ARIC Manuscript Proposal #4187

PC Reviewed: 1/10/23	**Status: _____**	**Priority: 2**
SC Reviewed: _____	**Status: _____**	**Priority: ____**

1.a. Full Title:
Timing of cognitive test score decline prior to dementia onset: The Atherosclerosis Risk in Communities (ARIC) Study

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

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

Writing group members: Yunzhi Wang; A Richey Sharrett; Josef Coresh
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I, the first author, confirm that all the coauthors have given their approval for this manuscript proposal. __YZW___ **[please confirm with your initials electronically or in writing]**

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3. Timeline:
Since the proposed project is an analysis of existing data, we anticipate that it will take <12 months from MSP approval to submission of the manuscript to the ARIC Publications Committee.

4. Rationale:

About 50million people worldwide live with dementia. The number of people with dementia is rising. The global age-standardised prevalence of dementia between 1990 and 2016 was relatively stable, but with an ageing and bigger population the number of people with dementia has more than doubled since 1990 (1). Prior studies have shown that cognitive tests, such as the Delayed Word Recall Test (DWRT), the Digit Symbol Substitution Test (DSST), and the Word Fluency Test (WFT) can show lower performance on average in persons who are starting on the spectrum of cognitive disease (2, 3, 4). A previous ARIC study showed that declining DWRT and DSST scores in 6-year period were strongly associated with dementia incidence (5). Amieva et al performed neuropsychological testing and dementia screening using DSM-III-R criteria at 8 time points over a period of up to 19 years to study the relationship between cognitive test scores and Alzheimer's disease and found that cognitive decline began at least 15-16 years prior to dementia with accelerated decline 7 years before dementia (6). Another Wilson et al study with cases limited to dementia of presumed Alzheimer's disease completed a mean of 7-years annual evaluations with a few participants followed up to 16 years found that cognitive decline accelerates during the 5 years prior to dementia due to Alzheimer's disease (7). This association has been supported by other large-scale cohort studies, including the Framingham Heart Study and the Cardiovascular Health Cognition Study (3, 8). However, with a few exceptions, previous studies on this topic were limited to a single-occasion assessment of cognitive function, shorter length of follow-up than in ARIC, non-adjudicated dementia definitions and/or focusing mostly on populations who were elderly at baseline.

Herein we propose to characterize the associations between cognitive test scores at visits 2, 4, 5 and 6 with incident dementia level 3 ascertainment in the ARIC Study. We seek to examine if cognitive test scores in participants with future dementia are significantly different in the years before the onset of dementia from those without incident dementia, and to characterize how many years before the dementia those differences were substantial or significant.

5.Main Hypothesis/Study Questions:

We hypothesize that participants will have lower mean cognitive function more than 20 years before the onset of dementia. This difference from persons without dementia will be stronger the closer to the onset of dementia and be independent of confounding by demographic factors.

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 of visit 2, 4, 5 and 6 cognitive test scores, respectively, and risk of incident dementia diagnosis. Cognitive function is assessed at four time points (visits 2, 4, 5 and 6) by the Digit Symbol Substitution Test (DSST), the Delayed Word Recall Test (DWRT), and the Word Fluency Test (WFT).

Study Population:

Study population will include all ARIC participants who survived and attended visit 2, 4, 5 or 6, respectively.

Exclusions: 1) diagnosis with dementia at or prior to the according baseline visit (2, 4, 5 or 6); 2) Those who did not have cognitive testing will be excluded, including those who died during the follow up, though we keep their contribution before they died. (For example: A participant who died before visit 5 but was examined at visit 2 and 4 will be kept in the count related to visit 2 and 4 scores.)

Exposures:
Cognitive function at visit 2, 4, 5 and 6 will be the exposure variable. In the ARIC Study, cognitive function was assessed using three standardized tests:

1) The DSST of the Wechsler Adult Intelligence Scale-Revised (WAIS-R), a test of attention, executive function and processing speed (9).
2) The DWRT, a test of verbal learning and recent memory required elaborative processing of to-be-remembered words and delayed free recall (10).
3) The WFT, also known as the Controlled Oral Word Association Test (COWA) of the Multilingual Aphasia Examination. It is a test of executive function and expressive language (11).

We will also use 3-test z-score at each visit calculated by summing the mean of the DWRT, the DSST, and the WFT z scores, also standardized to visit 2 by subtracting the mean of the combined z score and then dividing by the standard deviation of the combined score (12).

Covariates:
Age, sex, race-center (Washington-White, Forsyth-White, Forsyth Black, Jackson-Black, and Minneapolis-White), education level (< high school; high school graduate or equivalent; college or professional school).Age will be assessed at each baseline testing visit.

Stratifying variable:
We plan to conduct stratified analyses by dementia status and explore its association with cognitive function.

Outcome:
The study outcome will be the level 3 ARIC definition of dementia: namely, for dementia ascertained at a visit, expert reviewer diagnosis, an algorithmic diagnosis, and for first dementia assessed outside of a visit, AD8 (AD8 Dementia Screening Interview), SIS (Six Item Screener), or dementia codes from hospitalizations or death certificates. Diagnoses are prioritized, with the reviewer diagnosis being given highest priority, then the algorithmic diagnosis, AD8, SIS, hospitalization codes, and finally death certificate codes, however the date of the ascertainment is the first-recorded diagnosis, unless found not demented at a later visit (13). Visit 7 will be used as censoring end point.

Statistical Analysis:

We will compare the cognitive test scores at fixed intervals (We will calculate the interval between the date of dementia diagnosis or censoring date and the cognitive test date, and divide it into time intervals for every five years) prior to dementia in two groups - participants who were diagnosed with dementia within that interval vs. those who survived that interval but did not develop dementia. Also, we will use the Welch Two Sample T-test to evaluate the difference between each pair of groups (non-dementia vs. dementia) within same time interval.
The adjustment model will include age, gender, race-center and education level. We will fit a separate linear regression model for each visit to calculate the individual residuals. Then add the intercept to the average of all individual residuals in each time interval by dementia status to get adjusted z-scores for each test, interval and visit.

We will plot the mean test scores for dementia and non-dementia group within each time interval in figures, using different colors to distinguish between the different visits.

Limitation:
The main limitation of the study is that we do not have data with which to separate specific causes of dementia, such as vascular or Alzheimer's disease. It is difficult to know whether test differences would show similar time associations for separate dementia subgroups.

7.a. Will the data be used for non-ARIC analysis or by a for-profit organization in this manuscript? ____ Yes __√__ 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 __√__ 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

___√___ 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)?
Cognitive Function and Incident Dementia: The ARIC Study (MS1700) | Christman, A.

The association of microvascular retinal abnormalities with cognitive decline and cognitive status after 10 years. (ARIC Study) | Lesage, S.
Changes in cognitive test scores in the ARIC cohort over a 6-year period (Visit 2 to Visit 4) and their correlation with vascula | Knopman, D.

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* _____)

___ 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.

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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