

**ARIC Manuscript Proposal # 3330**

**PC Reviewed: 1/8/19**

**Status: \_\_\_\_\_**

**Priority: 2**

**SC Reviewed: \_\_\_\_\_**

**Status: \_\_\_\_\_**

**Priority: \_\_\_\_\_**

**1.a. Full Title:**

Correlates of Hypoglycemia among Older Adults: The Atherosclerosis Risk in Communities Study

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

Hypoglycemia in Older Adults

**2. Writing Group:**

Writing group members: Justin B. Echouffo-Tcheugui, Natalie Daya, James Pankow, B. Gwen Windham, Elizabeth Selvin; others welcome

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

Analysis to begin immediately after the approval of the proposal, and submission of a draft of the manuscript for review to ARIC for review within 6 months.

#### **4. Rationale:**

Hypoglycemia is a complication of treatment among individuals with diabetes. Older diabetic individuals (aged >65 years) experience hypoglycemia more frequently, with a doubling of risk in each additional decade of life after age 60 years.<sup>1</sup> This increase in risk can be explained, at least in part, by the age-related physiological changes in the metabolism of drugs (absorption, distribution, and renal elimination).<sup>3</sup>

Among older individuals, the determinants of hypoglycemia may differ from those observed among middle-aged adults, a group that we previously evaluated in the Atherosclerosis Risk in Communities (ARIC) study using data from visit 4 (1996–1998).<sup>2</sup> There are potentially unique aspects pertaining to hypoglycemia in an older population, with a maladaptive response to hypoglycemia.<sup>4</sup> Older patients also tend to have comorbidities including functional loss, frailty, muscle loss, cognitive dysfunction, and depression that may significantly interfere with the prevention, identification and appropriate treatment of hypoglycemia.<sup>5</sup> Older adults who suffer from hypoglycemia may also be at increased risk for exacerbation of conditions such as cognitive dysfunction and cardiac events, which may in turn affect their ability to self-manage hypoglycemia.<sup>5</sup>

Hitherto, the correlates of hypoglycemia have seldom been studied among older individuals in a community-based setting. The extant evidence mainly originates from clinic-based studies.<sup>6</sup> Identifying such correlates are critical to improving the assessment of the risk of hypoglycemia and its efficient management in older adults with type 2 diabetes.

Using data from visit 6 in the ARIC study, we aim to assess the correlates of hypoglycemia among older individuals with diabetes.

#### **5. Main Hypothesis/Study Questions:**

Among older adults (age 70 years or above) in a community-based sample and using multiple definitions of hypoglycemia, we aim to assess the prevalence and correlates of hypoglycemia.

#### **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).**

##### **Inclusion/Exclusion criteria**

ARIC participants with a diagnosis of diabetes based on either self-report or diabetes medication use at visit 6 (2016–2017). We will exclude individuals with missing data on the potential correlates of hypoglycemia.

##### **Outcomes**

The main outcome will be hypoglycemia. We will use three different definitions of hypoglycemia based on questionnaire data collected in adults with a diagnosis of diabetes at visit 6:

- Hypoglycemia defined as self-report of one or more episodes in the last year of a severe low blood sugar reactions such as passing out or needing help to treat the reaction;
- Hypoglycemia defined as self-report of two or more episodes in the last year of a severe low blood sugar reactions such as passing out or needing help to treat the reaction;

- Hypoglycemia defined as self-report of one or more episode in the last year of a severe low blood sugar reactions such as passing out or needing help to treat the reaction OR self-report of feeling that blood sugars have been unacceptably low in the past few weeks.

### **Covariates**

The covariates will include age, sex, race-center, educational level, smoking status, alcohol use, use of diabetes medications, duration of diabetes, hemoglobin A<sub>1C</sub> (HbA<sub>1C</sub>), estimated glomerular filtration rate (eGFR) based on cystatin C and serum creatinine in the CKD-EPI equation, albuminuria, body mass index (BMI), systolic blood pressure (SBP), diastolic blood pressure (DBP), pulse, use of hypertension medication, LDL-cholesterol, HDL-cholesterol, cholesterol-lowering medication use, history of myocardial infarction, prevalent coronary heart (CHD), heart failure, stroke, cognitive function and depression status.

### **Statistical analysis**

We will estimate the burden of hypoglycemia using three different definitions. We will present the baseline characteristics of the sample by hypoglycemia status, defined using each of the definitions.

We will use multivariable logistic regression models to investigate the associations of potential correlates of hypoglycemia. We will conduct sequential modelling as follows: Model 1 will adjust for age, sex, and race-center. Model 2 will additionally include educational level, smoking status, duration of diabetes, use of diabetes medication, glycemic control (assessed by HbA<sub>1C</sub> and fructosamine), eGFR, albuminuria, body mass index, systolic blood pressure, diastolic blood pressure, use of alcohol, HDL-cholesterol, LDL-cholesterol, use of lipid lowering medications, prevalent CHD, history of myocardial infarction, cognitive function, and depression status.

### **Limitations:**

The limitations of our study include a relatively small number of hypoglycemic events, which may limit our ability to identify some of the relevant correlates of hypoglycemia. Furthermore, the questionnaire-based definitions of hypoglycemia may lead to some inaccuracies. We also do not have detailed information on the diabetes medications, especially non-insulin therapies that may be related to hypoglycemia.

**7.a. Will the data be used for non-CVD analysis in this manuscript?  Yes  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  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.unc.edu/aric/mantrack/maintain/search/dtSearch.html>**

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)?**

ARIC 2833: Risk Factors for Severe Hypoglycemia in Black and White Older Adults with Diabetes

ARIC 2630: Severe hypoglycemia, mild cognitive impairment, dementia and brain volumes in older adults with type 2 diabetes: the Atherosclerosis Risk in Communities (ARIC) cohort study

**11.a. Is this manuscript proposal associated with any ARIC ancillary studies or use any ancillary study data?  Yes     No**

**11.b. If yes, is the proposal**

- A. primarily the result of an ancillary study (Study #2009.16 - PI: Selvin)**  
 **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 <https://www2.csc.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.csc.unc.edu/aric/index.php>, under Publications, Policies & Forms. [http://publicaccess.nih.gov/submit\\_process\\_journals.htm](http://publicaccess.nih.gov/submit_process_journals.htm) shows you which journals automatically upload articles to PubMed central.

## References

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- hypoglycemia in black and white adults with diabetes: The Atherosclerosis Risk in Communities (ARIC) Study. *Diabetes Care*. 2017;40:1661–1667.
3. Ligthelm RJ, Kaiser M, Vora J, Yale JF. Insulin use in elderly adults: Risk of hypoglycemia and strategies for care. *J Am Geriatr Soc*. 2012;60:1564–1570.
  4. Meneilly GS, Cheung E, Tuokko H. Counterregulatory hormone responses to hypoglycemia in the elderly patient with diabetes. *Diabetes*. 1994;43:403–410.
  5. Frier BM. Hypoglycaemia in diabetes mellitus: Epidemiology and clinical implications. *Nat. Rev. Endocrinol*. 2014;10:711–722.
  6. Silbert R, Salcido-Montenegro A, Rodriguez-Gutierrez R, Katabi A, McCoy RG. Hypoglycemia Among Patients with Type 2 Diabetes: Epidemiology, Risk Factors, and Prevention Strategies. *Curr. Diab. Rep*. 2018;18.