1.a. Full Title: Changes in Leisure-Time Physical Activity and Risk of Incident Atrial Fibrillation – The Atherosclerosis Risk in Communities (ARIC) Study

b. Abbreviated Title (Length 26 characters): Change in Physical Activity and AF

2. Writing Group: Sheila Hegde; Brian Claggett; Tor Biering-Sorensen, Susan Cheng, Amil Shah, Lin Y. Chen, Elsayed Soliman, Alvaro Alonso, Scott D. Solomon; others welcome

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

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3. Timeline: Analysis will begin following proposal approval with anticipated manuscript completion within 6 months.
4. **Rationale:**

Atrial fibrillation (AF) was estimated to affect 2.7 to 6.1 million Americans in 2010 and has a projected prevalence of 5.6 to 12.1 million in 2050, which is in part attributed to the growing older population in the United States (1, 2). The growing burden of AF is associated with increased hospitalizations and substantial morbidity and mortality (2). While leisure-time physical activity (LTPA) has been shown to reduce the risk of cardiovascular disease, several studies have suggested that regular exercise is associated with a higher risk of AF, particularly in young, endurance athletes (3, 4). One prospective study has reported that light to moderate LTPA was associated with a lower risk of AF (5) while findings from the MESA study demonstrated that higher LTPA is not associated with increased AF risk (6). Furthermore, a meta-analysis of four prospective cohort studies suggested that there is no association between regular LTPA and AF in nonathletes (7). These inconsistent results may be due to variable study populations and differences in analytic models. Additional studies have demonstrated the importance of obesity and weight change in mediating and modifying the relationship between LTPA and AF (8, 9). Given these incongruent findings, evaluating the change in LTPA in relation to incident AF may provide additional insight.

Previous work in ARIC on this topic has focused on the relationship of obesity and weight change with baseline LTPA at visit 1 and incident AF through December 31, 2009. This study aims to evaluate the change in LTPA between visits 1 and 3 and its relationship to incident AF and to further investigate the association between cumulative average LTPA and incident AF in those who remain active.

5. **Main Hypothesis/Study Questions:**

We hypothesize that those who maintain intermediate or ideal LTPA and increase their LTPA category between visits 1 and 3 will have a reduced incidence of AF relative to those who remain inactive and that there will be a dose-response relationship.

Aims:
1. To evaluate the association between change in LTPA and incident AF
   a. To evaluate whether this association differs by age, sex, race, BMI
2. To evaluate the association between cumulative average LTPA and incident AF in those who remain active.
   a. To evaluate whether this association differs by age, sex, race, BMI

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:

We will evaluate the prospective association between change in LTPA between visit 1 and visit 3 and incident AF after visit 3.

Inclusions:
1. Participants who do not develop AF between Visit 1 and Visit 3.
2. Participants with physical activity responses at visits 1 and 3.

Exclusions:
1. Missing physical activity information at visits 1 and 3.
2. Missing or unreadable ECGs at all visits.
3. Prevalent AF at visit 1 (defined as AF by ECG or AF hospitalization).
4. Missing variables for major covariates - BMI.

Exposure:

The primary exposure will be the change in physical activity level. Physical activity was measured using the modified Baecke physical activity questionnaire at visits 1 and 3. As previously done, the sports questionnaire responses will be converted to minutes per week of moderate or vigorous activity according to the metabolic equivalent as defined by the Compendium of Physical Activities, which will then be converted to ideal, intermediate, or poor LTPA according to AHA criteria. Ideal LTPA is defined as ≥ 150 min·wk⁻¹ of moderate activity, ≥ 75 min·wk⁻¹ of vigorous activity, or ≥ 150 min·wk⁻¹ of moderate + vigorous activity. Intermediate LTPA is defined as 1-149 min·wk⁻¹ of moderate activity, 1-74 min·wk⁻¹ of vigorous activity, or 1-149 min·wk⁻¹ of moderate + vigorous activity. Poor LTPA is defined as 0 min·wk⁻¹ of moderate + vigorous activity.

Change in activity will be categorized as follows: persistently poor activity, decreased activity, increased activity, or persistently active. Those who maintain intermediate or ideal LTPA over both visits will be categorized as persistently active. Those who maintain poor LTPA over both visits will be categorized as persistently poor activity. Those who increase or decrease their LTPA category between visit 1 and 3 will be categorized accordingly.

Leisure-time physical activity will also be measured as a continuous index. MET values using the updated Compendium of Physical Activities will be multiplied by the usual duration and frequency of the activity to obtain estimated total MET-minutes per week of sport activity. Total cumulative average LTPA in MET-min per week will be calculated by averaging the visit 1 and 3 values for each participant.

Outcome:

The primary outcome will be incident atrial fibrillation, defined by ECG diagnosis, ICD-9 code, or AF listed as cause of death, occurring after visit 3 until 1/1/12 (or most recent follow-up available). AF during hospitalizations for cardiac surgery will be excluded. Date of AF incidence will be the first date of any AF diagnosis.
Covariates of interest:

1. Demographics: Age, Sex, Race/ethnicity, Center, Education, Income, Education
2. Cardiovascular risk factors: Hypertension (SBP≥140 mmHg, DBP≥ 90 mmHg), anti-hypertensive medication use, Diabetes (A1C), Smoking status (current, former, never), Dyslipidemia, BMI, weight
3. Clinical characteristics: CVD (CHD, HF, valvular HD, CVA), COPD, CKD, resting heart rate, ECG PR interval
4. Social history: Alcohol intake
5. Laboratory data: TSH, fasting glucose

Analysis plan:

1. Primary analysis
   a. We will use Cox proportional hazard models to estimate the association between change in LTPA categories and incident AF after visit 3 using several models
      i. Model 1: age, sex, race
      ii. Model 2: Model 1 + education, smoking status, alcohol use
      iii. Model 3: Model 2 + SBP, anti-hypertensive use, diabetes, BMI, incident HF, incident MI
   b. The reference group will be those with persistent poor LTPA (poor LTPA activity and visit 1 and 3)
   c. We will use Visit 1 variables and adjust for change between visit1 and 3 variables. We will also do a sensitivity analysis adjusting for visit 1 only and visit 3 only covariates.
2. Secondary analysis
   a. In those who remain active, we will use the continuous measure of cumulative average LTPA over visits 1 and 3 to evaluate the association with incident AF using a Cox proportional hazards model with cubic spline function.
3. Additional analysis
   a. We will evaluate for interaction by age, sex, race, and BMI, acknowledging the potential for false positives due to multiple testing
   b. We will test for proportional hazards.

Descriptive statistics of the overall population will be presented by change in LTPA category. Continuous normally distributed data will be displayed as mean and standard deviation values. Continuous non-normally distributed data will be displayed as median and interquartile range values. Categorical data will be reported as percent frequencies and compared by chi-squared tests. Continuous data will be compared by Wilcoxon rank sum tests or t tests as appropriate. A two-sided p-value of < 0.05 will be considered statistically significant.
Limitations:

1. Baecke questionnaire for physical activity is a self-reported exposure, which may result in recall bias; however, this questionnaire has been well-validated.
2. We may not be able to fully account for changes in LTPA that occur between visits 1 and 3.
3. Incomplete AF incidence as there may be participants with asymptomatic AF or paroxysmal AF.
4. Residual confounding.

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 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 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.cscu.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)?

#2029: Obesity, physical activity and risk of incident atrial fibrillation: the Atherosclerosis Risk in Communities Study (ARIC)

#2548: Changes in Physical Activity and the Risk of Incident Heart Failure: The Atherosclerosis Risk in Communities (ARIC) Study
11a. Is this manuscript proposal associated with any ARIC ancillary studies or use any ancillary study data? _____ Yes ___x__ No

11b. 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.

13. Per Data Use Agreement Addendum for the Use of Linked ARIC CMS Data, approved manuscripts using linked ARIC CMS data shall be submitted by the Coordinating Center to CMS for informational purposes prior to publication. Approved manuscripts should be sent to Pingping Wu at CC, at pingping_wu@unc.edu. I will be using CMS data in my manuscript _____ Yes ___x__ No.

References


