1.a. Full Title: Body mass index (BMI) change after incident cardiovascular disease (CVD) event and recurrent CVD event

b. Abbreviated Title (Length 26 characters): BMI change and recurrent CVD

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)\(^1\).

Adults with a history of myocardial infarction and stroke often have additional co-morbidities (e.g. type 2 diabetes, hypertension) that increase their risk of a recurrent event \(^3\)\(^5\). Lifestyle modifications (e.g. improved diet, more physical activity, smoking cessation, moderate drinking) are often recommended to improve overall health and the reduce risk of recurrence. Weight change after a cardiovascular disease (CVD) event could be a result of these modifications or weight reduction could be unintentional and an indicator of declining health.

Numerous studies have shown that both body mass index (BMI) and weight change are associated with incident cardiovascular (CVD) events. Our research group found using data from the Atherosclerosis Risk in Communities (ARIC) study that a long-term weight gain between early and middle adulthood was associated with elevated incident CHD and stroke risk \(^6\). Interestingly, a short-term weight loss of >3% elevated immediate risk of incident CHD and stroke. This study suggests that such a weight loss, likely to be unintentional, could be used as a clinical marker or warning sign for cardiovascular episodes which would allow early detection and prevention of CVD events. We hypothesize that similar phenomena could occur with recurrent CVD events, and may be even more exaggerated.

The literature examining BMI, body composition and weight change is much smaller and inconclusive for recurrent compared to first CVD events. Asgari et al. examined the relationship between BMI and recurrent CVD in the Tehran lipid and glucose study (TLGS) and did not find a significant difference between the weight status groups after adjusting for age and gender\(^7\). 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). After also adding smoking, aspirin use and diabetes medication, overweight remained protective, but there was no significant difference between normal weight and obese adults. The authors concluded that “further studies with different ways to identify obesity are needed to fully understand the impacts responsible for the lower cardiovascular events and mortality in overweight/obese patients”. This study did not examine weight change, so it is possible that adults in the normal weight group were previously overweight and obese and had experienced unintentional weight loss due to illness or intentional weigh loss due to lifestyle modification.

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\(^8\). In contrast to the findings from Asgari et al.\(^7\), the authors in this study found higher BMI was associated with higher rates of recurrent MI, although associations were not found for recurrent stroke, all-cause mortality or CVD mortality. A large waist circumference and WHR were associated with higher rates of recurrent CVD, all-cause mortality, and CVD mortality but not stroke. These results illustrate the need to examine both BMI and measures of body shape.

Lopez-Jimenez et al. examined baseline BMI and 6 month weight change in the Enhancing Recovery in Coronary Heart Disease (ENRICH-D) trial\(^9\). The authors found that in adults with history of MI, underweight (BMI <20) were more likely to die compared to normal weight adults, but overweight and obese adults had rates similar to normal weight adults. Obese adults had lower rates of cardiovascular mortality compared to normal weight adults. After adjusting for baseline BMI and other covariates, the authors found that weight losers were at increased risk for all-cause mortality, cardiovascular mortality and non-fatal MI plus all-cause mortality compared to weight maintenance. Weight gain was not associated with increased risk. The authors did not measure the intentionality of the weight loss but they assumed “weight loss was unintentional and may be a consequence more of non-cardiac comorbidities”.

In summary, the high survival rates of the first MI or stroke has created a large population of adults at risk for a recurrent MI or stroke event. The literature on the impact of changes in weight and body shape on having a recurrent event is sparse, especially in relation to the current weight status and intentionality of weight loss. The ARIC study provides an excellent opportunity to examine both BMI and body shape (i.e. waist circumference, hip circumference, WHR) and percent body fat (or lean body mass). We can also examine change in weight/BMI post MI/stroke event. This proposed study can help fill some literature gaps:

- Are changes in body shape more informative in predicting risk of recurrence than changes in weight?
- What weight status groups are at risk for recurrent MI/stroke event? Will the findings support the Obesity Paradox, a phenomena in which obesity is protective for certain health outcomes and better survival rates. Whereas, underweight or normal weight adults experience more detrimental health outcomes and higher mortality. Are normal weight adults at higher risk for recurrent MI/stroke event after removing adults who lost weight without dieting (i.e. unintentional) from the referent group?
- Can weight maintenance reduce risk of recurrent MI/stroke event in diabetic adults? Is the weight change-recurrent event relationship different in adults diagnosed with diabetes before first CVD event versus after first CVD event?
- Does weight change post-incident MI provide any insight into the recurrent MI/stroke health disparity between Whites and African Americans?
- Does lean body mass predict recurrent events more strongly than BMI and is the effect different in Whites and African Americans?
5. Main Hypothesis/Study Questions:

1. To determine if changes in obesity related measures after the first (incident) non-fatal coronary heart disease (CHD) or stroke event are associated with the rate of a recurrent CHD or stroke event.
   We hypothesize that adults who maintained their body weight (i.e. BMI) will have the lowest rate of recurrence. Also, adults who lost weight with dieting will have lower rate of recurrence than adults who lost weight without dieting.
   We hypothesize the changes in waist circumference, waist-to-hip ratio and percent fat free mass body mass will be small; therefore, these change comparisons will be exploratory.

2. To determine if the post incident CHD/stroke event weight change and recurrent CHD or stroke event relationship differs by gender and race/ethnicity.
   We hypothesize that African American men and women who experience weight gain will have a greater risk for a recurrent event than White men and women.

3. To determine if the post incident CHD/stroke event weight change and recurrent CHD or stroke event relationship differs by diabetes status and when diagnosed.
   We hypothesize that post incident CHD or stroke event weight change and recurrent event relationship will differ based on diabetes status and when diagnosed. Adults with diabetes diagnosed prior to first CHD/stroke event and adults without diabetes will have similar weight change-recurrent event relationship. However, adults with diabetes diagnosed after first CHD/stroke event who experience weight loss without dieting will have a greater risk for a recurrent event than adults without diabetes who experience weight loss without dieting.

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 end of weight change interval (T3) to date of recurrent CHD or stroke event or censoring date (See diagram below).

Main exposure
The main exposure variable of interest for the proposed study is percent weight change after the first non-fatal CHD/stroke event. This will be calculated as follows:
% weight change_{T2,T3} = ((weight_{T3} - weight_{T2}) / (weight_{T2})) * 100
where, T2 = visit number after the incident CHD/stroke event (2\textsuperscript{nd} or 3\textsuperscript{rd} visit )
T3 = next visit (~3 years later: 3\textsuperscript{rd} or 4\textsuperscript{th} visit )
We will examine percent weight change as a continuous variable and also as a categorical variable (weight losers, weight gainers and weight maintainers (+/- 3.0%, referent)). For the categorical analysis, we will stratify weight losers by intentionality based on their self-reported response to “Are you currently on weight loss diet?”.

Additional exploratory main exposures that will be examined are waist circumference, hip circumference, WHR, percent body fat and percent fat free mass. Percent body fat will be calculated based on equations developed by Stevens et. al.\(^{(10)}\) Percent fat free mass will be calculated as 100 – percent body fat.

Covariates
The following variables will be included in models: age, ethnicity, gender, center, and education. Additional variables at Time 3 will be examined in selected models: BMI, smoking status, drinking status, diabetes status, physical activity, and dietary in takes

Exclusions
Non-African American or White participants
African American participants from the Minnesota or Maryland centers
Participants with prevalent CHD/stroke at baseline
Participants with no history of CHD or stroke

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 change will be evaluated as a categorical variable in some models and as a continuous variable in others. Following previous weight change analysis conducted by our group in ARIC, we will examine spline models and if appropriate, reduce to quadratic or linear 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(11). 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(12). 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 the associations of BMI, body composition and weight change with 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 ___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 at http://www.cscu.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.cscu.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