ARIC Manuscript Proposal #2284 (Amended)

PC Reviewed: 4/12/22	**Status: _____**	**Priority: 2**
SC Reviewed _____	**Status: _____**	**Priority:**

1.a. Full Title: Lifetime socioeconomic position and cognitive decline: the ARIC-NCS study

b. Abbreviated Title (Length 26 characters): **Lifetime SEP and cognition**

2. Writing Group:

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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]**

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3. Timeline: Complete manuscript by December 2022

4. Rationale:

Associations between low socioeconomic position (SEP) and poor cardiovascular health are well-established.[1] Previous work from the ARIC ancillary study (AS 1998.05 Socioeconomic Status and Health Across the Life Course (LCSES)) demonstrated a strong, inverse relationship of cumulative, life course SEP with subclinical atherosclerosis assessed in middle-age.[2] Extensive empirical evidence supports the importance of early life conditions and life course experiences in the onset and progression of adult chronic disease.[3,4] However, the role of lifetime SEP on cognitive function in older adults has not been sufficiently evaluated.

Several studies have examined associations between life course SEP and mid-life cognitive function, later-life decline, and incident dementia. Individuals with greater

socioeconomic disadvantage, in childhood or adulthood, have been consistently observed to exhibit poorer cognitive performance in various populations.[5-9] Most studies detected an independent association of childhood SEP with cognitive function, after accounting for adult socioeconomic achievement, whereas other studies questioned a direct effect of early life socioeconomic conditions on later-life cognition.[7,8] Regardless, early life conditions appear to play an important role in adult cognitive abilities.

While most studies have used individual attributes to define SEP, few have examined the role of neighborhood socioeconomic context on changes in cognitive function among older adults. Recent studies observed poorer cognitive functioning in adults residing in low SEP neighborhoods, independent of individual-level socioeconomic characteristics.[10-12] However, Zeki Al Hazzouri et al. found, among older (60+ years) Mexican-Americans, the association of neighborhood SEP with cognitive decline was predominantly explained by individual educational attainment.[11] A previous ARIC study of life course SEP and subclinical atherosclerosis did not observe a consistent relationship with neighborhood-level measures independent of individual SEP.[2] Where this study examined cumulative neighborhood context starting in childhood, Murray et al. focused on neighborhood changes from mid- to late-life and identified an association between distinct neighborhood socioeconomic trajectories (mobile and stable) and carotid IMT, which persisted, though not significant, after adjustment for individual adult SEP.[13] Given that neighborhood socioeconomic context appears to influence cardiovascular disease, more studies are needed to examine these processes as they relate to cognitive function among older adults.

In this manuscript, we will estimate the association of lifetime SEP with changes in objectively measured cognitive decline. Our objective will be to examine whether high SEP is protective with respect to cognitive decline overall or only within groups characterized by high cognitive decline. The ARIC-NCS study will provide extant data on 30- year changes in cognitive function in a well-characterized cohort, and we will use individual- and neighborhood-defined SEP indicators collected by the LCSES study to characterize lifetime socioeconomic context of cohort participants.

5. Main Hypothesis/Study Questions:

Our main hypothesis is that high SEP (defined by individual and neighborhood attributes) in childhood and maintained across the life course is associated with a low rate of cognitive decline from middle into old age. Based on recent findings from the Health and Retirement Study[14], we further hypothesize that the association of childhood SEP with the rate of cognitive decline in adulthood is mediated by midlife SEP and midlife cardiometabolic factors. Specific study aims are to:

Aim 1: Estimate the association of childhood individual and neighborhood SEP with a 30-year change in cognitive performance.

> **Sub-aim 1:** Examine potential mediation of the association of childhood SEP with a 30-year change in cognitive performance, by midlife SEP and cardiometabolic factors

Aim 2: Estimate the association of cumulative, lifetime SEP with a 30-year change in cognitive performance.

Aim 3: Estimate associations of socioeconomic mobility, between childhood, middle-age, and old age (e.g., upwardly mobile versus low stable) with a 30-year change in cognitive performance.

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

The study population will include those ARIC cohort participants who underwent cognitive testing at Visit 2 (N=14,201) and were queried on childhood and earlier life SEP in the LCSES ancillary study (N=12,716). We will exclude individuals of race other than Black or White and Black participants in Washington, MD and Minneapolis, MN (because of insufficient numbers).

Cognitive Decline

We will examine cognitive decline from Visit 2 to Visit 8. During Visits 2 and 4, cognitive performance was measured with three tests, Delayed Word Recall (DWR), Digit Substitution (DSS), and Word Fluency (WFT). At Visit 5 and during subsequent visits 6 and 7, the neurocognitive battery was expanded to include Incidental Learning (ILR), the Animal Naming Score (ANS), Logical Memory Test (LMT), Trail Making Test A (TMTA), Trail Making test B (TMTB), Digit Span Backwards (DSB) and the Boston Naming Test (BNT). Cognitive assessment at visit 8, which was conducted virtually over the phone due to the COVID-19 pandemic, consisted of a modified six-test battery that included the DSB, the ANS, a version of the WFT limited to the letters F and A, and three additional tests: Consortium to Establish a Registry for Alzheimer's Disease Word List (CERAD), Oral Trail Making Test A (OTMTA), and Oral Trail Making Test B (OTMTB).

To accommodate differences in cognitive tests that were administered at different visits utilizing different modes of administration (in-person and telephone at Visit 8) we will use co-calibrated factor scores. We will examine cognitive decline during follow-up periods depicted in Table 1, with splines applied as noted. In assessing cognitive decline through Visit 8, we will consider two options. The first option will include follow-up through the end of the in-person Visit 8 examination (March 2020). The second option will include follow-up through the end of Visit 8 (December 2020) and will include in-person and telephone assessments.

Table 1: Follow-up periods

Follow-up period	Splines
V2-V5	V4
V5-V8	V5
V2-V8	V4 and V5

Lifetime Socioeconomic Position (SEP)

Available data on individual and neighborhood attributes will be used to define SEP at various stages of the life course (Table 2). Individual and neighborhood SEP measures will be summarized into scores for each life stage and summed for a cumulative, lifetime SEP score using previously described methods[2,12]. Within each life stage, high, medium, and low SEP groups will be defined according to tertiles of the distribution. In sensitivity analyses, childhood and midlife SEP exposures will be categorized as deciles of the distribution.

Change in SEP from childhood to adulthood will be examined as continuous patterns of change over time. We will use the baseline intercept and the slope over time as exposures, testing the latent interaction between those over time. In a sensitivity analysis, patterns of change between childhood and adult SEP will be defined as five categories: low-to-high, high stable, medium stable, low stable, and high-to-low, which will be based on membership in tertiles of the exposure in childhood and at midlife (Visit

4) or in older adulthood (Visit 5).

Table 2. Individual and neighborhood socioeconomic measures in ARIC Life		
Life Stage	**Socioeconomic Measures**	
	Individual	**Neighborhood**
Childhood (age 10)	• Parental education • Parental occupation (non-manual or manual, managerial or non-managerial) • Parental home ownership	• Education among persons 25+ years old • Managerial occupations among persons 16+ years old • Value of owner-occupied homes • Family income
Young Adulthood (age 30)	• Education • Occupation (non-manual or manual, managerial or non-managerial) • Home ownership	• Education among persons 25+ years old • Managerial occupations among persons 16+ years old • Value of owner-occupied homes • Family income
Middle Age (ages 45 to 64)	• Family income • Occupation (non-manual or manual, managerial or non-managerial) • Home ownership	• Education among persons 25+ years old • Managerial occupations among persons 16+ years old • Value of owner-occupied homes • Household income
Old Age (ages 65+)	• Family income • Financial standing • Community standing	• Education among persons 25+ years old • Managerial occupations among persons 16+ years old • Value of owner-occupied homes • Household income
Adapted from Carson AP, et al. Cumulative Socioeconomic Status Across the Life Course and Subclinical Atherosclerosis. Ann Epidemiol. 2007		

Relevant Covariates

Participant age, sex, race, and study community were ascertained at baseline (Visit 1). Health-related behaviors and risk factors, measured at baseline and subsequent visits, will include cigarette smoking, obesity, diabetes, hypertension, anti-hypertensive medications, total cholesterol, LDL cholesterol, HDL cholesterol, cholesterol-lowering medications, and prevalent CHD and stroke.

We will examine potential effect measure modification of the association of childhood SEP with cognitive decline by midlife occupation complexity. Occupational status was ascertained at ARIC visit 1, during which participants' information on their most recent occupation was coded at each study center by two independent trained codes according to the 1980 U.S. Census Dictionary of Occupational Titles. An occupational complexity index has

been derived in ARIC by Anna Kucharska-Newton according to the following protocol: The 1980 occupational categories were cross-walked to the 1970 U.S. Census Dictionary of Occupational Titles (Mosbacher and Otner, 1989) so that the occupational complexity index could be calculated. Following protocols outlined by Jonaitis et al.,[15] a matrix developed by Roos and Trieman was used to assign work complexity classification for each occupational title[16] using three complexity ratings: complexity of work with data, complexity of work with people, and complexity of work with things. Scores ranged from 0 (most complex) to 6 (least complex) for complexity of work with data, 0 to 8 for complexity of work with people, and 0 to 7 for complexity of work with things. The scores were reverse coded to reflect correspondence of higher scores with greater work complexity. Analyses will be based on complexity of work with data, with lower scores representing least complex work. This continuous complexity of work with data index will be further categorized into tertiles of the distribution, with the lowest tertile representing the least complex work.

Statistical Analysis

We will estimate longitudinal changes in cognitive performance utilizing linear and quantile mixed effects models. Multiple imputation by chained equations will be employed to mitigate informative attrition. Baseline age and age^2 will be incorporated into the models as fixed effects. Random effects from each model denoting subject-specific estimates of annualized cognitive decline will be discretized into ordinal groups ranging from minimal cognitive decline to maximal cognitive decline. Iterations of each model will be tested including stratification by sex and race as well as the addition of sex, education, and race-center as fixed effects. Differences in how participants are classified into ordinal groups across models will be compared. Classifications from the most clinically meaningful model will be utilized as the primary outcome while classifications from the other models will be explored in sensitivity analyses. Ordinal and multinomial logistic regression models will examine the association of *a priori* specified SEP exposures with classifications of cognitive decline.

Multilevel analyses will account for both individual- and neighborhood-based measures. To address missing historical neighborhood information we will use multiple imputation methods as previously described.[17] We will examine effect measure modification by tertiles of the occupational complexity index. We will use multilevel causal mediation structural equation models to examine potential mediation of the association of childhood SEP with cognitive decline from midlife to older adulthood. Potential mediators will be considered at the individual level (e.g. education, cardiometabolic risk factors) and at the neighborhood level (e.g. neighborhood SEP).

The analytical approach described in this amended version of the proposal is intended to parallel the analytical approach specified in the amended version of MP#3207 (“Minimal cognitive decline”). For both proposals we will consider normative modeling approaches as additional sensitivity analyses.[18] Analyses conducted as part of MP#3207 will be used to inform potential use of multiple group structural equation modeling to examine differences in associations of SEP with cognitive decline across quantiles.

7.a. Will the data be used for non-CVD analysis in this manuscript? _X___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? _X___Yes

_____No
(This 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 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 926: Individual and Area-Level Lifecourse Socioeconomic Status and Subclinical Atherosclerosis

MS 960: Individual and area-level life-course SES and decline in renal function

MS 1858: Midlife occupation and 1990-2006 cognitive decline

MS 1982: Estimation of cognitive change from repeat measures in observational studies; associations with education: the ARIC NCS

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* 1998.05, 2008.06, Role of lifetime socioeconomic position in cognitive aging (PIs Patel/Heiss - AS proposal submitted **)**
____ 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/

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.

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.

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