ARIC Manuscript Proposal #2630

PC Reviewed: 9/8/15	**Status: A**	**Priority: 2**
SC Reviewed: _____	**Status: _____**	**Priority: ____**

1.a. Full Title: Hypoglycemia and cognitive function in older adults with diabetes

b. Abbreviated Title (Length 26 characters): Hypoglycemia and Cognition

2. Writing Group:

Writing group members: Alexandra Lee, Andreea Rawlings, Andrea Schneider, Elbert Huang, A. Richey Sharrett, Elizabeth Selvin; others welcome

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

First author: **Alexandra Lee**
Address: Welch Center
2024 E. Monument St, Ste 2-600
Baltimore, MD 21287

Phone: (510) 499-8037 Fax:
E-mail: alee160@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: Welch Center
2024 E. Monument St, Ste 2-600
Baltimore, MD 21287

Phone: 410-614-3752 Fax: 410-955-0476
E-mail: eselvin@jhu.edu

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

4. Rationale:

Severe hypoglycemia is an acute, potentially life-threatening complication of diabetes that may also cause permanent harm. Although more common in individuals with type 1 diabetes, in type 2 diabetes the incidence rate of hospitalization for hypoglycemia was estimated at 612 per 100,000 person-years among Medicare beneficiaries in 2010.[1] Older adults are particularly susceptible to hypoglycemia due to polypharmacy and reduced kidney clearance of insulin and sulfonylureas.[2] As the population of older adults with type 2 diabetes increases, it is important to characterize the impact of hypoglycemia and its associations with cognition in this population.

There is evidence that poor cognition contributes to an increased risk of hypoglycemia in persons with diabetes; people with poor cognition may be more likely to experience medication-dosing errors and/or may not recognize early signs of hypoglycemia. A link between poor cognition and hypoglycemia risk has been shown in several studies.[3,4] For example, a post-hoc analysis of the ACCORD trial found that individuals in the lowest tertile of cognitive function, as assessed by the digit symbol substitution test, were more than twice as likely to have a hypoglycemic event requiring medical services during a median of ~3 years of follow-up compared to those in the top two tertiles of cognitive function.[5]

Hypoglycemia may also accelerate cognitive decline in older adults, but the evidence for hypoglycemia leading to future cognitive decline is less clear. Because the brain, unlike other organs, relies almost exclusively on glucose for fuel, it may be uniquely vulnerable to low circulating glucose levels. Severe hypoglycemia has been associated with cortical injury and neuronal death.[6] In DCCT/EDIC, a well-characterized long-term study of persons with type 1 diabetes, severe hypoglycemia, defined by seizure or coma, had no effect on cognitive function after 18 years of follow-up.[7] However, participants had a mean age of 52 at the end of follow-up, and it is possible that the analysis did not have enough power to detect small cognitive changes. Two recent epidemiologic studies in patients with type 2 diabetes found that severe hypoglycemia requiring hospitalization and/or emergency department care were associated with incident dementia diagnoses, even after adjusting for comorbidities and hemoglobin A1c.[3,8]

It is possible that the association of hypoglycemia with cognition is bi-directional, with hypoglycemia contributing to future risk of cognitive decline and poor cognitive function also leading to episodes of hypoglycemia. Nonetheless, studying the long-term effects of hypoglycemic episodes on cognitive decline is complicated by the need for well-ascertained hypoglycemic events and long-term follow-up for cognitive outcomes. Thus, the evidence suggesting the hypoglycemic episodes can contribute to cognitive decline in an initially cognitively intact population is sparse.

Quantifying the effects of hypoglycemia can inform the debate regarding appropriate glucose targets for older adults with diabetes.[2] Most glucose-lowering trials have shown more intensive glucose control results in a higher risk of hypoglycemia.[7,9–13] Particularly in older adults, episodes of hypoglycemia can result in substantial harm, such as falls, cardiac arrhythmias, and even death.[14–17] Understanding the link between hypoglycemic

events and cognition can aid in the formulation of appropriate guidelines for glucose management in older adults with diabetes.

The Atherosclerosis Risk in Communities (ARIC) Study provides a unique opportunity to study the possible bi-directional association of hypoglycemia and cognition due to the availability of detailed phenotype data on diabetes, cognitive testing at multiple time points in all participants, and ascertainment of severe hypoglycemia via both ARIC hospitalizations and linkage to data from the Centers for Medicare Services and Medicaid (CMS). Using linkage to CMS data, we can evaluate risk of hypoglycemia over 10 years for most ARIC participants with diabetes. Repeat cognitive testing, beginning in middle-age, will permit us to better evaluate the directionality of associations between hypoglycemia and cognitive function. This analysis of ARIC will be the largest epidemiologic study of hypoglycemia and cognitive function with research-grade data.

5. Main Hypothesis/Study Questions:

AIM 1: Examine cross-sectional associations of history of severe hypoglycemia with prevalent cognitive dysfunction among participants with diabetes at Visit 5 (2011-2013).

> Hypothesis: History of severe hypoglycemia (versus not) will be associated with higher prevalence of cognitive dysfunction.

AIM 2: Quantify risk of severe hypoglycemia among older adults with diabetes. Compare risk of severe hypoglycemia by age group, race, medication use, and duration of diabetes.

> Hypothesis: Risk of hypoglycemia will be higher among older individuals and those with long duration of diabetes and insulin use.

AIM 3: To evaluate whether poor cognitive function in 1996-1998 (visit 4) among persons with diabetes is associated with future risk of severe hypoglycemia. We will also evaluate whether there is evidence for a 'dose-response' association between cognitive function and severe hypoglycemia or if there is a threshold below which there is no association.

> Hypothesis: Poor cognitive function will be independently associated with risk of severe hypoglycemic events, with evidence of a possible threshold effect.

AIM 4: To determine if severe hypoglycemia in diabetes is associated with cognitive decline from Visit 4 (1996-1998) to Visit 5 (2011-2013)

Hypothesis: Any severe hypoglycemia will be associated with greater cognitive decline.

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).

AIM 1: Examine cross-sectional associations of history of severe hypoglycemia with prevalent cognitive dysfunction among participants with diabetes at Visit 5 (2011-2013).

Study Design: Cross-sectional at Visit 5

Inclusion Criteria: Individuals with self-reported diagnosed diabetes or diabetes medication use through Visit 5 who completed the cognitive battery.

Exclusion Criteria: Individuals on medications known to affect cognition, non-white and non-black race, and blacks at the Maryland and Minnesota study sites.

Exposure: Severe hypoglycemia will be defined as hypoglycemia resulting in an emergency department visit, an observational hospital stay, or an inpatient hospital admission from the linked CMS data and ARIC hospitalizations. Hypoglycemia will be identified by ICD-9 diagnosis codes 251.0 (hypoglycemic coma), 251.1 (other specified hypoglycemia), 252.2 (hypoglycemia, unspecified), 962.3 (poisoning by insulins and antidiabetic agents) in first position with 250.x (diabetes) in any other position, and by 250.8 in first position (in the absence of 681.xx, 682.xx, 686.90, 707.xx, 730.27, and 731.8). This follows a validated algorithm by Ginde et al., but is modified slightly to exclude 270.3 (leucine-induced hypoglycemia), 775.0 (hypoglycemia in infants), and 775.6 (neonatal hypoglycemia). Sensitivity analysis will be conducted allowing the aforementioned codes to be in any position, rather than just first position. A second sensitivity analysis will exclude code 962.3 (poisoning by antidiabetic agents), as Ginde et al. found it had a low positive predictive value and the overall positive predictive value of the algorithm increased when this code was eliminated.[18]

Outcome: First, cognitive test scores from Visit 5 NCS will be examined individually as continuous outcomes.
Second, cognitive dysfunction will be defined within domains, using norms from the Brain MRI visit.[19] Three cognitive tests will be used to assess processing speed and executive function: Digit Symbol Substitution Test, and Trail Making Tests A and B. Memory will be assessed by the Delayed Word Recall Test, and the Logical Memory Test Parts I and II. Language and verbal fluency will be assessed by the Animal Naming test and the Word Fluency Test. A single cognitive test score worse than 1.5 standard deviations below age-, race- and education-specific normative data from healthy older adults will qualify an individual as having cognitive dysfunction in that domain.[19]

Third, we will use visit 5 to create a robust normative sample as described in the ARIC-NCS renewal proposal. The following criteria will be used to define a cognitively healthy group of participants:

1) No decline in DWR, DSST, or WFT from prior visits, as defined by the decline criteria in Manual of Procedure #17
2) An MMSE score ≥21 for whites and ≥19 for blacks
3) No clinical neurological disease, use of cholinomimetic medications, or diagnosed dementia at Visit 5
4) Two APOE ε4 alleles
5) No self-reported memory problems

Analysis: We will examine cognitive test scores as a continuous outcome with linear regression, adjusting for and/or stratifying by covariates listed above.
Crude prevalence of cognitive dysfunction by domain will be examined for individuals with and without a history of severe hypoglycemia. Prevalence ratios from Poisson regression with robust standard errors will be progressively adjusted for age, sex, race-center, education, hypertension, diabetes duration, prevalent CHD, prevalent stroke, drinking status, smoking status, and APOE ε4.

Limitations: Using ICD-9 codes to identify cases of hypoglycemia is common in the literature, but this algorithm has not been evaluated for sensitivity and specificity, only positive predictive value. Hypoglycemia requiring emergency medical care is likely only a small fraction of hypoglycemic episodes experienced by individuals with advanced type 2 diabetes. The need for medical care for hypoglycemia is likely due to many factors, including whether the individual lives alone and his/her cognitive and physical abilities. It is possible that severe hypoglycemia, as measured here, may be a marker of vulnerability. Recurrent mild hypoglycemia not requiring medical care may result in different physiological responses that would not be captured in this study.

This cross-sectional analysis will not enable conclusions about causality, but will provide relevant clinical information for doctors who treat older adults with diabetes and a history of severe hypoglycemia. The numerous biases present in this cross-sectional analysis will affect all cognitive domains equally, and so relative comparisons of domains should be valid.

AIM 2: Describe risk of severe hypoglycemia among older adults with diabetes. Compare risk of severe hypoglycemia by age group, race, medication use, and duration of diabetes.

Study Design: Prospective cohort.

Inclusion criteria: ARIC participants at least 65 years of age at or after visit 4 with diagnosed diabetes (updated with self-reported diabetes or medication use in the AFU and potentially two or more codes of 250.x in CMS) who are enrolled in at least 12 continuous months of Medicare FFS.

Exclusion criteria: Non-white and non-black race, and blacks at the Maryland and Minnesota study sites

Outcome: Severe hypoglycemia from the linked CMS data, as described above.

Analysis: Risk of hypoglycemia will be assessed both overall and in subgroups, defined by age, race, medication use, and duration of diabetes (categorical, based on the date of first self-report). Because identification of severe hypoglycemia as defined above requires enrollment in Medicare fee-for-service Parts A and B (FFS), and individuals must be at least age 65 to enter Medicare, individuals will have varying amounts of time in Medicare FFS. We will account for the amount of at-risk person-time in our analyses.

Limitations: Restricting our analytic population to individuals with FFS will reduce the sample size and thus result in less stable estimates of risk. However, the strength this particular analysis brings to the literature is a well-characterized population with known at-risk person-time. Previous studies on risk of hypoglycemia in the general population have used numerators and denominators from different data sources. Thus, rigorously quantifying the at-risk person time by restricting to individuals with FFS is a novel feature of this analysis.

Additionally, while it would be ideal to categorize diabetes medication use by type (insulin, sulfonylureas, or oral agents), we will likely only be able to categorize diabetes medication use as yes/no. All AFU calls ask whether or not participants are taking medications for diabetes, but lists of medication are only collected at in-person visits and in the AFU starting in 2006 (with version L of the AFU form). Thus, prior to 2006 it is only feasible to characterize diabetes medication use as yes/no, while after 2006 it might be possible to further categorize diabetes medication use by type, depending on sample size.

AIM 3: To evaluate whether poor cognitive function in 1996-1998 (visit 4) among persons with diabetes is associated with future risk of severe hypoglycemia. We will also evaluate whether there is evidence for a 'dose-response' association between cognitive function and severe hypoglycemia or if there is a threshold below which there is no association.

Study Design: Prospective cohort.

Inclusion criteria: Individuals with self-reported diagnosed diabetes or diabetes medication use at Visit 4.

Exclusion criteria: Missing cognitive assessments at visit 4, non-white and non-black race, and blacks at the Maryland and Minnesota study sites

Exposure: Poor cognitive function will be defined as the lowest quartile from each cognitive test from visit 4: the Digit Symbol Substitution Test, the Delayed Word Recall Test, the Word Fluency Test, and the global cognitive Z score.

Outcome: Severe hypoglycemia, defined using the ICD-9 codes described above, from CMS inpatient hospital admissions, emergency department visits, and observational hospital stays (no ARIC hospitalizations).

Analysis: For each of the four measures of cognition at visit 4, we will use Cox regression with visit 4 as the time origin. Late entries will be used for individuals who enroll in Medicare fee-for-service parts A and B after visit 4. The exposure, cognition, will be modeled first as quartiles and then with splines to look for evidence of either a dose-response or threshold effect. Analyses will adjust for age, sex, race-field center, educational attainment, APOE ε4 genotype (0, 1, or 2 alleles), and covariates at visit 4: BMI, alcohol use (current/former/never), smoking (current/former/never), hypertension (defined as systolic blood pressure ≥140, diastolic blood pressure ≥90, or blood pressure-lowering medication use), history of coronary heart disease, history of stroke, ESRD, duration of diabetes, and diabetes medication use. In the primary analysis, individuals who have a stroke after visit 4 will be censored at that date, since stroke frequently results in diminished cognitive function. A secondary analysis will use a time-varying variable for incident stroke to assess the possibility that stroke mediates the effect of cognition on risk of severe hypoglycemia.
As a sensitivity analysis, we will remove the requirement of fee-for-service enrollment and include ARIC hospitalization. This will address the main limitation (described below).

Limitations: The main limitation is a smaller sample size due to restriction of the analysis to individuals with Medicare fee-for-service enrollment in parts A and B. This is necessary to ensure all participants would have an emergency department hypoglycemic event captured in the data. A recent analysis found that only 27% of individuals who presented at the emergency department with hypoglycemia were admitted to the hospital.[20] The decision to hospitalize an individual from the emergency department is likely based both on severity of hypoglycemia and on other comorbidities present. Thus, if we were to include individuals' person-time before they were "at-risk" for emergency department visits, then the independent variables in the model might be more strongly associated with factors related to hospital admission rather than hypoglycemia per se.

AIM 4: To determine if severe hypoglycemia in diabetes is associated with cognitive decline from Visit 4 (1996-1998) to Visit 5 (2011-2013).

Study Design: Prospective cohort.

Inclusion criteria: Individuals with self-reported diagnosed diabetes or diabetes medication use at Visit 4. (We will explore imputation for these individuals as a sensitivity analysis.)

Exclusion criteria: Missing cognitive test scores at visit 4, non-white and non-black race, and blacks at the Maryland and Minnesota study sites

Exposure: Severe hypoglycemia from both CMS linkage and ARIC hospitalizations, categorized in two ways: 1) ever/never 2) ordinal categories.

Outcome: Cognitive decline, as measured by change from visit 4 to visit 5 in three cognitive tests (Delayed Word Recall, Digit Symbol Substitution, and Word Fluency) and global z-score. Cognitive scores for individuals who did not attend Visit 5 will be imputed with multiple imputation by chained equations (as in MP #2523).
We will also explore the possibility of using latent variables for cognitive change, so that all the cognitive tests at Visit 5 can be utilized (as described in MP #2215).

Analysis: Change in cognitive test score will be modeled with linear regression. Models will be adjusted for age, race-center, sex, education, hypertension, BMI, lipids, smoking status, duration of diabetes, APOE ε4, living alone, number of hospitalizations, and number of emergency department visits. Models will be run both adjusted and unadjusted for cognitive score at visit 4. We will guide our model-building with DAGs, taking into account Glymour's descriptions of potential biases when adjusting for baseline cognition in models of cognitive change.[21]

Limitations: Of the approximately 200 individuals who experienced severe hypoglycemia between Visits 4 and 5 and are alive at Visit 5, only 50 have cognitive test scores at Visit 5. To account for this potential selection bias, we will impute scores of participants who did not attend visit 5.
However, if all potential biases are correctly accounted for, this would be the first study to assess the prospective association between hypoglycemia and sub-clinical cognitive decline.

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?
__X__ 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"?
__X__ 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

__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)?

(MP#2160) Rawlings, AM, Sharrett, AR, Schneider, AL, Coresh, J, Albert, M, Couper, D, Griswald, M, Gottesman, RF, Wagenknetch, LE, Windham, BG, & Selvin, E (2014). Diabetes in midlife and cognitive change over 20 Years: A cohort study. *Annals of internal medicine*, *161*(11), 785-793.

MP #1967 Wruck, L, Alonso A, Bandeen-Roche K, Carlson M, Schneider A, Griswold M, Mosley T, Sharrett R. Adjusting for Measurement Error in Baseline Measures of Cognitive Function: The ARIC Neurocognitive Study.

MP #2523 Rawlings AM, Sang Y, Griswold M, Sharrett AR, Coresh J, Wruck LM, Deal JA, Power MC, Bandeen-Roche K. Imputing missing outcome data using multiple imputation by chained equations: simulation and validation in the ARIC study.

(MP #1121) Knopman D, Mosley T, Catellier D, Coker L. Fourteen-year longitudinal study of vascular risk factors, APOE genotype, and cognition: The ARIC MRI Study. Alzheimer's and Dementia 2009.

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

11.b. If yes, is the proposal
__X__ A. primarily the result of an ancillary study (list number* 2008.06)
___ 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 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.

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 __X__ Yes ____ No.

References

1. Lipska KJ, Ross JS, Wang Y, et al. National Trends in US Hospital Admissions for Hyperglycemia and Hypoglycemia Among Medicare Beneficiaries, 1999 to 2011. *JAMA Intern Med*. 2014;174(7):1116-1124. doi:10.1001/jamainternmed.2014.1824.

2. Seaquist ER, Anderson J, Childs B, et al. Hypoglycemia and diabetes: A report of a workgroup of the American diabetes association and the endocrine society. *Diabetes Care*. 2013;36(5):1384-1395. doi:10.2337/dc12-2480.

3. Yaffe K. Association Between Hypoglycemia and Dementia in a Biracial Cohort of Older Adults With Diabetes Mellitus. *JAMA Intern Med*. 2013;173(14):1300. doi:10.1001/jamainternmed.2013.6176.

4. De Galan BE, Zoungas S, Chalmers J, et al. Cognitive function and risks of cardiovascular disease and hypoglycaemia in patients with type 2 diabetes: The action in diabetes and vascular disease: Preterax and diamicron modified release controlled evaluation (ADVANCE) trial. *Diabetologia*. 2009;52(11):2328-2336. doi:10.1007/s00125-009-1484-7.

5. Punthakee Z, Miller ME, Launer LJ, et al. Poor Cognitive Function and Risk of Severe Hypoglycemia in Type 2 Diabetes. *Diabetes Care*. 2012;35:1-7. doi:10.2337/dc11-1855.

6. Warren RE, Frier BM. Hypoglycaemia and cognitive function. *Diabetes, Obes Metab*. 2005;7(5):493-503. doi:10.1111/j.1463-1326.2004.00421.x.

7. Jacobson AM, Musen G, Ryan CM, et al. Long-term effect of diabetes and its treatment on cognitive function. *N Engl J Med*. 2007;356(18):1842-1852. doi:10.1056/NEJMoa066397.

8. Whitmer R a, Karter AAJ, Yaffe K, Quesenberry CPC, Selby JVJJ V. Hypoglycemic episodes and risk of dementia in older patients with type 2 diabetes mellitus. *JAMA*. 2009;301(15):1565-1572. doi:10.1001/jama.2009.460.

9. ORIGIN Trial Investigators. Predictors of nonsevere and severe hypoglycemia during glucose-lowering treatment with insulin glargine or standard drugs in the ORIGIN trial. *Diabetes Care*. 2015;38(1):22-28. doi:10.2337/dc14-1329.

10. Zoungas S, Patel A, Chalmers J, et al. Severe hypoglycemia and risks of vascular events and death. *N Engl J Med*. 2010;363(15):1410-1418. doi:10.1056/NEJMoa1003795.

11. Bonds DE, Miller ME, Bergenstal RM, et al. The association between symptomatic, severe hypoglycaemia and mortality in type 2 diabetes: retrospective

epidemiological analysis of the ACCORD study. *BMJ*. 2010;340:b4909. doi:10.1136/bmj.b4909.

12. Duckworth W, Abraira C, Moritz T, et al. Glucose control and vascular complications in veterans with type 2 diabetes. *N Engl J Med*. 2009;360(2):129-139. doi:10.1056/NEJMoa0808431.

13. UK Prospective Diabetes Study Group. Intensive Blood-Glucose Control With Sulphonylureas or Insulin Compared With Conventional Treatment and Risk of Complications in Patients With Type 2 Diabetes. *Lancet*. 1998;352(Ukpds 33):837-853. doi:10.1016/S0140-6736(98)07019-6.

14. Johnston SS, Conner C, Aagren M, Ruiz K, Bouchard J. Association between hypoglycaemic events and fall-related fractures in Medicare-covered patients with type 2 diabetes. *Diabetes, Obes Metab*. 2012;14(7):634-643. doi:10.1111/j.1463-1326.2012.01583.x.

15. Johnston SS, Conner C, Aagren M, Smith DM, Bouchard J, Brett J. Evidence linking hypoglycemic events to an increased risk of acute cardiovascular events in patients with type 2 diabetes. *Diabetes Care*. 2011;34(5):1164-1170. doi:10.2337/dc10-1915.

16. Desouza C V., Bolli GB, Fonseca V. Hypoglycemia, diabetes, and cardiovascular events. *Diabetes Care*. 2010;33(6):1389-1394. doi:10.2337/dc09-2082.

17. McCoy RG, Van Houten HK, Ziegenfuss JY, Shah ND, Wermers R a., Smith S a. Increased Mortality of Patients With Diabetes Reporting Severe Hypoglycemia. *Diabetes Care*. 2012;35(9):1897-1901. doi:10.2337/dc11-2054.

18. Ginde A a, Blanc PG, Lieberman RM, Camargo C a. Validation of ICD-9-CM coding algorithm for improved identification of hypoglycemia visits. *BMC Endocr Disord*. 2008;8:4. doi:10.1186/1472-6823-8-4.

19. Schneider a L, Sharrett a R, Gottesman RF, et al. Normative Data for 8 Neuropsychological Tests in Older Blacks and Whites From the Atherosclerosis Risk in Communities (ARIC) Study. *Alzheimer Dis Assoc Disord*. 2014;29(1):32-44. doi:10.1097/WAD.0000000000000042.

20. Wang J, Geiss LS, Williams DE, Gregg EW. Trends in Emergency Department Visit Rates for Hypoglycemia and Hyperglycemic Crisis among Adults with Diabetes, United States, 2006-2011. *PLoS One*. 2015;10(8):e0134917. doi:10.1371/journal.pone.0134917.

21. Glymour MM, Weuve J, Berkman LF, Kawachi I, Robins JM. When is baseline adjustment useful in analyses of change? An example with education and cognitive change. *Am J Epidemiol*. 2005;162(3):267-278. doi:10.1093/aje/kwi187.