ARIC Manuscript Proposal #3454

1.a. Full Title: Is hemoglobin A1c associated with death and other outcomes in older adults with and without type 2 diabetes?

b. Abbreviated Title (Length 26 characters): **HbA1c & Mortality**

2. Writing Group:
Writing group members: Mary R Rooney, James S Pankow, Olive Tang, 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:
Data analysis to begin immediately. Manuscript completion within 1 year.

4. Rationale:
Among middle-aged adults, J-shaped curves between hemoglobin A1c (HbA1c) and mortality have been reported. However, there has been little characterization of this association among older adults. Moreover, given the uncertainty over what constitutes appropriate glycemic control in older adults, an examination of the HbA1c-mortality relationship specific to this life stage may inform diabetes care in older adults.

Few studies have examined the HbA1c-mortality relationship in older adult populations with and without diabetes.[6,12] As HbA1c is a treatment target in diabetes, explanations for any link between low HbA1c with mortality and other outcomes are likely to differ in the setting of diabetes compared to nondiabetic populations. For example, in individuals with diabetes, low HbA1c may reflect tight glycemic control or overtreatment.

Additionally, accumulating research suggest that strength of associations between risk factors and outcomes may differ across the life course; for example, risk factors in mid-life tend to be more strongly related to outcomes than in late-life.[15,16] Therefore, examining the HbA1c-mortality relationship among older adults with and without diabetes may extend our understanding of the association when assessed in mid-life.

HbA1c has been examined in relation to a variety of outcomes, such as microvascular outcomes (chronic kidney disease, end-stage renal disease, retinopathy),[1] cardiovascular disease,[2] and all-cause mortality[2,3] among ARIC participants without diagnosed diabetes, when they were middle-aged. When specific causes of death were examined, no one specific cause of death accounted for the elevated risk among individuals with low HbA1c.[3] Some[4-9] but not all[10-12] of the other studies conducted among individuals without diabetes have reported J-shaped curves between HbA1c and mortality.

Liver disease has been suggested as one explanation for low HbA1c and its association with elevated risk of mortality and other adverse health outcomes.[13] Among NHANES participants without diabetes who were aged <20 years old,[13] low HbA1c (<4.0%) was associated with higher odds of having elevated liver enzymes [alanine aminotransferase (ALT), aspartate aminotransferase (AST)], and steatosis as compared to those with HbA1c between 5.0-<5.5%.[13] In middle-aged ARIC participants without diabetes, a J-shaped curve between HbA1c and risk of liver hospitalizations has also been reported.[3] Anemia and conditions relating to red-cell turnover is another plausible explanation linking low HbA1c and mortality.[14]

We aim to test whether HbA1c is associated with mortality and other outcomes (CVD mortality, CVD, liver hospitalizations) in older adults with and without diabetes.

5. Main Hypothesis/Study Questions:
Is hemoglobin A1c associated with death and other outcomes (CVD mortality, CVD, liver hospitalizations) in older adults with and without diabetes?

We hypothesize that there will be a J-shaped association among older adults with diabetes and also without 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

This analysis will be prospective from visit 5 (baseline) through 2017 or most recent available, stratifying by prevalent type 2 diabetes. Participants who attended visit 5 and have an HbA1c measurement will be eligible for this analysis.

Participants with incomplete information on prevalent diabetes at visit 5 will be excluded. Additionally, participants who are neither black nor white as well as black participants at the Maryland and Minnesota centers will be excluded.

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.

Secondary exposures
We will include fructosamine and glycated albumin as secondary exposures to help interpret any non-linear associations with outcomes (glycemic vs non-glycemic) since these biomarkers both correlate so highly with HbA1c (Pearson's r~0.8 at ARIC visit 2).[17] Fructosamine and glycated albumin were both measured in serum. Fructosamine was analyzed using a colorimetric assay on the Roche Modular P800 Chemistry Analyzer (Roche Diagnostics). Glycated albumin was measured using a complex method by Asahi Kasei Pharma adapted to the Roche Modular P800 Chemistry Analyzer.

Primary outcome
All-cause mortality identified through semiannual follow-up telephone calls, state records, and National Death Index linkage.

Secondary outcomes
- Cardiovascular disease (CVD) mortality based on ICD-9 or ICD-10 codes from death certificates for cardiovascular causes (390-398, 401-404, 410-427, 430-438, 440-448, 451-459, I00-I78).
- 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.
- Liver hospitalizations based on hospital discharge records which include ICD-9 codes 570.0–573.9 or ICD-10 codes K70-K77 anywhere.

Covariates = age, sex, race-center, smoking status, drinking status, body mass index (BMI), systolic blood pressure, antihypertension medication use, estimated glomerular filtration rate (eGFR), high density lipoprotein (HDL) cholesterol, total cholesterol, cholesterol-lowering medication use

Stratification variable = Diagnosed type 2 diabetes will be defined as self-report physician diagnosis or current medication use for diabetes.

Data Analysis
We will present baseline (visit 5) participant characteristics across HbA1c categories, stratified by diagnosed diabetes status. We will also describe liver enzymes (ALT, AST, GGT) and hemoglobin measures across HbA1c and diabetes status. Restricted cubic splines will be used to more flexibly model associations between HbA1c and outcomes, stratified by diabetes status. We will categorize HbA1c among participants without diabetes as <5.0%, 5.0-<5.7%, 5.7-<6.5%, and ≥6.5% (undiagnosed diabetes), and among those with diagnosed diabetes as <6.5%, 6.5-<7.0%, 7.0-<7.5%, 7.5-<8.0%, and ≥8.0%.

Multivariable Cox proportional hazards regression models will be used to examine the association between HbA1c and outcomes among participants with and without diabetes. We will construct a series of models proposed below. A similar analytic approach will be used for the secondary exposures fructosamine and glycated albumin.

- Model 1 = age, sex, race-center
- Model 2 = Model 1 + educational attainment, smoking status, drinking status, physical activity score, BMI, systolic blood pressure, antihypertension medication use, eGFR, HDL, total cholesterol, cholesterol-lowering medication use

We will test for multiplicative effect measure modification by race and anemia (defined as hemoglobin <13.5g/dL for males and <12.0 g/dL for females). We will explore results stratified by race (given ongoing interest in possible HbA1c racial differences), and by anemia status (known to affect HbA1c measurements).

We will also consider using Fine and Gray's competing risks model when CVD mortality is the outcome of interest.

<u>Limitations</u>
Residual confounding is one potential limitation. We may also have limited power for testing for interaction and estimating moderate effects in subgroups. There may be few people with elevated HbA1c without a diagnosis of diabetes, limiting our power to detect associations of undiagnosed diabetes with clinical outcomes.

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

_____ Yes   ___x___ 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)?

Jung (MS #3029) = Glycemia and short-term outcomes in older adults with diabetes
Selvin (MS #3033) = Short-term mortality and cardiovascular risk in older adults with diabetes or prediabetes
Selvin (MS #1024) = Glycemic Control (HbA1c) and Coronary Heart Disease Risk in Persons with and Without Diabetes: The Atherosclerosis Risk in Communities Study

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.

References

1.	Selvin E, Ning Y, Steffes MW, et al. Glycated hemoglobin and the risk of kidney disease and retinopathy in adults with and without diabetes. *Diabetes.* 2011;60(1):298-305.
2.	Selvin E, Steffes MW, Zhu H, et al. Glycated hemoglobin, diabetes, and cardiovascular risk in nondiabetic adults. *The New England journal of medicine.* 2010;362(9):800-811.
3.	Aggarwal V, Schneider AL, Selvin E. Low hemoglobin A(1c) in nondiabetic adults: an elevated risk state? *Diabetes Care.* 2012;35(10):2055-2060.
4.	Carson AP, Fox CS, McGuire DK, et al. Low hemoglobin A1c and risk of all-cause mortality among US adults without diabetes. *Circ Cardiovasc Qual Outcomes.* 2010;3(6):661-667.
5.	Mongraw-Chaffin M, Bertoni AG, Golden SH, et al. Association of Low Fasting Glucose and HbA1c With Cardiovascular Disease and Mortality: The MESA Study. *J Endocr Soc.* 2019;3(5):892-901.
6.	Huang ES, Liu JY, Moffet HH, John PM, Karter AJ. Glycemic control, complications, and death in older diabetic patients: The diabetes and aging study. *Diabetes Care.* 2011;34(6):1329-1336.
7.	Brewer N, Wright CS, Travier N, et al. A New Zealand linkage study examining the associations between A1C concentration and mortality. *Diabetes Care.* 2008;31(6):1144-1149.
8.	Saydah S, Tao M, Imperatore G, Gregg E. GHb level and subsequent mortality among adults in the U.S. *Diabetes Care.* 2009;32(8):1440-1446.
9.	Levitan EB, Liu S, Stampfer MJ, et al. HbA1c measured in stored erythrocytes and mortality rate among middle-aged and older women. *Diabetologia.* 2008;51(2):267-275.
10.	Pfister R, Sharp SJ, Luben R, Khaw KT, Wareham NJ. No evidence of an increased mortality risk associated with low levels of glycated haemoglobin in a non-diabetic UK population. *Diabetologia.* 2011;54(8):2025-2032.
11.	Chonchol M, Katz R, Fried LF, et al. Glycosylated hemoglobin and the risk of death and cardiovascular mortality in the elderly. *Nutrition, Metabolism and Cardiovascular Diseases.* 2010;20(1):15-21.
12.	Palta P, Huang ES, Kalyani RR, Golden SH, Yeh HC. Hemoglobin A1c and Mortality in Older Adults With and Without Diabetes: Results From the National Health and Nutrition Examination Surveys (1988-2011). *Diabetes Care.* 2017;40(4):453-460.
13.	Christman AL, Lazo M, Clark JM, Selvin E. Low glycated hemoglobin and liver disease in the U.S. population. *Diabetes Care.* 2011;34(12):2548-2550.
14.	Zoppini G, Targher G, Chonchol M, et al. Anaemia, independent of chronic kidney disease, predicts all-cause and cardiovascular mortality in type 2 diabetic patients. *Atherosclerosis.* 2010;210(2):575-580.
15.	Lind L, Sundstrom J, Arnlov J, Lampa E. Impact of Aging on the Strength of Cardiovascular Risk Factors: A Longitudinal Study Over 40 Years. *Journal of the American Heart Association.* 2018;7(1).
16.	Sattar N, Rawshani A, Franzen S, et al. Age at Diagnosis of Type 2 Diabetes Mellitus and Associations With Cardiovascular and Mortality Risks. *Circulation.* 2019;139(19):2228-2237.
17.	Selvin E, Rawlings AM, Lutsey PL, et al. Fructosamine and Glycated Albumin and the Risk of Cardiovascular Outcomes and Death. *Circulation.* 2015;132(4):269-277.