ARIC Manuscript Proposal #4215

PC Reviewed: 03/14/23	**Status: _____**	**Priority: 2**
SC Reviewed: _____	**Status: _____**	**Priority: ____**

1.a. Full Title: To what extent are risks in prediabetes explained by progression to diabetes?

b. Abbreviated Title (Length 26 characters): **PreDM, incident DM & outcomes**

2. Writing Group:
Writing group members: Mary R. Rooney, Justin B. Echouffo Tcheugui, Michael Fang, Jiaqi Hu, Pamela L. Lutsey, Morgan E. Grams, Josef Coresh, Elizabeth Selvin. Others welcome.

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

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ARIC author to be contacted if there are questions about the manuscript and the first author does not respond or cannot be located (this must be an ARIC investigator).

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3. Timeline: All data is currently available. We plan to submit for publication within ~6 months of the approval of this manuscript proposal.

4. Rationale:
Prediabetes is a term to identify individuals at high risk of diabetes. According to the Center for Disease Control and Prevention (CDC), prediabetes is a "serious disease" but, using current CDC definitions, nearly 1 in 3 US adults have prediabetes.[1] Prediabetes prevalence is highest in older age, affecting nearly 1 in 2 adults aged 65+ according to current CDC definitions (fasting glucose ≥100mg/dL or HbA1c ≥5.7%).[2] Approximately 5 to 10% of middle-aged adults who meet current definitions for prediabetes will progress each year to diabetes.[3-5] However, only 1 to 2% of older adults with prediabetes by these definitions progress to diabetes each year.[6-8]
There are 5 definitions of prediabetes endorsed by clinical guidelines (**Table 1**), with substantial variation in prevalence. This inconsistency leads to confusion for clinicians: What cut-point to use for diagnosis? Which prediabetes definition is 'best'? What definition is most predictive of diabetes and its clinical complications?[9] Estimates of absolute risk of progression to diabetes vary by definition and population, e.g. adults with ADA-defined IFG have 10-year diabetes risk

of ~10% in middle-age and ~20% in adults 65+.[8]

Table 1: Prediabetes definitions in clinical guidelines			
	HbA1c	**IFG**	**IGT**
ADA	5.7-<6.5%	100-<126 mg/dL	140-<200 mg/dL
WHO	Not endorsed	110-<126 mg/dL	
IEC	6.0-<6.5%	Not endorsed	Not endorsed
Abbreviations: IFG, impaired fasting glucose; IGT, impaired glucose tolerance; ADA, American Diabetes Association; WHO, World Health Organization; IEC, International Expert Committee			

Current definitions of prediabetes have modest associations with future microvascular and macrovascular complications.[10] The strength of association of prediabetes with clinical outcomes varies by definition. We have shown in ARIC that baseline HbA1c in the prediabetic range is more strongly associated with future outcomes than definitions of prediabetes based on fasting glucose. However, the extent to which risk in prediabetes remains after accounting for progression to diabetes is uncharacterized. It is unknown whether prediabetes itself is associated with risk of outcomes or if risks in prediabetes are partially or wholly explained by progression to diabetes.

In ARIC, we will quantify the associations of midlife prediabetes with long-term risk of macrovascular and microvascular outcomes before and after accounting for intervening onset of diabetes. These findings can help inform diabetes prevention strategies by identifying which prediabetes definition(s) capture persons with the highest risk of diabetes and its complications.

5. Main Hypothesis/Study Questions:

Aim 1: To characterize the risks in midlife prediabetes with clinical outcomes before and after accounting for progression to incident diabetes.

Hypothesis 1: Prediabetes in midlife will be associated with modestly higher risks of clinical outcomes among individuals who do not develop diabetes. Progression from prediabetes to diabetes will explain a substantial amount of the risk for atherosclerotic cardiovascular disease (ASCVD), heart failure (HF), mortality, amputation, and end-stage kidney disease (ESKD).

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 (baseline visit 2 when HbA1c was first measured in ARIC)

Exclusions

- Did not attend visit 2
- Missing HbA1c at visit 2
- Non-fasting blood draw at visit 2
- Missing data for adjustment covariates measured at visit 2
- Prevalent total diabetes at visit 2 (based on diagnosis, medication, HbA1c≥6.5%, or FG ≥126mg/dl)
- Prevalent outcomes of interest (ASCVD, HF, amputation, ESKD) at visit 2 or missing information on outcome incidence

Exposure

We will examine associations of each of the prediabetes definitions (based on visit 2 fasting glucose and HbA1c) with outcomes. We will also examine combinations of the ADA prediabetes definitions (e.g. ADA HbA1c 5.7-<6.5% or ADA FG 100-<126 mg/dL; confirmatory definition: ADA HbA1c 5.7-<6.5% and ADA FG 100-<126 mg/dL).

1) ADA HbA1c 5.7-<6.5%
2) ADA FG 100-<126 mg/dL
3) WHO FG 110-<126 mg/dL

Outcome

Our primary outcomes will be defined based on adjudicated ARIC events where possible (~30 year follow-up, through 31 Dec 2019).

1) Atherosclerotic cardiovascular disease (ASCVD), including coronary heart disease and ischemic stroke (hospitalizations or death)
2) heart failure (hospitalizations or death)
3) end-stage kidney disease (ESKD) identified by the US Renal Data System registry
4) Amputation (CMS linkage and hospitalizations for non-traumatic amputations)
5) All-cause mortality

Covariates

- Visit 2 Age, sex, race (White, non-White), center, smoking (current/former/never), alcohol use (current/former/never), physical activity (sports index), body mass index, total cholesterol, HDL cholesterol, lipid-lowering medication use, systolic blood pressure, blood pressure lowering medication use
- Time-varying diabetes: The definition used to capture progression from prediabetes to incident diabetes may have an important impact on the interpretation of our findings. In sensitivity analyses, we will consider different definitions (combinations) to capture progression to diabetes.

  Incident treated diabetes:
  1) glucose-lowering medication use at subsequent visits (self-report or medication inventory) or during annual follow-up calls (self-report)

  Incident diagnosed diabetes:
  1) diagnosis (self-report) at subsequent visits or during annual follow-up calls, or
  2) glucose-lowering medication use at subsequent visits (self-report or medication inventory) or during annual follow-up calls (self-report)

  Incident total diabetes:
  1) diagnosis (self-report) at subsequent visits or during annual follow-up calls,
  2) glucose-lowering medication use at subsequent visits (self-report or medication inventory) or during annual follow-up calls (self-report),
  3) HbA1c≥6.5% at visits 5, 6, 7,
  4) FG≥126 mg/dL at all subsequent visits, or
  5) OGTT 2-hr glucose ≥140 mg/dL at visit 4

Statistical Analysis: We will report descriptive statistics of the participants at baseline according to prediabetes status. For each outcome, person-time will accrue based on date of the outcome, loss-to-follow-up, death, or whichever comes first. We will generate Kaplan-Meier curves for each outcome according to baseline prediabetes definitions and then according to age of diabetes onset among persons with prediabetes. We will use Cox regression to assess associations of prediabetes definitions with incidence of outcomes before and after adjusting for time-varying diabetes status. We will calculate the excess risk in prediabetes explained by progression to diabetes and generate bootstrapped 95% CI's for our excess risk estimate. We will calculate the median time to diabetes diagnosis and the percentage of participants who progress from prediabetes to diabetes prior to the outcome of interest. In additional analyses, we will account for progression to diabetes according to age of diabetes onset (e.g. <60, 60-79 or ≥80 years).

We will have 2 base adjustment models. To Models 1 and 2, we will additionally account for progression to incident (time-varying) diabetes prior to each event of interest.

- Model 1 = age, sex, race, center
- Model 2 = Variables in Model 1 + smoking, alcohol use, physical activity, BMI, total cholesterol, HDL cholesterol, lipid-lowering medication use, SBP, blood pressure lowering medication use

Potential limitations: After baseline (visit 2), HbA1c was not measured until visit 5. Additionally, OGTT was not performed at ARIC visit 2, which is needed to capture IGT. However, OGTT's are not routinely used to screen for hyperglycemia in clinical practice among non-pregnant individuals. We may consider using visit 4 as baseline in supplemental analyses for IGT.

7.a. Will the data be used for non-ARIC analysis or by a for-profit organization in this manuscript? ____ Yes __X__ 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" ? ____ 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: http://www.cscc.unc.edu/aricproposals/dtSearch.html

___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)?
#3904 (Jiaqi Hu) Prediabetes, Diabetes, and 30-year Dementia Risk
#2649 (Bethany Warren) Prediabetes and complications

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 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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