ARIC Manuscript Proposal # 1333

PC Reviewed: 01/15/08	**Status: ___A_**	**Priority: __2_**
SC Reviewed: _____	**Status: _____**	**Priority: ____**

1.a. Full Title: Socioeconomic indicators and the risk of sudden cardiac death.

b. Abbreviated Title (Length 26 characters): SES and sudden death

2. Writing Group:

Writing group members: Anna Kucharska-Newton, Wayne D. Rosamond, David Couper, Kennet Harald, Kathryn Rose, Veikko Salomaa, Thomas Rea; others welcome

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

F**irst author**: Anna Kucharska-Newton
Address:
Cardiovascular Disease Program
Department of Epidemiology
University of North Carolina at Chapel Hill
137 E. Franklin St. Suite306
Chapel Hill, NC 27514

Phone: 919 966 4564 Fax: 919 966 9800
E-mail: Anna_Newton@unc.edu

Corresponding/senior author (if different from first author correspondence will be sent to both the first author & the corresponding author):
Address:

Phone: Fax:

3. Timeline: Data analyses to begin July, 2008. Manuscript preparation: September-November 2008.

4. Rationale:

The decline in coronary heart disease (CHD) mortality, observed in developed countries over the past fifty years[1, 2], has not been uniform[3, 4]. Moreover, despite clinical and public health interventions, sudden cardiac death remains a significant public health burden continuing to contribute fifty percent of total coronary heart disease mortality[5, 6]. Identification of those at risk for sudden cardiac death is hampered by lack of specificity of the traditional risk factors[7]. This is especially an issue in the low to moderate risk populations, which contribute the largest overall proportion of sudden cardiac death cases[8]. It becomes important therefore, in an effort to conduct effective primary prevention, to identify sudden cardiac death risk factors, which may allow for more direct targeting of preventive strategies.

Numerous studies have pointed to the role of socioeconomic indicators in the incidence of sudden cardiac death. Mortality rates for sudden cardiac death, as for other cardiovascular events, show consistent and robust socioeconomic gradients, with higher death rates observed among those with higher levels of social deprivation[9], but the extent to which attributes of socioeconomic status (SES) influence the risk of sudden cardiac death in comparison with other, nonfatal, coronary outcomes has not been examined extensively.

The goal of this study is to determine if SES measures are preferentially associated with the risk of sudden cardiac death as compared to the risk of nonfatal myocardial infarction. To explore this hypothesis we will use data from two population-based studies: the Atherosclerosis Risk in Communities (ARIC) study and a Finnish population-based cardiovascular risk factor monitoring study, the National FINRISK study[10]. Finland, a country with a government-subsidized health care system, has experienced a remarkably steep decline in mortality and incidence of cardiovascular disease[11], attributed to effective primary and secondary prevention[12]. A social class gradient of cardiovascular mortality however, persists in Finland and a significant increase in mortality by occupational class has recently been observed[13]. A systematic comparison of the association of socioeconomic indicators with the risk of sudden cardiac death in these two different countries can provide a greater understanding of the role that social context plays in the incidence of sudden cardiac death

5. **Main Hypothesis/Study Questions**:

1. Among participants of the ARIC cohort, compare and contrast association of individual measures of socioeconomic status (SES) with the risk of sudden cardiac death to the association of those measures with the risk of nonfatal myocardial infarction.

1 a. Determine the association of individual measures of SES with the risk of sudden cardiac death

1 b. Determine the association of individual measures of SES with the risk of nonfatal myocardial infarction

1c. Compare the incidence rates and hazard ratios of the association of individual SES indicators with sudden cardiac death and nonfatal myocardial infarction. Evaluate the

potential effect modification of these associations by known cardiovascular disease risk factors.

2. Using data from the ARIC cohort determine if neighborhood measures of socioeconomic status modify the association of individual measures of socioeconomic status with the risk of sudden cardiac death.

3. Compare the socioeconomic gradient associated with the risk of sudden cardiac death and nonfatal myocardial infarction observed in the ARIC cohort to that observed in the National FINRISK study.

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 populations: This research is to be conducted as a comparative analysis of the risk of sudden cardiac death in the United States and Finland. The Atherosclerosis Risk in Communities (ARIC) study will constitute the basis for the United States component of this project. The National FINRISK study will be the basis of the Finnish component. All analyses will involve follow-up from 1987 through 2001.
The National FINRISK study is a series of population based surveys conducted every five years since 1972 among a stratified random sample of men and women aged 25-64 years, from four regions of Finland (North Karelia, Kuopio, Turku/Loimaa and Helsinki)[14]. At the time of the survey, all study participants are asked to complete a health behavior questionnaire and undergo a personal health examination. Analysis based on the FINRISK data will include information concerning the participants of surveys conducted in the years 1987, 1992 and the 1997. Participants of those surveys will have been followed-up for cardiovascular mortality and morbidity for up to 14 years. Cardiovascular diagnoses in the Finnish Causes-of-Death Register and in the Hospital Discharge Register have recently been validated[15]. Due to these registers, completeness of follow-up is 100 percent for deaths and hospitalizations that occur in Finland.
For the purposes of this study we will use data concerning only the 45-64 year age group to assure comparability of results between the FINRISK and ARIC studies.

Exposure measurement:

Individual level socioeconomic indicators: education and median household income will be used to measure the level of individual SES. Education will be defined as a dichotomous variable with the exposure category corresponding to high school or less years of education in the ARIC cohort and less than 9 years of education in the FINRISK study. Median household income will be defined as a categorical variable. In the ARIC study four race-specific income categories will determined on the basis of race-specific

income distributions[16]. In the FINRISK study, taxable income data are obtained from Statistics Finland and linked with mortality data using unique personal identifiers. Personal income is classified as low, middle and high, according to predetermined limits, which have been adjusted during duration of the study to account for inflation[17].
Neighborhood level socioeconomic indicators: Socioeconomic status of a neighborhood will be measured only in the ARIC study. This measurement will be based on the following neighborhood characteristics determined at a Census block level: median household income, median value of housing units, percentage of households receiving interest, dividend, or net rental income, percentage of adults 25 years or older who had completed high school, and percentage of persons 16 years or older who are employed in executive, managerial or professional specialty occupation. Addresses of ARIC study participants, collected at the time of baseline examination, are linked to the above indicators thus allowing for attribution of characteristics of the neighborhood of residence to each study participant. Additionally, a summary score of neighborhood socioeconomic status will be constructed, as per Diez-Roux et al.[16], as a summary score based on z scores determined separately for the component neighborhood SES measures. The z scores, reflecting deviation from the mean, will be estimated by subtracting from the value of the variable for a given census block, the overall mean and dividing that by the standard deviation for the entire population.

Outcome ascertainment:

Sudden cardiac death: In the ARIC study sudden cardiac death will be defined as death adjudicated by a physician panel to be a sudden, pulseless condition without a known non-cardiac cause, or death determined by death certificate codes indicating death due to underlying heart disease that occurred outside the hospital or in the emergency department[18, 19]. In the FINRISK study sudden cardiac death is defined as cardiac death that occurred out-of-hospital or in the emergency room or within 1 hour from the onset of symptoms[20]. All out-of-hospital deaths in the FINRISK study are ascertained on the basis of review of death certificates for each of the four geographical areas of the study. ICD-9 codes reflecting cardiac origin of the death are determined for each recorded out-of-hospital death. Information obtained from death certificates is cross-checked with the National Causes of Death Register.

Non-fatal MI. In both the FINRISK and ARIC study diagnosis of nonfatal myocardial infarction is based on hospital admission records specifying an incident definite or probable non-fatal myocardial infarction which did not result in a fatal outcome within 28 days.

Covariates: Demographic covariates, age, gender, study center, and in the case of the ARIC study, race/center, will be examined for inclusion into regression models used in the analyses. Biological (hypertension, diabetes, markers of inflammation) and behavioral (physical activity, alcohol intake, weight, smoking), with perhaps the exception of diabetes, would appear to be on the pathway of the association of SES with cardiovascular outcomes. They will therefore, not be included as confounders.

Statistical analysis: Cox proportional hazards regression and Poisson regression models will be used in analysis of the association of individual SES indexes with sudden cardiac death and with non-fatal myocardial infarction. To account for intra-class correlation, multilevel regression models, such as hierarchical linear models, will be explored as tools in the analysis of the effect of neighborhood measures of SES on the associations found for the individual SES measures (ARIC study only).
Comparison of the ARIC and FINRISK studies will be performed through analysis of z-scores based on estimates of the beta parameters and associated standard errors obtained from both studies.

Power analysis
An analysis of the power of both the ARIC and the FINRISK studies indicates that the size of both studies is adequate for observation, with 95 percent confidence and 90 percent power, of relative risk ratios ranging from 1.3 to 2.1, estimates comparable to those reported by existing studies. The range of estimates of relative risk of sudden cardiac death associated with low education was reported to be from 1.33 (95 percent CI 1.18, 1.51) to 2.2 ($p<0.001$)[17, 21-23]. The range of estimates of relative risk of sudden cardiac death associated with low median household income was reported to be from 1.3 (95 percent CI: 1.1, 1.7) to 2.11 (95 percent CI:1.82, 2.46)[17, 22].

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# 385 Socioeconomic status and incident cardiovascular disease
MS# 454 Neighborhood of residence and incidence of coronary heart disease
MS# 535 Trends in sudden coronary death, 1987-1995
MS# 780 Trends in the incidence and mortality of myocardial infarction by socioeconomic status, 1991-1999
MS#1086r Epidemiologic implications of the Cardiac Arrest Case Definition

11. a. Is this manuscript proposal associated with any ARIC ancillary studies or use any ancillary study data? __X__ Yes ____ No

1. MS#1086r: Epidemiologic Implications of the Cardiac Arrest Case Definition
This manuscript outlines a proposal to identify and validate sudden cardiac death cases in the ARIC and CHS cohorts and create a common cohort including data from both studies. As such it constitutes the basis for our proposed study. In the proposed study we will use the definition of sudden cardiac death developed as part of this manuscript. In our analysis we will not use the CHS cohort data.

2. ARIC Ancillary Lifecourse SES, Social Context and CVD Study, Gerardo Heiss, PI
This ancillary study will provide necessary reference for the use of neighborhood SES indicators.

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.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.

Literature cited:

1. Fox CS, Evans JC, Larson MG, Kannel WB, Levy D. Temporal Trends in Coronary Heart Disease Mortality and Sudden Cardiac Death From 1950 to 1999: The Framingham Heart Study. Circulation 2004;110:522-7.
2. Lewis RP. The ACC at 50: a giant grew in Bethesda: The impact of the ACC on cardiovascular medicine. Journal of the American College of Cardiology 2000;35:1061-6.
3. Ford ES, Capewell S. Coronary Heart Disease Mortality Among Young Adults in the U.S. From 1980 Through 2002: Concealed Leveling of Mortality Rates. Journal of the American College of Cardiology 2007;50:2128-32.

4. Gerber Y, Jacobsen SJ, Frye RL, Weston SA, Killian JM, Roger VL. Secular trends in deaths from cardiovascular diseases - A 25-year community study. Circulation 2006;113:2285-92.
5. Zipes DP, Wellnes HJJ. Sudden cardiac death. Circulation 1998;98:2334-51.
6. Sotoodehnia N, Zivin A, Bardy GH, Siscovick DS. Reducing mortality from sudden cardiac death in the community: lessons from epidemiology and clinical applications research. Cardiovascular Research 2001;50:197-209.
7. Kannel WB, Schatzkin A. Sudden death: lessons from subsets in population studies. Journal of the American College of Cardiology 1985;5:141B-9B.
8. Myerburg RJ. Sudden Cardiac Death: Exploring the Limits of Our Knowledge. Journal of Cardiovascular Electrophysiology 2001;12:369-81.
9. Hemingway H, Malik M, Marmot M. Social and psychosocial influences on sudden cardiac death, ventricular arrhythmia and cardiac autonomic function
Eur Heart J 2001;22:1082-101.
10. Vartiainen E, Jousilahti P, Alfthan G, Sundvall J, Pietinen P, Puska P. Cardiovascular risk factor changes in Finland, 1972-1997. Int J Epidemiol 2000;29:49-56.
11. Pajunen P, Paakkonen R, Juolevi A, et al. Trends in fatal and non-fatal coronary heart disease events in Finland during 1991-2001. Scand Cardiovasc J 2004;38:340-4.
12. Laatikainen T, Critchley J, Vartiainen E, Salomaa V, Ketonen M, Capewell S. Explaining the Decline in Coronary Heart Disease Mortality in Finland between 1982 and 1997. Am J Epidemiol 2005;162:764-73.
13. Mackenbach JP, Bos V, Andersen O, et al. Widening socioeconomic inequalities in mortality in six Western European countries. Int J Epidemiol 2003;32:830-7.
14. Vartiainen E, Puska P, Pekkanen J, Toumilehto J, Jousilahti P. Changes in risk factors explain changes in mortality from ischaemic heart disease in Finland. BMJ 1994;309:23-7.
15. Pajunen Pa, Koukkunen Hb, Ketonen Mc, et al. The validity of the Finnish Hospital Discharge Register and Causes of Death Register data on coronary heart disease. European Journal of Cardiovascular Prevention & Rehabilitation 2005;12:132-7.
16. Roux AVD, Merkin SS, Arnett D, et al. Neighborhood of Residence and Incidence of Coronary Heart Disease
N Engl J Med 2001;345:99-106.
17. Salomaa V, Miettinen H, Niemela M, et al. Relation of socioeconomic position to the case fatality, prognosis and treatment of myocardial infarction events; the FINMONICA MI Register Study. J Epidemiol Community Health 2001;55:475-82.
18. Ives DG, Fitzpatrick AL, Bild DE, et al. Surveillance and ascertainment of cardiovascular events : The Cardiovascular Health Study. Annals of Epidemiology 1995;5:278-85.
19. Sotoodehnia N, Siscovick DS, Vatta M, et al. {beta}2-Adrenergic Receptor Genetic Variants and Risk of Sudden Cardiac Death. Circulation 2006;113:1842-8.
20. Salomaa V, Ketonen M, Koukkunen H, et al. Decline in Out-of-Hospital Coronary Heart Disease Deaths Has Contributed the Main Part to the Overall Decline in Coronary Heart Disease Mortality Rates Among Persons 35 to 64 Years of Age in Finland: The FINAMI Study. Circulation 2003;108:691-6.
21. Ruberman W, Weinblatt E, Goldberg JD, Chaudhary BS. Education, psychosocial stress and sudden cardiac death. J Chronic Dis 1983;36:151-60.
22. Reinier K, Stecker EC, Vickers C, Gunson K, Jui J, Chugh SS. Incidence of sudden cardiac arrest is higher in areas of low socioeconomic status: A prospective two year study in a large United States community. Resuscitation 2006;70:186-92.
23. Yarnell J, Yu S, McCrum E, et al. Education, socioeconomic and lifestyle factors, and risk of coronary heart disease: the PRIME Study. Int J Epidemiol 2005;34:268-75.