**ARIC Manuscript Proposal #2518**

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| **PC Reviewed: 4/14/15** | **Status: A** | **Priority: 2** |
| **SC Reviewed: _____** | **Status: _____** | **Priority: ____** |

**1.a. Full Title**: Cognitive function and brain structure and risk for incident diabetes; The Atherosclerosis Risk in Communities (ARIC) Study

**b. Abbreviated Title (Length 26 characters)**: Brain health and diabetes

**2. Writing Group**:
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Others welcome

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

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**3. Timeline**: this project will comprise part of MPB's dissertation; to be completed and defended by May 2016 and submitted for journal review.

**4. Rationale**: An abundance of research supports the association between the traditional cardiovascular risk factor of diabetes (T2DM) and brain function and structure

(i.e., cognitive decline, dementia, and less favorable brain imaging).[1-5] Prospective research on the association between diabetes and brain function and structure has focused on assessing the change in brain function and structure according to previously determined glucose levels.[2] The underlying conceptual model assumes chronically elevated levels of glucose are detrimental to the brain and lead to structural damage (vascular and neurodegenerative) and cognitive impairment.[5-7] Important to note, T2DM and cognitive impairment share similar risk factors (e.g., obesity, insulin resistance, poor diet, and low levels of physical activity)[8-10].

Alternatively, research addressing the association between brain health and subsequent metabolic health may be of interest as it improves our understanding of the overall relationship between brain and metabolic health; however it is limited. The shared risk factor hypothesis was supported by researchers who found individuals with Alzheimer's were more vulnerable to the development of diabetes, proposing an underlying link between neurodegeneration and β-cell depletion.[11] Threats to short-term homeostasis of blood glucose are, in part, appropriately adjusted for by the central nervous system (CNS). It has also been proposed prolonged activation of the hypothalamic-pituitary-adrenal (HPA) axis and CNS has influential metabolic and hemodynamic consequences.[12] Any role of the CNS over time is unknown. To our knowledge only two studies have evaluated the association between baseline cognitive function and the subsequent development of diabetes over follow-up[13,14] and none have assessed baseline brain structure and the incidence of diabetes over follow-up.

We propose to evaluate the long-term effect of brain structure and cognitive function on metabolic health, specifically the association between brain MRI measures and cognitive function scores and the incidence of T2DM. This project will expound on the relationship between brain health and metabolic health, providing a multi-faceted assessment of brain function and structure and the incidence of diabetes.

*Previous literature*

In separate studies of younger and older adults, lower levels of cognitive functioning were found to be associated with increased risk for diabetes.[13,14] In a large study of healthy late-adolescent/early-adult males, when comparing those with cognitive functioning scores in the lowest 10% of the sample to those with cognitive scores in the highest 23% of the sample (4 categories for comparison, created according to cognitive score and not distribution), those with the lowest cognitive function had twofold greater risk for incident diabetes (95% CI 1.5, 3.1) in early adulthood after adjustment for age, BMI, glucose, family history of diabetes, SES and education, physical activity, smoking status, triglyceride level, breakfast consumption, and white blood cell count. Elevated risk for diabetes was also apparent for those with cognitive scores in the middle of the cohort distribution (HRs 1.6-1.7, excluding the null value), showing a consistent inverse association between cognitive functioning and risk for incident diabetes.[14] In an elderly population of men and women, cognitive impairment was associated with increased incidence of diabetes in women after adjustment for manifold demographic, behavior, and clinical characteristics. HRs for men were elevated (HR=1.6), however the confidence limits were wide and surrounded the null (~0.50 , 6.6).[13] Cognitive

impairment was more prevalent in women (28% in women vs. 10% in men) in this study and researchers questioned the inconsistent gender results possibly being due to differences in health-seeking behavior.[13]

*Potential mechanisms*

There are several possible explanations for the previous associations. Sub-clinical dementia and cognitive impairment may limit physical functioning, physical activity, or influence dietary choices and increase risk for T2DM through these pathways; however it is unclear if brain dysfunction actually causes altered metabolism. It is possible that reverse causation is occurring by way of prediabetes/undiagnosed diabetes. Prediabetes itself is recognized as a cardiovascular and cerebrovascular risk factor and metabolic disorder antecedent to diabetes[15]; levels of glycemia, below the threshold of diabetes, are shown to be associated with subsequent cognitive decline and brain atrohpy.[16,17]

It has also been suggested that impaired insulin signaling in the brain, proposed as "Type 3 diabetes" and associated with neurodegeneration, may explain the relationship between cognitive decline, Alzheimer's disease, and diabetes.[18,19] AD pathology and impaired insulin signaling observed in the absence of T2DM may suggest T2DM is not a sufficient factor of AD pathogenesis, likely a possible cofactor, and that AD is a unique neuroendocrine disorder of its own.[19] Alterations of the HPA axis may also explain the observed associations. Citing animal models of chronic stress exposure and enhanced levels of cortisol associated with increased levels of components of the metabolic syndrome and atherosclerosis[20], Pasquali et al, has proposed hyperactivity of the HPA axis integral to the accumulation of abdominal adiposity and development insulin resistance and as a potential effector organ for prevention of type 2 diabetes.[21,22]

*Implications*

*A. Behavioral health*

It is recognized, diabetes and elevated normal glycemia are associated with cognitive decline and brain atrophy/pathology. Diabetic individuals with lower cognitive functioning are at risk for mismanagement of their diabetes, opening the door for manifold adverse health events. It is reasonable to propose lower cognitive function in non-diabetic individuals may place them at risk for deterioration of health maintenance, understandably associated with and leading to deterioration of metabolic health.

*B. Biological and clinical health*

Clarifying the relationship between brain health (function and structure) and subsequent metabolic health in healthy individuals may identify populations in need of intervention to maintain cognitive and metabolic health. Establishing a point of intercession in this association could lead to a reduced burden of these maladies later in life.

Additionally, investigation of this association will better characterize the risk factors for diabetes and the overall relationship between brain and metabolic health. Specifically, identification of a cerebral component to the development of diabetes may advance potential cerebral-pharmacological treatment, at a minimum bolstering the emphasis of "cognitive exercise" and maintaining acuity throughout life in addition to the relationship of CVD risk factors and brain health.

Research is needed in otherwise healthy individuals examining the association between cognitive function over time, imaging measures of brain health, and incident diabetes. The increasing number of individuals living with diabetes and impaired cognitive function/dementia is a public health concern. The latest epidemiological research suggesting an alternative direction to the association between diabetes and adverse brain deserves scrutiny further elaboration, especially given the limitations of the studies. For example, general cognitive scores were used to assess cognitive function, not specific to a cognitive domain.[13,14] Second, it is possible this association is unique to specific populations, for example, younger populations at risk for early onset of diabetes.[14] Potential health-care seeking behavior may also explain the disparate results by gender in older populations, specifically increased diagnosis of diabetes in women.[13] Lastly, an evaluation of this association in ARIC, assessing both brain structure and cognitive function and risk for incident diabetes may provide elaboration to the observed results and offers a unique opportunity to assess this association with multifaceted measures of brain health (potentially contributing consistency of results across multiple forms of brain health).

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

1. Is lower cognitive function, assessed at ARIC visit 2, associated with increased incidence of diabetes (from post-visit 2 through visit 5)?

   Hypothesis 1 (H1): Lower cognitive function at ARIC visit 2 will be associated with increased incidence of diabetes (from post-visit 2 through visit 5), independent of known diabetes risk factors.

2. Is greater ventricular volume, sulcal size, and white matter hyperintensities (evaluated in subset of ARIC participants who underwent brain MRI at ARIC visit 3 (1993-95)) associated with increased incidence of diabetes (from post-visit 3 through visit 5)?

   Hypothesis 2 (H2): Greater ventricular volume, sulcal size, and white matter hyperintensities (measured at ARIC visit 3) will be associated with increased incidence of diabetes (from post-visit 3 through visit 5), independent of known diabetes 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).**

*Design:* Prospective analysis of cognitive function measures taken at ARIC visit 2 (1990-92) and incidence of diabetes defined over the years 1990 to 2013 (post-visit 2). Additionally, we look to prospectively analyze, in a subset of ARIC participants who underwent brain magnetic resonance imaging (MRI) at ARIC visit 3 (1993-95), the association between MRI measures (ventricular size, sulcal size, and white matter hyperintensities) taken at ARIC visit 3 and the incidence of diabetes defined over the years 1993 to 2013 (post-visit 2).

*Inclusion/exclusion:* Blacks from Minnesota and Maryland will be excluded from all analyses. We will try to eliminate any persons who may have cognitive impairment due to known vascular disease or a condition affecting the CNS. Therefore we will further exclude: those with a history of stroke, transient ischemic attack, or myocardial infarction between the visit 1 and visit 2 examinations and those taking medications with known central nervous system effects, such as antidepressants and antipsychotics, at visit 2 for H1 (and between visit 1 and 3 for H2). Participants free from clinical diabetes who attended ARIC visit 2 and any subsequent follow-up visit will be eligible for the assessment of cognitive function (measured at ARIC visit 2) and incidence of T2DM (from post-visit 2 through visit 5). For the assessment of brain imaging and incidence of T2DM, participants will be eligible if they were selected for and underwent a brain MRI scan at ARIC visit 3 (participants from MN and MD were not selected for brain MRI), and were free from diabetes at visit 3.

*Exposures:* The second clinical exam, ARIC visit 2, contained three neuropsychological tests to assess cognitive function. They included the Delayed Word Recall (DWR) Test, the Digit Symbol Substitution (DSS) Test (a subtest of the Wechsler Adult Intelligence Scale-Revised), and the Word Fluency (WF) Test. The **DWR** is a test designed for dementia screening, composed of a set of ten common nouns presented to participants and asked to recall after a 5-minute interval. The test shows fair test re-test reliability, with high specificity and sensitivity for dementia at a cut-off of 3 or more correct words recalled.[23] The **DSS** is a test requiring the subject to associate numbers with unique symbols, testing sustained attention and psychomotor speed.[24,25] Test-retest reliability in middle-aged adults is 0.82.[25] The **WFT** requires participants to produce as many words as possible that begin with three different letters of the alphabet.[26] This test measures verbal function and mental agility in retrieving words and is the sum of all three trials.[27,28] Forms of this test have high test-retest reliability over 19-42 days in normal middle –aged adults (r=0.81 to 0.88).[29]

We will test the association of baseline cognitive function and incidence of diabetes for each individual test score. We will also assess incidence of diabetes according to a global score of cognitive function, encompassing all three tests, outlined previously.[30] Briefly, a *z* score for each test will be calculated by subtracting the overall mean test score from each individuals' test score and dividing by the standard deviation. The global *z* score for each individual will be calculated by averaging the *z* scores of the three tests and subtracting the global mean *z* score and dividing by its standard deviation. This value can be interpreted as the cognitive performance per *z* standard deviations above/below the mean score.[30]

Details of magnetic resonance imaging protocol are available in the ARIC Visit 3 Manual 13a. Briefly, 1.5-Tesla MRI scanners (GE Signa or Picker) were used to capture brain images at both visits for selected participants at the Jackson, MS and Forsyth County, NC field centers. Scans were interpreted at the ARIC MRI Reading Center at Johns Hopkins Medical Institutions using a validated scoring protocol and assigned a grade.[31,32] Adjudicated grade will be used as exposure for brain structure analyses.

*Outcomes:* The outcome of interest will be incidence of diabetes. We will assess incidence of diabetes with combination of visit-based and self-reported data. **Diabetes status** will be determined at each ARIC visit by self-report of diabetes medication use, self-report of a physician diagnosis, or by fasting glucose ≥ 126 mg/dL (≥ 7.0 mmol/L) and at annual telephone follow-up (AFU) calls by self-report of physician diagnosis *(Questions on medication use which were routinely asked during the clinic visits have not routinely been asked during the Annual Follow-up interviews*). Percent HbA1c was measured at ARIC Visit 2 and values will be used to exclude any potential undetected diabetes cases with HbA1c ≥ 6.5%. Self-reported diabetes status was determined if individuals answer "yes" to any of the following questions: 1.) "Has a doctor ever said you have diabetes (sugar in the blood)?" 2.) "Were any of the medications you took during the past 2 weeks for diabetes or high blood sugar?"

For hypothesis 1, incident cases of diabetes occurring post-visit 2 through visit 5 will be assessed while for hypothesis 2, incidence of diabetes occurring post-visit 3 through visit 5 will be assessed.

*Other variables of interest (for descriptive and analytic purposes):*
Demographic/lifestyle:
Age, sex, race/field center (MN whites; MD whites; NC whites; NC blacks; MS blacks), education level, tobacco use (years and status), daily alcohol consumption, caloric intake, and regular physical activity.

Clinical:
Fasting time, fasting glucose (baseline value), percentage HbA1c (baseline value), blood pressure, body mass index (weight and height), waist-to-hip ratio, cholesterol (total, LDL, HDL), medication use (blood pressure lowering, cholesterol lowering, and glucose lowering), APOE genotype, and family history of diabetes.

*Statistical analysis:*
Individuals with missing covariate information at baseline (H1: visit 2; H2: visit 3) will be excluded. To address hypothesis 1, the main exposure will be cognitive function assessed at ARIC visit 2. To address hypothesis 2, data from the first brain MRI scan, adjudicated grade, (ARIC visit 3) will be used for the main exposure.

Cox proportional hazards will be used to quantify risk of incident diabetes (hazard ratios and 95% confidence limits) over the course of follow-up with each individual's contributed time to the analysis concluding with the date of exam or telephone interview at which diabetes was ascertained or administrative censoring of their last exam visit or telephone interview (i.e., individuals lost to follow-up, mortality, and end of follow-up). We will use restricted cubic splines to assess risk for T2DM by baseline cognitive function scores (each individual test and global *z* score) and for general descriptive purposes. Brain imaging will be analyzed according to adjudicated grade.

We will estimate hazards before and after adjustment for age, sex, race/field center, education level, family history of diabetes, APOE genotype, smoking status, alcohol consumption, physical activity level, caloric intake, BMI, waist-to-hip ratio, fasting glucose, hypertension (and blood pressure lowering medication use), low-density cholesterol and high-density cholesterol (and cholesterol lowering medication use).

We will perform formal tests for interaction by sex and race. Statistical tests will be based on 2-sided probability of alpha = 0.05.

Sensitivity analyses:
We will assess the robustness of our results in multiple fashions.

1. We will perform analyses after excluding the first 3 years of observation (to mitigate any reverse causation or underlying disease).
2. We will perform analyses stratified on baseline glycemic status: normal or prediabetes (baseline: cognition visit 2 and brain structure visit 3). This will identify if the association observed is driven by those with prediabetes.
3. We will also evaluate the association when diabetes is determined strictly from clinical values (fasting glucose ≥ 126 mg/dL (≥ 7.0 mmol/L) and medication use (all medications presented at exam visits), as impaired cognitive function could influence self-reporting of previous physician diagnosis. This will identify if the association is sensitive to self-report of diabetes.
4. Because lower baseline (visit 2) cognitive function would likely be associated with loss to follow-up we will use inverse probability of attrition weighting (IPAW).

*Limitations:* The brain MRIs performed in 1993-1995 are dated compared to current methods and were only performed in NC and MS. Our analysis uses crude and dated methods for exposure ascertainment relative to contemporary methods and has limited sample size for brain MRI measures. We will use a combination of self-reported and diagnostic test data to capture diabetes in addition to the other covariates of interest. Utility and clinical application of a global cognitive *z* score is unclear. With all observational studies, we cannot rule out the possibility of residual confounding or unknown confounding (e.g., intracranial volume). We cannot rule out the influence of Alzheimer's disease or dementia at earlier visits (not collected until MRI).

A valid comment of this proposal may be cognitive impairment leads to behaviors/characteristics that increase the risk of being diagnosed with diabetes. This is almost certainly true. For example, it is reasonable to suggest individuals with impaired cognitive function will have difficulty maintaining adequate levels of exercise, eating healthy, understanding glucose level in relation to general health, etc. and will place them at increased risk for diabetes. However, our concern is to estimate the overall effect of cognition and brain structure on incidence of diabetes, not the individual pathways by which impaired cognitive function or brain structure are possibly associated with diabetes (i.e. we do not anticipate mediation analyses for direct and indirect effects).

**7.a. Will the data be used for non-CVD analysis in this manuscript? ____ Yes _X_ 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 __X__ 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.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)?**

- ARIC #1119r: MRI predictors of global and domain specific cognitive function at 10 years follow-up: the ARIC MRI Study (Coker)
- ARIC #2288: Associations of Brain Imaging with Cognitive Change over 20 Years (Knopman)
- ARIC # 2315: Association of Diabetes with Brain Magnetic Resonance Imaging (Schneider)
- Rawlings AM, Sharrett AR, Schneider AL, et al. Diabetes in Midlife and Cognitive Change Over 20 Years: A Cohort Study. *Ann Intern Med*. 2014;161(11):785-793.

***Note:*** All related work use cognitive function or brain MRI measures as dependent variables (outcome of interest), not as the independent variable (exposure of interest) as we propose here.

**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**

**___ A. primarily the result of an ancillary study (list number* _____)**

**_X_ B. primarily based on ARIC data with ancillary data playing a minor role (usually control variables; list number(s)*** 1999.01 – ARIC MRI Study**)**

*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.**

**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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