ARIC Manuscript Proposal #4107

PC Reviewed: 8/9/22	**Status: _____**	**Priority: 2**
SC Reviewed: _____	**Status: _____**	**Priority: ____**

1. a. Full Title:
Self-rated health and risk of incident atrial fibrillation: Findings from the Atherosclerosis Risk in Communities (ARIC), the Multi-Ethnic Study of Atherosclerosis (MESA), and the Trøndelag Health Study (The HUNT Study)

b. Abbreviated Title:
SRH and risk of AF

2. Writing Group:
Parveen Garg, Aniqa Alam, Harpreet Bhatia, Imre Janszky, Malmo Vegard, Jan Pal Loennechen, Scott Mu, Randi Foraker, Elizabeth Selvin, Alvaro Alonso, Susan R. Heckbert

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

First author: Parveen Garg
Address: 1510 San Pablo St, #322
Los Angeles, CA
Phone: (323)-442-6131
Fax: (323)-442-6133
E-mail: parveeng@med.usc.edu

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).

Name: Alvaro Alonso
Address: Department of Epidemiology
Rollins School of Public Health
Emory University
1518 Clifton Rd NE, Room 3051
Atlanta, GA 30322
Phone: 4047278714
E-mail: alvaro.alonso@emory.edu

3. Timeline:
June 2022 – Submit proposal
August-September-October 2022– Complete primary data analysis
September-October-November 2022 – Additional data analysis/Manuscript preparation
December 2022 – Submit manuscript for P&P review

4. Rationale:
Atrial fibrillation (AF) is the most frequently encountered cardiac arrhythmia in clinical practice, with an estimated prevalence of 11 million people in Europe and 9 million people in the United States.[1, 2] The presence of AF is associated with an over two-fold increased risk of stroke, heart failure, and cardiovascular mortality.[3] After accounting for known modifiable risk factors,

nearly half of the population attributable risk for AF development remains unexplained.[4] Continued investigation into finding factors, particularly those that are readily assessable in the clinical setting, that can help further identify those at increased AF risk is important.

Self-rated health (SRH) is a simple, reproducible measure[5] of subjective health status that is assessed with one question and has been shown to be a sensitive reflection of current underlying disease or proxy for a subclinical state.[6-9] SRH is thought to reflect a variety of factors including measurable cardiovascular (CV) risk factors, sociodemographic factors, perceived control of risk factors, mental health factors—depression and anxiety, and social factors—social isolation and stress.[9] Previous studies of large cohorts across many countries have consistently shown that poorer SRH is independently associated with an increased risk of cardiovascular disease (CVD), CV mortality, and all-cause mortality even after adjustment for demographics and clinical risk factors.[10-15] Findings suggest SRH assessment may better represent psychological and sociodemographic factors as well as residual downstream effects of measured and unmeasured CV risk factors not otherwise captured by traditional risk factors.

AF and CVD share significant risk factor overlap across sociodemographic, traditional CV, and mental health domains; therefore, it is important to see if SRH is also associated with AF risk. The Trøndelag Health Study (The HUNT-3 Study), the Multi-Ethnic Study of Atherosclerosis (MESA), and the Atherosclerosis Risk in Communities (ARIC) offer an opportunity to prospectively examine the relationship between SRH and the development of AF in multiple large, well-defined populations with long-term follow-up. Examination of multiple prospective cohorts with very different baseline demographic characteristics will allow for increased generalizability of findings. Additionally, inclusion of multiple cohorts will provide better power to evaluate this relationship in gender- and race-specific analyses.

5. Main Hypothesis/Study Questions:

- Higher baseline SRH scores will be associated with a lower incidence of AF
- Higher SRH scores over time will also be associated with a lower incidence of atrial fibrillation

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).

Data:

ARIC

Study participants

Eligible participants will be from the ARIC cohort with data for self-reported health and without AF at baseline.

Exposure variable: Self-rated health

SRH was measured over telephone at baseline and at each annual follow-up (1987–2006) using the question, 'Over the past year, compared to other people your age, would you say that your health has been *excellent*, *good*, *fair* or *poor*?' SRH data are simple to collect,[17] yet may be difficult to interpret, since the SRH scale is not precisely ordinal. For trajectory analyses, SRH data was scored on a scale from 4 (excellent health) to 1 (poor health).[18, 19]

Outcome variable—Atrial Fibrillation

Incident AF will be defined as in previous ARIC analyses.[20] Study participants underwent ECG recordings at baseline (visit 1) and at the first four follow-up exams (visits 2 through 5). All ECG recordings automatically coded as AF were visually re-checked by a trained cardiologist to confirm the diagnosis. A trained abstractor obtained and recorded all ICD-9-CM hospital discharge diagnoses from each participant's hospitalizations reported in the annual follow-up interview. AF was defined as the presence of ICD-9-CM code 427.31 or 427.32 in the discharge codes (ICD-10-CM codes I48.xx starting in 2015). AF hospitalization diagnoses occurring

simultaneously with heart revascularization surgery or other cardiac surgery involving heart valves or septa, without evidence of AF in subsequent hospitalizations or study exams were excluded. ARIC participants were also labeled as AF cases if the underlying cause of death was AF. The incidence date of AF was defined as the date for the first ECG showing AF or the first hospital discharge with an AF diagnosis. Follow-up will be available through the end of 2019.

MESA

Study participants

Eligible participants are part of the MESA cohort (n=6814). Details of MESA have been reported previously.[16] A self-report of current AF was an exclusion criterion for enrollment in MESA; however, some participants were identified by Medicare claims data to have had an AF diagnosis assigned prior to enrollment. These individuals will also be excluded from this analysis.

Exposure variable: Self-rated health

An EVGGFP (excellent, very good, good, fair, and poor) measure of SRH was assessed in MESA via the single question: "Would you say, in general, your health is poor, fair, good, very good, or excellent?". SRH was assessed at Visit 1 (baseline) and every year after either by phone or in-person.

Outcome variable—Atrial Fibrillation

After the baseline examination, participants were followed up every 9-12 months by telephone to obtain information on hospitalizations and medical records, including discharge diagnoses. Incident AF through December 2018 was identified from study ECGs verified for AF at Visit 5 (2010-2012), ICD-9 or -10 hospital discharge diagnoses consistent with AF (427.31 or 427.32; I48), and, for participants enrolled in fee-for-service Medicare, inpatient and outpatient AF claims data.

The HUNT Study

Study participants

Eligible participants are those who participated in the 3rd phase of the HUNT Study (n=50,807, in 2006-2008) with data for SRH and without AF at baseline.

Exposure variable: Self-rated health

SRH was measured at the 3rd phase by the following question which appeared in the main questionnaire filled in by HUNT participants: "*How is your health at the moment?*" The possible answers were: "*poor, not so good, good, very good*".

Outcome variable—Atrial Fibrillation

AF diagnoses were retrieved from discharge registers at the two hospitals in Nord-Trøndelag County from HUNT-3 examination (2006-2008) until 01.01.2019. We used code I48 from the International Classification of Diseases Tenth Revision to screen for patients with possible AF. Medical records of these patients were then reviewed by specialists, and AF was adjudicated according to the electrocardiographic criteria recommended by the European Society of Cardiology (ESC).[21] Persons who only had an episode of AF within the first 7 days after cardiac surgery, during the acute phase of a myocardial infarction or during episodes of haemodynamic instability (e.g., sepsis or non-cardiac surgery) were not regarded as having incident AF. If information from medical records was insufficient for exact classification of the diagnosis, two physicians evaluated the available information separately. Only cases where both physicians concurred were regarded as AF. The rest were classified as possible AF and will not be regarded as AF cases in the main analyses.[22]

Other Variables of Interest (all cohorts)

Demographic - Age, Race/Ethnicity, Sex, Education, Height, Weight, Clinic site
Comorbidities - Cigarette smoking, SBP, DBP, CHD, HF
Laboratory data –Glucose, TC, HDL, BNP
Medication use – Anti-hypertensive use, Lipid lowering therapy, Anti-DM medication use
Others – Alcohol consumption, Physical activity levels

Exclusion criteria
Participants without self-rated health measured at baseline, with baseline AF, or without follow-up data for incident AF will excluded.

4) Analysis plan:
The following analysis will be performed separately in MESA, ARIC, and HUNT.
1) Comparison of baseline characteristics
Descriptive statistics will be computed for baseline variables. We will examine the distributions of demographic and clinical characteristics according to baseline categories of SRH. Categorical variables will be reported as frequency and percentage, and continuous variables as mean (standard deviation).
2) Associations of SRH with incident AF
Cox proportional hazards models will be used to calculate adjusted hazard ratios (HRs) and 95% confidence intervals (CIs) for the association of SRH with incident AF (referent=poor/fair). Person-years will accrue from baseline visit to the date of the participant's first AF event, loss to follow-up, death, or end of follow-up, whichever occurred first. Models will be run categorically according to the groupings described above (referent=poor/fair).
-Models will be adjusted for the following:

Model 1: Age, race, sex, education, and height
Model 2: Model 1 + BMI, cigarette smoking, DM, SBP, DBP, anti-hypertensive medication, physical activity, TC, HDL, alcohol consumption, CHD and HF (*if applicable*)

3) Stratified analyses
We will evaluate the effect modification by race/ethnicity, sex, and follow-up duration (<median vs. >median) using a stratification technique and comparing models with and without interaction terms.
4) Associations of SRH trajectories with incident AF
Because data for SRH was assessed annually in MESA and ARIC, we will determine how SRH over time (V1 to V4 for MESA (2000-2002 to 2005-2007) and ARIC (1988-1990 to 1996-1998)) affects AF risk. Participants will be separated into 4 groups based upon the number of times they rated their health as either excellent or very good. Multivariable models will be constructed as above with additional adjustment for V4 SRH score (Referent=highest number of excellent/very good SRH reports). Participants with data for all SRH assessments between V1 to V4 and without AF at V4 will be eligible for this analysis. Visit 4 will serve as the baseline visit for these analyses.

7.a. Will the data be used for non-CVD analysis in this manuscript? __ _ Yes _XX_ 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? _XX___ 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 __XX_ 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

   __XX__ 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)?**
    The author identifies no significantly related manuscript proposals. Co-authors with extensive ARIC experience for prior proposals related atrial fibrillation have been contacted to collaborate.

11. a. Is this manuscript proposal associated with any ARIC ancillary studies or use any ancillary study data? ____ Yes _XX_ 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/

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.cscc.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.

References

1) Krijthe BP, Kunst A, Benjamin EJ, Lip GY, Franco OH, Hofman A, Witteman JC, Stricker BH, Heeringa J. Projections on the number of individuals with atrial fibrillation in the European Union from 2000 to 2060. *Eur Heart J*. 2013;34:2746–2751.
2) Miyasaka Y, Barnes ME, Gersh BJ, Cha SS, Bailey KR, Abhayaratna WP, Seward JB, Tsang TS. Secular Trends in Incidence of Atrial Fibrillation in Olmsted County, Minnesota, 1980 to 2000, and Implications on the Projections for Future Prevalence. *Circulation*. 2006;114:119-125.
3) Odutayo A, Wong CX, Hsiao AJ, Hopewell S, Altman DG, Emdin CA. Atrial fibrillation and risks of cardiovascular disease, renal disease, and death: systematic review and meta-analysis. *BMJ*. 2016;354:i4482
4) Huxley RR, Lopez FL, Folsom AR, Agarwal SK, Loehr LR, Soliman EZ, Maclehose R, Konety S, Alonso A. Absolute and attributable risks of atrial fibrillation in relation to optimal and borderline risk factors: the atherosclerosis risk in communities (ARIC) study. *Circulation*. 2011;123:1501–1508.
5) Rumsfeld JS. Health status and clinical practice: when will they meet? *Circulation*. 2002;106(1):5-7.
6) Idler EL, Benyamini Y. Self-rated health and mortality: a review of twenty-seven community studies. *J Health Soc Behav* 1997;38:21–37.
7) Bailis DS, Segall A, Chipperfield JG. Two views of self-rated general health status. *Soc Sci Med* 2003;56:203–217.
8) Jylha M, Volpato S, Guralnik JM. Self-rated health showed a graded association with frequently used biomarkers in a large population sample. *J Clin Epidemiol* 2006;59: 465–471.
9) Kaplan G, Baron-Epel O. What lies behind the subjective evaluation of health status? *Soc Sci Med* 2003;56:1669–1676.
10) Orimoloye OA, Mibolouk M, Uddin SM, Dardari ZA, Miedema MD, Al-Mallah MH, et al. Association Between Self-rated Health, Coronary Artery Calcium Scores, and Atherosclerotic Cardiovascular Disease Risk: The Multi-Ethnic Study of Atherosclerosis (MESA). *JAMA Netw Open* 2019;2:e188023.
11) Ogunmoroti O, Utuama OA, Salami JA, et al. Association between self-rated health and ideal cardiovascular health: the Baptist Health South Florida Employee Study. *J Public Health* 2017;40:e456-e463.
12) Kaplan GA, Camacho T. Perceived health and mortality: a nine-year follow-up of the human population laboratory cohort. *Am J Epidemiol* 1983;117:292-304.
13) Barger SD, Cribbet MR, Muldoon MF. Participant-reported health status predicts cardiovascular and all-cause mortality independent of established and nontraditional biomarkers: evidence from a representative US sample. *J Am Heart Assoc*. 2016;5:e003741.
14) Dong W, Pan XF, Yu C, et al; China Kadoorie Biobank Collaborative Group. Self-rated health status and risk of ischemic heart disease in the China Kadoorie Biobank Study: a population-based cohort study. *J Am Heart Assoc* 2017;6:e006595.
15) DeSalvo KB, Fan VS, McDonell MB, Fihn SD. Predicting mortality and healthcare utilization with a single question. *Health Serv Res* 2005;40:1234-1246.
16) Bild DE, Bluemke DA, Burke GL, et al. Multi-ethnic study of atherosclerosis: objectives and design. *Am J Epidemiol* 2002;156:871-81.
17) McFadden E, Luben R, Bingham S, Wareham N, Kinmonth AL, Khaw KT. Social inequalities in self-rated health by age: cross-sectional study of 22,457 middle-aged men and women. *BMC Public Health* 2008;8:230.
18) Diehr P, Patrick DL. Trajectories of health for older adults over time: accounting fully for death. *Ann Intern Med* 2003;139:416-420.
19) Foraker RE, Rose KM, Chang PP, McNeill AM, Suchindran CM, Selvin E, et al. Socioeconomic status and the trajectory of self-rated health. *Age and Ageing* 2011;40:706–711.
20) Alonso A, Agarwal SK, Soliman EZ, et al. Incidence of atrial fibrillation in whites and African-Americans: the Atherosclerosis Risk in Communities (ARIC) Study. Am Heart J 2009;158:111–117.
21) Camm AJ, Kirchhof P, Lip GY, Schotten U, Savelieva I, Ernst S, Van Gelder IC, Al-Attar N, Hindricks G, Prendergast B. Guidelines for the management of atrial fibrillation. Eur Heart J 2010;31:2369–2429.
22) Malmo V, Langhammer A, Bønaa KH, Loennechen JP, Ellekjaer H. Validation of self-reported and hospital-diagnosed atrial fibrillation: the HUNT study. Clin Epidemiol 2016;8:185–193.