

ARIC Manuscript Proposal #3210

PC Reviewed: 8/14/18

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Priority: 2

SC Reviewed: _____

Status: _____

Priority: _____

1.a. Full Title: Life Course Individual and Neighborhood Socioeconomic Status and Risk of Dementia and MCI in the Atherosclerosis Risk in Communities (ARIC) Neurocognitive Study (NCS)

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

2. Writing Group:

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

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3. Timeline: Begin analysis after ARIC approval in August

4. Rationale:

There is increasing evidence that chronic diseases in adults are caused by a complex accumulation and interaction of lifetime exposures. [1] These exposures not only involve common behavioral and biologic risk factors like smoking or obesity, but also sociodemographic factors such as socioeconomic status (SES). SES, also referred to as socioeconomic position (SEP), is defined as “social and economic factors that influence which positions individuals or groups will hold within the structure of a society.” [2] Measures of SES collected across the life course can be used to quantify the accumulation of risk by incorporating time of exposure across generations and over the progression of life epochs. [3][4] Life epochs generally include stages related to childhood, young adulthood, active professional life, retirement/older adulthood and can be measured at the individual and neighborhood/area level (Table 1). LC-SES models hypothesize that life epochs do not occur independently of one another, but events occurring during these periods can accumulate and interact leading to increased risk of chronic disease over a lifetime. [3][4] Some SES measures may only be relevant during specific life epochs, such as parental education during childhood, but influence subsequent exposures and have a lasting impact on disease risk.

Life Epoch	Example SES Measures
Childhood	Birthweight, Parent’s education, Parent’s occupation, Household income, Household conditions, Overcrowding
Young Adulthood	Education
Active Professional Life	Occupation, Household income, Employment status, Wealth, Partner’s SES, Household conditions

Retirement/Older adulthood	Household income, Wealth/deprivation, Household conditions
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Table 1. Examples of SES measures at different life epochs. [3][4]

Applying a life course perspective to dementia research offers an opportunity to understand a complex, heterogeneous disease process. Boundaries between diseases associated with dementia (e.g. Alzheimer’s disease (AD), cerebrovascular disease, Parkinson’s disease) are not always well defined and often overlapping. [5] These dementias share biological and behavioral risk factors (particularly age) that are related to and complicated by LC-SES (Figure 1). [5] Evidence suggests that while mid-life vascular risk factors are significantly associated with incident dementia, this association is likely confounded by cumulative effects of LC-SES that cannot be fully adjusted for using midlife or late-life SES factors alone. [6][7][8] Further, SES is an especially crucial component in the development of dementia, versus other chronic diseases, due to the importance of education and cognitive reserve on disease risk. Cognitive reserve is based on the observation that brain pathology or damage is not directly related to cognitive function. [9] While there is no standard measure of reserve, measures of SES and education are widely used proxies, because they are associated with environmental exposures related to advantage. [9]

A number of studies have found a significant association between SES and cognitive decline and dementia.[10][11][12][13][14][15][16][17][18][19][20][21][22][23][24] However, the methods used to measure SES vary widely between studies and many rely on SES measured only at middle age or later adulthood. Taking a cumulative life course approach to understanding dementia is important in order to account for risk factors that may have an additive effect on disease risk that are (partially or fully) masked by only examining risk factors in middle age or after. [4][6] Among studies that have assessed LC-SES and cognitive function, very few have measured both individual and neighborhood-level SES factors. Further, the relationship between

SES and cognitive function independent of education has not been fully characterized, nor the relationship between individual and neighborhood LC-SES. Using ARIC-NCS, we can better assess the association of cumulative LC-SES with risk of dementia and MCI, as well as better understand how individual and neighborhood level SES influence dementia and MCI risk in a biracial cohort with over 25 years of follow-up.

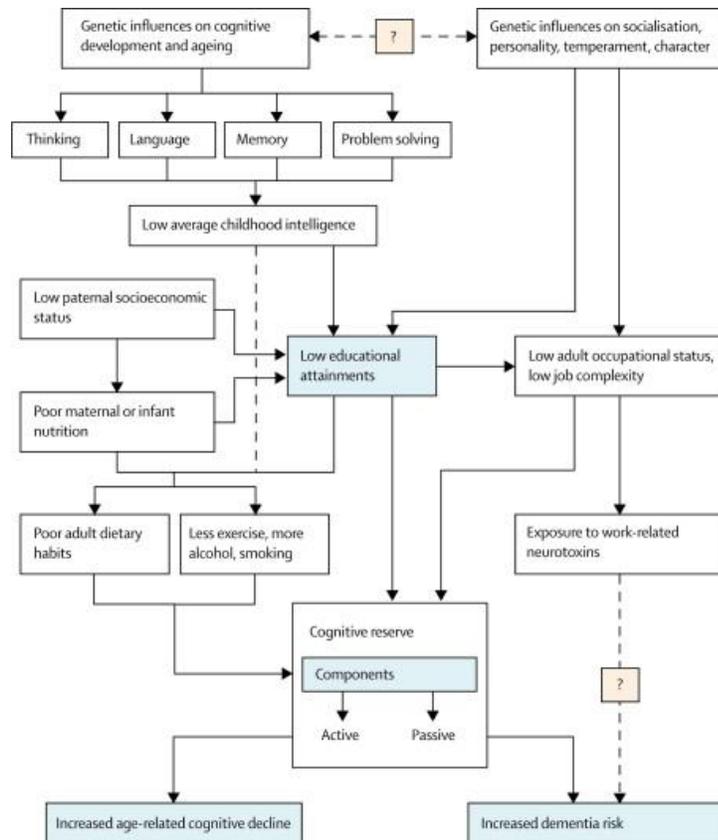


Figure 1. Pathways in cognitive decline and dementia [5]

5. Main Hypothesis/Study Questions:

Aim 1: Assess the association between cumulative individual-level LC-SES and dementia and mild cognitive impairment (MCI)

Hypothesis 1: We hypothesize that participants with the low cumulative individual-level LC-SES score will be at increased risk of dementia and MCI compared to participants with high cumulative individual-level LC-SES

Aim 2: Characterize the association between cumulative individual-level LC-SES and dementia and mild cognitive impairment independent of individual educational attainment

Hypothesis 1: We hypothesize that the individual-level LC-SES score will be associated with dementia and MCI independent of individual educational attainment

Aim 3: Assess the association between cumulative neighborhood-level LC-SES with dementia and mild cognitive impairment

Hypothesis 1: We hypothesize participants with low cumulative neighborhood-level LC-SES score will be at increased risk of dementia and MCI independent of their individual-level LC-SES score

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: Prospective Cohort Study: association between cumulative LC-SES (childhood through older adulthood) and dementia outcomes from visit 1 (1987-1989) through visit 5 (2011-2013)

Exclusions: Participants will be excluded if they are non-white or African American (as well as African Americans in MD or MN) or did not participate in the LC-SES ancillary study (2001-2002).

Exposure:

Cumulative LC-SES scores will be created for both the individual and neighborhood-level by summarizing SES variables related to each life epoch, childhood through older adulthood, following ARIC convention (Table 3). [25] For individual LC-SES, variables related to each epoch will have a range of possible values between 0 (lowest SES) and 5 (highest SES). [25] These epoch scores can be summed to get a cumulative individual LC-SES score ranging between 0 and 15. [25] Neighborhood LC-SES variables were identified in a factor analysis from available census data across several decades. [25] Because of segregation, race-specific z-scores were obtained for each census variable and summed to develop a summary z score for cumulative neighborhood LC-SES where a higher z score indicates higher SES. [25] Individual and neighborhood-level cumulative LC-SES scores will be used to create race-specific distribution-based tertiles of SES defined as low, medium, and high. However, a sensitivity analysis will be conducted using different categorical classifications of individual and neighborhood-level cumulative SES scores.

Table 3. Individual and neighborhood life course socioeconomic factors and scoring adapted from Carson AP, 2007 [25]

Life Epoch	Individual Variable	Individual Variable Value	Neighborhood Variable*
Childhood (age 10)	Parental Education	<8 th grade = 0	Adult Education
		8 th grade = 1	
		>8 th grade = 2	
	Parental Occupation	Manual = 0	Adult Occupation

		Non-manual = 1	
	Parental Occupational Role	Non-managerial = 0	Dwellings Occupied by Owner
		Managerial = 1	
	Parental Home Ownership	Rent or other = 0	Median Home Value
Own home = 1			
Young Adulthood (age 30 years)	Education	<High school = 0	Adult Education
		High school = 1	
		>High school = 2	
	Occupation	Manual = 0	Adult Occupation
		Non-manual = 1	
	Occupational Role	Non-managerial = 0	Median Income
		Managerial = 1	
	Home Ownership	Rent or other = 0	Dwellings Occupied by Owner
Own home = 1			
		Median Home Value	
Older Adulthood (age 45-65 years)	Income	<\$25,000 = 0	Adult Education
		\$25-34,999 = 1	
		≥\$35,000 = 2	
	Occupation	Manual = 0	Adult Occupation
		Non-manual = 1	
	Occupational Role	Non-managerial = 0	Median Income
		Managerial = 1	
	Home Ownership	Rent or other = 0	Dwellings Occupied by Owner
Own home = 1			
		Median Home Value	

*Neighborhood variables will be scored using summary z-score

Outcome:

We will use dementia and mild cognitive impairment (MCI) outcomes identified using three levels of criteria. The first level, involved adjudicated outcomes from visits 5 (2011-2013) NCS evaluations including the longitudinal cognitive assessments from visits 2, 4, and 5. [26] A standardized definition for dementia and MCI was used for level 1 classification to generate computer algorithmic diagnoses; a panel of physicians and neuropsychologists reviewed each

case of suspected cognitive impairment as well as a random sample of cognitively normal participants. [26]

Level 2 dementia and MCI includes cases identified in level 1 as well as participants who did not attend ARIC-NCS and were identified through telephone interview for cognitive status (TICS), informant telephone interview using a modified version of the Clinical Dementia Rating (CDR), and a random sample used to correct for missed cases. [26] This identification primarily occurred during visit 5 (2011–2013). [26] Finally, level 3 includes levels 1 and 2 as well as participants identified through surveillance for hospitalization discharge codes (ICD-9) or death certificate codes related to dementia which were primarily identified prior to visit 5. [26]

Separate analyses will be run using two definitions of dementia and MCI outcomes. The first definition will include all incident dementia cases from visit 2 through 5 (level 3 criteria). The second definition will only include adjudicated dementia and MCI cases (level 1 criteria), which were identified at ARIC visit 5 and include information on etiology (i.e. Alzheimer's disease vs. cerebrovascular vs. other determined by additional review of a participant's brain magnetic resonance imaging (MRI) scan).

Covariates from visit 1 (1987-1989): age, sex, race (MS-blacks, NC-whites, NC-blacks, MN-whites, and MD-whites), APOE ϵ 4, body mass index (BMI), smoking status, hypertension (defined as systolic blood pressure \geq 140 mm Hg, or diastolic blood pressure \geq 90 mm Hg, or self-report of antihypertensive medication use), diabetes, drinking status, HDL cholesterol, and total cholesterol

Covariates from LC-SES Ancillary Study (2001-2002): see Table 3 (above)

Analysis:

Analyses will follow ARIC NCS analysis working group recommendations. Incidence rates of dementia from visit 1, 1987-89, through visit 5, 2011-13, will be calculated using Poisson regression stratified by individual-level LC-SES, neighborhood-level LC-SES, and a cross-classification of individual and neighborhood LC-SES.

Aim 1, Assess the association between cumulative individual-level LC-SES and dementia and mild cognitive impairment (MCI). For aim 1, hypothesis 1, Cox regression with a competing risk of non-dementia related death will be used to assess the hazard of level 3 dementia between visits 1 and 5 in relation to cumulative individual LC-SES. We will repeat this analysis using level 1 cases in a relative risk regression to assess cumulative individual LC-SES and adjudicated dementia and MCI at visit 5. Relative risk regression will be conducted using generalized linear models with a Poisson distribution and a log link. To account for possible attrition over follow-up, we will follow ARIC NCS analysis working group recommendations by applying multiple imputation by chained equations (MICE). For both analyses, we will use marginal structural models to account for time-varying confounding by cumulative individual LC-SES from childhood through late adulthood on risk of dementia and MCI.

Aim 2: Characterize the association between cumulative individual-level LC-SES and dementia and mild cognitive impairment independent of individual educational attainment. For aim 2 hypothesis 1, Cox regression with a competing risk of non-dementia related death will be used to assess the hazard of dementia with individual-level LC-SES after removing educational attainment from the cumulative LC-SES score. This will allow us to characterize the association between non-education LC-SES factors and dementia independent of education. The analysis will be repeated using adjudicated dementia and MCI cases from visit 5 using relative risk

regression with a Poisson distribution, log link, and MICE. To account for time-varying confounders, models will use marginal structural models.

Aim 3: Assess the association between cumulative neighborhood-level LC-SES with dementia and mild cognitive impairment. For aim 2 hypothesis 1, Cox regression with a competing risk of non-dementia related death will be used to assess the hazard of dementia with cumulative neighborhood LC-SES using marginal structural models to adjust for time-varying individual and neighborhood LC-SES. Again, analysis will be repeated using adjudicated dementia and MCI cases using relative risk regression and MICE.

We will consider whether major risk factors for dementia measured at visit 1 (as confounders, effect modifiers, or mediators) and include adjustment for baseline covariates when appropriate. All analyses will be race-specific (African American and white).

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 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 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>

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)?

#880: Retrospective Ascertainment of Early Life SES: Experiences from the Life Course SES, Social Context, and Cardiovascular Disease Study

#930r: Lifecourse SES and Systemic Markers of Inflammation

#960: Individual and Area-Level Life-Course SES and Decline in Renal Function: The Atherosclerosis Risk in Communities Study

#972: A Descriptive Study of Socio-Environmental Exposures across the Life Course in the ARIC Study

#1099: SES Across the Life Course and the Metabolic Syndrome

#2284: Lifetime Socioeconomic Position and Cognitive Decline: The ARIC-NCS Study

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

11.b. If yes, is the proposal

A. primarily the result of an ancillary study (list number* 1998.02)

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.csc.unc.edu/atic/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.csc.unc.edu/atic/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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