ARIC Manuscript Proposal # 3259

PC Reviewed: 10/9/18  Status: _____  Priority: 2
SC Reviewed: _________  Status: ____  Priority: ____

1.a. Full Title: SES and Incident Cardiovascular Disease Among Individuals with Obesity and Diabetes

b. Abbreviated Title (Length 26 characters): SES and CVD in Obesity/Diabetes


I, the first author, confirm that all the coauthors have given their approval for this manuscript proposal. ___AC___ [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:**

Previous studies have demonstrated that lower socioeconomic status (SES) is associated with adverse clinical outcomes, including incident cardiovascular disease (CVD) events (1-3). Data suggests that mortality from CVD is higher among persons with lower occupational class or lower educational level (4,5). This may be partially explained by differences in healthy behaviors related to SES. Disparities in several healthy behaviors, including healthy diet, regular exercise and routine self-management in cooperation with health care professionals, are likely influenced by limited access to goods and services that would facilitate these behaviors. In addition, other factors such as psychosocial stress, health care access and inequalities in the distributions of comorbidities predisposing to CVD may further explain the relationship between SES and increased CVD risk. Indeed, prior research has shown that lower SES is associated with lower consumption of fruits and vegetables, less physical activity, less access to care and a higher prevalence of CVD risk factors compared to high SES groups (6-11).

Obesity and diabetes are increasingly prevalent and inter-related conditions that are also associated with increased CVD risk. Because obesity and diabetes are rapidly increasing in prevalence, understanding the factors relating to adverse outcomes in individuals with these conditions is increasingly important. Fundamental to the management of these conditions and the prevention of complications related to them is a healthy lifestyle and ability to adhere to recommended therapy, which is likely affected by financial resources, education, social networks, the built environment and other factors (6,9,12-13). Given the importance of lifestyle and access to care in managing obesity and diabetes, it is possible that SES plays a particularly significant role in the development of adverse outcomes in individuals with these conditions (14-16). There is limited data regarding how SES relates to CVD events and mortality among people with obesity and diabetes (17-18) and whether these conditions modify the risk associations of SES with incident CVD. Further, prior data indicates racial differences may exist in the relationship between SES and adverse CVD outcomes, with the protective association of high SES against CVD outcomes being larger in Whites than Blacks (19-20), but this has not been explored among individuals with obesity and diabetes.

In this analysis of the Atherosclerosis Risk in Communities (ARIC) Study, we aim to assess the association of SES with incident CVD events and mortality among those with obesity and/or diabetes, and to assess whether the risk association differs from that among those without these conditions. We hypothesize that low SES will be associated with greater CVD risk among individuals with obesity and diabetes than among those without these conditions. The CVD outcome of particular interest is incident HF, as there is excess HF risk among those with obesity and diabetes that is poorly explained by traditional risk mechanisms. We will also evaluate if the association between SES and CVD events among individuals with obesity and/or diabetes differs across demographic groups. We anticipate this analysis will provide additional insight into the relationship of SES with adverse clinical outcomes among individuals with obesity and diabetes. The finding that individuals with obesity and DM with low SES are
at particularly elevated risk for CVD would suggest that this group requires special clinical attention.

5. Main Hypothesis/Study Questions:

Aims:

1) We will assess the association of SES with incident CVD events and mortality among those with obesity and diabetes, and whether the association differs from that among those without these conditions.

2) We will test for race and sex differences in the association of SES with incident CVD events and mortality among those with obesity and diabetes.

Hypotheses:

1a) Among individuals with obesity and diabetes, lower SES will be associated with a higher likelihood of developing incident CVD events.

1b) The association between SES and incident CVD will be modified by the presence of obesity and diabetes and metabolic syndrome, being stronger among those with these conditions.

2) The association of SES with incident CVD events among those with obesity and diabetes will differ across subgroups defined by sex and race.

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 evaluate the prospective association between SES variables at Visit 1 and incident CVD events and mortality, performing analyses stratified by the presence of obesity and diabetes (assessed independently and compositely, as the presence of any one of these conditions). We will assess for effect modification of the association between SES and CVD by obesity and diabetes.

Exposures: The primary exposure will be SES, as reflected by income, education level, and area deprivation index. These SES variables will be evaluated individually and in combination with each other.

- As has been done previously, household income will be categorized into <$12,000, $12,000-$24,999, $25,000-$49,999, and ≥$50,000 in 1987–1989 (11,21)
($1 in 1987–1989 is about $2 in 2016) (22). In 1987, for an average household $12,000 corresponds to 150% of the federal poverty level (23).

- Educational attainment will be categorized as 1) grade school or high school without completion, 2) high school completion or vocational school, 3) college with or without completion and 4) graduate/professional school (24).
- ADI represents socioeconomic deprivation experienced by a neighborhood and was obtained using 17 different factors of SES from 2000 Census block group-level or the nine-digit ZIP data. The distribution of ADI values will be examined, and neighborhoods will be sorted into quartiles (4 equal groups) of ADI. The highest quartile of ADI will be used as the reference group for the SES score, with higher quartiles of ADI indicating greater deprivation. Progressively lower quartiles will represent less deprivation (11).
- Obesity and diabetes at Visit 1 will be evaluated as potential effect modifiers of the association between SES and incident CVD. Obesity will be defined as a measured BMI greater than or equal to 30 kg/m². Diabetes will be defined as a fasting glucose greater than or equal to 126 mg/dl, a non-fasting glucose level greater or equal to 200 mg/dl, a prior physician diagnosis of diabetes, or the use of hypoglycemic medication. We will evaluate these conditions individually and also collectively (e.g., both obesity and diabetes). In secondary analyses, we will also evaluate the effect modification of the association between SES and CVD by metabolic syndrome (among those with and without obesity and diabetes), given the link between metabolic syndrome and incident CVD, as well as the importance of lifestyle measures for optimal management of metabolic syndrome. Metabolic syndrome will be defined using AHA/NHLBI criteria by the presence of at least 3 of the following conditions: abdominal obesity (waist circumference ≥102 cm in males and ≥88 cm in females), low HDL cholesterol (<40 mg/dL in males and <50 mg/dL in females), elevated triglycerides (≥150 mg/dL), hypertension (≥130 mmHg systolic blood pressure and/or ≥85 mm Hg diastolic blood pressure and/or on anti-hypertensive drug treatment), and fasting hyperglycemia (≥100 mg/dL and/or on hypoglycemic drug treatment).

**Outcomes:**

Incident CVD events (defined as the outcomes of incident HF hospitalization or death, fatal and non-fatal incident CHD and fatal and non-fatal stroke, assessed individually and in composite) will be the outcomes of interest.

In secondary analyses, we will evaluate the association of SES with all-cause mortality as the secondary outcome.

**Exclusions:** We will exclude participants with a BMI less than 18.5 given the confounding frequently associated with underweight. We will exclude participants with known CVD at Visit 1 (self-reported CHD, HF or stroke or silent MI by ECG at Visit 1). We will exclude participants missing data for SES variables, metabolic syndrome
components, diabetes status, or BMI. We will exclude the small number of participants at baseline who are not black or white. We will also exclude the small number of black participants in the Minneapolis, MN and Washington County, MD field centers.

**Covariates:** Age, sex, race, occupation, smoking status, alcohol use, LDL-cholesterol, systolic blood pressure, anti-hypertensive medication use, estimated GFR, exercise physical activity (obtained by modified Baecke questionnaire and categorized as poor, intermediate and recommended [>= 150 minutes of moderate-vigorous activity or 75 minutes of vigorous activity]), healthy diet score (using healthy diet components of adequate fruits/vegetables, adequate fish, adequate whole grains, low sodium and low sugar sweetened beverages and categorized as poor [0-1 components] intermediate [2-3] and ideal [4-5]), insurance status and frequency of health care visits (all measured at Visit 1).

**Main Analyses:**
- As has been done in prior analyses, we will combine categorized measures of income, education and area deprivation as described above to develop a cumulative SES variable. We will first give equal weight to each of the 3 SES components, with scores from 0-3 as follows: household income scored as < $12,000 = 0, $12,000-$24,999 = 1, $25,000-$49,999 = 2, and ≥$50,000 = 3; educational attainment scored as grade school or high school without completion = 0, high school completion or vocational school = 1, college with or without completion = 2, graduate/professional school = 3; and ADI scored with the highest ADI quartile as the reference group, and progressively lower quartiles receiving scores of 1, 2, and 3. We will use these scores to create a cumulative SES score from 0-9, categorized as low (0-2), medium (3-5) and high (6-9) SES. We will also perform analyses using the risk associations of the individual SES components with incident CVD to weight each of the SES components in a cumulative SES score based on their strength of association with the primary outcome of interest.
- We will compare baseline demographics and clinical characteristics (including the prevalence of obesity and diabetes) of the study population across SES categories, using ANOVA for continuous variables and the chi-squared test for categorical variables.
- As we hypothesize that lifestyle factors and health care access may play a role in the relationship between SES and CVD among those with obesity and diabetes, we will logistic regression to assess the association of the individual and combined SES variables with levels of physical activity (odds of poor physical activity, defined as no moderate or vigorous exercise activity); poor diet (odds of poor diet); insurance (odds of no insurance) and frequency of health care visits (odds of no health care visits for routine health care).
- We will estimate incidence rates for CVD in association with lower SES category among those with and without obesity and diabetes. We will further evaluate the association between lower SES and incident CVD risk using Cox regression models with successive levels of adjustment. Model 1 will adjust for the confounders of age, sex, race, smoking and alcohol use. Model 2 will adjust for
Model 1 variables plus the traditional CVD mediators: SBP, LDL-C and eGFR. Model 3 will adjust for Model 2 variables, as well as the SES-related potential mediators of physical activity, diet, insurance, and visit frequency to seek health care. Analyses will be stratified by the presence of obesity and metabolic syndrome, with tests for interaction between SES and these conditions on CVD risk. We hypothesize more harmful associations of low SES with CVD events among those with obesity, metabolic syndrome and diabetes. We will evaluate the individual SES variables of income, education and area deprivation index (each categorized) as well as the composite SES score (categorized as low, medium and high). For estimating associations of the composite SES score with incident CVD, we will perform secondary analyses using multi-level modeling, given the inclusion of both individual and aggregate level attributes in the cumulative SES score.

- In secondary analyses, we will assess whether metabolic syndrome modifies the association between SES and incident CVD. We will also perform analyses stratifying those with metabolic syndrome as: 1) metabolic syndrome without obesity or diabetes; 2) metabolic syndrome with either obesity or diabetes; and 3) metabolic syndrome with both obesity and diabetes.
- Among those with obesity and diabetes, we will perform analyses stratified by race and sex, to assess whether the association between SES and CVD differs across these demographic subgroups.
- We will perform the analyses above using all-cause mortality as a secondary outcome, and perform competing risk regression to account for premature mortality associated with the exposure variables.

**Sensitivity Analyses:**

- In sensitivity analysis, we will model obesity and diabetes from Visit 1 through 4 as time varying exposures, to account for their onset after the baseline visit in evaluating risk associations.
- We will perform competing risk regression to account for the competing risk of premature mortality associated with the exposures of interest
- We will consider additional analyses including occupation subtype and home ownership as additional SES factors.

**Limitations:**

- SES is a theoretical construct encompassing individual, household, and/or community resources. Thus one individual measure of SES may not capture the entire SES of an individual. To partially address this, we will use household income, educational attainment, and area deprivation index as measures of SES in primary analyses. Additionally, we will consider further analyses including occupation subtype and home ownership as additional SES factors.
• It is unclear whether CVD outcomes are associated with individual or composite measures of SES. We will attempt to better understand the prognostic association of SES variables to CVD outcomes by performing analyses relating CVD outcomes to individual SES variables as well as analyses relating CVD outcomes to composite SES variables.

• As this is an observational study, there is a high likelihood of residual confounding.

7.a. Will the data be used for non-CVD analysis in this manuscript?  ____ Yes  ____ 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  ____ 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”?  ____ 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)?

SES across the Life Course and the Metabolic Syndrome ARIC Manuscript Proposal # 1099

Cross-sectional and Prospective Associations between Neighborhood Socioeconomic Status and Incident Diabetes. ARIC Manuscript Proposal # 2469

Individual and neighborhood SES and health among persons with and without type 2 diabetes: the Atherosclerosis Risk in Communities Study ARIC Manuscript Proposal # 1261
An evaluation of area-level measures of SES: CVD health outcomes in the ARIC study communities
ARIC Manuscript Proposal # 1114

Individual and Area-Level Lifecourse Socioeconomic Status and Subclinical Atherosclerosis: The Atherosclerosis Risk in Communities (ARIC) Study ARIC Manuscript Proposal # 926

Socioeconomic status and incidence of subclinical myocardial damage ARIC Manuscript Proposal #2307

Life Course Socioeconomic Exposures and Heart Failure in the Atherosclerosis Risk in Communities (ARIC) Study ARIC Manuscript Proposal # 1160r

Socioeconomic indicators and the risk of sudden cardiac death. ARIC Manuscript Proposal # 1333

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
__x__ A. primarily the result of an ancillary study (list number* __2009.16 and 2008.10____)

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.
References


