

## ARIC Manuscript Proposal #3452

PC Reviewed: 8/13/19  
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Priority: 2  
Priority: \_\_\_\_\_

**1.a. Full Title:** Sex Differences in Cognitive Decline: A Pooled Cohort Analysis of ARIC, CARDIA, CHS, FOS, and NOMAS

**b. Abbreviated Title (Length 26 characters):** Sex Differences in Cognitive Decline: A Pooled Cohort Analysis

### 2. Writing Group:

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

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**3. Timeline:** We plan to submit an abstract for submission to the International Stroke Conference (February 19-21, 2020, Los Angeles, CA), with a submission deadline of August 13, 2019. Manuscript preparation will be ongoing, with an expected draft completion date of 7/1/2020.

**4. Rationale:** Sex differences in dementia risk are unclear. We know that women have greater prevalence of Alzheimer's disease than men at least partly because women live longer.<sup>1,2,3</sup> Some, but not all, studies suggest that women have higher incidence of Alzheimer's disease.<sup>4,5,6</sup> Sex differences in biological and social factors, including CV risk and education levels, are hypothesized to contribute to sex differences in CID risk.<sup>7,8</sup> Yet, most studies have focused on the effects of CV risk and education on sex disparities in late-life CID. It is unclear how sex differences in CV risk and educational levels contribute to sex differences in cognitive trajectories. Leveraging an existing pooled cohort of five population-based cohort studies of individuals (blacks, whites, and Hispanics) aged 5 to 95 at cohort baseline with repeated objective measures of cognition, we will conduct a pooled cohort study to determine sex differences in later-life cognitive trajectories.

**5. Main Hypothesis/Study Questions:**

Main study question: Do women have greater risk for cognitive decline than men?

Hypothesis: Women have greater risk for cognitive decline than men.

**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 conduct a pooled cohort analysis using individual participant data from five well-characterized American prospective cohort studies with repeated measures of BP and cognition: Atherosclerosis Risk in Communities Study (ARIC), Coronary Artery Risk Development in Young Adults Study (CARDIA), Cardiovascular Health Study (CHS), Framingham Offspring Study (FOS), and Northern Manhattan Study (NOMAS) for years 1971 to 2017. We will require participants to have  $\geq 2$  measurements of cognition. Because cumulative mean BP is significantly associated with cognitive decline in this pooled cohort, we also require all cohort participants to have  $\geq 1$  measurement of BP at or before the first measurement of cognition. We will exclude participants reporting a baseline history of stroke and those with incident stroke or cohort-defined incident dementia at or before first measurement of cognition.

**Outcomes:** The primary outcome will be change in global cognition. Secondary outcomes will be change in memory and executive function. To make inferences about cognitive domains instead of individual cognitive test items, and to resolve the challenge of different cognitive tests administered across the cohorts, we have co-calibrated available cognitive test items into factors representing global cognition (global cognitive performance), memory (learning and delayed recall/recognition), and executive function (complex and/or speeded cognitive functions) using item response theory (IRT) methods that leverage all available cognitive information in common across cohorts and test items unique to particular cohorts.<sup>9</sup> In a pre-statistical harmonization phase, we have identified 126 test items from 32 cognitive instruments across the cohorts and determined shared items between cohorts.<sup>10</sup> Expert neuropsychologists (EMB, BJB) have assigned each test item to a cognitive domain. In IRT, each test item is weighted based on its correlation with other items and empirically assigned a relative location along the latent trait (e.g., global cognition) corresponding to its estimated difficulty. We have computed factor scores

from models for each domain using the regression-based method in Mplus version 8.1.<sup>11,12</sup> Cognitive outcomes have been set to a t-score metric (mean 50, SD 10 at a participant's first cognitive assessment); a 1-point difference represents a 0.1 SD difference in the distribution of cognition across the 5 cohorts.

**Covariates:** Covariates are factors that could influence sex and cognition. We will use covariate values measured closest to, but not after, the first cognitive assessment. We have harmonized covariates across cohorts by choosing common response categories for categorical variables and converting measurements to common units for continuous variables. Covariates are age (continuous), race/ethnicity (black, white, Hispanic), cohort (ARIC, CARDIA, CHS, FOS, NOMAS), education (eighth grade or less, grades 9-11, completed high school, some college but no degree, college graduate or more), alcoholic drinks per week (none, one to six, seven to thirteen, fourteen or more), current cigarette smoking, any physical activity, body mass index, waist circumference, history of atrial fibrillation, fasting glucose, LDL cholesterol, cumulative mean systolic blood pressure, anti-hypertensive medication use. Note: We cannot include other socioeconomic factors (e.g., literacy, quality of education, occupation, and childhood socioeconomic status) or depressive symptoms, because they are unavailable for all cohorts at or before the first cognitive assessment.

#### **Statistical Analysis:**

We will compare participant characteristics by sex using a 2-sample t-test with equal variance or  $\chi^2$  test as appropriate. Linear mixed-effects models will measure changes in each continuous cognitive outcome over time by sex. The models will include covariates, interaction terms for age at the time of first cognitive assessment\*follow-up time, sex\*follow-up time, and race\*follow-up time, as well as subject-specific random effects for intercepts and slopes. All continuous variables will be centered at the overall median, except cumulative mean SBP, which will be centered at 120 mmHg. Glucose, LDL cholesterol, and SBP values will be divided by 10 so that the parameter estimates reflect a 10-unit change in the variables. Time will be treated as a continuous measure defined as years since first measurement of each cognitive outcome.

For each outcome, all available cognitive observations will be used in the primary analysis except observations after the time of first cohort-adjudicated incident stroke during follow-up, because incident stroke alters the cognitive trajectory.<sup>13</sup> We will inspect residual plots to evaluate the assumptions of the linear mixed-effects models (e.g., linearity of relationships of interest and normality of residual errors). To estimate sex differences in cognitive decline, models will include a sex\*follow-up time interaction term. Statistical significance for all analyses will be set as  $P < 0.05$  (2-sided). All analyses were performed using SAS version 9.4 (SAS Institute, Cary, NC).

**Sensitivity Analyses:** We will repeat analyses including participants' cognitive observations after the time of incident stroke and also after adding kidney function (glomerular filtration rate, GFR<sup>14</sup>) and history of myocardial infarction because they may be on the causal pathway. To assess attrition bias, we will repeat analyses after adding death as a covariate to the models. We will repeat analyses within cohorts to assess heterogeneity in the associations between sex and cognitive decline.

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/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)?

Co-author Rebecca Gottesman has published articles on BP and cognition using ARIC data. Co-author Alden Gross has published article on harmonization of cognitive measures using ARIC data.

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\* 2008.06, ARIC-NCS, PI Coresh)

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 <https://www2.csc.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.csc.unc.edu/aric/index.php>, under Publications, Policies & Forms. [http://publicaccess.nih.gov/submit\\_process\\_journals.htm](http://publicaccess.nih.gov/submit_process_journals.htm) shows you which journals automatically upload articles to PubMed central.