ARIC Manuscript Proposal # 3108

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1.a. Full Title: Predictors of recurrent CVD current events

b. Abbreviated Title (Length 26 characters): Recurrent CVD predictors

2. Writing Group:
   Writing group members: Kimberly Truesdale, June Stevens, Jianwen Cai, Salim Virani

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

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3. Timeline: This work is a component of an R21 grant proposal that will be submitted in February of 2018. Dataset preparation and analysis will start immediately upon funding. If the R21 not funded, we will seek other support for this work. We plan to complete the analysis and manuscript before the manuscript approval period expires.
4. **Rationale:**

In the United States, each year about 580,000 adults have their first myocardial infarction (MI) and 610,000 adults have their first stroke\(^1\). The vast majority of these events are non-fatal, however, adults with a history of MI or stroke are more likely to have a recurrent MI or stroke event than adults without a history of MI or stroke to have their first MI or stroke event. This increased risk is an important public health issue given the estimated 7.6 million adults with history of myocardial infarction and 6.6 million adults with history of stroke\(^2\). It is also important to recognize and examine the health disparity in recurrent CVD events since a larger percentage of African American men and women who had their first MI between 45 to 64 years of age have a recurrent MI (fatal and non-fatal) within 5 years (22% and 32%, respectively) compared to White men and women (11% and 15%, respectively)\(^1\).

All adults with a history of MI or stroke are at increased risk for a recurrent event; however, everyone will not have a recurrent event. Therefore, it is important to identify risk factors for recurrent events, especially modifiable risk factors. Based on a recurrent risk score developed from the Framingham Study (Framingham Recurrent Risk Score), the key factors for predicting a recurrent event are age, total cholesterol, HDL cholesterol, diabetes status, systolic blood pressure (women only) and cigarette smoking (women only)\(^3\). BMI was considered but not selected as predictor of recurrent events.

In contrast, Wilson et al. examined over 33,000 adults from the Reduction of Atherothrombosis for Continued Health (REACH) Registry and found BMI <20 kg/m\(^2\) were increased risk for both recurrent CVD event and CVD death\(^4\). Whereas, Rea et al. found that adults with class I (BMI: 30-34.9 kg/m\(^2\)) or class II (BMI: 35-48 kg/m\(^2\)) obesity were at increased risk for recurrent MI compared to adults with healthy weight (BMI: 16-24.9 kg/m\(^2\))\(^5\). Baseline BMI was also included in the prediction model for cardiovascular mortality but not non-fatal MI or the combined end point of cardiovascular mortality, non-fatal MI and resuscitated cardiac arrest in the EURopean trial ON reduction of cardiac events with Perindopril in stable coronary Artery disease (EUROPA) study\(^6\). The inconclusive findings of BMI maybe related to the non-linear risk for BMI and/or different associations with non-fatal versus fatal CVD events.

Associations between other measures of body shape and recurrent CVD events have not been as extensively studied. Dagenais et al. examined the association between BMI, waist circumference and waist-to-hip (WHR) ratio with all-cause mortality, CVD mortality, recurrent MI, and recurrent stroke in adults from the Heart Outcomes Prevention Evaluation (HOPE) study\(^7\). They found waist and WHR were better predictors than BMI for all-cause mortality and CVD morality, equally predictive for MI. None of the measures were predictive of stroke. Asgari et al. examined the relationship between BMI and recurrent CVD in the Tehran lipid and glucose study (TLGS) and found the higher incidence of recurrent CVD in the normal weight adults compared to overweight and obese adults\(^8\). The authors did not find a significant difference between the weight status groups after adjusting for age and gender. However, the addition of waist circumference to the models, resulted in significant differences between normal weight and overweight and obese adults (overweight and obesity were protective).

Although BMI and percent body fat are highly correlated, everyone with a high BMI (obese) does not have excess fat mass and vice versa. One of the theories behind the Obesity Paradox, a
phenomena in which obese adults are a lower risk than normal weight adults, is that the muscle mass may differ among obese subjects. A recent review by Wannamethee and Atkins highlighted the importance of looking at both obesity and body composition in aging populations\(^9\). This is especially true since some adults could experience changes in body composition (loss of muscle mass and increase in fat mass) with no change in BMI. The authors concluded “to fully understand the effect of obesity on mortality in the elderly it is important to take muscle mass into account”\(^9\). While their conclusion focuses on mortality, it is reasonable that it also applies to recurrent CVD events. However, little research has been conducted related to sarcopenia, age related loss of muscle mass and recurrent events. Atkins et al. used data from the British Regional Heart Study to examine associations between four mutually exclusive sarcopenic obesity groups – optimal (not obese or sarcopenic), sarcopenic (but not obese), obese (but not sarcopenic) and sarcopenic obese and risk of CVD events and CVD mortality\(^10\). Atkins et al. found no significant difference between the optimal group and the other 3 groups for CVD events. Sarcopenic adults and obese adults but not sarcopenic obese adults were at increased risk for CVD mortality after adjusting for age, smoking, alcohol, occupational social class and physical activity. After additional adjustments for prevalent stroke, prevalent MI and CVD risk factors only sarcopenic adults remained at increased risk for CVD mortality. These findings underscore the importance of looking at body composition and BMI.

In summary, given increasing number of adults with a history of MI or stroke, it is of public health and clinical importance to identify the adults with the highest probability for having a recurrent event based on collection of risk factors. The Framingham Recurrent Risk Score is comprised 7 and 5 predictive variables in women and men, respectively that have been shown in other studies to be predictive of recurrent CVD events. The ARIC study provides an opportunity to examine the Framingham Recurrent Risk Score in White and African American men and women. Although BMI was not identified as a significant predictor in the Framingham study, it is possible that measures of body composition may improve the prediction of recurrent MI or stroke events.

5. Main Hypothesis/Study Questions:

1. To determine and compare the associations between obesity related measures post non-fatal coronary heart disease (CHD) or stroke event and recurrent events.

   We hypothesize the BMI relationship will be U-shaped, with thinner (BMI <20 kg/m\(^2\)) and heavier (BMI ≥30 kg/m\(^2\)) adults at increased rate of recurrent CVD events.

   We hypothesize that fat free mass will be independently associated with recurrent CVD events and it will be more predictive than BMI at predicting recurrent events.

2. To determine if the addition of obesity related measures will improve the performance of the Framingham Recurrent Risk Score for prediction of a recurrent CVD events.

   We hypothesize the addition of fat free mass to the Framingham Recurrent Risk Score model will the model as assessed by the concordance index (c-index).

   We hypothesize the addition of BMI (linear and quadratic terms) to the Framingham Recurrent Risk Score model will improve the model as assessed by the c-index.
3. To examine sex and race/ethnic differences in the associations between obesity related measures and recurrent CVD events after controlling for the Framingham Recurrent Risk Score.

We hypothesize that in models that include the Framingham Recurrent Risk Score, there will be stronger associations with percent fat free mass in Whites compared to Blacks and in females compared to males for the outcome of recurrent CVD event.

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).

Outcome
The outcome of interest for this study is recurrent coronary heart disease (CHD) or stroke. We will define coronary heart disease as definite or probable myocardial infarction. The recurrent event will be defined as the next recorded CHD or stroke event. Time to recurrent event is the number of years from post-event weight (T2) to date of recurrent CHD or stroke event or censoring date (See diagram below).

Main exposure
The exposure variable of interest for the proposed study is Framingham Recurrent Risk Score\(^3\). The components of this score are age, total cholesterol, HDL cholesterol, diabetes status, smoking status (women only) and systolic blood pressure (women only). The score will be calculated at the ARIC visit immediately following the incident MI/stroke event (T2).

At T2, percent body fat will be calculated based on equations developed by Stevens et al\(^{11}\). Percent fat free mass will be calculated as 100 – percent body fat.

\[
\text{Score, } \%\text{FFM} = \frac{E_2 - E_1}{T_2 - T_1}
\]

Covariates
The following variables at T2 will be examined: age, ethnicity, gender, center, education, BMI, waist circumference, drinking status, physical activity, and dietary intakes.

Exclusions
Non-African American or White participants
African American participants from the Minnesota or Maryland centers
Participants with prevalent CHD/stroke at baseline
Participants who did not have a CHD/stroke event or had incident CHD/stroke event
Participants who had recurrent CHD/stroke event before the next ARIC visit

Brief Summary Data Analysis
We will use the Cox regression model with time dependent covariates to calculate hazard ratios and the additive hazard model to calculate risk differences. Weight will be evaluated as a
categorical variable in some models and as a continuous variable in others. Following previous weight analysis conducted by our group in ARIC, we will examine spline models and if appropriate, reduce to quadratic or linear models. We will use the Harrell’s concordance index (c-index) to estimate how well the models performed and the Somer’s D statistic to compare the different models.

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.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)?

To our knowledge, only two published ARIC manuscripts have examined recurrent CVD.

ARIC 731: Wattanakit et al. examined the association between risk factors for cardiovascular disease and recurrent CVD using data from the baseline ARIC visit\(^\text{12}\). The authors examined the 766 adults who had prevalent CVD at baseline, and found that baseline levels of lipoprotein (a), white blood cells, fibrinogen, and creatine were associated with recurrent CVD events. They did not find an association with baseline waist-to-hip ratio and baseline BMI was not examined.

ARIC 818: Lee et al. compared the relative risk of having an MI event between adults with and without history of diabetes and MI at baseline\(^\text{13}\). They found non-diabetic adults with a history of MI had increased risk of having an MI event compared to diabetic adults without a history of MI. These two groups had similar risk of having a stroke event.
The proposed study differs from the previously published studies in that the study population is ARIC participants who had an incident CVD event after the baseline visit and our main hypotheses examine if adding percent fat free mass to the Framingham Recurrent Risk Score improves the prediction of recurrent MI and stroke.

We identified 7 additional ARIC proposals that examined recurrent MI or stroke events (outcome of interest) but none of them looked at BMI, body composition or weight change in relation to recurrent events.

MS #161  Risk of recurrent coronary heart disease in men and women

MS #1226  Psychosocial distress and risk for recurrent adverse cardiac events: The Atherosclerosis Risk in Communities (ARIC) Study

MS #1327  Association between initial etiological stroke subtype and recurrent etiological stroke subtype and vascular event type.

MS #1527  Joint modeling of longitudinal data and recurrent events in the presence of informative terminal event

MS #1757  The association of high sensitivity troponin with heart failure, mortality and recurrent coronary heart disease (CHD) in individuals with prevalent CHD

MS #2275  Semiparametric Regression Analysis of Current Status Data for Recurrent Events

MS #2773  Risk of recurrent ischemic complications in myocardial infarction (MI) and peripheral arterial disease (PAD)

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

References