ARIC Manuscript Proposal #1456

PC Reviewed: 12/9/ 08 **Status: A** **Priority: 2**

SC Reviewed:_____ **Status:_____** **Priority:_____**

1 **a. Full Title**: Measures of obesity in predicting different CVD outcomes by race and sex in the ARIC study

b. Abbreviated Title: Measures of obesity and CVD in ARIC

2 **Writing Group**:

Writing group members:

Hiroshi Yatsuya, Aaron Folsom, other co-authors welcome

I, the first author, confirm that all the coauthors have given their approval for this manuscript proposal. HY

First author: Hiroshi Yatsuya

Address: Division of Epidemiology and Community Health
1300 S. Second Street, Suite 300
Minneapolis, MN 55454

Phone: 612-625-6730 Fax: 612-624-0315

E-mail: yatsu002@umn.edu

ARIC author to be contacted if there are questions about the manuscript and the first author does not respond or cannot be located (this must be an ARIC investigator).

Name: **Aaron R. Folsom**

Address: Division of Epidemiology and Community Health
1300 S. Second Street, Suite 300
Minneapolis, MN 55454

Phone: 612-626-8862 Fax: 612-624-0315

E-mail: folso001@umn.edu

3 **Timeline**: Analysis will begin immediately, once the proposal is accepted, using surveillance datafiles through 2005. A draft will be prepared within four months and will be submitted to the Publications committee by 6 months.

4 **Rationale**:

There is no doubt that obesity is a serious medical and public health problem worldwide. A number of studies have been performed to relate within-population variations of body habitus and subsequent disease occurrence,[1, 2] although obesity trials with hard endpoints such as mortality or CVD incidence have been and

will still be scarce[3].

At present, uncertainties admittedly exist regarding which measurements at which cut-off points best predict cardiovascular diseases onset[4-7]. Furthermore, possible differences in the associations exist according to population characteristics, such as race, sex, age, disease history, follow-up duration, or type of endpoint, which makes the issue more complex[8-15].

From different perspective, however, knowing factors that may strengthen or weaken the effect of obesity on CVD incidence would be clinically useful. Such information might be used to efficiently provide public health messages to people who would benefit most from obesity treatment, or public health policy by estimating population attributable fraction for the each specific group.

We will attempt to address some of these issues in the ARIC Study. Compared with ARIC's previous report[1], we now have longer follow-up, outcomes like sudden cardiac death and ischemic stroke, and detailed stratified analyses will be possible.

It has been reported that possible effects of obesity on disease outcomes could more clearly be seen by excluding early events in the cohort in order to eliminate the confounding of occult diseases that might have present in lean subjects[8, 10]. We therefore will explore analysis for events after 10 years of follow-up.

5 **Main Hypothesis/Study Questions**:

Examine the associations of obesity-related measures with different (following) CVD endpoints

- Sudden cardiac death
- Stroke (ischemic stroke)
- CHD

Effect modification by the participants' baseline status

- By sex
- By race
- By age category
- By Framingham risk score
- By smoking status
- By past history of CHD

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 methodological limitations or challenges if present).

Study design: A prospective cohort study

Dependent variables: incident CHD (measured through 2005), incident ischemic stroke (measured through 2005–there will likely to be too few hemorrhagic strokes for analysis), sudden cardiac death, all CVD

Independent variable: BMI, waist, hip, waist/hip, waist/height

Covariates: age, smoking status, alcohol drinking, physical activity, family history score of CHD, study center

Modeling:

1. Assessing risk associated with the following categories of BMI and other obesity-related variables by COX proportional hazards model with time dependent variables of follow-up weight or other obesity-related variables within each race-, sex-group (categorical analyses).

   BMI: <18.5, 18.5 to <21.0, 21.0 to <23.5, 23.5 to <25.0, 25.0 to <26.5, 26.5 to <28.0, 28.0 to <30.0, 30.0 to <35.0, and 35.0 or more (reference group, 21.0 to <23.5)

   Other obesity-related variables (waist, hip, waist/hip, waist/height): decile of each variable
2. The relationships will also be evaluated with the use of nonparametric restricted cubic splines, with 4 knots defined at the 5th, 25th, 75th, and 95th percentiles of the anthropometric measurements within each race-, sex-group[16]. The reference point for BMI is the midpoint of the reference group (21.0 to <23.5) from the categorical analysis. The reference point for waist and hip circumference, waist/hip and waist/height are the sex-specific medians of these variables.
3. Estimating risks according to the NIH classification table of overweight and obesity by BMI, waist circumference, and associated disease risk [17].

   The reference group is normal weight and waist circumference 102 cm or less in men and 88 cm or less in women.

Table 4. Classification of Overweight and Obesity by Body Mass Index (BMI), Waist Circumference, and Associated Disease Risk

		Disease Risk* Relative to Normal Weight and Waist Circumference	
	BMI, kg/m²	Men, ≤102 cm; Women, ≤88 cm	Men, >102 cm; Women, >88 cm
Underweight	<18.5	. . .	. . .
Normal†	18.5-24.9	. . .	. . .
Overweight	25.0-29.9	Increased	High
Obesity, class			
I	30.0-34.9	High	Very high
II	35.0-39.9	Very high	Very high
III (extreme obesity)	≥40	Extremely high	Extremely high

** Disease risk for type 2 diabetes, hypertension, and cardiovascular disease. Ellipses indicate that no risk at these levels of BMI was assigned.*

† Increased waist circumference can also be a marker for increased risk even in persons of normal weight.

Arch Intern Med 1998; 158: 1855-67.

Analysis plan:

Inclusion/Exclusion: inclusion: all ARIC visit 1 participants free of cancer (not including skin cancer) or type 1 diabetes (or those with current insulin use). Except for the stratified analysis by past history of CHD, participants with CVD at visit 1 will also be excluded.

7 Will the data be used for non-CVD analysis in this manuscript?

_____Yes __x__No

8 a. Will the DNA data be used in this manuscript?

_____Yes __x__No

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”?

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

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.

___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# 343A Obesity and CHD; Body mass index, waist/hip ratio, and coronary heart disease incidence in African-Americans and whites

The paper evaluated relative importance of the obesity measurements by revealing that once significantly associated variable of BMI was no more significant after waist/hip ratio was included in the model in relation to CVD incidence during an average of 6.2 years of follow-up (Folsom AR, *Am J Epidemiol*, 1998) [1].

Others: References 1, 12 and 18 below [18]

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

_____Yes ___x___No

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

1. Folsom AR, Stevens J, Schreiner PJ, McGovern PG. Body mass index, waist/hip ratio, and coronary heart disease incidence in African Americans and whites. Atherosclerosis Risk in Communities Study Investigators. Am J Epidemiol 1998;148:1187-94.
2. Gelber RP, Gaziano JM, Orav EJ, Manson JE, Buring JE, Kurth T. Measures of obesity and cardiovascular risk among men and women. J Am Coll Cardiol 2008;52:605-15.
3. Curioni C, Andre C, Veras R. Weight reduction for primary prevention of stroke in adults with overweight or obesity. Cochrane Database Syst Rev 2006:CD006062.
4. Stevens J. BMI and mortality: sorting through the data to find the public health message. Int J Obes (Lond) 2008;32:727-9.
5. Litwin SE. Which measures of obesity best predict cardiovascular risk? J Am Coll Cardiol 2008;52:616-9.
6. Stevens J, McClain JE, Truesdale KP. Selection of measures in epidemiologic studies of the consequences

of obesity. Int J Obes (Lond) 2008;32 Suppl 3:S60-6.

7. Stevens J, Nowicki EM. Body mass index and mortality in asian populations: implications for obesity cut-points. Nutr Rev 2003;61:104-7.
8. Moore SC, Mayne ST, Graubard BI, et al. Past body mass index and risk of mortality among women. Int J Obes (Lond) 2008;32:730-9.
9. Sumner A, Ricks M, Sen S, Frempong B. How Current Guidelines for Obesity Underestimate Risk in Certain Ethnicities and Overestimate Risk in Others. Current Cardiovascular Risk Reports 2007;1:97-101.
10. Dyer AR, Stamler J, Garside DB, Greenland P. Long-term consequences of body mass index for cardiovascular mortality: the Chicago Heart Association Detection Project in Industry study. Ann Epidemiol 2004;14:101-8.
11. Flegal KM, Graubard BI, Williamson DF, Gail MH. Impact of smoking and preexisting illness on estimates of the fractions of deaths associated with underweight, overweight, and obesity in the US population. Am J Epidemiol 2007;166:975-82.
12. Stevens J, Juhaeri, Cai J, Jones DW. The effect of decision rules on the choice of a body mass index cutoff for obesity: examples from African American and white women. Am J Clin Nutr 2002;75:986-92.
13. Romero-Corral A, Montori VM, Somers VK, et al. Association of bodyweight with total mortality and with cardiovascular events in coronary artery disease: a systematic review of cohort studies. Lancet 2006;368:666-78.
14. Yusuf S, Hawken S, Ounpuu S, et al. Obesity and the risk of myocardial infarction in 27,000 participants from 52 countries: a case-control study. Lancet 2005;366:1640-9.
15. Pischon T, Boeing H, Hoffmann K, et al. General and abdominal adiposity and risk of death in Europe. N Engl J Med 2008;359:2105-20.
16. Durrleman S, Simon R. Flexible regression models with cubic splines. Stat Med 1989;8:551-61.
17. Executive summary of the clinical guidelines on the identification, evaluation, and treatment of overweight and obesity in adults. Arch Intern Med 1998;158:1855-67.
18. Folsom AR, Eckfeldt JH, Weitzman S, et al. Relation of carotid artery wall thickness to diabetes mellitus, fasting glucose and insulin, body size, and physical activity. Atherosclerosis Risk in Communities (ARIC) Study Investigators. Stroke 1994;25:66-73.