ARIC Manuscript Proposal #4192

PC Reviewed: 02/14/23	**Status: _____**	**Priority: 2**
SC Reviewed: _____	**Status: _____**	**Priority: ____**

1.a. Full Title:

Life-Course Neighborhood Socioeconomic Status and All-cause and Cause-specific Mortality: Atherosclerosis Risk in Communities Study

b. Abbreviated Title (Length 26 characters):

Neighborhood SES and Mortality

2. Writing Group [please provide a middle name if available; EX: Adam Lee Williams]:
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3. Timeline:

- Initiate analysis February 1, 2023
- Complete first draft of manuscript and submit to co-authors by July 1, 2023
- Send to National Cancer Institute clearance review by July 25, 2023
- Send to ARIC review August 10, 2023
- Submit for publication by September 1, 2023

4. Rationale:

The physical and social attributes of the neighborhood environment can affect health, including quality of life, through access to resources and opportunities.[1–4] Studies have implicated the neighborhood social and economic characteristics as a contributor to health disparities.[1,3,4] For instance, individuals residing in low socioeconomic status (SES) neighborhoods as compared to those residing in high SES neighborhoods, have greater chronic disease burden due to differences in access and quality of socioeconomic resources, such as education, employment, and health care.[1,5] Individuals that reside in low SES neighborhoods are more likely to have limited access to fresh foods, be exposed to greater environmental toxins, and have less areas to safely engage in physical activity, all which may influence health and longevity.[3]

Previous studies have linked socioeconomic disadvantaged neighborhoods to all-cause and premature mortality.[2,6] Given the documented relationship between neighborhood environment and chronic diseases, such as cardiovascular disease (CVD), cancer, type 2 diabetes, and respiratory diseases, it is plausible that low neighborhood SES would influence risk of various cause-specific mortality.[7–12] However, the relationship between neighborhood SES and cause-specific mortality remains understudied.

Majority of epidemiologic studies that evaluated the relationship between neighborhood SES and mortality have relied on measuring the neighborhood environment at one time point (most often mid- or late- life), thereby not accounting for early life exposures and changes in SES over life stages (childhood, and young, middle, and older adulthood).[3,6] For instance, low neighborhood SES in childhood could shape health behaviors (i.e., engagement in physical activity) that

persists into adulthood that may influence risk of chronic disease and mortality. A life course approach provides a more comprehensive understanding by determining the cumulative health effects of neighborhood SES across life stages.[13] Therefore, utilizing a life course approach would provide a better understanding of the dynamic relationship between neighborhood SES and mortality, especially the cumulative health effects of low neighborhood SES across life stages. Among studies that assessed life course SES and mortality, few have measured neighborhood-level SES. However, the influence life course neighborhood SES has on cause-specific and premature mortality remains not well understood.

The present study aims to investigate the relationship between neighborhood SES in childhood and young, middle, and older adulthood, as well as changes in neighborhood SES in adulthood on all-cause and cause-specific mortality. We will further investigate whether race and sex separately and jointly modify the relationship between life-course neighborhood SES and all-cause and cause-specific mortality.

5. Main Hypothesis/Study Questions:

A. We hypothesize that neighborhood SES at all life stages will be inversely associated with the risk of all-cause mortality.

B. We hypothesize that neighborhood SES in childhood, and young, middle, and older adulthood will be inversely associated with the risk of cardiovascular- and cancer-specific mortality.

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 Cohort

The present study will use data from the Atherosclerosis Risk in Communities Study (ARIC), a large multicenter prospective cohort study investigating the etiology and natural history of atherosclerosis and CVD from four U.S. communities (Washington County, Maryland; Forsyth County, North Carolina; Jackson, Mississippi; and the suburbs of Minneapolis, Minnesota). Details of the ARIC study has been previously described.[14] Briefly, the study cohort is comprised of 15,792 participants aged 45-64 years at baseline (visit 1) in 1987-1989. Participants were contacted annually to complete surveys on general health and hospitalization. Additionally, multiple follow-up visits were conducted from baseline through visit 9 (2020-2021). Between 2001-2002, participants provided their residential addresses at different life stages as part of the Life Course Socioeconomic, Social Context and Cardiovascular Disease (LCSES) Study, an ARIC ancillary study.[15] Since Visit 4 (1996-1998) aligned most closely in time with the LCSES study when neighborhood exposures in earlier life stages were evaluated, this visit will be considered as the baseline for the current analysis. Participants will be excluded if they did not participate in visit 4 and the LCSES ancillary study. Participants identifying as neither Black nor White (n=47) will be considered together with White cohort participants. We will include in analyses Black participants from the Washington County, MD and Minnesota field centers. These participants were traditionally excluded from ARIC analyses due to small numbers, especially in analyses stratified by a combined race-center variable. We will stratify analyses by

center to account for potential geographic differences in SES and separately by race. In a sensitivity analysis, we will add a stratification by race-center, in which Black participants from Washington County and Minnesota as well as participants who identify as neither Black or White will be excluded. Additionally, participants will be excluded for missing information on baseline study covariates. All participants provided informed consent and Institutional Review Board approval was obtained at each study site.

Life course neighborhood socioeconomic status

As part of the LCSES study, participants reported their addresses for the following age periods: approximately at age 10 (childhood), age 30 (young adulthood), age 40-50 (middle adulthood), and visit 4 will be considered older adulthood (visit 4 median age 62 years; range 52-75 years). Addresses collected were geocoded and linked to U.S. Census data. Childhood neighborhood SES was based on approximate census information (1930-1950) at the county-level, as this was the smallest geographic unit with aggregated data for all participating areas during this period. Middle and young adulthood neighborhood SES was evaluated on the bases of the most proximate census (1960-1980) at the census tract-level. Finally, older adulthood neighborhood SES was evaluated using data from the 2000 Census at the census tract-level. Previous validation studies reported high repeatability and accuracy of geocodes in the ARIC study.[16,17]

Prior studies have described the analytical details on the derivation of neighborhood SES measures at different life stages.[15,18] Briefly, composite measures of neighborhood SES were derived by summing *z* scores for multiple census variables representing neighborhood-level education, home ownership, income, occupation, and property value at different life stages.[15] For childhood and young adulthood neighborhood SES, we will use ages 10 and 30 years as the midpoints, respectively, because participants reported their address information for these ages of their life stages. For middle adulthood, we will use age 45 years as it represents the midpoint of the age period of 40-50 years for which address information was collected. Finally, for older adulthood, we will use the median age at visit 4 (62 years), as everyone was older than 52 years of age and occurred most closely in time with the LCSES Study when neighborhood exposure at earlier life stages was evaluated.

We will calculate *z* scores for each census variable to develop a summary *z*-score for Life course neighborhood SES, where higher z scores indicate greater SES. Quartiles based on the population distribution for neighborhood SES at different life stages will then be created.[1,3,19,20] Additionally, we will derive variables to evaluate changes in neighborhood SES between adulthood life stages. This will be performed by dichotomizing each adult life stage at the median split z-score for each racial group. For example, the neighborhood SES patterns between young and middle adulthood will include four categories: low-to-high or improvement (below the median in young adulthood and at or above the median in middle adulthood), high-to-low (decline), low-to-low (stable low), and high-to-high (stable high). This approach will be used to estimate the neighborhood-SES patterns at two periods: young-to-middle adulthood and middle-to-older adulthood. We will not examine changes from childhood since neighborhood SES derived from county-level information, which would not be comparable to the census-level information obtained at older ages.

Mortality

The study outcomes will include all-cause and cause-specific mortality. Follow-up time will be defined as time (in days) between baseline visit and mortality event or last contact date, whichever occurred first. The follow-up mortality outcomes will extend through December 31, 2019. In the event of study participant death, ARIC interviewers contacted participant proxy, obituaries, hospital records, death certificates, or vital statistics from the National Death Index. All-cause mortality determined as death from any cause, and cause-specific mortality will be based on the underlying cause reported on death certificates. Cardiovascular mortality will be defined as death due to stroke, myocardial infarction, coronary heart disease or other cardiovascular disease. Moreover, since cardiovascular disease and cancer are the leading causes of death in the U.S., cardiovascular- and cancer-specific mortality will constitute the cause-specific mortality of interest in this study.

Covariates

Information obtained at baseline for descriptive assessments will include the following characteristics: participants' self-reported age, education, income, marital status, race, sex, alcohol consumption, smoking status, and physical activity, body mass index [weight(kg)/height(m)2], blood pressure (diastolic and systolic blood pressure, estimated by averaging second and third of three blood pressure measurements), hypertension (defined as diastolic blood pressure of >90mm Hg, systolic blood pressure of >140 mm Hg, or self-reported antihypertensive medication use), and diabetes (defined as fasting glucose ≥126 mg/dL, non-fasting serum glucose of ≥ 200mg/dL, documented taking medication for diabetes or high blood sugar, or self-reported diabetes diagnosis from a physician).

Statistical analysis

To address missingness, we will apply multiple imputation by chained equations, including all covariates, with a minimum of ten imputed datasets created.[21] Descriptive statistics will be calculated using the original dataset without imputation to describe the study population characteristics.[22,23] Categorial variable will be presented as percentages, continuous variables with normal distribution will be shown as the mean with standard deviation, and continuous variables that are skewed will be presented as the median with interquartile range.

We will perform Cox regression analyses to assess the association between life-course neighborhood SES and mortality (all-cause and cause-specific) to estimate hazard ratios (HRs) and corresponding 95% confidence intervals (95% CI). Guided by conceptual models of neighborhood and health, we identified potential confounders, defined as factors that influence both living in certain neighborhoods and mortality, but not mediators of the association.[3,9] In Model 1, we will adjust for age, sex, and race. In model 2, we will adjust for Model 1+ education, income, marital status, and study site.

Since prior studies have shown associations of low neighborhood environment SES characteristics with the risk of premature mortality, we will leverage ARIC life course and mortality data to perform sensitivity analysis examining the relationship between neighborhood SES at different life stages and premature mortality (all-cause and cause-specific).[24,25] We will define premature mortality as death before 70 years of age according to Sustainable Development Goals adopted by the United Nations in 2015.[26] Participants who survived to age 70 years (or older) will be censored.

P for trend will be calculated by modeling quartiles of neighborhood SES as a continuous variable. We will further evaluate the interactions between neighborhood SES and race and sex using the likelihood ratio test comparing models with and without the cross-product term. The threshold of $P < 0.10$ will be used to assess significance of the interaction terms.[27] All analysis will be performed using R 4.0.2 and SAS 9.4.

7.a. Will the data be used for non-ARIC analysis or by a for-profit organization in this manuscript? ____ Yes _X_ No

b. If Yes, is the author aware that the current derived consent file ICTDER05 must be used to exclude persons with a value RES_OTH and/or RES_DNA = "ARIC only" and/or "Not for Profit" ? ____ Yes ____ No
(The file ICTDER 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 current derived consent file ICTDER05 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/mantrack/maintain/search/dtSearch.html

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)?

Life-Course Individual and Neighborhood Socioeconomic Status and Risk of Dementia in the Atherosclerosis Risk in Communities Neurocognitive Study

Life-Course Neighborhood Socioeconomic Status and Cardiovascular Events in Black and White Adults in the Atherosclerosis Risk in Communities Study

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*** 2004.05**)**

___ 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 https://sites.cscc.unc.edu/aric/approved-ancillary-studies

12a. 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.

We will complete this within three years.

12b. The NIH instituted a Public Access Policy in April, 2008 which ensures that the public has access to the published results of NIH funded research. It is **your responsibility to upload manuscripts to PubMed Central** whenever the journal does not and be in compliance with this policy. Four files about the public access policy from http://publicaccess.nih.gov/ are posted in http://www.cscc.unc.edu/aric/index.php, under Publications, Policies & Forms. http://publicaccess.nih.gov/submit_process_journals.htm shows you which journals automatically upload articles to PubMed central.

As an employee at the National Institutes of Health, we are required to adhere to this for all publications.

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