ARIC Manuscript Proposal #2649

PC Reviewed: 10/13/15	**Status: A**	**Priority: 2**
SC Reviewed: _____	**Status: _____**	**Priority: ____**

1.a. Full Title: Comparative Prognostic Performance of Different Definitions of Prediabetes

1.b. Abbreviated Title (Length 26 characters):

Prediabetes definitions

2. Writing Group: Bethany Warren; James Pankow; Mark Woodward; Elizabeth Selvin; others welcome

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

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3. Timeline:

We intend to complete this proposal within a year of approval, as the data necessary for these analyses are currently available.

4. Rationale:

As of 2010, there were approximately 21 million adults in the U.S. with diabetes, a disease associated with numerous microvascular and macrovascular complications.[1] Clinically, diabetes is characterized by hyperglycemia, defined by a fasting glucose $\geq$ 126 mg/dL, a 2-hour glucose following a 75-g oral glucose tolerance test $\geq$ 200 mg/dL, or a glycated hemoglobin (HbA_{1C}) $\geq$ 6.5%, confirmed by a follow-up test.[2] In addition to diabetes, "prediabetes", or persons at increased risk for diabetes, is a pressing clinical and public health problem, which affects approximately 12 to 30% of U.S. adults age 18 years and older, depending on the definition used.[1] The American Diabetes Association recommends identifying persons with prediabetes using the following definitions: a fasting glucose between 100 mg/dL and 125 mg/dL ("impaired fasting glucose"), a 2-hour glucose following a 75-g oral glucose tolerance test between 140 mg/dL and 199 mg/dL ("impaired glucose tolerance"), or a HbA_{1C} between 5.7% and 6.4% ("impaired glycated hemoglobin").[2] International diabetes and health organizations largely agree on the clinical definitions of diabetes and have universally adopted an HbA_{1C} 6.5% as the appropriate diagnostic threshold in addition to fasting glucose and 2-hour glucose criteria.[3–5] By contrast, the category of prediabetes does not have a uniform agreed-upon definition. In fact, some researchers in the field believe that the category of prediabetes should not exist by any definition and that the construct unnecessarily labels patients, causes harm, and is not directly indicative of adverse outcomes.[6]

Further, a source of controversy and concern with the various categories for prediabetes is that there is discordance among them, meaning they identify different individuals. The lack of alignment of prediabetes categories has important implications for their use for screening and population burden estimation. For example, Selvin et al found that utilizing fasting glucose to quantify the prevalence of prediabetes (30%) resulted in an estimation that was more than double the prevalence identified by HbA_{1C} (12%) in the same population.[1] This is because, as described by an International Expert Committee and confirmed by Knowler et al, the HbA_{1C} cut-point for diabetes diagnosis was chosen to favor specificity over sensitivity, and therefore identifies fewer individuals than fasting glucose or 2-hour glucose.[7,8] In a recent pooled analysis of 96 population-based studies conducted by the NCD Risk Factor Collaboration, HbA_{1C} of $\geq$ 6.5% for diagnosis of diabetes was found to have an overall sensitivity of 30.5%, but an overall specificity of 99.69% when compared to fasting plasma glucose or a 2-hour oral glucose tolerance test.[9]

Complicating this debate is the ambiguity regarding which definition(s) of prediabetes best identify those individuals who are at risk of hard clinical outcomes.[6–8] For example, the DECODE trial suggested that 2-hour glucose definitions of prediabetes and diabetes are more closely associated with outcomes than fasting glucose.[13] However, Selvin et al found that the HbA_{1C} was more strongly associated with risks of cardiovascular disease and death compared to fasting glucose.[12] Different conclusions were put forth by the Emerging Risk Factors Collaboration, who resolved that adding information on HbA_{1C} in order to predict cardiovascular disease was at least equal to the improvement gained when including information on fasting glucose and 2-hour glucose. Further, Pankow et al found in the ARIC study that prediabetes defined by fasting glucose and 2-hour glucose identified groups that had similar rates of death from incident coronary heart disease, although their median follow-up time was 6.3 years.[11,14]

Combinations of definitions for diabetes have also been explored. Selvin et al 2011 identified that those with diabetes diagnosed by both an elevated fasting glucose and HbA_{1C} are at the

highest risk.[12] Many investigators have recommended the routine use of both fasting glucose and HbA_{1C} in combination for diabetes diagnosis to best indicate future outcomes, an approach that could also be considered for prediabetes. [15–17]

Nonetheless, there remains uncertainty regarding which definition or combination of definitions of prediabetes are most informative for identifying those at risk for adverse clinical outcomes. The over two decades of follow-up of ARIC participants, the availability of fasting glucose, 2-hour glucose, and HbA1c data, and the large numbers of events presents the opportunity to formally compare definitions of prediabetes, singly and in combination, in their associations with future outcomes.

5. Main Hypothesis/Study Questions:

The overarching objective of these analyses is to examine the different definitions of prediabetes and determine which identifies the individuals most at risk for future outcomes:

Aim 1: To conduct cross-sectional analyses to compare risk factor profiles among the different definitions of prediabetes

> *Hypothesis 1*: HbA_{1C}, with its cut off that emphasizes specificity, is the definition of prediabetes that will identify participants with the most adverse risk profiles

Aim 2: To conduct prospective analyses to compare the magnitude of associations of different prediabetes definitions (based on HbA1c, fasting glucose, or 2-hour glucose) and future outcomes (i.e., incident diabetes, cardiovascular disease [coronary heart disease and/or ischemic stroke], heart failure, chronic kidney disease, end stage renal disease, and all-cause mortality)

> *Hypothesis 2.a*: The combination of the HbA_{1C} and fasting glucose definitions of prediabetes will be more associated with future outcomes over other definition combinations or a single definition alone
>
> *Hypothesis 2.b*: The single definition of prediabetes by HbA_{1C} will be more associated with future outcomes than any other single definition
>
> *Hypothesis 2.c*: The associations between the definitions and outcomes will be similar by race group

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):

<u>Study Design</u>

We will prospectively assess the relationship of the different prediabetes definitions and incident outcomes using fasting glucose and HbA_{1C} measured at visit 2 (1990-1992) attended by 14,348 participants and 2-hour glucose and fasting glucose at visit 4 (1996-1998) attended by 11,656

participants. Since HbA_{1C} is only available at visit 2 and 2-hour glucose is only available at visit 4, head-to-head comparisons of HbA_{1C} and 2-hour glucose on the same visit will not be feasible. To address this, two different sets of analyses will be conducted.

For the primary analysis, the definitions of the measures assessed at the same visit will be directly compared. For fasting glucose and HbA_{1C} baseline will be visit 2 (visit 2 analyses), and for fasting glucose and 2-hour glucose visit 4 will serve as baseline (visit 4 analyses). In addition, utilizing age as the time scale in the cox proportional hazards model will also be explored to address this issue, as described further in the analysis section below.

Exclusions

Participants will be excluded from the analyses if they had prevalent diabetes (i.e., self-report of a physician diagnosis of diabetes or self-report of medications for diabetes), cardiovascular disease [coronary heart disease and/or ischemic stroke], heart failure, chronic kidney disease, or end stage renal disease at the relevant baseline visit, are missing information on covariates, or did not fast for 8 or more hours. The prevalent disease(s) that will be excluded will depend on the outcome being assessed. Participants will also be excluded from visit 2 analyses if they are missing fasting glucose or HbA_{1C} data and will be excluded from visit 4 analyses if they are missing 2-hour glucose or fasting glucose data.

Variables

Exposure. As mentioned above, those with diagnosed diabetes at baseline will be excluded from analyses. For those without prevalent diagnosed diabetes, three categories will be utilized to characterize diabetes status (i.e., no prediabetes/diabetes, prediabetes, and undiagnosed diabetes at baseline):

Category	Definitions
Diagnosed diabetes	• Self-report of a physician diagnosis of diabetes at an ARIC visit • Self-report use of an anti-diabetic medication at an ARIC visit
No prediabetes/ diabetes	• Fasting glucose level < 100 mg/dL; • $HbA_{1C} < 5.7\%$; or • 2-hour glucose < 140 mg/dL following a 75-g oral glucose tolerance test
Prediabetes	• Fasting glucose level ≥ 100 mg/dL & < 126 mg/dL; • $HbA_{1C} \geq 5.7\%$ and $\leq 6.4\%$; or • 2-hour glucose ≥ 140 mg/dL and ≤ 199 mg/dL following a 75-g oral glucose tolerance test
Undiagnosed diabetes	• Fasting glucose level ≥ 126 mg/dL; • $HbA_{1C} \geq 6.5\%$; or • 2-hour glucose ≥ 200 mg/dL following a 75-g oral glucose tolerance test[2]

Outcomes. Several outcomes will be assessed prospectively, per the definitions below:

Category	Definition

Incident diagnosed diabetes	• Self-report of a physician diagnosis of diabetes at an ARIC visit or during an annual follow-up telephone call through 2014; or • Self-report use of an anti-diabetic medication at an ARIC visit or during an annual follow-up telephone call through 2014
Cardiovascular Disease	• Coronary heart disease hospitalization; or • Coronary heart disease death; or • Ischemic stroke hospitalization; or • Ischemic stroke death
Heart failure	• Heart failure hospitalization; or • Heart failure death
Chronic Kidney Disease	• An estimated glomerular filtration rate-creatinine (eGFR-Cr) < 60 mL/min/1.73 m^2 at a subsequent study visit and an eGFR-Cr decline from baseline visit of at least 25%; or • Hospitalization or death related to chronic kidney disease; or • An end stage renal disease event identified by the United States Renal Data System registry
End Stage Renal Disease	• An end stage renal disease event identified by the United States Renal Data System registry
All-cause mortality	• Death from any cause

Covariates. Model 1 covariates will be measured at the relevant baseline and will be limited to age, sex, and race since these analyses aim to understand risk. Model 2 covariates will include Model 1 covariates and risk factors for diabetes and cardiovascular disease (i.e., body mass index, waist-to-hip ratio, LDL, HDL, triglycerides, eGFR-Cr, systolic blood pressure, smoking, alcohol, family history of diabetes, family history of cardiovascular disease, blood pressure-lowering medications, and lipid-lowering medications).

Statistical Analyses

For all analyses, fasting glucose, 2-hour glucose, and HbA_{1C} will be modeled categorically (no prediabetes or diabetes, prediabetes, undiagnosed diabetes). Additionally, the different combinations of the definitions will be assessed (i.e., 9 groups per visit based analysis).

Cross-sectional analyses at baseline will be conducted to understand which definition is associated with the most adverse risk profile. Means, standard deviations and frequencies will be compared stratified by the various categorical definitions. Characteristics that will be considered include: age, sex, race, body mass index, waist-to-hip ratio, family history of diabetes, family history of cardiovascular disease, smoking status, alcohol use, systolic blood pressure, LDL-cholesterol, HDL-cholesterol, triglycerides, eGFR, use of blood pressure-lowering medication, use of a lipid-lowering medication.

Prospective analyses to assess which definition is most closely associated with clinical outcomes will involve Cox regression models to estimate hazard ratios of the categories within each definition for the various outcomes (i.e., incident diabetes, cardiovascular disease [coronary heart disease and/or ischemic stroke], heart failure, chronic kidney disease, end stage renal disease, and all-cause mortality).

Both unadjusted and adjusted models for age, sex, and race-center (Model 1) will be generated. Model 2 will contain the variables in Model 1 plus risk factors for diabetes and cardiovascular disease (i.e., body mass index, waist-to-hip ratio, LDL, HDL, triglycerides, eGFR-Cr, systolic blood pressure, smoking, alcohol, family history of diabetes, family history of cardiovascular disease, blood pressure-lowering medications, and lipid-lowering medications). In addition to analyzing each definition separately, combinations (both fasting glucose and HbA_{1C} and fasting glucose and 2-hour glucose) will be assessed. We will also evaluate whether there are differences in the associations of the various definitions with outcomes by race. We will include an interaction term in the models and perform likelihood ratio tests to assess the a priori hypothesis that these relationships will not be significantly modified by race (with $p < 0.10$ as significant). Race-stratified analyses will also be conducted. Poisson regression will be used to estimate incidence rates of each outcome for each definition and combination of definitions and Kaplan-Meier graphs will be generated. Additionally, a sensitivity analysis will be conducted using the previous FG threshold for diabetes of 110 mg/dL (instead of 100 mg/dL).

These analyses will be performed utilizing two time scales for comparative purposes:

(1) Time from enrollment will be used as the time scale in the cox models and visit 2 and visit 4 analyses will be analyzed separately
(2) Age will be used as the time scale in the cox models, allowing for overlap between the timing of the visit 2 and visit 4 tests to promote comparability of the definitions

Limitations

HbA_{1C} and 2-hour glucose are measured at different times (visit 2 and visit 4, respectively). This makes direct comparison more challenging, since the 2-hour glucose was measured approximately 6 years after HbA_{1C}, when the participants were older, and likely to be further along in the disease process. Additionally, these analyses rely on a single measure of fasting glucose, HbA_{1C}, and/or a 2-hour glucose, which may result in some misclassification especially relative to formal definitions, which require confirmation of any elevated test by a second test at a later time point.

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

__ 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)?

1. Selvin, E., Steffes, M. W., Gregg, E., Brancati, F. L. & Coresh, J. Performance of A1C for the classification and prediction of diabetes. *Diabetes Care* **34,** 84–89 (2011).

2. Pankow, J. S. *et al.* Cardiometabolic risk in impaired fasting glucose and impaired glucose tolerance: The atherosclerosis risk in communities study. *Diabetes Care* **30,** 325–331 (2007).

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* 2006.15)

___ 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/

12.a. 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.

12.b. 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.

References

1. Selvin, E., Parrinello, C. M., Sacks, D. B. & Coresh, J. Trends in Prevalence and Control of Diabetes in the United States, 1988-1994 and 1999-2010. *Ann. Intern. Med.* **160,** 517–526 (2014).

2. American Diabetes Association. Standards of Medical Care in Diabetes - 2015. *Diabetes Care* **38,** S1–S93 (2015).

3. World Health Organization. Use of glycated haemoglobin (HbA1c) in the diagnosis of diabetes mellitus: abbreviated report of a WHO consultation. 25 (2011).

4. International Diabetes Federation Clinical Guideline Task Force. *Global Guideline for Type 2 Diabetes*. (2012).

5. Rydén, L. *et al.* European Society of Cardiology (ESC) guidelines on diabetes, pre-diabetes, and cardiovascular diseases developed in collaboration with the European ASsociation for the Study of Diabetes (EASD). *Eur. Heart J.* **34,** 3035–3087 (2013).

6. Yudkin, J. & Montori, V. The epidemic of pre-diabetes : the medicine and the politics. *Bmj* **4485,** 1–6 (2014).

7. International Expert Committee. International Expert Committee report on the role of the A1C assay in the diagnosis of diabetes. *Diabetes Care* **32,** 1327–34 (2009).

8. Diabetes Prevention Program Research Group, prepared by Knowler, W. C. *et al.* HbA1c as a Predictor of Diabetes and as an Outcome in the Diabetes Prevention Program: A Randomized Clinical Trial. *Diabetes Care* **38,** 51–58 (2015).

9. NCD Risk Factor Collaboration. Effects of diabetes defi nition on global surveillance of diabetes prevalence and diagnosis : a pooled analysis of 96 population-based studies with 331 288 participants. *LANCET Diabetes Endocrinol.* **8587,** 1–14 (2015).

10. Nathan, D. M. *et al.* Impaired fasting glucose and impaired glucose tolerance: Implications for care. *Diabetes Care* **30,** 753–759 (2007).

11. Pankow, J. S. *et al.* Cardiometabolic risk in impaired fasting glucose and impaired glucose tolerance: The atherosclerosis risk in communities study. *Diabetes Care* **30,** 325–331 (2007).

12. Selvin, E., Steffes, M. W., Gregg, E., Brancati, F. L. & Coresh, J. Performance of A1C for the classification and prediction of diabetes. *Diabetes Care* **34,** 84–89 (2011).

13. The DECODE Study Group, on behalf of the European Diabetes Epidemiology Group. Glucose Tolerance and Cardiovascular Mortality. *Arch. Intern. Med.* **161,** 397–405 (2001).

14. Emerging Risk Factors Collaboration. Glycated hemoglobin measurement and prediction of cardiovascular disease. *JAMA* **311,** 1225–33 (2014).

15. Christophi, C. A. *et al.* Confirming Glycemic Status in the Diabetes Prevention Program: Implications for Diagnosing Diabetes in High Risk Adults. *J. Diabetes Complicat.* **27,** 150–157 (2013).

16. Fajans, S. S., Herman, W. H. & Oral, E. A. Insufficient Sensitivty of Hemoglobin A1c (A1C) Determination in Diagnosis or Screening of Early Diabetic States. *Metabolism* **60,** 86–91 (2011).

17. Heianza, Y. *et al.* HbA1c 5.7-6.4% and impaired fasting plasma glucose for diagnosis of prediabetes and risk of progression to diabetes in Japan (TOPICS 3): A longitudinal cohort study. *Lancet* **378,** 147–155 (2011).