ARIC Manuscript Proposal Form

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Publication Committee Review Date: 7/8/2025
ARIC Manuscript Proposal Number#: 4707

1.a. Full Title: Burden of hypoglycemia in older adults with type 2 diabetes

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

2. Writing Group [please provide a middle initial if available; EX: Adam L Williams]:
Writing group numbers: Michael Fang, Yein Jeon, Natalie Daya Malek, Justin Echouffo-Tcheugui, Scott Zeger, Elizabeth Selvin

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

First author [please provide a middle initial; EX: Adam L Williams]:

Natalie	Daya	Malek
First name	Middle initial	Last name

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ARIC sponsor to be contacted if there are questions about the manuscript and the first author does not respond or cannot be located. The ARIC sponsor is responsible for **carefully reviewing the proposal and ensuring its soundness prior to submission to the ARIC Publications Committee.** (The ARIC sponsor should be involved enough in ARIC to be able to point the lead author to appropriate ancillary study PIs and to be able to search ARIC manuscript proposals if the lead author doesn't have the access needed to do such a search).

Name: Elizabeth Selvin
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3. Timeline:

- Analyze data: July 2025
- Write paper: July – August 2025
- Submit for publication: August 2025

4. Rationale:

Frequent episodes of mild hypoglycemia may be a major risk factor for severe hypoglycemic events. In older adults with diabetes, the American Diabetes Association (ADA) recommends spending <1% of the time with a glucose <70 mg/dl. Clinical guidelines describe frequent hypoglycemia as an "absolute indication" for relaxed glycemic targets and treatment deintensification.

Continuous glucose monitoring (CGM) devices measure glucose every 1-15 minutes and comprehensively identify biochemical hypoglycemia. However, studies of CGM have largely focused on younger adult populations with type 1 diabetes in clinical trials.[4] Community-based studies in older patients are lacking, particularly for those with type 2 diabetes. Understanding the burden and risk factors of mild hypoglycemia in older adults can enhance prevention in clinical practice.

Our objective was to characterize the burden and risk factors of CGM-detected hypoglycemia in older adults with type 2 diabetes. To accomplish this aim, we collected and analyzed CGM data in a large, diverse cohort of older adults with type 2 diabetes.

5. Main Hypothesis/Study Aims:

1) What is the burden of CGM-detected hypoglycemia in very old adults with type 2 diabetes
2) How does the occurrence of CGM-detected hypoglycemia vary across time of day
3) What are risk factors for CGM-detected hypoglycemia in very old adults with type 2 diabetes

6. Design and analysis - please address the following aspects:

a) **Inclusion/exclusion**
b) **Study design**
c) **Outcome and other variables of interest with specific reference to the time of their collection**
d) **Summary of data analysis**
e) **Any anticipated methodologic limitations or challenges if present**

Study design: Cross-sectional (study visit 9)

Study population: Persons with diabetes (defined as a physician diagnosis or use of glucose lowering medication at prior study visits) who had CGM at visit 9.

Outcomes: Definitions of hypoglycemia are summarized in **Table 1** and are based on clinical CGM guidelines.[6,7] Our primary outcome will be percentage of time spent with hypoglycemia, defined as CGM-glucose <70 mg/dl. We will also characterize the proportion of participants who spent>=1% of time with hypoglycemia. We will examine the number and duration of hypoglycemic episodes. We will define an episode as having at least two consecutive (>15 minutes) CGM glucose readings <70 mg/dl, and an "extended" episode as at least eight consecutive (120 minutes) CGM glucose readings <70 mg/dl. A hypoglycemic

episode will be considered "resolved" when CGM glucose is ≥70 mg/dl for two consecutive readings. In secondary analyses, we will repeat all analyses using lower glucose cutpoints to define hypoglycemia (<60 mg/dl; <54 mg/dl).

Table 1 – Defintion of hypoglycemic outcomes

Outcome	Definition
Time with hypoglycemia	Percentage of time with CGM glucose <70 mg/dl (continuous measure)
"Excessive" hypoglycemia	Proportion of participants that spent >1% of time with CGM glucose <70 mg/dl (binary measure)
Number of hypoglycemic episodes	An episode is defined as having at least two consecutive CGM glucose readings <70 mg/dl. An episode is considered "resolved" when glucose is above ≥70 mg/dl for two consecutive readings (continuous measure)
Duration of hypoglycemic episodes	Total duration of time (minutes) between the start and end of each hypoglycemia episode (continuous measure)

Risk factors

Based on prior studies of hypoglycemia risk factors,[8,9] we will examine the following comorbidities:

Measure	Defintion
History of severe hypoglycemia	ICD 9 or 10 code for severe hypoglycemia in hospital records or CMS claims
Chronic kidney disease	eGFR<60 or ACR>30. eGFR will be estimated used the new race-free CKD-EPI equation.
Heart disease	Coronary heart disease, stroke, or heart failure – adjudicated events at or prior to visit 9
Frailty	Any 3 of exhaustion, low physical activity, weakness, slow walking speed, unintentional weight loss (only up to visit 8 currently – to be updated as soon as data are available)
Poor physical functioning	Score <7 on Short Physical Performance Battery (only up to visit 8 currently – to be updated as soon as data are available)
Dementia or mild cognitive impairment	Based on neurocognitive testing and dementia adjudication (only up to visit 8 currently – to be updated as soon as data are available)

Statistical analysis

1. Baseline characteristics, by medication use (those using versus not using insulin or sulfonylurea)
2. Characterize distribution of time spent with hypoglycemia, by medication use
    a. Generate histograms of percentage of time spent with CGM glucose<70 mg/dl
    b. Calculate % with >=1% time in hypoglycemia

3. Characterize distribution of time spent with hypoglycemia across time of day, by medication use
    a. Calculate the median amount of time spent with hypoglycemia across each hour of the day
    b. Calculate the median amount of time spent with hypoglycemia during daytime (6:00 am to 11:59 pm) and nighttime (12:00 am to 5:59 am)
4. Characterize number and duration of hypoglycemic events, by medication use
    a. Generate histograms of number and duration of hypoglycemic episodes
    b. Calculate median and mean # of episodes
    c. Calculate median and mean duration hypoglycemic episodes
5. Examine risk factors of hypoglycemia
    a. Examine associations between risk factors and median time with hypoglycemia using quintile regression, adjusted for age and sex
    b. Estimate models overall and by medication use

f) **Will the author need Limited data to complete the proposed manuscript?**

☐ Yes, Limited data is needed. (Provide a brief (2-3 sentences) justification for requesting PHF data)

☒ No, De-identified data will be sufficient.

Please note, Limited dataset access is strict and rarely provided. Limited data includes identifiable information such as dates (birthdays, visit dates, etc.). CMS, Genomic, Geocoded, Proteomics/Somalogic, and other -omic data all fall under the limited data category. De-identified data does not include dates. All dates are date adjusted to "Days since Visit 1".

7. Will the data be used by a for-profit organization in this manuscript? ☐ Yes* ☒ No

8. Will the DNA data be used in this manuscript? ☐ Yes* ☒ No

* Please carefully review the instructions and documentation on the ARIC website at: https://aric.cscc.unc.edu/aric9/researchers/Obtain_Submit_Data [ARIC website > Researchers > Obtain/Submit Data] for instructions on proper data use.

9. The lead author or the ARIC sponsor 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 website at: https://aric.cscc.unc.edu/aric9/proposalsearch [ARIC Website >Publications >Proposal Search]

☒ 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)?

- #2833 - Risk Factors for Severe Hypoglycemia in Black and White Older Adults with Diabetes
- # 3330 - Correlates of Hypoglycemia among Older Adults: The Atherosclerosis Risk in Communities Study
- #3792 - Glucose Patterns in Older Adults: A Pilot Study in a Community-based Population
- #4417 – Symptoms of hypoglycemia in older adults with and without diabetes

11.a. Is this manuscript proposal associated with any ARIC ancillary studies or does it use current [or ongoing] ancillary study data (this includes ACHIEVE)?

☒ Yes ☐ No→ **Skip to question 12**

11.b. If yes to 11.a., is the proposal

☒ A. primarily the result of an ancillary study
☐ B. primarily based on ARIC data with ancillary data playing a minor role (usually control variables)

- **11.c. If yes to 11.a., list number*** 2019.28

*ancillary studies are listed by number
https://aric.cscc.unc.edu/aric9/researchers/ancillary_studies/approved_ancillary_studies [ARIC Website >Ancillary Studies >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. The NIH-NHLBI Public Access Brochure about the public access policy from http://publicaccess.nih.gov/ is posted in https://aric.cscc.unc.edu/aric9/publications/policies_forms_and_guidelines [ARIC Website > Publications >Publication Policies, Forms, and Guidelines]. http://publicaccess.nih.gov/submit_process_journals.htm shows you which journals automatically upload articles to PubMed central.

References:

1. Lee AK, Warren B, Lee CJ, et al. The association of severe hypoglycemia with incident cardiovascular events and mortality in adults with type 2 diabetes. Diabetes Care 2018;41(1):104-111.
2. Huang ES, Laiteerapong N, Liu JY, John PM, Moffet HH, Karter AJ. Rates of complications and mortality in older patients with diabetes mellitus: the diabetes and aging study. JAMA Intern Med 2014;174(2):251-258.
3. Assessment G. 6. Glycemic Targets: Standards of Medical Care in Diabetes—2022. Diabetes Care 2022;45:S83.
4. Maiorino MI, Signoriello S, Maio A, et al. Effects of continuous glucose monitoring on metrics of glycemic control in diabetes: a systematic review with meta-analysis of randomized controlled trials. Diabetes Care 2020;43(5):1146-1156.
5. 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;18:1-16.
6. Battelino T, Danne T, Bergenstal RM, et al. C42(8):1593-1603.
7. Danne T, Nimri R, Battelino T, et al. International consensus on use of continuous glucose monitoring. Diabetes Care 2017;40(12):1631-1640.
8. Association AD. 12. Older Adults: Standards of Medical Care in Diabetes—2020. Diabetes Care 2020;43(Supplement 1):S152-S162.
9. Lee AK, Lee CJ, Huang ES, Sharrett AR, Coresh J, Selvin E. Risk factors for severe hypoglycemia in black and white adults with diabetes: the Atherosclerosis Risk in Communities (ARIC) Study. Diabetes Care 2017;40(12):1661-1667.

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