ARIC Manuscript Proposal # 1775

PC Reviewed: 4/8/11	**Status: A**	**Priority: 2**
SC Reviewed: _____	**Status: _____**	**Priority: ____**

1.a. Full Title: **Risk of Sudden Cardiac Death in Relation to Obesity in the General Population**

b. Abbreviated Title (Length 26 characters): **Sudden Death in Obesity**

2. Writing Group:

Writing group members: Selcuk Adabag, Lin Y. Chen, Alvaro Alonso, Suma Konety, Aaron R. Folsom, Nona Sotoodehnia, David Siskovick, Jorge Kizer, Kenneth Mukamal, Michael Rosenberg.

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

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3. Timeline:

Statistical Analysis: 3 months

Manuscript preparation: 3 months

4. Rationale:

The objective of this proposal is to examine the association between obesity and sudden cardiac death in the general population.

Sudden cardiac death (SCD) is an important public health problem held responsible from 300,000 deaths in the US and 4-5 million deaths worldwide each year (1-4). Indeed, >50% of deaths due to coronary heart disease (CHD) and 10% of total mortality in the US is attributed to SCD (1-4). At autopsy, 80% of the SCD cases are found to have severe CHD (1,5). Thus, many demographic and clinical risk factors for CHD are also predictors of SCD.

Obesity has reached global epidemic proportions in both adults and children. In the US, 2/3rd of adults and 1/3rd of children are overweight or obese (6,7). Obesity has been associated with hypertension, diabetes mellitus, sleep-disordered breathing and CHD. Indeed, among older men and women who participated in the cardiovascular health study, incidence of diabetes mellitus and CHD increased with measures of obesity including BMI and waist/hip ratio (8,9). Obesity has also been recognized as a moderate risk factor for SCD (10-15). However, whether the influence of obesity on SCD is strictly through CHD or mediated by an independent propensity for developing cardiac arrhythmias is unknown. Indeed, obesity has been linked to a cardiomyopathy, specified by left ventricular hypertrophy and dilatation, and leads to insulin resistance and obstructive sleep apnea (16-20). Each one of these conditions has been associated with cardiac arrhythmias in obese individuals (20-24). Further, obesity has been associated with electrocardiogram (ECG) abnormalities including left ventricular hypertrophy and prolonged QT interval, both of which are recognized as risk markers for SCD in the general population (16,25-27). Signal averaged ECG, another marker for arrhythmias, is also abnormal in obese individuals. Further, cardiac arrhythmias such as frequent and complex premature ventricular contractions, non-sustained ventricular tachycardias, atrial fibrillation and appropriate shocks from implantable defibrillators occur more commonly in obese individuals than lean ones (21,24,28,29). Most notably, obesity has been associated with 1.6 to 2.2 times increase in the risk of SCD in population studies among men and women (12,14,15).

However, there are several gaps in the literature on obesity and SCD. First, the relation between body mass index (BMI) and SCD has not been examined in detail in the general population. Further, the association between SCD and other measures of obesity such as waist circumference has also not been investigated. This is in marked contrast to detailed examination of the relation between SCD and other CHD risk factors such as sex, race, diabetes, smoking etc. Second, no attempt has been made to separate the effect of obesity on SCD from its effect on CHD. The objective of this proposal is to fill these gaps.

5. Main Hypothesis/Study Questions:

Aim #1: To examine the relation between BMI and SCD in the general population

Hypothesis #1: Risk of SCD is lowest in individuals with BMI in normal range. The SCD risk increases with BMI above or below normal range.

Aim #2: To separately assess the influence of obesity on SCD from its influence on CHD

Hypothesis #2: There is an independent association between obesity and SCD separate from the association between obesity and CHD

Aim #3: To assess the relation between SCD and other markers of obesity such as waist circumference and waist to hip ratio

Hypothesis #3: Risk of SCD will increase with each marker of obesity

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 population

We will study the entire ARIC and CHS cohorts (a separate form will be completed for CHS). ARIC and CHS are population-based prospective cohort studies with similar study protocols. The two cohorts have been jointly analyzed in the past. For the purposes of the present investigation pooled analysis of the two cohorts will be performed.

Exclusion criteria: Subjects with missing covariates will be excluded. For the analysis of Aim #2, subjects with a history of CHD or heart failure at baseline will be excluded.

Exposures measurement

BMI: at study enrollment and at follow-up visits

Underweight	<18.5
Healthy weight	18.5-24.9
Overweight	25-29.9
Obese	30-39.9
Morbidly obese	≥40

Other predictor variables:
Waist circumference (women, < 88 cm vs. ≥ 88 cm; men <102 cm vs. ≥ 102 cm)
Waist to hip ratio (women, <0.8 vs. ≥ 0.8; men < 0.95 vs. ≥ 0.95)

Outcomes measurement

SCD

SCD was adjudicated by a committee of physicians in ARIC and CHS through 2001. All events classified as fatal coronary heart disease (CHD) (definite MI, definite fatal CHD, or possible fatal CHD, in and out of hospital) were reviewed. SCD was defined as unexpected deaths that occurred within 1 hour of the onset of symptoms, when death was witnessed, and within 24 hours of last being seen alive, when it was unwitnessed. Circumstances of the event, medical comorbidities and body position of the victim were also considered when adjudicating SCD cases. After review of available data, cases were classified as definite sudden arrhythmic death, possible arrhythmic death, not sudden arrhythmic death, or unclassifiable. For the purposes of this analysis all patients with possible or definite SCD will be considered as SCD.

CHD event

Non-fatal myocardial infarction, deaths due to CHD which did not meet criteria for SCD, myocardial infarction on ECG, history of CHD

Covariates

Age, sex, race, education, study center, smoking status, family history of CHD.

Statistical analysis

Participants will be coded according to whether or not they had SCD. Kaplan-Meier curves for SCD and BMI categories will be generated by quintiles of its sex-specific distribution and also by commonly-used categories. In the latter case BMI in the normal range (22-24) will be taken as reference. Interaction terms for race (black vs. white), age and smoking status (current vs. former vs. never) will be examined.

Cox proportional hazards regression models will be used to determine the demographic and clinical variables associated with the risk of SCD. In addition to BMI, the covariates to be included in the analyses are age, sex, race, smoking status, education (less than high school, high-school graduate, college or higher) and family history of CHD. Diabetes mellitus, fasting blood glucose, systolic and diastolic blood pressure, and serum levels of LDL, HDL and triglycerides might be on the causal pathway and thus will not be adjusted in the analysis. Variables that are significantly associated with each outcome will be determined. Because low BMI has reflected comorbidity, subgroup analyses among nonsmokers in good self-reported health will be performed.

Secondary analyses:

-The association between BMI and SCD will be examined separately for blacks vs. whites as the relation might differ between races.

-The association between BMI and SCD will be examined separately for smoking status (current, former, never)

-If the relation between BMI and SCD are different for ARIC vs. CHS, we will repeat the analysis using BMI at age 50 in CHS, based on the self-reported weight at 50. This measure has correlated better with BMI in ARIC before. It also has had a stronger association with CHD than baseline BMI in CHS (9).

Aim #2

To statistically separate the effects of obesity on SCD from its influence on CHD we will use the methods below:

1- Censor the subject when CHD event occurs: In addition to SCD, participants will also be coded as to whether or not they had an incident CHD event (MI/CHD/non-sudden CHD death/ECG MI) during follow-up. Participants who had no event or had a non-CHD death will be censored in the analysis at their date of last contact or death. Individuals who had CHD events prior to SCD will be coded as CHD events (ie. 1st outcome, whether CHD event or SCD, will be considered).
2- Include CHD as a time-dependent variable in the multivariable model
3- A secondary analysis adjusting for carotid IMT thickness will be performed to account for subclinical CHD

Aim #3

Correlations between obesity measures will be assessed by computing Spearman coefficients. Each measure will be classified by quintiles of its sex-specific distribution and also by commonly-used categories. Cox models will be fit to calculate the relative risk of incident events by using the lowest quintile as the reference category. To assess monotonic associations, test for trend will be performed using a grouped linear variable. Relative risks will be evaluated by using partition values recommended for waist circumference and waist/hip ratio by scientific and governmental organizations. Same methods outlined in Aim #1 will be used.

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

8.c. If yes, is the author aware that the participants with RES_DNA = 'not for profit' restriction must be excluded if the data are used by a for profit group?
____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 tocontact lead authors of these proposals for comments on the new proposal or collaboration)?

- MS #1557: Prineas – ECG predictors of SCD
- MS #1196: Peacock – Magnesium and SCD

We have included some authors above as co-authors in the current manuscript.

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

_x_ B. primarily based on ARIC data with ancillary data playing a minor role (usually control variables; list number(s)* ___2004.03_____ _____ _____)

*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.

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