trauma, no PTSD	27/392,546	0.77 (0.45, 1.33)
1-3 PTSD symptoms	25/288,113	0.80 (0.46, 1.39)
4-5 PTSD symptoms, remitted	11/67,065	1.14 (0.55, 2.33)
4-5 PTSD symptoms, active	6/55,406	1.71 (0.69, 4.27)
6-7 PTSD symptoms, remitted	10/34,031	1.91 (0.91, 4.04)
6-7 PTSD symptoms, active	6/36,518	2.57 (1.03, 6.41)*

Analyses regarding whether PTSD and co-occurring distress exacerbate risk of OvCA associated with PTSD will start in November 2018.

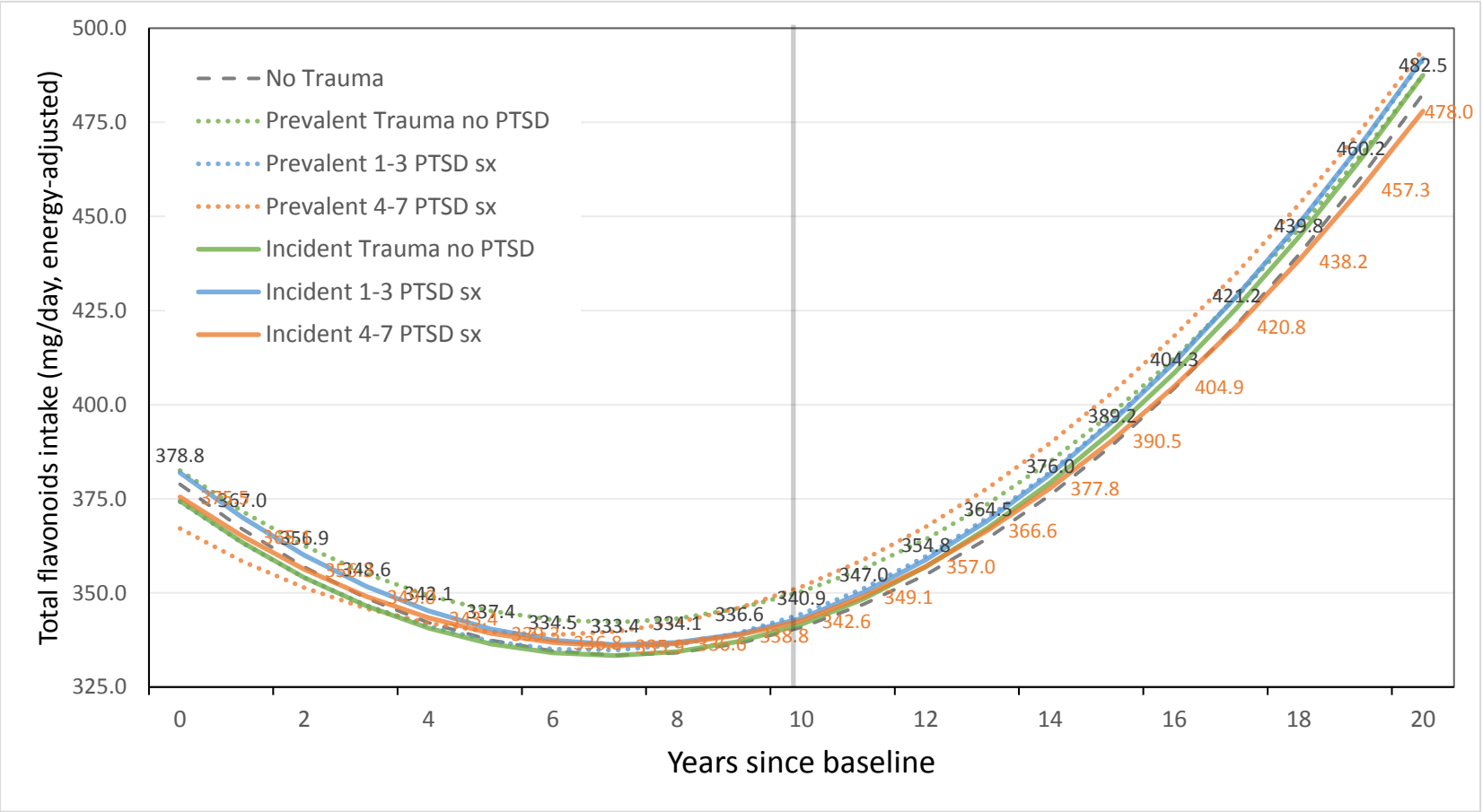
For Specific Aim 2, tasks are 50-70% completed. Specifically, we have identified existing measures of biomarkers including as CRP, IL-6, TNFR2, and leukocyte telomeres among women with trauma and PTSD symptoms measured and we are currently analyzing relevant associations. We have completed analyses linking PTSD with diet. Findings from PTSD and diet analysis have been written up and the manuscript is circulated among co-authors. A final

manuscript is planned for submission to a peer-review journal in October 2018. We have conducted preliminary analyses examining the association between PTSD and HT and findings from these analyses were presented at a scientific conference (Society for Epidemiologic Research 51th Annual Meeting in June 2018). Additional analyses for this study are underway and the write-up of these findings for submission to a peer-review journal is ongoing (planned for submission, January 2019).

For the study examining the association between PTSD and dietary intake, specific objectives were to examine whether women with PTSD would be more likely to have a diet low in flavonoids and poor in quality than women with no trauma exposure. Trauma exposure and PTSD symptoms were measured with the same tools as stated above. Information on dietary intake was obtained via a validated food frequency questionnaire. We performed linear mixed effects spline models, a statistical modeling approach to handle data with repeated measures over time, to test differences in trajectories of total flavonoids intake and diet quality by trauma/PTSD status over 20-year's follow-up among more than 50,000 women. Total flavonoids intake (mg/day) was calculated after accounting for total energy consumption. Overall diet quality was measured using the Alternative Healthy Eating Index-2010 (AHEI), in which the higher score indicates the healthier diet.

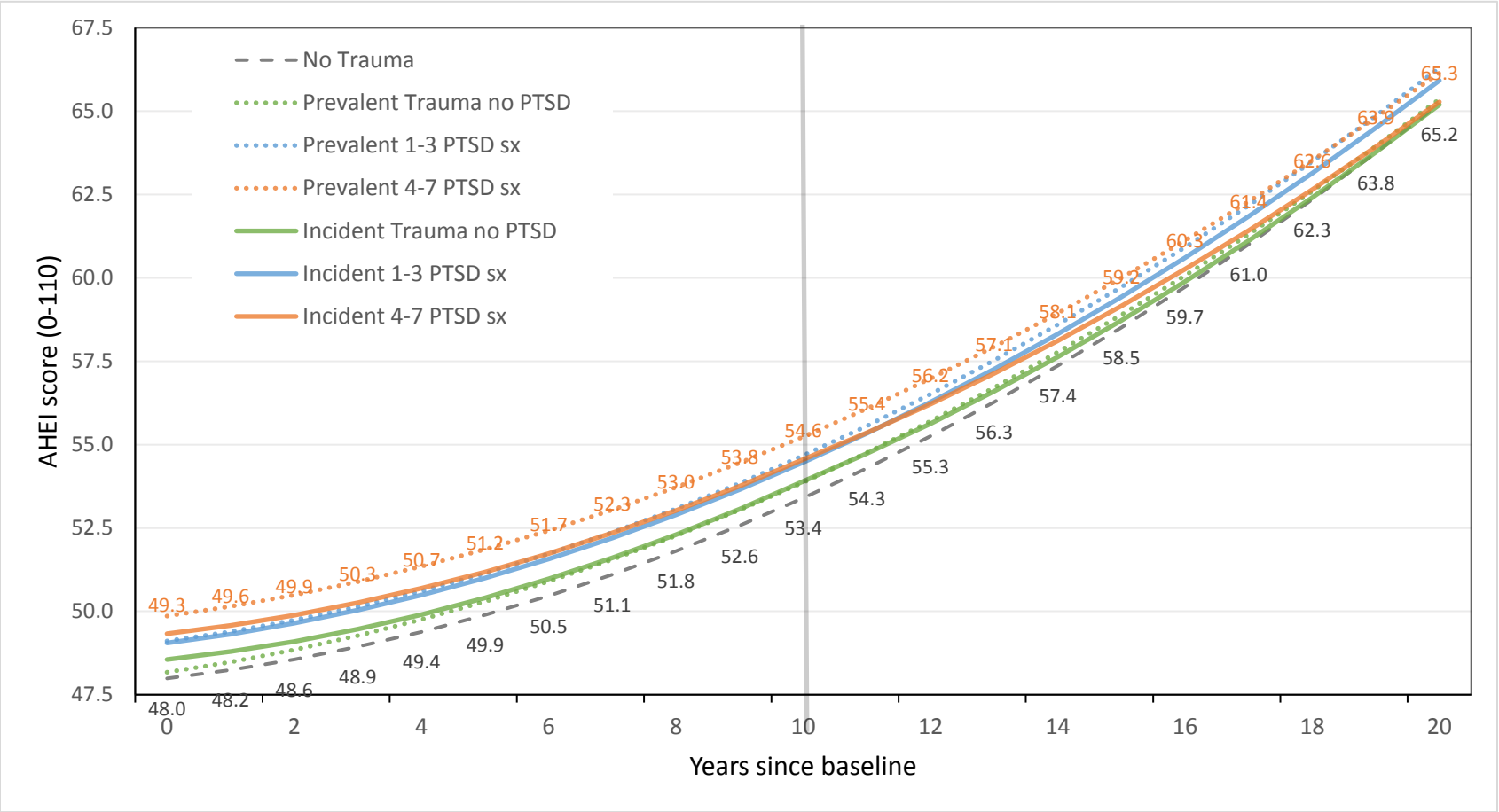
During the 20 years of follow-up, there was an overall improvement in total flavonoid intake (i.e., J-shaped) and diet quality (i.e., accelerated increase) among the full sample. Therefore, we developed statistical models to capture such secular trends with quadratic terms including year since baseline (both quadratic and linear terms) and time-updated age (both quadratic and linear terms). Overall, we found women with new onset PTSD during the course of our follow-up tended to have decreased intake of total flavonoids and poorer diet quality by 2.0-2.5% over a 10-year period after the onset of PTSD, compared with women with no trauma exposure. As shown in Figure 2, while women with no trauma exposure increased intake of total flavonoids from an average of 340.9 to 482.5 mg/day, energy-adjusted, women with new onset PTSD showed less of an increase in intake (from an average of 342.6 to 478.0 mg/day, energy-adjusted) during the 10-years since PTSD onset, after accounting for age. Similarly, as shown in Figure 3, while women with no trauma exposure showed increases in overall diet quality, measured by AHEI score, over a 10-year period, women with new onset PTSD did not show as much of an increase during the 10-years since PTSD onset, after accounting for age. These findings were consistently significant after accounting for an extensive range of sociodemographic (parental education, region at birth, living arrangement), medical (menopausal status, history of depression and severe chronic condition), and behavioral factors (smoking and physical activity). Among the subclasses of flavonoids, women who developed new onset PTSD had decreased intake of anthocyanins, flavonoid polymers, and proanthocyanidins, particularly, after the PTSD onset, relative to women with no trauma exposure. Among the components of overall diet quality, women who developed new onset PTSD were more likely to eat unhealthy foods such as red/processed meats and trans fat, less likely to eat healthful foods such as whole grain and omega fat, and more likely to consume inappropriate amounts of alcohol.

Figure 2. Age-adjusted predicted values of total flavonoids intake (mg/day, energy-adjusted) by trauma/PTSD status over 20 years.



Note. The median age at baseline (age of 35 years old) for all women and median onset year (10 years after baseline, represented as the gray vertical line) for women with incident trauma/PTSD were used to predict the total flavonoids intake (mg/d, energy adjusted) by trauma/PTSD status, based on linear mixed effects spline model, which included the following covariates, age (time-updated, squared and linear terms), time since baseline (squared and linear terms, centered at median year since baseline), trauma/PTSD X time since baseline (squared and linear terms) interaction terms, time to onset (linear term), and interaction between trauma/PTSD X time to onset (linear term), as well as random intercept and random slopes for time since baseline (squared and linear terms) and time to onset (linear term).

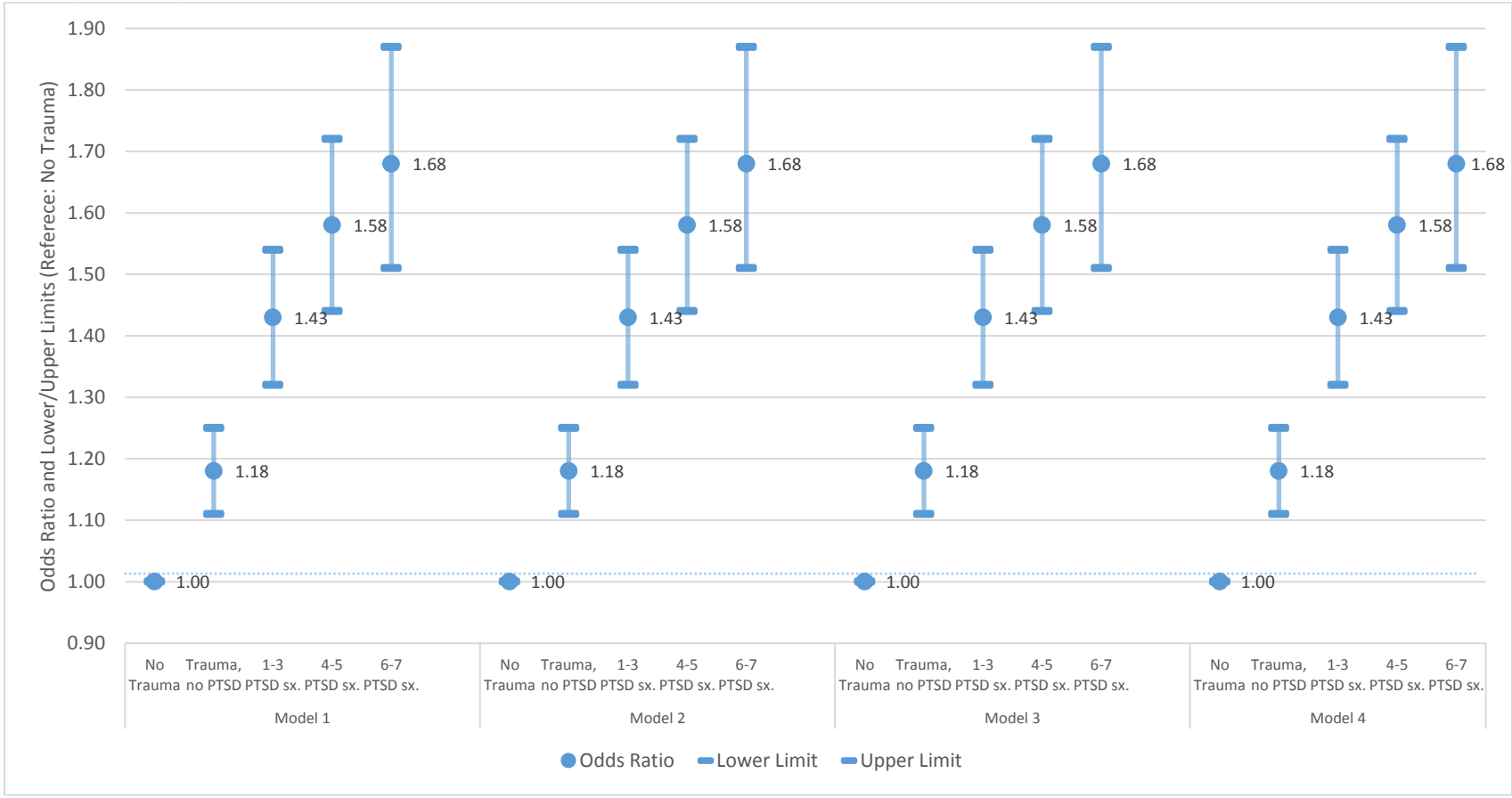
Figure 3. Age-adjusted predicted values of AHEI scores (ranging from 0-110) by trauma/PTSD status over 20 years.



Note. The median age at baseline (age of 35 years old) for all women and median onset year (10 years after baseline, represented as the gray vertical line) for women with incident trauma/PTSD were used to predict the AHEI scores by trauma/PTSD status, based on linear mixed effects spline model, which included the following covariates, age (time-updated, squared and linear terms), time since baseline (squared and linear terms, centered at median year since baseline), trauma/PTSD X time since baseline (squared and linear terms) interaction terms, time to onset (linear term), and interaction between trauma/PTSD X time to onset (linear term), as well as random intercept and random slopes for time since baseline (squared and linear terms) and time to onset (linear term).

For the study seeking to understand the association between PTSD and the use of hormone replacement therapy (HT), specific objectives were to examine if women with PTSD would be more likely to use HT than women with no trauma exposure. Information on HT was measured via a biennial questionnaire in NHS2, regarding use of prescription and/or over-the-counter hormones. As stated above, the information on trauma exposure and PTSD symptoms were measured with the validated screening tools at 2008. Initial analyses examined whether the use of HT measured in 2009 follow-up survey was different by trauma/PTSD status measured in 2008 survey. To test this, we performed multivariable logistic regression models to evaluate differences in HT use by trauma/PTSD status among nearly 35,000 women for whom relevant data are available. In brief, we found women with high PTSD symptoms were more likely to use HT than those with no trauma exposure, with a statistically significant dose-response trend evident. For instance, compared to women with no trauma, likelihood of HT use was higher by 57% for women with trauma plus 4-5 PTSD symptoms, and by 67% for women with trauma plus 6-7 PTSD symptoms (p-value for dose-response trend test was statistically significant, $p<0.001$) after accounting for age (see Figure 3). This relationship was robust even after further adjusting for sociodemographic factors (e.g., parental education), reproductive factors (e.g., parity), other comorbidities (e.g., diabetes, depression), and health-related behaviors (e.g., cigarette smoking).

Figure 4. Cross-sectional analysis of association between PTSD at 2008 and Hormone Replacement Therapy use after menopause in 2009 in NHS2 (N=34,461)



Model 1. Adjusted for age;
Model 2. Model 1+ Additionally adjusted for early childhood factor (race, parental education, somatotype at age 5);
Model 3. Model 2+Additionally adjusted for reproductive factors (parity, hysterectomy and breast cancer);
Model 4. Model3 + Additionally adjusted for other comorbidities (hypertension, diabetes, hypercholesterolemia, RA, SLE, osteoporosis, myocardinal infarct, stroke, and depression);
Model 5. Model4 + Additionally adjusted for behavioral factors (physical activity, cigarette smoking, alcohol consumption, and diet quality)

We have also cleaned the data and further identified information on existing biomarkers among women who responded to Trauma and PTSD screening survey in NHS2. The overarching goal for analyses planned with these data is to understand if PTSD influences biological processes linked to increased risk of OvCa. More specifically, we will examine whether women with PTSD have higher concentrations of inflammatory markers such as CRP, IL-6, and sTNFr2 and telomere length. These analyses will utilize biomarkers already assayed in NHS2. To achieve this aim, we searched information on such biomarkers thru the biorepository of NHS2, and combined information on biomarkers with our primary dataset with data on trauma and PTSD status. To date, we have identified a total n=3,491 women who have information on both CRP level and trauma/PTSD status, n=3740 women who have information on both IL-6 and trauma/PTSD status; and n=2025 women who have information on both TNFRII and trauma/PTSD status. We have also identified nearly n=2500 of women with information on telomere length among those who participated in trauma and PTSD screening surveys in NHS 2.

With regard to examining PTSD in relation to novel biomarkers, tasks are 25% completed. Currently, we have identified and selected samples for novel biomarker assays, and sent them to the lab that will conduct the assays (Dr. Oto Martinez's Lab, UCLA, CA). Thus, we will obtain assays for 6 novel biomarkers (IL-8, IL-10, BAFF [B-cell activating factor], CXCL13 [BLC/BCA1], soluble IL-2 receptor alpha, and soluble IL-6 receptor [sIL-6R]) among women who underwent a gold-standard phone interview to assess PTSD. Among women who responded the PTSD gold-standard phone interview, plasma samples were selected from a total of n=30 women based on three criteria: (1) women who met the PTSD diagnostic criteria by the gold-standard interview and had the highest PTSD symptom scores among the interview respondents; (2) women who had PTSD onset (worst trauma) at least 1-year prior to the relevant blood draw; (3) women who had their most recent PTSD symptoms after the relevant blood draw (active PTSD); and (4) women who did not have any cancer prior to the relevant blood draw. We are in the process of selecting appropriate samples with tumor tissue, which will also be sent for assay once selected. These samples will provide us with preliminary data with which to assess which biomarkers to assay in the larger sample for further investigation.

We have not yet begun working on tasks for Specific Aim 3.

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

While the project was not initially designed to provide training opportunities, it has provided Dr. Yongjoo Kim, a postdoctoral research fellow working on the project, with opportunities to receive training on a number of valuable research tasks. These include managing data from a large prospective cohort study, learning advanced statistical modeling such as linear mixed effects spline models and Cox proportional hazard models, and statistical programing of these kinds of model with statistical software packages such as SAS. Training occurs through one-on-one sessions and group meetings.

3.4 How were the results disseminated to communities of interest?

Nothing to Report

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

To accomplish our goals and objectives for the next year, during the next reporting period, we plan to do a range of activities as follows. For Specific Aim 1, we will refine analyses testing whether women with chronic PTSD have shorter survival than those with no trauma and/or PTSD symptoms, among women with OvCa. We will also begin conducting exploratory analyses to understand whether women with both PTSD and co-occurring psychological distress have highest risk of OvCa relative to women with only PTSD but without co-occurring distress or to women with no trauma. We will write up the findings from the analyses and submit them to peer-reviewed journals. We will submit findings to relevant conferences for presentation.

For Specific Aim 2, we will continue conducting analyses to determine whether women with PTSD (vs. women with no trauma) have more inflammation, by using existing biomarkers such as CRP, IL-6, and TNFR2, and shorter telomere length. We will report findings from analyses of inflammatory markers and telomere length in separate manuscripts and submit all resulting manuscripts to peer reviewed journals. In addition, we will present the findings from PTSD-diet analyses at an upcoming scientific conference. Time permitting, we will begin writing up the findings from the analyses linking PTSD to HR use for submission to a peer-reviewed journal.

We expect to receive data for the novel biomarkers from blood samples in the next several months. We will then begin conducting analyses to understand the association between PTSD and novel biomarkers, to see which biomarkers can be validly assessed and may be worth pursuing in further research. We will also select samples from tumor tissues and send to the laboratory for assays, obtain information, create data sets, and conduct analyses.

With respect to Specific Aim 3, we will begin conducting more formal mediation analyses to test whether adverse behaviors mediate the elevated risk of OvCa related to PTSD.

4.0 IMPACT:

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

The current findings of the project are beginning to provide evidence showing that high levels of PTSD can increase the risk of developing ovarian cancer. Plausible pathways may be by increasing likelihood of having a diet with low flavonoid and poor quality, and using hormone therapy use. Such findings may have impact for several disciplines – both mental health and cancer epidemiology. With regard to mental health (the principal discipline), assuming our findings hold and continue to be consistent, they suggest the value of surveillance and screening of trauma and PTSD symptoms among general public as well as high risk populations, since trauma and PTSD may have significant effects not only on mental but also physical health. They may also suggest the value of careful screening for cancer among trauma-exposed women who develop PTSD. Our results further suggest it may be valuable to incorporate behavioral modification in clinical practice for managing PTSD. Physical activity and nutritional intake are important factors that affect the development of ovarian cancer (and other chronic diseases). Although a growing evidence points to the impact of PTSD on these behaviors, seeking to

manage these behaviors is not a common goal incorporated in the management of PTSD in clinical settings. The findings of the current project add to the scientific knowledge by providing evidence that PTSD alters dietary behaviors in a harmful direction that can lead to ovarian cancer, above and beyond the role of sociodemographic factors, depression, chronic conditions, and other behaviors. This supports the recommendation from our earlier work (Kubzansky, 2014; Winning, 2017), calling for the importance of incorporating promotion and modification of health-related behaviors such as physical activity and healthy eating into the current practice for PTSD management in clinical settings. In public health practice, behavior-change interventions that promote healthy diet and physical activity may be particularly valuable for individuals affected by PTSD.

4.2 What was the impact on other disciplines?

The findings of the project are also likely to make substantial impacts on the field of epidemiology by providing evidence that the impacts of chronic stress in relation to traumatic event can go beyond the scope of psychological health and functioning and affect physical health, and specifically cancer risk. Specifically, the findings of the project suggest that PTSD can result in higher risk of developing ovarian cancer. Moreover, the results suggest that such chronic stress-related reactions can alter health-related behavioral decision making process such as dietary intake and HR use in harmful directions, which can increase risk for developing ovarian cancer and other severe chronic disorders.

4.3 What was the impact on technology transfer?

Nothing to report

4.4 What was the impact on society beyond science and technology?

Nothing to report

5. CHANGES/PROBLEMS:

5.1 Changes in approach and reasons for change

Nothing to report

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

Nothing to report

5.3 Changes that had a significant impact on expenditures

Nothing to report

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

Not applicable

5.5 Significant changes in use or care of human subjects

Not applicable

5.6 Significant changes in use or care of vertebrate animals.

Not applicable

5.7 Significant changes in use of biohazards and/or select agents

Not applicable

6. PRODUCTS:

6.1 Publications, conference papers, and presentations

6.1.1 Journal publications.

Nothing to report

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

Nothing to report

6.1.3 Other publications, conference papers, and presentations.

Sun Jae Jung, Jennifer Sumner, Carolyn Gibson, Yongjoo Kim, Andrea Roberts, Qixuan Chen, Laura Kubzansky, Eric Rimm, Karestan Koenen; (0746 S/P) Trauma exposure, posttraumatic stress disorder symptoms, and hormone replacement therapy after menopause in women. Poster presentation at the Society for Epidemiologic Research 51st Annual Meeting, Baltimore, June 2018

7. PARTICIPANTS & OTHER COLLABORATING ORGANIZATIONS

7.1 What individuals have worked on the project?

Name:	Laura Diane Kubzansky
Project Role:	PD/PI
Researcher Identifier (e.g. ORCID ID):	0000-0002-4039-2235

Nearest person month worked:	1
Contribution to Project:	Dr. Kubzansky has led the project by working closely with Dr. Yongjoo Kim (Post-doctoral Fellow) to build appropriate datasets, identify and send appropriate samples for assay for novel biomarkers. Dr. Kubzansky has also been involved in overseeing and interpreting all analyses throughout the project. Dr. Kubzansky has led the bi-weekly conference calls for the project and involved in manuscript preparation and submission to peer-reviewed journals as well as presentation of data at professional meetings.
Funding Support:	Other Support page included in Appendix

Name:	Shelley S. Tworoger
Project Role:	Co-Investigator
Researcher Identifier (e.g. ORCID ID):	0000-0002-6986-7046
Nearest person month worked:	1
Contribution to Project:	Dr. Tworoger has collaborated on the project by working with Drs. Kubzansky and Kim to identify and send appropriate samples for assay for novel biomarkers. She has also been involved with interpreting analyses and preparing manuscripts describing the findings from analyses (PTSD and incident ovarian cancer; PTSD and diet; PTSD and HR), and participated in the bi-weekly conference calls for the project.
Funding Support:	Other Support page included in Appendix

Name:	Karestan C. Koenen
Project Role:	Co-Investigator
Researcher Identifier (e.g. ORCID ID):	0000-0003-2978-7655
Nearest person month worked:	1
Contribution to Project:	Dr. Koenen has collaborated on all aspects of the project with Drs. Kubzansky, Kim and Tworoger to accomplish the proposed aims. She has participated in regular meetings with Dr. Kubzansky and

	the other co-investigators, and has been involved with characterizing PTSD in the most rigorous way possible, interpreting analyses and preparing manuscripts describing the findings from analyses (PTSD and incident ovarian cancer; PTSD and diet; PTSD and HR), and in writing them up for submission to peer-review journals.
Funding Support:	Other Support page included in Appendix

Name:	Andrea Lynne Roberts
Project Role:	Co-Investigator
Researcher Identifier (e.g. ORCID ID):	0000-0001-5023-4399
Nearest person month worked:	1
Contribution to Project:	Dr. Roberts has conducted the statistical analyses linking PTSD and risk of developing ovarian cancer and drafted the findings. Dr. Roberts has also participated in bi-weekly conference calls for the projects and in manuscripts and presentation related to study findings.
Funding Support:	N/A

Name:	*Yongjoo Kim*
Project Role:	*Postdoctoral Research Fellow*
Researcher Identifier (e.g. ORCID ID):	0000-0002-0768-9256
Nearest person month worked:	8
Contribution to Project:	Dr. Kim has been involved in all aspects of the project, including data cleaning and management, sample selection for novel biomarkers, identification of existing biomarkers, and statistical analyses linking PTSD with diet and manuscript preparation for the findings, under the direction of Dr. Kubzansky. He has also participated in the bi-weekly conference calls for the project.

Funding Support:	N/A

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

There have been several changes in in effort level for key personnel.
Dr. Andrea Roberts is no longer on this project because she moved to another department. We are using the savings from her departure to increase the effort for our post-doctoral fellow to 100% effort.

Drs. Kubzansky's and Koenen's effort has changed slightly from 10% effort to 9.26%, this is due to our changes in fringe rate which went from 24.6% to 25.3%.

Dr. Tworoger (Moffitt Center) effort has gone from 5% in year 1 to 2.5% in year 2, also to accommodate sustaining greater effort than originally budgeted for the postdoctoral fellow.

7.3 What other organizations were involved as partners?

Provide the following information for each partnership:

1. **Organization Name:** H. Lee Moffitt Cancer Center and Research Institute
2. **Location of Organization:** Tampa, Florida
3. **Partner's contribution to the projec**t: Dr. Shelley Tworoger is a Co-Investigator

a. **Financial support;** $34,379
b. **In-kind support**: n/a
c. **Facilities** n/a
d. **Collaboration** n/a
e. **Personnel exchanges** n/a
f. **Other:** n/a

8. SPECIAL REPORTING REQUIREMENTS

- Invention Disclosures and Patent Application reporting
- Quad Chart

9. APPENDICES:

Invention Disclosures and Patent Applications form
Quad Chart
Presentation at SER 2018 - PPTSD.HT poster presentation
Laura Kubzansky - Other Support Page
Shelley Tworoger - Other Support Page
Karestan Koenen - Other Support Page

REPORT OF INVENTIONS AND SUBCONTRACTS

(Pursuant to "Patent Rights" Contract Clause) (See Instructions on back)

Form Approved
OMB No. 9000-0095
Expires Jan 31, 2008

PLEASE DO NOT RETURN YOUR COMPLETED FORM TO THE ABOVE ORGANIZATION. RETURN COMPLETED FORM TO THE CONTRACTING OFFICER.

1.a. NAME OF CONTRACTOR/SUBCONTRACTOR	c. CONTRACT NUMBER	2.a. NAME OF GOVERNMENT PRIME CONTRACTOR	c. CONTRACT NUMBER	3. TYPE OF REPORT *(X one)*
President and Fellows of Harvard College	W81XWH-17-1-0153	Chris Baker	0010989017	X a. INTERIM ☐ b. FINAL

b. ADDRESS *(Include ZIP Code)*	d. AWARD DATE *(YYYYMMDD)*	b. ADDRESS *(Include ZIP Code)*	d. AWARD DATE *(YYYYMMDD)*	4. REPORTING PERIOD *(YYYYMMDD)*
677 Huntington Avenue Boston, MA 02115-6028	20170930	USA MED Research ACQ Activity 820 Chandler St., Fort Detrick, MD 21702-5014	20170504	a. FROM 20170930 b. TO 20180929

SECTION I - SUBJECT INVENTIONS

5. "SUBJECT INVENTIONS" REQUIRED TO BE REPORTED BY CONTRACTOR/SUBCONTRACTOR *(If "None," so state)*

NAME(S) OF INVENTOR(S) *(Last, First, Middle Initial)* a.	TITLE OF INVENTION(S) b.	DISCLOSURE NUMBER, PATENT APPLICATION SERIAL NUMBER OR PATENT NUMBER c.	ELECTION TO FILE PATENT APPLICATIONS *(X)* d.				CONFIRMATORY INSTRUMENT OR ASSIGNMENT FORWARDED TO CONTRACTING OFFICER *(X)* e.	
			(1) UNITED STATES		(2) FOREIGN			
			(a) YES	(b) NO	(a) YES	(b) NO	(a) YES	(b) NO
None								

f. EMPLOYER OF INVENTOR(S) NOT EMPLOYED BY CONTRACTOR/SUBCONTRACTOR		g. ELECTED FOREIGN COUNTRIES IN WHICH A PATENT APPLICATION WILL BE FILED	
(1) (a) NAME OF INVENTOR *(Last, First, Middle Initial)*	(2) (a) NAME OF INVENTOR *(Last, First, Middle Initial)*	(1) TITLE OF INVENTION	(2) FOREIGN COUNTRIES OF PATENT APPLICATION
(b) NAME OF EMPLOYER	(b) NAME OF EMPLOYER		
(c) ADDRESS OF EMPLOYER *(Include ZIP Code)*	(c) ADDRESS OF EMPLOYER *(Include ZIP Code)*		

SECTION II - SUBCONTRACTS *(Containing a "Patent Rights" clause)*

6. SUBCONTRACTS AWARDED BY CONTRACTOR/SUBCONTRACTOR *(If "None," so state)*

NAME OF SUBCONTRACTOR(S) a.	ADDRESS *(Include ZIP Code)* b.	SUBCONTRACT NUMBER(S) c.	FAR "PATENT RIGHTS" d.		DESCRIPTION OF WORK TO BE PERFORMED UNDER SUBCONTRACT(S) e.	SUBCONTRACT DATES *(YYYYMMDD)* f.	
			(1) CLAUSE NUMBER	(2) DATE *(YYYYMM)*		(1) AWARD	(2) ESTIMATED COMPLETION
None							

SECTION III - CERTIFICATION

7. CERTIFICATION OF REPORT BY CONTRACTOR/SUBCONTRACTOR *(Not required if: (X as appropriate))* ☐ SMALL BUSINESS or X NONPROFIT ORGANIZATION

I certify that the reporting party has procedures for prompt identification and timely disclosure of "Subject Inventions," that such procedures have been followed and that all "Subject Inventions" have been reported.

a. NAME OF AUTHORIZED CONTRACTOR/SUBCONTRACTOR OFFICIAL *(Last, First, Middle Initial)*	b. TITLE	c. SIGNATURE	d. DATE SIGNED
Angie Suriel	Assistant Director of Sponsored programs Administration		

DD FORM 882 INSTRUCTIONS

GENERAL

This form is for use in submitting INTERIM and FINAL invention reports to the Contracting Officer and for use in reporting the award of subcontracts containing a "Patent Rights" clause. If the form does not afford sufficient space, multiple forms may be used or plain sheets of paper with proper identification of information by item number may be attached.

An INTERIM report is due at least every 12 months from the date of contract award and shall include (a) a listing of "Subject Inventions" during the reporting period, (b) a certification of compliance with required invention identification and disclosure procedures together with a certification of reporting of all "Subject Inventions," and (c) any required information not previously reported on subcontracts containing a "Patent Rights" clause.

A FINAL report is due within 6 months if contractor is a small business firm or domestic nonprofit organization and within 3 months for all others after completion of the contract work and shall include (a) a listing of all "Subject Inventions" required by the contract to be reported, and (b) any required information not previously reported on subcontracts awarded during the course of or under the contract and containing a "Patent Rights" clause.

While the form may be used for simultaneously reporting inventions and subcontracts, it may also be used for reporting, promptly after award, subcontracts containing a "Patent Rights" clause.

Dates shall be entered where indicated in certain items on this form and shall be entered in six or eight digit numbers in the order of year and month (YYYYMM) or year, month and day (YYYYMMDD). Example: April 2005 should be entered as 200504 and April 15, 2005 should be entered as 20050415.

1.a. Self-explanatory.

1.b. Self-explanatory.

1.c. If "same" as Item 2.c., so state.

1.d. Self-explanatory.

2.a. If "same" as Item 1.a., so state.

2.b. Self-explanatory.

2.c. Procurement Instrument Identification (PII) number of contract (DFARS 204.7003).

2.d. through 5.e. Self-explanatory.

5.f. The name and address of the employer of each inventor not employed by the contractor or subcontractor is needed because the Government's rights in a reported invention may not be determined solely by the terms of the "Patent Rights" clause in the contract.

Example 1: If an invention is made by a Government employee assigned to work with a contractor, the Government rights in such an invention will be determined under Executive Order 10096.

Example 2: If an invention is made under a contract by joint inventors and one of the inventors is a Government employee, the Government's rights in such an inventor's interest in the invention will also be determined under Executive Order 10096, except where the contractor is a small business or nonprofit organization, in which case the provisions of 35 U.S.C. 202(e) will apply.

5.g.(1) Self-explanatory.

5.g.(2) Self-explanatory with the exception that the contractor or subcontractor shall indicate, if known at the time of this report, whether applications will be filed under either the Patent Cooperation Treaty (PCT) or the European Patent Convention (EPC). If such is known, the letters PCT or EPC shall be entered after each listed country.

6.a. Self-explanatory.

6.b. Self-explanatory.

6.c. Self-explanatory.

6.d. Patent Rights Clauses are located in FAR 52.227.

6.e. Self-explanatory.

6.f. Self-explanatory.

7. Certification not required by small business firms and domestic nonprofit organizations.

7.a. through 7.d. Self-explanatory.

Posttraumatic Stress Disorder and Ovarian Cancer Risk

W81XWH-17-1-0153

PI: Kubzansky, Laura **Org:** President and Fellows of Harvard College **Award Amount:** $638,672.00

Study/Product Aim(s)

We have identified several stress-related factors as increasing risk for incident ovarian cancer (OvCa); these findings are consistent with work conducted in animal models of ovarian carcinogenesis. Thus, we propose that posttraumatic stress disorder (PTSD) may be a risk factor for OvCa, with the specific aims to (a) determine if PTSD is longitudinally associated with increased risk of developing OvCa; (b) identify if PTSD influences biological and behavior related processes also linked to increased OvCa risk; and (c) evaluate if behavior-related pathways mediate the association between PTSD and risk of developing OvCa.

Approach

We are using the unique resource of the Nurses' Health Study 2 PTSD sub-study (N=54,282), to conduct prospective analyses linking PTSD, biological and behavioral risk factors, and OvCa. We are enriching existing data resources by obtaining novel biomarkers related to OvCa, including interleukin-8, interleukin-10, soluble interleukin-2 receptor alpha, soluble interleukin-6 receptor, CXCL13, and B-cell activating factor (BAFF).

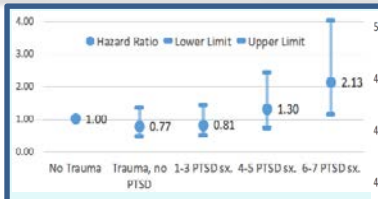


Figure 1. Association between Trauma/PTSD status (vs. no Trauma) and OvCa diagnosis

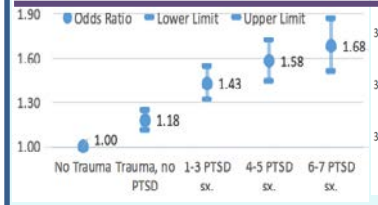


Figure 2. Association between Trauma/PTSD status (vs. no Trauma) and hormone therapy use

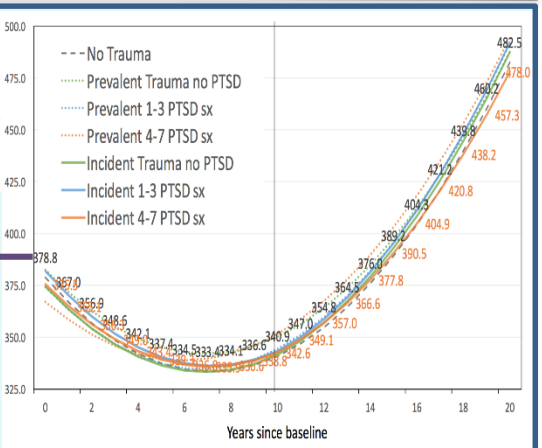


Figure 3. Age-adjusted predicted plots of total flavonoids intake (mg/day, energy-adjusted) by Trauma/PTSD status over 20 years

Women with high PTSD symptoms (vs. no trauma) were more likely to develop OvCa (>2-fold greater risk), (b) have a diet low in flavonoids and poor in quality (by 2.0-2.5%), and (c) use hormone therapy in a dose-response fashion.

Timeline and Cost

Activities	CY 17	18	19	20
Obtain IRB approval by 2 months; clean and prepare data sets for existing measures.				
Spec. Aim 1 –conduct analysis linking PTSD with risk of OvCa development and shorter survival; draft and submit findings for peer review.				
Spec. Aim 2 - select samples for novel biomarkers; conduct analyses of PTSD with OvCa-related biological and behavioral factors, and draft and submit findings for peer review.				
Spec. Aim 3 - conduct formal mediation analyses on behavior pathways mediating PTSD-OvCa association; draft and submit findings for peer-review.				
Estimated Budget ($K)	**$000**	**$000**	**$000**	**$000**

Updated: (August 28, 2018)

Goals/Milestones

CY17 Goal – Overall project tasks (IRB approval, data management)

☑ submit IRB approval for DoD HRPO approval (2 months)

☑ clean and prepare data sets for existing measures (8 months)

CY18 Goal – Specific Aim 1: PTSD and OvCa incidence and survival

☐ conduct analyses, draft and submit to peer-review journals (19-22 months)

CY19 Goal – Specific Aim 2: PTSD and OvCa-related biological and behavioral (flavonoids and hormone therapy) processes

☐ select samples and obtain novel biomarkers, conduct analyses, draft and submit to peer-review journals (26-32 months)

CY20 Goal – Specific Aim 3: behavior pathways mediating PTSD-OvCa association

☐ conduct analyses, draft and submit to peer-review journals (35 months)

Comments/Challenges/Issues/Concerns: The project is progressing well and we have no comments/challenges/issues/concerns.

Budget Expenditure to Date

Projected Expenditure: $207,258

Actual Expenditure: $ 186,303

0744

NO ASSOCIATION BETWEEN NEIGHBORHOOD DISADVANTAGE AND DEPRESSIVE SYMPTOMS AMONG ADOLESCENTS FOLLOWED INTO EMERGING ADULTHOOD Rise B. Goldstein* Rise B. Goldstein, Awapuhi K. Lee, Jacob S. Jeffers, Brian J. Fairman, Jeremy W. Luk, Denise L. Haynie, Bruce G. Simons-Morton, Stephen E. GIlman, , (Health Behavior Branch, Division of Intramural Population Health Research, Eunice Kennedy Shriver National Institute of Child Health and Human Development)

Introduction According to recent studies, residents of disadvantaged neighborhoods have higher levels of depressive symptoms; however, most of these studies have focused on adults and used cross-sectional designs. Therefore, we prospectively examined associations of two aspects of neighborhood disadvantage (social fragmentation and income inequality) with depressive symptoms over six yearly waves of a nationally representative survey of adolescents. Methods The NEXT Generation Health Study enrolled 10th-grade students from 80 United States high schools in 2010. Depressive symptoms were assessed with the pediatric Patient Reported Outcome Measurement Information System (PROMIS) from Waves 2-6. Social fragmentation and income inequality were measured at the census-tract level using geolinked data from the American Community Survey 5-year estimates. We used linear mixed-effects models to relate time-varying neighborhood disadvantage to PROMIS T-scores at Waves 2-6 controlling for neighborhood racial composition, respondent sex, age, race/ethnicity, family affluence, and Wave 1 depressive symptoms. Results Respondents (n=2647) were 55% female, 16.3 years old at Wave 1, and completed an average of 4 follow-up assessments. Neighborhood disadvantage was not associated with depressive symptoms. Regression coefficients (SE) for the 2nd through 4th (vs. first) quartiles of social fragmentation were 0.25 (0.29), -0.07 (0.39), and 0.35 (0.43). Coefficients for income inequality were 0.15 (0.30), -0.37 (0.31), and -0.33 (0.34). Conclusion Social fragmentation and income inequality, which were associated with depressive symptoms in prior studies of adults, were not associated with scores on an established measure of depressive symptoms in a nationally representative cohort of adolescents. These findings raise questions for future research regarding developmental timing of neighborhood effects on mental health and their potential heterogeneity across the United States.

0745

ACCESS TO AFFORDABLE DAYCARE AND WOMEN'S MENTAL HEALTH IN RAJASTHAN, INDIA: EVIDENCE FROM A CLUSTER-RANDOMIZED SOCIAL INTERVENTION Arijit Nandi* Arijit Nandi, Sam Harper, (McGill University)

The provision of affordable and reliable daycare services is a potentially important policy lever for reducing gender inequality, improving health and socioeconomic well-being, and empowering women in resource limited settings. This cluster-randomized trial uses data from a sample of 2859 mothers with age eligible children to evaluate the impact of providing access to a community-based daycare program on women's mental health roughly two years later. The study takes places in 160 village hamlets in rural Rajasthan, India, which were randomized to intervention or control groups after a baseline survey. Symptoms of common mental disorders were assessed using a Hindi version of the 12-item General Health Questionnaire (GHQ-12). At baseline, the mean number of GHQ-12 symptoms was 2.12 (SD=2.45). Treatment assignment increased the probability that a respondent used a daycare by 33 percentage points. Mothers living in treated hamlets reported 0.17 fewer symptoms of distress (95%CI=-0.41, 0.07) at follow-up. We found some variability in treatment effects according to block of residence and baseline characteristics, with the largest reductions in mental distress observed among women employed year round prior to the intervention. Analyses exploring the impact of maternal use of a daycare using two-stage least squares (2SLS) instrumental variables analysis showed that daycare use decreased symptoms of mental distress by 0.44 (95%CI=-0.97, 0.09) symptoms, or roughly 21% compared to the baseline mean. The provision of affordable, community-based daycare was associated with substantial uptake and showed potential for improving mothers' mental health in a lower-income, rural context.

0746 S/P

TRAUMA EXPOSURE, POSTTRAUMATIC STRESS DISORDER SYMPTOMS, AND HORMONE REPLACEMENT THERAPY AFTER MENOPAUSE IN WOMEN Sun Jae Jung* Sun Jae Jung, Jennifer Sumner, Carolyn Gibson, Yongjoo Kim, Andrea L Roberts, Qixuan Chen, Laura Kubzansky, Eric B Rimm, Karestan C Koenen, (Harvard University T.H. Chan School of Public Health)

Background: Posttraumatic stress disorder (PTSD) is a common and often persistent psychiatric disorder that occurs twice as frequently in women as in men. PTSD has been linked to increased cardiometabolic risk, and use of female hormone therapy may potentially contribute to or reduce the risk of these health conditions. We hypothesized that women with PTSD and trauma exposure will have increased use of hormone therapy compared to women with no trauma exposure. Method: We used data from 34,461 women in Nurses' Health Study II which began in 1989. History of trauma and PTSD were asked with Short Screening Scale for DSM-4 PTSD in 2008. Use of hormone replacement therapy (HRT) after menopause was assessed in every survey from 1989, and we utilized the data from 2009 to compare baseline association. We made bivariate outcome (yes/no) for HRT use. Logistic regression was used to estimate multivariate-adjusted odds ratios and 95% confidence intervals for HRT use, adjusting age, childhood factors, reproductive factors, other comorbidities, and behavioral factors in the final model. Result: In multivariable adjusted models, we found significant associations for PTSD with HRT use (p-trend <0.001; trauma with no PTSD symptoms, 1.12 [95% CI:1.05-1.20]; 1-3 PTSD symptoms, 1.34 [95% CI:1.36-1.45]; 4-5 PTSD symptoms, 1.47 [95% CI:1.33-1.61]; and 6-7 PTSD symptoms, 1.46 [95% CI:1.30-1.64]). Conclusion: PTSD was associated with higher likelihood of HRT use in a dose-dependent pattern. Further research is needed to explore the role of HRT as a possible mediating mechanism between PTSD and cardiometabolic diseases.

OTHER SUPPORT: KUBZANSKY, LAURA

ACTIVE:

W81XWH-17-1-0153 (Kubzansky) 09/30/17-09/29/20 0.96 calendar
DoD $150,000
Contract Specialist: Lisa Wells Roark
Phone: 301-619-2086
Email: lisa.l.wellsroark.civ@mail.mil

Posttraumatic Stress Disorder and Ovarian Cancer Risk

The goal of this project is to assess the role of PTSD in risk of developing ovarian cancer. This project will also consider underlying biological (e.g., inflammation) or behavioral (e.g., poor diet) processes that may explain how PTSD alters risk of ovarian cancer. It will also differentiate effects of trauma alone from effects of trauma and PTSD.
Role: PI

Grant # 215 (Spengler) 03/01/2014-02/28/2019 0.60 calendar
JPB Foundation $35,359
Grants Manager: Julio Bautista
The JPB Foundation
875 Third Avenue, 29th Floor
New York, NY 10022

JPB Environmental Health Fellows Program

To train scholars in studying and addressing the environmental and social determinants that contribute to health disparities through an innovative, interdisciplinary training program integrating social, behavioral and environmental sciences.
Role: Faculty

R01 AR057327 (Costenbader) 09/21/2015-08/31/2020 0.96 calendar
NIH/NIAMS / BWH $43,999 (sub)
National Institute of Arthritis and Musculoskeletal and Skin Diseases
Program Official: William P Tonkins
1 AMS Circle
Bethesda, MD 20892-3675
Email: tonkinsw2@mail.nih.gov

Sociodemographic Disparities in SLE Incidence: Behavioral and Psychosocial Factors

Harvard T.H. Chan School of Public Health is collaborating with Brigham and Women's Hospital, Boston in the detailed assessment of depression and chronic stress in relation to incident systematic lupus erythematosus (SLE). Harvard investigators are involved in evaluating stress and distress measures and constructing appropriate scales for analysis, as well as in integrating the subjective and biological data and evaluating linkages between them.
Role: Co-Investigator

5R01AG051600-02 (Hankinson/Kubzansky 09/15/2017-05/31/2021 1.44 calendar
NIH/NIA/University of Massachusetts, Amherst $26,549 (sub)
National Institute of Health
Program Official: Lisbeth Nielsen

9000 Rockville Pike
Bethesda, Maryland 20892
Email: nielsenli@nia.nih.gov

Development and Application of a Metabolic Profile of Chronic Distress to Cardiometabolic Risk
The Harvard T.H. Chan School of Public Health is collaborating with University of Massachusetts, Amherst in the assessment of chronic distress and relevant covariates using data from the Nurses' Health Studies and the Women's Health Initiative. The Harvard team is coordinating the metabolomics assays using banked blood samples, and involved in integrating existing data with the assay data, as well as with developing and implementing plans for statistical analyses.
Role: Co-PI

5R01AG05327-03(Grodstein/Kubzansky) 09/01/2016-03/31/2020 0.91 calendar
NIH/NIA $288,990
National Institute of Health
Program Official: Lisbeth Nielsen
9000 Rockville Pike
Bethesda, Maryland 20892
Email: nielsenli@nia.nih.gov

Optimism and Exceptional Longevity
Survival has steadily increased in industrialized countries and exceptional longevity beyond 85 years is becoming increasingly common but who achieves exceptional longevity and why is not well understood. The goal of this work is to gain greater understanding of factors that promote longer healthier lives by considering whether and how optimism enhances the likelihood of attaining exceptional longevity (i.e., survival to 85+ years).
Role: Co-PI

3R01AG053273-03S1 (Grodstein/Kubzansky) 07/15/2018-03/31/2020 0.91 calendar
NIH/NIA $287,791
National Institute of Health
Program Official: Lisbeth Nielsen
9000 Rockville Pike
Bethesda, Maryland 20892
Email: nielsenli@nia.nih.gov

Optimism and Exceptional Longevity
This application expands the scope of the current R01, and will assess whether and how optimism may influence longevity across diverse populations. In addition, the project seeks to develop a novel social-media derived measure of optimism, combining insights from psychology, natural language processing, and machine learning.
Role: Co-PI

5R01MH101269-05 (Koenen/Kubzansky) 06/02/2014-06/30/2022 0.96 calendar
NIH/NIMH $682,950
National Institute of Mental Health
6001 Executive Boulevard, Room 7113, MSC 9634
Bethesda, MD 20892-9663
Program Official: Jovier D Evans

Email: jevans1@mail.nih.gov

Post Traumatic Stress Disorder and Accelerated Aging in Women

The purpose of this research is to understand whether posttraumatic stress disorder (PTSD) causes accelerated aging in women and to identify underlying disease mechanisms. This research may point to new strategies for ameliorating the adverse effects of PTSD and for comparing effectiveness of various prevention or intervention strategies.

Role: Co-PI

74575 (Berkman) 08/15/2017-08/14/2020 0.60 calendar
RWJF $13,190
Roger Wood Johnson Foundation
50 College Road East
Princeton, NJ 08540-6614
Senior Program Officer: Paul Tarini
Email: ptarini@rwjf.org

Workplace Redesign for Worker Well-Being: Blueprint for Resilience

The goal of this project is to provide novel insight into sustainable practices for enhancing worker well-being and will assess evidence that investing in employee well-being and engagement leads to better organizational outcomes.

Role: Co-PI

07252252-01 (Clougherty) 09/01/2017-07/31/2019 1.20 calendar
Health Effects/Drexel University $ 23,515 (sub)
Drexel University
1505 Race Street, 10th Floor
Philadelphia, PA 19102
POC: Brianna Thompson, Research Accountant
Email: Bnt34@drexel.edu

Susceptibility to Multiple Air Pollutants in Cardiovascular Disease

The goal of this project is to conduct research to assess the interplay between chronic stressor exposure, multiple air pollutants and cardiovascular disease. The project will consider whether exposure effects of multiple pollutants on risk of cardiovascular disease vary depending on exposure to community stressors or socioeconomic position.

Role: Co-Investigator

PENDING:

R01 AG053273 (Kubzansky) 09/01/17-03/31/20 0.70 calendar
NIH/NIA Competing Revision/Supplement $241,315

Optimism and Exceptional Longevity

This application expands the scope of the current R01, and will assess whether and how optimism may influence longevity across diverse populations. In addition, the project seeks to develop a novel social-media derived measure of optimism, combining insights from psychology, natural language processing, and machine learning.

Role: PI

No number (Spengler/Kubzansky) 01/01/20-06/30/21 1.20 calendar
Magnolia Quality Development Corporation $331,243 phase 2

Assessing the influence of nature on physical health and wellbeing in an urban development prototype
This proposal outlines research led by the Center for Health and the Global Environment (CHGE) in conjunction with the Lee Kum Sheung Center for Health and Happiness at the Harvard Chan School of Public Health and the University of Hong Kong's Urban Planning and Design faculties to investigate ways in which setting an urban development amidst a forested environment may reconnect three elements-humans, nature, and living creatures- to benefit the health and happiness of residential occupants.
Role: Co-Investigator

U01 Intense longitudinal behaviors (Chavarro/Onnela) 07/01/18-06/31/21 0.60 calendar
NIH/NICHD $126,193
Digital Phenotypes of Emotion, Health Behaviors, and Geographic Context within a Prospective Cohort
The objective of this proposal is to accurately quantify and understand the interdependent relationships of dynamically-measured emotional and contextual factors with three established, modifiable risk factors for cancer (e.g., physical activity, diet, and sleep).
Role: Multi-PI

No number (Berkman) 07/01/18 – 06/30/23 0.00 calendar
NICHD
Pop Center Infrastructure
This Multi-PI project will provide infrastructure support, plus the creation of a seed grant program for faculty affiliated with our center. The mission of the Harvard Center for Population and Development Studies (HCPDS) is to improve well-being around the world by better understanding the interaction of demographic changes with social, economic, and biological processes.
Role: Faculty

OVERLAP:

If one or more of the pending proposals should be awarded Dr. Kubzansky's effort will be adjusted accordingly.

COMPLETED: (Last 3 years)
5R01 MH101269-03 (Koenen/Kubzansky) 06/02/2014-05/31/2017 2.40 calendar
NIH/NIMH / Columbia University $147,089
National Institute of Mental Health
Program Official: Farris K. Tuma
6001 Executive Blvd.
Room 8184, MSC 9663
Bethesda, MD 20892-9663
Email: ftuma@mail.nih.gov
Assessing Causality: Is PTSD Cardio-Toxic
Harvard T.H. Chan School of Public Health is working with Columbia University to assess the role of PTSD in developing stroke and coronary heart disease.

R03 AG046342 (Boehm) 09/30/2013-08/31/2016 0.24 calendar
NIH/NIA / Chapman University $28,688
National Institute on Aging
Program Official: Lisbeth Nielsen
31 Center Drive, #5c27

Bethesda, MD 20892
Email: nielsenli@nia.nih.gov

Adaptive Aging: Psychological Well-Being and Favorable Cardiovascular Health

Harvard T.H. Chan School of Public Health is working with Chapman University to use existing data from the CARDIA study and from the English Longitudinal Study of Aging to evaluate the role of positive psychological factors in attaining and maintaining favorable cardiovascular health.

053572 (Berkman)	09/01/2006-08/31/2016	2.32 calendar.
Robert Wood Johnson Foundation	$27,870	

Senior Program Officer: Pamela G. Russo, M.D.
1 College Road
Princeton, NJ 08540
Phone: 609-627-7577
Email: prusso@rwjf.org

Health and Society Scholars Program

To train scholars in the social determinants of health through a tightly knit, interdisciplinary training program integrating social, behavioral and biological sciences with a rich historical perspective.

R01CA163451 (Tworoger)	09/01/2012-07/31/217 (NCE)	0.84 calendar
NIH/NCI / BWH	$16,177 (sub)	

National Cancer Institute
Program Official: Paige A. Green
8717 Grovemont Circle #115
Bethesda, MD 20892
Email: mcdonalp@mail.nih.gov

Psychological stress, associated biologic mediators, and ovarian cancer risk

This innovative application will translate experimental research into prospective human studies and potentially could improve our understanding of ovarian carcinogenesis and our ability to prevent this fatal disease

OTHER SUPPORT: TWOROGER, SHELLEY

ACTIVE:

W81XWH-17-1-0153 (Kubzansky) 09/30/2017 - 09/29/2020 0.60 calendar
DoD $19,988 (sub)
Contract Specialist: Lisa Wells Roark
Phone: 301-619-2086
Email: lisa.l.wellsroark.civ@mail.mil

Posttraumatic Stress Disorder and Ovarian Cancer Risk

The goal of this project is to assess the role of PTSD in risk of developing ovarian cancer. This project will also consider underlying biological (e.g., inflammation) or behavioral (e.g., poor diet) processes that may explain how PTSD alters risk of ovarian cancer. It will also differentiate effects of trauma alone from effects of trauma and PTSD.

Role: Co-Investigator

P01 CA87969 (Stampfer) 07/01/2015 - 06/30/2020 2.40 calendar
NIH/NCI $47,002

Grants Officer: Somdat Mahabir, Ph.D., MPH., Epidemiology and Genomics Research Program, Division of Cancer Control and Population Sciences, National Cancer Institute, National Institutes of Health, 9609 Medical Center Drive, Rm. 4E106, MSC 9763,Bethesda, MD 20892,Telephone: (240) 276-6941, Fax: (240) 276-7920, mahabir@mail.nih.gov

Dietary and Hormonal Determinants of Cancer in Women, Project 3: Ovarian Cancer

The goal of this project is to improve ovarian cancer prevention, which is key for reducing morbidity and mortality. This proposal examines two key, but understudied putative pathways in ovarian carcinogenesis, metabolism and inflammation. We will examine several key lipid classes using a metabolomics profiling platform as well as an agnostic evaluation of all measured metabolites. For inflammation, we propose to focus on modifiable factors, such as diet, sedentary behavior, premenopausal NSAID use, as well as biomarkers of prostaglandins and chlamydia antibodies. We also will consider tumor characteristics including mRNA expression with inflammatory exposures. Finally, for the first time, we will consider post-diagnosis modifiable exposures with ovarian cancer survival.

Specific Aims: The major focus of the current proposal is on modifiable or treatable factors within two key, yet underexplored, pathways in Ovarian Cancer etiology: lipids and Inflammation. For the lipid pathway, we will examine plasma total cholesterol, HDL, and LDL as these markers can be altered by medication or lifestyle changes, as well as several other promising lipid classes, Lysophosphatidylcholines and Sphingomyelins, which have been suggested as early detection markers and also be important etiologically. These will be measured on a validated, semi-targeted metabolomics platform; this also will allow us to conduct a comprehensive discovery-based analysis of other small molecule metabolites that may be important in Ovarian carcinogenesis. The inflammation aims will build on work from the current P01 and cross-project collaboration with Project 2 (colorectal Cancer), taking an innovative approach that considers multiple facets of the Inflammatory milieu, including lifestyle factors (pro-inflammatory Diet, sedentary behavior, strength training), analgesic related factors (premenopausal NSAID use, urinary Prostaglandins), and chlamydia infection status. Importantly, we will explore potential underlying biologic mechanisms of action by evaluating risk factor associations by tumor aggressiveness, the amount of tumor-associated macrophage Infiltration, and global tumor gene expression to identify transcriptional alterations in tumors of patients with varying Inflammatory exposures. We propose to provide the first detailed evaluation of modifiable factors after diagnosis, including physical activity, Smoking, NSAIDs, and a pro-inflammatory Diet, and survival in stage I/II patients; no evidence-based recommendations currently are available.

Role: Proj 3 Leader

59607 (Shields) 06/01/2017 – 02/28/2019 0.72 calendar
John Templeton Foundation/BWH/MGH $41,128
Grants Officer: Partners Research Management, Brigham and Women's Hospital and Massachusetts General Hospital, 399 Revolution Drive, Suite 740, Somerville, MA 02145, mghsubs@partners.org

National Spirituality and Health Consortium

The goal of this application is to create the National Consortium on Spirituality and Health, comprised of six leading national cohorts who will contribute standardized questions on religiosity and spirituality (R/S), demographic, clinical, and DNA for ~ 1,200 of their participants to create the first prospective R/S research database. We will then evaluate the relationship of R/S measures with DNA methylation in five stress-related and serotonergic genes (i.e., glucocorticoid receptor [*GCR*], *HSD11ß1*, *HSD11ß2*, catechol-O-methyltransferase [*COMT*], and serotonin transporter gene [*SLC6A4*]) and telomere shortening as well as risk of hypertension, cardiovascular disease, and mortality

Specific Aims: Cutting-edge studies increasingly include genetic, social, cultural, environmental, and behavioral factors in complex research designs in an attempt to move from identifying associations related to disease to understanding the underlying mechanisms or pathways that explain disease etiology. These complex research designs require well-characterized and representative participants with large sample sizes, and thus the pooling of data across cohorts is a critical necessity. Consequently, only those measures that are available across all cohorts from which samples are drawn can be included in these aggregated analyses. Measures of religion or spirituality (R/S) cannot usually be included in these innovative research designs because so few cohorts prioritize and collect these data, and, if they do, each collects different measures. The dearth of R/S measures currently collected within U.S. prospective studies thus curbs consideration of the role of R/S in many of the highest-quality health research studies conducted. This proposal aims to conduct state-of-the-art, transformative research on R/S and health within the context of U.S. prospective cohort studies, and

use the results of this research to identify those R/S measures that have the most biological resonance and would thus be most valuable to collect going forward. The robustness of the research upon which our measure selection will be based will position our investigative team to campaign for these measures to be adopted by U.S. cohort studies nationally, which in turn will make possible a new generation of cutting-edge R/S research that leverages the massive amounts of high-quality data already available within the nation's leading prospective studies.

Role: Co Investigator

R01 CA193965 (Terry) 04/01/2017 – 05/31/20201 1.08 calendar
NIH/NCI $20,684
Grants Officer: Christos F. Patriotis, Cancer Biomarkers Research Group, Division of Cancer Prevention National Cancer Institute, 9609 Medical Center Drive, MSC 9790, Bethesda, MD 20892-9790, Phone: (240) 276-7040, Fax: (240) 276-7845, patriotisc@mail.nih.gov

Redefining Normal: Personalized CA125 Cutpoints for Ovarian Cancer Screening

CA125 has been proven to be the single best marker for ovarian cancer detection, yet variation of CA125 in healthy women has prevented its utility as a biomarker for ovarian cancer screening. Here we propose to develop personalized CA125 cutpoints using individual characteristics to improve the sensitivity and specificity for screening and assess if CA125 can improve risk modeling. We hypothesize that by reducing the background noise introduced by exposures that elevate or lower CA125; these personalized cutpoints will improve CA125 as an ovarian cancer screening biomarker for population based ovarian cancer screening.

Specific Aims: Dr. Tworoger will oversee the selection of NHS samples for the study and will collaborate with Dr. Terry on all aspects of study design, analysis, quality control assessment and manuscript preparation. Dr. Tworoger has published extensively on ovarian cancer risk factors and biomarker analyses in epidemiologic studies, including a recent paper incorporating biomarkers into a breast cancer risk prediction model (Tworoger et al., JCO 2014).

Role: Co-Investigator

P30 CA076292 (Sellers) 02/18/1998 - 01/31/2022 2.4 calendar
NIH/NCI $1,565,039
Grants Officer: Peter Ogunbiyi, Ph.D., D.V.M., Center to Reduce Cancer Health Disparities, National Cancer Institute, 9609 Medical Center Drive, MSC 9746, Sixth Floor, West Tower, Bethesda, MD 20892, Phone: 240-276-6170, Fax: 240-276-7862, ogunbiyp@mail.nih.gov
Moffitt Cancer Center Support Grant
Specific Aims: The grant provides support for key personnel involved in the cancer center's research mission. The 142 MCC members span the basic, clinical, and population sciences. They are organized into five highly collaborative, multidisciplinary programs with exceptional levels of intra- (35%) and inter-programmatic (18%) publications. Under the leadership of Dr. Thomas Sellers, the third MCC Director, a Research Strategic Plan (RSP) was developed and implemented for "Moffitt 3.0." Four of six Associate Center Directors are new; and new leaders have been appointed in every program, with bold goals and specific aims. Two of the 13 shared resources have been significantly restructured (Chemical Biology, Molecular Genomics), and one new resource created (Collaborative Data Services) to better meet the changing needs of MCC scientists. Implementation of the strategic plan has been bolstered by substantial institutional investment, especially in basic science, immunotherapy, and clinical research infrastructure, including the recruitment of 45 new faculty members, of whom 32 are CCSG members. MCC is a leader in immunotherapy, and more than 40% of overall clinical trial accrual is to investigator-initiated studies. MCC population scientists initiated significant new efforts in cancer prevention and outcomes that include vaccines, tobacco cessation, and health disparities. This is particularly true in the unique Cancer problems in the catchment area – notably lung Cancer, melanoma, and HPV-prevention. MCC's Total Cancer Care protocol, the ground-breaking research strategy to realize the promise of personalized medicine, has continued to thrive, resulting in dramatic utilization of the Tissue Core and the formation of the oncology Research Information Exchange Network (ORIEN) that now includes eleven cancer centers across the nation, with several more poised to join the consortium this year. MCC requests funding for: five scientific programs, 13 shared resources, two clinical research components, planning and evaluation, administration, leadership, four staff investigators, and developmental funds. CCSG funds are leveraged more than 10-fold with institutional resources to maximize impact on Cancer prevention, treatment, and cure in the catchment area, the state of Florida and beyond.
Role: Associate Center Director

P30 CA076292 (Sellers) 02/18/1998 - 01/31/2022 0.60 calendar
NIH/NCI $1,565,039
Grants Officer: Peter Ogunbiyi, Ph.D., D.V.M., Center to Reduce Cancer Health Disparities, National Cancer Institute, 9609 Medical Center Drive, MSC 9746, Sixth Floor, West Tower, Bethesda, MD 20892, Phone: 240-276-6170, Fax: 240-276-7862, ogunbiyp@mail.nih.gov
Moffitt Cancer Center Support Grant
The Survey Methods Core was established to provide critical and standardized services for survey research and cognitive interviews in population-based and clinical settings.
Role: Director

PENDING:
1K01HL143034 (Huang) 07/01/2018 – 06/30/2023
NHLBI
Elucidating Inflammatory and Metabolic Pathways in Obstructive Sleep Apnea Development
Goals: Understanding the pathogenic pathways, including the heterogeneity by sex and the potential gene-environment interaction, is critical for targeted prevention and screening of obstructive sleep apnea. This

application integrates genetic and biomarker-based approaches to elucidate the roles of inflammatory and metabolic pathways in obstructive sleep apnea development. Findings from this work may lead to new strategies that target these pathways for obstructive sleep apnea prevention and treatment.
Role: Mentor

R01 (Being Resubmitted) (Kaaks) 07/01/2019 – 06/30/2024 0.72 calendar
NIH Cohort Consortium $36,871
Identification of immuno-proteomic markers for ovarian cancer detection
The goal of the application is discover and validate autoantibody [TAAb] biomarker panels for early detection of ovarian cancer, overall and by tumor sub-types (histology; stage & grade at original clinical diagnosis), as complementary markers to CA125 and HE4.
Specific Aims: 1a. Using cohort-nested case-control studies, identify novel diagnostically useful TAAb markers through a three-stage discovery study by a combination of protein binding arrays (stages 1 & 2) and ELISA immunoassays (stage 3).
1b. Using samples of the Brigham & Women's Hospital biorepository, ascertain the potential of selected TAAbs (ELISA assays) to diagnostically discriminate patients with invasive epithelial ovarian cancer from patients with benign pelvic disease.
2. Within the nested case-control studies and samples from Brigham & Women's Hospital, in addition to the TAAbs identified under study aim 1, cross-validate further promising TAAb biomarkers that may be identified through literature review of discovery studies conducted independently.
3. Assess the joint diagnostic discrimination potential of the TAAbs individually identified and confirmed to be diagnostically useful under study aims 1-2.
Role: Co-Investigator

OVERLAP:
Should any other pending grants be awarded, Dr. Tworoger's active research effort will be adjusted accordingly and as necessary.

COMPLETED: (Last 3 years)
No Grant Number (Poole) 04/01/2015 - 03/31/2016
Marsha Rivkin Center for Ovarian Cancer Research
Medication Use and Ovarian Cancer Survival
The goal of this application is to develop ovarian cancer survivorship research in the Nurses' Health Study cohorts. We will evaluate a signature of optimal cytoreductive surgery and apply it in a study of common medication use among ovarian cancer patients.

R01 CA138580 (Tworoger) 07/01/2010 - 04/30/2016 (NCE)
NIH/NCI
Growth Hormones and Breast Cancer Risk
In this proposal, we will conduct a detailed evaluation of prolactin, IGF-I, and IGFBP-3 associations with breast cancer risk. This study will use a prospective nested case-control design (913 cases diagnosed through 2011, 1,826 controls) and blood samples collected between 1996-1999 from 29,611 women, ages 32 to 52 years, in the Nurses' Health Study II. To increase our power, we also will include 354 invasive cancers diagnosed through 2006 in Nurses' Health Study participants who were premenopausal at blood collection in 1989-1990.
TREC
Role: PI

No number available (Tworoger) 06/01/2015 - 05/31/2016
NIH
Sleep quality in relation to metabolomics prouiles and canonical stress hormones

In this application, we propose to examine the relationship of self-reported sleep quality (using the Pittsburgh Sleep Quality Index, PSQI) and circadian factors (chronotype and shiftwork) with metabolic and stress hormone biomarkers. We will use data from the Mind-Body Study (MBS), a sub-study from the Nurses' Health Study II (NHSII), in which 226 women provided fasting blood samples to conduct metabolomic profiling, first morning urine samples to assess catecholamines, and five timed saliva samples over a day to measure diurnal cortisol rhythms. At biospecimen collection, women completed the PSQI, information on other stressors (e.g., discrimination, depression, social isolation, mindfulness, etc.), and weight, with corresponding detailed behavioral and co-morbidity data from the NHSII questionnaires.

R01CA163451 (Tworoger) 09/13/2012 - 07/31/2016
NIH/NCI
Psychological stress, associate biologic mediators, and ovarian cancer risk
This innovative application will translate experimental research into prospective human studies and potentially could improve our understanding of ovarian carcinogenesis and our ability to prevent this fatal disease.

U01CA049449 (Hankinson) 05/01/2012 - 08/31/2016
NIH/NCI
Biochemical Markers in the Nurses' Health Study Cohort
We propose to continue our work identifying and validating biomarkers – particularly hormonal markers – that predict risk of invasive breast cancer in postmenopausal women. Using a prospective nested case-control design, we plan to analyze blood samples collected from the 32,826 participants in the Nurses' Health Study (NHS) who provided a blood sample in 1989-90 and, for 18,743 of these women, a second sample in 1999-2000. We propose to evaluate markers from several inter-related pathways to determine their role in cancer risk; a number of these aims are entirely new, while others extend our work in the most promising areas from the current grant cycle.

W81XWH-12-1-0561 (Tworoger) 09/30/2012 – 09/29/2016 (NCE)
DOD
Development of the Ovarian Cancer Cohort Consortium: Risk factor associations by heterogeneity of disease
The overall goal of this project is topool data from at least 20 cohort studies from around the world to evaluate whether risk factor associations for ovarian cancer differ by various metrics of tumor heterogeniety. We will focus on known and putative ovarian cancer risk factors, such as parity, oral co ntraceptive use, tubal ligation, postmenopausal hormone use, etc. and will evaluate associations by histology, tumor dominance (as a surrogate for cell of origin), and tumor aggressiveness (defined by women who died within 3 years of diagnosis versus not). We will then use this information to develop an improved risk prediction model for ovarian cancer that accounts for heterogenous associations by tumor subtype. The other goal of this application is to develop the infrastructure of the Ovarian Cancer Cohort Consortium to allow future analyses.

W81XWH-13-1-0493 (Poole) 09/30/2013 – 04/30/2017
DOD
Psychosocial stress and ovarian cancer risk: metabolomics and perceived stress
The objective of this application is to study the role of psychosocial stress in ovarian cancer risk, particularly for the aggressive forms of the disease, including high stage and rapidly fatal cancers. The Nurses' Health Study (NHS) and NHSII are two large, prospective cohorts with repeated measures of self-reported stress as well as blood and tumor tissue specimens; they are the ideal setting in which to prospectively evaluate the role of chronic stress in humans. This application will provide a translational link between animal models and human studies, and has substantial potential to improve our understanding of ovarian cancer and its prevention.

W81XWH-14-1-04999 (Oaklander) 09/30/2014 – 09/29/2017 *Effort ended 05/31/2017

U.S. Army Medical Research Acquisition Activity

Characterizing Treatable Causes of Small Fiber Polyneuropathy in Gulf War Veterans

This grant would support global development of a case definition for small-fiber polyneuropathy using the Delphi method among a cohort of experts, and then test the hypothesis that small-fiber polyneuropathy underlies a significant proportion of cases of Gulf War Illness.

OTHER SUPPORT: KOENEN, KATESTAN

ACTIVE:

W81XWH-17-1-0153 (Kubzansky) 09/30/2017 - 09/29/2020 0.93 calendar
DoD $150,000
Contract Specialist: Lisa Wells Roark
Phone: 301-619-2086
Email: lisa.l.wellsroark.civ@mail.mil
Posttraumatic Stress Disorder and Ovarian Cancer Risk
The goal of this project is to assess the role of PTSD in risk of developing ovarian cancer. This project will also consider underlying biological (e.g., inflammation) or behavioral (e.g., poor diet) processes that may explain how PTSD alters risk of ovarian cancer. It will also differentiate effects of trauma alone from effects of trauma and PTSD.
Role: Co-Investigator

R01MH101269 (Koenen, Kubzansky) 09/18/2017 – 06/30/2022 2.40 calendar
NIH/NIMH $682,950
National Institute of Mental Health
6001 Executive Boulevard, Room 7113, MSC 9634
Bethesda, MD 20892-9663
Program Official: Jovier D Evans
Email: jevans1@mail.nih.gov
Post Traumatic Stress Disorder and Accelerated Aging in Women
The purpose of this research is to understand whether posttraumatic stress disorder (PTSD) causes accelerated aging in women and to identify underlying disease mechanisms. This research may point to new strategies for ameliorating the adverse effects of PTSD and for comparing effectiveness of various prevention or intervention strategies.
Role: Co-PI

R01MH101227 (Koenen, Kessler, Shalev) 07/21/2014 - 04/30/2019 (NCE) 0.96 calendar
NIMH $465,869
National Institute of Mental Health
Program Official: Farris K. Tuma
Email: ftuma@mail.nih.gov
Identifying Risk Factors for PTSD by Pooled Analysis of Current Prospective Studies
The purpose of this research project is to develop predictive models for PTSD from pooled data from prospective studies, combining and analyzing individual-level data across numerous studies using coordinated coding and analysis methods that maximize precision of comparisons.
Role: Principal Investigator

U01MH109539 (Daly) 07/01/2016 - 03/31/2021 0.96 calendar
NIH/NIMH/MGH $20,444 (subcontract direct costs)
National Institute of Mental Health
6001 Executive Boulevard, Room 7113, MSC 9634
Bethesda, MD 20892-9663
Program Official: Jovier D Evans
Email: jevans1@mail.nih.gov
2/7 Psychiatric Genomics Consortium: Finding actionable variation

The purpose of the Psychiatric Genomics Consortium is to conduct mega-analyses of genome-wide genetic data for psychiatric disorders. The idea is that individual studies are too small to identify robust and replicable associations. Meta-analysis is a widely-used technique that can combine information across studies. The term "mega-analysis" represents the fact that our analyses are based on individual genotype data.
Role: Co-Investigator / Site PI

R01MH106595 (Nievergelt) 08/19/2016 - 06/30/2019 1.98 calendar
NIH/NIMH/UCSD $56,714 (subcontract direct costs)
National Institute of Mental Health
6001 Executive Boulevard, Room 7113, MSC 9634
Bethesda, MD 20892-9663
Program Official: Jovier D Evans
Email: jevans1@mail.nih.gov
Psychiatric Genomics Consortium for PTSD
The goal of this project is to detect novel genetic variations associated with risk for PTSD and dissect the genetic architecture of PTSD in the broader genetic and environmental context.
Role: Co-Principal Investigator / Site PI

U01MH110925 (McLean) 09/23/2016 - 07/31/2021 1.17 calendar
NIH/NIMH/UNC $82,058 (subcontract direct costs)
National Institute of Mental Health
6001 Executive Boulevard, Room 7113, MSC 9634
Bethesda, MD 20892-9663
Program Official: Jovier D Evans
Email: jevans1@mail.nih.gov
Longitudinal Assessment of Post-traumatic Syndromes
This study will use a structural equation modeling approach to (1) identify and characterize the development and early course of the most common adverse posttraumatic neuropsychiatric sequeale (APNS) of trauma in 5,000 trauma-exposed individuals using the RDoC framework, (2) gain important new insights into the pathogenesis of APNS, and (3) develop tiered clinical decision support algorithms that identify those at high risk of specific APNS in the early aftermath of trauma.
Role: Co-Investigator / Site PI

R01MD011728 (Uddin) 08/16/2017 - 05/31/2021 0.60 calendar
NIH/NIMHD/University of Illinois $25,563 (subcontract direct costs)
National Institute of Mental Health
6001 Executive Boulevard, Room 7113, MSC 9634
Bethesda, MD 20892-9663
Program Official: Jovier D Evans
Email: jevans1@mail.nih.gov
Epigenomic Predictors of PTSD and Traumatic Stress in an African American Cohort
This project will characterize genome wide patterns of leukocyte DNA methylation in African American participants in the Detroit Neighborhood Health Study, a population-based study of mental disorders among adult Detroit residents. Analysis will be targeted toward glucocorticoid receptor regulatory network genes and will test the effects of social adversity on DNA methylation levels in this gene network. The project will also prospectively compare trauma-exposed participants who either did or did not develop post-traumatic stress disorder (PTSD) in order to test whether social adversity impacts longitudinal patterns of DNA methylation in stress response genes.
Role: Co-Investigator / Site PI

6910075-5500000736 (Koenen) 07/01/2015 - 06/30/2020 1.20 calendar
The Broad Institute $1,099,898
415 Main Street
Cambridge, MA 02142
Phone: 617-714-7000
Stanley Center for Psychiatric Research
This project involves developing neuropsychiatric genetics initiatives in Africa and Latin America including capacity building and new sample collections. This includes the design and implementation of genetic epidemiological studies of neuropsychiatric disorders including schizophrenia, bipolar disorder, autism, ADHD and PTSD and the development of a post-doctoral program for collaborators form participating countries.
Role: Principal Investigator

R01AG051600 (Hankinson/Kubzansky) 09/15/2017 - 05/31/2021 0.60 calendar
NIH/NIA/University of Massachusetts, Amherst $26,549 (subcontract direct costs)
National Institute of Health
Program Official: Lisbeth Nielsen
9000 Rockville Pike
Bethesda, Maryland 20892
Email: nielsenli@nia.nih.gov
Development and Application of a Metabolomic Profile of Chronic Distress to Cardiometabolic Risk
The Harvard T.H. Chan School of Public Health is collaborating with University of Massachusetts, Amherst in the assessment of chronic distress and relevant covariates using data from the Nurses' Health Studies and the Women's Health Initiative. The Harvard team is coordinating the metabolomics assays using banked blood samples, and involved in integrating existing data with the assay data, as well as with developing and implementing plans for statistical analyses.
Role: Co-Investigator

PENDING:

R21 (Gelaye, Koenen) 07/01/2018 - 06/30/2020 1.20 calendar
NIH $125,000
The Role of Hypothalamic Pituitary- Adrenal Axis Dysregulation in Preterm Birth
The goal of this proposal is to examine the role of hypothalamic-pituitary-adrenal (HPA) axis dysregulation in the observed association between exposure to traumatic events and PTB. The proposed project will be the first investigation to assess the hypothesized association between time-integrated measures of cortisol secretion (using scalp hair cortisol concentrations [HCC]) and PTB in a large cohort of pregnant women.
Role: Co-Principal Investigator

R01 (Gelaye) 04/01/2019 - 03/31/2024 0.60 calendar
NIH
Intergenerational impact of maternal trauma history on preschoolers' behavior and health outcomes: Assessing links with caregiving sensitivity and DNA methylation
This study builds on an existing cohort of high-risk births to examine how characteristics of maternal lifetime trauma history, maternal psychopathology, and maternal caregiving sensitivity are associated with their 3-year old children's behavior, physical health problems, salivary DNA methylation, and salivary peripheral biomarkers.
Role: Co-Investigator

R01 (Joffe, Chavarro) 09/01/2018 - 08/31/2023 0.36 calendar

NIH
SCOR Clinical Project 2
Role: Co-Investigator

R01 (Roberts) 09/01/2018 - 08/31/2023 0.36 calendar
NIH
Maternal exposure to childhood abuse and disparities in offspring neurodevelopment: Identifying mechanisms
This project will seek to determine whether maternal childhood abuse is associated with differences in pregnancy hormonal homeostasis known to harm offspring neurodevelopment,and whether maternal childhood abuse is associated with pregnancy markers of systemic inflammation known to harm offspring neurodevelopment. We also seek to determine whether stressors experienced during pregnancy mediate any association between childhood abuse and hormonal and inflammatory homeostasis during pregnancy, and if women who experienced childhood abuse carry higher genetic loading for neuropsychiatric disorders, including ASD and ADHD.
Role: Co-Investigator

R21 (Basu) 04/01/2019 - 03/31/2021 0.30 calendar
NIH $150,000
Post-trauma Transdiagnostic Psychopathology in Children: Risk and Resilience in a Population-based Longitudinal Cohort
This is a large general population-based trauma cohort study of children that will identify subgroups of multidimensional psychopathology following trauma. The use of an existing registry from an unselected population and rigorous epidemiologic methods will allow us to efficiently examine predictor combinations (e.g., pre-morbid psychopathology, treatments, demographic variables). Results from this study can be replicated and expanded in other samples.
Role: Co-Investigator

OVERLAP:
If any pending grants are awarded which would result in over-commitment, Dr. Koenen will adjust effort accordingly so as to remain under 12.0 calendar months. She will seek NIH approval where required for any changes reflecting a greater than 25% adjustment of effort.

COMPLETED: (Last 3 years)
1R21MH106715-01 Koenen; Hariri (PIs) 09/27/2014-08/31/2015
NIH / Columbia University $140,107
National Institute of Mental Health
Program Official: Andrea C. Beckel-Mitchener
Email: amitchen@mail.nih.gov
Epigenetic links between the social environment and emotional brain function
This project is aimed at revealing potential pathways for how modifiable social exposure(s) that act through DNA methylation processes produce changes in brain function known to be behaviorally and clinically relevant.
Role: PI