ARIC Manuscript Proposal #3889

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

1.a. Full Title: Natural history of prediabetes in middle-aged adults and long-term risk of chronic kidney disease and mortality: the Atherosclerosis Risk in Communities (ARIC) study

  b. Abbreviated Title (Length 26 characters): Prediabetes and risk of chronic kidney disease

2.   Writing Group:
    Writing group members: Amelia S Wallace, Mary R Rooney, Michael Fang, Justin Echouffo-Tcheugui, Morgan Grams, Elizabeth Selvin.
    Others welcome.

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

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3.   Timeline: <mark>All data are available. We will submit the manuscript to ARIC <12 months from approval.</mark>

4.   Rationale:

    Prediabetes is an intermediate state of hyperglycemia intended to identify people at high risk for development of diabetes[1]. However, estimates of risk of progression to diabetes vary greatly by prediabetes definition and population[1], and rates of regression to normal glycemic levels are not often estimated[1]. There are three laboratory measurements used to define diabetes and

prediabetes: hemoglobin A1c (HbA1c), fasting glucose (FG), and 2-hour post-load glucose (2hBG). Cut-points are not universally agreed upon and different definitions of prediabetes used in clinical practice identify different individuals[2]. Prevention trials, including the Diabetes Prevention Program (DPP)[3], have shown that interventions can delay or prevent progression to diabetes in persons with impaired glucose tolerance (IGT), but eligibility criteria for diabetes prevention trials have differed and it is not clear how these results apply to other (non-IGT) prediabetes populations.

Some prior studies have shown that regression to normoglycemia from IGT prediabetes was associated with lower risk of diabetes[4], 10-year CVD risk[5], and CVD mortality[6], but other studies have shown no reduction in incidence of CVD[7] or all-cause mortality[6]. Regression to normoglycemia from non-IGT definitions of prediabetes has not consistently been shown to be associated with improved outcomes[7,8]. The association between regression to normoglycemia and microvascular disease, including CKD, is less well understood. A study in the DPP Outcomes Study showed a reduction in the risk of microvascular disease for adults with IGT who achieved normal glucose regulation at any point during the DPP trial, but this risk reduction was attenuated when adjustments for measures of glycemia over follow-up were included[9].

We aim to characterize rates and correlates of progression from prediabetes to diabetes or normoglycemia, in a population of middle-aged adults. We will use data from ARIC visits 2 and 4. We will also evaluate risk of incident chronic kidney disease, cardiovascular disease, and mortality, comparing participants who regressed to normoglycemia by visit 4 and those who remained prediabetic or who progressed to diabetes.

5.   Main Hypothesis/Study Questions:

We hypothesize that most participants with prediabetes will maintain status within the prediabetes category or regress to normoglycemia, while a minority will progress to diabetes between visits 2 and 4. We hypothesize that the participants who progress in glycemic status will have higher incidence of chronic kidney disease, cardiovascular disease, and mortality than those that regress or maintain their glycemic status.

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
Inclusion:
We will include participants at visit 2 with normoglycemia [defined using HbA1c <5.7% and FG <100 mg/dL] or prediabetes [defined using HbA1c 5.7-<6.5% or FG 100-125 mg/dL] and who also attended ARIC visit 4.

Exclusion:
We will exclude participants who:
1) are missing data on HbA1c or FG,
2) have prevalent diabetes at visit 2 [defined using HbA1c ≥6.5%, FG ≥126 mg/dL, self-reported prior physician diagnosis, or diabetes medication use],

4) are neither black nor white or blacks at the MN and MD study centers.

Variables

Exposure
At visit 2, HbA1c was measured in whole blood using the Tosoh 2.2 and Tosoh G7 automated high-performance liquid chromatography analyzers (Tosoh Bioscience), which was standardized to the Diabetes Control and Complications Trial assay. Fasting glucose was measured using a hexokinase method in serum. To ensure comparability across visits, we recalibrated all glucose measurements using Deming regression coefficients from a previous recalibration sub-study in ARIC[10].

Four definitions of prediabetes using HbA1c and FG are currently in clinical use: FG 100-126 mg/dL (American Diabetes Association Impaired Fasting Glucose, ADA-IFG); FG 110-126 mg/dL (World Health Organization IFG, WHO-IFG); HbA1c 5.7-6.4% (ADA-HbA1c); and HbA1c 6.0-6.4% (International Expert Committee HbA1c, IEC-HbA1c). For our primary analysis, we will evaluate the ADA IFG and ADA A1c definitions separately and in combination with each other. In secondary analyses, we will evaluate the WHO and IEC definitions separately and in combination with each other.

Glycemic Outcomes
HbA1c was not measured at visit 4. However, glycated albumin was measured in plasma at the Baylor College of Medicine using the Lucica-GA assay (Asahi Kasei Pharma Corp). The correlation between glycated albumin and HbA1c is high (~0.86). Thus, we will estimate visit 4 HbA1c using these glycated albumin data using a linear regression model developed using measured HbA1c and GA at visit 2.

Primary outcomes: the possible outcomes at visit 4 are:
   1) Progression to diabetes: estimated HbA1c (eHbA1c) ≥6.5% and FG ≥126 mg/dL, self-report physician diagnosis, or diabetes medication at visits 3 or 4
   2) Reversion to normoglycemia: eHbA1c <5.7% and FG < 100 mg/dL
   3) No change in prediabetes status
   4) All-cause mortality

Secondary outcomes: the possible outcomes at visit 4 are:
   1) Progression to diabetes: estimated HbA1c (eHbA1c) ≥6.5% and FG ≥126 mg/dL, self-report physician diagnosis, or diabetes medication at visits 3 or 4
   2) Reversion to normoglycemia: eHbA1c <6.0% and FG < 110 mg/dL
   3) No change in prediabetes status
   4) All-cause mortality

Clinical Kidney Disease
Chronic kidney disease will be defined using a composite of (1) visit-based decrease in eGFR to <60 mL/min/1.73m^2 and ≥ 25% decline from baseline, (2) hospitalizations or deaths with CKD

related ICD codes, (3) USRDS-identified ESRD events (Definition 3). Baseline for this outcome will be visit 4, and follow-up will be through 2018 (2017 for USRDS data). For this aim, all participants with CKD at visit 4 will be excluded.

Cardiovascular Disease
CVD events will include coronary heart disease (defined as either definite or probable myocardial infarction or definite fatal CHD), stroke (definite or probable), and heart failure. For this analysis, all participants with prevalent CVD at visit 4 will be excluded.

Mortality
All-cause mortality will be based on semi-annual follow-up calls participants or their proxies, state records, and linkage to the National Death Index.

Other variables:
Visit 2 = age, sex, race-study center, body mass index, family history of diabetes, smoking status, alcohol use, systolic blood pressure, blood pressure-lowering medication use, total cholesterol, HDL cholesterol, lipid-lowering medication use, eGFR, prevalent cardiovascular disease (CHD, HF, stroke). Potentially also include modifiable lifestyle factors (physical activity, diet) to evaluate potential for prevention. These will be the adjustment variables in determining who is at risk of progression to diabetes or regression to normoglycemia.

Visit 4 = age, sex, race-study center, body mass index, family history of diabetes, smoking status, alcohol use, systolic blood pressure, blood pressure-lowering medication use, total cholesterol, HDL cholesterol, lipid-lowering medication use, eGFR, log-transformed urine albumin-to-creatinine ratio, prevalent cardiovascular disease (CHD, HF, stroke). Potentially also include modifiable lifestyle factors (physical activity, diet) to evaluate potential for prevention. These will be the adjustment variables for the association between prediabetes progression status at visit 4 and subsequent outcomes.

Data Analysis

Natural history of prediabetes over 6 years
    We will report characteristics of participants at visit 2 using means and proportions. We will also report the proportion of participants who maintain their status in the prediabetes category, progress to diabetes, or regress to normoglycemia by visit 4. Additionally, we will report unadjusted and age-adjusted 6-year odds ratios of 1) progression from pre-diabetes to diabetes, 2) reversion to normoglycemia, 3) stability of pre-diabetes. In sensitivity analysis, we will also determine the rate of mortality. Person-years will be calculated based on time to whichever event comes first. We will present these rates stratified by age (split at median), sex, and race group.
    Multinomial logistic regression models will be used to calculate odds ratios and 95% confidence intervals for correlates of the outcomes: progression to diabetes, reversion to normoglycemia, or mortality (if substantial). We will test whether there are differences in the association by age, sex, and race.

Model 1 = age, sex, race-center

Model 2 = Model 1 + BMI, family history of DM, current smoking, systolic blood pressure, blood pressure-lowering medication use, total cholesterol, HDL cholesterol, lipid-lowering medication use, eGFR, prevalent cardiovascular disease

Long-term clinical implications: Incident CKD, CVD and mortality
To assess the effect of change in glycemic status on risk of outcomes, we will use Cox proportional hazards models to estimate the hazard of incident CKD, CVD, and mortality after visit 4 in the following groups (1) participants who had prediabetes at visit 2 but were normoglycemic at visit 4, (2) participants who had prediabetes at visit 2 and were diagnosed with diabetes by visit 4, (3) participants who had normoglycemia at visit 2 and had either prediabetes or diabetes at visit 4, (4) participants with stable prediabetes at both visits, and (5) participants with stable normoglycemia at both visits.

For this analysis, we will exclude participants who have CKD or CVD at visit 4, those missing data on glycemic markers at visit 2 or visit 4, and those missing key covariates.

Model 1 = age, sex, race-center
Model 2 = Model 1 + BMI, family history of DM, current smoking, systolic blood pressure, blood pressure-lowering medication use, total cholesterol, HDL cholesterol, lipid-lowering medication use, visit 4 eGFR

Limitations:
This study has a few limitations; primarily, not all biomarkers of interest were measured at all of the visits. In particular, HbA1c was not measured at visit 4, but we do have measurements of glycated albumin and fructosamine, which are highly correlated with HbA1c. We also do not have an oral glucose tolerance test at visit 2, limiting our ability to assess all prediabetes states. We only have information on black and white individuals, which may limit generalizability of our study. As with all observational studies, we may also have residual confounding.

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)?
MS #3477 (Rooney) – Diabetes progression in older adults
MS #2649 (Warren) – Comparative prognostic performance of prediabetes
MS # 2613 (Virtanen) – Long-term glycemic status, cardiovascular events and mortality
MS # 3734 (Rooney) – Simultaneous consideration of HbA1c and insulin resistance for risk assessment of future cardiometabolic disease in Black and White adults

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)* __2009.16_____ _____ _____)**

*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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