ARIC Manuscript Proposal #2608

PC Reviewed: 9/8/15  Status: A  Priority: 2
SC Reviewed: _________  Status: _____  Priority: ____

1.a. Full Title: Prevalence of cognitive dysfunction among older adults with diabetes and prediabetes

b. Abbreviated Title (Length 26 characters): prevalence of cog dysfunction

2. Writing Group:
Writing group members: Andreea M. Rawlings; A. Richey Sharrett; David S. Knopman; Priya Palta; Karen Bandeen-Roche; Rebecca F. Gottesman; Marilyn Albert; Josef Coresh; Thomas H. Mosley; Elizabeth Selvin, others welcome

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]

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3. Timeline: All data is currently available, we plan to submit for publication within 6 months of approval of the manuscript proposal.
4. **Rationale:**
The U.S. population is rapidly aging. Currently 14% of the population is 65 and older and the number is expected to nearly double, reaching more than 70 million, by 2030\(^1\). In this population of older adults, the prevalence of diabetes and prediabetes is 26% and 50%, respectively\(^2\). The burden accompanying diabetes is considerable, as diabetes is associated with a number of micro- and macrovascular complications, including retinopathy, nephropathy, stroke, and heart disease\(^3,4\).

A growing body of evidence has found that diabetes also affects a wide range of cognitive domains, including motor function, processing speed, memory, and attention\(^5\), and persons with diabetes are at increased risk of dementia and increased cognitive decline\(^6-8\). Further, among U.S. adults age 70 and older, an estimated 14% have dementia\(^9\). As a result, the number of adults with both diabetes and cognitive dysfunction is growing, and represents challenges for care of patients with diabetes, especially relating to medication adherence and side-effects (hypo- and hyper-glycemia).

It is important to characterize the burden of cognitive dysfunction among older adults with diabetes and prediabetes, and the bi-ethnic, community-based population of the ARIC-NCS is well-suited for this task. Characterizing this prevalence has important clinical and public health implications.

5. **Main Study Questions:**

**Aim 1**
The first aim of the study is to determine if the prevalence of cognitive dysfunction in older adults differ by diabetes, clinical categories of HbA1c, pre-diabetes, and diabetes duration. We will also look at associations by continuous values of each cognitive measure.

**Aim 2**
The second is to determine if the prevalence of cognitive dysfunction in the groups describe above (diabetes, HbA1c categories, and diabetes duration) differ by race.

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**
Cross-sectional study using data from visit 5 (2011-2013)

**Exclusions**
We will exclude participants who meet any of the following criteria:
- Did not attend visit 5
- Race other than black or white, and blacks in Minneapolis or Washington County centers
- Missing cognitive tests at visit 5 (as a sensitivity analysis, we will impute scores for these persons, see below)
- Missing covariates included in statistical models (listed below)

**Exposure**
- We will examine prevalence of cognitive dysfunction by the following categories:
  - Diabetes (yes/no) defined based on self-reported doctor diagnosis or medication use at visit 5
  - Clinical categories of HbA1c:
    - Among persons without a self-report of diabetes: <5.7%, 5.7-6.4% (prediabetes), ≥6.5% (undiagnosed diabetes)
    - Among persons with a self-report of diabetes: <7%, ≥7%
  - Among persons with diabetes, by duration of diabetes using prior visit information to characterize diabetes duration:
    - We will categorize duration into newly diagnosed diabetes (<3 years), diabetes of intermediate duration (3-10 years), and long-standing diabetes (>10 years). We will also characterize duration by tertiles and quartiles.
- We will examine the 3 groups above by race, to see if race is a modifier of these associations.

**Outcomes**
The outcomes for this study are the cognitive function tests, which were assessed in all participants at visits 5 using the following standardized tests:
- Delayed word recall test (DWRT)
- Digit symbol substitution test (DSST)
- Word fluency test (WFT)
- Logical memory, parts I and II (LM-I, LM-II)
- Trail making test, parts A and B (TMT-A, TMT-B)
- Boston naming (BN)
- Animal naming (AN)
- Digit Span backwards (DSB)
- Mini-mental state exam (MMSE)
- Clock time (and pentagons, a subset of the MMSE)

We will examine these tests individually, and grouped by domains. For each test, we will calculate a Z score by subtracting the test mean and dividing by the standard deviation. To create the domains, we will average the Z scores of tests in each domain and standardize scores so that each domain has a mean of 0 and a standard deviation of 1.

The domains are:
- Language: AN, BN, WFT
- Processing speed and executive function: TMT-A, TMT-B, DSST, DSB
- Memory: DWRT, LM-I, LM-II
- Visuospatial: Clock-time and pentagons
We will consider two definitions of cognitive dysfunction (a binary variable). First, we will define cognitive dysfunction as scores that are 1.5 or more standard deviations below age, race, and education-adjusted norms on each test as established in ARIC using data from the rigorously defined “normal” subset of the brain MRI\textsuperscript{10}. This is a common cut-point for defining mild cognitive impairment and dementia\textsuperscript{11–13}. Dysfunction in a cognitive domain will be defined as failure of 2 or more tests in that domain.

Second, we will use visit 5 to define a robust visit 5 normative sample as described in the ARIC-NCS renewal proposal. Briefly, we will define a cognitively health group of participants as those who meet the following criteria:

1) No decline in DWR, DSST, or WFT from previous visits as defined by the decline criteria in Manual of Procedure #17
2) MMSE $\geq$21 for whites, $\geq$19 for blacks
3) Do not have clinical neurologic disease, use cholinomimetic meds, or have dementia at or within 4 years of visit 5
4) Do not have ApoE ε4/4 genotype
5) Do not self-report memory problems

We will use this group of participants to define age, education, and race-specific cognitive norms. Scores 1.5 or more standard deviations below this robust normative sample will be classified as having cognitive dysfunction.

Statistical Analysis:
We will characterize our analytic population using means (standard deviations) or N (%) for all covariates. Covariates include age, race/center, body mass index, education, hypertension, hypertension medication use, apoE genotype, smoking, alcohol use, physical activity, eGFR, and depression. We will also examine associations adjusted for (and stratified) by diabetes treatment modality (oral medication, insulin use) to potentially account for disease severity.

We will analyze the association between the exposure groups for cognitive dysfunction using log-binomial or Poisson regression to estimate prevalence ratios using the following models:

Model 1: Crude/unadjusted
Model 2: Model 1 + age, gender, race/field center, education
Model 3: Model 2 + physical activity, alcohol consumption, smoking, body mass index, apoE, hypertension, hypertension medication use, depression

Effect Modification
In addition to race, we will examine possible effect modification by sex and depression status.

Challenges/Limitations
- The observational cross-sectional design limits our ability to draw firm conclusions regarding temporality or causality of any observed associations
This analysis is limited to participants who attended visit 5, which may be a select group of participants. As a sensitivity analysis, we will impute global Z scores for persons who did not attend visit 5, but who were alive at the time of visit 5. Because diabetes is assessed at each study visit and through annual follow-up, diabetes (yes/no) will be complete for nearly all participants. We will explore the potential use of Heckman selection models to account for selective attrition due to dropout and death when using cross-sectional data.

We will not be able to rule out the possibility of residual confounding.

7.a. Will the data be used for non-CVD analysis in this manuscript? __X__ 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? __X__ 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? __X__ 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”? __X__ 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.cscce.unc.edu/ARIC/search.php __X__ 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#1418: Glycemic control (hemoglobin A1c), cognitive decline and dementia risk: The Atherosclerosis Risk in Communities (ARIC) Study (Selvin)
MSP#1067: Glycemia (haemoglobin A1c) and incident stroke: The ARIC Study (Selvin)
MSP #2302: Risk factor control in older adults with diabetes (Parrinello)
MSP #2160: Diabetes and cognitive change over 20 years: the Atherosclerosis Risk in Communities Study (Rawlings)
MSP #672: Changes in cognitive test scores in the ARIC cohort over a 6-year period (visit 2 to visit 4) and their correlation with vascular risk factors (Knopman)
11.a. Is this manuscript proposal associated with any ARIC ancillary studies or use any ancillary study data? __X__ Yes    ____ No

11.b. If yes, is the proposal

__X__   A. primarily the result of an ancillary study (list number* 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.cscc.unc.edu/aric/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. Accepted

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.
References


