ARIC Manuscript Proposal #3904

PC Reviewed: 7/13/21	**Status: _____**	**Priority: 2**
SC Reviewed: _____	**Status: _____**	**Priority: ____**

1.a. Full Title: Midlife prediabetes and diabetes with 30-year risk of dementia: the Atherosclerosis Risk in Communities Study

b. Abbreviated Title (Length 26 characters): Prediabetes and dementia

2. Writing Group:

Writing group members: Jiaqi Hu, James R. Pike, Pamela L. Lutsey, A. Richey Sharrett, Lynne Wagenknecht, Timothy Hughes, Jesse Seegmiller, Rebecca F. Gottesman, Thomas H. Mosley, Josef Coresh, Elizabeth Selvin, others welcome

I, the first author, confirm that all the coauthors have given their approval for this manuscript proposal. JH **[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:

Prediabetes is an intermediate stage of hyperglycemia, defined by elevated blood sugar that does not meet the criteria for a clinical diagnosis of diabetes. Mid-life prediabetes is known to be associated with an elevated risk of cardiovascular disease, kidney disease and mortality[1]. While diabetes is a well-established risk factor for cognitive decline and dementia, the association of prediabetes with neurocognitive outcomes including dementia has been less well studied. Prior studies have reported prediabetes as a risk factor for cognitive decline, vascular dementia and Alzheimer's dementia risks[2–4]. However, prior work tended to be limited by short follow-up time or inability to adjudicate dementia.

ACCORD-MIND showed no associated of intensive glycemic control on cognitive or brain outcomes[5]. There were a number of limitations to this trial including substantial loss to follow-up and bias towards cognitively healthier cohort. The duration of follow-up in ACCORD-MIND was approximately 80 months, potentially too short to observe potential effects of diabetes on brain structure and cognition. Large-scale observational studies have shown that among persons with diabetes, earlier onset, longer duration, poorly controlled glucose, more complications, and glucose variability were associated with faster cognitive decline and risk of clinical dementia[2,6,7]. While these components of diabetes can partially explain the risk of dementia, it is unknown whether and to what extent the association of prediabetes with dementia is mediated by the development of clinical diabetes. That is, it is not clear whether persons with prediabetes who do not go on to develop diabetes have an elevated risk of dementia.

We will conduct an analysis of ARIC participants to quantify the associations of midlife prediabetes and diabetes with 30-year risk of dementia.

5. Main Hypothesis/Study Questions:

Aim 1: To characterize the association of prediabetes and diabetes in mid-life with 30-year risk of dementia.

> **Aim 1a**: To characterize the direct and indirect associations (mediation by clinical diabetes) of prediabetes in mid-life with 30-year dementia risk.

Hypothesis 1a: Prediabetes is associated with greater risk of incident dementia as compared to persons without prediabetes. Most of the association will be mediated by clinical diabetes.

> **Aim 1b**: To characterize the extent to which level of glycemic control (HbA1C) and duration of diabetes explain the graded risk of dementia in persons with diabetes and without diabetes at baseline.

Hypothesis 1b: Poor glycemic control and longer duration of diabetes have graded associations with incident dementia.

Aim 2: To quantify the absolute risk (30-year incidence) of dementia in by diabetes status at baseline (normoglycemia, prediabetes, diabetes).

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 (the first visit with HbA1c available)

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

- Did not attend visit 2
- Are missing HbA1C tests at visit 2
- Are not fasting for blood glucose test
- Are missing cognitive tests at visit 2
- Race other than black or white, and blacks in Minneapolis or Washington County centers
- Are missing covariates included in statistical models (see below)

Exposures
Prediabetes will be defined based on HbA1C 5.7-6.4% among people without a history of diagnosed diabetes or medication use for diabetes. Diabetes will be defined based on self-reported physician diagnosis or diabetes medication use or HbA1C level of 6.5% or greater. Persons without diabetes (no diagnosis, no medication use and A1C<5.7) will serve as the reference group. We will conduct sensitivity analyses using prediabetes defined by fasting glucose (<100, 100-125, >=125 mg/dL).

Among persons with diagnosed diabetes, we will examination duration of diabetes using various approaches including self-reported date of diagnosis (asked at visit 3) and using information on timing of diabetes diagnosis from visits 1- 4 (baseline will be visit 4 for the analysis). For example, among persons with diabetes at visit 4, we will calculate using diagnosis date if participants were diagnosed at or after visit 4 using information at any one of the prior visits and self-reported age of diagnosis if participants were diagnosed at or prior to visit 3. We will categorize duration of diabetes will be as 0-5 years, 5-10 years, or 10 or more years. A diagnosis of diabetes was not given if an individual had a single elevation in blood glucose on a visit with a normal glucose measurement on subsequent visit in the absence of medication use or physician diagnosis.

Covariates
Age, race-center, body mass index, education, total cholesterol, HDL cholesterol, hypertension, hypertension medication use, apoE carrier status, smoking, alcohol use, and physical activity. Covariates will be treated as fixed (such as in the case of education) or time-varying where available (e.g. hypertension, hypercholesterolemia).

Outcomes
Incident Dementia will be defined using the recommended criteria. Briefly:

Cognitive function[8] has been assessed in ARIC since 1990-1992 through in-person administration of a 3-test cognitive battery and since 2011-2013 in ARIC-NCS through an expanded 10-test battery, the Mini-Mental State Examination (MMSE), and informant interviews that include the Clinical Dementia Rating (CDR) scale and the Functional Activities Questionnaire (FAQ). A computer algorithm generated preliminary diagnoses that were verified by an expert panel of clinicians and neuropsychologists.[9,10]

Among participants who did not return for an in-person follow-up evaluation, dementia was ascertained from a Telephone Interview for Cognitive Status-Modified (TICSm) or Six-Item Cognitive Screener administered to the participant and an informant interview comprised of the CDR, FAQ, and the Ascertain Dementia Eight-Item Informant Questionnaire. If the participant was lost to follow-up or deceased, dementia cases were identified solely by surveillance based on a prior discharge hospitalization ICD-9 or death certificate code through the date of last participant contact[9,11,12] up to December 31st, 2019.

Statistical Analysis

Aim 1:

Descriptive statistics by diabetes status will be performed using means (standard deviations) or N (%) for all the covariates. At visit 2 (baseline) as well as subsequent visits noting new cases of diabetes which will be incorporated into the time-dependent covariate.

We will use **Cox proportional hazards models** to analyze **dementia incidence** before and after adjusting for the covariates. Pre-diabetes and diabetes will be modeled as follows:

Aim 1a:

- Model 1: Baseline diabetes status (no diabetes, prediabetes, diabetes)
    - 1A: Baseline age, race-center, education, apoE genotype
    - 1B: 1A + body mass index, smoking, alcohol use, and physical activity
    - 1C (includes variables altered substantially by diabetes): 1B+ total cholesterol, HDL cholesterol, hypertension, hypertension medication use.
- Model 2: model 1 + incident diabetes (time-varying covariate)
- Model 3: Time-varying updated mid-life pre-diabetes (based on fasting glucose and other markers of hyperglycemia measured at ARIC visits 2-4) in the models above.

Aim 1b:

- Add baseline HbA1c, continuous (per 1-SD and using splines) to the models in Aim 1a and examine the extent to which HbA1c is associated with dementia risk among people with and without diabetes at baseline.
- Among people with diabetes, duration of diabetes will also be modeled.

For all models, we will test the proportional hazards assumption using log(-log) plots and testing risk-factor-by-time interactions.

Aim 2: Crude incidence rates of dementia (according to the exposure categories defined above) per 1000 person-years by 5-year age categories will be calculated. We will calculate cumulative incidence using the Kaplan-Meier method. We will examine both follow-up time (which has the

benefits of similar measurements are study visits synchronized by follow-up time) and age (where left censoring allows for estimation of dementia risk for meaningful age ranges such age from age 50 to 95; ARIC follow-up is long enough to approximate the lifetime cumulative incidence of dementia). We will also conduct a competing risks analysis to better reflect the real-life situation where a higher risk of death prior to the diagnosis of dementia reduces the actual experienced cumulative risk of dementia among individuals with diabetes. Absolute risk differences of dementia will be calculated for prediabetes and diabetes, comparing to participants without diabetes at specified ages (or follow-up time, e.g. 10, 20, 30 years or by age 70, 80, 90) after taking into account death as a competing risk.

Challenges/Limitations

- We will not be able to rule out the possibility of residual confounding.
- Measures of hyperglycemia are not available at every visit and the visit frequency is limited, particularly between visits 4 and 5.
- The definition of prediabetes is not settled in the clinical practice and we will consider alternative definitions.

7.a. Will the data be used for non-ARIC analysis or by a for-profit organization in this manuscript? __x__ Yes ____ No

b. If Yes, is the author aware that the current derived consent file ICTDER05 must be used to exclude persons with a value RES_OTH and/or RES_DNA = "ARIC only" and/or "Not for Profit" ? __x__ Yes ____ No
(The 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 current derived consent file ICTDER05 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:

__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#1418: Glycated haemoglobin and cognitive decline: the Atherosclerosis Risk in Communities (ARIC) study[13]

Shorter follow-up in this 2011 publication which precedes visit 5 and the dementia adjudication process.

MP#2160: Diabetes in Midlife and Cognitive Change Over 20 Years: A Cohort Study[2]

This paper focuses on cognitive function, not dementia.

MP##3058: The Association of Late-Life Diabetes Status and Hyperglycemia With Incident Mild Cognitive Impairment and Dementia: The ARIC Study[14]

This paper focused on visit 5 as the baseline at late-life rather than mid-life which is the focus of this proposal.

MP#2511: Association Between Midlife Vascular Risk Factors and Estimated Brain Amyloid Deposition[9]

This paper focuses on multiple risk factors with less emphasis on diabetes itself and no focus on pre-diabetes.

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, 2006.15 and 2019.28)

___ 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 https://sites.cscc.unc.edu/aric/approved-ancillary-studies

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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