

ARIC Manuscript Proposal #2723

PC Reviewed: 3/8/2016
SC Reviewed: _____

Status: A
Status: _____

Priority: 2
Priority: _____

1.a. Full Title: The Relationship between Vital Exhaustion and Sudden Cardiac Death

b. Abbreviated Title (Length 26 characters): VE and SCD

2. Writing Group:

Writing group members: Brittany Bogle, Nona Sotoodehnia, Wayne Rosamond, others welcome

I, the first author, confirm that all the coauthors have given their approval for this manuscript proposal. __BB__ [**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: Analysis can begin immediately upon approval. Goal of a complete manuscript submitted by June 2016.

4. Rationale:

Vital exhaustion (VE) is characterized by lack of energy and increased fatigue and irritability, along with feelings of demoralization. VE was first formally defined by Appels after the observation of psychological precursors to sudden cardiac death (SCD)

and myocardial infarction (MI). [1] The Maastricht questionnaire was originally developed to assess the VE prior to an MI or SCD. [1] Appels reported that kin-reported VE scores were significantly higher for SCD victims when compared to kin-reported healthy controls, after adjusting for cardiovascular risk factors. [2]

Some characteristics of VE overlap with depression criteria. Several studies have explored self-reported depression and the risk of SCD. Whang et al reported that within The Nurses' Health Study, those in the highest quartile of self-reported depression had approximately twice the hazard of SCD compared to those in the reference group. [3] In the Canadian Amiodarone MI Arrhythmia Trial (671 MI patients), both fatigue and depression were significantly associated with an increased risk of SCD within 2 years after the patient's first MI, after adjusting for cardiovascular risk factors. [4] A study of over 1000 elderly in Northern Finland demonstrated that depressive symptoms were a significant predictor of SCD in death certificate reported events, but not nonfatal MI.[5]

Interestingly, while the relationship between SCD and VE has not been examined in ARIC, other cardiac events have been studied as a primary outcome. A positive association between a high VE score and acute MI or fatal CHD was reported by Williams et al. [6] Smoking status and VE independently, and the interaction between them, were found to be associated with an increased risk of ischemic stroke in ARIC by Schwartz et al. [7] The ARIC cohort provides a unique opportunity to study the link between VE and SCD with a much larger sample size, adjudicated SCD events, and self-reported VE.

5. Main Hypothesis/Study Questions:

- Question: Is vital exhaustion associated with time to sudden cardiac death?
- Hypothesis: Vital exhaustion will be significantly associated with sudden cardiac death, independent of established CVD risk factors

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).

We will use self-reported VE scores from Exam 2. Any participants without VE scores will be excluded from analysis. VE scores will be split into tertiles and those in the tertile with the highest score will be compared to all others. Cox Proportional hazards ratio analysis will be used to compute the hazards ratio between these groups. We will adjust for other cardiovascular risk factors (age, sex, blood pressure, cholesterol, etc). Potential confounders will also be examined.

The primary endpoint will be time to SCD, but two different definitions of SCD will be used in two separate analyses: 1-hour SCD and an updated SCD event definition that is not restricted by time criteria. 1-hour SCD is defined as death due to coronary artery disease within one hour of the onset of acute symptoms. The updated SCD endpoint is the result of an ARIC ancillary study where SCD was defined as a "sudden pulseless condition from a cardiac origin in a previously stable individual." [8]

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 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 ICTDER 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 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.csc.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)?

MS#537: The Relationship of Excess Fatigue to Incident Myocardial Infarction. Paul G. McGovern, Ph.D.

MS#625: Does vital exhaustion increase CHD risk? Janice Williams, Catherine Paton, Herman A. Tyroler

MS#1181: Vital Exhaustion and incident coronary heart disease. Tom Mosley, Woody Chambless, Sue Everson-Rose, Ken Butler, Maria Bryant, Kimberly Truesdale, June Stevens.

Full Manuscript:

Nagayoshi, Mako, Susan A. Everson-Rose, Hiroyasu Iso, Thomas H. Mosley, Kathryn M. Rose, and Pamela L. Lutsey. "Social network, social support, and risk of incident stroke atherosclerosis risk in communities study." Stroke 45, no. 10 (2014): 2868-2873.
Clinical outcomes in depression and heart failure. Janice Williams, Anna Kucharska-Newton, Laura Loehr, Sharon Wyatt, Thomas Mosley, David Couper

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.csc.unc.edu/aric/forms/>

12a. 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.

12b. The NIH instituted a Public Access Policy in April, 2008 which ensures that the public has access to the published results of NIH funded research. It is **your responsibility to upload manuscripts to PUBMED Central** whenever the journal does not and be in compliance with this policy. Four files about the public access policy from <http://publicaccess.nih.gov/> are posted in <http://www.csc.unc.edu/aric/index.php>, under Publications, Policies & Forms. http://publicaccess.nih.gov/submit_process_journals.htm shows you which journals automatically upload articles to PubMed central.

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2. Appels, A., B. Golombeck, A. Gorgels, J. De Vreede, and G. Van Breukelen. "Psychological risk factors of sudden cardiac arrest." *Psychology and Health* 17, no. 6 (2002): 773-781.
3. Whang, William, Laura D. Kubzansky, Ichiro Kawachi, Kathryn M. Rexrode, Candyce H. Kroenke, Robert J. Glynn, Hasan Garan, and Christine M. Albert. "Depression and risk of sudden cardiac death and coronary heart disease in women: results from the Nurses' Health Study." *Journal of the American College of Cardiology* 53, no. 11 (2009): 950-958.
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5. Luukinen, Heikki, P. Laippala, and H. V. Huikuri. "Depressive symptoms and the risk of sudden cardiac death among the elderly." *European Heart Journal* 24, no. 22 (2003): 2021-2026.

6. Williams, Janice E., Thomas H. Mosley, Willem J. Kop, David J. Couper, Verna L. Welch, and Wayne D. Rosamond. "Vital exhaustion as a risk factor for adverse cardiac events (from the Atherosclerosis Risk In Communities [ARIC] study)." *The American journal of cardiology* 105, no. 12 (2010): 1661-1665.
7. Schwartz, Skai W., Cheryl Carlucci, Lloyd E. Chambless, and Wayne D. Rosamond. "Synergism between smoking and vital exhaustion in the risk of ischemic stroke: evidence from the ARIC study." *Annals of epidemiology* 14, no. 6 (2004): 416-424.
8. Peacock, James M., Tetsuya Ohira, Wendy Post, Nona Sotoodehnia, Wayne Rosamond, and Aaron R. Folsom. "Serum magnesium and risk of sudden cardiac death in the Atherosclerosis Risk in Communities (ARIC) Study." *American heart journal* 160, no. 3 (2010): 464-470.