

ARIC Manuscript Proposal # 1858

PC Reviewed: 10/08/19

Status: A

Priority: 2

SC Reviewed: _____

Status: _____

Priority: _____

1.a. Full Title: Midlife occupation and cognitive decline: the ARIC-NCS study

b. Abbreviated Title (Length 26 characters): Occupation and cognition

2. Writing Group:

Writing group members: Mehul Patel, Rebecca Gottesman, Thomas Mosley, Andrea Schneider, Ola Selnes, Josef Coresh, A. Richey Sharrett

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:

Preliminary results presented at 2012 SER meeting (Minneapolis, MN). Begin analysis of currently available ARIC-NCS Visit 5 data; complete manuscript within 6 months of final NCS Stage 1 data distribution.

4. Rationale:

Cognitive, or brain, reserve is a theoretical property of the central nervous system characterized by the capacity to preserve cognitive performance in the presence of brain disease, like Alzheimer's Disease or vascular dementia. Factors that may have these effects, such as education, occupational complexity, and mental activities (e.g. crossword puzzles), might influence either the level of cognitive performance or the rate of cognitive decline.

A recent systematic review presents evidence for the protective effects of higher education, more complex occupation, and more stimulating mental activities (individually and combined) on rate of cognitive decline [1]. However, much of the evidence on which the review was based was questioned by Glymour et al [2]. Also, results are difficult to compare between studies since there is significant heterogeneity in the way cognitive performance is tested. Furthermore, while education is generally defined in terms of years of school completed, various occupational classifications and status scores are used as proxies for the intellectual complexity of occupations. Studies of the independent effect of occupation on cognitive decline have produced mixed results, with either insignificant or a minimally significant benefit of higher occupation [3-7], except for a recent study that found a greater decline in the high occupation group [8]. Discrepancies in reported findings can be attributed not only to differences in occupation and cognitive performance measures but also in the covariates adjusted for in analyses.

We aim to estimate the association of midlife occupation with baseline level of cognitive performance and cognitive decline later in life in the Atherosclerosis Risk in Communities (ARIC) cohort, adjusting for age, gender, race, education and other relevant covariates. The ARIC study offers an ideal setting given the detailed education and occupation data that were collected at baseline and cognitive function testing covering a range of cognition domains that was conducted at multiple follow-up visits. Furthermore, the ARIC study is one of the largest population-based studies of white and black, men and women in the US.

5. Main Hypothesis/Study Questions:

Main Hypothesis: Higher occupational position at midlife is associated with increased levels of baseline cognitive performance and decreased cognitive decline later in life

Primary Aim: Estimate the association of participant's occupational position (1987-89) with baseline levels and declines in cognitive test scores (Delayed Word Recall, DWR; Digit Substitution, DSS; Word Fluency, WF) from 1990-92 to 2011-13, adjusting for educational attainment and other relevant covariates

Secondary Aim: Estimate the joint association of occupation and education on baseline levels and declines in cognitive test scores

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 ARIC cohort consists of 15,792 white and black, men and women ages 45–64 years at the onset of the study (1987-89). The proposed study will include follow-up from Visit 2 (1990-92) through Visit 5 (2011-13) for cohort participants. Repeat cognitive performance scores from Visits 2, 4, and 5 will be analyzed. We will not include cognitive testing at Visit 3 and the Brain and Carotid MRI visits since these were conducted on a non-random subsample of participants.

For this analysis, we will exclude individuals of race other than white or black race and blacks in Washington, MD and Minneapolis, MN (because of insufficient numbers). Participants with missing occupation and education information will also be excluded.

Additional Exclusions

Participants who did not undergo cognitive testing at Visit 2 will be excluded from the analysis of cognitive performance. For weighted analyses of cognitive decline, we will also exclude participants missing data on relevant time-fixed and time-varying covariates (see “Inverse Probability of Selection Weighting” section on page 5).

Exposure: Occupation

For the aims of this analysis, occupation will be defined in two ways: a categorical occupation classification and a continuous occupational status score. Based on each participant’s report of his/her current employment status and most recent occupation, we will code participant’s occupation into the six Census summary groupings, which are based on the 1977 Standard Occupational Classification (shown in ARIC Cohort Procedures Manual 2a Visit 1 Appendix III), and additional groups will be created for “retired” and “homemaker” employment status. Table 1 displays the distribution of occupation groups by gender. We hypothesize that the highest status group (i.e. managerial and professional specialty occupation) will be associated with the highest baseline cognitive function and the lowest cognitive decline.

Table 1. Distribution of occupational groups by gender, ARIC Visit 1 (1987-89)

Derived Occupation Groups	Men, n	Women, n
Census Summary Groupings*		
Managerial and Professional Specialty Occupations	1,903	1,607
Technical, Sales, and Administrative Support Occupations	1,053	2,059
Service Occupations	353	1,339
Farming, Forestry, and Fishing Occupations	100	17
Precision Production, Craft, and Repair Occupations	1,100	151
Operators, Fabricators, and Laborers	970	598
Homemakers	15	1,546
Retired	1,567	949
missing/never worked	21	444

*Based on 1977 Standard Occupational Classification

Since occupational summary groups can be heterogeneous with respect to type of job, we will also characterize occupation using a socioeconomic status (SES) score. The Nam-Powers occupational status score (ranging from 0 to 100) ranks by the median education and median income of the persons employed in that occupation for each decennial US Census since 1940 [9]. While there are several such scores to consider, we chose Nam-Powers since it has been created for the 1980 Census and can be readily coded from the available data in ARIC. Furthermore, a previous study found a strong association between cognitive impairment and low SES, as measured by the Nam-Powers occupation score [10]. Finally, although occupational status scores are mainly a measure of social standing, we feel the Nam-Powers score is a reasonable, yet limited, proxy for occupational complexity. We hypothesize that an increase in Nam-Powers occupational status score will be associated with a higher baseline cognitive function and a lower cognitive decline.

Outcome: Cognitive Performance and Decline

Cognition 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 (Table 2). The same protocols were used at all visits. Baseline levels of cognitive function will be determined by Visit 2 cognitive test scores. Cognitive decline will be defined as a decrease in test scores over the follow-up period (i.e., ~20 years).

Table 2. Number of ARIC participants administered cognitive tests by visit

	Visit 2 (1990-92)	Visit 4 (1996-98)	Visit 5 (2011-13)
Examined, N	14,348	11,656	6,533
Cognitive testing, N	14,201	11,343	6,515

Relevant Covariates

Demographic variables will include age, gender, and race-center. To test effect measure modification by education, categories of less than high school, high school or equivalent (GED/vocational school), and more than high school will be used. Other relevant covariates will include smoking, diabetes, hypertension, previous CHD/stroke, and ApoE genotype. Time interactions with all covariates will also be considered as covariates. Covariates believed to affect both occupation and cognitive decline, directly or indirectly, will be treated as potential confounders.

Statistical Analysis

Cognitive test scores will be individually normalized into race-specific Z scores, defined on the basis of visit 2 means and standard deviations, and averaged to a global Z score. To estimate associations between cognitive decline and occupation, we will use a random-effects linear model for repeated measures within individuals. Changes in cognitive performance between Visits 2, 4, and 5 will be analyzed by a linear mixed

model with random intercept and slope effects. Two-piece splines, as used in other change papers and discussed in the Analysis Workgroup, will be considered to handle non-linear changes. Models with occupational categories will be gender-stratified since a much larger proportion of female participants were homemakers (19%) compared to males. Race-center interactions will be examined to determine the possible necessity of race stratified models. The main regression models will include demographic variables and education. To assess an occupation-education interaction, we will fit models with product terms between occupational status score and education level.

Inverse Probability of Selection Weighting

Since substantial cohort attrition occurred over the course of follow-up, inverse probability weighting (IPW) will be used to account for potential selection bias [11]. For each follow-up visit (i.e., Visits 4 and 5), we will fit logistic models separately estimating the probability of being alive and undergoing cognitive testing. The Visit 4 selection models will include the main “exposure” (i.e., occupation group), time-fixed covariates (i.e., gender, race-center, education, and age at Visit 2), and time-varying covariates (i.e., Visit 2 global cognitive Z score, current smoking, current drinking, hypertension, diabetes, previous CHD, and previous stroke). Visit 5 selection models will include these variables in addition to time-varying covariate information at Visit 4. Important variables may include those collected at follow-up interviews, such as functional status or self-perceived health relative to others. These variables are likely to influence death and dropout and have minimal missing data.

Informally, the weight for each participant at a particular follow-up visit is the inverse of the cumulative probability of being alive and tested at the visit. We will examine the distribution of constructed weights for any highly weighted individuals and will winsorize and stabilize weights accordingly. These weights will then be incorporated into linear mixed models.

Additional Analytical Considerations

In additional analyses, we will exclude participants with a neurologic disorder that could affect cognitive performance – stroke/TIA, multiple sclerosis, Parkinson’s disease, dementia, brain tumor, or surgery or radiation therapy involving skull or brain. Since certain medications can affect cognitive performance, we will drop test scores if the participants was taking CNS-altering medications (anxiolytics, antipsychotics, hypnotics/sedatives, anticonvulsants, and dementia drugs or nootropics) at the time of the visit.

Lastly, we will consider a sensitivity analysis of the bias due to exclusion of dementia cases from cognitive decline studies. For the 663 whites and 76 blacks who did not attend Visit 5 but completed the Telephone Interview for Cognitive Status (TICS) assessment, we could impute a global cognitive performance Z score and repeat analyses. In a separate analysis, we could multiple impute cognitive performance scores for dementia cases who did not attend or died before Visit 5. This approach will be further developed after dementia case ascertainment and validation is completed.

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

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)?

MS 1742 Education and cognitive change from 1990-92 to 2004-06 (First author: Gottesman)

MS 1982 Estimation of cognitive change from repeat measures in observational studies; associations with education (First author: Gottesman)

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

Brain MRI (Mosley)
ARIC-NCS (Coresh)

11.b. If yes, is the proposal

A. primarily the result of an ancillary study (list number* 1999.01, 2008.06)

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/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

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