

ARIC Manuscript Proposal #3477

PC Reviewed: 10/8/19
SC Reviewed: _____

Status: _____
Status: _____

Priority: 2
Priority: _____

1.a. Full Title: Diabetes progression in older adults: the Atherosclerosis Risk in Communities (ARIC) study

b. Abbreviated Title (Length 26 characters): Diabetes progression in older adults

2. Writing Group:

Writing group members: Mary R Rooney, James S Pankow, Justin Echouffo Tcheugui; Josef Coresh; A. Richey Sharrett; Elizabeth Selvin; Others welcome.

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

First author: Mary Rooney

Address: 2024 E. Monument St. Suite 2-600
Baltimore, MD 21287

Phone: (630) 995-5772 Fax:
E-mail: mroone12@jhu.edu

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).

Name: Elizabeth Selvin

Address: 2024 E. Monument St. Suite 2-600
Baltimore, MD 21287

Phone: 410-955-0495 Fax:
E-mail: eselvin@jhu.edu

3. Timeline: We expect to submit an abstract based on preliminary results to the AHA Epi|Lifestyle Scientific Sessions 2020 based on visits 5-6 (submission deadline: October 2019; conference held March 2020). We will finalize the manuscript after all data from visit 7 is complete (anticipated manuscript preparation = 12 months).

4. Rationale:

The prevalence of prediabetes and diabetes increases with age.¹ In the United States, an estimated 25% of adults aged ≥ 65 years old have diabetes while over 50% meet the criteria for prediabetes, depending on the definition used.² Despite the high prevalence of both diabetes and

prediabetes among older adults, the epidemiology of these conditions in older adults is not sufficiently characterized.

The American Diabetes Association highlighted prognostic implications of hyperglycemia among older adults as a critical knowledge gap.^{3,4} While glucose increases with age, the risk factors and likelihood of progression of hyperglycemia—including the transition from prediabetes to diabetes in older adults are inadequately understood. Additionally, hyperglycemia among older adults is heterogeneous with regard to presentation, outcomes, and treatment considerations.^{4,5}

Previously, a population-based Swedish study examined the natural progression of prediabetes (defined as HbA1c 5.7- $<$ 6.5%) among adults aged \geq 60 years during 12 years of follow-up.⁶ Among 3,363 participants with pre-diabetes they reported that the majority maintained prediabetes status (~42%), while 13% progressed to overt diabetes, 22% reverted to normoglycemia, and 23% died by year 12. The investigators also reported that baseline BMI, systolic blood pressure and prevalent heart disease were the major predictors for progression to diabetes.⁶ Few other data exist on this topic.

We aim to characterize rates and correlates of progression from normal to pre-diabetes, pre-diabetes to diabetes, normoglycemia, or mortality using ARIC visit 5 as baseline, when participants were aged 71-90 years with follow-up through visits 6 (2016-2017) and 7 (2018-2019).

5. Main Hypothesis/Study Questions:

We hypothesize that the majority of participants with pre-diabetes will remain prediabetic, while the minority will progress to diabetes between visits 5 and 7.

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

We will include all participants who attended visit 5 and had relevant measures of hyperglycemia and no history of diagnosed diabetes. We will exclude participants who are neither black nor white or blacks at the MN and MD study centers.

Variables

Exposure

HbA1c was measured in whole blood using a Tosoh G7 automated high-performance liquid chromatography analyzer (Tosoh Bioscience), which was standardized to the Diabetes Control and Complications Trial assay. Glucose was measured in serum using the hexokinase method on the Beckman Coulter Olympus AU400e analyzer.

Outcomes

- 1) Progression to diabetes: HbA1c $\geq 6.5\%$, self-report physician diagnosis, or diabetes medication at visits 6 or 7
- 2) Reversion to normoglycemia: HbA1c $< 5.7\%$
- 3) All-cause mortality

Other variables:

Visit 5 = 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), prevalent dementia or mild cognitive impairment

Data Analysis

We will report characteristics of participants at visit 5 using means and proportions. We will also report the proportion of participants who maintain their status in the prediabetes category, progress to diabetes, or die by the end of visit 7. Additionally, we will report unadjusted and age-adjusted incidence rates of 1) progression from no diabetes/prediabetes to prediabetes, 2) progression from pre-diabetes to diabetes, 3) reversion to normoglycemia, or 4) 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.

Mixed models will be used to examine HbA1c and fasting glucose continuously among participants. 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. 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 + current smoking, systolic blood pressure, blood pressure-lowering medication use, total cholesterol, HDL cholesterol, lipid-lowering medication use, eGFR, prevalent cardiovascular disease

Limitations

This analysis has visit-based outcomes among older adults. As such, non-random attrition is of potential concern, particularly because inclusion in the proposed analysis is conditional upon the ARIC participant both surviving and agreeing to attend later ARIC visits. To attempt to account for this informative missingness, we plan to conduct a sensitivity analysis incorporating inverse probability of attrition weighting (IPAW),^{7,8} and multiple imputation by chained equations (MICE).^{9,10} These attrition weights will be derived using the variables listed above under “other variables” to estimate the probability of non-participation, and the probability of death at subsequent ARIC visits. We will use multiple imputation prediction models regressing variables with missing data on all other variables, including prior imputations.

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.csc.c.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)?

None

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.csc.c.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.csc.c.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. Richter B, Hemmingsen B, Metzendorf MI, Takwoingi Y. Development of type 2 diabetes mellitus in people with intermediate hyperglycaemia. *Cochrane Database Syst Reviews*. 2018(10).
2. Centers for Disease Control and Prevention. *National Diabetes Statistics Report [Internet]*. 2017.
3. Sinclair A, Dunning T, Rodriguez-Manas L. Diabetes in older people: new insights and remaining challenges. *The lancet Diabetes & endocrinology*. 2015;3(4):275-285.
4. Kirkman MS, Briscoe VJ, Clark N, et al. Diabetes in older adults. *Diabetes Care*. 2012;35(12):2650-2664.
5. Halter JB, Musi N, McFarland Horne F, et al. Diabetes and cardiovascular disease in older adults: current status and future directions. *Diabetes*. 2014;63(8):2578-2589.
6. Shang Y, Marseglia A, Fratiglioni L, et al. Natural history of prediabetes in older adults from a population-based longitudinal study. *Journal of Internal Medicine*. 2019;0(0).
7. Cole SR, Hernan MA. Constructing inverse probability weights for marginal structural models. *Am J Epidemiol*. 2008;168(6):656-664.
8. Weuve J, Tchetgen Tchetgen EJ, Glymour MM, et al. Accounting for bias due to selective attrition: the example of smoking and cognitive decline. *Epidemiology (Cambridge, Mass)*. 2012;23(1):119-128.
9. Romaniuk H, Patton GC, Carlin JB. Multiple imputation in a longitudinal cohort study: a case study of sensitivity to imputation methods. *Am J Epidemiol*. 2014;180(9):920-932.
10. White IR, Royston P, Wood AM. Multiple imputation using chained equations: Issues and guidance for practice. *Statistics in medicine*. 2011;30(4):377-399.