ARIC Manuscript Proposal #2606

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

1.a. Full Title: Biomarkers of hyperglycemia, 20-year cognitive decline, and dementia risk: the Atherosclerosis Risk in Communities Study

b. Abbreviated Title (Length 26 characters): Hyperglycemia, cognition v2-v5

2. Writing Group:
Writing group members: Andreea M. Rawlings, A Richey Sharrett; Thomas Mosley; Shoshana H. Ballew; Jennifer A. Deal; Michael W Steffes; 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 prevalence of diabetes has substantially increased in the past few decades, currently affecting over 20 million adults in the U.S[1,2]. In addition, the U.S. population is rapidly aging, with the number of persons 65 and older expected to reach nearly 70 million by 2030[3]. The health burden of diabetes in older adults is substantial, as diabetes is associated with a number of micro- and macro-vascular complications, including cardiovascular disease, retinopathy, nephropathy, and stroke[4–8]. Additionally, a growing body of evidence has found that diabetes affects performance in several cognitive domains and is associated with greater cognitive decline and dementia[9–12].

Glucose and hemoglobin A1c (HbA1c) are the standard clinical measures used in the diagnosis and management of diabetes[13]. However, interest is growing in the use of non-traditional biomarkers of hyperglycemia, specifically glycated albumin, fructosamine, and 1,5-anhydroglucitol (1,5-AG)[14–17], and prior studies have shown strong associations of these non-traditional biomarkers with microvascular and microvascular outcomes, independent of HbA1c[18–21].

1,5-AG is a monosaccharide, similar to glucose in structure. In the presence of hyperglycemic episodes (levels above the renal threshold, approximately 180 mg/dL), 1,5-AG competes with glucose for renal re-absorption, which causes serum levels to fall. As a result, 1,5-AG reflects hyperglycemic excursions over a short period of time (1-2 weeks)[22]. Fructosamine and glycated albumin are measures of protein glycation, and reflect glycemia over 2-3 weeks, and a recent study proposed a biological mechanism by which glycated albumin may also reflect hyperglycemic excursions[23]. The separate biology and different time-windows of glycemic exposure indicates that these non-traditional biomarkers can be used to evaluate aspects of glycemia not captured by HbA1c or fasting glucose. Their short-term interpretation may have advantages for adjusting therapeutic regimens from one clinic visit to the next.

Fluctuations in glycemia have been shown to adversely affect endothelial function and may lead to vascular damage and cognitive decline[24,25]. A few studies using continuous glucose monitors (CGMs) have found associations between glycemic variability, higher mean amplitude of glycemic excursions (MAGE), and cognitive dysfunction and brain atrophy, independent of mean levels of glycemia and hypoglycemic episodes[26–28]. These aspects of glycemia not captured by HbA1c, which responds to long-term glucose levels without special sensitivity to glycemic peaks, may be particularly important to long-term cognitive decline; however no long-term prospective studies have been conducted.

Our aim is to characterize the prospective association between glycated albumin, fructosamine, and 1,5-anhydroglucitol and 20-year cognitive decline and incident dementia.

5. Main Study Questions:

<u>Aim 1</u>

To examine the association between fructosamine, glycated albumin, and 1,5-AG and cognitive decline over 20 years, independently of HbA1c and other risk factors.

Aim 2
To examine the association between fructosamine, glycated albumin, and 1,5-AG and incident dementia, independently of HbA1c and other risk 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, using visit 2 as baseline

Exclusions
We will 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
- Missing cognitive tests at visit 2 (as a sensitivity analysis, we will impute scores for these persons, see below)

Exposure
All biomarkers were measured at visit 2. We will examine the associations both continuously and categorically for each marker, with categories based on HbA1c rank-order equivalent values. For example, at visit 2, the five clinical cut-points of HbA1c correspond to approximately the 75^{th}, $75\text{-}95^{th}$, and $>95^{th}$ percentile among persons without diabetes, and the 35^{th} percentile among persons with diabetes. We can use these percentiles to similarly categorize the non-traditional markers, as has been done with these markers previously in ARIC[18,29]. We can also look at these markers dichotomized at the median within each category of HbA1c. We will also compare persons with high values of each marker (or low levels of 1,5-AG) but a normal value of HbA1c, and stratify by diabetes status.

Finally we will examine the markers together by potentially classifying participants into groups. For example, participants who may have normal A1c and fasting glucose but have elevated levels of 1 or more marker or all markers (for example). We will do exploratory analyses to determining how best to combine the markers.

Outcomes
Aim 1:
Cognitive function was assessed in all participants at visits 2, 4, and 5 using the following standardized tests:
- Delayed word recall test (DWRT)

- Digit symbol substitution test (DSST)
- Word fluency test (WFT)

For each test, we will calculate a Z score by subtracting the test mean and dividing by the standard deviation. We will also create a global measure of cognitive performance by averaging the Z scores the three tests. We will also consider the use of latent variables in place of the individual tests (work developed by Alden Gross, MP#2215)

Aim 2:
Incident dementia will be defined as a hospitalization with an ICD-9 code of dementia. As a sensitivity analysis, we will also examine the coordinating center-created definitions of dementia (levels 1, 2, and 3). However these variables lack time-of-diagnosis, so a time-to-event analysis cannot be completed.

Statistical Analysis:
Aim 1:
We will characterize our analytic population using means (standard deviations) or N (%) for all covariates. Covariates include age, sex, race/center, education, body mass index, hypertension, hypertension medication use, apoE genotype, smoking, alcohol use, physical activity, and eGFR

We will analyze the relationship between each marker and cognitive function using regression analysis and the following statistical models:

Model 1: Crude/unadjusted
Model 2: Model 1 + age, sex, race/field center, education
Model 3: Model 2 + body mass index, hypertension, hypertension medication use, apoE genotype, smoking, alcohol use, physical activity, and eGFR
Model 4: Model 3 + A1c

We will model the associations using mixed-effects models, which account for the correlations between repeated measures of persons over time. We will include a random intercept, random slope for time, and will assume that the random effects are independent.

Aim 2:
For analysis between the non-traditional markers and incident dementia, we will use Cox proportional hazards regression. Follow-up will begin at the time of Visit 2 and will continue to incident dementia hospitalization, dropout, death, or the administrative censoring date December 31, 2012. We will test the non-proportional hazards assumption using log(-log) plots and testing risk-factor-by-time interactions. We will use the same models described above.

Effect Modification
We will examine possible effect modification by race, sex, and diabetes status and duration

Sensitivity analyses

Propensity score analysis:

Persons with different categories of both traditional and non-traditional biomarkers, regardless of diabetes status, may differ substantially on a number of demographic, behavioral, and clinical characteristics (such as A1c). The lack of comparability between these groups may limit the ability to control for confounding using traditional methods. As an alternative, we will use a stratified, propensity score matching approach to account for confounding.

Missing data:

Participants who do not attend follow-up visits are likely informatively different from those who do, and may lead to biased estimated associations between the risk factors and cognitive function. To account for dropout, we will use multiple imputation by chained equations (MICE) to impute cognitive scores and missing covariates for persons who do not attend follow-up visits.

Challenges/Limitations

- Single measurement of the non-traditional markers and each cognitive test
- We will not be able to rule out the possibility of residual confounding
- Dropout bias is of great concern, but use of MICE may reduce this bias

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.cscc.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)?

MP #2112: The prognostic value of 1,5-anhydroglucitol (Selvin)
MP#1418: Glycemic control (hemoglobin A1c), cognitive decline and dementia risk: The Atherosclerosis Risk in Communities (ARIC) Study (Selvin)
MP#1067: Glycemia (haemoglobin A1c) and incident stroke: The ARIC Study (Selvin)
MP #1973: Cardiovascular exposures, cognitive decline, and depression in whites and blacks (Al Hazzouri)
MP#2160: Diabetes and cognitive change over 20 years: the Atherosclerosis Risk in Communities Study (Rawlings)
MP #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)
MP #2215: Development of longitudinal measures of general and domain-specific latent factors for cognitive performance (Gross)

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

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.

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