ARIC Manuscript Proposal #2029

PC Reviewed: 11/13/12	**Status: A**	**Priority: 2**
SC Reviewed: _____	**Status: _____**	**Priority: ____**

1.a. Full Title: Obesity, physical activity and risk of incident atrial fibrillation: the Atherosclerosis Risk in Communities Study (ARIC)

b. Abbreviated Title (Length 26 characters): Obesity, physical activity and atrial fibrillation

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

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3. Timeline:
Data analysis – 3 months
First draft of the manuscript – 3 months

4. Rationale:

Excess weight is an established risk factor for many chronic conditions including cardiovascular disease. A meta-analysis based on data from 16 studies reported that

obesity increased the risk of atrial fibrillation (AF) by nearly 50% (Hazard Ratio 1.49, 95% Confidence Intervals 1.36 to 1.64) (Wanahita et al. 2008). It has however been suggested that physical activity and good physical fitness could ameliorate the adverse effect of obesity on cardiovascular mortality (Fogelholm 2010). In a recent study of 2014 middle-aged men among whom there were 253 AF events during follow-up, weight gain in adult life was predictive of AF, but the associated risk was confined to those men with a relatively low level of physical fitness; weight gain in men with above the median levels of physical fitness was not associated with increased risk of AF (Grundvold et al 2012). These findings have yet to be replicated but such a study would have possible public health potential given that interventions to increase levels of physical activity are more often successful than those aimed at long-term weight loss.

The ARIC study provides an excellent for a prospective study of the association between weight gain, physical activity and incident AF in both whites and African-Americans. Further, information on a large number of socio-demographic, physiological, and biochemical risk factors will enable adjustment for known and unknown confounders allowing a more accurate estimate of the association to be determined.

5. Main Hypothesis/Study Questions:

We hypothesize that there is an interaction between weight gain, obesity and physical activity on the risk of incident AF such that the detrimental effect of weight gain on risk of AF is attenuated by increasing level of physical activity. Specifically, this proposal has four aims:

i. To quantify the relationship between BMI and risk of incident AF
ii. To determine the relationship between weight change during follow-up and incident AF
iii. To examine the association between level of physical activity (poor, intermediate or ideal) with risk of AF
iv. To determine whether test level of physical activity modifies the relationship between BMI, weight change and risk of AF

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).

Inclusions

1. Those individuals who do not develop AF between Visit 1 and Visit 4 (this leaves a population in whom there were more than 700 AF events)
2. Those with information on physical activity status at baseline and/or at visit 2 (ideally we will use the mean of the physical activity values at Visit 1 and Visit
3. Those with information on BMI at Visit 1 and at Visit 4

Exclusions
The following individuals will be excluded from all analyses:

- Those with missing or unreadable ECGs at visit 1
- Those with prevalent AF at visit 1 (defined as AF by ECG or AF hospitalization)
- Those other than white or African-American
- Those with missing information on physical activity and BMI at baseline
- Those with missing information on BMI at visit 4
- Those with missing variables for any of the major covariates

Exposure
There are three primary exposures in this proposal: BMI, weight change during study follow-up and level of physical activity:

i. Body mass index
BMI at baseline and during follow-up will be calculated (weight [kg]/height [m]2. The crude and adjusted relationship between BMI and incident AF will be explored first as a continuous association and again after categorizing individuals according to the World Health Organization's categories for normal weight (BMI 18.5 – 24.9kg/m^2), overweight (25 – 29.9 kg/m^2) and obese ($\geq$ 30 kg/m^2).

ii. Weight change during study follow-up will be classified into the following groups: weight loss, weight gain 0 – 4.9 kg (reference group), weight gain 5 – 9.9 kg and weight gain $\geq$ 10 kg.

iii. Physical activity levels will be categorized according to the American Heart Association's ideal CVD health guidelines: Ideal physical activity was defined as ≥150 min/wk moderate or ≥75 min/wk vigorous or ≥150 min/wk moderate + vigorous activity; intermediate as 1-149 min/wk moderate or 1-74 min/wk vigorous or 1-149 min/wk moderate + vigorous activity; and poor physical activity as 0 min/wk of activity.

Outcome
Incident cases of AF identified in the follow-up through the end of 2010 from three sources: ECGs done at study visits, presence of AF ICD9 (427.31 or 427.32) code in a hospital discharge, or AF listed as any cause of death. Hospitalizations with AF associated with cardiac surgery will not be considered events. Date of AF incidence will be the earliest of any AF diagnosis.

Statistical analysis
Means and standard deviations (SD) for the continuous variables and percentages for the categorical variables will be obtained separately for men and women and for white and African-American participants. Associations between BMI, weight change during follow-up and physical activity level with incidence of AF will be estimated using time-

dependent Cox proportional hazards models. Separate analyses will be conducted in men and women, and models will adjust for baseline age, ethnicity, study site, education, income, height, prior history of cardiovascular disease, cigarette smoking and alcohol consumption. Models will additionally include the following covariates from Visit 4: prior CVD, body height, cigarette smoking and alcohol consumption. We will explore the assumption of proportional hazards adding to the model an interaction term between follow-up time and exposure of interest, computing Schoenfeld residuals, and by inspection of the log(-log[survival function]) curves.

An interaction term for physical activity will be added to the models of the association between BMI and weight change with risk of AF. If there is evidence of an interaction between BMI and/or weight change and physical activity level with risk of AF, men and women will be stratified according to their age-adjusted baseline level of physical activity (poor, intermediate or ideal) and sex-specific Cox models of the association between BMI or category of weight change with incident AF with adjustment for age, race, study site, education, income, prior history of cardiovascular disease, smoking and alcohol consumption will be obtained. (It is likely that we will have to combine African-Americans with whites in this analysis due to issues of power).

Limitations

A limitation of this analysis is the lack of information on physical fitness and reliance on self-report levels of physical activity, which may dilute any relationship with incident AF. Moreover, misclassification may exist in outcome ascertainment although preliminary analyses suggest a positive predictive value of ~90% for AF diagnosis done through hospital discharge codes, implying a limited amount of misclassification. Additional limitations include residual confounding and misclassification of the exposure at baseline and due to their time-varying nature.

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

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

8.c. If yes, is the author aware that the participants with RES_DNA = 'not for profit' restriction must be excluded if the data are used by a for profit group?
____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

_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)?

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

X A. primarily the result of an ancillary study (list number* 2006.15 and 2008.12)

___ 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/

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

Wanahita N, Messerli FH, Bangalore S, Gami AS, Somers VK, Steinberg JS. Atrial fibrillation and obesity--results of a meta-analysis. Am Heart J. 2008 Feb;155(2):310-5

Fogelholm M. Physical activity, fitness and fatness: relations to mortality, morbidity and disease risk factors. A systematic review. Obes Rev. 2010 Mar;11(3):202-21

Grundvold I, Skretteberg PT, Liestøl K, Gjesdal K, Erikssen G, Kjeldsen SE, Arnesen H, Erikssen J, Bodegard J. Importance of physical fitness on predictive effect of body mass index and weight gain on incident atrial fibrillation in healthy middle-age men. Am J Cardiol. 2012 Aug 1;110(3):425-32

Table 1. Baseline characteristics

Variable	Blacks		Whites	
	Men	Women	Men	Women
Age, years				
Study site, n (%)				
Forsyth County				
Jackson				
Minneapolis suburbs				
Washington County				
< High school education, n (%)				
< $35,000 per year income, n (%)				
Body height (cm)				
Body weight (kg)				
Body mass index (kg/m2)				
Mean weight change during follow-up				
Physical activity (mins/per week)				
Prior cardiovascular disease				
Alcohol consumption				
Cigarette smoking				
Systolic blood pressure				
Blood pressure lowering medication				
Diabetes				
Diabetes lowering medication				

Table 2 Association between overweight and obesity with risk of AF

	No of AF cases	Model 1			p-for trend	Model 2			p-for trend
		Per unit increase	Overweight	Obese		Per unit increase	Overweight	Obese	
Black men									
Black women									
White men									
White women									

Ref group = normal weight; Model 1 = adjusted for age, study site, education and income; Model 2 = Model 1 + prior CVD, height, cigarette smoking, physical activity and alcohol consumption. (*We may also include a final model that includes SBP and diabetes and association medications but given that these variables are on the causal pathway between obesity and AF this could be considered over-adjustment).

Table 3 Association between weight change during follow-up with risk of AF

	No of AF cases	Model 1			p-for trend	Model 2			p-for trend
		0-4.9 kg	5- 9.9 kg	$\geq$ 10 kg		0-4.9 kg	5- 9.9 kg	$\geq$ 10 kg	
Black men									
Black women									
White men									
White women									

Ref group = 0-4.9 kg group; Model 1 = adjusted for age, study site, education and income; Model 2 = Model 1 + prior CVD, height, cigarette smoking, physical activity and alcohol consumption.

Table 4. Impact of level of physical activity on the association between overweight and obesity with risk of AF in men and women

	Level of PA	Model 1			p-for trend	Model 2			p-for trend
		Normal weight	Overweight	Obese		Normal weight	Overweight	Obese	
Men	Poor	Ref							
	Intermediate	Ref							
	Ideal	Ref							
Women	Poor	Ref							
	Intermediate	Ref							
	Ideal	Ref							

Ref group = normal weight; Model 1 = adjusted for age, race, study site, education and income; Model 2 = Model 1 + prior CVD, height, cigarette smoking, and alcohol consumption

Table 5. Impact of level of physical activity on the association between weight change during follow up with risk of AF in men and women

	Level of PA	Model 1			p-for trend	Model 2			p-for trend
		0-4.9kg	5-9.9 kg	≥10kg		0-4.9kg	5-9.9 kg	≥10kg	
Men	Poor	Ref							
	Intermediate	Ref							
	Ideal	Ref							
Women	Poor	Ref							
	Intermediate	Ref							
	Ideal	Ref							

Ref group = 0-4.9kg weight change; Model 1 = adjusted for age, race, study site, education and income; Model 2 = Model 1 + prior CVD, height, cigarette smoking, and alcohol consumption