ARIC Manuscript Proposal # 1580

PC Reviewed: 12/8/09	**Status: A**	**Priority: 2**
SC Reviewed: _____	**Status: _____**	**Priority: ____**

1.a. Full Title: Social Isolation, Psychological Distress, and the Risk of Incident Heart Failure: Findings from the Atherosclerosis Risk in Communities Study

b. Abbreviated Title (Length 26 characters):
Social Isolation and Heart Failure

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

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3. Timeline:

- Preliminary analysis to be completed by: December 22, 2009
- Final analysis to be completed by: Feb 12, 2010
- Initial draft of manuscript to be completed by: April 5, 2010
- Manuscript to be submitted for publication by: July 9, 2010

4. Rationale:

Chronic Heart Failure (HF) is a highly prevalent clinical syndrome, affecting over 5 million Americans, with HF incidence approaching 10 per 1000 in people after age 65.[1] It is a major cause of morbidity and mortality among the elderly. Furthermore, the prevalence and associated economic costs of this disease are increasing as a result changing demographics in the USA. [2] Chronic HF results in reduced quality of life because of symptoms, physical limitations, and repeated hospital admissions.[3,4]

The role of psychosocial factors (e.g. depression/exhaustion, anger/hostility, and social support) in coronary heart disease has been demonstrated in a number of epidemiologic studies, [5]but few studies have been conducted to examine the extent to which these factors are associated with heart failure. Studies examining the influence of social relationships on health generally suggest a protective effect of social ties on survival as well as on general physical and mental health. [6-9]

The majority of evidence regarding social relationships and long-term health outcomes has come from studies using social integration measures.[10] Social integration, considered a measure of structural social support is the extent to which an individual participates in a broad range of social relationships. Health risks associated with social isolation have been comparable in magnitude to the well-known dangers of smoking and obesity.[8] Studies show that more socially integrated individuals live longer and are less likely to report being depressed. [9]In fact, one hypothesized mechanism by which social integration is thought to be related to health outcomes is through its effects on one's affect (e.g. depression). [10] Vital exhaustion is a construct related to depression although two key features of depression (guilt and low self-esteem) have been found to be absent among exhausted people. 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. [11]Studies show that exhaustion is positively associated with the onset of acute Myocardial Infarction, [11,12] but no published studies show a relationship between exhaustion and HF.

Data on the relationship between social support and outcomes for patients with HF is very limited. [13-16] To my knowledge no study has examined the association between social isolation, in particular, and the development of heart failure ("incident" heart failure) or evaluated whether this relationship might be mediated through psychological distress (vital exhaustion).

5. Main Hypothesis/Study Questions:

The aim of this study is to determine whether social isolation, is associated with incident heart failure independent of behavioral factors, socioeconomic status, and other major risk factors for heart failure. We hypothesize that individuals with higher scores on the Lubben Social Network Scale (i.e. more socially isolated individuals), will be at higher risk for the development of heart failure, even after controlling for factors known to be associated with incident heart failure. We further hypothesize that this association will be partially mediated by psychological distress (assessed using the Maastricht Questionnaire for Vital Exhaustion).

6. Design and analysis (study design, inclusion/exclusion, outcome and other variables of interest with specific reference to the time of their collection, summary of data analysis, and any anticipated methodologic limitations or challenges if present).

Analytic sample: The cohort for this analysis consists of subjects who participated in Visit 2 of the ARIC Cohort Component survey. We will use Visit 2 as our "baseline" since our prior exposure variable of interest, the Lubben Social Network Scale, was collected at visit 2 and not before. The analyses will include cases that developed incident HF after Visit 2. We will exclude subjects with prevalent heart failure at baseline and subjects who developed heart failure prior to visit 2.

Dependent variable: The dependent variable in this analysis is a diagnosis of incident heart failure occurring from visit 2 onward. Incident HF was determined through surveillance of hospitalization and death certificate ICD (International Classification of Diseases, 9th Revision, Clinical Modification ICD-9) codes. Incident HF will be defined by an ICD code of either (1) a hospitalization that includes an ICD-9 discharge code of 428 (428.0 to 428.9) or (2) a death certificate with a 428 or ICD-10 code 150. Prevalent HF at baseline and all hospitalizations before visit 2 will be excluded.

Follow-up years will be calculated from the visit 2 year until the date of the hospitalization or death that resulted in a diagnosis of incident heart failure, the date of last contact if the subject was lost to follow-up, the date of death, or December 31, 2004, whichever comes first.

Independent variable: The primary independent variable for this analysis will be the Lubben Social Network Scale- an indicator of social isolation. This 10-item scale assesses the size of the subject's active social network and the perceived social support received by family, friends, and neighbors. The total score is an equally weighted sum, with scores ranging from 0-50; the higher the score, the greater the level of social support. A score <20 indicates a person who may have an extremely limited social network. Score interpretation: <20= isolated; 21-25= high risk for isolation; 26-30= moderate risk for isolation; ≥31= low risk for isolation.

In a secondary analysis, we will focus on the Interpersonal Support Evaluation List (ISEL)- a measure of functional social support and conduct the same analyses as are proposed below.

Mediator variable: Maastricht Questionnaire for Vital Exhaustion
This measure assesses a participant's outlook on life and symptoms of fatigue and depression and is considered a measure of psychological distress. It has been shown to increase the risk of incident coronary heart disease.

Covariates: age, race, gender, educational level, living status, smoking status, alcohol use, BMI, coronary heart disease, hypertension, diabetes

Analyses: Descriptive statistics will be generated for demographic variables and for select covariates. We will use the Cox Proportional hazards model to estimate crude and adjusted hazards ratios for incident heart failure, stratified by categories of the LSNS.

Model 1: Adjust for age, gender, race-center, educational level, and socioeconomic status
Model 2: Adjusted for behavioral risk factors
Model 3: Adjusted for major disease risk factors

Mediation and Moderation Analyses:
A mediation analysis will be conducted to examine whether psychological distress (vital exhaustion) mediates the relationship between social isolation and incident HF. Mediation is commonly used in social psychological research and represents the generative mechanism through which the focal independent variable is able to influence the dependent variable of interest. [17] In our analysis, psychological stress will meet criteria to be considered a mediator if: (a) variations in the levels of the independent variable (social isolation) significantly account for variations in the presumed mediator (psychological stress); (b) variation in the mediator (psychological distress) significantly account for variations in the dependent variable (incident heart failure), and (c) when you control for the paths in (a) and (b), a previously significant relation between the independent and dependent variables is no longer significant, with the strongest demonstration of mediation occurring when the past articulated in (c) is zero. [17] One approach typically used to assess for mediation is to simply include the mediator in a statistical models with other potential confounders. Per published methodology borrowed from the field of psychology (161-163), a percentage change of >15% in the beta coefficient for the independent variable of interest (social isolation) when psychological stress is removed from the statistical model suggests the presence of mediation, while a percent change of >30% would strongly suggest mediation. [18-20] We are aware of the pitfalls in mediation analyses and of the controversy surrounding it. To inform a wider range of scientists active in this field, we will include mediation analyses in our work to a limited degree and use deliberate caution in making interpretations based on these results.

We will also separately examine whether race and gender moderate the relationships between social isolation and incident heart failure. Race or gender would be considered

moderators of the relationship between the independent (social isolation) and dependent (incident heart failure) variables if the interaction of race X social isolation or gender X social isolation is significantly associated with incident heart failure. In addition we will examine other whether the moderator variable is correlated with the independent and the dependent variables. It is desirable that moderator variables be uncorrelated with the independent and dependent variables to provide a clearly interpretable interaction term. [17]

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

b. If Yes, is the author aware that the file ICTDER03 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 ICTDER03 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 __X_ No

8.b. If yes, is the author aware that either DNA data distributed by the Coordinating Center must be used, or the file ICTDER03 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.cscc.unc.edu/ARIC/search.php

___X___ 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)?
MS Proposal #1160r Life Course Socioeconomic Exposures and Heart Failure in the AtherosclerosisRisk in Communities (ARIC) Study, Calpurnyia Roberts, Kathy Rose, Wayne Rosamond, Diane Catellier, Herman Taylor, Gerardo Heiss

MS #1276 Exhaustion and risk for congestive heart failure: The Atherosclerosis Risk in Communities (ARIC) Study, Janice Williams, Kathryn Rose, Moyses Szklo, David Couper

MS #691 The Moderating Effects of Social Support on the Association Between Negative Emotions and CHD Events, Carotid Arterial Wall Thickness, and

Mortality, Thomas Mosley, Pat Dubbert, Tom Payne, Cecil Burchfiel, Herman Taylor, Paul McGovern, Mike Andrew

There are authors from each one of these manuscripts that are included in this proposal.

11. a. Is this manuscript proposal associated with any ARIC ancillary studies or use any ancillary study data? ____ Yes __X__ No

11.b. If yes, is the proposal

___ A. primarily the result of an ancillary study (list number* _____)

___ B. primarily based on ARIC data with ancillary data playing a minor role (usually control variables; list number(s)* _____ _____ _____)

*ancillary studies are listed by number at http://www.cscc.unc.edu/aric/forms/

12. 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.

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