ARIC Manuscript Proposal #4146

PC Reviewed: 10/11/22	**Status: _____**	**Priority: 2**
SC Reviewed: _____	**Status: _____**	**Priority: ____**

1.a. Full Title:
Association of alcohol intake with the incidence of atrial fibrillation in persons ≥65 y.o. in the Atherosclerosis Risk in Communities (ARIC) cohort

b. Abbreviated Title (Length 26 characters):
Alcohol intake and AF in persons ≥65

2. Writing Group:
Writing group members:
Louis Li, Linzi Li, Lin Yee Chen, Elsayed Z. Soliman, Alvaro Alonso, others welcome

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

First author: **Louis Li**
Address: Dept. of Epidemiology, Rollins School of Public Health
1518 Clifton Rd NE
Atlanta, GA 30322

Phone: 484-238-6333
E-mail: louis.li@emory.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: Dept of Epidemiology, Rollins School of Public Health
Emory University
1518 Clifton Rd NE, CNR 3051
Atlanta, GA 30322

Phone: 404-727-8714
E-mail: alvaro.alonso@emory.edu

3. Timeline:
Analysis to begin immediately upon proposal approval. A formal manuscript is to be expected by May 2023.

4. Rationale:

Atrial fibrillation (AF) is the most common arrhythmia, and its incidence and prevalence continue to increase.[1] The Framingham Heart Study (FHS) indicated that the prevalence of AF has increased 3-fold over the last 50 years, and the worldwide prevalence is expected to double or triple by 2050 based on 2021 estimates.[1,2] While increased awareness and enhanced detection of AF have contributed in part to these increases, the aging population has significantly increased the burden of AF as age is the most important risk factor for AF.

Alcohol intake has been associated with AF both in acute settings and in long-term consumption.[3,4] Acute alcohol consumption has direct effects on cellular, autonomic, and electrophysiological functions involved in arrhythmogenicity. Long-term heavy alcohol consumption has direct effects on left atrial substrate including left atrial remodeling, dilation, and fibrosis as well as indirect effects via interactions with other AF risk factors such as hypertension and cardiomyopathy. However, results on light-moderate long-term alcohol intake have not been as conclusive.[5,6] Furthermore, previous literature addressing alcohol intake and AF in elderly populations is limited. Only one study specifically focused on a population of adults ≥65 years in the U.S. which concluded that current moderate alcohol consumption was not associated with risk of AF and former drinking was associated with higher risk.[7] A previous ARIC study addressed the association of alcohol intake and incident AF in participants aged 45-64 years old and found that, among former drinkers, the number of years of drinking and the amount of alcohol consumed were associated with increased risk of AF. However, among former drinkers, they also found that a longer duration of abstinence was associated with a decreased risk of AF. Additionally, their results indicated that former drinkers were at higher risk compared to never drinkers and current drinkers.[8]

To further explore and confirm these findings, this study will investigate the understudied population of patients ≥65 years who are at increased risk of incident AF. Additionally, we hope to better characterize the relationship between more detailed characteristics of abstinence among former drinkers including number of years of drinking, number of years of abstinence, and amount of alcohol consumed. We hypothesize that former drinkers and current drinkers will have a higher risk of incident AF than non-drinkers. We hypothesize that, within the former drinkers, the number of years of abstinence will be associated with decreased risk of AF and that the number of years of drinking and amount of alcohol consumed with be associated with increased risk of AF.

5. Main Hypothesis/Study Questions:

1. What is the association between alcohol intake history in early-to-mid adulthood and the incidence of atrial fibrillation among the elderly (≥65 years) in the ARIC cohort?
2. In former drinkers, what is the association between characteristics of alcohol intake history—number of years of drinking, amount of alcohol consumed, and number of years of abstinence—and the incidence of atrial fibrillation?

We hypothesize that there will be:

- a higher risk of incident AF for former drinkers and current drinkers than never drinkers.
- a higher risk of incident AF for current drinkers than former drinkers.
- within former drinkers, a lower risk of incident AF with fewer years of drinking, lower amount of alcohol consumed, and more years of abstinence.

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).

1. **Study Design**
   Cohort study starting from visit 5
2. **Inclusion/Exclusion**
   Inclusion
   - Participants attending visit 5

   Exclusion
   - Participants with prevalent AF at visit 5 and missing information on alcohol consumption history.
     - Prevalent AF will be determined via study ECGs and hospital discharge codes (ICD-9-CM: 428.3x, ICD-10-CM: I48.x)
   - Standard ARIC exclusions by race/center: non-White and non-Black participants, non-White participants from the Minnesota and Washington County sites.

3. **Main Independent Variable (Alcohol Intake)**
   Alcohol intake will be assessed from the ARIC Smoking and Alcohol Use Form from visit 5. Participants were asked 1) if they had ever consumed alcoholic beverages, 2) if they presently drink alcoholic beverages, 3) approximately how many years ago they stopped drinking, 4) how many and what type of alcohol they consumed daily and weekly.
   Participants will be stratified on their responses on drinking status: never drinker, former drinker, and current drinker.
   Amount of alcohol consumed weekly will be calculated assuming the following alcohol content: 4oz wine (10.8g), 12oz beer (13.2g), 1.5oz hard liquor (15.1g)[8,9]
   Weekly alcohol consumption will be stratified into 4 cohorts:[10,11]
   Light drinkers: ≤1 drink per week
   Moderate drinkers: 2-7 drinks per week
   Heavy drinkers: 8-14 drinks per week
   Excessive drinkers: ≥ 14 drinks per week

4. **Outcome**
   Incident AF between visit 5 (2011-13) and 2019.
   Atrial fibrillation will be identified via hospital discharge codes (ICD-9-CM: 428.3x, ICD-10-CM: I48.x) not occurring in the context of cardiac surgery and from death certificates with AF as an underlying or contributing cause of death (ICD-10: I48)[8,12]

5. **Covariates**
   Age, sex, race/center, education, prevalent CVD (CAD, HF, stroke), cardiovascular risk factors (systolic and diastolic BP, HDL-C, LDL-C, use of antihypertensive medications, use of anticoagulants, diabetes, smoking, body mass index) at visit 5 will be considered as potential confounders. Covariates will be defined based on previous ARIC study analyses and/or ACC/AHA guidelines.[8]

6. **Statistical Analysis**
   Continuous variables with normal distribution will be reported as means ± SDs.
   Continuous variables with non-normal distribution will be reported as medians with IQRs.
   Categorical variables will be reported as frequencies with percentages.
   Associations between drinker status and past drinking characteristics and incident AF will be analyzed via Cox proportional hazard models both before and after controlling for potential confounders listed above. Additionally, the proportional hazards assumption will be assessed using Kaplan-Meier versus predicted survival plots and log-minus-log survival plots.[8]
   Within former drinkers, longitudinal data of number of years of drinking, number of years of abstinence, and amount of alcohol consumed (to be analyzed as categorical variable with 4 cohorts as described above) will be analyzed via Cox proportional hazard models.
   Statistical analysis will be conducted in SAS software (Version 9.4; SAS Institute, Cary, NC, US).

7.a. Will the data be used for non-ARIC analysis or by a for-profit organization in this manuscript? ____ Yes __X__ No

b. If Yes, is the author aware that the current derived consent file ICTDER05 must be used to exclude persons with a value RES_OTH and/or RES_DNA = "ARIC only" and/or "Not for Profit" ? ____ Yes ____ No
(The 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 __X__ No

8.b. If yes, is the author aware that either DNA data distributed by the Coordinating Center must be used, or the current derived consent file ICTDER05 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/aricproposals/dtSearch.html

_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)?

- Dixit S, Alonso A, Vittinghoff E, Soliman EZ, Chen LY, Marcus GM. Past alcohol consumption and incident atrial fibrillation: The Atherosclerosis Risk in Communities (ARIC) Study [published correction appears in PLoS One. 2017 Dec 21;12 (12):e0190329]. *PLoS One*. 2017;12(10):e0185228. Published 2017 Oct 18. doi:10.1371/journal.pone.0185228
- Hu EA, Lazo M, Rosenberg SD, et al. Alcohol Consumption and Incident Kidney Disease: Results From the Atherosclerosis Risk in Communities Study. *J Ren Nutr*. 2020;30(1):22-30. doi:10.1053/j.jrn.2019.01.011
- He X, Rebholz CM, Daya N, Lazo M, Selvin E. Alcohol consumption and incident diabetes: The Atherosclerosis Risk in Communities (ARIC) study. *Diabetologia*. 2019;62(5):770-778. doi:10.1007/s00125-019-4833-1

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 https://sites.cscc.unc.edu/aric/approved-ancillary-studies

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.

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2. Kornej J, Börschel CS, Benjamin EJ, Schnabel RB. Epidemiology of Atrial Fibrillation in the 21st Century: Novel Methods and New Insights. *Circ Res*. 2020;127(1):4-20. doi:10.1161/CIRCRESAHA.120.316340
3. Marcus GM, Vittinghoff E, Whitman IR, et al. Acute Consumption of Alcohol and Discrete Atrial Fibrillation Events. *Ann Intern Med*. 2021;174(11):1503-1509. doi:10.7326/M21-0228
4. Djoussé L, Levy D, Benjamin EJ, et al. Long-term alcohol consumption and the risk of atrial fibrillation in the Framingham Study. *Am J Cardiol*. 2004;93(6):710-713. doi:10.1016/j.amjcard.2003.12.004
5. Voskoboinik A, Prabhu S, Ling LH, Kalman JM, Kistler PM. Alcohol and Atrial Fibrillation: A Sobering Review. *J Am Coll Cardiol*. 2016;68(23):2567-2576. doi:10.1016/j.jacc.2016.08.074
6. Voskoboinik A, Kalman JM, De Silva A, et al. Alcohol Abstinence in Drinkers with Atrial Fibrillation. *N Engl J Med*. 2020;382(1):20-28. doi:10.1056/NEJMoa1817591
7. Mukamal KJ, Psaty BM, Rautaharju PM, et al. Alcohol consumption and risk and prognosis of atrial fibrillation among older adults: the Cardiovascular Health Study. *Am Heart J*. 2007;153(2):260-266. doi:10.1016/j.ahj.2006.10.039
8. Dixit S, Alonso A, Vittinghoff E, Soliman EZ, Chen LY, Marcus GM. Past alcohol consumption and incident atrial fibrillation: The Atherosclerosis Risk in Communities (ARIC) Study [published correction appears in PLoS One. 2017 Dec 21;12 (12):e0190329]. *PLoS One*. 2017;12(10):e0185228. Published 2017 Oct 18. doi:10.1371/journal.pone.0185228
9. Eigenbrodt ML, Mosley TH Jr, Hutchinson RG, Watson RL, Chambless LE, Szklo M. Alcohol consumption with age: a cross-sectional and longitudinal study of the Atherosclerosis Risk in Communities (ARIC) study, 1987-1995. *Am J Epidemiol*. 2001;153(11):1102-1111. doi:10.1093/aje/153.11.1102
10. Hu EA, Lazo M, Rosenberg SD, et al. Alcohol Consumption and Incident Kidney Disease: Results From the Atherosclerosis Risk in Communities Study. *J Ren Nutr*. 2020;30(1):22-30. doi:10.1053/j.jrn.2019.01.011
11. He X, Rebholz CM, Daya N, Lazo M, Selvin E. Alcohol consumption and incident diabetes: The Atherosclerosis Risk in Communities (ARIC) study. *Diabetologia*. 2019;62(5):770-778. doi:10.1007/s00125-019-4833-1
12. 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(1):111-117. doi:10.1016/j.ahj.2009.05.010