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:
   Writing group members (in alphabetical order): Benjamin Capistrant, Laura Coker, Gerardo Heiss (senior), Dmitry Kats, Thomas Mosley, Priya Palta, Mehul Patel (first), John Preisser, Michelle Snyder, others welcome

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

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3. Timeline: Begin preliminary analyses immediately. Submit ancillary study proposal for funding in June 2014. Complete manuscript within 12 months of ancillary study onset.

4. Rationale:

   Associations between lower 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 performance. In other words, we will explore the role of SEP on resilient cognitive aging. The ARIC-NCS study will provide extant data on 20-year changes in cognitive function in a well-characterized biracial 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 higher SEP (defined by individual and neighborhood attributes) across the life course is associated with a lower rate of cognitive decline from middle into old age (Visit 2 to 5). Specific study aims include:
1. Estimate the association of cumulative, lifetime SEP with 20-year cognitive decline.
2. Estimate the association of childhood SEP with 20-year cognitive decline, independent of adult and older age SEP.
3. Estimate associations of socioeconomic mobility, between childhood, middle-age, and old age, (e.g., upwardly mobile versus low stable) with 20-year cognitive decline.

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 use data from the ARIC cohort (Visits 1-4, 1987-89) and the ARIC Neurocognitive Study (Visit 5, 2011-13) (Table 1). Childhood and adult SEP information, as collected in the LCSES ancillary study (2001-2002), will also be used. 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 study (N=12,716). We will exclude individuals of race other than Black or White and Blacks in Washington, MD and Minneapolis, MN (because of insufficient numbers).

<table>
<thead>
<tr>
<th>Table 1. Number of ARIC participants administered cognitive tests by visit</th>
</tr>
</thead>
<tbody>
<tr>
<td>Examined, N</td>
</tr>
<tr>
<td>Cognitive testing, N</td>
</tr>
</tbody>
</table>

**Cognitive Decline**

Cognitive performance was measured with three tests, Delayed Word Recall (DWR), Digit Substitution (DSS), and Word Fluency (WF), in all ARIC participants who attended Visits 2, 4, and 5. Baseline levels of cognitive function will be defined as Visit 2 cognitive test scores. Cognitive decline will be defined by repeat testing over the follow-up period (i.e., ~20 years). For analyses, cognitive test scores will be individually normalized to Z scores, based on means and standard deviations of scores at Visit 2, and then averaged and standardized to a global Z score.

**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). An ARIC ancillary study has been proposed to extend the SEP characterization of the cohort to older ages. In Aim 1, 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). Tertile statistics for the entire population will be used to define high, medium, and low SEP groups. We will estimate the crude association of childhood SEP
(individual and neighborhood) and adjusted for later life SEP in Aim 2. Trajectories between childhood and adult SEP will be defined as five categories: low-to-high, high stable, medium stable, low stable, and high-to-low (Aim 3).

Table 2. Individual and neighborhood socioeconomic measures in ARIC

<table>
<thead>
<tr>
<th>Life Stage</th>
<th>Individual Socioeconomic Measures</th>
<th>Neighborhood Socioeconomic Measures</th>
</tr>
</thead>
<tbody>
<tr>
<td>Childhood (age 10)</td>
<td>• Parental education</td>
<td>• Education among persons 25+ years old</td>
</tr>
<tr>
<td></td>
<td>• Parental occupation (non-manual or manual, managerial or non-managerial)</td>
<td>• Managerial occupations among persons 16+ years old</td>
</tr>
<tr>
<td></td>
<td>• Parental home ownership</td>
<td>• Value of owner-occupied homes</td>
</tr>
<tr>
<td></td>
<td>• Education among persons 25+ years old</td>
<td>• Family income</td>
</tr>
<tr>
<td>Young Adulthood (age 30)</td>
<td>• Education</td>
<td>• Education among persons 25+ years old</td>
</tr>
<tr>
<td></td>
<td>• Occupation (non-manual or manual, managerial or non-managerial)</td>
<td>• Managerial occupations among persons 16+ years old</td>
</tr>
<tr>
<td></td>
<td>• Home ownership</td>
<td>• Value of owner-occupied homes</td>
</tr>
<tr>
<td></td>
<td>• Education among persons 25+ years old</td>
<td>• Family income</td>
</tr>
<tr>
<td>Middle Age (ages 45 to 64)</td>
<td>• Family income</td>
<td>• Education among persons 25+ years old</td>
</tr>
<tr>
<td></td>
<td>• Occupation (non-manual or manual, managerial or non-managerial)</td>
<td>• Managerial occupations among persons 16+ years old</td>
</tr>
<tr>
<td></td>
<td>• Home ownership</td>
<td>• Value of owner-occupied homes</td>
</tr>
<tr>
<td></td>
<td>• Education among persons 25+ years old</td>
<td>• Household income</td>
</tr>
<tr>
<td>Old Age (ages 65+)</td>
<td>• Family income</td>
<td>• Education among persons 25+ years old</td>
</tr>
<tr>
<td></td>
<td>• Financial standing</td>
<td>• Managerial occupations among persons 16+ years old</td>
</tr>
<tr>
<td></td>
<td>• Community standing</td>
<td>• Value of owner-occupied homes</td>
</tr>
<tr>
<td></td>
<td>• Education among persons 25+ years old</td>
<td>• Household income</td>
</tr>
</tbody>
</table>


**Relevant Covariates**

Participant age, gender, race, and study community were measured 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.

**Statistical Analysis**

We will analyze longitudinal changes in cognitive performance with linear mixed models or generalized estimating equations, depending on recommendations from the ARIC-NCS data analysis working group. Multi-level 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 (2, 15). Inverse probability weighting will be used to account for potential selection bias due to deaths and losses to follow-up (16). Since race in the ARIC study is, by design, structurally confounded with geographic region, we will stratify analyses by Blacks and Whites.

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.csc.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.

References