

ARIC Manuscript Proposal # 1276

PC Reviewed: 8/21/07

Status: D

Priority: _____

SC Reviewed: _____

Status: _____

Priority: _____

1.a. Full Title: Exhaustion and risk for congestive heart failure: The Atherosclerosis Risk in Communities (ARIC) Study

b. Abbreviated Title (Length 26 characters): exhaustion and heart failure

2. Writing Group (list individual with lead responsibility first):

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I, the first author, confirm that all the coauthors have given their approval for this manuscript proposal. jew [please confirm with your initials electronically or in writing]

3. Timeline: Manuscript completed December 2008

4. Rationale:

Heart failure is a rapidly growing public health problem. According to the most recent statistics provided by the American Heart Association, approximately 5 million Americans are living with heart failure, and 550,000 new cases are diagnosed each year (1). The economic burden of this disease, in terms of both direct and indirect costs, is estimated at \$29.6 billion yearly (1). Of this figure, costs for hospitalization far outweigh all others.

The role of psychosocial factors (e.g., such as depression/exhaustion, anger/hostility, and social support) in CHD, particularly acute myocardial infarction (MI), has been demonstrated in a number of epidemiologic studies (2), but few studies have been conducted to examine the extent to which these factors are associated with heart failure. Of the psychosocial factors, depression has received the greatest amount of research attention as regards heart failure. A recent study reported that depressed elderly men and women with isolated systolic hypertension had a 2.82 times greater risk for incident heart failure compared to their nondepressed counterparts - findings that were independent of MI history and traditional CHD risk factors (3). It has been reported that depression existed in up to 51% of patients hospitalized for congestive heart failure (4).

Exhaustion is a construct akin to depression although guilt and low self-esteem – key ingredients of depression – have been found absent among exhausted persons. Exhaustion is a syndrome defined as excessive fatigue, feelings of demoralization, and increased irritability, and is often considered to be an adaptation to prolonged psychological distress (5). Studies show that

exhaustion is positively associated with the onset of acute MI (5, 6), and MI is a major risk factor for heart failure. In turn, exhaustion may be a risk factor for heart failure. Plausible physiologic mechanisms that link exhaustion and heart failure has not been articulated. The most recent hypothesis regarding the pathophysiology of heart failure implicates neurohormonal and cytokine activation as key elements (7). These processes have been observed among exhausted persons and therefore suggest a possible pathway by which exhaustion may be associated with heart failure (8-10).

The purpose of the proposed analyses is to examine the cross-sectional and prospective associations between exhaustion and heart failure, thereby constituting two companion paper proposals: a) the relationship of exhaustion to prevalent heart failure, and b) the relationship of exhaustion to incident heart failure. The results of these analyses have the potential to add to a growing body of reports that have shown a positive association between psychosocial factors and cardiovascular disease.

5. Main Hypothesis/Study Questions:

Proposal A: Exhaustion and prevalent heart failure

- 1) Participants with high exhaustion compared with their low exhaustion counterparts will have a significantly greater odds of having heart failure. (Note: For this hypothesis, exhaustion scores will be obtained from Visit 2 only.)

Proposal B: Exhaustion and incident heart failure

- 1) Participants with high exhaustion compared with their low exhaustion counterparts will have a significantly greater risk for incident heart failure, independent of MI history and the traditional CHD risk factors. (Note: For this hypothesis, the baseline will be Visit 2; to assess the effect of any change in exhaustion from Visit 2 to Visit 4, we will include in the Cox model a time-dependent exhaustion variable).
- 2) There will be a monotonic increase in the risk for heart failure by level of exhaustion.

6. Data (variables, time window, source, inclusions/exclusions):

Variables: Exhaustion scores at Visits 2 and 4, age, center, race/ethnicity, educational level, HDL cholesterol, LDL-cholesterol, systolic blood pressure, diastolic blood pressure, cigarette smoking, diabetes mellitus, prevalent MI, prevalent heart failure at baseline (defined as having taken any medication for heart failure, or qualifying for the Gothenberg Criteria), incident hospitalized heart failure.

By 2003, 1416 incident hospitalized heart failure cases were reported for all participants in the cohort. Somewhat fewer cases will be present for the current analysis since Visit 2 is the baseline and all participants with an incident heart failure before Visit 2 will be excluded.

7.a. Will the data be used for non-CVD analysis in this manuscript? Yes No

b. If Yes, is the author aware that the file ICTDER02 must be used to exclude persons with a value RES_OTH = "CVD Research" for non-DNA analysis, and for DNA analysis RES_DNA = "CVD Research" would be used? Yes No

(This file ICTDER02 has been distributed to ARIC PIs, and contains the responses to consent updates related to stored sample use for research.)

8.a. Will the DNA data be used in this manuscript? Yes No

8.b. If yes, is the author aware that either DNA data distributed by the Coordinating Center must be used, or the file ICTDER02 must be used to exclude those with value RES_DNA = “No use/storage DNA”? Yes No

9. The lead author of this manuscript proposal has reviewed the list of existing ARIC Study manuscript proposals and has found no overlap between this proposal and previously approved manuscript proposals either published or still in active status. ARIC Investigators have access to the publications lists under the Study Members Area of the web site at: <http://www.csc.c.unc.edu/ARIC/search.php>

Yes No

10. What are the most related manuscript proposals in ARIC (authors are encouraged to contact lead authors of these proposals for comments on the new proposal or collaboration)?

#640 (Convergence of trait anger and exhaustion and incident CHD risk)

11. Manuscript preparation is expected to be completed in one to three years. If a manuscript is not submitted for ARIC review at the end of the 3-years from the date of the approval, the manuscript proposal will expire.

References

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4. Freedland KE, Rich MW, Skala JA, Carney RM, Dávila-Román VG, Jaffe AS. Prevalence of depression in hospitalized patients with congestive heart failure. *Psychosom Med* 2003;65:119-128.
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8. Sjogren E, Leanderson P, Kristenson M, Ernerudh J. Interleukin-6 levels in relation to psychosocial factors: studies on serum, saliva, and in vitro production by blood mononuclear cells. *Brain Behav Immun* 2006;20:270-278.
9. Toker S, Shirom A, Shapira I, Berliner S, Melamed S. The association between burnout, depression, anxiety, and inflammation biomarkers: C-reactive protein and fibrinogen in men and women. *J Occup Health Psychol* 2005;10:344-362.
10. Melamed S, Shirom A, Toker S, Berliner S, Shapira I. Burnout and risk of cardiovascular disease: evidence, possible causal paths, and promising research directions. *Psych Bull* 2006;132:327-353.