ARIC Manuscript Proposal #2315

1.a. Full Title:
Association of Diabetes with Brain Magnetic Resonance Imaging

1.b. Abbreviated Title (Length 26 characters):
Diabetes and Brain Imaging

2.   Writing Group: Writing group members:

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

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3.   Timeline:
The visit 5 brain MRI data is now available and a set of derived variables will soon be distributed; we plan to submit for publication within 6 months.

4.   Rationale:

In the United States, diabetes is estimated to affect approximately 26 million individuals aged 20 years or older (11.3% of individuals in this age group). The burden of diabetes is high among the elderly (individuals aged 65 years or older) where 26.9% of the population are affected (1). It has been suggested that "mid-life onset" and "late-life onset" of diabetes represent distinct clinical entities. Although "mid-life onset" and "late-life onset" have similar burdens of clinical macrovascular disease (stroke, cardiovascular disease, coronary heart disease), "mid-life onset" diabetes has a higher burden of clinical microvascular disease (retinopathy) (2).

Diabetes is associated with increased risk for many common neurologic diseases, including dementia (3) and stroke (4). Recently, the American Diabetes Association recognized cognitive impairment as a "common comorbid condition" that clinicians should consider screening for in individuals with diabetes (5). Mechanisms by which diabetes may be associated with neurologic disorders include chronic hyperglycemia, microvascular disease, glucose toxicity and abnormal cerebral insulin homeostasis (6, 7). Brain imaging studies have the potential to help clarify the pathogenesis underlying these clinical manifestations. Indeed, diabetes has previously associated with both neurodegenerative pathology (e.g., brain volume (8); hippocampal volume (9)) and with vascular pathology (e.g. white matter hyperintensities [WMH] (10); infarcts [lacunar (11), non-lacunar (12)]) on brain magnetic resonance imaging (MRI), many of which are caused by cerebral microvascular disease. Less is known about the association of diabetes with cerebral microbleeds, other than co-occurring with retinopathy, possibly representative of microangiopathy involving multiple organs (13). Little is known about potential differences in the strength of the associations with brain MRI findings for diabetes diagnosed in mid-life versus in late-life. Two studies report that longer duration of diabetes is associated with increased WMH severity (14, 15), but both of these studies were comprised of <200 participants. To our knowledge, there have not been any studies comparing the association of mid-life glycemic control versus late-life glycemic control with brain MRI findings, although a microvascular etiology of many of these brain MRI findings supports a more important role of mid-life glycemic status.

One important limitation in the interpretation of previous work in this area is the use of inconsistent definitions and nomenclature for different types of brain MRI findings (16). Indeed, in a meta-analysis of 25 studies on the association between diabetes and WMHs, no clear association was found. The conclusions from this meta-analysis suggest that the inconsistency in the association between diabetes and WMHs was due, at least in part, to differences in the definition of WMHs across studies, with some studies using crude measures of volume and others using ordinal scales (7, 16). Recent standards for reporting vascular changes of neuroimaging (STRIVE) have been published to facilitate comparison across future studies (17). WMHs are defined as hyperintensities on T2-weighted images without cavitation occurring in cortical areas. By STRIVE recommendations, lacunar infarcts are defined as round/ovoid, subcortical lesions between 3 mm and 15 mm in diameter. Microbleeds are defined as small (generally 2-5 mm) areas of signal void on T2*-weighted images (17). Although brain volumes and atrophy are not considered pathognomonic for vascular disease of the brain, and are likely multifactorial, the STRIVE guidelines also include atrophy as a marker of brain vascular disease,

supporting the importance of evaluating its association with vascular disease.

In order to comprehensively characterize the relationship of diabetes status with brain MRI findings, and particularly microvascular MRI findings, we propose to examine the association between diabetes status (defined by categories of duration over the 1987-2013 time period), glycemic control ("mid-life": 1990-1992, "late-life": 2011-2013) and late-life brain MRI findings (2011-2013) including brain volume, WMH volume, number of infarcts, and number of microbleeds in the Atherosclerosis Risk in Communities (ARIC) Study. We hypothesize that mid-life diabetes/ MRI associations will be stronger than those with late-life diabetes.

5. **Main Hypothesis/Study Questions**:
   1. Is diabetes associated with brain volume, WMH volume, number of infarcts, and number of microbleeds on brain MRI scans performed in late-life?

      Hypothesis 1: Diabetes, regardless of time of measurement, will be associated with lower brain volume, higher WMH volume, increased number of infarcts and increased number of microbleeds on brain MRI scans performed in late-life, independent of known risk factors.

   2. Is "mid-life onset" of diabetes or "late-life onset" of diabetes more strongly associated with brain volume, WMH volume, number of infarcts, and number of microbleeds on brain MRI scans performed in late-life?

      Hypothesis 2: "Mid-life onset" of diabetes will be more strongly associated with lower brain volume, higher WMH volume, increased number of infarcts and increased number of microbleeds on brain MRI scans performed in late-life than "late-life onset" of diabetes, independent of known risk factors.

   3. Are "mid-life" and "late-life" glycemic control (HbA1c), among individuals with and without diabetes diagnoses at the time of HbA1c measurement, associated with brain volume, WMH volume, number of infarcts, and number of microbleeds on brain MRI scans performed in late-life?

      Hypothesis 3: Both "mid-life" and "late-life" glycemic control (HbA1c), among individuals with and without diabetes diagnoses at the time of HbA1c measurement, will be associated with lower brain volume, higher WMH volume, increased number of infarcts and increased number of microbleeds on brain MRI scans performed in late-life. The associations with "mid-life" glycemic control will be stronger than with "late-life" glycemic control.

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

Non-concurrent cross-sectional analysis of diabetes status defined over the years of 1987 to 2013 with brain MRI data obtained from 2011 to 2013.

Study Population (Inclusion/Exclusion Criteria)
Participants who attended ARIC visit 5 (2011-2013), who were selected for a brain MRI scan, and who completed a brain MRI scan of adequate quality will be eligible for this analysis. A detailed description of the selection criteria for brain MRI at visit 5 is available in the *ARIC Neurocognitive Exam (Stages 2 and 3) Manual 17*.

Briefly, selection criteria for a brain MRI scan at visit 5 included:
1. Absence of any contraindications to MRI: cardiac pacemaker, defibrillator or valvular prosthesis, histories of meningioma, arachnoid cyst, craniotomy, with resection or radiation therapy involving the skull or brain, or normal pressure hydrocephalus, metal fragments in the eyes, brain or spinal cord, cochlear implant, spinal cord stimulator, or other internal electrical device, permanent eyeliner, or weight >350 pounds.
2. All 2004-2006 ARIC brain MRI participants (regardless of their visit 5 cognitive status).
3. All "atypical" participants (goal recruitment n~1,200), defined as either low Mini-Mental State Exam score (visit 5 MMSE <21 for whites and <19 for blacks) *or* (low visit 5 domain z-scores on 2 or more cognitive domains [domain z-score < -1.5 SD] *and* definite cognitive decline on the Delayed Word Recall Test, Digit Symbol Substitution Test, Word Fluency Test [defined as current score minus highest prior score <20th percentile on 1 or more tests or <10th percentile on 2 or more tests]).
4. A random sample of "typical" participants (those who did not meet above criteria for "atypical") (goal recruitment n~800). Sampling fractions were set for participants <80 years and ≥80 years (10% for MN, MD, and MS and 5% in NC to compensate for recruitment of brain MRI study participants).

According to the "*Participant Recruitment Status and Visit Scheduling for Stage 3 by Field Center*" document dated January 22, 2014, 1,962 participants have completed the visit 5 brain MRI scan (MN n=444, MD n=511, NC n=493, MS n=514).

Of those who completed a brain MRI at visit 5, we will additionally exclude any individuals missing covariates included in our statistical models (see below).

Exposure: Diabetes
Our primary exposure will be diabetes status defined over the years of 1987 to 2013. Diabetes status will be defined by self-report of a physician diagnosis or by self-report of diabetes medication use. We will use self-report so that diabetes status can be updated at each visit and at each annual follow-up telephone call occurring after visit 4 (when diabetes questions were added to the annual follow-up questionnaire). Self-report diabetes status has been previously shown to be 55%-80% sensitive and 84%-97% specific, depending on the reference definition (18).

We will classify participants as having diabetes if they answered "yes" to any one of the following questions: 1.) "Has a doctor ever said you have diabetes (sugar in the blood)?" (asked at in-person visits and during annual telephone calls); 2.) "Were any of the medications you took during the past 2 weeks for diabetes or high blood sugar?" (asked at in-person visits) and 3.)

"Did you take any medications during the past 2 weeks for diabetes or high blood sugar?" (asked during annual telephone calls).

Diabetes will be classified in two ways:
1. Binary exposure defined as ever diabetes versus never diabetes defined over the 1987-2013 time period.
2. Categorical exposures where we will divide individuals who have diabetes at baseline or who develop diabetes over the 1987-2013 time period into groups based on the time when the individual developed diabetes. *These categories will help us to examine potential differences in association by "mid-life onset" and "late-life onset" of diabetes.* We will consider two ways of defining these categories:
    a. Define binary variable of diabetes status incorporating age diabetes diagnosis occurred: <65 years "mid-life onset" versus ≥65 years "late-life onset". We will also consider a categorical variable divided into more age groups defined using age when diabetes diagnosis occurred: <55 years; 55-60 years; 60-65 years; 65-70 years; 70-75 years; ≥75 years. The reference group will be participants without a diagnosis of diabetes.
    b. Define categories as diabetes diagnosis occurring <5 years; 5-10 years; 10-20 years; and ≥20 years prior to the visit 5 brain MRI (this last group approximately corresponds to those with prevalent diabetes at visit 1, 1987-1989). The reference group will be participants without diabetes over the entire 1987-2013 time period.

We will also consider glycemic control using hemoglobin A1c (HbA1c), which was measured at visit 2 (1990-1992) and visit 5 (2011-2013). We will consider two separate analyses: 1) using HbA1c data from visit 2 ("mid-life glycemic control"), and 2) using HbA1c data from visit 5 ("late-life glycemic control"). We will create the following categories for HbA1c measured visit 2 and visit 5 (based on the American Diabetes Association's 2014 clinical practice guidelines (5)):
- No diabetes at time of HbA1c measurement
    - <5.7% (reference)
    - 5.7-<6.5% (pre-diabetes)
    - ≥6.5% (undiagnosed diabetes)
- Diabetes at the time of HbA1c measurement:
    - <7% (controlled)
    - ≥7% (uncontrolled)

Outcome: Visit 5 Brain MRI Data
A detailed description of the visit 5 brain MRI protocol is available in the *ARIC NCS MRI Manual 13*. Briefly, visit 5 brain MRI scans (2011-2013) were performed using 3 Tesla scanners (MN: Siemens Trio [vb17 software]; MD: Siemens Verio [vb17 software]; MS: Siemens Skyra [D13 software]; NC: Siemens Skyra [D11 software]. The following sequences were obtained: Localizer, MP-RAGE (1.2 mm slices), Axial T2*GRE (4 mm slices), Axial T2 FLAIR (5 mm slices), Field Mapping (3 mm slices), Axial DTI (2.7 mm slices for Skyra and Verio scanners and 3 mm slices for Trio scanners).

We will investigate the association of diabetes with the following brain MRI variables:

1. Brain volume (from MP-RAGE)
    - Total brain volume
    - Regional brain volumes thought to be associated with Alzheimer's disease (19):
        - Medial temporal cortex
        - Temporoparietal cortices
        - Hippocampus
        - Frontal cortex
2. Total WMH Volume (from T2 FLAIR)
3. Number of Infarcts (from T2 FLAIR)
    - Lacunar
    - Non-lacunar
4. Number of Microbleeds (from T2*GRE)

Covariates
Covariates included in our statistical models include: age (years; continuous), sex (male; female), race/field center (MN whites; MD whites; NC whites; NC blacks; MS blacks), smoking status (current; former; never), and hypertension (self-report of physician diagnosis; self-report of hypertension medication use).

We will update the covariates of smoking status and hypertension at each visit and annual follow-up call. We will define hypertension as self-report so that we can use the same definition to update this variable at each visit and annual follow-up call (systolic and diastolic blood pressure is only available at in-person visits).

Covariates selected for inclusion in our statistical models were chosen a priori based on hypotheses about variables that may confound the association and based on variables identified as possible confounders used in prior papers on this topic (7).

Potential Effect Modifiers
We will formally test for interaction by age, sex, and race. We will perform stratified analysis if we observe evidence for significant effect modification.

Statistical Analysis
All statistical analyses will be performed incorporating sampling weights (derived by the ARIC coordinating center) to account for the visit 5 brain MRI selection process that was designed to oversample cognitively impaired individuals (see above). Incorporating sampling weights is particularly important for this analysis, as cognitive impairment is associated both with diabetes and with brain MRI findings.

We will tabulate participant characteristics for the overall population and by diabetes groups as defined above. Participant characteristics will be presented as means for continuous variables and as % for categorical variables.

We will use adjusted linear regression models to assess the association of diabetes status with brain volume (total; regional) and WMH volume. The distributions of these volumes may be non-normal, so we will explore and transform distributions of these data as appropriate. We will

use adjusted poisson models to assess the association of diabetes status with number of infarcts (lacunar; non-lacunar) and number of microbleeds. We will also consider adjusted logistic regression to assess the association of diabetes status with the binary outcome variables of presence/absence of infarcts and presence/absence of microbleeds. We will use the same models to assess the association of "mid-life" and "late-life" glycemic control (HbA1c) with each of the brain MRI outcomes.

We will perform three statistical models:
- Model 1: adjusted for demographic variables: age, sex, and race/field center.
- Model 2: adjusted for Model 1 + smoking status.
- Model 3: adjusted for Models 1 and 2 + hypertension.

Sensitivity Analysis
To assess the robustness of our results to visit 5 brain MRI selection criteria (where cognitively impaired individuals were oversampled), we will repeat all analyses without incorporating sampling weights. We expect that our findings will become stronger in unweighted analyses.

Because we know that individuals who attended visit 5 were in general healthier than those who did not attend visit 5, we will also consider an analysis where we incorporate the visit 5 brain MRI selection weights (which make our results approximately representative of participants who attended visit 5) plus other weights to make our results approximately representative of the broader community-based ARIC population (e.g. using inverse probability of attrition weighting [IPAW] to weight back to the visit 1 population).

As an additional sensitivity analysis, we will compare associations of diabetes with two different definitions of lacunar infarct:
1. Lacunar infarct defined as 3-15 mm to be consistent with the recent standards for reporting vascular changes on neuroimaging (STRIVE) (17).
2. Lacunar infarct defined as 3-20 mm to be consistent with previous ARIC publications using earlier brain MRI scans (1993-1995, 2004-2006) (11).

Limitations
Although brain MRIs have now been performed on a subset of ARIC participants at three time points (1993-1995, 2004-2006, 2011-2013), we will not be performing analyses of change in brain MRI variables over time. The brain MRIs performed in 1993-1995 and 2004-1006 were only performed in NC and MS, which would limit the sample size for analyses of change over the three brain MRI scans. Additionally, brain MRIs performed in 1993-1995 and 2004-2006 were performed on 1.5 Tesla scanners, while the brain MRIs performed at visit 5 were performed on 3 Tesla scanners, making comparisons across the three scans more challenging.

Another limitation of this study is the use of self-reported data to define diabetes status. We chose to use self-report so that diabetes status can be updated at each visit and at each annual follow-up telephone. We have previously shown that self-report diabetes status is 55%-80% sensitive and 84%-97% specific, depending on the reference definition (18). Additionally, we do not have exact measures of diabetes duration as we do not have dates of diagnosis or reliable data on age at diagnosis. For individuals with prevalent diabetes at ARIC visit 1, we will not

have any indication of the duration of diabetes because there is not reliable data on age at diabetes diagnosis, all that we will know about these individuals is that they have had diabetes for >20 years (time between visits 1 and 5). However, the exact date of any diagnosis for diabetes is inherently arbitrary, as the pathologic changes have likely existed for many months, if not years, prior to clinical presentation and diagnosis.

Lastly, as with any observational study, we will also 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? _____ Yes
 X No**

7.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)?

MSP #2266: Associations Between Brain Vascular Imaging Features and Regional Volumetrics (Graff-Radford/Knopman)

MSP #2288: Associations of Brain Imaging with Cognitive Change over 20 Years (Knopman)

MSP #2136: Abnormal Sleep Characteristics and Brain MRI Markers of Cerebral Vascular Disease and Alzheimer's Disease: the Atherosclerosis Risk in Communities Study (Lutsey)

MSP #2272: Subclinical Arrhythmias, Cognitive Function, and Brain MRI Abnormalities in the Elderly: the Atherosclerosis Risk in Communities (ARIC) Study (Chen)

MSP #1771: Cognitive, Vascular Risk Factors, and APOE Genotype Predictors of Hippocampal Volume (Knopman)

MSP #1553: Associations Between Vascular Risk Factors and Longitudinal Changes in Ventricular Size: a 14-Year Longitudinal Study (Knopman)

MSP #1902: The Metabolic Syndrome, MRI Volumetrics and Cognitive Outcomes: Brain Structure and Function in the ARIC Cohort (Dearborn)

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

11.b. If yes, is the proposal
**   ___   A. primarily the result of an ancillary study (list number* _____)**
**   ___   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.

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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