

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

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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).

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- 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 scarce³.

At present, uncertainties admittedly exist regarding which measurements at which cut-off points best predict cardiovascular diseases onset⁴⁻⁷. 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 complex⁸⁻¹⁵.

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 report¹, 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-group¹⁶. 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 risk¹⁷.

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

	BMI, kg/m ²	Disease Risk* Relative to Normal Weight and Waist Circumference	
		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 No

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

_____ Yes 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.

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 below¹⁸

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

Yes 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.

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