

ARIC Manuscript Proposal #2833

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Priority: 2
Priority: _____

1.a. Full Title: Risk Factors for Severe Hypoglycemia in Black and White Older Adults with Diabetes

b. Abbreviated Title (Length 26 characters): Hypoglycemia Risk Factors

2. Writing Group:

Writing group members: Alexandra K. Lee, Elbert S. Huang, Clare Lee, A. Richey Sharrett, Josef Coresh, Elizabeth Selvin; others welcome

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

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3. Timeline: All data are available. From time of approval of manuscript proposal, we expect to have a manuscript ready for submission in 1 year.

4. Rationale:

Current American Diabetes Association (ADA) clinical practice guidelines recommend individualizing A1c targets for older adults with diabetes based on their risk of hypoglycemia and remaining life expectancy.¹ ADA guidelines highlight insulin deficiency, renal insufficiency, and cognitive impairment as risk factors for hypoglycemia that might warrant modification of treatment, but do not mention any other risk factors explicitly. Identification of key risk factors for hypoglycemia in the community is important to inform clinical management of diabetes in older adults and preventing hypoglycemic events.

Overall, risk factors for hypoglycemia are not firmly established in the literature.^{2,3} There are few factors, other than age, dementia, chronic kidney disease, and insulin use, that have been consistently associated with hypoglycemia across studies.⁴⁻¹⁰ In general, there is lack of agreement regarding which factors should be routinely considered when identifying persons at high risk for hypoglycemia.

“Unidentified cognitive deficits” are discussed in ADA guidelines as an important risk factor for hypoglycemia given the complexity of self-care needed to manage diabetes such as glucose monitoring and proper timing of insulin with meals;¹ however, there is relatively little epidemiologic evidence for this statement. Indeed, the association of pre-dementia cognitive deficits with hypoglycemia is almost completely uncharacterized, despite its biologic plausibility and mention by the clinical guidelines. While several studies have demonstrated that dementia increases the risk of severe hypoglycemia,⁶⁻⁹ only three studies have examined the association of lesser cognitive impairments with hypoglycemia.^{9,11,12} Two prior studies on this topic were observational analyses of randomized trials of intensive glucose control. The first study, in ADVANCE, showed that only participants with “severe dysfunction,” as defined by a Mini Mental Status Exam (MMSE) score <24, but not “mild dysfunction,” MMSE 24-27, were at increased risk of severe hypoglycemia, after adjustment.¹¹ In ACCORD, of several cognitive tests (digit symbol substitution test (DSST), Rey Auditory verbal leaning test, the Stroop test, and the MMSE), only the DSST score was associated with increased risk of mild, but not severe, hypoglycemia after adjustment.¹² The third study was an observational analysis of Veterans Affairs administrative data that used ICD-9 codes and showed that dementia and cognitive impairment were associated with hypoglycemia after adjustment.⁹ Given that the slow process of cognitive decline begins at least 10 years prior to a dementia diagnosis, it is important to identify the level of cognitive impairment at which risk of hypoglycemia increases.¹³

Additionally, to our knowledge, no studies have examined the association of difficulty with activities of daily living (ADLs) or instrumental activities of daily living (IADLs) with severe hypoglycemia. Since “difficulty in complex self-care activities” is the hypothesized mechanism by which poor cognitive function results in hypoglycemia, it follows that self-reported difficulty in IADLs or ADLs would be associated with increased risk of hypoglycemia.¹ Additionally, simple questions querying these tasks may be more feasible than standardized cognitive testing in a clinical setting. However,

difficulties in IADLs or ADLs may be less sensitive to smaller cognitive deficits that would impact the capacity for diabetes self-management.

Other markers known to indicate poor prognosis and predict all-cause mortality could also be associated with severe hypoglycemia. These markers include self-rated health, c-reactive protein, high-sensitivity cardiac troponin T, and serum albumin.¹⁴⁻¹⁷ Several other factors have been inconsistently associated with hypoglycemia in the literature including: female sex, low BMI, and history of CVD.^{4,5,7,18} Additionally, blacks have a roughly twofold higher rate of severe hypoglycemia, but most studies of hypoglycemia and its risk factors have occurred in majority white populations.^{4,7,10,20,21}

Given the clinical importance of reducing hypoglycemia and the lack of clear epidemiologic evidence for key risk factors for hypoglycemia, our overarching goal is to comprehensively evaluate risk factors for hypoglycemia and determine which are most important for clinicians to consider when assessing a patient's risk of severe hypoglycemic episodes. This study of hypoglycemic risk factors in the ARIC cohort is poised to make a unique contribution to the existing literature. Most studies of hypoglycemia risk factors have been conducted in the setting of a randomized controlled trial of glucose control (highly selective group of participants) or using administrative claims data, which rely on ICD-9 codes to identify comorbidities, and are frequently missing important clinical characteristics, such as duration of diabetes, HbA1c, and BMI. In contrast, the community-based ARIC cohort is both representative of a broad diabetes patient population and has rigorously measured risk factors conducted by trained personnel in all participants using standardized protocols.

5. Main Hypothesis/Study Questions:

Aim 1: To identify risk factors for severe hypoglycemia, and to determine if risk factors differ for blacks and whites.

Hypothesis: Risk factors for hypoglycemia will include: older age, poor baseline cognitive function, longer duration of diabetes, insulin and oral diabetes medication use, poor kidney function, low socioeconomic status, mobility limitations, IADLs, and ADLs. Risk factors for hypoglycemia will be similar for blacks and whites.

Aim 2: To identify a small set of risk factors (5-8) that are most predictive of severe hypoglycemia.

Hypothesis: Age, medication use, poor kidney function, and any IADLs or ADLs will be most predictive of severe 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).

Study Design: Prospective cohort, using Visit 4 as baseline

Inclusion Criteria: Diagnosed diabetes (by medication use or self-report)

Ascertainment of Severe Hypoglycemia: We will use a widely used algorithm to identify episodes of severe hypoglycemia from ARIC hospitalization and linked CMS claims data for hospitalizations, ambulance services, and emergency department visits (**Table 1**). The original algorithm has a positive predictive value of 89%.²² As others have done, we will modify the algorithm slightly to exclude neonatal hypoglycemia and leucine-induced hypoglycemia, which are very unlikely to occur in type 2 diabetes.^{21,23}

Table 1. ICD-9 Coding Algorithm for Identification of Severe Hypoglycemia

ICD-9 codes in 1 st position	Other restrictions
251.0x: Hypoglycemic coma 251.1x: Other specified hypoglycemia 251.2x: Hypoglycemia, unspecified 962.3x: Poisoning by insulins or other anti-diabetic agents	(none)
250.8x: Diabetes with other specified manifestations	Must not have codes specifying other diabetes complications used for 250.8: 259.8: Secondary diabetic glycosuria 272.7: Diabetic lipodystrophy 681.xx, 682.xx, 686.9x: Cellulitis 707.1 – 707.9: Ulcers of the lower extremity 709.3: Oppenheim-Urbach syndrome 730.0 – 730.2, 731.8: Osteomyelitis

Approximately 75% of cases of severe hypoglycemia that present to the emergency department are discharged without being admitted to the hospital.²³ Claims for the emergency department visits in ARIC are only available if a participant is enrolled in CMS fee-for-service Part B. Thus, we believe it is important to account for possible differential ascertainment of severe hypoglycemia related to the use of claims data. To address this potential bias, we will examine and compare associations in the following scenarios: 1) an analysis of all participants, identifying severe hypoglycemia only with ARIC hospitalizations data (continuous eligibility, but prone to underascertainment since will only capture hospitalized events); 2) an analysis of all participants using both ARIC and CMS data to identify severe hypoglycemia, recognizing that not all participants in the denominator will be continuously eligible for CMS-defined events; and 3) an analysis limited to participants enrolled in CMS fee-for-service Part B at or within 2 years of Visit 4, recognizing that this approach may be associated with lower power (smallest number of participants).

Hypoglycemia risk factors we will examine are (measured at visit 4 unless otherwise noted):

- Age
- Sex
- BMI, both continuous and categorical (normal weight, overweight, obese)
- Kidney function:
 - eGFR estimated by creatinine, creatinine and cystatin, and cystatin alone
 - Albuminuria, by categories of ACR <30, 30-<300, and ≥300mg/L
 - CKD Stage by KDIGO classification, combining eGFR and albuminuria²⁴
- Diabetes duration, calculated based on the first report of a diabetes diagnosis to ARIC. This will be categorized into 2 or 3 groups since it will not be continuous.
- Diabetes Medication use, classified into categories of no medication, oral medication(s) only, or any insulin.
- Income from SESA, classified into race-specific tertiles
- Education from Visit 1 (variable elevel02 in the derived dataset)
- Occupation (retired/white collar/blue collar/homemaker), from Visit 1 and updated at Visit 3 and Visit 4 if occupation status changed.
- Cognitive function, from the digit symbol substitution test (DSST), the delayed word recall test (DWRT), the word fluency test (WFT), as well as the global z-score by averaging the z-scores of these cognitive tests. These will be examined as continuous variables and as quartiles, both overall and race-specific. Cognitive impairment for those 65+ will be based on the normative data published by Schneider 2014.²⁵
- History of cardiovascular disease (prvchd43, prvstr41)
- Liver function: ALT, AST, GGT will be examined continuously and in quartiles
- Percentiles of glycated albumin will be used to account for glycemic control; previous research has suggested that A1c <6% and >9% is associated with increased risk of hypoglycemia. We will identify the glycated albumin level corresponding to those values of A1c at visit 2, and then create categories of glycated albumin measured at Visit 4 based on these cutpoints.
- Alcohol consumption (current/former/never)
- Physical functioning, ADLs, & IADLs from PAQA, following the classification made in Houston 2005²⁶
 - Mobility limitation defined by self-report of any difficulty with: walking a quarter mile, walking 10 steps without resting, stooping/crouching/kneeling, lifting or carrying something up to 10 pounds, and standing up from an armless chair
 - IADL problems defined by self-report of any difficulty with: preparing own meals, managing money, and chores around the house.
 - ADL problems defined by self-report of any difficulty with: eating, dressing, getting in or out of bed, and walking from one room to another on the same level.
- Self-rated health (excellent/good/fair/poor) from Annual Follow-Up phone calls, taken from the AFU immediately following Visit 4
- Biomarkers of general poor health/prognosis, including: high-sensitivity cardiac troponin T, serum albumin, and CRP.

Statistical Analysis: We will examine demographic and clinical characteristics of participants at Visit 4 by race (black or white). We will examine the prevalence of established (albuminuria, low eGFR, duration of diabetes, older age, medication use) and suspected (female sex, low BMI, low cognitive function, poor liver function, history of cardiovascular disease, low SES, mobility limitations, IADLs, ADLs) risk factors for severe hypoglycemia according to race.

We will create race-specific quartiles for variables that have substantially different distributions by race (income and cognitive test scores). Cognitive test scores are known to show substantial differences by race and education that are not reflective of cognitive ability.²⁵ Because it is likely that blacks and whites at the same income level still have different socioeconomic status (for example, less wealth), adjusting for race-specific tertiles of income will account for the relative difference in SES within race but not differences in SES across race.²⁷

We will then conduct stratified Cox regression by race to compare the strength of risk factors by race. If there are not notable differences in the strength of the risk factors on hypoglycemia, then the models will be combined for better precision. If there are only a few risk factors that appear different, then blacks and whites will be combined into one model and an interaction term between race and the risk factor will be evaluated.

To determine which set of risk factors are most predictive, we will choose risk factors that are strongly associated with hypoglycemia and will prioritize those that are readily clinically available. We will compare models using the C-statistic to determine which set of risk factors best discriminates risk of severe hypoglycemia.

We will conduct several sensitivity analyses to determine how robust our results are. In one sensitivity analysis, we will use intervening events as time-varying exposures, including incident CKD/ESRD (by hospitalization and/or dialysis), incident stroke (by ARIC adjudication) and incident dementia (by hospitalization). We will look to see if these time-varying exposures are associated with risk of hypoglycemia and if they attenuate the associations of the other risk factors in the model with hypoglycemia.

We will also conduct a sensitivity analysis to try to exclude individuals with type 1 diabetes by excluding participants who reported a diabetes diagnosis at Visit 1 and have reported taking insulin only (no oral diabetes medications) at Visits 1 through 4.

Our third sensitivity analysis will be to separate oral medications into sulfonylureas and non-sulfonylureas, given that sulfonylureas are known to increase risk of hypoglycemia more than other oral hypoglycemic agents.²⁸⁻³⁰ However, due to the time of Visit 4 (1996-1998), few other oral medications were available clinically, and thus we anticipate very small numbers of individuals on oral medications other than sulfonylureas.

Our fourth sensitivity analysis will be to attempt to exclude cases of hypoglycemia that were caused by acute illness, such as pneumonia, sepsis or liver disease.³¹ We will do this

by looking for ICD-9 codes for acute conditions that may trigger hypoglycemia in hospitalization records. We expect that the exclusion of these cases of hypoglycemia will strengthen the association of hypoglycemia with baseline risk factors.

Limitations

A primary limitation of our study will be the relatively small number of severe hypoglycemia events (estimated to be N~110) and correspondingly low power to examine subgroups and conduct extensive multivariable adjustment. Indeed, following the rule of thumb of one covariate per ten events will limit the number of covariates that can be included in the final model to 11 covariates.

While we can evaluate type of medication use at visit 4 (insulin vs. oral vs. none), we do not have detailed information on medication use during the entire follow-up time. Beginning in 2007, annual follow-up phone calls included questions on all medications taken during the last two weeks, but did not record drug dosage. With the initiation of Medicare Part D in 2006, pharmacy claims with drug dosage are available for individuals who enrolled in Part D. We will consider using time-updated medication use in the regression models if it available for enough participants.

Finally, depression may also be linked to hypoglycemia risk, since depressive symptoms such as eating less may result in hypoglycemia. However, we do not have a valid measure of depressive symptoms, such as the CES-D, available at Visit 4. We will consider using the Vital Exhaustion Questionnaire at Visit 2, but there would likely not be enough signal to see an association with hypoglycemia.

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.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)?

MP#2630: Hypoglycemia and Cognitive Function in Older Adults with Diabetes.
Alexandra Lee, Andreea Rawlings, Andrea Schneider, Elbert Huang, A. Richey Sharrett, Elizabeth Selvin

MP#2707: Severe Hypoglycemia and Subclinical Myocardial Damage in Older Adults with Diabetes. Alexandra Lee, William McEvoy, Ron Hoogeveen, Christie Ballantyne, Elizabeth Selvin

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 (list number* _____)
 B. primarily based on ARIC data with ancillary data playing a minor role (usually control variables; list number(s)* 2008.06, 2002.02, 2009.16)

*ancillary studies are listed by number at <http://www.csc.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.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.

13. Per Data Use Agreement Addendum for the Use of Linked ARIC CMS Data, approved manuscripts using linked ARIC CMS data shall be submitted by the Coordinating Center to CMS for informational purposes prior to publication.

Approved manuscripts should be sent to Pingping Wu at CC, at pingping_wu@unc.edu. I will be using CMS data in my manuscript Yes No.

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