ARIC Manuscript Proposal # 2139

PC Reviewed: 5/14/13            Status: A            Priority: 2
SC Reviewed: _________            Status: _____            Priority: ____

1.a. Full Title: Social Isolation, Social Support, and the Risk of Incident Stroke: the Atherosclerosis Risk in Communities Study

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

2. Writing Group:
Writing group members: Mako Nagayoshi, PhD; Pamela L. Lutsey, PhD MPH; Hiroyasu Iso, MD, PhD; Thomas H. Mosley Jr., PhD; Susan Everson-Rose, PhD, MPH.; Kathryn Rose, PhD; Others welcome.

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

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ARIC author to be contacted if there are questions about the manuscript and the first author does not respond or cannot be located (this must be an ARIC investigator).

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3. Timeline:
• Preliminary analysis to be completed by: June 31, 2013
• Final analysis to be completed by: Sep 30, 2013
• Initial draft of manuscript to be completed by: Dec 31, 2013
• Manuscript to be submitted for publication by: Mar 31, 2014

4. Rationale:
Stroke is a highly prevalent clinical syndrome, and the third leading cause of death in the United States. Approximately 795,000 stroke events and 130,000 stroke deaths occur in the United States each year (1). Stroke results in reduced quality of life for both patients and their families through the serious, long-term disability caused by stroke. Therefore the prevention of stroke is a public health priority.

The social environment has a tremendous influence on physical and psychological health and well-being. Social isolation is absence of social ties or relationships. A number of epidemiological studies have demonstrated that social isolation is positively associated with incidence of coronary heart disease (2), and heart failure (3), but few studies have examined whether these factors are associated with incident stroke.

Vogt et al showed that social isolation predicted ischemic heart disease incidence, but none of the other morbidities explored (including incident stroke), among a randomly sampled cohort of 2603 HMO members in 1970-71 (4). In a separate study, Kawachi et al demonstrated that strong social networks were associated with reduced incidence of stroke among 32 624 US male health professionals aged 42 to 77 years. In that study, socially isolated men experienced a 2-times higher risk of incident stroke during 4-years of follow-up (5). Rutledge also demonstrated that socially isolated women with suspected myocardial ischemia were at a 2.7-times greater risk of nonfatal stroke events than those with more social relationships over 5.9 years of follow-up (6).

The mechanisms underlying the association between social isolation and incident cardiovascular diseases have not been fully elucidated but likely include both behavioral and physiological components. Individuals who are socially isolated may be less likely to take part in health-promoting behaviors (e.g. consuming a healthy diet, exercising, not smoking) (7). Psychological stress related to social isolation may impact the cardiovascular system via various mental and physical changes (8). Activation of the hypothalamic–pituitary adrenal (HPA) axis is an adaptive response to stress, although, prolonged stress or HPA activation is deleterious because of sustained elevations in glucocorticoids (cortisol) may compromise the neuroimmune system or neuronal
survival following an ischemic attack. Epidemiologic studies have reported that people who have a low social network score are more likely to have elevated circulating levels of C-reactive protein and interleukin-6 (9).

5. Main Hypothesis/Study Questions:
The aim of this study is to determine whether social isolation and perceived social support are associated with incident stroke independent of behavioral factors, and other major risk factors for stroke.

We hypothesize that individuals with higher scores on the Lubben Social Network Scale (10, 11) (i.e. more socially isolated individuals), and individuals with lower scores on the Interpersonal Support Evaluation List-Short Form (ISEL-SF) (12, 13), will be at higher risk of developing stroke, even after controlling for traditional stroke risk factors.

We further hypothesize that these associations will be partially mediated by vital exhaustion (assessed by using the 21-item Maastricht Questionnaire) (14) and inflammatory biomarkers.

We will also explore whether the magnitude of these relations differs by sex and race.

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).

Study Design: Prospective cohort starting at visit 2 (1990-1992), when social isolation was measured, and continuing until the end of follow-up (2010).

Inclusion/Exclusion: We will exclude those with prevalent stroke at visit 2.

Outcome variable: Incident stroke from visit 2 onward, as defined using standardized criteria, including ischemic stroke and hemorrhagic stroke. In secondary analyses we will look separately at ischemic and hemorrhagic stroke. Follow-up time will be calculated from the date of the visit 2 exam until the date of the hospitalization or death that resulted in a diagnosis of incident stroke, the date of last contact if the subject was lost to follow-up, the date of death, or December 31, 2010, whichever comes first.
Independent variable: Social isolation.

- Social isolation will be calculated by using the Lubben Social Network Scale (10, 11). This 10-item scale assesses the size of the participant’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. The score is frequently interpreted as follows: <20= isolated; 21-25= high risk for isolation; 26-30= moderate risk for isolation; ≥31= low risk for isolation.

- The Interpersonal Support Evaluation List-Short Form (ISEL-SF) will also be used to calculate perceived social support. (12) This 16-item scale was constructed by the original ARIC investigators from the original 40-item full scale (13), and assesses perceived social support with four subscales in the scale; (a) appraisal support, (b) tangible assets support, (c) belonging support, and (d) self-esteem support. The total score is an equally weighted sum, with scores ranging from 0-48; the higher the score, the greater perceived social support.

Mediator variables: Vital exhaustion and inflammatory biomarkers (e.g. CRP).

- Vital exhaustion will be calculated by using the 21-item Maastricht Questionnaire (14). The total score is an equally weighted sum, with scores ranging from 0-42; the higher the score, the more exhausted. A score of ≥ 14 will be used for present vital exhaustion (3), which is the suggested cut-off point for a clinical diagnosis; its Cronbach alpha has been reported as 0.89 (15).
- CRP (inflammatory biomarker)

Covariates: age, race, gender, marital status, smoking status, alcohol use, BMI, coronary heart disease, hypertension, diabetes, individual socioeconomic status (SES).

- Individual SES will be calculated as education attainment, income and wealth, and occupation.

Analyses: Descriptive statistics will be generated for demographic variables and for select covariates. We will use the Cox Proportional hazards model to estimate hazards ratios for incident stroke, stratified by categories of social isolation and social support.

  Model 1: Adjust for age, gender and race-center
  Model 2: Adjusted for Model 1 + individual SES + marital status
  Model 3: Adjusted for Model 2 + behavioral risk factors
Model 4: Adjusted for Model 3 + major disease risk factors

Model 5 (Mediation model): Adjusted for Model 4 + vital exhaustion.
Model 6 (Mediation model): Adjusted for Model 4 + CRP.

Mediation will be considered present if the beta for the social isolation or perceived social support and stroke relation changes by 10% or more upon inclusion of the potential mediator in the model. We will also separately examine whether race and gender modify the relationships between social isolation and incident stroke, by including cross-product terms in the models. Additionally, in secondary analyses we will look separately at risk of ischemic stroke, and risk of hemorrhagic stroke.

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
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.cscce.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 #1580 Social Isolation, Psychological Distress, and the Risk of Incident Heart Failure: Findings from the Atherosclerosis Risk in Communities Study, Crystal Wiley Cené, Wizdom Powell-Hammond, Giselle Corbie-Smith, Randi Foraker, Laura Loehr, Kathy Rose, Tom Mosley

There are authors from this manuscript that are included in this proposal.

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

11.b. If yes, is the proposal ___ A. primarily the result of an ancillary study (list number* _________) __ X _ 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/

2009.16 (Selvin PI)

- “Short-term markers of glycemia and long-term outcomes”
- CRP will be explored as a potential mediator. Dr. Selvin has granted us permission to use this variable.

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.

References

1. Executive Summary: Heart Disease and Stroke Statistics—2013 Update. A Report From the American Heart Association


