SUMMARY STATEMENT

PROGRAM CONTACT: **(Privileged Communication)** ***Release Date:*** **12/12/2013**

Farris Tuma
301-443-3648
ftuma@mail.nih.gov

Application Number: **1 R01 MH101269-01A1**

Principal Investigators (Listed Alphabetically):
KOENEN, KARESTAN C PHD (Contact)
KUBZANSKY, LAURA D PHD

Applicant Organization: COLUMBIA UNIVERSITY HEALTH SCIENCES

Review Group: **BGES**
Behavioral Genetics and Epidemiology Study Section

Meeting Date: **12/05/2013**
Council: **JAN 2014**
Requested Start: **04/01/2014**

RFA/PA: **PA11-260**
PCC: **AD-TS**
Dual IC(s): **NR, HL**

Project Title: **Assessing causality: Is post-traumatic stress disorder cardio-toxic?**

SRG Action: **Impact Score: 20 Percentile: 4**
Next Steps: **Visit http://grants.nih.gov/grants/next_steps.htm**
Human Subjects: **30-Human subjects involved - Certified, no SRG concerns**
Animal Subjects: **10-No live vertebrate animals involved for competing appl.**
Gender: **2A-Only women, scientifically acceptable**
Minority: **1A-Minorities and non-minorities, scientifically acceptable**
Children: **3A-No children included, scientifically acceptable**

Project Year	Direct Costs Requested	Estimated Total Cost
1	499,623	822,675
2	499,966	823,240
3	499,513	822,494
4	499,810	822,983
5	497,557	819,273
TOTAL	2,496,469	4,110,664

ADMINISTRATIVE BUDGET NOTE: The budget shown is the requested budget and has not been adjusted to reflect any recommendations made by reviewers. If an award is planned, the costs will be calculated by Institute grants management staff based on the recommendations outlined below in the COMMITTEE BUDGET RECOMMENDATIONS section.

1R01MH101269-01A1 Koenen, Karestan

RESUME AND SUMMARY OF DISCUSSION: The influence of posttraumatic stress disorder (PTSD) as a potential causal risk factor for coronary heart disease (CHD) will be assessed using longitudinal observational data from the Nurses' Health Study II to determine if PTSD causally influences CHD onset and myocardial infarction severity, to assess whether PTSD influences health behaviors, and to evaluate if PTSD affects biological pathways associated with increased CHD risk. Since PTSD is not currently considered to be a risk factor of CHD requiring attention, the proposed work has the potential for exceptionally high significance by convincingly establishing a causal relationship between PTSD and CHD risk, as suggested by the preliminary data. In this resubmission, the investigators, who have an outstanding record of productive research in this area, have addressed the concerns raised in the previous review by providing evidence that there will be adequate statistical power and by reducing emphasis on the less compelling aim, now considered exploratory, of evaluating genetic risk markers. Use of data from the Nurses' Health Study II makes effective use of an informative existing large resource, although findings might be limited in generalizability. While the rationale for the hypothesis that remission of PTSD would lead to reduced health risk behaviors is somewhat weak, and the complex issue of comorbidity with substance use and depression is challenging to address effectively, reviewers felt that these minor weaknesses do not diminish overall strong enthusiasm for the proposed work. Reviewers concluded that the study would have a high impact by establishing PTSD as a causal risk factor for cardiovascular disease and in identifying potential mechanisms underlying this relationship.

DESCRIPTION (provided by applicant): Posttraumatic stress disorder (PTSD) is a pervasive and debilitating mental disorder in the U.S. population; 1 in 9 women will meet criteria for the diagnosis during their lives. PTSD, the sentinel stress-related mental disorder, has been declared 'a life sentence' based on the belief that the disorder leads to a host of adverse physical health problems. The association between PTSD and coronary heart disease (CHD) has received particular attention, with observational studies suggesting PTSD contributes to early development of CHD, and also that mitigating CHD risk in this population might reduce overall burden of CHD. Despite consistent findings from these studies, whether PTSD causes CHD has not been established and PTSD is not ranked in the American Heart Association (AHA) 2010 impact goals as a risk factor that requires attention. As a result, neither systematic surveillance nor treatment is provided persons with PTSD to reduce potential risk of developing CHD. Informed by these concerns, we propose 3 strategies to address if PTSD is causally related to CHD, using state-of-the-science approaches for inferring causality in observational data. First, we will apply innovative analytic designs not previously been applied in this research area, including consideration of effects when PTSD remits. Second, we will examine if PTSD influences both CHD onset and severity; to date, effects of PTSD on myocardial infarction (MI) severity has only been examined cross-sectionally. Third, evidence that PTSD affects CHD-related behavioral and biological pathways would offer further support for causation but a recent review noted "mechanistic evidence on the progression of adverse cardiac outcomes in PTSD is lacking." PTSD is linked with CHD risk related behavior and biomarkers. Because cross-sectional studies cannot test if such behaviors and biomarkers are vulnerabilities for or consequences of PTSD, longitudinal studies are needed. We propose the following Specific Aims: (1) To determine if PTSD influences risk of CHD onset and MI severity with conventional and marginal structural models; (2) To examine whether PTSD changes health behaviors; (3) To identify if PTSD influences biological pathways associated with increased CHD risk. We will examine if new onset of PTSD among CHD-free women, produces changes in novel and conventional biomarkers associated with CHD risk. We will also explore using Mendelian Randomization (MR) to test whether the relation between PTSD and CHD, health behaviors, and CHD risk markers is explained by shared genetic risk or reverse causality. Taken together, the proposed research moves forward not only our understanding of the relation between PTSD and CHD but also the pathophysiology of PTSD in relation to health more broadly and has direct implications for population health.

PUBLIC HEALTH RELEVANCE: This purpose of this research is to better understand whether posttraumatic stress disorder (PTSD) causes cardiovascular disease (CVD) and to identify underlying disease mechanisms. If PTSD truly contributes to CVD etiology, then new avenues for reducing the burden of CVD must be considered and the effectiveness of various prevention or intervention strategies compared. For example, effective treatment of PTSD may reduce risk of CVD. Even if PTSD is resistant to treatment, persons with PTSD may yet benefit from greater surveillance of CVD risk factors and early interventions (e.g. statins) to prevent the development of CVD.

CRITIQUE 1:

Significance: 2
Investigator(s): 1
Innovation: 3
Approach: 3
Environment: 1

Overall Impact: This study utilizes data from the Nurses' Health Study II, which has 20 years of follow-up data involving cohort data and biological samples and has the ability to test the timing of traumatic events on CHD risk. To that end, the proposed work will test causal relationships between PTSD (both onset and remission) and CHD as well as underlying mechanisms. The study will also evaluate effects of PTSD on health risk behaviors for CHD, as well as whether new onset PTSD among CHD-free women is associated with changes in biomarkers associated with CHD risk. Strengths include unique data available from the Nurses' Health Study II, as well as the strong investigative team and resources, which increase feasibility. Weaknesses include limited rationale for certain hypotheses. Overall, this project is anticipated to have high impact. Knowing whether PTSD does (or does not) increase risk for CHD would have important implications for care delivery and prevention of CHD. Even if PTSD is not directly and causally related, health behaviors that impact risk for CHD or other health conditions might be important to incorporate into PTSD treatments, which will in turn decrease risk for CHD.

1. Significance:
Strengths

- PTSD and CVD are major public health concerns.
- Understanding whether PTSD causes CHD would be a significant contribution to the scientific literature and for women's health; CHD prevention and incorporation of health related behaviors could become an important piece of PTSD treatment as a recognized risk factor.
- Findings should help to more specifically target most fruitful factors that contribute to CHD risk.

Weaknesses

- None noted.

2. Investigator(s):
Strengths

- Drs. Koenan and Kubzanski have an established collaborative relationship.
- The investigative team is highly qualified.

Weaknesses

- None.

3. Innovation:
Strengths

- State of the art approaches to infer causality in observational data.

- Analyses will address PTSD onset, duration, and remission on CHD, as well as alterations in behavior and biological processes over time, which few studies can do. No study has evaluated biomarker levels with respect to onset and remission of PTSD.

Weaknesses

- The association between PTSD and CVD is already established, albeit not in this manner.

4. Approach:

Strengths

- Analyses account for trauma exposure as a confounding variable, as well as comorbid depression.
- Two reference groups (no trauma; trauma exposed without PTSD) allow for teasing apart the effects of trauma exposure vs. PTSD vs. both on CHD.
- Individuals reporting MI, angina, stroke, or transient ischemic attack at baseline will be excluded for the main analyses to reduce risk for reverse causation.

Weaknesses

- Sufficient evidence wasn't presented to support the hypothesis that remission of PTSD would lead to reduced health risk behaviors (e.g., smoking, physical activity). It could be that risk behaviors persist even when PTSD remits; old habits die hard.
- A rationale was not provided with the timeline to justify how long various aims will take to complete.

5. Environment:

Strengths

- The institutional support and resources of Columbia, Harvard and UCSF are very strong.

Weaknesses

- None noted.

Protections for Human Subjects

Acceptable Risks and/or Adequate Protections

- Procedures will be implemented to safeguard confidentiality of data.

Inclusion of Women, Minorities and Children:

G2A - Only Women, Acceptable
M1A - Minority and Non-minority, Acceptable
C3A - No Children Included, Acceptable

- Only women are included as PTSD occurs at higher rates in women. Minorities are represented. Children are not included because CHD does not occur at high rates in children.

Vertebrate Animals

Not Applicable (No Vertebrate Animals)

Biohazards

Not Applicable (No Biohazards)

Resubmission:

- The investigators were responsive to prior reviewer comments.

Budget and Period of Support

Recommend as Requested

CRITIQUE 2:

Significance: 1
Investigator(s): 1
Innovation: 3
Approach: 3
Environment: 1

Overall Impact: This dataset and team of investigators are well poised to investigate definitively the impact of PTSD on cardiovascular disease. It should inform future public health efforts as to how much attention should be paid to PTSD with regard to CVD.

1. Significance:
Strengths
- CVD and PTSD are both major health problems. Sorting out the impact of PTSD on CVD is important in order to guide public health decisions aimed at preventing CVD.

Weaknesses
- None noted.

2. Investigator(s):
Strengths
- The Principal Investigators and investigative team are first rate and well qualified to carry out this work.

Weaknesses
- None noted.

3. Innovation:
Strengths
- This is an innovative study in its comprehensive use of data and statistical methods.

Weaknesses
- None noted.

4. Approach:
Strengths
- The data set is extensive and statistical plans are well thought out. Issues raised in the last review concerning power and utility of the genetic risk factor analyses have been addressed in this resubmission.

Weaknesses
- Comorbidities, such as depression and substance abuse, might be important confounding variables which should probably be taken more into consideration in the modeling. In this resubmitted application, the investigators have proposed a good plan to incorporate depression ratings in the analyses.

5. Environment:
Strengths
- Environment at Columbia and Harvard Universities are first rate and likely to support the investigators well in accomplishing the research.

Weaknesses
- None noted.

Protections for Human Subjects:
Acceptable Risks and/or Adequate Protections

Inclusion of Women, Minorities and Children:
G2A - Only Women, Acceptable
M1A - Minority and Non-minority, Acceptable
C3A - No Children Included, Acceptable

Vertebrate Animals:
Not Applicable (No Vertebrate Animals)

Biohazards:
Not Applicable (No Biohazards)

Budget and Period of Support:
Recommended as Requested

CRITIQUE 3:

Significance: 1
Investigator(s): 1
Innovation: 2
Approach: 2
Environment: 1

Overall Impact: This is a resubmission of an application that capitalizes on the Nurses Health Study II cohort and examines PTSD and CHD. This is an undestudied topic that has major health implications. The investigators have been responsive to the concerns raised by the reviewers and have addressed them well within the contraints of the available data set. Limitations include teasing apart the potential contribution of confounding factors is a challenge and the generalizability from white educated women to other groups. It remains to be seen if and how findings will impact cardiac care of women with PTSD.

1. Significance:
Strengths
- Determining if PTSD influences risk for onset of CHD and MI severity is important.

Weaknesses
- None of note.

2. Investigator(s):
Strengths
- Highly established and productive.

Weaknesses
- None noted.

3. Innovation:
Strengths
- Systematic approach in an available cohort that will provide data currently not available.

Weaknesses
- Limitation to primarily white women.

4. Approach:
Strengths

- Complementary strategies – behavioral and biologic measures.

Weaknesses

- The complexity of presentation and comorbidity.

5. Environment:

Strengths

- Resources are fully in place.

Weaknesses

- None of note.

Protections for Human Subjects

Acceptable Risks and/or Adequate Protections

Inclusion of Women, Minorities and Children:

G2A - Only Women, Acceptable
M1A - Minority and Non-minority, Acceptable
C3A - No Children Included, Acceptable

- While relying on the Nurses' Health Study II cohort, PTSD and CHD are common in African Americans

Vertebrate Animals

Not Applicable (No Vertebrate Animals)

Biohazards

Not Applicable (No Biohazards)

Resource Sharing Plans:

Acceptable

Budget and Period of Support

Recommend as Requested

THE FOLLOWING RESUME SECTIONS WERE PREPARED BY THE SCIENTIFIC REVIEW OFFICER TO SUMMARIZE THE OUTCOME OF DISCUSSIONS OF THE REVIEW COMMITTEE ON THE FOLLOWING ISSUES:

PROTECTION OF HUMAN SUBJECTS (Resume): ACCEPTABLE

INCLUSION OF WOMEN PLAN (Resume): ACCEPTABLE

INCLUSION OF MINORITIES PLAN (Resume): ACCEPTABLE

INCLUSION OF CHILDREN PLAN (Resume): ACCEPTABLE

COMMITTEE BUDGET RECOMMENDATIONS: The budget was recommended as requested.

NIH has modified its policy regarding the receipt of resubmissions (amended applications). See Guide Notice NOT-OD-10-080 at http://grants.nih.gov/grants/guide/notice-files/NOT-OD-10-080.html.
The impact/priority score is calculated after discussion of an application by averaging the overall scores (1-9) given by all voting reviewers on the committee and multiplying by 10. The criterion scores are submitted prior to the meeting by the individual reviewers assigned to an application, and are not discussed specifically at the review meeting or calculated into the overall impact score. Some applications also receive a percentile ranking. For details on the review process, see http://grants.nih.gov/grants/peer_review_process.htm#scoring.

MEETING ROSTER

Behavioral Genetics and Epidemiology Study Section
Population Sciences and Epidemiology Integrated Review Group
CENTER FOR SCIENTIFIC REVIEW
BGES
October 08, 2013

CHAIRPERSON

JOHNSON, ERIC O, PHD
PROGRAM DIRECTOR
BEHAVIORAL HEALTH EPIDEMIOLOGY
RESEARCH TRIANGLE INSTITUTE INTERNATIONAL
RESEARCH TRIANGLE PARK, NC 27709

MEMBERS

BAKER, LAURA A, PHD
PROFESSOR
DEPARTMENT OF PSYCHOLOGY
UNIVERSITY OF SOUTHERN CALIFORNIA
LOS ANGELES, CA 90089

BRKANAC, ZORAN , MD
ASSOCIATE PROFESSOR
DEPARTMENT OF PSYCHIATRY
AND BEHAVIORAL SCIENCES
UNIVERSITY OF WASHINGTON
SEATTLE, WA 98195

BURT, S ALEXANDRA, PHD
ASSOCIATE PROFESSOR
DEPARTMENT OF PSYCHOLOGY
MICHIGAN STATE UNIVERSITY
EAST LANSING, MI 48824

COFFEY, SCOTT FRANKLIN, PHD *
PROFESSOR
DEPARTMENT OF PSYCHIATRY
AND HUMAN BEHAVIOR
UNIVERSITY OF MISSISSIPPI MEDICAL CENTER
JACKSON, MS 39216

COOPER, HANNAH L, SCD *
ASSOCIATE PROFESSOR
DEPARTMENT OF BEHAVIORAL SCIENCES AND
HEALTH EDUCATION
ROLLINS SCHOOL OF PUBLIC HEALTH
EMORY UNIVERSITY
ATLANTA, GA 30322

EATON, WILLIAM W, PHD
SYLVIA AND HAROLD HALPERT PROFESSOR AND CHAIR
DEPARTMENT OF MENTAL HEALTH
BLOOMBERG SCHOOL OF PUBLIC HEALTH
JOHNS HOPKINS UNIVERSITY
BALTIMORE, MD 21205

ESCAMILLA, MICHAEL A, MD
PROFESSOR AND CHAIR
DEPARTMENT OF PSYCHIATRY
DIRECTOR, CENTER OF EXCELLENCE IN
NEUROSCIENCES
TEXAS TECH UNIVERSITY HEALTH SCIENCES CENTER
EL PASO, TX 79905

GILMAN, STEPHEN E, SCD
ASSOCIATE PROFESSOR
DEPARTMENT OF SOCIETY, HUMAN DEVELOPMENT
AND HEALTH EPIDEMIOLOGY
SCHOOL OF PUBLIC HEALTH
HARVARD UNIVERSITY
BOSTON , MA 02115

GUR, RAQUEL E, MD, PHD
THE KARL AND LINDA RICKELS PROFESSOR
DEPARTMENTS OF PSYCHIATRY, NEUROLOGY
AND RADIOLOGY
UNIVERSITY OF PENNSYLVANIA
PHILADELPHIA, PA 19104

KNOPIK, VALERIE S, PHD
ASSOCIATE PROFESSOR
DEPARTMENT OF PSYCHIATRY AND HUMAN BEHAVIOR
BROWN UNIVERSITY
PROVIDENCE, RI 02903

MARMORSTEIN, NAOMI R, PHD *
PROFESSOR
DEPARTMENT OF PSYCHOLOGY
RUTGERS UNIVERSITY, CAMDEN
311 NORTH 5TH STREET
CAMDEN, NJ 08102

MCMAHON, FRANCIS J, MD
CHIEF
HUMAN GENETICS BRANCH
NATIONAL INSTITUTE OF MENTAL HEALTH
NATIONAL INSTITUTES OF HEALTH
BETHESDA, MD 20892

MORISSETTE, SANDRA BAKER, PHD *
ASSOCIATE PROFESSOR AND ASSESSMENT CORE
CHIEF
VETERANS AFFAIRS VISN 17 CENTER FOR EXCELLENCE
FOR RESEARCH ON RETURNING WAR VETERANS
TEXAS A&M HEALTH SCIENCES CENTER
CENTRAL TEXAS VETERANS HEALTHCARE SYSTEM
COLLEGE OF MEDICINE
WACO, TX 76711

NIMGAONKAR, VISHWAJIT LAXMIKANT, MD, PHD
PROFESSOR
DEPARTMENT OF PSYCHIATRY AND HUMAN GENETICS
SCHOOL OF MEDICINE
UNIVERSITY OF PITTSBURGH
PITTTSBURGH, PA 15213

RILEY, BRIEN P, PHD
ASSOCIATE PROFESSOR
DEPARTMENTS OF PSYCHIATRY AND HUMAN
AND MOLECULAR GENETICS
VIRGINIA COMMONWEALTH UNIVERSITY
RICHMOND, VA 23219

SACCONE, NANCY L, PHD *
ASSOCIATE PROFESSOR
DEPARTMENT OF GENETICS
SCHOOL OF MEDICINE
WASHINGTON UNIVERSITY
ST. LOUIS, MO 63110

SCIENTIFIC REVIEW ADMINISTRATOR

VOGLER, GEORGE , PHD
SCIENTIFIC REVIEW OFFICER
CENTER FOR SCIENTIFIC REVIEW
NATIONAL INSTITUTES OF HEALTH
BETHESDA, MD 20892

GRANTS TECHNICAL ASSISTANT

BURGESS, ANGELA
EXTRAMURAL SUPPORT ASSISTANT
CENTER FOR SCIENTIFIC REVIEW
NATIONAL INSTITUTES OF HEALTH
BETHESDA, MD 20892

* Temporary Member. For grant applications, temporary members may participate in the entire meeting or may review only selected applications as needed.

Consultants are required to absent themselves from the room during the review of any application if their presence would constitute or appear to constitute a conflict of interest.