ARIC Manuscript Proposal #

PC Reviewed: 6/10/14	**Status: A**	**Priority: 2**
SC Reviewed: _____	**Status: _____**	**Priority: ____**

1.a. Full Title: The Relative Associations of Obesity With Subtypes of Cardiovascular Disease: The Atherosclerosis Risk in Communities (ARIC) Study

b. Abbreviated Title (Length 26 characters): Obesity and Forms of CVD

2. Writing Group: Chiadi E. Ndumele; Kunihiro Matsushita; Mariana Lazo; Natalie A. Bello; Roger S. Blumenthal; Gary Gerstenblith; Vijay Nambi; Christie M. Ballantyne; Scott Solomon; Elizabeth Selvin; Aaron Folsom; Josef Coresh; others welcome

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

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3. Timeline: We aim to submit this manuscript to the ARIC publications committee <6 months from the date of approval of this manuscript proposal.

4. Rationale:

Obesity is a common risk factor for various subtypes of cardiovascular disease (CVD), including coronary heart disease (CHD), heart failure (HF) and stroke(1-4). However, there are divergent pathways by which obesity leads to different forms of CVD. For example, hypertension, insulin resistance and dyslipidemia are some of the primary mechanisms by which obesity increases the risk of CHD(5, 6). In contrast, elevated metabolic demand, abnormal cardiac remodeling and toxic effects of obesity on the myocardium represent important pathways, beyond traditional risk factors, by which obesity leads to HF(7, 8).

Differences in the mechanisms by which obesity leads to various forms of CVD may translate into differences in the strength of associations among obesity and subtypes of CVD. Understanding differences in the associations among obesity and various subtypes of CVD could have important clinical implications, particularly with regard to guiding efforts to manage CVD risk in individuals with obesity and overweight. Furthermore, the extent to which traditional risk factors explain the cardiovascular risk associated with obesity may differ for distinct subtypes of CVD. Subtypes of CVD for which the risk association with obesity is largely unexplained by traditional risk factors may indicate relationships for which further investigation is needed to elucidate pathways and devise preventive strategies. Despite the clinical importance of understanding obesity-associated CVD risk associations, there have been limited prospective analyses to date comparing the relationships of obesity with different subtypes of CVD, while also examining the contribution of traditional risk factors to the risk associations.

In this prospective, community-based analysis of middle aged men and women in the Atherosclerosis Risk in Communities (ARIC) study, we will evaluate the relative associations of obesity with CHD, HF, stroke and all-cause mortality and the degree of their attenuation accounted for by traditional risk factors. We will also assess several non-traditional risk factors that may mediate the association of obesity and CVD subtypes.

5. Main Hypothesis/Study Questions:

Aims:

1) To evaluate and compare the relative associations of higher BMI with different subtypes of incident CVD

2) To evaluate and compare the extent to which the associations of higher BMI with different subtypes of incident CVD are explained by traditional and non-traditional cardiovascular risk factors

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 examine and compare the prospective associations of higher BMI with incident CHD, CHD mortality, HF, stroke and total mortality. The baseline for this analysis will be ARIC Visit 2 (1990-1992).

Exposures: The exposure of interest will be BMI (height in kilograms divided by meters squared), measured at ARIC Visit 2. BMI will be categorized as normal (BMI 18.5-24.9 kg/m^2), overweight (25-29.9 kg/m^2), obese (30-34.9 kg/m^2) and severely obese (>35 kg/m^2). BMI will also be modeled as a continuous variable (risk per 5 kg/m^2 higher BMI). We will also use waist circumference as a secondary measure of adiposity.

Outcomes: The primary outcomes will be incident CHD, fatal CHD, HF, stroke and total mortality occurring after Visit 2 through January 1, 2012 (or most recent follow-up available). Incident CHD will be defined as definite or probable nonfatal myocardial infarction or fatal CHD. Incident HF will be defined as a HF-related hospitalization or death. Incident stroke will be defined as a definite or probable stroke of either ischemic or hemorrhagic etiology.

Exclusions: We will exclude the small number of participants at Visit 2 who are not black or white, and those participants missing covariates of interest at baseline. We will also exclude participants with prevalent CVD at baseline.

Covariates: Age, sex, race, SES, smoking status, SBP, anti-hypertension medication use, diabetes, LDL-cholesterol, HDL-cholesterol, triglycerides, alcohol use, estimated GFR, hs-CRP, hs-cTnT and NT-proBNP will be assessed at Visit 2. Smoking status, hypertension, diabetes and LDL-cholesterol will also be evaluated as time varying covariates.

Main Analyses: We will evaluate the prospective association of obesity with different subtypes of CVD, and compare the coefficients for the different risk associations using methods that account for correlations in error terms for multiple outcomes within a given subject.

1) We will perform univariate comparisons of baseline characteristics across BMI categories.

2) We will construct Cox proportional hazards models to estimate the hazard ratios and related 95% confidence intervals for each CVD outcome that are associated with higher BMI. We will construct models with sequential levels of adjustment as follows:

    - Model 1: age-adjusted
    - Model 2: adjusted for Model 1 + gender, race, SES, alcohol intake and smoking status

- Model 3: adjusted for Model 2 + diabetes, SBP, anti-hypertension medication use, LDL-C, HDL-C, triglycerides, and estimated GFR (all measured at Visit 2)
- Model 4: adjusted for Model 3 + non-traditional risk factors, as follows:
    - Model 4a: adjusted for Model 3 + hs-CRP
    - Model 4b: adjusted for Model 3 + NT-proBNP
    - Model 4c: adjusted for Model 3 + hs-cTnT
    - Model 4d: adjusted for Model 3 + hs-CRP, NT-proBNP and hs-cTnT

3) We will compare coefficients for the risk associations between obesity and subtypes of CVD, using seemingly unrelated regression to account for correlations in error terms

4) We will construct Poisson models to estimate age- and multivariable- adjusted incidence rates for each CVD outcome that are associated with higher BMI, using models with successive levels of adjustment, as described above.

5) In assessing absolute risk with Poisson models, we will perform additional analyses using competing risk regression to account for competing events (e.g. death from other causes) that may prevent the development of the outcomes of interest.

6) We will perform analyses stratified by race and gender, and if differences are observed we will test for statistically significant interactions between these demographic variables and BMI on the outcomes of interest

Sensitivity Analysis:

- In sensitivity analyses, we will adjust for smoking status, hypertension, diabetes and LDL-cholesterol as time varying covariates
- In additional sensitivity analyses, we will consider restricting events to those occurring from 2005 onwards (when HF event adjudication began)

Limitations:

- There is the likelihood for some residual confounding in our efforts to evaluate the relationship between higher BMI category and subtypes of CVD
- The use of hospitalization and discharge codes for the diagnosis of incident HF may have resulted in some misclassification

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

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)?

MS #815: The associations between weight maintenance and metabolic risk factors for cardiovascular disease

MS # 683: Obesity and concomitant risk for cardiovascular disease: implications of obesity guidelines

MS #2025: Obesity and Subclinical Myocardial Injury: The Atherosclerosis Risk in Communities (ARIC) Study

MS #1456: Measures of obesity in predicting different CVD outcomes by race and sex in the ARIC study

ARIC Manuscripts:

Folsom et al. Am J Epidemiol 1998;148:1187-94.

Chambless et al. J Clin Epid 2003; 56:880-90.

Folsom et al. Diabetes Care 1999;22:1077-83

Yatsuya et al. Stroke 2010;41:417-425.

Chambless et al. Am J Epidemiol 2004;160:259-69.

Stevens J et al. Am J Clin Nutr 2002;75:986-992.

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

___ A. primarily the result of an ancillary study (list number* __)

X B. primarily based on ARIC data with ancillary data playing a minor role (usually control variables; list number(s)* 2009.16)

*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.

Reference List

1. Jousilahti P, Tuomilehto J, Vartiainen E, Pekkanen J, Puska P. Body weight, cardiovascular risk factors, and coronary mortality. 15-year follow-up of middle-aged men and women in eastern Finland. Circulation 1996; 93:1372-9.

2. Kenchaiah S, Evans JC, Levy D, et al. Obesity and the risk of heart failure. N Engl J Med 2002; 347:305-13.

3. Wong CY, O'Moore-Sullivan T, Leano R, Byrne N, Beller E, Marwick TH. Alterations of left ventricular myocardial characteristics associated with obesity. Circulation 2004; 110:3081-7.

4. Yatsuya H, Folsom AR, Yamagishi K, North KE, Brancati FL, Stevens J. Race- and sex-specific associations of obesity measures with ischemic stroke incidence in the Atherosclerosis Risk in Communities (ARIC) study. Stroke 2010; 41:417-25.

5. Poirier P, Giles TD, Bray GA, et al. Obesity and cardiovascular disease: pathophysiology, evaluation, and effect of weight loss: an update of the 1997 American Heart Association Scientific Statement on Obesity and Heart Disease from the Obesity Committee of the Council on Nutrition, Physical Activity, and Metabolism. Circulation 2006; 113:898-918.

6. Lavie CJ, Milani RV, Ventura HO. Obesity and cardiovascular disease: risk factor, paradox, and impact of weight loss. J Am Coll Cardiol 2009; 53:1925-32.

7. Lavie CJ, Alpert MA, Arena R, Mehra MR, Milani RV, Ventura HO. Impact of obesity and the obesity paradox on prevalence and prognosis in heart failure. JACC Heart Fail 2013; 1:93-102.

8. Abel ED, Litwin SE, Sweeney G. Cardiac remodeling in obesity. Physiol Rev 2008; 88:389-419.