

ARIC Manuscript Proposal #2160

PC Reviewed: 6/11/13
SC Reviewed: _____

Status: A
Status: _____

Priority: 2
Priority: _____

1.a. Full Title: Diabetes and cognitive change over 20 years: the Atherosclerosis Risk in Communities Study

b. Abbreviated Title (Length 26 characters): diabetes and cog change

2. Writing Group:

Writing group members: Andreea Rawlings, and (alphabetically) Marilyn Albert, David Couper, Ronald Klein, Barbara Klein, David Knopman, Elizabeth Mayeda, Elizabeth Selvin, A. Richey Sharrett, Bruce Wasserman

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

First author: Andreea M. Rawlings
Address: Welch Center
2024 E. Monument St., STE 2-600
Baltimore, MD 21287

Phone: 410 502 2509 Fax: 410 955 0476
E-mail: arawling@jhsph.edu

ARIC author to be contacted if there are questions about the manuscript and the first author does not respond or cannot be located (this must be an ARIC investigator).

Name: A. Richey Sharrett
Address: Dept. Epidemiology
Johns Hopkins Bloomberg School of Public Health
615 N Wolfe St
Baltimore MD 21205
Phone: 443 287 6178 Fax: 410 955 0863
E-mail: rsharret@jhsph.edu

3. Timeline: Begin analyses using visit 5 data currently available. Complete paper within one month of ARIC NCS Stage 1 data closure.

4. Rationale:

Diabetes is associated with greater cognitive decline and the development of dementia (Biessels 2012(1)). However, most studies examining the association of diabetes with cognition have been limited either by the older age of the study population, relatively

short duration of follow-up time, or both. Furthermore, many studies collected data too limited for adequate adjustment for potential confounding and/or have not examined the effects of selective attrition. ARIC and NCS provide a unique opportunity to study the associations of diabetes in midlife on long-term (20+ years) cognitive trajectories. An analysis of diabetes and short-term cognitive change is underway as MSP#1871.

5. Main Study Questions:

Aim 1: Is diabetes at baseline associated with greater cognitive decline over time?

Hypothesis 1: Diabetes at baseline will be association with greater cognitive decline over time, compared to those without diabetes at baseline.

Aim 2: Among persons with diabetes at baseline, is cognitive decline greater among those whose diabetes is less controlled (based on glycated hemoglobin levels) than among those whose diabetes is well controlled?

Hypothesis 2: Participants with less controlled diabetes at baseline will show greater cognitive decline, compared to participants with well controlled diabetes at baseline.

Aim 3: Is development of diabetes after baseline associated with greater cognitive decline over time?

Hypothesis 3: Development of diabetes after baseline will be associated with greater cognitive decline, compared to those who do not develop diabetes after baseline.

Aim 4: Is the age of diabetes onset (or other measures of duration of diabetes) associated with 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 Design: Prospective cohort study with visit 2 as baseline.

Exclusions:

We'll exclude participants who meet any of the following criteria:

- Did not attend visit 2
- Race other than black or white, and blacks in Minneapolis or Washington County centers
- Are missing cognitive tests at visit 2
- Are missing covariates included in statistical models (see below)
- For aim 2, those without diagnosed diabetes at visit 2
- For aim 3, those with history of diagnosed diabetes at visit 2

Exposure:

Aim 1: Diabetes will be defined in 2 ways:

1. A 3-level definition of diabetes to separate participants into those with a history of diagnosed diabetes (based on self-reported doctor diagnosis or medication use), those without a history of diabetes, and those with undiagnosed diabetes based on elevated glycated hemoglobin values.
2. A 2-level definition of diabetes based on history of diagnosed diabetes. This definition combines the undiagnosed participants with those without a history of diabetes from definition 1 above.

Aim 2: We will use the 2-level definition of diabetes described above.

Aim 3: Incident diabetes will be defined using self-reported doctor diagnosis or self-reported diabetes medication use, assessed at visits 3, 4, and 5, and during the annual follow up (AFU) telephone calls.

Covariates: age, race/center, body mass index, education, total cholesterol, HDL cholesterol, hypertension, hypertension medication use, apoE genotype, smoking, alcohol use, and physical activity. Covariates will be treated as fixed (such as in the case of education) or time-varying where available.

Outcome:

Cognitive function was assessed in all participants at visits 2, 4, and 5 using three standardized tests: the Digit Symbol Substitution Test (DSST) of the Wechsler Adult Intelligence Scale-Revised (WAIS-R), the Delayed Word Recall Test (DWRT), and the Word Fluency Test (WFT), also known as the Controlled Oral Word Association Test (COWA) of the Multilingual Aphasia Examination. The DSST is a test of memory, executive function and processing speed, the DWRT is a test of verbal learning and recent memory, and the WFT is a test of executive function and expressive language.

We will create a global measure of cognition by averaging the race-specific, baseline Z scores of the three tests and dividing by the standard deviation; the resulting average scores will be standardized to their visit 2 means and standard deviations.

For participants who did not attend visit 5, but for whom we have Telephone Interview for Cognitive Status (TICS) data, we'll use the DWRT equivalent from the TICS. In addition the TICS might provide useful drop out data which may be incorporated in our models.

We will model change in each test separately and change in the global measure.

Models:

There is a concern of differential drop-out for both the exposure and outcome. Prior work has shown that drop out is informative in this setting; participants who had lower cognitive scores at baseline or who had diabetes at baseline were less likely to attend subsequent visits. In addition, those with diabetes are at higher risk of competing events

such as death. Both of these types of dropout are likely to bias our results in a conservative direction, to show a smaller association between diabetes and cognitive decline.

Therefore, in order to address this potential bias, we will utilize random effects longitudinal models and shared parameter models as described in Gottesman MSP#1982, Schneider 2012 (MSP#1418), and Griswold#2115, to examine the associations of diabetes with cognitive change. The variables found to be associated with attrition in MSP#1982 will be considered for these analyses.

Duration Metric:

We will use time since visit 2 as the time metric in our longitudinal models. We will also consider age as the time metric to assure that the conclusions are similar.

Effect Modification/Sensitivity analyses:

We will examine possible effect modification by race, sex, and apoE genotype.

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)?

MSP#1871: Type 2 diabetes and cognitive decline over 14 years, accounting for mortality (Mayeda (doctoral student UCSF))

MSP#1982: Estimation of cognitive change from repeat measures in observational studies; associations with education: the ARIC NCS

