THE EPIDEMIOLOGY OF SEVERE HYPOGLYCEMIA IN TYPE 2 DIABETES

by

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Abstract

The purpose of this dissertation is to explore the epidemiology of severe hypoglycemia in type 2 diabetes by examining risk factors and health outcomes associated with severe hypoglycemia. Severe hypoglycemia is more common with older age and reduced kidney function, but few studies have examined other factors contributing to hypoglycemia risk. Additionally, prior research has demonstrated associations of severe hypoglycemia with cardiovascular disease and dementia, but it is unclear whether such associations are causal.

The first aim of this dissertation evaluates risk factors for severe hypoglycemia among community-dwelling adults with diabetes in the Atherosclerosis Risk in Communities (ARIC) Study. In this prospective analysis, we show that poor glycemic control, older age, black race, macroalbuminuria, disability, and worse cognition are independently associated with severe hypoglycemia.

The second aim, addressed in a cross-sectional analysis, shows that the prevalence of elevated high-sensitivity cardiac troponin T (a biomarker of subclinical myocardial damage) is higher in those with a history of severe hypoglycemia as compared to those without. After adjustment for demographic variables, glycated hemoglobin (HbA1c), and diabetes duration, the association is attenuated and not statistically significant, suggesting that diabetes severity may partially explain this association.

The third aim examines the association of severe hypoglycemia with individual cardiovascular outcomes and cause-specific mortality. This prospective

analysis in the ARIC Study finds that hypoglycemia is associated with coronary heart disease (HR 2.02, 95%CI 1.27-3.20) and is suggestive of an association with peripheral artery disease. We find no association of hypoglycemia with other types of cardiovascular events, indicating hypoglycemia may contribute specifically to atherosclerotic disease.

The fourth aim investigates cognitive outcomes in older adults in the ARIC study. In a cross-sectional analysis, we show that persons with a history of severe hypoglycemia have smaller total and frontal brain volumes compared to persons without hypoglycemia. In a prospective analysis, we find that severe hypoglycemia is associated with substantially increased risk of dementia (HR 2.44, 95% CI 1.70-3.49).

Overall, this dissertation provides essential information on risk factors for severe hypoglycemia as well as the associated health risks, enabling providers to better weigh the pros and cons of glucose-lowering treatment in type 2 diabetes.

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List of Abbreviations

1,5-AG	1,5-anhydroglucitol
ACCORD	Action to Control Cardiovascular Risk in Diabetes (trial)
ACCORD-MIND	ACCORD-Memory in Diabetes
ACR	Albumin-to-creatinine ratio
ADVANCE	Action in Diabetes and Vascular Disease – preterax and diamicron MR controlled evaluation (trial)
ADA	American Diabetes Association
ADL	Activity of daily living
ALT	Alanine aminotransferase
ARIC	Atherosclerosis Risk in Communities (study)
AST	Aspartate aminotransferase
BMI	Body mass index
CES-D	Center for Epidemiologic Studies Depression Scale
CGM	Continuous glucose monitoring
CHD	Coronary heart disease
CI	Confidence interval
DCCT/EDIC	Diabetes Complications and Control Trial/Epidemiology of Diabetes Interventions and Complications
DPP-4	Dipeptidyl peptidase 4
DSST	Digit Symbol Substitution Test
EASD	European Association for the Study of Diabetes
ECG	Electrocardiogram
eGFR	Estimated Glomerular Filtration Rate
GGT	Gamma-glutamyl transferase
GLP-1	Glucagon-like peptide 1
HbA1c (A1c)	Glycated hemoglobin
HDL	High-density lipoprotein
HF	Heart failure
HIV	Human Immunodeficiency Virus
HR	Hazard ratio
hsCRP	High-sensitivity c-reactive protein
hs-cTnT	High-sensitivity cardiac troponin T
IADL	Instrumental activity of daily living
ICD-9	International Classification of Diseases – 9th Revision
LDL	Low-density lipoprotein
MCI	Mild cognitive impairment
MRI	Magnetic resonance imaging
NT-proBNP	N-terminal pro b-type natriuretic peptide
OR	Odds ratio
ORIGIN	Outcome Reduction with an Initial Glargine Intervention (trial)
PR	Prevalence ratio
SGLT2	Sodium glucose cotransporter 2
SD	Standard deviation

UKPDS	United Kingdom Prospective Diabetes Study
VADT	Veterans Affairs Diabetes Trial

Introduction

This dissertation examines the epidemiology of severe hypoglycemia in adults with type 2 diabetes. It describes the risks and rates of severe hypoglycemia in a community-based cohort. An overarching aim of this research was to comprehensively characterize the risk factors for severe hypoglycemia and its clinical consequences, with a focus on potential differences by race. Specifically, we examine the associations of severe hypoglycemia with important health outcomes, including subclinical heart damage, cardiovascular events, death, and cognitive outcomes. We also attempt to clarify whether severe hypoglycemia is a marker or a cause of increased risk.

Hypoglycemia

Hypoglycemia is a low blood glucose concentration, typically defined as either at least one blood glucose reading of <70 mg/dL or the appearance of symptoms that resolve upon administration of carbohydrates (1). Hypoglycemia can be either asymptomatic or accompanied by symptoms including tachycardia, shakiness, sweating, nervousness, hunger, and confusion (2). The appearance of symptoms is highly variable, as individuals with frequent hypoglycemia have an onset of symptoms at lower blood glucose concentrations (1-3). Declining blood glucose levels trigger an autonomic nervous system response, promoting hepatic and renal gluconeogenesis via glucagon secretion and increased epinephrine (**Table 1**) (2,4). The severity of symptoms increases at lower blood

glucose concentrations, with loss of consciousness and seizures typically occurring around 30 mg/dL (2).

Hypoglycemia is more common among individuals with type 1 compared to type 2 diabetes (5-6). Type 1 diabetes is characterized by an absolute insulin deficiency due to beta cell failure which is accompanied by the loss of the glucagon response from alpha cells (2). In type 1 diabetes and advanced type 2 diabetes, many of the counter-regulatory processes are blunted, resulting in a reduced ability to endogenously correct falling glucose concentrations (2).

Hypoglycemia can have a range of triggers. In most cases among patients with diabetes, hypoglycemia is considered to be iatrogenic, caused by excess glucose-lowering medication. Hypoglycemia is the most common adverse event associated with diabetes medications and is considered the primary barrier to achieving good glycemic control (2). Medications differ substantially regarding their risk of hypoglycemia: insulin is typically mostly strongly associated with hypoglycemia risk, followed by sulfonylureas (7). Medications such as metformin and newer classes of diabetes medications (thiazolidinediones, DPP-4 inhibitors, GLP-1 receptor agonists, and SGLT2 inhibitors) are associated with lower risks of hypoglycemia (7). Hypoglycemia may also be precipitated by excess alcohol consumption, liver failure, vigorous physical activity, and poor nutritional intake (2,8,9).

Hypoglycemia Definitions in Clinical Studies

There is no uniform definition or approach to assessment of hypoglycemia in research studies of type 2 diabetes. In most trials of glucose-lowering treatments, hypoglycemia is self-reported as either mild (symptomatic or asymptomatic with a blood glucose reading of <70 mg/dL) or severe (requiring assistance from another person) (10). Self-reported severe hypoglycemia is quite sensitive and generally also highly specific within a relatively short period of recall, up to one year, but mild hypoglycemia is less reliable (11).

Recently, a Joint Position Statement from the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD) provided guidance on reporting of hypoglycemia in clinical trials (3). These are: Level 1, glucose value of ≤3.9 mmol/L (70 mg/dL) as an alert value; Level 2, glucose value of <3.0mmol/L (54 mg/dL), indicating clinically significant hypoglycemia; Level 3, severe hypoglycemia, requiring third-party assistance due to cognitive difficulties. These cutpoints were chosen because a single glucose reading of <70 mg/dL may be due to random error in a finger-stick or continuous glucose monitoring system, or it could resolve on its own without symptoms, the clinical significance of which is unknown. In contrast, episodes of hypoglycemia with blood glucose <54 mg/dL were associated with increased mortality in several randomized clinical trials, thus indicating a clinically significant event. Finally, the category of severe hypoglycemia did not include blood glucose readings because they are not always available, but requiring assistance from another person is clearly an important adverse event (3).

In observational studies, hypoglycemia is sometimes assessed by self-report, but is more commonly assessed from ICD-9 codes on medical claims. A paper published in 2008 by Ginde and colleagues validated an algorithm based on ICD-9 codes at three academic emergency departments in the United States (12). The investigators reviewed charts for all observations identified by the algorithm; their gold standard definition of severe hypoglycemia was a documented blood glucose level of <3.9 mmol/L (70 mg/dL) either in the emergency department or prior to arrival, or a physician diagnosis of hypoglycemia. Their study reported a positive predictive value of 89% for the ICD-9 codes in any position and 93% for ICD-9 codes in the primary position. This definition is likely highly specific and fairly sensitive for hypoglycemia that does require emergency medical treatment, although an Italian study has noted that ICD-9 codes for hypoglycemia may be under-recorded (13). This definition misses hypoglycemia that is severe enough to warrant third-party intervention but does not result in treatment by medical professionals, and it is unclear what fraction of cases this represents.

Incidence Rate of Severe Hypoglycemia

Documented incidence rates of severe hypoglycemia vary depending on the definition of hypoglycemia used. Among individuals who present to the emergency department with hypoglycemia, only about one-quarter are admitted to the hospital (14). Thus, rates of hypoglycemia that include emergency

department records are substantially higher than those derived only from hospitalization records.

In most community-based studies, the incidence rate for middle- to older-aged adults with type 2 diabetes ranges from 1 to 16 events per 100 person-years (5,6,15,16,17). Studies have documented that the incidence rate is higher among insulin users, individuals with long duration of diabetes, and older adults (5,6,15,17,18).

In landmark randomized controlled trials in which participants were randomized to an HbA1c goal, incidence rates of severe hypoglycemia were two to three times higher in the intensive glucose treatment arms compared to the control arms (19). Despite similar methods of reporting, rates still varied from 0.4 per 100 diabetic person-years in the ADVANCE trial to 3.8 per 100 diabetic person-years in the VADT trial (19). Thus, estimates of the rate of severe hypoglycemia are known to vary dramatically by data source, method of ascertainment, and patient characteristics. One review found that on average, rates of severe hypoglycemia were higher in observational settings compared to randomized controlled trials, perhaps due in part to the practice of excluding individuals with previous hypoglycemia from trials (20, 21).

Trends in Severe Hypoglycemia in the U.S.

Based on data from the National Hospital Ambulatory Medical Care Survey, the rate of severe hypoglycemia treated in the emergency room was roughly constant between 1993 to 2005, ranging between 26 to 43 per 1,000

diabetic person-years (12). Based on data from the Nationwide Emergency Department Sample, the rate of severe hypoglycemia declined from 1.8 per 100 diabetic person-years (95% CI, 1.7-1.9) in 2006 to 1.4 per 100 diabetic person-years (95% CI, 1.3-1.5) in 2011 (14).

For hospitalized hypoglycemia, among adults aged 65 and over with Medicare, the rate has declined since the early 2000's, from a high of 7.81 per 1,000 diabetic person-years in 2001 to 6.12 per 1,000 diabetic person-years in 2010 (22). These data also show that hospitalization for severe hypoglycemia is now more common than hospitalization for acute hyperglycemia among Medicare beneficiaries, raising concern about overtreatment among this older population (22). Additionally, among Medicare beneficiaries on diabetes medications, the rate of hospitalized hypoglycemia has remained stable from 2006 to 2013, suggesting that the increased use of newer glucose-lowering agents (that have lower risk of hypoglycemia) has not translated to lower rates of hypoglycemia at the population level (23,24).

Racial Differences in Risk of Severe Hypoglycemia

Numerous studies have documented a higher incidence rate of severe hypoglycemia among black compared to white adults with type 2 diabetes (22,25-29). After accounting for age and sex, the incidence rate is approximately two times higher in blacks compared to whites. While several factors associated with increased risk of severe hypoglycemia are also more common in blacks compared to whites, including poor glycemic control (27,30) and poor kidney

function (27,31,32), even after accounting for these factors, hypoglycemia was more frequent in blacks compared to whites (27, 33-36). Socioeconomic status also likely plays a role; studies have shown that hypoglycemia is more common in those with low income or education and in food-insecure adults (5,37-39). However, it is difficult to fully account for socioeconomic status when examining racial differences; disparities in wealth and economic opportunities remain across races even when adjusting for income or education (40). Thus, the underlying reasons for higher risk of hypoglycemia in blacks than whites remain unclear.

Risk Factors for Severe Hypoglycemia

Overall, risk factors for hypoglycemia are not firmly established in the literature (1,16). There are few factors, other than age, dementia, chronic kidney disease, and insulin use, that have been consistently associated with hypoglycemia across studies (27,32,41-45). In general, there is lack of agreement regarding which factors should be routinely considered when identifying persons at high risk for hypoglycemia.

The relationships between HbA1c targets, observed HbA1c, and hypoglycemia are complex. In randomized controlled trials, incidence rates are higher in the treatment arm with the lower HbA1c goals (19). However, within the intensively treated arm in the ACCORD trial, there was a linear association between achieved HbA1c and hypoglycemia, with higher rates of hypoglycemia at higher HbA1c, suggesting that individuals who have trouble attaining a low HbA1c goal are those at highest risk of hypoglycemia (27). In contrast, in the

control arm, the association between achieved HbA1c and hypoglycemia was much weaker, and there was a weak U-shaped association between HbA1c and hypoglycemia. In another observational study, this U shape was also observed, suggesting that individuals who have low HbA1c (<6%), likely for reasons other than a very low glycemic goal, may also be at risk for severe hypoglycemia (30). Further studies are needed to clarify these associations, particularly in observational data.

Glycemic variability has also been associated with hypoglycemia (46-48). However, it remains unclear which metrics are best to use to identify those with greater glycemic variability and thus risk of severe hypoglycemia (48).

“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; however, there is relatively little epidemiologic evidence for this statement (8). While several studies have demonstrated that dementia increases the risk of severe hypoglycemia (42-44), only three studies have examined the association of lesser cognitive impairments with hypoglycemia (45, 49,50). Two prior studies on this topic were observational analyses of randomized trials of intensive glucose control. Data from the ADVANCE trial 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 (49). 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 (50). 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 (45). 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 (51).

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 (8). This association is likely mediated by social support, as having a caregiver to assist with diabetes self-management would likely ameliorate this potential mechanism. 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.

Factors that have been inconsistently associated with hypoglycemia in the literature include female sex, low BMI, and presence of cardiovascular disease (27,41,43,52). Because many have hypothesized that hypoglycemia may affect

those with general vulnerability, it is worth investigating if any factors that are generally predictive of mortality may also be associated with severe hypoglycemia (19,53). These factors include self-rated health, inflammation, and serum albumin (54-56).

Potential Mechanisms Linking Hypoglycemia and Cardiovascular Disease

There are several possible biological pathways that could increase the risk of cardiovascular disease following a hypoglycemic event. During hypoglycemia, the release of epinephrine increases the heart rate, peripheral systolic blood pressure, and myocardial contractility (57). Additionally, the release of catecholamines during hypoglycemia may cause hypokalemia, resulting in ECG abnormalities and arrhythmias (58). In small clinical studies in which participants with type 2 diabetes wore both continuous glucose monitors and Holter monitors; hypoglycemia (blood glucose <70 mg/dL) was associated with ventricular arrhythmias and abnormal T wave morphology (59,60).

Hypoglycemia is also thought to trigger an inflammatory response; studies have demonstrated increased concentrations of C-reactive protein, interleukin-6, interleukin-8, and tumor necrosis factor-α during and up to 48 hours following an episode of hypoglycemia (16,61). In addition to increasing proinflammatory markers in the blood, hypoglycemia also changes the functional status of circulating immune cells (62). Hypoglycemia also results in platelet activation and higher concentrations of factor VIII and von Willebrand factor lead to increased coagulation (58,61). Additionally, changes in vessel wall stiffness may contribute

to endothelial dysfunction (61,63). Overall, increases in coagulation, endothelial dysfunction, and inflammation resulting from hypoglycemia are thought to contribute to an atherogenic state that may contribute to long-term risk of cardiovascular events.

Hypoglycemia and Cardiovascular Disease: Epidemiologic Studies

Evidence from epidemiologic studies suggests that severe hypoglycemia is associated with increased risk of cardiovascular disease and all-cause mortality in type 2 diabetes (41,64-68). A recent meta-analysis found that individuals with a history of hypoglycemia have nearly a two-fold increased risk of cardiovascular disease compared to those without hypoglycemia (69). Nonetheless, concerns remain that hypoglycemia itself does not increase cardiovascular risk, but rather that individuals who are vulnerable and in poor health experience higher risks of both hypoglycemia and subsequent cardiovascular disease (19,41). Additionally, it remains unclear whether hypoglycemia is associated with all subtypes of cardiovascular disease. Prior studies have focused on composite cardiovascular outcomes (41,66,67,69) or coronary heart disease (70).

Another possibility is that hypoglycemia may trigger cardiovascular events in vulnerable individuals, specifically those with existing cardiovascular disease or a high burden of cardiovascular risk factors, but not in those at low cardiovascular risk (19). This hypothesis is supported by one study that found no association between hypoglycemia and cardiovascular disease in individuals with low

vascular risk, but a strong association in those at high vascular risk (70). This hypothesis also seems to be borne out by largely null associations of hypoglycemia with cardiovascular disease in type 1 diabetes, who on average have lower cardiovascular risk than their type 2 counterparts (66,71). Residual confounding by diabetes severity is also a possible explanation for the observed associations. It remains unclear which particular cardiovascular risk factors may be altering the association of hypoglycemia with cardiovascular disease and death.

Hypoglycemia and Cognition

Cognitive functioning is reduced during episodes of hypoglycemia. Studies have demonstrated impairments in word fluency, mathematical skills, and processing speed during clamp studies with induced hypoglycemia (72). Cognitive abilities are restored within an hour after a return to euglycemia, but there is concern about lasting damage.

Additionally, case studies of patients who are hospitalized in hypoglycemic comas (blood glucose ~20mg/dL) have shown extensive brain lesions on diffusion-weighted MRIs, indicating damage from neuroglycopenia (73-75). However, among cases that do survive, the imaging abnormalities are localized and disappear upon resolution to normoglycemia. Thus, it is unclear whether there is permanent harm to neurons, and, if so, at what concentration and duration of low blood glucose the harm occurs.

Complicating epidemiologic studies, however, is the fact that the association between hypoglycemia and cognitive function is thought to be bi-directional (43,76). Several studies have shown that dementia is a risk factor for severe hypoglycemia (42,43,44). Additionally, among individuals without dementia, there is some evidence that poor cognitive function and recent declines in cognitive function are associated with subsequent severe hypoglycemia (49,50,77). It is hypothesized that even small decrements in cognitive function result in decreased abilities in diabetes self-care. For these reasons, the current ADA guidelines recommend annual screening for cognitive impairments to prevent episodes of hypoglycemia among individuals whose cognitive decline may contribute to difficulties in diabetes self-management (8).

Severe hypoglycemia has been associated with incident dementia (43,78-81). However, given the long period of cognitive decline that precedes dementia, typically a decade or more (51), it is unclear whether the association of hypoglycemia with subsequent dementia is independent of the underlying cognitive decline causing hypoglycemia and dementia. While some prospective studies have attempted to control for this by excluding individuals with cognitive impairment at the start of follow-up (43), whether hypoglycemia independently contributes to cognitive decline is unclear. A few studies have examined hypoglycemia and cognitive decline as measured by change on neuropsychological tests among older adults with type 2 diabetes, but results have been mixed (42,77). Among individuals with type 1 diabetes, for whom hypoglycemia is far more frequent, no association was seen between

hypoglycemia and cognitive decline in the landmark DCCT/EDIC trial (82). It has been suggested that the relatively young age of participants makes their brains more resilient and less prone to cognitive decline, or, alternatively, that the study may be underpowered to detect small decrements in cognitive performance in this younger population.

Studies with brain imaging can also shed light on this topic. There has only been one epidemiologic study employing brain MRIs to look at the effects of hypoglycemia. The ACCORD-MIND MRI study examined changes in total brain volume and abnormal white matter volume over 40 months, and found no greater decrease in those with compared to without hypoglycemia (defined as glucose <50mg/dL or assistance from another person) during that period (83). Given the importance of identifying modifiable risk factors for cognitive decline, it is important to determine if hypoglycemia is a direct cause of cognitive decline among older adults with diabetes.

Dissertation Aims

The goal of this dissertation was to answer the following overarching question: *What are the risk factors and health consequences of severe hypoglycemia among adults with diabetes in a community-based population?*

Specifically, this dissertation sought to address the following questions:

- What is the incidence rate of severe hypoglycemia in a community-based sample of adults with diabetes, and how does the incidence rate differ by age, sex, and race?
- What are the independent risk factors for severe hypoglycemia among adults with diabetes, and is there effect modification of these risk factors by race?
- Is severe hypoglycemia independently associated with subtypes of cardiovascular disease and mortality, after accounting for diabetes severity and other shared risk factors, in adults with diabetes? Is there any effect modification of these associations by age, sex, race, diabetes duration, or level of vascular risk at baseline?
- What is the association of severe hypoglycemia with cognitive outcomes among older adults with diabetes, and are these associations independent of other causes of cognitive decline, including education, APOE alleles, and diabetes severity?

The answers to these questions are of crucial importance for individuals with diabetes on glucose-lowering medications. Since hypoglycemia is a major barrier to achieving glycemic control in diabetes, the risks of hypoglycemia have to be balanced against the potential benefit of lowered blood glucose. Depending on a patient's age, duration of diabetes, and overall health, the risk-benefit tradeoff of glucose-lowering medications may vary. Accurate estimates of the absolute risk of severe hypoglycemia are important to quantify in community-based samples to provide context for decision-making by patients and their

doctors. Additionally, current clinical guidelines by ADA recommend considering an older adult's risk of hypoglycemia when determining an appropriate glycemic target and medication use. A better understanding of risk factors for severe hypoglycemia will aid health care decision-making and inform guidelines. It is also vital to understand the link between severe hypoglycemia and major health outcomes, including cognitive decline, cardiovascular disease, and death, so that we understand the complete risks of glucose-lowering treatment. If hypoglycemia is merely a marker, and not a cause, of these health outcomes, then avoiding hypoglycemia will not reduce the frequency of these other health outcomes. Thus, these questions have an important role in the larger debate regarding appropriate glycemic targets, especially for older adults.

Conceptual Framework

The conceptual framework guiding this dissertation is found in **Figure 1**. The risk factors for severe hypoglycemia and the possible effect modification by race are examined in Aim 1. These risk factors also influence the development of other health outcomes. Aims 2-4 examine the association of severe hypoglycemia with health outcomes (subclinical myocardial damage, cardiovascular diseases and mortality, and cognitive function and brain volumes), while accounting for the other factors that influence both these outcomes and severe hypoglycemia.

Organization of Dissertation

This dissertation includes four chapters formatted as publishable manuscripts. The first chapter describes the incidence rate of severe hypoglycemia by age and race in the Atherosclerosis Risk in Communities (ARIC) Study among adults with diabetes. It assesses both traditional and novel risk factors for severe hypoglycemia, and tests for effect modification of risk factors by race.

The second chapter is a cross-sectional analysis of the association of a history of severe hypoglycemia with high sensitivity cardiac troponin T among older adults with diabetes in the ARIC Study. Because of the strong association of hypoglycemia with cardiovascular disease, we hypothesized that hypoglycemia would also be associated with elevated cardiac troponin T, a biomarker of myocardial damage. This is the first study of hypoglycemia and subclinical myocardial damage, and was published in the *Journal of the American College of Cardiology* as a research letter in 2016 (84).

The third chapter examines the association of severe hypoglycemia with subtypes of cardiovascular disease, including coronary artery disease, stroke, heart failure, atrial fibrillation, and peripheral artery disease, and all-cause and cause-specific mortality in the ARIC Study. Previous studies have typically reported only the association of hypoglycemia with coronary artery disease or with all-cause mortality, and have noted the caveat that the observed associations could be explained by residual confounding. We examined many cardiovascular outcomes to determine the specificity of the association of

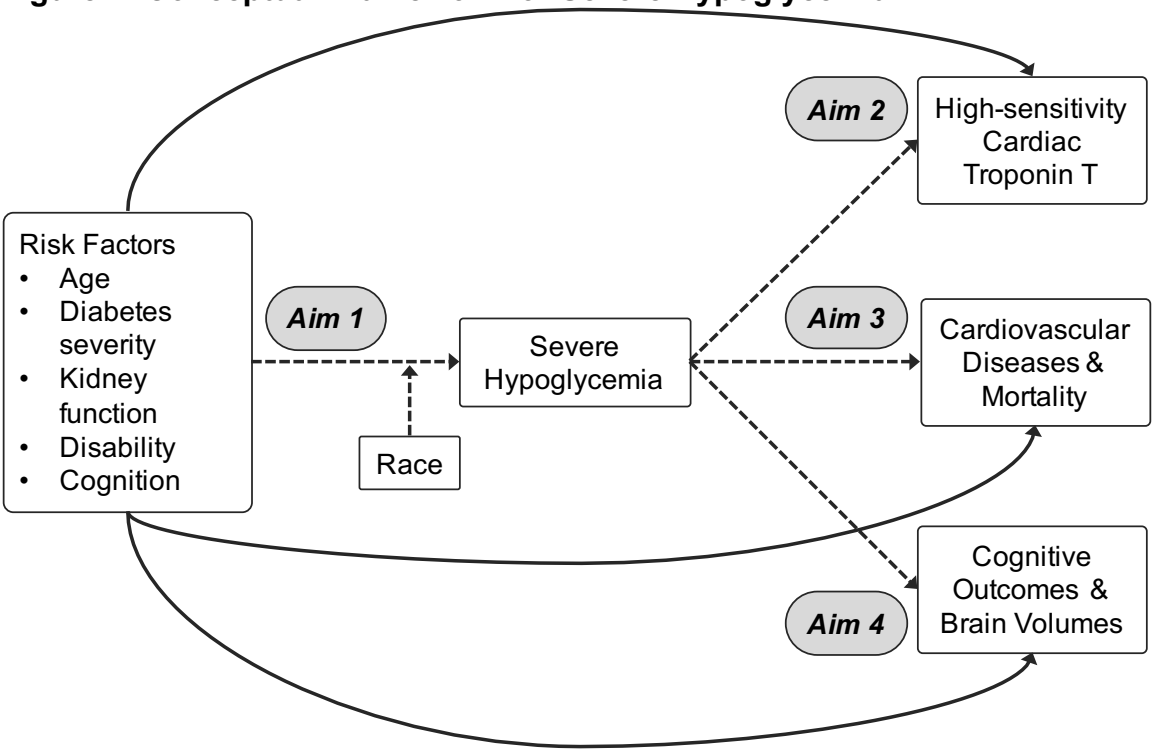
hypoglycemia to coronary heart disease, and since residual confounding would not be expected to influence each cardiovascular outcome differently, an association of severe hypoglycemia with coronary heart disease but not other outcomes would suggest the association is real rather than biased.

The fourth chapter evaluates the association of severe hypoglycemia with cognitive outcomes in the ARIC Study. It looks at the cross-sectional association of a history of severe hypoglycemia with overall cognitive status (normal, mild cognitive impairment, or dementia) and with brain volumes (total and by brain region). It also evaluates whether severe hypoglycemia during the preceding fifteen years is associated with cognitive decline over the same fifteen-year time span. Finally, it includes a prospective analysis of severe hypoglycemia with incident dementia. The dissertation concludes with a summary of findings and implications for future research.

Table 1. Immediate physiologic responses during hypoglycemia

Blood Glucose Concentration	Neurogenic Response (from autonomic nervous system)	Neuroglycopenic Response (due to reduced glucose in the brain)
80-85 mg/dL	Decreased insulin secretion increases glucose production by liver and kidneys	
65-70 mg/dL	Increased glucagon increases hepatic glucose production Epinephrine decreases glucose uptake by muscles and fat, increases hepatic and renal gluconeogenesis, and increases hepatic glycogenolysis	
50-55 mg/dL	Increased norepinephrine and acetylcholine cause symptoms of tremors, palpitations, sweating, and hunger	Impairments in cognitive function
~30 mg/dL		Reduced consciousness, seizures, coma

Figure 1: Conceptual Framework for Severe Hypoglycemia



Chapter 1: Risk Factors for Severe Hypoglycemia in Black and White Adults with Diabetes: the Atherosclerosis Risk in Communities (ARIC) Study

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Abstract

Objective: Severe hypoglycemia is a rare but important complication of type 2 diabetes. Few studies have examined the epidemiology of hypoglycemia in a community-based population.

Research Design and Methods: We included 1,206 Atherosclerosis Risk in Communities (ARIC) Study participants with diagnosed diabetes (baseline, 1996-1998). Severe hypoglycemic events were identified through 2013 by ICD-9 codes from claims for hospitalizations, emergency department visits, and ambulance use. We used Cox regression to evaluate risk factors for severe hypoglycemia.

Results: The mean age was 64 years, 32% black, 54% female. During a median follow-up of 15.2 years, there were 185 severe hypoglycemic events. Important risk factors after multivariable adjustment were: age (per 5 years; HR=1.24 95%CI, 1.07-1.43), black race (HR 1.39, 1.02-1.88), diabetes medications (any insulin use vs. no medications HR 3.00, 1.71-5.28; oral medications only vs. no medications HR 2.20, 1.28-3.76), glycemic control (moderate vs. good; HR 1.78, 1.11-2.83; poor vs. good HR 2.62, 1.67-4.10), macroalbuminuria (HR 1.95, 1.23–3.07), and poor cognitive function (DSST z-score: HR 1.57, 1.33-1.84). In an analysis of non-traditional risk factors, low 1,5-anhydroglucitol, difficulty with

activities of daily living, Medicaid insurance, and anti-depressant use were positively associated with severe hypoglycemia after multivariate adjustment. **Conclusions**: Poor glycemic control, glycemic variability as captured by 1,5-anhydroglucitol, kidney damage, and measures of cognitive and functional impairments were strongly associated with increased risk of severe hypoglycemia. Future studies should determine whether these characteristics can discriminate clinically meaningful levels of hypoglycemia risk.

Introduction

Hypoglycemia is an important complication of type 2 diabetes that can have a major impact on quality of life and health outcomes (1-3). Severe hypoglycemia is more common in older age, approximately doubling with each decade of life after age 60 (4). Because of the increased risk of hypoglycemia associated with tight glycemic control, clinical guidelines typically recommend individualizing glycemic targets for older adults based on a personalized assessment of risk for hypoglycemia and expected benefit from tight glycemic control (5). The 2017 Standards of Medical Care highlight “renal insufficiency” and cognitive dysfunction as important risk factors for hypoglycemia, but other risk factors remain less well documented. For instance, there is conflicting evidence that female sex or cardiovascular disease increase the risk of hypoglycemia (2,6,7). Advancing our understanding of risk factors for hypoglycemia can lead to improvements in the clinical assessment of hypoglycemia risk and contribute to the personalized and safe diabetes care.

There are also substantial racial disparities in rates of hypoglycemia (8,9,10). Blacks have approximately two-fold higher rates of severe hypoglycemia, and this excess risk persists after multivariate adjustment, suggesting that other factors may contribute to hypoglycemia risk in blacks (6). To date, previous studies have not specifically examined whether hypoglycemia risk factors may be different in blacks compared to whites.

Most prior studies of risk factors for hypoglycemia have been conducted either as post-hoc analyses of randomized clinical trials or as retrospective

studies of routinely collected clinical or administrative data. In clinical trials, patients are selected based on strict criteria and thus are unlikely to be representative of typical older adults with diabetes (11). Studies of administrative data may be more representative but lack standardized clinical assessments and are often missing important clinical characteristics, such as duration of diabetes. Epidemiologic cohort studies can fill a crucial gap in the literature, as they are typically more representative and have detailed demographic and clinical characteristics collected in a standardized fashion.

Our study aims were 1) to characterize incidence rates of severe hypoglycemia in a community-based epidemiologic cohort of older black and white adults with type 2 diabetes, 2) to rigorously evaluate traditional and non-traditional risk factors for severe hypoglycemia in older adults with diabetes, and 3) to determine if risk factor associations for hypoglycemia differ in blacks compared to whites.

Methods

Study Population

The Atherosclerosis Risk in Communities (ARIC) Study is an ongoing prospective cohort study which recruited participants in 1987-1989 from four U.S. communities: Jackson, Mississippi, Forsyth, North Carolina, Washington County, Maryland, and suburbs of Minneapolis, Minnesota (12). During the first twelve years of the study, study visits with physical exams and detailed questionnaires occurred every three years. The fourth study visit occurred in 1996-1998 and is

the baseline for the present analysis. At visit 4, there were 1,511 individuals with self-reported physician-diagnosed diabetes or currently taking diabetes medications. For the present analysis, we excluded 4 participants who self-identified as a race other than black or white. For the main analysis of traditional risk factors, we excluded individuals who were missing any risk factors of interest (n=301), leaving a final sample size of 1,206. For the analysis of non-traditional risk factors, we additionally excluded individuals who were missing any of the additional variables of interest (n=62), leaving a sample size of 1,144.

Risk Factors for Severe Hypoglycemia

Based on the existing literature, we classified risk factors as either "traditional" or "non-traditional." "Traditional" risk factors were those where there was existing evidence of an association with hypoglycemia in the literature and strong biologic plausibility: age, sex, race, BMI, duration of diabetes, glucose-lowering medication use, glycemic control, kidney function, albuminuria, and cognition. BMI was calculated from measured height and weight at visit 4. Because exact date of diagnosis was not available, we calculated diabetes duration based on time since the participant first reported a diagnosis or medication use. Diabetes duration was categorized as ≥9 years (reported at the first ARIC visit in 1987-1989) or <9 years. To assess medication use, participants brought in all medications taken in the past two weeks to each study visit. Diabetes medication use was classified as either "no medication use," "oral medications only," and "any insulin use" at the baseline visit (1996-1998). Since

the vast majority of participants in the “oral medication only” category were taking sulfonylureas, it was not possible to examine the association of other types of oral medications with severe hypoglycemia due to small sample size. Because HbA1c was not measured at visit 4, we used fructosamine (categorized into tertiles) as a proxy for glycemic control. Reduced kidney function was defined as an estimated glomerular filtration rate (eGFR) <60 mL/min/1.73 m^2, using the CKD-EPI equation for serum creatinine (13). Albuminuria was categorized by albumin-to-creatinine ratio (ACR): <30mg/g, 30-<300mg/g, and ≥300 mg/g. Cognitive function was assessed using the Digit Symbol Substitution Test (DSST), a neuropsychological test of executive function that has previously been associated with hypoglycemia (14). Because of large differences in the mean values between blacks and whites, race-specific z-scores were used in all analyses.

“Non-traditional” risk factors were items that were plausible but untested, or factors that had more limited biological plausibility but had been shown in one or two studies to be associated with severe hypoglycemia. Non-traditional risk factors included functional disabilities, self-reported health, history of cardiovascular disease, and a number of different biomarkers. Disability was based on assessment of any difficulty with activities of daily living (ADLs: eating, dressing, getting out of bed, or walking between rooms), any difficulty with instrumental activities of daily living (IADLs: managing money, preparing meals, or vacuuming/other light housework). We included two measures of general health asked via telephone within 12 months prior to Visit 4: self-rated health

(poor or fair vs. good or excellent), and ≥10 pounds unintentional weight loss. We created a count of comorbidities, based on adjudicated coronary heart disease or stroke, heart failure hospitalization, and self-report of the following: lung disease, liver cirrhosis, Parkinson's, cancer within past 5 years, recent spine or hip fracture, arthritis, or a blood clot in lung or legs. The count of comorbidities was categorized into zero, one, two, and three or more. Since previous studies have reported that a history of cardiovascular disease was associated with severe hypoglycemia, we also looked individually at prevalent coronary heart disease and stroke (2,7). Additional "non-traditional" risk factors included family history of diabetes, education, Medicaid insurance, anti-depressants, and beta-blockers (15-17). We also considered family history of diabetes, as it may indicate genetic risk of reduced insulin secretion and more labile diabetes that may predispose individuals to hypoglycemia (18).

Finally, we examined biomarkers that are plausible contributors to hypoglycemia risk, but have not been rigorously examined in prior studies. This included the liver enzymes alanine transaminase (ALT), aspartate transaminase (AST), and gamma-glutamyl transferase (GGT), since hepatic glucogenolysis and gluconeogenesis are crucial auto-regulatory responses when blood glucose levels are low (19). We also examined N-terminal pro b-type natriuretic peptide (NT-proBNP) and high-sensitivity cardiac troponin T (hs-cTnT) as markers of poor prognosis, and since hs-cTnT is more likely to be elevated in those with a history of severe hypoglycemia (20). Finally, since glycemic variability has been associated with hypoglycemia (21,22), we hypothesized that low 1,5-

anhydroglucitol (1,5-AG), a biomarker of glucose excursions, would be associated with increased risk of hypoglycemia independent of average glycemia.

Severe Hypoglycemia

We assessed severe hypoglycemia using a validated algorithm with ICD-9 codes in the primary position from hospitalizations, emergency department visits, and ambulance calls through December 31, 2013 (23). Records of hospitalizations are obtained for all ARIC participants through surveillance of local community hospital records and through medical records request for hospitalizations that occurred outside of the ARIC hospital surveillance system (12). For participants enrolled in Medicare, linkage to Centers for Medicare and Medicaid Services (CMS) provided claims for hospitalizations, emergency department visits, and ambulance use from 1991 through 2013.

Statistical Analysis

We used Poisson regression with robust standard errors to calculate incidence rates and incidence rate ratios by race, age, and sex. We used Cox proportional hazards regression models to evaluate the associations of traditional and non-traditional risk factors with severe hypoglycemia. For the Cox proportional hazard models, Model 1 was adjusted for age, sex, and race. Model 2 included all variables in Model 1 plus all traditional risk factors (obesity, duration of diabetes, diabetes medication use, glycemic control, low eGFR,

albuminuria, cognitive function). Non-traditional risk factors were evaluated individually in Models 1 and 2. We evaluated the proportional hazards assumption by visually examining the log-log survival plots. We tested for effect modification by race using the likelihood ratio test.

We conducted a number of sensitivity analyses to examine the robustness of results. First, we repeated our analyses in the subgroup of participants aged 65 and over with CMS Part B fee-for-service coverage. In this analysis, we censored participants if they died or changed to a different type of insurance. We also examined associations after excluding participants with possible type 1 diabetes defined by exclusive insulin use at all four ARIC study visits.

Results

At baseline (Visit 4, 1996-1998), the mean age was 64 years, 54% were female, and 55% were obese (BMI $\geq$30 kg/m^2) (**Table 1**). Overall, 42% had diabetes for at least nine years, 46% were taking oral medication(s) only, and 28% used insulin. Kidney function was relatively preserved: only 11% had eGFR <60 mL/min/1.73 m^2; 7.5% had an ACR $\geq$300 mg/g. There were substantial racial differences in baseline characteristics. Reflective of the overall ARIC study population, blacks were more likely to be female and to be obese. Blacks were also more likely to be on insulin, and to have poorer glycemic control and albuminuria.

There were 185 severe hypoglycemia events during a median of 15.2 years of follow-up in the 1,206 participants. The sex-adjusted incidence rates

ranged from 6.2 per 1000 person-years for whites age 60-69 years to 24.5 per 1000 person-years for blacks age 80-89 years (**Figure 1**). The incidence rate of severe hypoglycemia was almost two times greater for blacks compared to whites (age- and sex-adjusted incidence rate ratio (IRR) for black race: 1.88, 95%CI: 1.39-2.53). There was no difference in incidence rates by sex (age- and race-adjusted IRR for female sex: 1.00, p=0.99).

All traditional risk factors, with the exception of sex, were significantly associated with severe hypoglycemia after adjustment for age, sex, and race (Model 1; **Table 2**). Patterns of association were similar but attenuated after additional adjustment for all traditional risk factors (Model 2; Table 2). Risk factors that remained significant in Model 2 were age, black race, fructosamine, medication use, ACR ≥300 mg/g, and race-specific standard deviation lower DSST score. We did not find robust evidence for any interactions by race (**Supplemental Table S1**).

In our analysis of non-traditional risk factors, we found that measures of disability were associated with severe hypoglycemia but other general health metrics were not. Difficulty with ADLs was strongly associated with hypoglycemia (HR 1.95, 95%CI: 1.41-2.69), while difficulty with IADLs was marginally not statistically significant (HR 1.37, 95%CI: 0.99–1.90; Model 2, **Figure 2, numeric results in Supplemental Table S2**). There appeared to be a dose-relationship for the number of ADLs or IADLs and increasing risk of hypoglycemia. Several other metrics of general health, including unintentional weight loss, fair or poor self-rated health, prevalent coronary heart disease, and prevalent stroke, were

not associated with hypoglycemia. Number of comorbidities was associated with hypoglycemia only when the count reached 3 or more comorbidities (HR for 3+ vs. 0 comorbidities, 2.17, 95%CI: 1.44–3.28; Model 2, Figure 2).

Family history of diabetes was weakly but not statistically significantly associated with hypoglycemia (Model 2, Figure 2). Similarly, although not statistically significant, those with less education appeared to have higher risk of hypoglycemia. Having Medicaid insurance was strongly associated with hypoglycemia (HR 1.70, 95%CI: 1.14–2.53; Model 2).

After adjustment for traditional risk factors, 1,5-AG was linearly associated with severe hypoglycemia (HR per 5μg/mL, 1.22, 95%CI: 1.05-1.41; Model 2, **Figure 2**). For the cardiac biomarkers, both hs-cTnT and NT-proBNP were associated with severe hypoglycemia in the model adjusted only for age, sex, and race, but the hazard ratios were substantially attenuated and were no longer statistically significant after adjustment for traditional risk factors. There was no association for hsCRP. The findings for the liver enzymes ALT, AST, and GGT were also null (**Supplemental Figure S1**).

Anti-depressant use was strongly associated with hypoglycemia (HR 1.83, 95%CI: 1.11–3.04; Model 2). In a post-hoc analysis looking at type of anti-depressant, tricyclics were more strongly associated with risk of severe hypoglycemia than SSRIs (tricylics HR 2.08, 95%CI: 1.18 – 3.66; SSRI HR 1.28, 95%CI: 0.59-2.75; Model 2). Beta-blockers were not associated with hypoglycemia.

In the sensitivity analyses restricting to participants aged 65 and over with CMS Fee-For-Service Part B insurance coverage, estimates for the traditional and non-traditional risk factors were similar but had much wider confidence intervals, likely owing to the much smaller sample size (n=463, 76 hypoglycemic events) (**Supplemental Table S3 – S4, Figure S2**). After exclusion of 68 participants with possible type 1 diabetes, results for traditional risk factors were largely similar, although obesity became significantly associated with hypoglycemia (HR 1.62, 95% CI: 1.15-2.15, Model 2; **Supplemental Table S5**).

Conclusions

The incidence rates of severe hypoglycemia in our study (ranging in demographic groups from 6 to 25 per 1000 person-years) are similar to other studies of persons with type 2 diabetes and attest to the high burden of hypoglycemia in the community (4,10,14,23). Our results extend the evidence for risk factors previously identified in the literature. We found that older age, black race, poor glycemic control, glucose-lowering medication use, kidney damage, and poor cognition were all independently associated with risk of severe hypoglycemia. We also identified several novel risk factors: low 1,5-AG, anti-depressant use, difficulty with any ADL, and Medicaid insurance.

To our knowledge, our study is the first to examine 1,5-AG as a risk factor for hypoglycemia. We observed a strong association between 1,5-AG and severe hypoglycemia independent of average glucose. This finding is consistent with the biology of 1,5-AG as a biomarker of glucose excursions, and the variability

captured by low 1,5-AG may indicate greater insulin deficiency. Measuring 1,5-AG together with average glucose may identify a subgroup of diabetes patients with high glycemic instability and at high risk of future hypoglycemia.

Our finding that poor glycemic control was strongly associated with severe hypoglycemia extends the existing epidemiologic literature in type 2 diabetes (25). Although this may seem counter to the findings of clinical trials that have found higher rates of hypoglycemia associated with intensive glucose-lowering interventions, it is in concordance with an analysis of the ACCORD trial, which found that hypoglycemic events primarily occurred in those with high A1c values during the trial who were unable to attain the glycemic target despite intensive treatment (2,6,26). Combined with the findings for 1,5-AG, our results suggest that concern about hypoglycemia should be greatest in those with high A1c values and glycemic variability, rather than in those with well-controlled A1c.

Our study is also the first to provide rigorous evidence on the association of disability with severe hypoglycemia, in the form of difficulty with either ADLs or IADLs. Difficulty with these tasks, such as eating, dressing, and preparing meals, are easily assessed with a few questions. Combined with the strong influence of cognitive score on hypoglycemia risk, these findings highlight that difficulty with diabetes self-care can arise due to either mental or physical incapacities.

Our finding that blacks are at higher risk of hypoglycemia is consistent with prior studies demonstrating major racial disparities in hypoglycemia risk (6,8,9,10,33). In sensitivity analyses, we found that the observed racial disparities were not entirely explained by available metrics of socioeconomic status. Indeed,

neither education nor income was strongly associated with severe hypoglycemia risk in our study population after adjustment for traditional risk factors. However, we identified Medicaid insurance status as an important and robust predictor of hypoglycemia, which may reflect both low socioeconomic status and disability. Unmeasured health care access, utilization, medication adherence, and other socioeconomic and geographic disparities may play a major role in the racial differences in hypoglycemia risk. Future studies are needed to better identify those modifiable factors that can help ameliorate racial disparities in hypoglycemia risk and improve health outcomes in blacks.

We observed an increased risk of severe hypoglycemia among individuals using anti-depressant medications. Prior studies of anti-depressants have found that the association with hypoglycemia varied either by the duration of use or by the type of medication (16,17). With respect to depression and depressive symptoms, several cross-sectional studies have shown that a history of severe hypoglycemia is associated with the severity of depressive symptoms, but the directionality of causation is unclear: depressive symptoms such as lack of appetite could lead to increased risk of hypoglycemia, or previous episodes of hypoglycemia could lead to fear of hypoglycemia and withdrawal from daily activities, leading to depressive symptoms (27,28). Prospective cohort studies looking at depression and subsequent hypoglycemia have been mixed, with several null and one positive association (15,26,29,30).

Contrary to other studies (6,15), we did not observe an association of beta-blockers with severe hypoglycemia. While beta-blockers are known to

suppress symptoms of hypoglycemia and also may interfere with hepatic glycogenolysis and gluconeogenesis, there is some evidence that non-selective beta-blockers are more strongly associated with hypoglycemia than cardio-selective beta-blockers (31,32). In our study, 82% of participants taking beta-blockers were using cardio-selective beta-blockers, and in a post-hoc analysis looking by type of beta-blocker, the hazard ratio for non-selective beta-blockers was 1.25 (95%CI 0.50-3.09) and for cardio-selective beta-blockers was 0.93 (95%CI 0.58-1.49).

Previous studies of BMI and hypoglycemia have been mixed. In our minimally adjusted analyses, obesity appeared to be associated with increased risk of hypoglycemia, but after adjustment, this association was no longer statistically significant. Because several prior studies have shown increased risk of hypoglycemia among normal weight rather than obese persons, we conducted a post-hoc analysis examining waist circumference and waist-to-hip ratio (2,6,33). Neither of these alternative measures were associated with hypoglycemia. Ultimately, we did not observe a clear link between adiposity and hypoglycemia.

Kidney disease is a well-known risk factor for hypoglycemia due to its role in gluconeogenesis and drug clearance. We found a robust association of albuminuria with hypoglycemia, similar to previous studies (6,34,35). While eGFR was associated with hypoglycemia prior to multivariable adjustment, the association remained positive but was attenuated and was no longer significant after adjustment. It is likely that our study had limited power to detect a moderate

association with reduced kidney function; indeed, there were few people with very poor kidney function (only 45 participants with eGFR <45). Other studies have found a strong dose-response relationship between lower eGFR and increased risk of severe hypoglycemia (33,35).

There are several limitations of our study that are important to consider in the interpretation of these results. First, we had fewer than 200 severe hypoglycemic events, which limited our power to detect small to moderate associations. However, this is a similar or greater number of severe hypoglycemic events compared to other studies (7,14,30,34,36). Second, we were not able to look in detail at medication class and risk of hypoglycemia, since at the baseline exam for our study (1996-1998) many newer classes of medication were not yet available. Third, we did not have A1c data at baseline, but we were able to account for glycemic control using fructosamine. Fourth, within the ARIC study, race and geographic location are conflated: blacks and whites were recruited at different study sites in ARIC, with overlap only at the Forsyth County study site. Thus, while we cannot be certain that the difference between blacks and whites is due to racial disparities and not due to geographic differences, other studies have found similarly higher rates among African-Americans compared to whites (6,8,9,10). Fifth, we only had single baseline measurements of the risk factors examined here and cannot evaluate how changes in risk factors, including diabetes medications, during follow-up may have affected hypoglycemia risk. Sixth, as with all epidemiologic studies, under ascertainment of hypoglycemia is a general concern and it is possible that we

may have missed some severe hypoglycemia events, especially those treated by ambulance or in the emergency department among participants who are not covered by CMS Fee-For-Service Part B. In analyses restricted to participants with CMS coverage at baseline, our results were generally similar.

Strengths of our study included the well-characterized epidemiological cohort with rigorous measurements of both traditional and non-traditional risk factors. The large percentage of black participants (32%) allowed us to examine black-white disparities and evaluate potential effect modification by race. Lastly, linkage to CMS claims allowed us to include hypoglycemic events that were treated by ambulance or in the emergency room, and not just events treated in the hospital. This may have resulted in better identification of risk factors for hypoglycemia itself rather than factors that would lead a person with hypoglycemia to be hospitalized.

Greater awareness of the risk of hypoglycemia is sorely needed. Numerous studies have documented use of sulfonylureas and insulin in patients with chronic kidney disease, dementia, and/or low A1c values among older adults (37,38). In a recent survey in the Veteran's Affairs, 45% of primary care providers did not see any potential harm in continuing to treat a 77-year-old man with an eGFR of 26 with sulfonylureas (39). In contrast, patients' choices about diabetes medication are strongly influenced by risk of hypoglycemia, followed by long-term A1c (40). As calls for shared decision-making in diabetes care grow louder, there is a greater need for accurate characterization of patients' risk of hypoglycemia (41).

In conclusion, our results add to the paucity of data on incidence rates and risk factors for severe hypoglycemia. Given the aging population and increasing burden of diabetes, the importance of hypoglycemia and the risks and benefits from glycemic control will continue be of great significance.

Table 1. Baseline Characteristics of Black and White ARIC Study Participants with Diagnosed Diabetes (Visit 4, 1996-1998)

	Overall (n=1206) Mean (SD) or n (%)	**Blacks (n=391)** Mean (SD) or n (%)	**Whites (n=815)** Mean (SD) or n (%)
Age	63.7 (5.66)	62.7 (5.74)	64.2 (5.56)
Female sex	651 (54.0)	275 (70.3)	376 (46.1)
BMI category			
Overweight	413 (34.4)	126 (32.2)	290 (35.6)
Obese	657 (54.8)	239 (61.1)	421 (51.7)
Diabetes duration ≥9 years	508 (42.1)	178 (45.5)	330 (40.5)
Diabetes Medication use			
No medication	323 (26.8)	82 (21.0)	241 (29.6)
Oral medication(s) only	550 (45.6)	151 (38.6)	399 (49.0)
Any insulin	333 (27.6)	158 (40.4)	175 (21.5)
Fructosamine			
Middle tertile (296-350 μmol/L)	397 (32.9)	127 (32.5)	270 (33.1)
Highest tertile (>350 μmol/L)	499 (33.1)	168 (43.0)	231 (28.3)
eGFR <60 mL/min/1.73 m^2	138 (11.4)	49 (12.5)	89 (10.9)
Albumin to Creatinine Ratio			
30 - <300 mg/g	176 (14.6)	65 (16.6)	111 (13.6)
≥300 mg/g	90 (7.5)	41 (10.5)	49 (6.0)
Digit Symbol Substitution Test	38.0 (13.8)	28.0 (12.9)	42.8 (11.5)

Figure 1. Incidence Rates of Severe Hypoglycemia by Age and Race, Adjusted for Sex

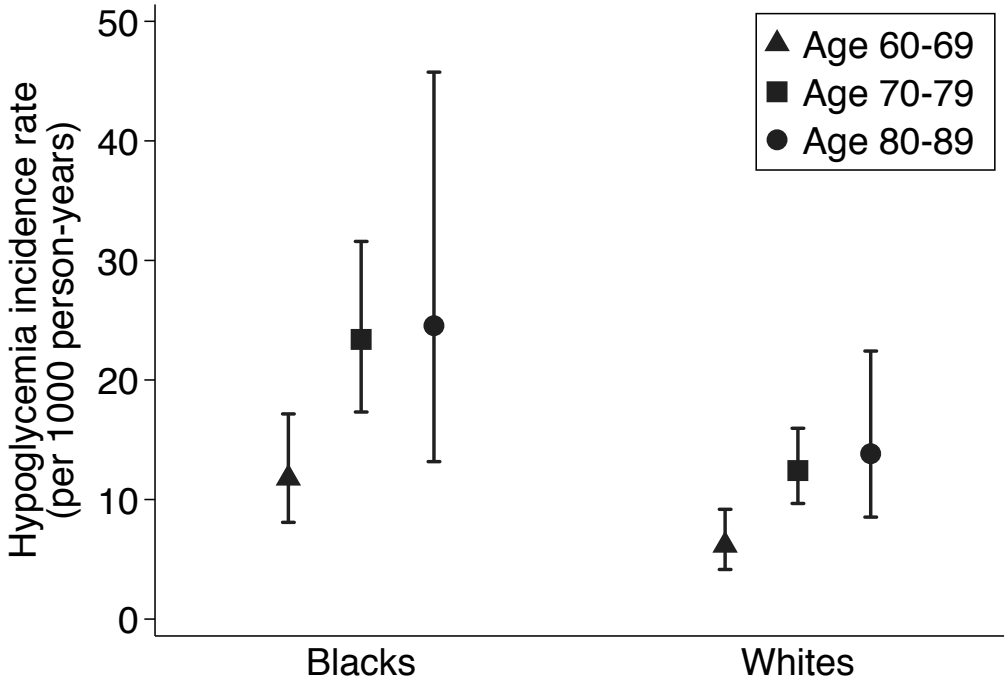
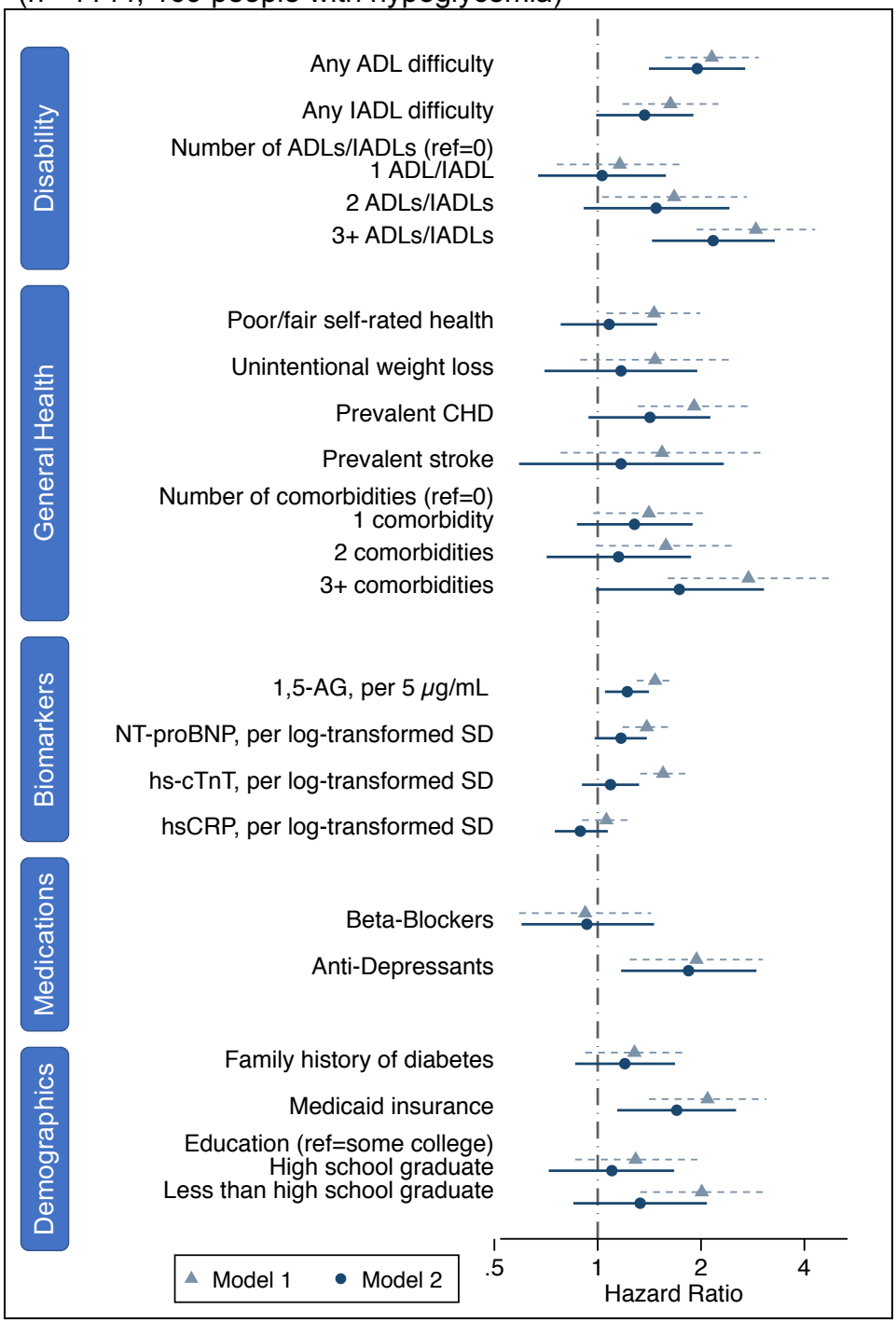


Table 2. Adjusted* Hazard Ratios and 95% Confidence Intervals for Traditional Risk Factors for Severe Hypoglycemia
(n=1206, 185 people with hypoglycemia)

	Model 1* HR (95% CI)	Model 2* HR (95% CI)
Age, per 5 years	1.42 (1.25 – 1.62)	1.24 (1.07 – 1.43)
Female sex	0.96 (0.71 – 1.30)	1.09 (0.80 – 1.48)
Black race	1.92 (1.42 – 2.60)	1.39 (1.02 – 1.88)
Obese**	1.46 (1.07 – 1.97)	1.31 (0.96 – 1.78)
Fructosamine (vs. lowest tertile)		
Middle tertile (296-350 μmol/L)	2.30 (1.46 – 3.62)	1.78 (1.11 – 2.83)
Highest tertile (>350 μmol/L)	4.04 (2.62 – 6.21)	2.62 (1.67 – 4.10)
Diabetes duration ≥9 years	1.75 (1.31 – 2.35)	1.19 (0.86 – 1.65)
Diabetes Medication (vs. none)		
Oral only	3.01 (1.78 – 5.07)	2.20 (1.28 – 3.76)
Any insulin use	5.51 (3.25 – 9.34)	3.00 (1.71 – 5.28)
eGFR <60 mL/min/1.73 m^2 (creatinine)	2.00 (1.35 – 2.97)	1.40 (0.92 – 2.13)
Albumin to Creatinine Ratio		
30 - <300 mg/g	1.51 (1.02 – 2.24)	1.16 (0.78 – 1.74)
≥300 mg/g	3.07 (2.00 – 4.72)	1.95 (1.23 – 3.07)
DSST***, per 1 lower race-specific standard deviation	1.67 (1.42 – 1.96)	1.57 (1.33 – 1.84)

*Model 1 included each covariate individually and was adjusted for age, sex, and race. Model 2 included all covariates listed in the table.
**Overweight and normal weight were collapsed into one reference group due to small numbers of normal weight participants.
***DSST: Digit Symbol Substitution Test

Figure 2. Hazard Ratios and 95% Confidence Intervals for Novel Risk Factors for Hypoglycemia
(n =1144, 169 people with hypoglycemia)



ADL: activity of daily living. IADL, Instrumental activity of daily living. CHD, coronary heart disease. 1,5-AG: 1,5-anhydroglucitol. NT-proBNP, N-terminal pro-B-type natriuretic peptide. hs-cTnT, high sensitivity cardiac troponin T. hsCRP, high sensitivity c-reactive protein.

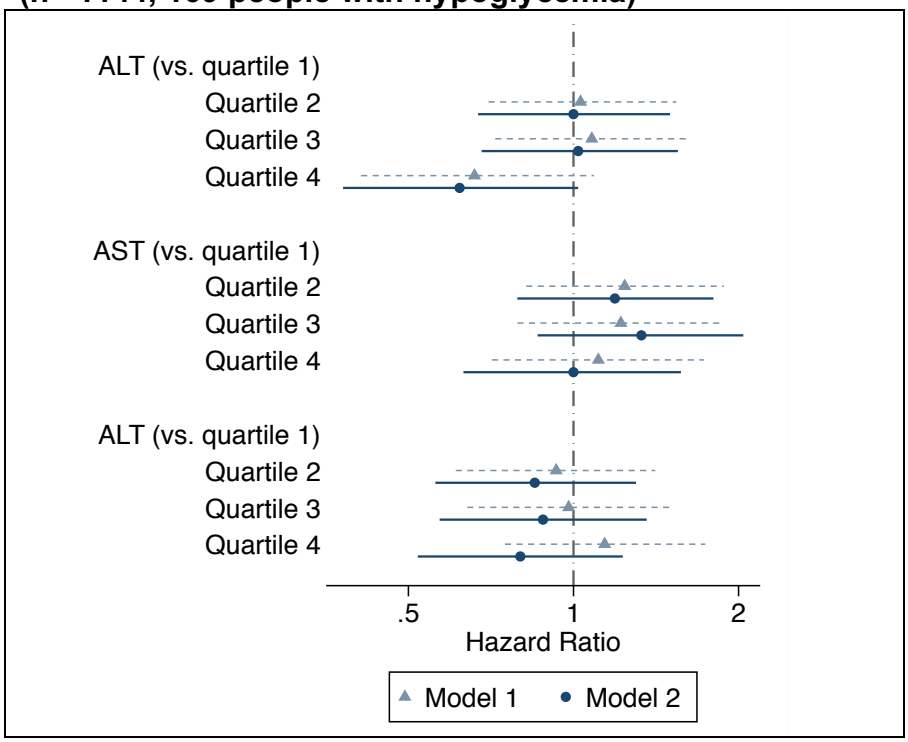
Supplement

Table S1: Hazard Ratios from Interactions by Race for Traditional Risk Factors of Severe Hypoglycemia n=1206

	Model 1*			Model 2*		
	Black HR (95% CI)	**White HR (95% CI)**	**p-value****	**Black HR (95% CI)**	**White HR (95% CI)**	**p-value****
Age, per 5 years	1.38 (1.15 – 1.67)	1.48 (1.23 – 1.77)	0.63	1.22 (1.00 – 1.47)	1.28 (1.05 – 1.55)	0.72
Sex	0.90 (0.56 – 1.47)	0.97 (0.66 – 1.43)	0.82	1.14 (0.70 – 1.86)	1.02 (0.69 – 1.52)	0.73
Obese***	1.74 (1.07 – 2.82)	1.31 (0.88 – 1.94)	0.36	1.61 (0.99 – 2.61)	1.15 (0.77 – 1.71)	0.29
Fructosamine						
Middle tertile	3.15 (1.28 – 7.73)	2.14 (1.26 – 3.66)	<0.0001	2.71 (1.10 – 6.68)	1.55 (0.90 – 2.67)	0.21
Highest tertile	6.05 (2.60 – 14.1)	3.16 (1.87 – 5.32)		4.38 (1.87 – 10.3)	1.89 (1.10 – 3.26)	
Diabetes duration ≥9 years	1.58 (1.02 – 2.46)	1.92 (1.29 – 2.84)	0.52	1.14 (0.72 – 1.81)	1.19 (0.78 – 1.82)	0.88
Diabetes Medications						
Oral only	2.09 (0.99 – 4.38)	4.04 (1.91 – 8.50)	<0.0001	1.62 (0.77 – 3.44)	2.88 (1.35 – 6.15)	0.43
Any Insulin use	3.07 (1.49 – 6.31)	9.11 (4.26 – 19.46)		2.10 (1.00 – 4.38)	4.24 (1.90 – 9.46)	
eGFR <60 mL/min/1.73 m^2	1.92 (1.07 – 3.44)	2.07 (1.23 – 3.48)	0.84	1.44 (0.79 – 2.65)	1.36 (0.79 – 2.34)	0.89
Albumin to Creatinine Ratio						
30 – < 300mg/g	1.13 (0.60 – 2.10)	1.94 (1.17 – 3.23)	<0.0001	0.88 (0.47 – 1.64)	1.48 (0.89 – 2.48)	0.39
≥300mg/g	2.28 (1.24 – 4.17)	4.34 (2.39 – 7.88)		1.68 (0.90 – 3.14)	2.26 (1.21 – 4.23)	
DSST, per 1 lower race-specific standard deviation	1.69 (1.32 – 2.18)	1.68 (1.38 – 2.04)	0.96	1.58 (1.22 – 2.04)	1.58 (1.29 – 1.93)	0.99

*Model 1 included age and sex. Model 2 included all variables in Model 1 plus all covariates listed in the table. **P-value for interaction from a model with only that variable's interaction terms in the model. ***Overweight and normal weight were collapsed into one reference group due to small numbers of normal weight participants.

Figure S1. Hazard Ratios and 95% Confidence Intervals for Liver Enzymes for Severe Hypoglycemia (n =1144, 169 people with hypoglycemia)



Quartiles of ALT were quartile 1: 1-10U/L, quartile 2: 11-14U/L, quartile 3: 15-19U/L, quartile 4: ≥20U/L. Quartiles of AST were quartile 1: 5-14U/L, quartile 2: 15-17U/L, quartile 3: 18-21U/L, quartile 4: ≥22U/L. Quartiles of GGT were quartile 1: 1-19U/L, quartile 2: 20-27U/L, quartile 3: 28-40U/L, quartile 4: ≥41U/L.
Fully adjusted models were adjusted for all traditional risk factors (age, sex, race, obesity, fructosamine tertiles, diabetes duration >9 years, diabetes medication use (no medication, oral only, any insulin), eGFR <60 mL/min/1.73 m^2, albuminuria (<30mg/g, 30-<300mg/g, ≥300 mg/g), DSST race-specific z-score).

Table S2. Hazard Ratios and 95% Confidence Intervals for Novel Risk Factors for Hypoglycemia

(n=1144, 169 people with hypoglycemia, numerical table of results from Figure 2)

	Model 1 HR (95% CI)	Model 2 HR (95% CI)
Disability		
Any ADL difficulty	1.95 (1.38-2.75)	1.74 (1.22-2.47)
Any IADL difficulty	1.79 (1.27-2.53)	1.45 (1.02-2.06)
Number of ADLs/IADLs (ref=0)		
1 ADL/IADL	1.17 (0.73-1.87)	1.02 (0.63-1.63)
2 ADLs/IADLs	1.56 (0.92-2.67)	1.43 (0.84-2.45)
3+ ADLs/IADLs	2.66 (1.72-4.14)	1.93 (1.22-3.05)
General Health		
Poor/fair self-rated health	1.47 (1.05-2.06)	1.06 (0.75-1.51)
Unintentional weight loss	1.66 (0.99-2.80)	1.27 (0.75-2.16)
Prevalent CHD	2.00 (1.34-3.00)	1.52 (0.98-2.35)
Prevalent stroke	1.58 (0.74-3.39)	1.08 (0.49-2.37)
Number of comorbidities (ref=0)		
1 comorbidity	1.51 (1.00-2.26)	1.40 (0.93-2.11)
2 comorbidities	1.50 (0.90-2.50)	1.13 (0.66-1.92)
3+ comorbidities	3.16 (1.78-5.60)	1.97 (1.08-3.60)
Biomarkers		
1,5-AG, per 5ug/mL	1.48 (1.29-1.68)	1.24 (1.06-1.45)
NT-proBNP, per log-transformed SD	1.41 (1.17-1.69)	1.16 (0.97-1.41)
hs-cTnT, per log-transformed SD	1.54 (1.31-1.81)	1.06 (0.87-1.30)
hsCRP, per log-transformed SD	1.03 (0.87-1.23)	0.88 (0.73-1.07)
Medications		
Beta-Blockers	0.95 (0.60-8.82)	0.95 (0.59-1.52)
Anti-Depressants	1.78 (1.08-2.93)	1.83 (1.11-3.04)
Demographics		
Family history of diabetes	1.27 (0.89-1.81)	1.19 (0.83-1.70)
Medicaid insurance	2.28 (1.50-3.46)	1.97 (1.29-3.02)
Education (ref = some college)		
High school graduate	1.46 (0.94-2.29)	1.25 (0.79-1.97)
Less than high school graduate	2.24 (1.43-3.52)	1.48 (0.91-2.42)

Table S3. Baseline Characteristics of Black and White ARIC Study Participants Aged 65 and Over with Diagnosed Diabetes and CMS Fee-For-Service Part B Coverage (Visit 4, 1996-1998)

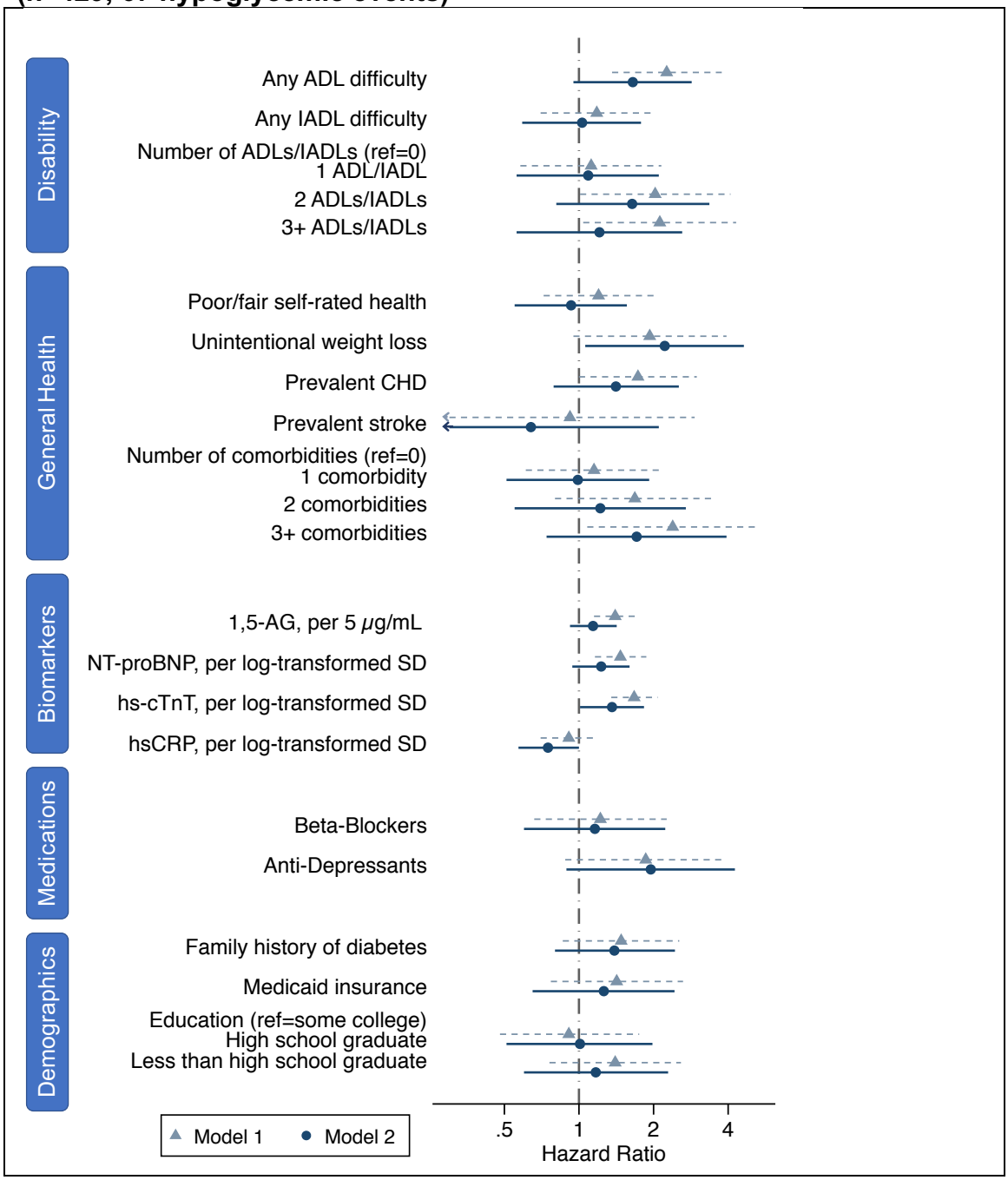
	Overall (n=463) Mean (SD) or n (%)	Blacks (n=139) Mean (SD) or n (%)	Whites (n=324) Mean (SD) or n (%)
Age	69.0 (2.53)	68.9 (2.65)	69.0 (2.48)
Female sex	242 (52.3)	101 (72.7)	141 (43.5)
BMI			
Overweight, %	176 (38.0)	48 (34.5)	128 (39.5)
Obese, %	236 (51.0)	78 (56.1)	158 (48.8)
Diabetes duration ≥9 years	225 (48.6)	80 (57.6)	145 (44.8)
Diabetes Medications			
No medication use	109 (23.5)	28 (20.1)	81 (25.0)
Oral medication use only	222 (48.0)	53 (38.1)	169 (52.2)
Any insulin use	132 (28.5)	58 (41.7)	74 (22.8)
Fructosamine			
Middle tertile (299-347 μmol/L)	154 (33.3)	46 (33.1)	108 (33.3)
Highest tertile (>347 μmol/L)	154 (33.3)	60 (43.2)	94 (29.0)
eGFR <60 mL/min/1.73 m^2	85 (18.4)	29 (20.9)	56 (17.3)
Albumin to Creatinine Ratio			
30 - <300mg/g	71 (15.3)	23 (16.7)	48 (14.8)
≥300mg/g	34 (7.3)	14 (10.1)	20 (6.2)
Digit Symbol Substitution Test	34.0 (12.9)	23.1 (10.2)	38.7 (11.0)

Table S4. Adjusted* Hazard Ratios and 95% Confidence Intervals for Traditional Risk Factors in ARIC Participants Aged 65 and Over with Diagnosed Diabetes and CMS Fee-For-Service Part B (n=463, 76 hypoglycemic events)

	Model 1* HR (95% CI)	Model 2* HR (95% CI)
Age, per 5 years	1.49 (0.95 – 2.33)	1.34 (0.83 – 2.15)
Female sex	0.96 (0.60 – 1.53)	1.07 (0.66 – 1.72)
Black race	2.00 (1.25 – 3.21)	1.48 (0.91 – 2.40)
Obese	1.44 (0.90 – 2.31)	1.22 (0.75 – 1.98)
Fructosamine (vs. lowest tertile)		
Middle tertile (299-347 μmol/L)	1.38 (0.71 – 2.66)	1.06 (0.54 – 2.09)
Highest tertile (>347 μmol/L)	2.63 (1.44 – 4.83)	1.68 (0.90 – 3.14)
Diabetes duration ≥9 years	1.86 (1.15 – 2.99)	1.15 (0.68 – 1.93)
Diabetes Medication (vs. none)		
Oral only	2.40 (0.99 – 5.77)	2.27 (0.92 – 5.61)
Any insulin use	6.18 (2.59 – 14.72)	4.72 (1.92 – 11.63)
eGFR <60 mL/min/1.73 m^2	2.32 (1.38 – 3.89)	1.92 (1.09 – 3.40)
Albumin to Creatinine Ratio		
30 – <300 mg/g	1.17 (0.59 – 2.31)	0.74 (0.36 – 1.52)
≥300 mg/g	4.01 (2.10 – 7.68)	2.97 (1.49 – 5.89)
DSST**, per 1 lower race-specific standard deviation	1.66 (1.30 – 2.13)	1.55 (1.21 – 1.99)

*Model 1 included age, sex, and race. Model 2 included all variables in Model 1 plus all covariates listed in the table.
**DSST: Digit Symbol Substitution Test

Figure S2. Hazard Ratios and 95% Confidence Intervals for Novel Risk Factors for Hypoglycemia in ARIC Participants Aged 65 and Over with Diagnosed Diabetes and CMS Fee-For-Service Part B (n=429, 67 hypoglycemic events)



Fully adjusted models were adjusted for all traditional risk factors (age, sex, race, obesity, fructosamine tertiles, diabetes duration >9 years, diabetes medication use (no medication, oral only, any insulin), eGFR <60 mL/min/1.73 m^2, albuminuria (<30mg/g, 30-<300mg/g, ≥300 mg/g), DSST race-specific z-score).

Figure S3: Incidence Rate of Severe Hypoglycemia among ARIC Participants Aged 65 and Over with Diagnosed Diabetes and CMS Fee-For-Service Part B.

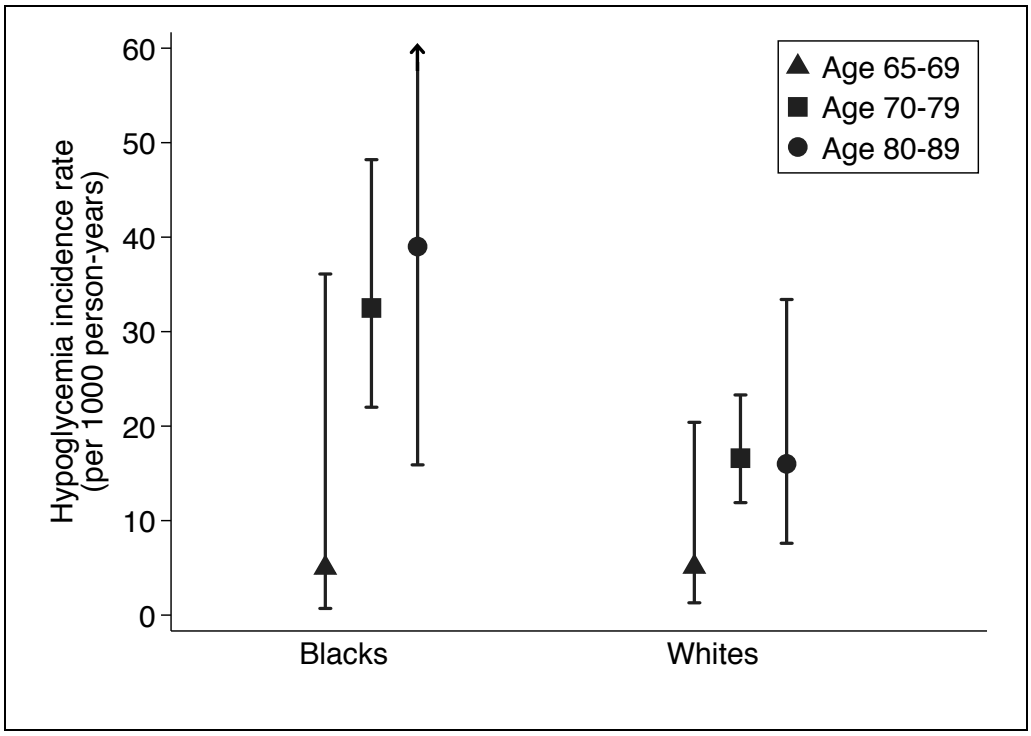


Table S5. Hazard Ratios and 95% Confidence Intervals for Traditional Risk Factors in ARIC Participants with Diagnosed Diabetes, excluding individuals with insulin only use at all four study visits (possible type 1) (n=1138, 158 hypoglycemic events)

	Model 1* HR (95% CI)	Model 2* HR (95% CI)
Age, per 5 years	1.39 (1.21 – 1.61)	1.26 (1.08 – 1.47)
Female sex	0.95 (0.69 – 1.32)	0.98 (0.70 – 1.37)
Black race	1.76 (1.27 – 2.45)	1.31 (0.94 – 1.84)
Obese	1.67 (1.20 – 2.33)	1.62 (1.15 – 2.15)
Fructosamine (vs. lowest tertile)		
Middle tertile (296-350 μmol/L)	1.91 (1.19 – 3.06)	1.54 (0.95 – 2.50)
Highest tertile (>350 μmol/L)	3.83 (2.47 – 5.94)	2.67 (1.69 – 4.21)
Diabetes duration ≥9 years	1.47 (1.07 – 2.01)	1.14 (0.82 – 1.61)
Diabetes Medications (vs. none)		
Oral only	3.02 (1.79 – 5.09)	2.14 (1.25 – 3.67)
Any insulin use	4.58 (2.65 – 7.93)	2.66 (1.49 – 4.73)
eGFR <60 mL/min/1.73 m^2	1.98 (1.28 – 3.08)	1.57 (0.99 – 2.51)
Albumin to Creatinine Ratio		
30 – <300mg/g	1.75 (1.16 – 2.62)	1.43 (0.95 – 2.15)
≥300mg/g	3.16 (1.91 – 5.23)	2.26 (1.33 – 3.85)
DSST**, per 1 lower race-specific standard deviation	1.64 (1.38 – 1.94)	1.55 (1.30 – 1.84)

*Model 1 included age, sex, and race. Model 2 included all variables in Model 1 plus all covariates listed in the table.
** DSST: Digit Symbol Substitution Test

Chapter 2: Severe Hypoglycemia and Elevated High-Sensitivity Cardiac Troponin T in Older Adults with Diabetes: The ARIC Study

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Persons with diabetes mellitus who have a history of severe hypoglycemia are at increased risk of cardiovascular disease (CVD)(1). However, it remains unclear whether hypoglycemia is causally linked to cardiovascular risk or is merely a proxy of vulnerability. Cardiac troponin T measured with a high-sensitivity assay (hs-cTnT) is a blood-based biomarker of subclinical myocardial damage and is strongly associated with future cardiovascular events(2).

Our objective was to quantify the association of severe hypoglycemia with elevated hs-cTnT in older adults with diabetes before and after adjustment for potential confounding factors.

We examined hs-cTnT in adults, 67 to 89 years of age, with diagnosed diabetes during visit 5 (2011 to 2013) of the ARIC (Atherosclerosis Risk In Communities) study. Past severe hypoglycemia events from 1991 to 2013 were identified from primary position International Classification of Diseases-Ninth Revision codes in Medicare fee-for-service claims for ambulance services, emergency department visits, and hospitalizations(3). Hs-cTnT was measured with a pre-commercial assay (Elecsys Troponin T, Roche Diagnostics, Indianapolis, Indiana). Given the advanced age of participants, we used age- and

sex-specific 99th percentile reference values for adults>65 years of age to define elevated hs-cTnT: >31 ng/l for men and>17 ng/l for women(4).

Because hs-cTnT is strongly associated with clinical CVD, we conducted analyses overall and stratified by prior coronary heart disease (CHD) or heart failure (HF) (adjudicated CHD event or HF hospitalization). We used Poisson regression with robust standard errors to generate prevalence ratios of elevated hs-cTnT, adjusted, first, for age, race-center, sex, and then additionally HbA1c and diabetes duration. We also tested for effect modification by prior CHD or HF. In a sensitivity analysis, we further adjusted for estimated glomerular filtration rate because troponin T is filtered by the kidney and poor kidney function increases risk of hypoglycemia.

After exclusions for missing data (n=50), 2,148 participants remained for analysis. Mean age was 76 years, 31% were black, and 72 (3%) had a history of severe hypoglycemia. Individuals with prior severe hypoglycemia were more likely to be black (48% vs.31%; p=0.002), have prior CHD or HF (51% vs. 25%; p<0.001), or have a longer duration of diabetes (median 20 years vs. 9 years; p<0.001). Median time from severe hypoglycemic episode to hs-cTnT measurement was 4.3 years (25^{th} to 75^{th} percentile:1.9 to 8.0 years).

Hs-cTnT values were substantially higher for individuals with a history of severe hypoglycemia compared to those without that history, regardless of prior CHD or HF status, after standardization to sex-specific reference values (Figure 1). The prevalence of elevated hs-cTnT in persons with both prior severe hypoglycemia and history of CHD or HF was extremely high, 70%. A history of

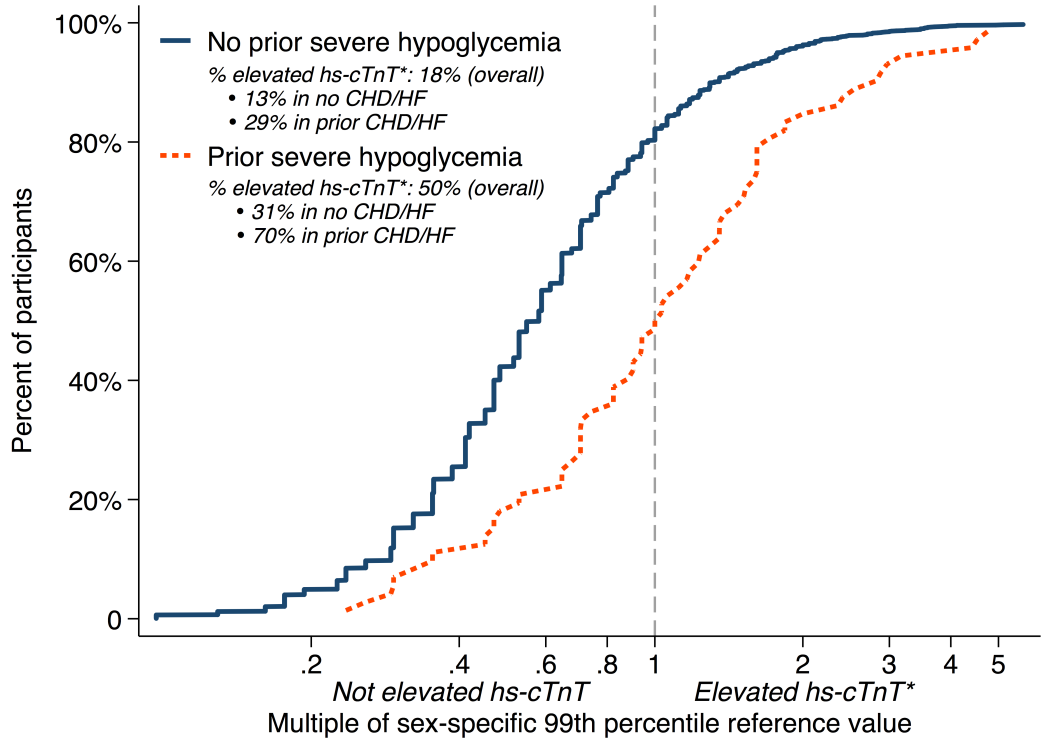
CHD or HF did not modify the adjusted association between prior severe hypoglycemia and elevated hs-cTnT (p=for interaction=0.58). The prevalence of elevated hs-cTnT was nearly twice as high in those with prior severe hypoglycemia after adjustment for age, sex, race-center, and prior CHD or HF (adjusted prevalence ratio [aPR]: 1.85; 95% confidence interval [CI]: 1.40 to 2.43). The effect estimate remained elevated but was attenuated and became nonsignificant after adjustment for HbA1c and diabetes duration (aPR: 1.34; 95% CI: 0.99 to 1.81) and additional adjustment for estimated glomerular filtration rate (aPR: 1.15; 95% CI: 0.89 to 1.49).

Limitations of this study include: 1) hypoglycemic events in this community-based population were rare and thus limited the precision of our estimates; 2) we were only able to capture severe hypoglycemic episodes, as many persons with hypoglycemia do not seek immediate medical attention(5); 3) selection bias is a concern because participants with severe hypoglycemia were less likely to attend visit 5; and 4) we were unable to assess medication use at the time of hypoglycemia.

To our knowledge, this is the first study to demonstrate an association between severe hypoglycemia and elevated hs-cTnT in older adults with diabetes. By decreasing energy supply to the myocardium, hypoglycemia may result in myocardial damage and, consequently, elevated hs-cTnT, particularly among persons prone to ischemia. As such, subclinical elevation in hs-cTnT could represent an intermediate step linking hypoglycemia to cardiovascular risk.

Whether causal or a marker of risk, severe hypoglycemia should raise concern about subclinical as well as clinical CVD risk.

Figure 1. Cumulative Distribution Curve for hs-cTnT, Standardized to Sex-Specific 99th percentile Reference Values, by Prior Severe Hypoglycemia



Legend for Figure 1: Analysis of 2,148 older adults with diagnosed diabetes in the ARIC (Atherosclerosis Risk In Communities) study (2011 to 2013). *Elevated high-sensitivity cardiac troponin T (hs-cTnT) was defined as hs-cTnT values greater than sex-specific 99th percentile reference values of 17 ng/l for women and 31 ng/l for men. The x-axis values are multiples of the sex-specific 99th percentile reference values (i.e., a value of 2 indicates an hs-cTnT of 34 ng/l in women and 62 ng/l in men). Overall, 18% of individuals without prior severe hypoglycemia and 50% of individuals with prior severe hypoglycemia had elevated hs-cTnT. CHD = coronary heart disease; HF = heart failure.

Chapter 3: The Association of Severe Hypoglycemia with Cardiovascular Disease and Mortality in Adults with Diabetes

Co-Authors: Bethany Warren, Clare J. Lee, John W. McEvoy, Kunihiro Matsushita, Elbert S. Huang, A. Richey Sharrett, Josef Coresh, Elizabeth Selvin

Abstract

Background: There is suggestive evidence linking hypoglycemia with cardiovascular disease, but there are few data collected in a community-based setting. Information is lacking on individual cardiovascular outcomes and cause-specific mortality.

Methods: We conducted a prospective cohort analysis of 1209 participants with diagnosed diabetes from the Atherosclerosis Risk in Communities (ARIC) Study (analytic baseline, 1996-1998). Severe hypoglycemic episodes were identified using first position ICD-9 codes from hospitalizations, emergency department visits, and ambulance calls through 2013. Cardiovascular events and deaths were captured through 2013. We used adjusted Cox regression models with hypoglycemia as a time-varying exposure.

Results: There were 195 participants with at least one severe hypoglycemic episode during a median fellow-up of 15.3 years. Following severe hypoglycemia, three-year cumulative incidence of coronary heart disease was 10.8% and of mortality was 28.3%. After adjustment, severe hypoglycemia was associated with coronary heart disease (hazard ratio (HR) 2.02, 95%CI 1.27-3.20), all-cause mortality (HR 1.73, 1.38-2.17), cardiovascular mortality (HR 1.64, 1.15-2.34), and cancer mortality (HR 2.49, 1.46-4.24). Hypoglycemia was not

associated with stroke, heart failure, atrial fibrillation, or non-cardiovascular and non-cancer death. Results were robust within subgroups defined by age, sex, race, and baseline cardiovascular risk.

Conclusions: Severe hypoglycemia was indicative of high absolute risk of cardiovascular events and mortality and was strongly and independently associated with coronary heart disease but not with macrovascular complications less related to atherosclerosis. Our results suggest that it is imperative to identify those at high risk for hypoglycemia to prevent major clinical outcomes.

Introduction

There is suggestive evidence that hypoglycemia is associated with substantially increased risk of cardiovascular disease; however, the mechanisms underlying this association remain unclear (1-6). Severe hypoglycemia, defined as hypoglycemia requiring assistance (7), could be merely a marker of vulnerability or could play a causal role in the development of cardiovascular disease. Severe hypoglycemia has been associated with a wide range of conditions, including respiratory, digestive, and skin diseases (6), and this lack of specificity to cardiovascular disease suggests that poor or failing health may be the underlying cause of both hypoglycemia and other diseases. It is also likely that hypoglycemia is a marker of the severity and duration of diabetes, as it is more common among those with poor glycemic control and who use insulin (8-10). However, several prior studies of severe hypoglycemia and cardiovascular disease have not accounted for these characteristics (1,11).

There are several pathways through which episodes of hypoglycemia may trigger arrhythmic events or promote atherosclerosis. During hypoglycemia, the sympathetic nervous system releases catecholamines, which induce tachycardia and stimulate cardiac contraction (12). Additionally, the activated sympathetic nervous system leads to hypokalemia in the myocardium, potentially causing arrhythmias (13,14). Hypoglycemia also triggers an acute inflammatory response, promoting coagulation through factor VIII and von Willebrand factor (12, 15). Endothelial dysfunction may also be increased due to an increase in C-reactive protein and platelet activation, promoting atherosclerosis (12).

Much of the epidemiologic evidence on this topic comes from secondary analyses of randomized clinical trials, which often recruit high-risk populations that are less representative of the general population (16). It has been suggested that the association of severe hypoglycemia with cardiovascular disease may be limited to those at high cardiovascular risk, and few studies have been conducted in relatively low risk diabetes populations (2,5). Another source of evidence is from retrospective analyses of medical claims databases, which often lack data on important characteristics such as duration of diabetes and kidney function. Thus, evidence is needed from community-based cohort studies that are both representative of the general population and have standardized, high-quality data on clinical characteristics.

The objective of our study was to rigorously quantify and compare associations of severe hypoglycemia with cardiovascular outcomes, including coronary heart disease, stroke, heart failure, atrial fibrillation, and peripheral

artery disease, as well as all-cause and cause-specific mortality in a community-based population with diabetes. We also sought to determine if the association of severe hypoglycemia with these outcomes varied by baseline characteristics, such as cardiovascular risk.

Methods

Study Population

The ARIC study recruited 15,792 participants from four US communities (17). Following the first study visit in 1987-1989, participants returned for subsequent study visits and had annual phone calls. The fourth study visit in 1996-1998 is the baseline visit for this analysis and was selected to maximize the number of participants with Medicare claims at baseline. Our study population was participants with diagnosed diabetes identified by self-report of a physician diagnosis or use of glucose-lowering medication use (n=1,511) among 11,656 participants at Visit 4. We excluded 4 participants who did not identify as either black or white, 6 black participants from the Minnesota or Maryland study sites, and those missing covariates (n=292). For analyses of mortality, our final analytic population was 1209 participants. For analyses of the different cardiovascular events, we excluded participants with prevalent disease at Visit 4, resulting in sample sizes ranging from 992 to 1190.

Each study site had institutional review board approval and all participants provided informed written consent.

Severe Hypoglycemia

Severe hypoglycemic events were identified from hospitalizations, emergency department visits, and ambulance calls with a validated algorithm, using ICD-9 codes in the primary position through December 31, 2013 (18). Hospitalization records were available from ARIC surveillance of local hospitals. Linked Medicare claims for hospitalizations, emergency department visits, and ambulance use were available for participants enrolled in Medicare fee-for-service part B.

Cardiovascular Outcomes and Mortality

Coronary heart disease was defined as non-fatal myocardial infarction and fatal coronary heart disease. Stroke was defined as definite or probable ischemic or hemorrhagic strokes. All coronary heart disease and stroke events since the inception of the study have been adjudicated by an expert committee (17).

For heart failure, adjudication began in 2005; all heart failure events prior to 2005 were based on hospitalization with a primary position ICD-9 code (428) (19). Incident atrial fibrillation was based on hospitalizations with ICD-9 codes for atrial fibrillation or atrial flutter (327.31 or 437.32) in the absence of cardiac surgery (procedure codes 35.x or 36.x) (20). Prevalent atrial fibrillation at Visit 4 was also identified from electrocardiograms conducted at Visits 1-4 (n=47). Peripheral artery disease events were identified from hospitalizations on the basis of ICD-9 diagnosis codes for peripheral artery disease (440.2, 440.3,

440.4) or ICD-9 procedure codes for leg revascularization (38.18, 39.25, 39.29, 39.50). Ascertainment for all events occurred through December 31, 2013.

Mortality was assessed via proxy, coroner reports, and the National Death Index through 2013. Cause-specific mortality was classified by the underlying cause of death listed on the death certificate: cardiovascular mortality (ICD-9 codes: 390-459, ICD-10 codes: I00-I99), cancer mortality (ICD-9 codes: 140-239, ICD-10 codes: C00-D49), and all other causes of death. Twenty-nine participants were missing cause of death and were censored at time of death.

Covariates

Since we did not have the exact date of diabetes diagnosis, we dichotomized diabetes duration as ≥9 years or <9 years, based on whether a participant had reported diabetes at the first ARIC study visit. Participants were asked to bring in all medications taken within the past 2 weeks to each study visit. We classified diabetes medication use as follows: no diabetes medication use, oral medication use only, or any insulin use. Because hemoglobin A1c was not available at Visit 4, we used fructosamine to characterize glycemic control.

Estimated glomerular filtration rate (eGFR) was calculated using the CKD-EPI equation from serum creatinine (21). Albuminuria was categorized based on the urinary albumin to creatinine ratio (ACR). The mean of two seated blood pressure measurements was used. Fasting total cholesterol and HDL cholesterol were measured, and LDL cholesterol was calculated using the Friedewald equation. Smoking status and household income were based on self-report.

Disability was based on self-report of any difficulty with activities of daily living (eating, dressing, getting out of bed, or walking between rooms).

For comparison to prior findings (2, 22), we classified participants as high or low cardiovascular risk based on the ACCORD trial inclusion criteria: ≥55 years of age, fructosamine ≥300μmol/L (instead of A1c >7.5%), and either a history of cardiovascular disease or at least two of the following risk factors: hypertension (systolic blood pressure >140mmHg or diastolic blood pressure >95mmHg, with or without treatment), BMI >32, LDL >130mg/dL with or without cholesterol-lowering medication, low HDL (<40mg/dL for men, <50mg/dL for women), current smoking.

Statistical Analysis

In all analyses, we considered severe hypoglycemia to be a time-varying exposure, conceptualized as either "no history of severe hypoglycemia," or "history of severe hypoglycemia."

For the main analysis, we examined the association of severe hypoglycemia with cardiovascular outcomes and mortality using Cox regression. We progressively adjusted the models for potential confounders. Model 1 included age, sex, and race-center (blacks from Jackson, blacks from Forsyth County, whites from Forsyth County, whites from Minneapolis, and whites from Washington County). Model 2 included all variables in Model 1 plus shared risk factors for hypoglycemia and cardiovascular events and mortality: diabetes medication use (none, orals only, any insulin), duration of diabetes (≥9 years, <9

years), tertiles of fructosamine (<296μmol/L, 296-351μmol/L, ≥352μmol/L), low eGFR (<60 mL/min/1.73 m^2), albuminuria (ACR <30, 30-300, ≥300mg/g), income (<$12,000, $12,000-$23,999, $24,000-$49,999, ≥$50,000), and disability. Model 3 additionally included cardiovascular risk factors: systolic blood pressure, hypertension medication use, LDL cholesterol, HDL cholesterol, cholesterol-lowering medication use, and smoking status (current, former, never). We verified that the proportional hazards assumption was met by inspecting negative log-log survival plots.

We examined the association of the number of hypoglycemia events (zero, one, or two or more) with cardiovascular disease and mortality. To examine the effect of time since hypoglycemia on risk of events, we classified each individual's person-time into one of three categories: no hypoglycemia, hypoglycemia within the past year, or hypoglycemia more than one year ago, using time-varying indicator variables. As others have observed, we expected to see the highest risk of cardiovascular events in the first year following severe hypoglycemia (2,6,11).

We hypothesized that severe hypoglycemia may represent failing health due to other illnesses, such as cancer. We looked to see if incidence rates of severe hypoglycemia were higher among participants with high fatality cancers compared to lower fatality cancers, as defined by five-year survival rates. High fatality cancers included cancers of the pancreas, liver, lung, stomach, brain, and of unknown primary site (23,24). Cancer diagnoses were identified from ARIC hospitalization surveillance and through linkage to state or county cancer

registries until December 31, 2012 (25,26). All incident cancer analyses were administratively censored at December 31, 2012 and additionally excluded participants who did not consent to research on non-cardiovascular topics (n=2).

We conducted two sensitivity analyses. First, we excluded participants with a history of severe hypoglycemia at Visit 4 (n=14) to reduce the possible influence of survival bias. Second, we replaced fructosamine with hemoglobin A1c measured at Visit 2 (6 years prior).

All analyses were conducted using Stata 13.1 (College Station, Texas).

Results

Among the 1,209 participants with diagnosed diabetes, 14 had a history of hypoglycemia at baseline and 186 experienced at least one event of severe hypoglycemia during a median follow-up time of 15.3 years (median time from baseline to severe hypoglycemic event: 7.7 years). Individuals with severe hypoglycemia were, at baseline, older, more likely to be black or using insulin, and have poor glycemic control and longer duration of diabetes (**Table 1**). They were also more likely to have poor kidney function, kidney damage, and to be disabled. The cardiovascular risk profile was slightly worse in those with severe hypoglycemia.

Of the 195 participants with severe hypoglycemia, 118 died; the median (25^{th} and 75^{th} percentiles) time between severe hypoglycemia and death was 3.8 (1.2 to 7.3) years. In three years following severe hypoglycemia, cumulative mortality was 28.3% and 10.8% experienced incident coronary heart disease.

The median time between the severe hypoglycemic episode and the different incident cardiovascular outcomes was approximately 3 years, with the exception of atrial fibrillation, where the median time was 5.6 years. The crude incidence rates of cardiovascular events and mortality were two to four times higher after severe hypoglycemia compared to without hypoglycemia, with the exception of stroke (**Table 2**).

In minimally adjusted models, severe hypoglycemia was associated with more than two times higher risk of each type of cardiovascular event except for stroke and atrial fibrillation (**Table 2**; Model 1). The association with coronary heart disease was most robust and remained statistically significant even in Model 3 (HR 2.02, 95%CI 1.27-3.20). For heart failure, the initially strong association in Model 1 (HR 2.35, 95%CI 1.72-3.20) was substantially attenuated and not statistically significant in Models 2 or 3 (Model 2, HR 1.37, 95% CI 0.98-1.91). For peripheral artery disease, adjustment for covariates also attenuated the association (Model 3: HR 1.55, 95%CI 0.86-2.80). For atrial fibrillation, the modest association in Model 1 was no longer observed after further adjustment (Model 3, HR 1.05, 95%CI 0.68-1.60). For stroke, there was no association with hypoglycemia in any model.

After adjustment, severe hypoglycemia was associated with more than two times greater risk of all-cause mortality and cardiovascular mortality in Model 1; the associations were substantially attenuated in Model 2, but changed little after additional adjustment (Model 3: all-cause mortality HR 1.73, 95%CI 1.38-2.17; cardiovascular mortality HR 1.64, 1.15-2.34). In contrast, hypoglycemia

was associated with approximately 2.5 times greater risk of cancer mortality regardless of adjustment. For other causes of death, hypoglycemia was associated with more than two times greater risk of death from other causes in Model 1, but was not significantly associated after additional adjustment (Model 3, HR 1.40, 0.95-2.03).

We examined the findings by subgroups of age, sex, race, diabetes duration at baseline, history of cardiovascular disease, and cardiovascular risk status. In Model 3, there was no significant effect modification (all p-values for interaction ≥0.2), and all hazard ratios were between 1.5 and 2.0 for all-cause mortality (**Figure 1**). For other outcomes, the results were similar, with a few, likely spurious, interactions for some outcomes (**Supplemental Tables S1 and S2**).

For most outcomes, the risk was highest in the first year following the hypoglycemic event (**Figure 2**). This difference was most pronounced for cancer mortality: within one year of the hypoglycemic event, the hazard ratio was 5.58 (95%CI: 2.53-12.28), and for more than one year since the hypoglycemic event, the hazard ratio was 1.89 (1.02-3.51).

Across outcomes, the hazard ratios for two or more severe hypoglycemic events were slightly stronger than for one severe hypoglycemic event, but there were only 59 participants with two or more events (**Supplemental Figure 1**).

In a sensitivity analysis excluding individuals with a history of severe hypoglycemia at Visit 4, the associations with hypoglycemia were slightly stronger for most outcomes (**Supplemental Table 3**). In a second sensitivity

analysis using HbA1c measured 6 years prior to baseline instead of fructosamine, results were similar (**Supplemental Table 4**).

Incident hypoglycemia in participants with cancer

There were only 21 episodes of severe hypoglycemia among participants with cancer diagnoses, and only four episodes following a diagnosis of a high fatality cancer. Although not statistically significant, the risk of severe hypoglycemia was nominally twice as high among those with more fatal cancers (HR 1.89, 95%CI 0.68-5.20) compared to those without cancer, whereas the risk of severe hypoglycemia was similar in those with less fatal cancers (HR 0.84, 0.56-1.27).

Discussion

Severe hypoglycemia is a major risk factor for cardiovascular events and deaths in persons with diabetes in the community. The strong associations of severe hypoglycemia with coronary heart disease and all-cause mortality persisted after adjustment for a wide range of potential confounders. Further, the risk of cardiovascular outcomes and mortality was highest in the first year following severe hypoglycemia. Overall, severe hypoglycemia was strongly indicative of poor prognosis, with nearly 30% cumulative mortality after 3 years. These results suggest that clinicians should pay particular attention to the potential for morbidity and mortality in the first year following a severe hypoglycemic event.

Our findings suggested that effects of severe hypoglycemia may be most pronounced for atherosclerotic disease, rather than cardiovascular conditions more broadly. The adjusted association of hypoglycemia with coronary heart disease was strong while the associations were essentially null for stroke and atrial fibrillation. It is possible that the long-term cardiovascular effects of hypoglycemia are more likely to result from the endothelial dysfunction and pro-inflammatory state induced by severe hypoglycemia rather than the temporary arrhythmic effects. Only two other studies have examined subtypes of cardiovascular disease, with inconsistent results (27,28).

We found no evidence of difference in the association between hypoglycemia and cardiovascular disease by level of baseline vascular risk, contrary to the thinking that hypoglycemia may be associated with cardiovascular events only in individuals with existing high cardiovascular risk (2,5). This suggests that an episode of severe hypoglycemia could have deleterious consequences for all adults with type 2 diabetes, not just the oldest or highest risk individuals.

We found some evidence of a dose-response association for a few cardiovascular outcomes. However, given the small number of people with two or more severe hypoglycemic events (n=59), these results are tentative. It is worth considering that the lack of many people with repeated severe hypoglycemic events may be indicative of the strong competing risk of all-cause mortality, rather than the absence of a dose-response per se.

Similar to other studies, severe hypoglycemia was strongly associated with all-cause mortality, and our analysis of cause-specific mortality extends this literature (4,6,29,30). There was no association of severe hypoglycemia with non-cardiovascular, non-cancer ("other") mortality after adjustment. For cancer mortality, adjustment for covariates had almost no impact, suggesting that the elevated risk of cancer death may be due to other factors. Our analysis suggested a higher incidence rate of hypoglycemia among those with more fatal cancers. Alternatively, individuals with reduced physiologic reserve may be more likely to experience severe hypoglycemia and to die from their cancer.

For cardiovascular mortality, even after adjustment for a history of cardiovascular disease, the strong association of hypoglycemia with cardiovascular mortality remained. Given the robust association of severe hypoglycemia with incident coronary heart disease, a reasonable conclusion from these results is that severe hypoglycemia has a causal contribution to cardiovascular mortality.

Overall, individuals who have severe hypoglycemia are clearly at high risk for both coronary heart disease and mortality, and this risk is highest in the first year after severe hypoglycemia. Severe hypoglycemia may be a sign of rapidly declining health, and it may be timely for providers comprehensively evaluate a patient's physical and mental status to determine if any adjustments to treatment may be necessary, to both prevent future hypoglycemia and reduce the risk of cardiovascular disease.

It is important to consider our study limitations. First, similar to other studies that have relied on claims data for identifying episodes of severe hypoglycemia, we were able to capture only the episodes that resulted in immediate, professional medical treatment. The sensitivity of this measure of severe hypoglycemia is likely low to moderate. However, with our restriction to ICD-9 codes for hypoglycemia in the primary position, our definition of severe hypoglycemia is likely highly specific, with a positive predictive value of 93% (18). Additionally, we were not able to account for factors that likely changed over time, such as diabetes medications and kidney function, and the number of events limits the precision of adjusted relative hazard estimates.

Our study also has important strengths. First, we were able to adjust for numerous rigorously measured covariates including aspects of diabetes severity and disability. Second, our study includes primarily incident cases of severe hypoglycemia, avoiding “prevalent case bias.” Given the high rate of death following severe hypoglycemia (28% cumulative mortality in 3 years), prevalent cases of hypoglycemia are likely non-representative, since the highest-risk individuals have already died. Thus, other studies that only captured a history of hypoglycemia at baseline likely underestimate the risk of cardiovascular events and mortality associated with severe hypoglycemia (2,30). Indeed, we saw stronger associations with coronary heart disease and mortality after excluding individuals with a history of hypoglycemia at baseline from our analysis. Third, the long duration of follow-up (approximately 15 years) resulted in a relatively large number of hypoglycemic events, cardiovascular events, and deaths.

In conclusion, whether severe hypoglycemia is a marker or a cause, our findings reinforce the concern about severe hypoglycemia and its sequelae, particularly the progression of atherosclerotic disease. In both middle-aged and older adults, severe hypoglycemia is followed by high absolute risk of mortality and cardiovascular events, suggesting the need to identify those at high risk for hypoglycemia and to increase monitoring of those with a recent episode of severe hypoglycemia. Further studies are needed to determine if interventions reducing severe hypoglycemia would reduce risk of coronary heart disease or death.

Table 1. Baseline Characteristics of ARIC Participants with Diagnosed Diabetes at Visit 4 (1996-1998) by Severe Hypoglycemia (n=1209)

	No Severe Hypoglycemia n=1014 mean ± SD or %	**Severe Hypoglycemia** n=195* mean ± SD or n (%)
Age	63.4 ± 5.7	64.7 ± 5.6
Female	53.7	57.9
Black	31.2	46.7
BMI	31.4 ± 5.9	32.4 ± 5.8
Diabetes medications		
None	30.2	8.2
Oral medication(s) only	45.4	41.5
Any insulin	24.5	50.3
Fructosamine tertiles		
Middle tertile (296-351μmol/L)	33.2	32.3
Highest tertile (≥352μmol/L)	29.4	51.8
Long duration of diabetes (≥9 years)	40.4	60.0
eGFR <60 mL/min/1.73 m^2	10.7	19.0
Albuminuria		
ACR** 30 - <300 mg/g	13.8	20.0
ACR ≥300 mg/g	6.6	14.9
Household income		
<$12,000	16.9	32.3
$12,000 – 23,999	27.0	26.7
$24,000 – 49,999	32.9	27.7
≥$50,000	23.3	13.3
Any difficulty with ADLs***	23.9	37.9
Systolic blood pressure	131.6 ± 19.5	135.6 ± 19.5
Hypertension medication	68.3	76.4
LDL cholesterol, mg/dL	116.6 ± 35.1	122.2 ± 38.5
HDL cholesterol, mg/dL	44.1 ± 13.7	46.4 ± 15.9
Cholesterol-lowering medication	24.1	27.2
Smoking status		
Current smoker	12.7	14.9
Former smoker	48.1	41.0
Prevalent CHD	17.4	21.0

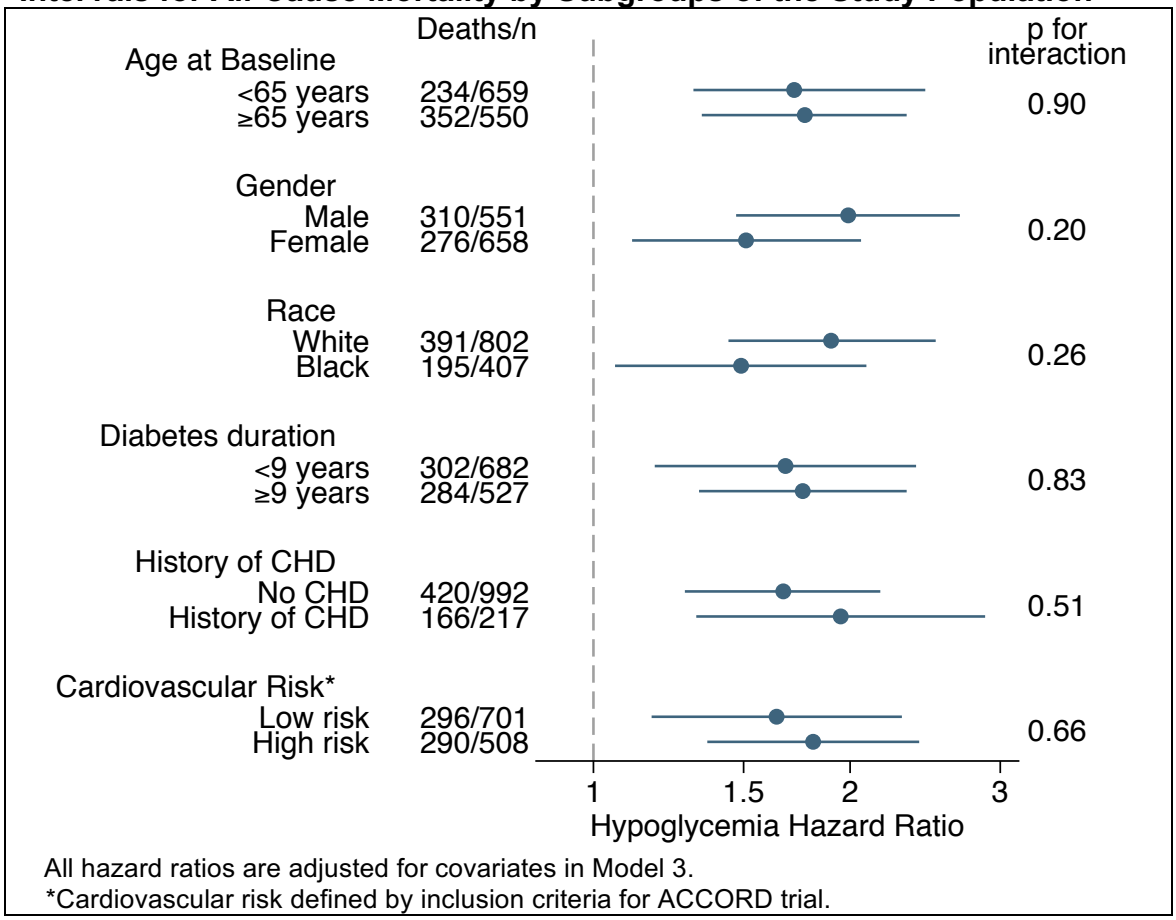
*14 had severe hypoglycemia prior to Visit 4, all others had hypoglycemia during follow-up. ** ACR, albumin-to-creatinine ratio. ***ADLs, activity of daily living: eating, dressing, getting out of bed, or walking between rooms at home.

Table 2. Crude Incidence Rates and Adjusted Hazard Ratios (95% Confidence Intervals) for Incident Cardiovascular Events and Mortality by Severe Hypoglycemia

	events / n	Crude incidence rate per 100PY* without hypoglycemia (95% CI)	Crude incidence rate per 100PY* after hypoglycemia (95%CI)	Model 1** Hazard Ratio (95%CI)	Model 2** Hazard Ratio (95%CI)	Model 3** Hazard Ratio (95%CI)
Incident Cardiovascular Events						
Coronary Heart Disease	173/992	1.24 (1.05 - 1.46)	3.87 (2.65 - 5.64)	2.78 (1.81 - 4.38)	2.23 (1.23 – 3.52)	2.02 (1.27 – 3.20)
Stroke	120/1163	0.81 (0.67 - 0.98)	1.17 (0.63 - 2.17)	1.15 (0.59 - 2.23)	0.91 (0.46 - 1.81)	0.81 (0.40 - 1.63)
Heart Failure	300/1190	1.82 (1.61 - 2.06)	6.61 (5.04 - 8.67)	2.35 (1.72 - 3.20)	1.37 (0.98 - 1.91)	1.35 (0.96 - 1.89)
Atrial Fibrillation	254/1162	1.70 (1.49 - 1.94)	3.36 (2.32 - 4.87)	1.55 (1.03 - 2.32)	1.13 (0.74 - 1.73)	1.05 (0.68 - 1.60)
Peripheral Artery Disease	89/1128	0.53 (0.42 - 0.67)	2.07 (1.30 - 3.29)	3.35 (1.94 - 5.78)	1.85 (1.04 - 3.30)	1.55 (0.86 - 2.80)
Mortality						
All-Cause Mortality	586/1209	3.20 (2.92 - 3.50)	11.43 (9.54 - 13.68)	2.56 (2.08 - 3.17)	1.86 (1.49 - 2.33)	1.73 (1.38 - 2.17)
Cardiovascular Mortality**	218/1209	1.15 (0.99 - 1.34)	4.74 (3.59 - 6.28)	2.80 (2.00 - 3.91)	1.76 (1.23 - 2.51)	1.64 (1.15 - 2.34)
Cancer Mortality**	121/1209	0.68 (0.56 - 0.83)	2.03 (1.33 - 3.12)	2.44 (1.49 - 3.99)	2.61 (1.55 - 4.38)	2.49 (1.46 - 4.24)
Other Mortality**	218/1209	1.21 (1.04 - 1.40)	3.97 (2.92 - 5.39)	2.31 (1.62 - 3.30)	1.47 (1.01 - 2.15)	1.40 (0.95 – 2.03)

Severe hypoglycemia was modeled as a time dependent covariate. *PY: person-years. **Model 1 was adjusted for age, sex, and race-center. Model 2 additionally included diabetes medications, fructosamine tertiles, duration of diabetes, low eGFR, albuminuria, income, and any difficulty with ADLs. Model 3 additionally included systolic blood pressure, hypertension medication use, LDL, HDL, cholesterol-lowering medication use, and smoking status. **29 individuals were missing cause of death and were censored at the time of death in the analyses of cause-specific death.

Figure 1: Severe Hypoglycemia Hazard Ratios and 95% Confidence Intervals for All-Cause Mortality by Subgroups of the Study Population



All hazard ratios are adjusted for covariates in Model 3.
*Cardiovascular risk defined by inclusion criteria for ACCORD trial.

Figure 2: Hypoglycemia Hazard Ratios and 95% Confidence Intervals for CVD and Mortality Outcomes, By Time Since Severe Hypoglycemic Event.

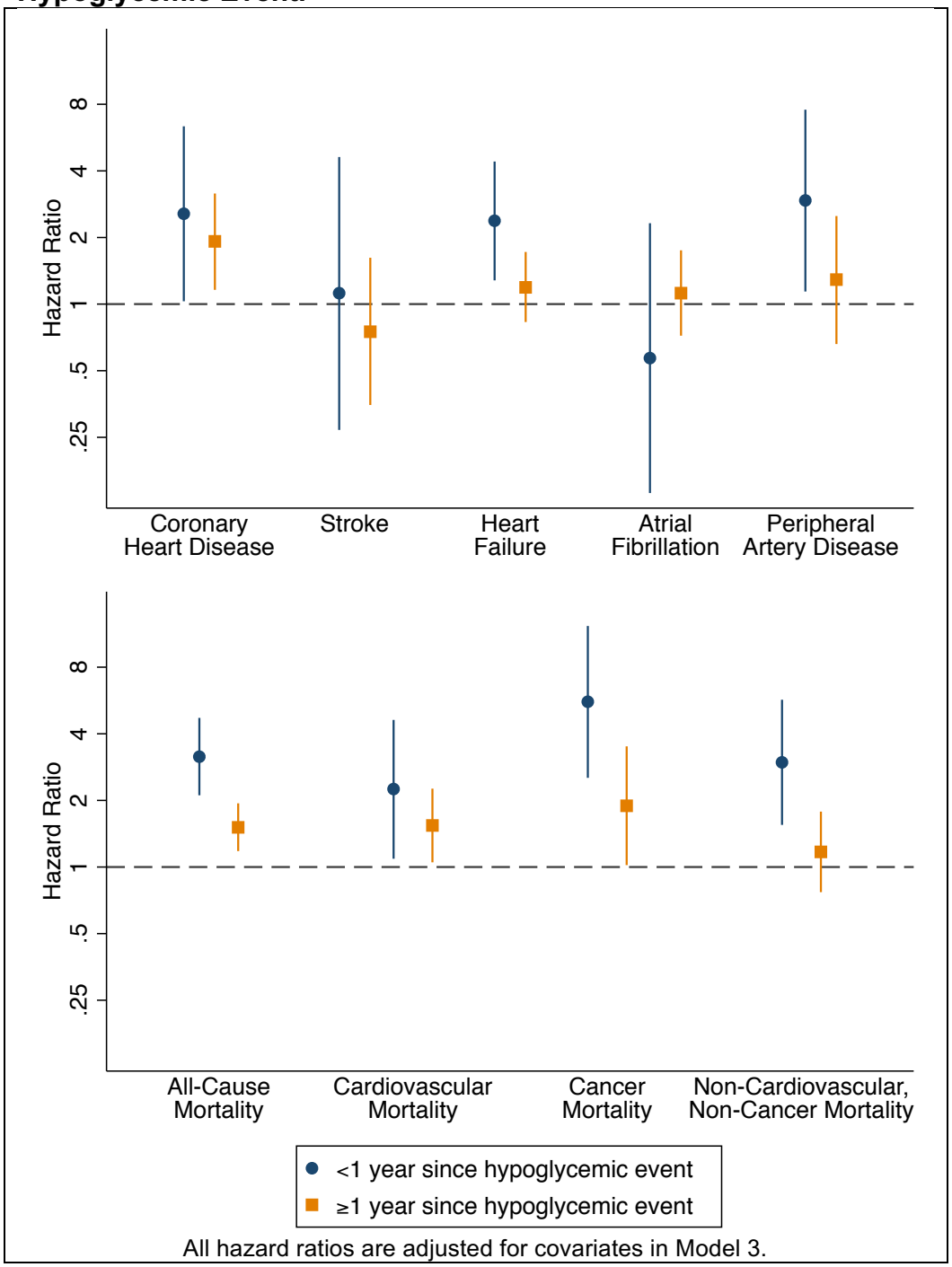


Table S1. Hypoglycemia Hazard Ratios and 95% Confidence Intervals for All-Cause and Cause-Specific Mortality, by subgroups
(n=1209)

	All-cause Mortality			Cardiovascular Mortality			Cancer Mortality			Other Mortality		
	HR	95% CI	p-value*	HR	95% CI	p-value*	HR	95% CI	p-value*	HR	95% CI	p-value*
Age												
<65 years	1.72	(1.21, 2.45)	0.90	1.44	(0.81, 2.57)	0.56	3.02	(1.43, 6.38)	0.60	1.56	(0.86, 2.84)	0.69
≥65 years	1.77	(1.34, 2.33)		1.77	(1.15, 2.74)		2.32	(1.15, 4.67)		1.35	(0.85, 2.13)	
Sex												
Male	1.99	(1.47, 2.69)	0.20	1.73	(1.07, 2.80)	0.74	2.16	(1.07, 4.37)	0.52	2.14	(1.31, 3.50)	**0.02**
Female	1.51	(1.11, 2.06)		1.54	(0.94, 2.53)		2.97	(1.42, 6.21)		0.91	(0.53, 1.58)	
Race												
White	1.90	(1.44, 2.52)	0.26	1.91	(1.20, 3.03)	0.44	2.68	(1.42, 5.05)	0.72	1.53	(0.97, 2.43)	0.47
Black	1.49	(1.06, 2.09)		1.47	(0.89, 2.44)		2.23	(0.96, 5.15)		1.17	(0.65, 2.10)	
Duration of Diabetes												
<9 years	1.68	(1.18, 2.39)	0.83	1.43	(0.80, 2.58)	0.57	2.25	(1.11, 4.57)	0.66	1.46	(0.78, 2.73)	0.87
≥9 years	1.76	(1.33, 2.33)		1.76	(1.14, 2.71)		2.82	(1.33, 5.96)		1.37	(0.87, 2.15)	
Prevalent CHD												
No	1.67	(1.28, 2.17)	0.51	1.92	(1.25, 2.95)	0.31	2.36	(1.25, 4.44)	0.85	1.08	(0.69, 1.68)	**0.01**
Yes	1.95	(1.32, 2.88)		1.33	(0.73, 2.44)		2.62	(1.08, 6.35)		3.10	(1.59, 6.02)	
Cardiovascular Risk**												
Low risk	1.64	(1.17, 2.30)	0.66	1.40	(0.78, 2.53)	0.48	1.48	(0.61, 3.60)	0.10	1.71	(1.01, 2.89)	0.32
High risk	1.81	(1.36, 2.41)		1.81	(1.17, 2.79)		3.54	(1.84, 6.80)		1.19	(0.71, 1.98)	

*p-value for interaction by the listed categories. **Cardiovascular Risk defined by inclusion criteria for the ACCORD trial. Hazard Ratios were from interaction terms in Model 3; the likelihood ratio test was used to generate the p-value for interaction.

Table S2. Hypoglycemia Hazard Ratios and 95% Confidence Intervals for Coronary Heart Disease, Stroke, Heart Failure, Atrial Fibrillation, and Peripheral Artery Disease, by subgroups

	Coronary Heart Disease			Stroke			Heart Failure			Atrial Fibrillation		
	HR	95% CI	p-value*	HR	95% CI	p-value*	HR	95% CI	p-value*	HR	95% CI	p-value*
Age												
<65 years	2.33	(1.18, 4.57)	0.59	0.14	(0.02, 1.07)	**0.01**	1.53	(0.94, 2.49)	0.51	1.40	(0.75, 2.63)	0.26
≥65 years	1.83	(1.01, 3.32)		1.48	(0.70, 3.14)		1.24	(0.80, 1.91)		0.87	(0.50, 1.51)	
Sex												
Male	1.79	(0.91, 3.51)	0.62	0.75	(0.26, 2.20)	0.86	1.53	(0.94, 2.49)	0.23	1.58	(0.88, 2.83)	0.08
Female	2.23	(1.23, 4.02)		0.85	(0.35, 2.06)		1.24	(0.80, 1.91)		0.76	(0.42, 1.37)	
Race												
White	1.69	(0.86, 3.31)	0.40	0.82	(0.32, 2.12)	0.91	1.50	(0.96, 2.35)	0.60	0.79	(0.46, 1.39)	0.09
Black	2.45	(1.34, 2.50)		0.76	(0.29, 2.00)		1.27	(0.80, 2.01)		1.63	(0.86, 3.07)	
Duration of Diabetes												
<9 years	1.94	(0.87, 4.33)	0.90	0.46	(0.11, 1.94)	0.31	1.50	(0.83, 2.71)	0.67	0.84	(0.38, 1.84)	0.49
≥9 years	2.05	(1.20, 3.52)		1.02	(0.46, 2.26)		1.29	(0.87, 1.91)		1.16	(0.70, 1.91)	
Cardiovascular Risk**												
Low risk	1.60	(0.81, 3.19)	0.30	1.05	(0.40, 2.74)	0.48	1.24	(0.74, 2.06)	0.61	0.92	(0.47, 1.80)	0.57
High risk	2.54	(1.41, 4.59)		0.65	(0.25, 1.70)		1.46	(0.96, 2.21)		1.16	(0.69, 1.97)	

*p-value for interaction by the listed categories. **Cardiovascular Risk defined by inclusion criteria for the ACCORD trial. Hazard Ratios were from interaction terms in Model 3; the likelihood ratio test was used to generate the p-value for interaction.

Table S2. Hypoglycemia Hazard Ratios and 95% Confidence Intervals for Coronary Heart Disease, Stroke, Heart Failure, Atrial Fibrillation, and Peripheral Artery Disease, by subgroups (continued from previous page)

	Peripheral Artery Disease		
	HR	95% CI	p-value*
Age			
<65 years	2.37	(1.10, 5.14)	0.13
≥65 years	1.01	(0.43, 2.41)	
Sex			
Male	2.38	(1.08, 5.21)	0.14
Female	1.06	(0.46, 2.41)	
Race			
White	1.01	(.41, 2.52)	0.17
Black	2.16	(1.03, 4.56)	
Duration of Diabetes			
<9 years	1.11	(0.32, 3.81)	0.51
≥9 years	1.72	(0.89, 3.32)	
Cardiovascular Risk**			
Low risk	0.70	(0.16, 3.05)	0.19
High risk	1.84	(0.96, 3.55)	

Figure S1: Hypoglycemia Hazard Ratios and 95% Confidence Intervals for Cardiovascular Events and Mortality by Frequency of Hypoglycemia.

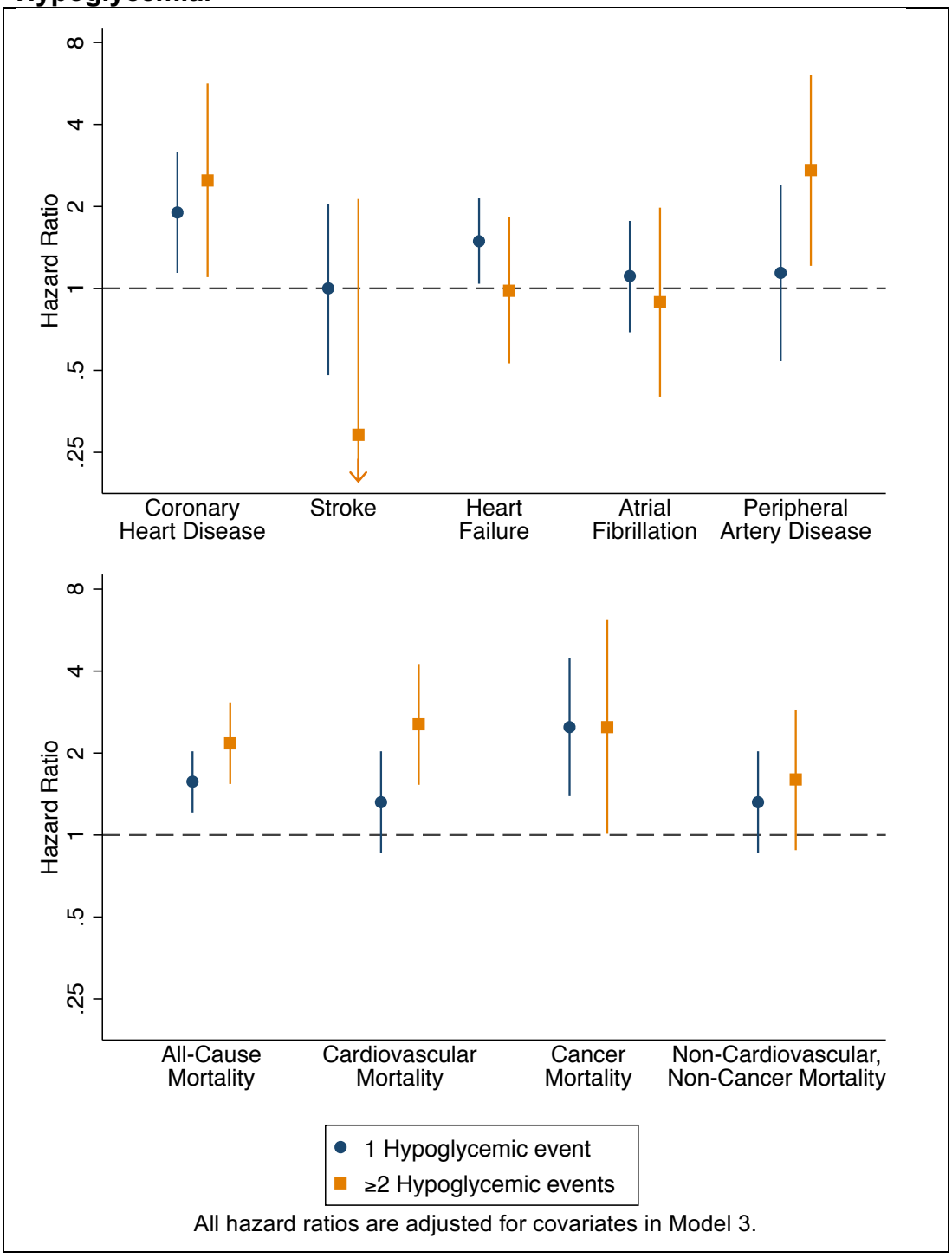


Table S3. Hazard Ratios (95% Confidence Intervals) for the Association of Severe Hypoglycemia with Incident Cardiovascular Disease Subtypes and Mortality, excluding 14 individuals with a history of severe hypoglycemia at Visit 4

	events / n	Model 1* HR (95%CI)	Model 2* HR (95%CI)	Model 3* HR (95%CI)
Incident Cardiovascular Events				
Coronary Heart Disease	168/980	2.73 (1.70 - 4.39)	2.19 (1.34 - 3.59)	2.18 (1.32 - 3.60)
Stroke	117/1150	0.93 (0.42 - 2.03)	0.74 (0.33 - 1.65)	0.67 (0.30 - 1.51)
Heart Failure	292/1176	2.26 (1.62 - 3.16)	1.35 (0.95 - 1.91)	1.36 (0.95 - 1.94)
Atrial Fibrillation	250/1148	1.52 (0.98 - 2.34)	1.13 (0.72 - 1.77)	1.07 (0.68 - 1.68)
Peripheral Artery Disease	85/1115	3.14 (1.71 - 5.78)	1.80 (0.95 - 3.39)	1.60 (0.84 - 3.06)
Mortality				
All-Cause Mortality	574/1195	2.61 (2.09 - 3.25)	1.97 (1.56 - 2.49)	1.89 (1.50 - 2.39)
CVD Mortality**	212/1195	2.80 (1.97 - 3.99)	1.90 (1.31 - 2.77)	1.85 (1.27 - 2.68)
Cancer Mortality**	119/1195	2.52 (1.51 - 4.21)	2.74 (1.60 - 4.68)	2.74 (1.59 - 4.72)
Other Mortality**	214/1195	2.35 (1.63 - 3.41)	1.53 (1.04 - 2.26)	1.47 (1.00 - 2.17)

*Model 1 was adjusted for age, sex, and race-center. Model 2 additionally included diabetes medications, fructosamine tertiles, duration of diabetes, low eGFR, albuminuria, income, and any difficulty with ADLs. Model 3 additionally included systolic blood pressure, hypertension medication use, LDL, HDL, cholesterol-lowering medication use, and smoking status.

**29 individuals were missing cause of death and were censored at the time of death in the analyses of cause-specific death.

Table S4. Hazard Ratios (95% Confidence Intervals) for the Association of Severe Hypoglycemia with Incident Cardiovascular Disease Subtypes and Mortality, using HbA1c measured 6 years prior instead of fructosamine to account for glycemic control

	events / n	Model 1* HR (95%CI)	Model 2* HR (95%CI)	Model 3* HR (95%CI)
Incident Cardiovascular Events				
Coronary Heart Disease	166/942	2.73 (1.74 - 4.26)	2.23 (1.40 - 3.59)	2.00 (1.23 - 3.24)
Stroke	113/1105	1.19 (0.61 - 2.33)	0.98 (0.49 - 1.96)	0.89 (0.44 - 1.79)
Heart Failure	284/1131	2.27 (1.64 - 3.13)	1.29 (0.91 - 1.83)	1.26 (0.89 - 1.79)
Atrial Fibrillation	248/1103	1.55 (1.03 - 2.33)	1.14 (0.74 - 1.76)	1.03 (0.66 - 1.58)
Peripheral Artery Disease	86/1072	3.33 (1.90 - 5.83)	1.89 (1.04 - 3.41)	1.61 (0.88 – 2.97)
Mortality				
All-Cause Mortality	550/1149	2.67 (2.15 - 3.32)	1.93 (1.53 - 2.43)	1.75 (1.38 - 2.21)
CVD Mortality**	201/1149	2.98 (2.11 - 4.20)	1.87 (1.29 - 2.72)	1.71 (1.18 - 2.49)
Cancer Mortality**	113/1149	2.42 (1.44 - 4.04)	2.56 (1.48 - 4.42)	2.39 (1.36 - 4.18)
Other Mortality**	209/1149	2.41 (1.68 - 3.45)	1.60 (1.09 - 2.35)	1.47 (1.00 - 2.17)

*Model 1 was adjusted for age, sex, and race-center. Model 2 additionally included diabetes medications, HbA1c tertiles (<6.3%, 6.3-7.6%, ≥7.7%), duration of diabetes, low eGFR, albuminuria, income, and any difficulty with ADLs. Model 3 additionally included systolic blood pressure, hypertension medication use, LDL, HDL, cholesterol-lowering medication use, and smoking status.

**27 individuals were missing cause of death and were censored at the time of death in the analyses of cause-specific death.

Chapter 4: Severe Hypoglycemia, Cognitive Impairment, Brain Volume, and Dementia in Older Adults with Diabetes

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Abstract

Background: Few studies have examined whether severe hypoglycemia is associated with domain-specific cognitive decline, smaller brain volumes, and dementia in a community-based setting.

Methods: We conducted cross-sectional analyses of prior severe hypoglycemia with cognitive status, recent cognitive decline, and brain volumes in participants with diagnosed diabetes from the Atherosclerosis Risk in Communities (ARIC) Study at Visit 5 (2011-2013). We also conducted prospective analyses of incident dementia (baseline, Visit 4 in 1996-1998) with follow-up through 2013. Severe hypoglycemia was identified using ICD-9 codes from hospitalizations, emergency department visits, and ambulance records. Cognitive decline over the past fifteen years was determined based on a battery of neuropsychological tests conducted at Visits 4 (1996-1998) and 5 (2011-2013). Cognitive status at visit 5 was classified as normal, mild cognitive impairment, or dementia. Brain volumes were assessed in a subset with brain MRI at visit 5. All analyses were adjusted for demographics, education, number of APOE alleles, diabetes medication use, diabetes duration, and HbA1c.

Results: Among 2,001 participants with diabetes at Visit 5 (mean age 76, 3.1% with history of severe hypoglycemia), a history of severe hypoglycemia was associated with dementia (vs. normal cognitive status): odds ratio 2.35, 95%CI 1.05-5.35. Among 1,755 participants with measurements of 15-year cognitive change, hypoglycemia was associated with greater decline in global cognitive performance by 0.20 standard deviations (SDs) (95%CI -0.39, -0.01) with minimal adjustment but was no longer statistically significant after additional adjustment. In the brain MRI subset (n=580), hypoglycemia was associated with smaller total brain volume (-0.309 SDs, 95%CI: -0.612, -0.006). In the prospective analysis, hypoglycemia was strongly associated with incident dementia (hazard ratio 2.44, 95% CI 1.70-3.49).

Conclusions: Severe hypoglycemia was associated with a high burden of cognitive dysfunction, smaller total brain volume, and incident dementia, suggesting that severe hypoglycemia is a strong marker of poor cognitive outcomes.

Introduction

The association between severe hypoglycemia and cognitive decline is thought to be bi-directional, although the evidence is far from conclusive (1-4). Several studies have shown that poor cognitive function and declining cognition are associated with incident hypoglycemia, likely mediated by impairment in diabetes self-management (5-6). Indeed, individuals with dementia are at high risk for hypoglycemia (3,7,8). Additionally, several studies have shown that severe hypoglycemia is associated with incident dementia, suggesting that hypoglycemia may have damaging effects on the brain (3,9,10). However, the literature on severe hypoglycemia and earlier changes in cognition have been inconsistent (7,11,12).

Hypoglycemia is well-known to cause symptoms of confusion and cognitive difficulties, with experimental studies documenting the onset of these neuroglycopenic symptoms occurring at blood glucose concentrations of 41-56 mg/dL (13,14). While cognition appears to improve within an hour of restoration to normal blood glucose levels, there is concern about lasting brain damage (13). There have been case reports documenting abnormalities by diffusion-weighted imaging among individuals in hypoglycemic comas (typically blood glucose <20mg/dL), but many abnormalities reverse upon restoration to normal glucose levels, among cases that survived (15-17). Thus, neuronal cell death may occur during hypoglycemia, but likely only during prolonged hypoglycemia at very low blood glucose concentrations, a threshold which many patients with severe hypoglycemia likely do not reach (18-20).

The overarching objective of our study was to comprehensively evaluate the association of severe hypoglycemia with cognitive measures in a community-based population of adults with diabetes. We had several specific aims: first, to describe the prevalence of cognitive impairment and dementia in old age among those with and without a history of severe hypoglycemia ("Cross-sectional Cognitive Status"); second, to determine whether severe hypoglycemia was associated with a faster rate of cognitive decline ("Prior Cognitive Decline"); third, to compare total and regional brain volumes measured by MRI among those with and without a history of severe hypoglycemia ("Cross-sectional Brain MRI Substudy"); and fourth, to determine the magnitude of the association of severe hypoglycemia with incident dementia in a prospective cohort analysis ("Prospective Incident Dementia").

Methods

Study Population

The Atherosclerosis Risk in Communities (ARIC) Study began in 1987 with the recruitment of 15,792 participants from four U.S. communities: Jackson, Mississippi, Forsyth County, North Carolina, Washington County, Maryland, and selected suburbs of Minneapolis, Minnesota (21). Since baseline, participants have attended up to six study visits and received annual follow-up phone calls. In the present study, we included participants with diagnosed diabetes and who were not missing covariates. We excluded a very small number of participants who reported a race other than black or white from the Minnesota and Maryland

study sites (**Supplementary Figure S1**). For the analyses of “Cross-sectional Cognitive Status,” “Prior Cognitive Decline,” and “Cross-sectional Brain MRI Substudy”, participants were selected from Visit 5 (2011-2013) for final analytic samples of 2,001, 1,755, and 580, respectively. The “Prospective Incident Dementia” analysis included 1,263 participants; baseline was Visit 4 (1996-1998) with follow-up through 2013.

Severe Hypoglycemia

Severe hypoglycemia episodes were identified with a widely-used algorithm using ICD-9 codes from hospitalizations, emergency department visits, and ambulance call records (22). The ICD-9 code for hypoglycemia was required to be in the primary position. Hospitalization records for ARIC participants were available from two sources: 1) ARIC active hospital surveillance, which captures all hospitalizations from local hospitals and also includes hospital records for participants who report hospitalizations outside the local catchment area (21), and 2) linkage to CMS claims for hospitalizations among ARIC participants enrolled in Medicare. Emergency department visits and ambulance calls were identified from outpatient claims for participants enrolled in Medicare fee-for-service Part B. Severe hypoglycemic events were ascertained through December 31, 2013.

Latent Factor z-scores for Cognitive Function

To examine cognitive decline, we compared changes in neuropsychological test scores from Visit 4 (1996-1998) to Visit 5 (2011-2013). All participants who attended these two visits were administered the digit symbol substitution test, the word fluency test, and the delayed word recall test. At Visit 5, seven additional tests were conducted. To compare cognitive function across study visits while utilizing all the cognitive tests administered at Visit 5, Gross et al. created factor scores using a confirmatory factor analysis approach for each cognitive domain (23). At Visit 5, the executive function domain factor score was based on the digit symbol substitution test, digit span backwards test, and trail making parts A and B. The language domain included the word fluency test, the Boston naming test, and the animal naming test. The memory domain included the delayed word recall test, incidental learning, and the logical memory test parts 1 and 2. For analysis, factor scores were standardized to a normal distribution with mean of 0 and standard deviation of 1 (z scores).

Brain Volumes

Brain volumes were measured by magnetic resonance imaging (MRI) (3 Tesla Siemens) in a substudy at Visit 5. Detailed selection criteria have been published elsewhere (24). In brief, participants were selected based on their cognitive performance; individuals with cognitive impairment or cognitive decline were oversampled.

Incident Dementia

Dementia diagnoses were based on a combination of evidence including cognitive test scores, informant interviews, hospitalization records, and death certificates (25). Follow-up for dementia ascertainment was complete through December 31, 2013.

Statistical Analysis

Based on previous evidence for a bi-directional association between hypoglycemia and cognition, we adjusted for educational attainment and number of APOE alleles to account for baseline cognitive performance and the rate of cognitive decline, respectively, which are important predictors of incident severe hypoglycemia (3,7,8). By accounting for these factors, we aimed to identify the association of severe hypoglycemia with cognitive measures independent of other known risk factors. Additionally, since the progression and severity of diabetes strongly influence the rate of hypoglycemia (26-28), we controlled for diabetes duration, medication use, and HbA1c. Model 1 was adjusted for demographics only: age, sex, and race-center (blacks from Jackson, blacks from Forsyth, whites from Forsyth, whites from Minneapolis suburbs, whites from Washington County). Model 2 was adjusted for all variables in Model 1 plus number of APOE alleles (0, 1, or 2) and education level (less than high school, high school graduate, or some college). Model 3 was adjusted for all variables in Model 2 plus diabetes duration, diabetes medication use (none, orals only, any insulin use), and HbA1c.

For the “Cross-sectional Cognitive Status” analysis, we calculated the age-adjusted prevalence and compared the odds of having cognitive impairment or dementia among those with and without severe hypoglycemia using multinomial logistic regression.

For the analysis of “Prior Cognitive Decline”, we evaluated the association of any severe hypoglycemia during the past 15 years with 15-year cognitive decline. We conducted linear regression using the latent z-scores for global cognitive function and for each cognitive domain (executive function, language, memory).

In the “Cross-sectional Brain MRI Substudy” analysis, we used linear regression to examine the association of a history of severe hypoglycemia with current brain volume. Due to small numbers and the need for a more parsimonious model, we used the same series of models but used race rather than race-center and insulin use (yes/no) instead of three categories of medication use. Per ARIC statistical analysis guidelines, all results were weighted to the original Visit 5 attendee sample using the probability of selection to the Brain MRI substudy (29).

To provide context for the magnitude of these results, we compared the results for hypoglycemia to those for age from the same model, since age-related cognitive decline is well recognized. We calculated the number of additional years of cognitive aging that severe hypoglycemia was equivalent to. For example, if our model found that hypoglycemia was associated with a 0.20 standard deviation (SD) decline, and age (per year) was associated with a 0.05

SD decline, then hypoglycemia would be equivalent to a four-year difference in age, e.g., the difference in cognitive performance of a 76-year-old person compared to an 80-year-old person (30).

For the “Prospective Incident Dementia” analysis, we modeled severe hypoglycemia as a time-varying exposure in a Cox regression model for incident dementia. At the start of follow-up time, the person-time for all participants were classified as “no severe hypoglycemia” unless they had had an episode of severe hypoglycemia prior to Visit 4 (n=16), in which case their person-time was classified as “any history of severe hypoglycemia”. During the follow-up time, an individual’s person-time was changed to “any history of severe hypoglycemia” at the time of their first severe hypoglycemic episode. The assumption of proportional hazards was verified with inspection of negative log log survival curves. Because HbA1c was not measured at Visit 4, the baseline for this analysis, we adjusted for fructosamine as a measure of glycemic control. Results were similar when HbA1c from a visit six years prior was used.

All analyses were conducted in Stata version 13.1 (StataCorp LP, College Station, TX).

Results

Cross-Sectional Cognitive Status

Of the 2,001 participants, 3.1% (n=63) had a history of severe hypoglycemia. Individuals with a history of severe hypoglycemia were, on average, older, more likely to be black, have less education, have a longer

duration of diabetes, be on insulin, and have more APOE alleles (**Table 1**). The median time between hypoglycemia and the study visit was 5.6 years (25^{th} and 75^{th} percentiles, 2.3 and 8.1 years).

Cognitive status was strongly associated with a history of severe hypoglycemia (**Figure 1**). After adjustment, persons with a history of severe hypoglycemia were significantly more likely to have dementia (odds ratio (OR) 2.35, 95%CI 1.05-5.35; Model 3). Differences by history of severe hypoglycemia comparing mild cognitive impairment to normal cognitive function were evident but not statistically significant after adjustment (OR 1.51, 95%CI 0.82-2.76).

As a sensitivity analysis, we also examined the prevalence of dementia among those who did not attend visit 5. As expected, the prevalence of dementia was higher among those who did not attend visit 5 compared to those to who did (in persons without hypoglycemia: 14.5% vs. 5.1%, respectively). Comparing those with and without a history of hypoglycemia, the odds ratio for dementia was slightly lower in those who did not attend visit 5 (OR 1.82, 95%CI 1.15-2.87) compared to those who did attend visit 5 (OR 2.36, 95%CI 1.26-4.44), after adjustment for age, sex, and race-center.

Prior Cognitive Decline

Among the 1,755 participants in the analysis of Prior Cognitive Decline, there were 2.8% (n=50) with a history of severe hypoglycemia. Individuals with severe hypoglycemia had greater cognitive decline (global factor score) compared to those without severe hypoglycemia in the minimally adjusted model

(-0.20 SD, 95%CI -0.39, -0.01; Model 1; **Table 2**). After further adjustment, severe hypoglycemia was no longer significantly associated with cognitive decline (-0.14 SD, 95%CI -0.33, 0.06; Model 3) but the point estimate remained sizeable and was equivalent to the difference in cognitive performance of two individuals differing in age by 4.6 years. Similarly, hypoglycemia was not statistically significantly associated with domain-specific cognitive decline, but the point estimates in Model 3 were large and equivalent to four to five years' difference in age.

In sensitivity analyses, we additionally adjusted for CES-D score, albuminuria, hypertension, and percent weight change from Visit 4 to Visit 5. While many of these variables were strongly associated with cognitive decline, they did not notably change the association between hypoglycemia and cognitive decline.

Brain Volumes

In the Brain MRI Substudy (n=580), 2.1% of participants (n=12) had a history of severe hypoglycemia. After adjustment, severe hypoglycemia was associated with smaller total brain volume (-0.309 SD, 95% CI: -0.612 to -0.006; Model 3, **Table 3**), equivalent to 45 cubic centimeters or a difference in age of 6.9 years (**Supplementary Table S1**). A history of severe hypoglycemia also was also associated with a smaller volume of the frontal lobe (-0.384 SD, 95% CI -0.766, -0.003; Model 3). The associations for other areas of the brain were weaker or absent.

Incident Dementia

Of 1,263 participants from Visit 4 (1996-1998; mean age, 64 years), 15.5% (n=196) experienced an episode of severe hypoglycemia. The median follow-up time was 13.9 years. Individuals who experienced severe hypoglycemia were more likely to be older, black, and to have lower cognitive scores at Visit 4 (**Supplementary Table S2)**.

The incidence of dementia following an episode of severe hypoglycemia was approximately five times greater than the incidence in the absence of any severe hypoglycemia (with severe hypoglycemia: 51.3 per 1000 person-years (PY), 95%CI 38.7-68.1; without severe hypoglycemia: 9.7 per 1000PY, 95%CI 8.2-11.4; **Table 4**). After adjustment, severe hypoglycemia was associated with two and a half times greater risk of dementia, which was only minimally attenuated with adjustment (Model 1 HR 2.55, 95%CI 1.81-3.59; Model 3 HR 2.44, 95%CI 1.70-3.49). Among the 48 participants with hypoglycemia and subsequent dementia, the median time between these events was 3.5 years (25^{th} and 75^{th} percentiles: 1.2 and 7.2 years).

When stratifying on baseline (visit 4) cognitive function, we found statistically significant effect modification with severe hypoglycemia (p-for-interaction = 0.004). There was a strong gradient for the hypoglycemia hazard ratio: among those in the lower two tertiles of cognitive function, hypoglycemia was not associated with incident dementia, but was very strongly associated with dementia in the highest tertile of baseline function (Model 4, lowest tertile HR:

1.45, 95%CI 0.87-2.40, highest tertile HR: 4.79, 95%CI 1.99-11.54; **Supplementary Table S3**).

Discussion

Our study documents the extensive cognitive deficits that accompany severe hypoglycemia among older adults with diabetes. In the study population at visit 5 (mean age 76), among those with a history of hypoglycemia, about half were cognitively normal and the other half had either mild cognitive impairment or dementia. The prevalence of dementia was approximately two times higher in individuals with a history of severe hypoglycemia compared to those without hypoglycemia, after accounting for demographic characteristics. With respect to both past cognitive decline and total brain volume, the deficits among those with hypoglycemia were equivalent to an age difference of four to eleven years. By nature of our study design, we cannot determine whether these deficits occurred prior to or following a hypoglycemic event, but it is clear that individuals with a history of hypoglycemia have a high burden of cognitive dysfunction.

Our study is the first epidemiologic inquiry to find smaller brain volumes in individuals with a history of severe hypoglycemia compared to those without hypoglycemia. While there have been case reports documenting imaging abnormalities during hypoglycemic comas (15-17), there has been only one other epidemiologic inquiry into the association of severe hypoglycemia with brain MRI parameters in type 2 diabetes (31). The ACCORD-MIND MRI substudy measured brain volumes at baseline and 40 months. Contrary to expectations,

they found that individuals with severe hypoglycemia had significantly *less* brain atrophy over 40 months than those without severe hypoglycemia (31). Additionally, there was no difference in change in abnormal white matter volume. The authors concluded that the brain was resilient to hypoglycemia insults when hypoglycemia did not lead to a coma. Our results are not incompatible with the results from the ACCORD-MIND MRI study; because our study was cross-sectional, we cannot know if the smaller brain volumes we observed preceded the hypoglycemic episode or if atrophy occurred as a result of the hypoglycemic episode. However, it is also worth noting that in ACCORD, participants were on average 10 years younger than in our study, and brain resilience may decline with increasing age.

Our study also adds to the existing literature on the association of severe hypoglycemia with subclinical cognitive decline assessed using neuropsychological tests. This association is difficult to evaluate due to the challenges of finding the ideal time interval over which to evaluate cognitive change. Over a short period of time, there may be only small declines that studies lack power to detect. Over a long period of time, the competing risk of mortality likely biases the results towards the null, since individuals who have less decline are more likely to survive and to attend study visits (30,32). Indeed, a prior study examining 18-month cognitive decline found no association with severe hypoglycemia, while a study of four years' duration found a significant association of severe hypoglycemia with cognitive decline (7,11). Our study, examining 15-year cognitive decline, found large effect sizes but most results

were not statistically significant, likely due to the relatively small number of participants with a history of severe hypoglycemia who also attended the study visit (n=50).

Previous research has shown that diabetes and poor glycemic control are most strongly associated with declines in the executive function domain (30). In our analysis, the association of hypoglycemia was weakest with the executive function domain and strongest for memory. This suggests that declines in memory are either causing severe hypoglycemia or brought about by episodes of severe hypoglycemia. It seems plausible that worsening short-term memory could cause severe hypoglycemia, especially if it impairs diabetes self-management skills.

ADA clinical guidelines currently recommend annual screening for cognitive impairments among older adults with diabetes, but this may not be adequate in individuals with severe hypoglycemia. Our results show that a severe hypoglycemic event is a strong indicator of poor cognitive prognosis, with nearly two and half times higher risk of dementia compared to those without hypoglycemia, similar to other studies (4,9,10). Severe hypoglycemia is likely associated with ongoing cognitive decline, since the median time between hypoglycemia and a dementia diagnosis was only 3.5 years in our study and cognitive decline typically precedes dementia diagnosis by a decade or more (33). ADA guidelines recommend using either the Mini-Mental Status Exam (MMSE) or the Montreal Cognitive Assessment (MoCA) for cognitive screening, but the MoCA is far more sensitive for detection of mild cognitive impairment

compared to the MMSE, with good specificity (1,34,35). Our results suggest that the MoCA should be the preferred cognitive screening test for individuals with hypoglycemia to more accurately detect mild cognitive impairment.

For adults with mild cognitive impairment or dementia, current ADA clinical guidelines recommend adjusting glucose-lowering therapies to avoid hypoglycemia (1). Although a recent study found that following a dementia diagnosis, there was a greater decline in the number of diabetes medications compared to a matched control group without a dementia diagnosis, there remain substantial concerns about overtreatment among older adults with cognitive dysfunction (36,37). Several studies have documented that many older adults take sulfonylureas and insulin and have an A1c <7% despite complex comorbidities that put them at high risk for hypoglycemia (38-41). More specific strategies on how to de-intensify medication use, particularly for patients on insulin with presumed beta-cell failure, are necessary to facilitate translation of this guideline into clinical practice (42,43).

It is not clear if hypoglycemia is a marker or direct cause of cognitive decline. Hypoglycemia can cause neuronal cell death through a variety of mechanisms, including increased production of glutamate, reactive oxygen species, and activation of poly(ADP-ribose) polymerase (44). However, in studies of insulin-induced hypoglycemia in monkeys, blood glucose concentrations of <20 mg/dL were required for five to six hours before neurologic damage occurred, and such durations of hypoglycemia in diabetes are very uncommon (44). With respect to our findings, although prior studies have shown that

neurons in the hippocampus are particularly vulnerable to hypoglycemia (45), we found no difference in hippocampal volume between individuals with and without a history of severe hypoglycemia. Additionally, contrary to what might be expected, we saw a difference by history of severe hypoglycemia in the volume of the prefrontal region, which is thought to have hyperprofusion during hypoglycemia to prevent damage (13). Thus, it is unclear if the observed differences in brain volume are due to severe hypoglycemia.

The connections from brain pathology to cognitive decline are complex and not fully understood. While it is generally understood that losing neurons eventually translates to loss of cognitive function, the theory of cognitive reserve posits that individuals with higher education and intellectual attainment are more resilient to increasing brain pathology because they are more able to find compensatory methods to maintain cognitive function (46). Thus, compared to their peers with lower education, these individuals maintain good cognitive function for longer given the same amount of brain pathology. However, at some point, the pathology overwhelms their compensatory abilities, and they experience rapid cognitive decline. Applying the theory of cognitive reserve to our stratified analysis by baseline cognitive function, we would expect that the insult of hypoglycemia would more strongly impact individuals with lower baseline cognitive function. However, we see the opposite, and indeed the highest incidence rates of dementia among those with severe hypoglycemia and high baseline cognitive function. Thus, we hypothesize that among those with high baseline cognitive function, hypoglycemia occurs after the inflection point, during

a time of rapid cognitive decline that leads to quickly to dementia. In this interpretation, hypoglycemia is most likely a marker, rather than a cause, of cognitive decline and dementia.

There could be other possible social mechanisms through which hypoglycemia contributes to cognitive decline. Withdrawal from daily activities and depressive symptoms can be due to fear of hypoglycemia, and these could contribute to dementia risk (47-49). Additionally, episodes of severe hypoglycemia may result in a de-intensification of treatment and more hyperglycemia-related cognitive decline (30,50,51). These potential mechanisms should be clarified in order to determine if hypoglycemia-related cognitive decline can be avoided.

Our study has several limitations. First, most analyses were cross-sectional, and given the strong bi-directional associations between severe hypoglycemia and poor cognition (3,4), the lack of temporality makes statements about causality inconclusive. Second, there may be survival bias in which individuals with severe hypoglycemia who attend the study visits are likely healthier than those who could not attend the study visit. However, in our study, the odds of dementia comparing individuals with and without hypoglycemia were similar whether or not participants attended the study visit.

There are also several strengths to our analyses. First, our assessments of mild cognitive impairment and dementia were based on robust criteria with a wide range of data, and each case was reviewed by an expert dementia committee to determine the diagnosis and likely etiology (25). Second, we were

able to adjust for likely confounders including educational attainment and APOE genotype, which affect baseline cognitive function and rate of cognitive decline, respectively.

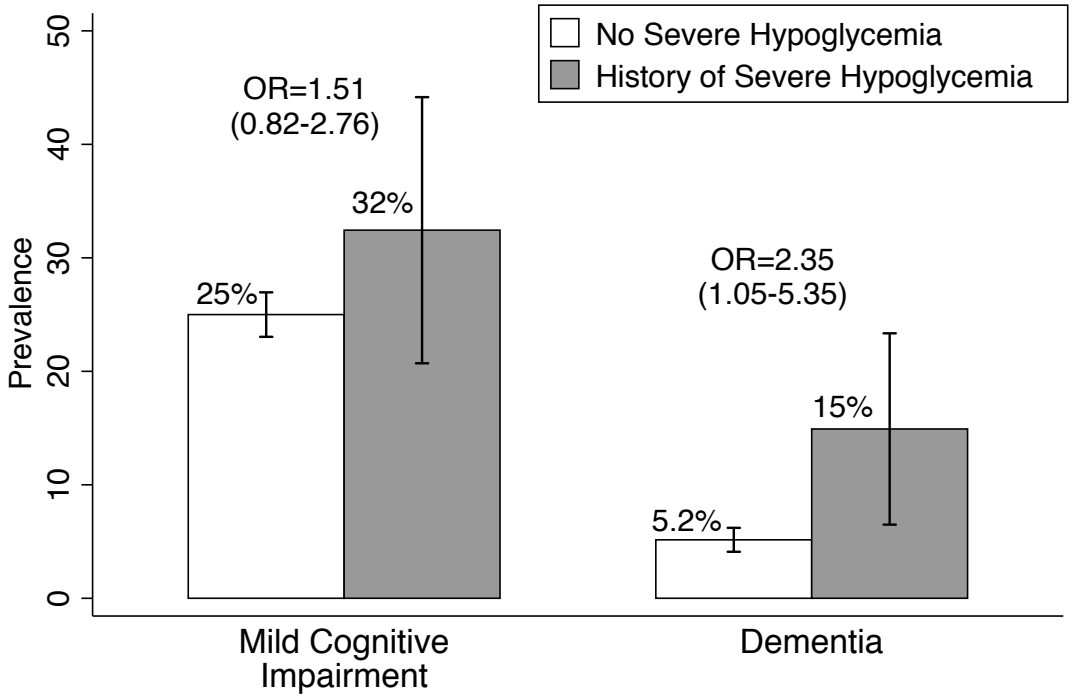
In conclusion, among older adults with type 2 diabetes, those with severe hypoglycemia have a high burden of cognitive dysfunction and are at increased risk for dementia. Severe hypoglycemia is a strong marker of cognitive decline and may be clinically useful as an early warning sign of cognitive impairment. Adjusting the ADA clinical guidelines to recommend the use of the MoCA questionnaire over the MMSE to improve screening for mild cognitive impairment may help identify those at high risk for hypoglycemia and future cognitive decline. Additionally, more specific approaches to medication deintensification among older adults with dementia may help reduce the risk of hypoglycemia. Further studies are needed to determine if interventions designed to reduce severe hypoglycemia also reduce cognitive decline and dementia.

Table 1. Characteristics of ARIC Participants with Diagnosed Diabetes at Visit 5 (2011-2013), by History of Severe Hypoglycemia, n=2001 for "Cross-Sectional Cognitive Status"

	No History of Severe Hypoglycemia n=1938 mean (SD) or %	History of Severe Hypoglycemia n=63 mean (SD) or %	p-value*
Age	75.7 (5.19)	77.2 (5.59)	0.04
Female	57%	65%	0.33
Black	30%	47%	<0.001
Education Not high school graduate High school graduate Some college or more	 20% 43% 37%	 33% 44% 23%	0.007
BMI**	30.6 (6.01)	31.0 (6.12)	0.93
Hypertension**	85%	89%	0.50
HbA1c (%)	6.6 (1.13)	7.1 (1.18)	<0.001
Diabetes duration (years)	9.8 (6.5)	18.0 (6.2)	<0.001
Diabetes Medications None Oral only Any insulin	 40% 45% 15%	 12% 30% 58%	<0.001
APOE alleles 0 (TT) 1 (CT) 2 (CC)	 72% 26% 2.6%	 59% 37% 4.8%	0.07

*P-values were calculated with chi-squared test for categorical variables and t-tests for continuous variables. **Missing BMI: 87 for no hypoglycemia, 7 for hypoglycemia. Missing hypertension: 25 for no hypoglycemia, 2 for hypoglycemia.

Figure 1. Age-Adjusted Prevalence and 95% Confidence Intervals of Mild Cognitive Impairment or Dementia, With Odds Ratios (OR) Compared to Normal Cognitive Status, by History of Severe Hypoglycemia at Visit 5 ("Cross-Sectional Cognitive Status" n=2001, 63 with history of hypoglycemia)



Prevalence of normal cognitive status: 70% in those without hypoglycemia, 53% in those with hypoglycemia. Odds ratios are compared to normal cognitive status and are adjusted for age, sex, race-center, education, APOE, diabetes duration, diabetes medication, HbA1c (Model 3)

Table 2. Association of Severe Hypoglycemia with 15-year Cognitive Decline, as Assessed by Change in Latent Cognitive Z-scores from Visit 4 (1996-1998) to Visit 5 (2011-2013)
("Prior Cognitive Decline" n=1755; 50 with a history of hypoglycemia)

	Model 1*		Model 2*		Model 3*		Beta for age from Model 3	Hypoglycemia year equivalents**
	Beta	(95% CI)	Beta	(95% CI)	Beta	(95% CI)		
Global Z	-0.20*	(-0.39, -0.01)	-0.18	(-0.37, 0.01)	-0.14	(-0.33, 0.06)	-0.03	4.6
Memory	-0.42	(-0.89, 0.05)	-0.33	(-0.80, 0.13)	-0.33	(-0.81, 0.15)	-0.07	4.9
Language	-0.26	(-0.54, 0.03)	-0.23	(-0.52, 0.06)	-0.22	(-0.52, 0.08)	-0.06	3.8
Executive Function	-0.14	(-0.32, 0.04)	-0.13	(-0.31, 0.04)	-0.07	(-0.25, 0.11)	-0.02	4.6

*Model 1: Age, sex, race-center. Model 2: Age, sex, race-center, education, # APOE alleles. Model 3: Age, sex, race-center, education, # APOE alleles, diabetes duration, diabetes medication, HbA1c.
**Hypoglycemia year equivalents were calculated by dividing the beta for hypoglycemia from Model 3 by the beta for 1 year of age from Model 3.

Table 3. Association of History of Severe Hypoglycemia with Brain Volumes in Standard Deviations ("Cross-sectional Brain MRI substudy," n=580, 12 with severe hypoglycemia)

	Model 1		Model 2		Model 3		Beta for age from Model 2	Hypoglycemia year equivalents**
	Beta	(95% CI)	Beta	(95% CI)	Beta	(95% CI)		
Total Brain	-0.448	(-0.731, -0.165)	-0.398	(-0.702, -0.094)	-0.309	(-0.612, -0.006)	-0.045	6.9
Frontal	-0.431	(-0.810, -0.052)	-0.399	(-0.788, -0.009)	-0.384	(-0.766, -0.003)	-0.034	11.3
Temporal	-0.443	(-0.847, -0.040)	-0.368	(-0.758, 0.022)	-0.293	(-0.706, 0.121)	-0.055	5.3
Deep Grey	-0.378	(-0.792, 0.037)	-0.236	(-0.631, 0.158)	-0.171	(-0.577, 0.235)	-0.029	5.9
Hippocampal	-0.170	(-0.680, 0.340)	-0.084	(-0.586, 0.418)	0.029	(-0.498, 0.556)	-0.080	-0.4
Occipital	-0.442	(-0.869, -0.015)	-0.400	(-0.843, 0.042)	-0.344	(-0.793, 0.105)	-0.049	7.0
Parietal	-0.315	(-0.670, 0.040)	-0.223	(-0.572, 0.127)	-0.127	(-0.496, 0.242)	-0.038	3.3
Alzheimer's Disease region	-0.420	(-0.840, -0.000)	-0.315	(-0.735, 0.104)	-0.223	(-0.655, 0.209)	-0.049	4.6

*p-value < 0.05. **Hypoglycemia year equivalents were calculated by dividing the beta for hypoglycemia from Model 3 by the beta for 1 year of age from Model 3. Model 1: Age, sex, race, intra-cranial volume, sex*intra-cranial volume; Model 2: Model 1 + education, # APOE alleles; Model 3: Model 2 + diabetes duration, insulin use, A1c

Table 4. Association of Severe Hypoglycemia with Incident Dementia among ARIC Participants with Diagnosed Diabetes at Visit 4, n=1263

	Incident Dementia	Dementia Incidence Rate (per 1000)	Model 1 HR (95% CI)	Model 2 HR (95% CI)	Model 3 HR (95% CI)	Model 4 HR (95% CI)
No severe hypoglycemia	138	9.7 (8.2-11.4)	1 [ref]	1 [ref]	1 [ref]	1 [ref]
With severe hypoglycemia	48	51.3 (38.7 – 68.1)	2.55 (1.81 - 3.59)	2.54 (1.80 - 3.59)	2.52 (1.77 - 3.61)	2.44 (1.70 – 3.49)

Model 1: Age, sex, race-center; Model 2: Model 1+ education, APOE alleles; Model 3: Model 2 + diabetes duration, diabetes medication, fructosamine; Model 4: Model 3+ systolic blood pressure, hypertension medication use, albuminuria, eGFR <60

Figure S1. Flow Chart of Analytic Samples

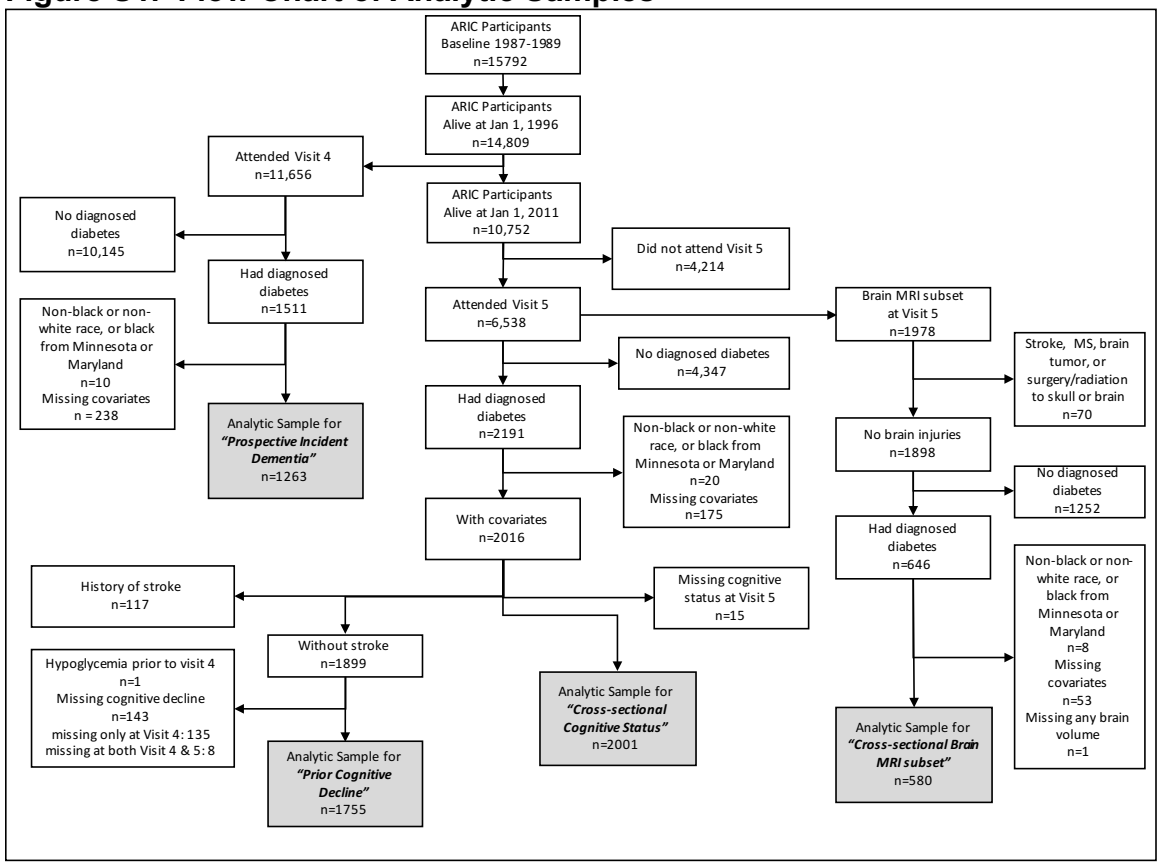


Table S1. Association of History of Severe Hypoglycemia with Brain Volumes in cubic centimeters, from MRI Substudy
("Cross-sectional Brain MRI subset" n=580, 12 with severe hypoglycemia)

	Model 1		Model 2		Model 3	
	Beta	**(95% CI)**	**Beta**	**(95% CI)**	**Beta**	**(95% CI)**
Total Brain	-45.24	(-73.85, -16.64)	-40.18	(-70.91, -9.45)	-31.19	(-61.77, -0.60)
Frontal	-6.67	(-12.53, -0.80)	-6.17	(-12.20, -0.14)	-5.95	(-11.85, -0.05)
Temporal	-4.89	(-9.33, -0.44)	-4.06	(-8.35, 0.24)	-3.22	(-7.78, 1.33)
Deep Grey	-1.18	(-2.47, 0.12)	-0.74	(-1.96, 0.49)	-0.53	(-1.80, 0.73)
Hippocampal	-0.16	(-0.63, 0.32)	-0.08	(-0.54, 0.39)	0.03	(-0.46, 0.52)
Occipital	-2.35	(-4.63, -0.08)	-2.13	(-4.49, 0.22)	-1.83	(-4.22, 0.56)
Parietal	-3.72	(-7.92, 0.48)	-2.64	(-6.77, 1.50)	-1.50	(-5.86, 2.86)
Alzheimer's Disease region	-2.75	(-5.50, -0.001)	-2.06	(-4.81, 0.68)	-1.46	(-4.29, 1.37)

Model 1: Age, sex, race, intra-cranial volume, sex*intra-cranial volume
Model 2: Age, sex, race, intra-cranial volume, sex*intra-cranial volume, education, # APOE alleles
Model 3: Age, sex, race, intra-cranial volume, sex*intra-cranial volume, education, # APOE alleles, diabetes duration, insulin use, A1c

Table S2. Characteristics of ARIC Participants at Visit 4 with Diagnosed Diabetes, by Severe Hypoglycemia, n=1263

	No Severe Hypoglycemia n=1067 mean (SD) or %	Any Severe Hypoglycemia n=196 mean (SD) or %	p-value
Age	63.5 (5.7)	64.7 (5.6)	0.007
Female	54.6%	57.7%	0.44
Black	33.5%	48.5%	<0.001
Education			0.01
Not high school graduate	28.4%	38.8%	
High school graduate	40.9%	37.8%	
Some college or more	30.7%	23.5%	
BMI*	31.4 (5.9)	32.1 (6.1)	0.10
Systolic blood pressure	132.1 (19.8)	134.8 (19.6)	0.07
Hypertension medication use	68.3%	75.5%	0.045
Fructosamine			<0.001
Middle tertile (297 -352μmol/L)	33.8%	30.6%	
Highest tertile (≥352μmol/L)	29.8%	52.0%	
Diabetes Duration >8 years	41.0%	60.7%	<0.001
Diabetes Medications			<0.001
None	29.6%	10.2%	
Oral only	45.9%	38.8%	
Any insulin	24.5%	51.0%	
Low eGFR (<60mL/min/1.73m^2)	10.3%	21.4%	<0.001
Albuminuria			<0.001
ACR** < 30mg/g	79.3%	63.3%	
ACR** 30-<300mg/g	14.6%	19.9%	
ACR** ≥300mg/g	6.1%	16.8%	
APOE alleles			0.005
0 (TT)	73.3%	62.8%	
1 (CT)	24.3%	32.1%	
2 (CC)	2.4%	5.1%	
Cognitive function			<0.001
Lowest tertile***	30.6%	51.5%	
Middle tertile	33.7%	30.6%	
Highest tertile	35.8%	17.9%	

*BMI was missing for 2 participants with severe hypoglycemia. **ACR, albumin to creatinine ratio. ***Lowest tertile of cognitive function included 7 participants missing the latent score for cognition.

Table S3. Incidence Rates and Hazard Ratios of Dementia Among Diabetes by Severe Hypoglycemia, Stratified by Baseline Cognitive Function, n=1263

	Incident Dementia Cases	Incidence Rate of Dementia per 1000 person-years (95% CI)	Model 4 HR (95% CI)
Lowest Tertile of Baseline Cognitive Function (n=427)*			
No severe hypoglycemia	74	17.8 (14.2 – 22.3)	1 [ref]
With severe hypoglycemia	23	49.6 (33.0 – 75.0)	1.45 (0.87 – 2.40)
Middle Tertile of Baseline Cognitive Function (n=419)			
No severe hypoglycemia	39	8.23 (6.01 – 11.3)	1 [ref]
With severe hypoglycemia	13	40.0 (23.2 – 68.8)	1.47 (0.65 – 3.33)
Highest Tertile of Baseline Cognitive Function (n=417)			
No severe hypoglycemia	23	4.3 (2.9 – 6.5)	1 [ref]
With severe hypoglycemia	12	83.5 (47.4 – 147.1)	4.79 (1.99 – 11.54)

*Lowest tertile includes 7 individuals with missing baseline cognitive function. P-value for interaction: 0.0036. Model 4 is adjusted for age, sex, race-center, education, number of APOE alleles, diabetes duration, diabetes medication, fructosamine, systolic blood pressure, hypertension medication use, albuminuria, and eGFR <60

Conclusion

This dissertation examined the risk factors and health outcomes associated with severe hypoglycemia in type 2 diabetes. In addition, we attempted to provide new evidence about the question of whether hypoglycemia was a marker or a cause of increased risk of cardiovascular and cognitive outcomes.

Summary of Findings

In Chapter 1, we described the incidence rate of severe hypoglycemia by subgroups of age and race and comprehensively evaluated traditional and novel risk factors for severe hypoglycemia in the community-based ARIC Study. We found that the incidence rate of severe hypoglycemia was higher at older ages and was approximately two times higher in blacks compared to whites (blacks vs. whites, for age <65: IRR=2.10, p=0.001; for 65-69: IRR=1.62, p=0.11; for ≥70: IRR=1.60, p=0.10). In a model including all traditional risk factors for hypoglycemia, the independent predictors were age (HR per five years 1.24, 95%CI 1.07-1.43), black race (HR 1.39, 95%CI 1.02-1.88), poor glycemic control (middle vs. lowest tertile of fructosamine HR 1.78, 95%CI 1.11-2.83; highest vs. lowest tertile of fructosamine HR 2.62, 95%CI 1.67-4.10), diabetes medication use (orals only vs. no medications HR 2.20, 95%CI 1.28-3.76, any insulin vs. no medications HR 3.00, 95%CI 1.71-5.28), macroalbuminuria (ACR ≥300mg/g vs. <30mg/g HR 1.95, 95%CI 1.23-3.07), and poorer cognitive function (per 1 lower race-specific standard deviation of the Digit Symbol Substitution Test HR 1.57,

95%CI 1.33-1.84). We did not find any significant effect modification of traditional risk factors by race. In the analysis of novel risk factors, we found additional prognostic factors were 1,5-AG (per 5 μg/mL HR 1.24, 95%CI 1.06-1.45), difficulty with ADLs (HR 1.74, 95%CI 1.22-2.47), difficulty with IADLs (HR 1.45, 95%CI 1.02-2.06), anti-depressant use (HR 1.77, 95%CI 1.07-2.93), and Medicaid insurance (HR 1.97, 95%CI 1.29-3.02). These results suggest that both average glucose and glycemic variability play an important role in identifying those risk of severe hypoglycemia, in addition to the more established risk factors such as kidney function, kidney damage, and poor cognition.

In Chapter 2 (1), we examined the cross-sectional association of a history of severe hypoglycemia with high-sensitivity cardiac troponin T (hs-cTnT), a measure of subclinical myocardial damage, among participants with diagnosed diabetes at ARIC Visit 5. Among individuals without a history of CHD or HF, the prevalence of elevated hs-cTnT was 13% in those without prior severe hypoglycemia and 31% with prior severe hypoglycemia. For those with a history of CHD or HF, the prevalence of elevated hs-cTnT was 29% in those without prior severe hypoglycemia and 70% in those with prior severe hypoglycemia. After adjustment, the association of severe hypoglycemia with elevated hs-cTnT was not statistically significant (PR 1.15, 95%CI 0.89-1.49). These findings suggest that individuals with severe hypoglycemia have a high burden of subclinical myocardial damage, although given the small number with a history of severe hypoglycemia (n=72), it was not clear if this association was fully independent of diabetes characteristics and kidney function.

In Chapter 3, we sought to determine the prospective association of severe hypoglycemia with subtypes of cardiovascular disease and death in the ARIC Study. Among 1209 participants with diabetes, 195 had at least one episode of severe hypoglycemia. During a median of 15 years follow-up, severe hypoglycemia was independently associated with coronary heart disease (HR 2.02, 95%CI 1.27-3.20), all-cause mortality (HR 1.73, 95%CI 1.38-2.17), cardiovascular mortality (HR 1.64, 95%CI 1.15-2.34), and cancer mortality (2.49, 1.46-4.24). The absence of association of severe hypoglycemia with stroke, heart failure, atrial fibrillation, and an apparent but not statistically significant association with peripheral artery disease (HR 1.55, 95%CI 0.86-2.80) suggested that severe hypoglycemia was specifically related to the development of cardiovascular outcomes that were more atherosclerotic in nature. Since few other studies have examined the subtypes of cardiovascular disease, future studies are needed to confirm these findings and to determine if severe hypoglycemia is associated with subclinical measures of atherosclerosis, such as coronary artery calcium and carotid intima-media thickness.

In Chapter 4, we aimed to thoroughly investigate the association of severe hypoglycemia with rigorously measured cognitive outcomes, including brain volume. Severe hypoglycemia was strongly associated with dementia in both cross-sectional (OR 2.35, 95%CI 1.05-5.35) and prospective analyses (HR 2.44, 95% CI 1.70-3.49). A history of severe hypoglycemia was also associated with smaller total brain volume (-0.309 SDs, 95%CI: -0.612, -0.006) and with 15-year cognitive decline (-0.20 SD, 95%CI -0.39, -0.01). These findings demonstrate

that hypoglycemia is a strong marker of poor cognitive outcomes, but given that cognitive decline has a long trajectory before dementia, it remains possible that cognitive decline may contribute to the incidence of severe hypoglycemia.

Implications for Glycemic Control in Older Adults

Current Guidelines for Glycemic Control in Older Adults

Recommendations for glycemic targets in older adults with diabetes differ across medical societies in the U.S. and Europe, although they all recommend individualizing treatment based on patient characteristics and preferences (2). The American Diabetes Association (ADA) and the American Geriatrics Society (AGS) have three tiers for recommended glycemic targets (**Tables 1 & 2**), while the European Diabetes Working Party for Older People has two tiers (3-5). The European Diabetes Working Party for Older People's two tiers include one for individuals without major comorbidities, for whom the HbA1c target is 7.0-7.5%, and the other for frail patients, for whom the HbA1c target is 7.6-8.5%. In contrast, the three tiers of the ADA and AGS are 1) healthy, 2) those with moderate comorbidities, and 3) those with end-stage diseases, and while the HbA1c targets are generally similar for each group, there are substantial differences in how each group is defined.

The AGS defines "healthy" individuals as those with "newly diagnosed" diabetes, few comorbidities or geriatric syndromes, and at least 10 years life expectancy; they also explicitly note that few older adults with diabetes meet these criteria (4). In contrast, the ADA defines "healthy" as those with few comorbidities and intact cognitive and physical functioning, but does not mention

diabetes duration (3). For these “healthy” groups, the AGS HbA1c target is 7.0-7.5%, while the ADA HbA1c target is <7.5%. It is important to note that the ADA HbA1c target does not have a lower limit, in contrast to the AGS target’s lower limit of 7.0%. The AGS specifically mentions that there is potential harm to lowering the HbA1c below 6.5% (5), whereas the ADA states that “[p]atients who can be expected to live long enough to reap the benefits of long-term intensive diabetes management, who have good cognitive and physical function, and who choose to do so via shared decision making may be treated using therapeutic interventions and goals similar to those for younger adults with diabetes” (3). This highlights the difference in approaches between the AGS and the ADA: the ADA is more amenable to aggressive glucose treatment in older adults, whereas the AGS highlights the dangers of aggressive glucose treatment.

The intermediate groups for both the AGS and ADA are characterized by some comorbidities and moderate remaining life expectancy, which the AGS defines as 5-10 years, and the ADA does not define. A major difference between the two organizations’ intermediate groups is that the ADA guidelines include individuals with IADL difficulties or “mild-to-moderate cognitive impairment” in the intermediate group, whereas the AGS guidelines classify those individuals in the poor health group. The HbA1c targets are similar despite these differences in grouping individuals: <8.0% by ADA and 7.5-8.0% by AGS.

The poor health groups are characterized by the presence of numerous comorbidities, end-stage diseases, and/or short life expectancy (<5 years by AGS). The AGS guidelines also include individuals with “any functional or

cognitive impairments," while the ADA guidelines include individuals with "moderate-to-severe cognitive impairments" or "2+ ADL dependencies." The HbA1c targets for these groups are <8.5% by ADA and 8.0-9.0% by AGS. Thus, while the labels for the three groups are similar between ADA and AGS, there is substantial discordance in the characteristics of each group, with the AGS generally classifying more people in the poorer health groups.

Although they differ in the operationalization of individualized glycemic targets, the medical societies all agree on the fundamental reasons for personalizing treatment in older adults. In brief, randomized clinical trials have robustly shown that lower HbA1c targets directly cause higher rates of hypoglycemia (2). At the same time, the benefits of more intensive glucose treatment are minimal for cardiovascular mortality (the primary cause of death among older adults with diabetes), and the benefits for clinical microvascular events, such as kidney failure, take a decade or more to accrue (2). Thus, individuals with limited or moderate life expectancy may not benefit from intensive glucose treatment (6).

However, this current conceptualization is one-dimensional: it seems to assume that the glycemic target is the primary driver of hypoglycemia risk, and thus by shifting the HbA1c target higher, the hypoglycemia risk is minimized to approximately balance with the benefits of glycemic control. Indeed, the ADA's official recommendation with respect to hypoglycemia states: "Hypoglycemia should be avoided in older adults with diabetes. It should be assessed and managed by adjusting glycemic targets and pharmacologic interventions" (grade

B evidence) (3). There are no other risk factors mentioned for hypoglycemia in the AGS guidelines, and the only risk factors the ADA mentions are “insulin deficiency necessitating insulin therapy,” “progressive renal insufficiency,” and “unidentified cognitive deficits causing difficulty with self-care activities” (3). These factors are not specifically incorporated into the framework for glycemic targets described above, only mentioned briefly with a statement that “glycemic targets and pharmacologic interventions may need to be adjusted to accommodate for the changing needs of the older adult” (3). Thus, there is no formal structure for identifying risk of hypoglycemia in older adults.

Improving Assessment of Hypoglycemia Risk and Implications for Glycemic Control Guidelines

We identified numerous factors that were associated with increased risk of hypoglycemia, including older age, black race, poor glycemic control, glycemic variability, insulin use, macroalbuminuria, Medicaid insurance, poor cognitive function, and functional impairments. Several other factors have inconclusive evidence and deserve further study, including low BMI, cancer, anti-depressant use, depression, and beta-blocker use (7-10). Some of these hypoglycemia risk factors overlap with known predictors of mortality, such as older age and functional impairments, and potentially also low BMI and cancer (11-13). However, there are other factors that increase risk of death, such as male sex, but do not increase risk of hypoglycemia (7-13). The differences and similarities in predictors of hypoglycemia and mortality risk should be fully explored.

I think that the guidelines should consider the use of a two-dimensional framework for glycemic control in older adults, with one axis for risk of hypoglycemia, and the other axis for expected benefit of glycemic control given life expectancy. Particularly for individuals currently in the “intermediate” health group, there could be a wide range in the absolute risk of hypoglycemia, depending on an individual’s age, race, and types of comorbidities. This would likely require the adoption of risk equations for both hypoglycemia and life expectancy among older adults with diabetes.

There are currently several research groups working on hypoglycemia risk prediction models for clinical use (14,15). Their models are primarily based on data from electronic health records and range from complex (with over 100 variables) to simple (with only 6 variables). The complex model, developed at the Veterans Affairs, are designed to be programmed into the electronic health record and calculated by the computer, showing only the result (predicted hypoglycemia risk in one year) to the provider (14). By contrast, the simple model, developed by Andy Karter at Kaiser Permanente Northern California, has 6 variables for ease of use by clinicians: number of previous hypoglycemia episodes, insulin use, sulfonylurea use, age, chronic kidney disease stage, and number of prior emergency department visits (for any reason) (15). This model is designed to discriminate between high, medium, and low risk individuals, but does not provide absolute risk estimates. These models are still in development, and it remains to be seen which models become used in clinical practice and adopted into clinical practice guidelines.

In contrast, there seems to be little momentum to quantify life expectancy among older adults with diabetes. There are several published equations estimating the probability of 4-14 year survival (11-13) that were developed in the general population. However, I am not aware of any evaluations of these equations' calibration or discrimination specifically among patients with diabetes. Mortality prediction equations among patients with diabetes may be beneficial because they could incorporate other diabetes-specific metrics, such as glycemic control and duration of diabetes, which would likely improve discrimination.

In addition, the importance of shared decision-making for individualizing glycemic targets cannot be overlooked (16-17). Because the HbA1c target for older adults depends on balancing the potential risks and benefits of glycemic control, which are generally poorly quantified, patient preferences are important in determining the appropriate target for each patient. Research on clinical decision aids is ongoing and is an important component of clinical implementation of individualized glycemic targets (17).

Complex Relationship of HbA1c and Hypoglycemia

It is important to distinguish between target (goal) HbA1c and achieved HbA1c when considering HbA1c and hypoglycemia risk. The only scenarios in which we explicitly know both the target and the achieved HbA1c are randomized clinical trials of HbA1c targets, namely ACCORD, ADVANCE, and VADT. An analysis by Miller and colleagues of the ACCORD trial data provide the definitive study on this topic (10). They showed that among individuals in the intensive treatment arm (HbA1c target <6.0%), there was a linear relationship between the

most recent observed HbA1c and hypoglycemia risk: individuals with higher HbA1c had higher incidence rates of hypoglycemia. In contrast, among individuals in the standard treatment arm (HbA1c target 7.0-7.9%), there was a slight J-shaped relationship between most recent HbA1c and hypoglycemia risk. The authors concluded that individuals who are having trouble meeting their HbA1c goal should not have their treatment repeatedly intensified, as this appears to increase risk of hypoglycemia.

In epidemiologic cohort studies, we do not know the target HbA1c; we only observe the achieved HbA1c. However, similar to the standard arm of the ACCORD trial, an observational study by Lipska and colleagues found a J-shaped relationship between HbA1c and hypoglycemia risk, which was substantially attenuated and became marginally not statistically significant after adjustment for demographics and comorbidities (18). The highest risk groups were those with HbA1c <6% and HbA1c ≥9%; there was almost no difference in risk in the range of 6.0% to 8.9% after adjustment.

In contrast, we found only a graded increase in hypoglycemia risk with higher average glycemia. However, we lacked power to look at the low end of the glycemic range. In our study, the lowest tertile of fructosamine was <296μmol/L, roughly equivalent to an HbA1c of 7%, and so it is possible that there is heterogeneity of hypoglycemia risk within this group that we were not able to examine. Thus, while our work re-iterates the importance of high glycemia as a risk factor for hypoglycemia, the absence of a J-shaped association in our study should not be used to argue that the J-shaped association does not exist.

The importance of the increased risk of hypoglycemia with high HbA1c cannot be understated. Currently, ADA clinical guidelines state that to reduce hypoglycemia risk, the HbA1c target should be raised (3). However, for individuals with an HbA1c ≥9% who are at highest risk of hypoglycemia, raising their HbA1c goal from <7% to 8% without substantially changing their medications may not reduce their risk of severe hypoglycemia.

Future research is needed to determine whether the majority of severe hypoglycemic episodes occur among individuals with low (<6%) or high (≥9%) HbA1c, and how this might vary by age group. For example, it is possible that given the high prevalence of poor control in younger age groups (19), the majority of severe hypoglycemic events in younger adults occur among individuals with high HbA1c, whereas among older adults, low HbA1c is more common and thus the majority of hypoglycemia events occur among those with low HbA1c. These results would have implications for approaches to reduce the burden of hypoglycemia. If the majority of hypoglycemia events occur among individuals with high HbA1c, then increasing their HbA1c target may not be enough to reduce hypoglycemia risk; other medications or methods to reduce glycemic variability, for example, might be necessary. In contrast, if the majority of hypoglycemic episodes occur among individuals whose HbA1c <6%, then reducing their medications and allowing the HbA1c to increase to a higher target of 7.0-8.0% might be appropriate and productive towards reducing severe hypoglycemia rates.

Importance of Screening for Cognitive and Functional Impairments

Our work underscores the importance of screening for cognitive and functional impairments to help prevent hypoglycemia. Our results suggest that mild cognitive deficits occurring at earlier ages (50s and 60s) can contribute to increased risk of severe hypoglycemia. Our findings are consistent with results from observational re-analyses of the intensive vs standard treatment arms in the landmark ACCORD-MIND and ADVANCE trials which also linked cognitive scores in middle-age to subsequent hypoglycemia (20,21).

Current ADA clinical guidelines recommend annual screening for cognitive impairment among older adults with diabetes (3). Because mild cognitive impairment is a relatively new clinical construct, increased awareness about its identification, prognosis, and clinical importance may be needed (22). Additionally, while the ADA guidelines recommend the use of either the Mini-Mental Status Exam (MMSE) or the Montreal Cognitive Assessment (MoCA), the MoCA has been found to be much more sensitive for mild cognitive impairment compared to the MMSE (which was designed as a rule-out test for dementia) (23,24). Thus, with respect to identifying cognitive deficits that may impair diabetes self-care, the MoCA is likely a better screening test, and the MMSE would not add any value (25). Further research is needed to understand the specific association of the MoCA score with risk of hypoglycemia.

Since we found that hypoglycemia is a strong predictor of subsequent dementia, a comprehensive cognitive evaluation may also be warranted following an episode of severe hypoglycemia, even in middle-aged adults. Since an

episode of severe hypoglycemia is a strong risk factor for subsequent hypoglycemia (7,8), it is important to consider any possible cognitive deficits when deciding diabetes treatments to prevent future hypoglycemia.

While we found that functional impairments (difficulties with IADLs or ADLs) was associated with increased risk of hypoglycemia, there are currently no formal recommendations on the assessment of functional impairments in older adults with diabetes in the ADA clinical guidelines. The guidelines recommend prioritizing screening for diabetes complications that could lead to functional impairments, but do not address functional impairments directly (3,26). It is worth considering whether the addition of screening for IADL and ADL difficulties would help identify potential difficulties with diabetes self-care that would increase risk of hypoglycemia.

Clinical Utility of Severe Hypoglycemia as a Cardiovascular Risk Marker

Among individuals with type 2 diabetes, severe hypoglycemia is a strong marker of poor prognosis. Severe hypoglycemia is strongly associated with coronary heart disease, mortality, and dementia and these associations do not appear to be explained by other commonly considered risk factors. For clinical practice and for future research, this utility of hypoglycemia as a risk marker has several implications.

Severe hypoglycemia should be considered a marker of increased cardiovascular risk among patients with type 2 diabetes. To guide statin and antiplatelet treatment in adults with diabetes, current ADA clinical guidelines

name several cardiovascular risk factors in patients with diabetes (LDL cholesterol >100 mg/dL, hypertension, smoking, chronic kidney disease, albuminuria, and family history of premature atherosclerotic cardiovascular disease). Adding a history of severe hypoglycemia to this list of cardiovascular risk factors in the ADA clinical guidelines may help draw attention to the strong prognostic value of severe hypoglycemia. An important new direction for research is to formally evaluate whether adding severe hypoglycemia to cardiovascular risk prediction scores improves discrimination in persons with diabetes.

Additionally, future studies should evaluate whether a policy to re-evaluate and optimize cardiovascular risk factor management immediately following an episode of severe hypoglycemia would result in a reduction of cardiovascular events. These studies would need to carefully consider the competing risk of death and the treatment burden among older adults who may already be experiencing negative side effects of polypharmacy.

As the evidence mounts for improved cardiovascular outcomes with newer glucose-lowering agents such GLP-1 receptor agonists and SGLT-2 inhibitors (27), it may also be worth considering reducing medications that have high risk of hypoglycemia (insulin and sulfonylureas) and replacing them with medications that have lower hypoglycemia risk and possible cardiovascular benefits. For the first time in 2017, the ADA clinical guidelines included a recommendation to consider adding these new agents for individuals with pre-existing cardiovascular disease to reduce mortality risk. It should be evaluated whether individuals with a

history of severe hypoglycemia would also benefit from these medications, given their increased risk of coronary heart disease and cardiovascular mortality.

Future Research on Hypoglycemia

Future Epidemiologic Studies on Severe Hypoglycemia

There is clearly additional work needed to fully understand severe hypoglycemia. A standard set of risk factors for hypoglycemia should be developed, as well as risk prediction tools that provide clinical utility in discriminating between those at high vs. low risk of severe hypoglycemia. Additional outcomes following severe hypoglycemia should also be examined, in particular, other markers of subclinical cardiovascular disease, falls and fractures, and car crashes. The timing of cognitive decline and hypoglycemia needs to be clarified to fully understand the potential bi-directional relationship. Finally, a full picture of the relationships of general vulnerability and risk of hypoglycemia is needed to determine the causal contribution of hypoglycemia to all-cause mortality. Specifically, studies examining the association of the frailty phenotype and its components with severe hypoglycemia may help clarify whether declining physiologic reserve is an underlying cause of both severe hypoglycemia and mortality.

Implications for Future Epidemiologic Research on Severe Hypoglycemia

Our findings have important implications for the design of future studies on severe hypoglycemia. The observed 28% three-year cumulative mortality

following an episode of severe hypoglycemia shows that there is a substantial selection pressure after severe hypoglycemia. Indeed, we found that subsequent cardiovascular events and mortality were most likely to occur in the one year following the severe hypoglycemic episode. For research, this suggests that individuals with a history of severe hypoglycemia (e.g, any episodes in the last ten years) are different than those with incident severe hypoglycemia (e.g., within the past month), because they have survived the initially high mortality following severe hypoglycemia. Thus, studies that define hypoglycemia at baseline as any individuals with a history of severe hypoglycemia are likely to have a “prevalent case bias,” a type of left truncation that has been previously described in other topic areas of epidemiology, including occupational epidemiology, HIV epidemiology, and perinatal epidemiology (28-30). When studying the association of severe hypoglycemia with subsequent health outcomes, the bias is most likely towards the null because those with prevalent severe hypoglycemia are not representative: they are healthier than those who have already died. This potential bias is of crucial importance and should be considered in the study design for future epidemiologic research on hypoglycemia. Researchers should prioritize study designs that use incident rather than prevalent cases of severe hypoglycemia. In practice, this will require using hypoglycemia as a time-varying exposure in survival analyses, and for cross-sectional studies, measuring the other covariates as close in time to the hypoglycemic event as possible.

Continuous Glucose Monitoring – The Future of Hypoglycemia Research?

Continuous glucose monitoring (CGM) shows great promise for clarifying the importance of both mild and severe episodes of hypoglycemia (31). CGM measures interstitial glucose every few minutes and can provide alerts if the glucose concentration is too low. CGMs can provide average glucose, time spent in an ideal range, time spent in hyperglycemia, time spent in hypoglycemia, area under the curve, and many metrics of glycemic variability. Currently, the relationship of severe hypoglycemia with mild hypoglycemia is unclear, and it is unknown whether individuals with severe hypoglycemia are also suffering frequent and possibly unidentified episodes of mild hypoglycemia. Additionally, the long-term significance of mild hypoglycemia (55-70mg/dL) is unclear, with one study surprisingly showing it to have a protective effect (9,32). Research is needed to clarify the association of mild hypoglycemia with microvascular and macrovascular complications.

CGM should also be able to clarify the associations of hypoglycemia, glycemic variability, and long-term outcomes. Since we found, similar to other studies, that higher glycemic variability as assessed by the novel biomarker 1,5-AG was associated with increased risk of severe hypoglycemia, it is important to clarify whether it is hypoglycemia or glycemic variability that is associated with long-term outcomes, or both (33,34). While there is ongoing debate on whether glycemic variability itself should become a treatment target (31,35), it is clear that CGMs will be able to quantify hypoglycemia in terms of glucose concentrations

and duration in ways that have not previously been done in research of hypoglycemia in type 2 diabetes.

Interventions to Reduce Hypoglycemia

Currently, patient-level interventions are being designed to reduce hypoglycemia in older adults by reducing insulin doses and adding non-insulin agents (36). In a pilot study without a control arm, the researchers found that the number of minutes spent in mild hypoglycemia (blood glucose <70mg/dL, as measured by CGM) decreased significant with the intervention. However, because they only included individuals who had mild hypoglycemia during a 5-day baseline evaluation, it is possible that the results are due to regression to the mean. They did not assess episodes of severe hypoglycemia, and larger studies with a control arm will be needed to assess the efficacy of this intervention for severe and mild hypoglycemia. Because of the rarity of severe hypoglycemia (1-2 events per 100 people with type 2 diabetes per year, (37,38)), it will be difficult to design a trial large enough to determine if an intervention that reduced the incidence of severe hypoglycemia would also reduce the incidence of coronary heart disease or death.

At a system level, the U.S. Department of Veterans Affairs began the Hypoglycemia Safety Initiative in 2014 to prevent hypoglycemia among high-risk individuals (39). An evaluation of this initiative in several New England hospitals found that the clinical reminder built into the electronic health record and other educational materials reduced the number of patients defined as overtreated

(A1c <7% with use of insulin or sulfonylureas and either age 75+ or dementia) over an 18-month period. It is not yet clear whether this intervention reduced the number of severe hypoglycemic events or other associated health outcomes.

Summary

This dissertation evaluated risk factors and health outcomes associated with severe hypoglycemia in a community-based population of persons with type 2 diabetes. We showed that independent risk factors for severe hypoglycemia include poor glycemic control, glycemic variability as measured by 1,5-AG, macroalbuminuria, age, black race, disability, and poor cognition. The novel findings for 1,5-AG and disability suggest new areas of research to investigate whether these indicators could be useful to improve hypoglycemia risk prediction. We also demonstrated that severe hypoglycemia was associated with both subclinical myocardial damage as well as increased risk of coronary heart disease, but not other types of cardiovascular disease, suggesting that hypoglycemia may contribute to vascular risk via cardiac ischemia and/or atherosclerotic-specific mechanisms. Our preliminary investigation into the risk of hypoglycemia among patients with cancer suggested that diabetes patients with rapidly failing health may be at increased risk of hypoglycemia; this topic merits further study. Additionally, we documented a high burden of mild cognitive impairment and dementia, as well as smaller brain volume, among older adults with a history of severe hypoglycemia. Ultimately, these studies show that hypoglycemia is a strong marker of poor prognosis, a potential contributor to

vascular risk, and reinforce the need to develop and test novel interventions to reduce hypoglycemia and evaluate if such interventions can reduce the burden of vascular disease and cognitive outcomes in persons with type 2 diabetes.

Table 1. ADA Framework for Glycemic Targets in Older Adults

Patient Characteristics	Rationale	Reasonable A1c Goal
Healthy *All of the following:* • Few other chronic diseases* • Intact cognitively • Normal physical function	Longer remaining life expectancy	<7.5%
Complex/Intermediate *Any of the following:* • Multiple chronic diseases* • Mild-to-moderate cognitive impairments • 2+ IADL impairments	Intermediate remaining life expectancy, high treatment burden, hypoglycemia vulnerability, fall risk	<8.0%
Very complex/poor health *Any of the following:* • In long-term care facility (nursing home) • End-stage chronic illnesses** • Moderate-to-severe cognitive impairments • 2+ ADL impairments	Limited remaining life expectancy makes benefit uncertain	<8.5%
*Chronic diseases are serious enough to require medications or lifestyle management and may include arthritis, cancer, congestive heart failure, depression, emphysema, falls, hypertension, incontinence, stage 3 or worse chronic kidney disease, myocardial infarction, and stroke. 'Multiple' means at least three. **End-stage chronic illnesses include stage 3-4 congestive heart failure, oxygen-dependent lung disease, kidney disease requiring dialysis, or uncontrolled metastatic cancer. Adopted from ADA Standards of Medical Care in Diabetes, 2017, Table 11.1 (3)		

Table 2. AGS Framework for Glycemic Targets in Older Adults

Patient Characteristics	Reasonable A1c Target	Comments
Healthy *All of the following:* • Newly diagnosed diabetes • Little comorbidity • Long life expectancy (>10 years) • Few established vascular complications	7.0 - 7.5%	Few adults >65 years of age meet these criteria. There is potential harm in lowering HbA1c to <6.5%
Moderate health • Moderate comorbidities • Moderate life expectancy (5 -10 years)	7.5 – 8.0%	This is the majority of older adults. Metformin should be used unless contraindicated, and medications should not be used to achieve HbA1c <7.5%.
Poor health • Multiple comorbidities • Functional or cognitive impairments • Short life expectancy (<5 years, includes most nursing home residents)	8.0 – 9.0%	
Adopted from American Geriatrics Society Guidelines, 2013, and AGS "Choosing Wisely" Campaign (4,5)		

References for Introduction

1. 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.
2. Cryer PE. The barrier of hypoglycemia in diabetes. *Diabetes*. 2008;57(12):3169-3176.
3. International Hypoglycaemia Study Group. Glucose Concentrations of Less Than 3.0 mmol/L (54 mg/dL) Should Be Reported in Clinical Trials: A Joint Position Statement of the American Diabetes Association and the European Association for the Study of Diabetes. *Diabetes Care*. 2017;40(1):155-157.
4. Woerle HJ, Meyer C, Popa EM, Cryer PE, Gerich JE. Renal Compensation for Impaired Hepatic Glucose Release During Hypoglycemia in Type 2 Diabetes Further Evidence for Hepatorenal Reciprocity. *Diabetes*. 2003;52:1386-1392.
5. Leese GP, Wang J, Broomhall J, et al. Frequency of Severe Hypoglycemia Requiring Emergency Treatment in Type 1 and Type 2 Diabetes. *Diabetes Care*. 2003;26(4):1176-1180.
6. Donnelly L a., Morris a. D, Frier BM, et al. Frequency and predictors of hypoglycaemia in Type 1 and insulin-treated Type 2 diabetes: A population-based study. *Diabet Med*. 2005;22(6):749-755.
7. Inzucchi SE, Bergenstal RM, Buse JB, et al. Management of hyperglycemia in type 2 diabetes, 2015: a patient-centered approach: Update to a position statement of the American Diabetes Association and the European Association for the Study of Diabetes. *Diabetes Care*. 2015;38:140-149.
8. American Diabetes Association. Standards of Medical Care in Diabetes--2017. *Diabetes Care*. 2017;40(Supplement 1).
9. Marchesini G, Veronese G, Forlani G, Forlani G, Ricciardi LM, Fabbri A. The management of severe hypoglycemia by the emergency system: The HYPOTHESIS study. *Nutr Metab Cardiovasc Dis*. 2014;24(11):1181-1188.
10. Bonds DE, Kurashige EM, Bergenstal R, et al. Severe hypoglycemia monitoring and risk management procedures in the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial. *Am J Cardiol*. 2007;99(12A):80i-89i.
11. Akram K, Pedersen-Bjergaard U, Carstensen B, Borch-Johnsen K, Thorsteinsson B. Prospective and retrospective recording of severe hypoglycemia, and assessment of hypoglycemia awareness in insulin-treated Type 2 diabetes. *Diabet Med*. 2009;26(12):1306-1307.
12. Ginde AA, Blanc PG, Lieberman RM, Camargo CA. Validation of ICD-9-CM coding algorithm for improved identification of hypoglycemia visits. *BMC Endocr Disord*. 2008;8:4.

13. Veronese G, Marchesini G, Forlani G, Fabbri A. Are severe hypoglycemic episodes in diabetes correctly identified by administrative data? Evidence of underreporting from the HYPOTHESIS study. *Acta Diabetol*. 2016.
14. 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.
15. Akram K, Pedersen-Bjergaard U, Borch-Johnsen K, Thorsteinsson B. Frequency and risk factors of severe hypoglycemia in insulin-treated type 2 diabetes: a literature survey. *J Diabetes Complications*. 2006;20:402-408.
16. Frier BM. Hypoglycaemia in diabetes mellitus: epidemiology and clinical implications. *Nat Rev Endocrinol*. 2014;10(12):711-722.
17. 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.
18. UK Hypoglycemia Study Group. Risk of hypoglycaemia in types 1 and 2 diabetes: effects of treatment modalities and their duration. *Diabetologia*. 2007;50(6):1140-1147.
19. Pistrosch F, Hanefeld M. Hypoglycemia and Cardiovascular Disease: Lessons from Outcome Studies. *Curr Diab Rep*. 2015;15(12):117.
20. Elliott L, Fidler C, Ditchfield A, Stissing T. Hypoglycemia Event Rates: A Comparison Between Real-World Data and Randomized Controlled Trial Populations in Insulin-Treated Diabetes. *Diabetes Ther*. 2016.
21. The ACCORD Study Group. Action to Control Cardiovascular Risk in Diabetes (ACCORD) Trial: Design and Methods. *Am J Cardiol*. 2007;99(12A):S21-S33.
22. 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.
23. Lipska KJ, Yao X, Herrin J, et al. Trends in Drug Utilization, Glycemic Control, and Rates of Severe Hypoglycemia, 2006–2013. *Diabetes Care*. 2016;(3):dc160985.
24. Müller N, Lehmann T, Gerste B, et al. Increase in the incidence of severe hypoglycaemia in people with Type 2 diabetes in spite of new drugs: analysis based on health insurance data from Germany. *Diabet Med*. 2017;38(1):42-49.
25. Karter AJ, Laiteerapong N, Chin MH, et al. Ethnic Differences in Geriatric Conditions and Diabetes Complications Among Older, Insured Adults With Diabetes: The Diabetes and Aging Study. *J Aging Health*. 2015;27(5):894-918.
26. Karter AJ, Lipska KJ, O'Connor PJ, et al. High rates of severe hypoglycemia among African American patients with diabetes: the surveillance, prevention, and Management of Diabetes Mellitus (SUPREME-DM) network. *J Diabetes Complications*. 2017;31(5):869–873.

27. Miller ME, Bonds DE, Gerstein HC, et al. The effects of baseline characteristics, glycaemia treatment approach, and glycated haemoglobin concentration on the risk of severe hypoglycaemia: post hoc epidemiological analysis of the ACCORD study. *BMJ*. 2010;340:b5444.
28. Ginde A a, Espinola JA, Camargo C a. Trends and Disparities in U.S. Emergency Department Visits for Hypoglycemia, 1993-2005. *Diabetes Care*. 2008;31(3):511-513.
29. Diamantidis CJ, Seliger SL, Zhan M, et al. A varying patient safety profile between black and nonblack adults with decreased estimated GFR. *Am J Kidney Dis*. 2012;60(1):47-53.
30. Lipska KJ, Warton EM, Huang ES, et al. HbA1c and risk of severe hypoglycemia in type 2 diabetes : the diabetes and aging study. *Diabetes Care*. 2013;36(11):3535-3542.
31. Hodge M, McArthur E, Garg AX, Tangri N, Clemens KK. Hypoglycemia Incidence in Older Adults by Estimated GFR. *Am J Kidney Dis*. 2017:1-10.
32. Cahn A, Raz I, Mosenzon O, et al. Predisposing Factors for Any and Major Hypoglycemia With Saxagliptin Versus Placebo and Overall: Analysis From the SAVOR-TIMI 53 Trial. *Diabetes Care*. 2016;39(8):1329-1337.
33. Parrinello CM, Rastegar I, Godino JG, Miedema MD, Matsushita K, Selvin E. Prevalence of and Racial Disparities in Risk Factor Control in Older Adults With Diabetes: The Atherosclerosis Risk in Communities Study. *Diabetes Care*. 2015:dc150016..
34. Selvin E, Parrinello CM, Sacks DB, Coresh J. Trends in prevalence and control of diabetes in the United States, 1988-1994 and 1999-2010. *Ann Intern Med*. 2014;160(8):517-525.
35. Parsa A, Kao WHL, Xie D, et al. *APOL1* Risk Variants, Race, and Progression of Chronic Kidney Disease. *N Engl J Med*. 2013;369(23):2183-2196.
36. McClellan W. Racial Differences in the Prevalence of Chronic Kidney Disease among Participants in the Reasons for Geographic and Racial Differences in Stroke (REGARDS) Cohort Study. *J Am Soc Nephrol*. 2006;17(6):1710-1715.
37. Berkowitz SA, Karter AJ, Lyles CR, et al. Low socioeconomic status is associated with increased risk for hypoglycemia in diabetes patients: the Diabetes Study of Northern California (DISTANCE). *J Health Care Poor Underserved*. 2014;25(2):478-490.
38. Seligman HK, Bolger AF, Guzman D, L??pez A, Bibbins-Domingo K. Exhaustion of food budgets at month's end and hospital admissions for hypoglycemia. *Health Aff*. 2014;33(1):116-123.
39. Seligman HK, Jacobs EA, Lopez A, Sarkar U, Tschann J, Fernandez A. Food Insecurity and Hypoglycemia Among Safety Net Patients with Diabetes. *Arch Intern Med*. 2011;171(13):1204-1205.
40. Kaufman JS, Cooper RS, McGee DL. Socioeconomic status and health in blacks and whites: the problem of residual confounding and the resiliency of race. *Epidemiology*. 1997;8(6):621-628.

41. 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.
42. Bruce DG, Davis W a., Casey GP, et al. Severe hypoglycaemia and cognitive impairment in older patients with diabetes: The Fremantle Diabetes Study. *Diabetologia*. 2009;52(9):1808-1815.
43. Yaffe K, Falvey CM, Hamilton N, et al. Association between hypoglycemia and dementia in a biracial cohort of older adults with diabetes mellitus. *JAMA Intern Med*. 2013;173(14):1300-1306.
44. Prinz N, Stingl J, Dapp A, et al. High rate of hypoglycemia in 6770 type 2 diabetes patients with comorbid dementia: A multicenter cohort study on 215,932 patients from the German/Austrian diabetes registry. *Diabetes Res Clin Pract*. 2015:1-9.
45. Feil DG, Rajan M, Soroka O, Tseng CL, Miller DR, Pogach LM. Risk of hypoglycemia in older veterans with dementia and cognitive impairment: Implications for practice and policy. *J Am Geriatr Soc*. 2011;59(12):2263-2272.
46. Murata GH, Hoffman RM, Shah JH, Wendel CS, Duckworth WC. A Probabilistic Model for Predicting Hypoglycemia in Type 2 Diabetes Mellitus: The Diabetes Outcomes in Veterans Study (DOVES). *Arch Intern Med.* 2004;164(13):1445-1450.
47. Klimontov VV, Myakina NE. Glucose variability indices predict the episodes of nocturnal hypoglycemia in elderly type 2 diabetic patients treated with insulin. *Diabetes Metab Syndr*. 2016:8-13.
48. Kovatchev B, Cobelli C. Glucose Variability: Timing, Risk Analysis, and Relationship to Hypoglycemia in Diabetes. *Diabetes Care*. 2016;39:502-510.
49. 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.
50. Punthakee Z, Miller ME, Launer LJ, et al. Poor cognitive function and risk of severe hypoglycemia in type 2 diabetes: post hoc epidemiologic analysis of the ACCORD trial. *Diabetes Care*. 2012;35(4):787-793.
51. Schneider ALC, Gottesman RF, Mosley T, et al. Cognition and incident dementia hospitalization: Results from the atherosclerosis risk in communities study. *Neuroepidemiology*. 2013;40(2):117-124.
52. 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.
53. Abdelhafiz AH, McNicholas E, Sinclair AJ. Hypoglycemia, frailty and dementia in older people with diabetes: Reciprocal relations and clinical implications. *J Diabetes Complications*. 2016;30(8):1548-1554.
54. Idler E, Benyamini Y. Self-Rated Health and Mortality: A Review of Twenty-Seven Community Studies. *J Health Soc Behav*. 1997;38(1), 21-37.

55. Corti MC, Guralnik JM, Salive ME, Sorkin JD. Serum albumin level and physical disability as predictors of mortality in older persons. *J Am Med Assoc*. 1994;272(13):1036-1042.
56. The Emerging Risk Factors Collaboration. C-reactive protein concentration and risk of coronary heart disease, stroke, and mortality: an individual participant meta-analysis. *Lancet*. 2010;375(9709):132-140.
57. Wright RJ, Frier BM. Vascular disease and diabetes: is hypoglycaemia an aggravating factor? *Diabetes Metab Res Rev*. 2014;24(5):353-363.
58. Frier BM, Schernthaner G, Heller SR. Hypoglycemia and Cardiovascular Risks. *Diabetes Care*. 2011;34:S132-S137.
59. Chow E, Bernjak A, Williams S, et al. Risk of cardiac arrhythmias during hypoglycemia in patients with type 2 diabetes and cardiovascular risk. *Diabetes*. 2014;63(5):1738-1747.
60. Stahn A, Pistrosch F, Ganz X, et al. Relationship between hypoglycemic episodes and ventricular arrhythmias in patients with type 2 diabetes and cardiovascular diseases: Silent hypoglycemias and silent arrhythmias. *Diabetes Care*. 2014;37(2):516-520.
61. Desouza C V., Bolli GB, Fonseca V. Hypoglycemia, diabetes, and cardiovascular events. *Diabetes Care*. 2010;33(6):1389-1394.
62. Ratter JM, Rooijackers HMM, Tack CJ, et al. Pro-inflammatory Effects of Hypoglycemia in Humans with or without Diabetes. *Diabetes*. 2017;66(April):db161091.
63. Jialal I, Dhindsa S. Hypoglycemia and the predisposition to cardiovascular disease: Is the pro-inflammatory-pro-coagulant diathesis a plausible explanation? *Atherosclerosis*. 2016;251:504-506.
64. 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.
65. 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.
66. Khunti K, Davies M, Majeed A, Thorsted BL, Wolden ML, Paul SK. Hypoglycemia and Risk of Cardiovascular Disease and All-Cause Mortality in Insulin-Treated People With Type 1 and Type 2 Diabetes: A Cohort Study. *Diabetes Care*. 2015;38(2):316-322.
67. Mellbin LG, Rydén L, Riddle MC, et al. Does hypoglycaemia increase the risk of cardiovascular events? A report from the ORIGIN trial. *Eur Heart J*. 2013;29(24):3137-3144.
68. Hsu PF, Sung SH, Cheng HM, et al. Association of clinical symptomatic hypoglycemia with cardiovascular events and total mortality in type 2 diabetes: A nationwide population-based study. *Diabetes Care*. 2013;36(4):894-900.

69. Goto A, Goto M, Terauchi Y, Yamaguchi N, Noda M. Association Between Severe Hypoglycemia and Cardiovascular Disease Risk in Japanese Patients With Type 2 Diabetes. *J Am Heart Assoc*. 2016;5(3):e002875.
70. Leong A, Berkowitz SA, Triant VA, et al. Hypoglycemia in diabetes mellitus as a coronary artery disease risk factor in patients at elevated vascular risk. *J Clin Endocrinol Metab*. 2015;101(2):659-668.
71. Gruden G, Barutta F, Chaturvedi N, et al. Severe hypoglycemia and cardiovascular disease incidence in type 1 diabetes: The EURODIAB prospective complications study. *Diabetes Care*. 2012;35(7):1598-1604.
72. Warren RE, Frier BM. Hypoglycaemia and cognitive function. *Diabetes, Obes Metab*. 2005;7(5):493-503.
73. Kang E, Jeon S, Choi S, Song C, Yu I. Diffusion MR Imaging of Hypoglycemic Encephalopathy. *Am J Neuroradiol*. 2010;31:559-564.
74. Lo L, Tan C, Umapathi T, Lim C. Diffusion-Weighted MR Imaging in Early Diagnosis and Prognosis of Hypoglycemia. *Am J Neuroradiol*. 2006;27:1222-1224.
75. Ma J, Kim Y-J, Yoo W, et al. MR imaging of hypoglycemic encephalopathy: lesion distribution and prognosis prediction by diffusion-weighted imaging. *Neuroradiology*. 2009;51(10):641-649.
76. Mattishent K, Loke YK. Bi-directional interaction between hypoglycaemia and cognitive impairment in elderly patients treated with glucose-lowering agents: a systematic review and meta-analysis. *Diabetes Obes Metab*. 2016;18(2):135-141.
77. Feinkohl I, Aung PP, Keller M, et al. Severe hypoglycemia and cognitive decline in older people with type 2 diabetes: The edinburgh type 2 diabetes study. *Diabetes Care*. 2014;37(2):507-515.
78. 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.
79. Lin CH, Sheu WHH. Hypoglycaemic episodes and risk of dementia in diabetes mellitus: 7-year follow-up study. *J Intern Med*. 2013;273(1):102-110.
80. Mehta HB, Mehta V, Goodwin JS. Association of Hypoglycemia With Subsequent Dementia in Older Patients With Type 2 Diabetes Mellitus. *Journals Gerontol Ser A Biol Sci Med Sci*. 2016;0(0):glw217.
81. Chin SO, Rhee SY, Chon S, et al. Hypoglycemia is associated with dementia in elderly patients with type 2 diabetes mellitus: An analysis based on the Korea National Diabetes Program Cohort. *Diabetes Res Clin Pract*. 2016;122:54-61.
82. 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.
83. Zhang Z, Lovato J, Battapady H, et al. Effect of Hypoglycemia on Brain Structure in People With Type 2 Diabetes: Epidemiological Analysis of the ACCORD-MIND MRI Trial. *Diabetes Care*. 2014;37(12):3279-3285.

84. Lee AK, McEvoy JW, Hoogeveen RC, Ballantyne CM, Selvin E. Severe Hypoglycemia and Elevated High-Sensitivity Cardiac Troponin T in Older Adults With Diabetes. *J Am Coll Cardiol*. 2016;68(12):1370-1371.

References for Chapter 1

1. Laiteerapong N, Karter AJ, Liu JY, et al. Correlates of quality of life in older adults with diabetes: the diabetes & aging study. *Diabetes Care*. 2011;34(8):1749-1753.
2. 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.
3. 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.
4. 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.
5. American Diabetes Association. Standards of Medical Care in Diabetes--2017. *Diabetes Care*. 2017;40(Supplement 1).
6. Miller ME, Bonds DE, Gerstein HC, et al. The effects of baseline characteristics, glycaemia treatment approach, and glycated haemoglobin concentration on the risk of severe hypoglycaemia: post hoc epidemiological analysis of the ACCORD study. *BMJ*. 2010;340:b5444.
7. Yun J, Ko S, Ko S, et al. Cardiovascular Disease Predicts Severe Hypoglycemia in Patients with Type 2 Diabetes. *Diabetes Metab*. 2015:39(6):498-506.
8. 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.
9. Karter AJ, Laiteerapong N, Chin MH, et al. Ethnic Differences in Geriatric Conditions and Diabetes Complications Among Older, Insured Adults with Diabetes: The Diabetes and Aging Study. *J Aging Health*. 2015:27(5):894-918
10. Karter AJ, Lipska KJ, O'Connor PJ, et al. High rates of severe hypoglycemia among African American patients with diabetes: the surveillance, prevention, and Management of Diabetes Mellitus (SUPREME-DM) network. *J Diabetes Complications*. 2017:31(5); 869–873.
11. Cruz-Jentoft AJ, Carpena-Ruiz M, Montero-Errasquín B, Sánchez-Castellano C, Sánchez-García E. Exclusion of older adults from ongoing clinical trials about type 2 diabetes mellitus. *J Am Geriatr Soc*. 2013;61(5):734-738.
12. ARIC Investigators. The Atherosclerosis Risk in Communities (ARIC) Study: Design And Objectives. *Am J Epidemiol*. 1989;129(4):687-702.
13. Levey AS, Stevens LA, Schmid CH, et al. A New Equation to Estimate Glomerular Filtration Rate. *Ann Intern Med*. 2009;150(9):604-612.

14. Punthakee Z, Miller ME, Launer LJ, et al. Poor Cognitive Function and Risk of Severe Hypoglycemia in Type 2 Diabetes. *Diabetes Care*. 2012;35(4):787-793.
15. Pathak R, Schroeder EB, Seaquist ER, et al. Severe Hypoglycemia in a Large Cohort of Adults with Diabetes Mellitus Treated in U. S. Integrated Health Care Delivery Systems, 2005-2011. *Diabetes Care*. 2016;39(3):363-370.
16. Derijks HJ, Heerdink ER, De Koning FH, Janknegt R, Klungel OH, Egberts AC. The association between antidepressant use and hypoglycaemia in diabetic patients: a nested case-control study. *Pharmacoepidemiol Drug Saf*. 2008;17(4):336-344.
17. McIntyre RS, Soczynska JK, Konarski JZ, Kennedy SH. The effect of antidepressants on glucose homeostasis and insulin sensitivity: synthesis and mechanisms. *Expert Opin Drug Saf*. 2006;5(1):157-168.
18. Gerich JE. The genetic basis of type 2 diabetes mellitus: Impaired insulin secretion versus impaired insulin sensitivity. *Endocr Rev*. 1998;19(4):491-503.
19. Cryer PE. The barrier of hypoglycemia in diabetes. *Diabetes*. 2008;57(12):3169-3176.
20. Lee AK, McEvoy JW, Hoogeveen RC, Ballantyne CM, Selvin E. Severe Hypoglycemia and Elevated High-Sensitivity Cardiac Troponin T in Older Adults With Diabetes. *J Am Coll Cardiol*. 2016;68(12):1370-1371.
21. Klimontov VV, Myakina NE. Glucose variability indices predict the episodes of nocturnal hypoglycemia in elderly type 2 diabetic patients treated with insulin. *Diabetes Metab Syndr Clin Res Rev*. 2016. 10.1016/j.dsx.2016.08.023 Accessed April 19, 2017.
22. Qu Y, Jacober SJ, Zhang Q, Wolka LL, DeVries JH. Rate of hypoglycemia in insulin-treated patients with type 2 diabetes can be predicted from glycemic variability data. *Diabetes Technol Ther*. 2012;14(11):1008-1012.
23. Ginde A, Blanc PG, Lieberman RM, Camargo C. Validation of ICD-9-CM coding algorithm for improved identification of hypoglycemia visits. *BMC Endocr Disord*. 2008;8:4.
24. Leese GP, Wang J, Broomhall J, et al. Frequency of Severe Hypoglycemia Requiring Emergency Treatment in Type 1 and Type 2 Diabetes. *Diabetes Care*. 2003;26(4):1176-1180.
25. Lipska KJ, Warton EM, Huang ES, et al. HbA1c and risk of severe hypoglycemia in type 2 diabetes: the diabetes and aging study. *Diabetes Care*. 2013;36(11):3535-3542.
26. 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.
27. Green AJ, Fox KM, Grandy S. Self-reported hypoglycemia and impact on quality of life and depression among adults with type 2 diabetes mellitus. *Diabetes Res Clin Pract*. 2012;96(3):313-318.

28. Kikuchi Y, Iwase M, Fujii H, et al. Association of severe hypoglycemia with depressive symptoms in patients with type 2 diabetes: the Fukuoka Diabetes Registry. *BMJ Open Diabetes Res Care*. 2015;3(1):e000063.
29. Bruce DG, Davis W a., Casey GP, et al. Severe hypoglycaemia and cognitive impairment in older patients with diabetes: The Fremantle Diabetes Study. *Diabetologia*. 2009;52(9):1808-1815.
30. Yaffe K, Falvey CM, Hamilton N, et al. Association between hypoglycemia and dementia in a biracial cohort of older adults with diabetes mellitus. *JAMA Intern Med*. 2013;173(14):1300-1306.
31. Sawicki PT, Siebenhofer A. Betablocker treatment in diabetes mellitus. *J Intern Med*. 2001;250(1):11-17.
32. Braak EW, Appelman AM, van de Laak M, Stolk RP, van Haeften TW, Erkelens DW. Clinical characteristics of type 1 diabetic patients with and without severe hypoglycemia. *Diabetes Care*. 2000;23(10):1467-1471.
33. Cahn A, Raz I, Mosenzon O, et al. Predisposing Factors for Any and Major Hypoglycemia with Saxagliptin Versus Placebo and Overall: Analysis From the SAVOR-TIMI 53 Trial. *Diabetes Care*. 2016:39(8):1329-1337.
34. Yun JS, Ko SH, Ko SH, et al. Presence of macroalbuminuria predicts severe hypoglycemia in patients with type 2 diabetes: a 10-year follow-up study. *Diabetes Care*. 2013;36(5):1283-1289.
35. Hodge M, McArthur E, Garg AX, Tangri N, Clemens KK. Hypoglycemia Incidence in Older Adults by Estimated GFR. *Am J Kidney Dis*. 2017;70(1):59-68.
36. Davis TME, Brown SGA, Jacobs IG, Bulsara M, Bruce DG, Davis WA. Determinants of severe hypoglycemia complicating type 2 diabetes: The Fremantle diabetes study. *J Clin Endocrinol Metab*. 2010;95(5):2240-2247.
37. Lipska KJ, Ross JS, Miao Y, Shah ND, Lee SJ, Steinman MA. Potential Overtreatment of Diabetes Mellitus in Older Adults with Tight Glycemic Control. *JAMA Intern Med*. 2015;175(3):356-362.
38. Thorpe CT, Gellad WF, Good CB, et al. Tight glycemic control and use of hypoglycemic medications in older veterans with type 2 diabetes and comorbid dementia. *Diabetes Care*. 2015;38(4):588-595.
39. Caverly TJ, Fagerlin A, Zikmund-Fisher BJ, et al. Appropriate Prescribing for Patients with Diabetes at High Risk for Hypoglycemia. *JAMA Intern Med*. 2015:175(12):1994-1996.
40. Muhlbacher A, Bethge S. What matters in type 2 diabetes mellitus oral treatment? A discrete choice experiment to evaluate patient preferences. *Eur J Heal Econ*. 2016;17:1125-1140.
41. Rodriguez-Gutierrez R, Gionfriddo MR, Ospina NS, et al. Shared decision making in endocrinology: present and future directions. *Lancet Diabetes Endocrinol*. 2016;4:706-716.

References for Chapter 2

1. Goto A, Arah OA, Goto M, Terauchi Y, Noda M. Severe hypoglycaemia and cardiovascular disease: systematic review and meta-analysis with bias analysis. *BMJ* 2013;347:f4533.
2. Saunders JT, Nambi V, de Lemos JA, et al. Cardiac troponin T measured by a highly sensitive assay predicts coronary heart disease, heart failure, and mortality in the Atherosclerosis Risk in Communities Study. *Circulation* 2011;123:1367–76.
3. Ginde AA, Blanc PG, Lieberman RM, Camargo MA. Validation of ICD-9-CM coding algorithm for improved identification of hypoglycemia visits. *BMC Endocr Disord* 2008;8:4.
4. Gore MO, Seliger SL, deFilippi CR, et al. Age- and sex-dependent upper reference limits for the high-sensitivity cardiac troponin T assay. *J Am Coll Cardiol* 2014;63:1441–8.
5. 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;36:1384–95.

References for Chapter 3

1. Goto A, Goto M, Terauchi Y, Yamaguchi N, Noda M. Association Between Severe Hypoglycemia and Cardiovascular Disease Risk in Japanese Patients With Type 2 Diabetes. *J Am Heart Assoc*. 2016;5(3):e002875.
2. Leong A, Berkowitz SA, Triant VA, et al. Hypoglycemia in diabetes mellitus as a coronary artery disease risk factor in patients at elevated vascular risk. *J Clin Endocrinol Metab*. 2015:101(2);659-668.
3. Khunti K, Davies M, Majeed A, Thorsted BL, Wolden ML, Paul SK. Hypoglycemia and Risk of Cardiovascular Disease and All-Cause Mortality in Insulin-Treated People With Type 1 and Type 2 Diabetes: A Cohort Study. *Diabetes Care*. 2015;38(2):316-322.
4. Mellbin LG, Rydén L, Riddle MC, et al. Does hypoglycaemia increase the risk of cardiovascular events? A report from the ORIGIN trial. *Eur Heart J*. 2013;29(24):3137-3144.
5. Pistrosch F, Hanefeld M. Hypoglycemia and Cardiovascular Disease: Lessons from Outcome Studies. *Curr Diab Rep*. 2015;15(12):117.
6. 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.
7. International Hypoglycaemia Study Group. Glucose Concentrations of Less Than 3.0 mmol/L (54 mg/dL) Should Be Reported in Clinical Trials: A Joint Position Statement of the American Diabetes Association and the European Association for the Study of Diabetes. *Diabetes Care*. 2017;40(1):155-157.
8. 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.
9. Lipska KJ, Warton EM, Huang ES, et al. HbA1c and risk of severe hypoglycemia in type 2 diabetes: the diabetes and aging study. *Diabetes Care*. 2013;36(11):3535-3542.
10. Miller ME, Bonds DE, Gerstein HC, et al. The effects of baseline characteristics, glycaemia treatment approach, and glycated haemoglobin concentration on the risk of severe hypoglycaemia: post hoc epidemiological analysis of the ACCORD study. *BMJ*. 2010;340:b5444.
11. Hsu PF, Sung SH, Cheng HM, et al. Association of clinical symptomatic hypoglycemia with cardiovascular events and total mortality in type 2 diabetes: A nationwide population-based study. *Diabetes Care*. 2013;36(4):894-900.
12. Frier BM, Schernthaner G, Heller SR. Hypoglycemia and Cardiovascular Risks. *Diabetes Care*. 2011;34(Supplement 2): S132-S137.
13. Chow E, Bernjak A, Williams S, et al. Risk of cardiac arrhythmias during hypoglycemia in patients with type 2 diabetes and cardiovascular risk. *Diabetes*. 2014;63(5):1738-1747.
14. Stahn A, Pistrosch F, Ganz X, et al. Relationship between hypoglycemic episodes and ventricular arrhythmias in patients with type 2 diabetes and

cardiovascular diseases: Silent hypoglycemias and silent arrhythmias. *Diabetes Care*. 2014;37(2):516-520.
15. Jialal I, Dhindsa S. Hypoglycemia and the predisposition to cardiovascular disease: Is the pro-inflammatory-pro-coagulant diathesis a plausible explanation? *Atherosclerosis*. 2016;251:504-506.
16. Cruz-Jentoft AJ, Carpena-Ruiz M, Montero-Errasquín B, Sánchez-Castellano C, Sánchez-García E. Exclusion of older adults from ongoing clinical trials about type 2 diabetes mellitus. *J Am Geriatr Soc*. 2013;61(5):734-738.
17. ARIC Investigators. The Atherosclerosis Risk In Communities (ARIC) Study: Design And Objectives. *Am J Epidemiol.* 1989;129(4):687-702.
18. Ginde A a, Blanc PG, Lieberman RM, Camargo CA. Validation of ICD-9-CM coding algorithm for improved identification of hypoglycemia visits. *BMC Endocr Disord*. 2008;8:4.
19. Rosamond WD, Chang PP, Baggett C, et al. Classification of Heart Failure in the Atherosclerosis Risk in Communities (ARIC) Study: a Comparison of Diagnostic Criteria. *Circ Hear Fail*. 2012;5(2):152-159.
20. Alonso A, Agarwal SK, Soliman EZ, et al. Incidence of atrial fibrillation in whites and African-Americans: The Atherosclerosis Risk in Communities (ARIC) study. *Am Heart J*. 2009;158(1):111-117.
21. Levey AS, Stevens LA, Schmid CH, et al. A new equation to estimate glomerular filtration rate. Ann Intern Med. 2009;150(9):604-612.
22. The ACCORD Study Group. Action to Control Cardiovascular Risk in Diabetes (ACCORD) Trial: Design and Methods. *Am J Cardiol*. 2007;99(12A):S21-S33.
23. Howlader N, Noone AM, Krapcho M, Miller D, Bishop K, Kosary CL, Yu M, Ruhl J, Tatalovich Z, Mariotto A, Lewis DR, Chen HS, Feuer EJ, Cronin KA (eds). SEER Cancer Statistics Review, 1975-2014, National Cancer Institute. Bethesda, MD, https://seer.cancer.gov/csr/1975_2014/, Accessed Apr 24, 2017.
24. Fizazi K, Greco FA, Pavlidis N, Daugaard G, Oien K, Pentheroudakis G. Cancers of unknown primary site: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol*. 2015;26(Supplement 5):v133-v138.
25. Mertens AJ, Sweeney C, Shahar E, Rosamond WD, Folsom AR. Physical activity and breast cancer incidence in middle-aged women: A prospective cohort study. *Breast Cancer Res Treat.* 2006;97(2):209-214.
26. Prizment AE, Anderson KE, Visvanathan K, Folsom AR. Inverse Association of Eosinophil Count with Colorectal Cancer Incidence: Atherosclerosis Risk in Communities Study. *Cancer Epidemiol Biomarkers Prev*. 2011;20(9):1861-1864.
27. Bedenis R, Price AH, Robertson CM, et al. Association Between Severe Hypoglycemia, Adverse Macrovascular Events, and Inflammation in the Edinburgh Type 2 Diabetes Study. *Diabetes Care*. 2014;37(12):3301-3308.

28. Zhao Y, Campbell CR, Fonseca V, Shi L. Impact of hypoglycemia associated with antihyperglycemic medications on vascular risks in veterans with type 2 diabetes. *Diabetes Care*. 2012;35(5):1126-1132.
29. 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.
30. McCoy RG, Van Houten HK, Ziegenfuss JY, Shah ND, Wermers RA., Smith SA. Increased Mortality of Patients With Diabetes Reporting Severe Hypoglycemia. *Diabetes Care*. 2012;35(9):1897-1901.

References for Chapter 4

1. American Diabetes Association. Standards of Medical Care in Diabetes--2017. *Diabetes Care*. 2017;40(Supplement 1).
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.
3. Mattishent K, Loke YK. Bi-directional Interaction Between Hypoglycaemia And Cognitive Impairment In Elderly Patients Treated with Glucose Lowering Agents: Systematic Review and Meta-analysis. *Diabetes Obes Metab*. 2015.
4. Yaffe K, Falvey CM, Hamilton N, et al. Association between hypoglycemia and dementia in a biracial cohort of older adults with diabetes mellitus. *JAMA Intern Med*. 2013;173(14):1300-1306.
5. Punthakee Z, Miller ME, Launer LJ, et al. Poor cognitive function and risk of severe hypoglycemia in type 2 diabetes: post hoc epidemiologic analysis of the ACCORD trial. *Diabetes Care*. 2012;35(4):787-793.
6. 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.
7. Bruce DG, Davis WA, Casey GP, et al. Severe hypoglycaemia and cognitive impairment in older patients with diabetes: The Fremantle Diabetes Study. *Diabetologia*. 2009;52(9):1808-1815.
8. Prinz N, Stingl J, Dapp A, et al. High rate of hypoglycemia in 6770 type 2 diabetes patients with comorbid dementia: A multicenter cohort study on 215,932 patients from the German/Austrian diabetes registry. *Diabetes Res Clin Pract*. 2015:1-9.
9. Whitmer RA, 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.
10. Lin CH, Sheu WHH. Hypoglycaemic episodes and risk of dementia in diabetes mellitus: 7-year follow-up study. *J Intern Med*. 2013;273(1):102-110.
11. Feinkohl I, Aung PP, Keller M, et al. Severe hypoglycemia and cognitive decline in older people with type 2 diabetes: The Edinburgh type 2 diabetes study. *Diabetes Care*. 2014;37(2):507-515.
12. 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.
13. Warren RE, Frier BM. Hypoglycaemia and cognitive function. *Diabetes, Obes Metab*. 2005;7(5):493-503.
14. Cryer PE. The barrier of hypoglycemia in diabetes. *Diabetes*. 2008;57(12):3169-3176.

15. Kang E, Jeon S, Choi S, Song C, Yu I. Diffusion MR Imaging of Hypoglycemic Encephalopathy. *Am J Neuroradiol*. 2010;31:559-564.
16. Lo L, Tan C, Umapathi T, Lim C. Diffusion-Weighted MR Imaging in Early Diagnosis and Prognosis of Hypoglycemia. *Am J Neuroradiol*. 2006;27:1222-1224.
17. Ma J, Kim Y-J, Yoo W, et al. MR imaging of hypoglycemic encephalopathy: lesion distribution and prognosis prediction by diffusion-weighted imaging. *Neuroradiology*. 2009;51(10):641-649.
18. Fanelli CG, Porcellati F, Pampanelli S, Bolli GB. Insulin therapy and hypoglycaemia: The size of the problem. *Diabetes Metab Res Rev*. 2004;20(SUPPL. 2):32-42.
19. Tsujimoto T, Yamamoto-Honda R, Kajio H, et al. Vital signs, QT prolongation, and newly diagnosed cardiovascular disease during severe hypoglycemia in type 1 and type 2 diabetic patients. *Diabetes Care*. 2014;37(1):217-225.
20. Marchesini G, Veronese G, Forlani G, Forlani G, Ricciardi LM, Fabbri A. The management of severe hypoglycemia by the emergency system: The HYPOTHESIS study. *Nutr Metab Cardiovasc Dis*. 2014;24(11):1181-1188.
21. ARIC Investigators. The Atherosclerosis Risk In Communities (ARIC) Study: Design And Objectives. *Am J Epidemiol*. 1989;129(4):687-702.
22. Ginde AA, Blanc PG, Lieberman RM, Camargo CA. Validation of ICD-9-CM coding algorithm for improved identification of hypoglycemia visits. *BMC Endocr Disord*. 2008;8:4.
23. Gross AL, Power MC, Albert MS, et al. Application of Latent Variable Methods to the Study of Cognitive Decline When Tests Change over Time. *Epidemiology*. 2015;26(6):878-887.
24. Knopman DS, Griswold ME, Lirette ST, et al. Vascular Imaging abnormalities and cognition: Mediation by cortical volume in nondemented individuals: Atherosclerosis risk in communities-neurocognitive study. *Stroke*. 2015;46(2):433-440.
25. Knopman DS, Gottesman RF, Sharrett AR, et al. Mild cognitive impairment and dementia prevalence: The Atherosclerosis Risk in Communities Neurocognitive Study. *Alzheimer's Dement Diagnosis, Assess Dis Monit*. 2016;2:1-11.
26. 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.
27. Miller ME, Bonds DE, Gerstein HC, et al. The effects of baseline characteristics, glycaemia treatment approach, and glycated haemoglobin concentration on the risk of severe hypoglycaemia: post hoc epidemiological analysis of the ACCORD study. *BMJ*. 2010;340:b5444.
28. Leese GP, Wang J, Broomhall J, et al. Frequency of Severe Hypoglycemia Requiring Emergency Treatment in Type 1 and Type 2 Diabetes. *Diabetes Care*. 2003;26(4):1176-1180. doi:10.2337/diacare.26.4.1176.

29. ARIC Investigators. ARIC Visit 5/NCS Analysis Manual. Available at: https://www2.cscc.unc.edu/aric/sites/default/files/public/listings/V5%20NCS%20Analysis%20Manual_150901%20v1.pdf. Accessed June 3, 2017.
30. Rawlings AM, Sharrett a. R, Schneider ALC, et al. Diabetes in Midlife and Cognitive Change Over 20 Years. *Ann Intern Med*. 2014;161(11):785.
31. Zhang Z, Lovato J, Battapady H, et al. Effect of Hypoglycemia on Brain Structure in People With Type 2 Diabetes: Epidemiological Analysis of the ACCORD-MIND MRI Trial. *Diabetes Care*. 2014;37(12):3279-3285.
32. Weuve J, Proust-Lima C, Power MC, et al. Guidelines for reporting methodological challenges and evaluating potential bias in dementia research. *Alzheimer's Dement*. 2015;11(9):1098-1109.
33. Schneider ALC, Gottesman RF, Mosley T, et al. Cognition and incident dementia hospitalization: Results from the atherosclerosis risk in communities study. *Neuroepidemiology*. 2013;40(2):117-124.
34. Julayanont P, Nasreddine ZS. Chapter 7: Montreal Cognitive Assessment (MoCA): Concept and Clinical Review. In: *Cognitive Screening Instruments*; 2016:139-195.
35. Nasreddine ZS, Phillips NA, Bedirian V, et al. The Montreal Cognitive Assessment, MoCA : A Brief Screening Tool for Mild Cognitive Impairment. *J Am Geriatr Soc*. 2005;53:695-699.
36. Sarkar U, Lyles C, Steinman M, et al. Changes in Medication Use After Dementia Diagnosis in an Observational Cohort of Individuals with Diabetes Mellitus. *J Am Geriatr Soc*. 2017;65(1):77-82.
37. Huang ES. Management of diabetes mellitus in older people with comorbidities. *BMJ*. 2016;353:i2200.
38. Lipska KJ, Ross JS, Miao Y, Shah ND, Lee SJ, Steinman M a. Potential overtreatment of diabetes mellitus in older adults with tight glycemic control. *JAMA Intern Med*. 2015;175(3):356-362.
39. Thorpe CT, Gellad WF, Good CB, et al. Tight glycemic control and use of hypoglycemic medications in older veterans with type 2 diabetes and comorbid dementia. *Diabetes Care*. 2015;38(4):588-595.
40. Tseng C-L, Soroka O, Maney M, Aron DC, Pogach LM. Assessing Potential Glycemic Overtreatment in Persons at Hypoglycemic Risk. *JAMA Intern Med*. 2014;174(2):259.
41. McCoy RG, Lipska KJ, Yao X, Ross JS, Montori VM, Shah ND. Intensive Treatment and Severe Hypoglycemia Among Adults With Type 2 Diabetes. *JAMA Intern Med*. 2016:1-9.
42. Munshi MN, Slyne C, Segal AR, Saul N, Lyons C, Weinger K. Simplification of Insulin Regimen in Older Adults and Risk of Hypoglycemia. *JAMA Intern Med*. 2016:176(7):1023-1025.
43. Sussman JB, Kerr EA, Saini SD, et al. Rates of Deintensification of Blood Pressure and Glycemic Medication Treatment Based on Levels of Control and Life Expectancy in Older Patients With Diabetes Mellitus. *JAMA Intern Med*. 2015;175(12):1942-1949.
44. Cryer PE. Hypoglycemia, functional brain failure, and brain death. *J Clin Invest*. 2007;117(4):868-870.

45. Auer RN, Siesjo BK. Hypoglycaemia: brain neurochemistry and neuropathology. *Baillieres Clin Endocrinol Metab*. 1993;7(3):611-625.
46. Stern Y. Cognitive reserve in ageing and Alzheimer's disease. *Lancet Neurol*. 2012;11:1006-1012.
47. Fratiglioni L, Paillard-Borg S, Winblad B. An active and socially integrated lifestyle in late life might protect against dementia. *Lancet Neurol*. 2004;3(6):343-353.
48. Green AJ, Fox KM, Grandy S. Self-reported hypoglycemia and impact on quality of life and depression among adults with type 2 diabetes mellitus. *Diabetes Res Clin Pract*. 2012;96(3):313-318.
49. Diniz BS, Butters M a., Albert SM, Dew M a., Reynolds CF. Late-life depression and risk of vascular dementia and Alzheimer's disease: systematic review and meta-analysis of community-based cohort studies. *Br J Psychiatry*. 2013;202(5):329-335.
50. Leiter L, Yale J, Chiasson J, Harris S, Kleinstiver P, Sauriol L. Assessment of the impact of fear of hypoglycemic episodes on glycemic and hypoglycemia management. *Can J Diabetes*. 2005;29(3):1-7.
51. Wild D, von Maltzahn R, Brohan E, Christensen T, Clauson P, Gonder-Frederick L. A critical review of the literature on fear of hypoglycemia in diabetes: Implications for diabetes management and patient education. *Patient Educ Couns*. 2007;68(1):10-15.

References for Conclusion

1. Lee AK, McEvoy JW, Hoogeveen RC, Ballantyne CM, Selvin E. Severe Hypoglycemia and Elevated High-Sensitivity Cardiac Troponin T in Older Adults With Diabetes. *J Am Coll Cardiol*. 2016;68(12):1370-1371.
2. Huang ES. Management of diabetes mellitus in older people with comorbidities. *BMJ*. 2016;353:i2200.
3. American Diabetes Association. Standards of Medical Care in Diabetes--2017. *Diabetes Care*. 2017;40(Supplement 1).
4. AGS Choosing Wisely Workgroup. American Geriatrics Society Identifies Five Things That Healthcare Providers and Patients Should Question. *J Am Geriatr Soc*. 2013;61:622-631.
5. American Geriatrics Society Expert Panel on the Care of Older Adults with Diabetes Mellitus. Guidelines abstracted from the American Geriatrics Society guidelines for improving the care of older adults with diabetes mellitus: 2013 update. *J Am Geriatr Soc*. 2013;61:2020-2026.
6. Huang ES, Zhang Q, Gandra N, Chin MH, Meltzer DO. The effect of comorbid illness and functional status on the expected benefits of intensive glucose control in older patients with type 2 diabetes: A decision analysis. *Ann Intern Med*. 2008;149:11-19.
7. Davis TME, Brown SGA, Jacobs IG, Bulsara M, Bruce DG, Davis WA. Determinants of severe hypoglycemia complicating type 2 diabetes: The Fremantle diabetes study. *J Clin Endocrinol Metab*. 2010;95(5):2240-2247.
8. Bruce DG, Davis W a., Casey GP, et al. Severe hypoglycaemia and cognitive impairment in older patients with diabetes: The Fremantle Diabetes Study. *Diabetologia*. 2009;52(9):1808-1815.
9. 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.
10. Miller ME, Bonds DE, Gerstein HC, et al. The effects of baseline characteristics, glycaemia treatment approach, and glycated haemoglobin concentration on the risk of severe hypoglycaemia: post hoc epidemiological analysis of the ACCORD study. *BMJ*. 2010;340:b5444.
11. Schonberg M a, Davis RB, McCarthy EP, Marcantonio ER. Index to predict 5-year mortality of community-dwelling adults aged 65 and older using data from the National Health Interview Survey. *J Gen Intern Med*. 2009;24(10):1115-1122. doi:10.1007/s11606-009-1073-y.
12. Schonberg MA, Li V, Marcantonio ER, Davis RB, McCarthy EP. Predicting Mortality up to 14 Years Among Community-Dwelling Adults Aged 65 and Older. *J Am Geriatr Soc*. 2017.
13. Lee SJ, Lindquist K, Segal MR, Covinsky KE. Development and validation of a prognostic index for 4-year mortality in older adults. *Jama*. 2006;295(7):801-808.
14. Miller D. VA Hypoglycemia Prediction Model. In: *American Diabetes Association Conference*. San Diego; 2017.

15. Karter AJ. Kaiser Permanente Hypoglycemia Prediction Model. In: *American Diabetes Association Conference*. San Diego; 2017.
16. Tamhane S, Rodriguez-Gutierrez R, Hargraves I, Montori VM. Shared Decision-Making in Diabetes Care. *Curr Diab Rep*. 2015;15(12). doi:10.1007/s11892-015-0688-0.
17. Rodriguez-Gutierrez R, Gionfriddo MR, Ospina NS, et al. Shared decision making in endocrinology: present and future directions. *Lancet Diabetes Endocrinol*. 2016;4:706-716. doi:10.1016/S2213-8587(15)00468-4.
18. Lipska KJ, Warton EM, Huang ES, et al. HbA1c and risk of severe hypoglycemia in type 2 diabetes: the diabetes and aging study. *Diabetes Care*. 2013;36(11):3535-3542.
19. Selvin E, Parrinello CM, Sacks DB, Coresh J. Trends in prevalence and control of diabetes in the United States, 1988-1994 and 1999-2010. *Ann Intern Med*. 2014;160(8):517-525.
20. 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.
21. Punthakee Z, Miller ME, Launer LJ, et al. Poor cognitive function and risk of severe hypoglycemia in type 2 diabetes: post hoc epidemiologic analysis of the ACCORD trial. *Diabetes Care*. 2012;35(4):787-793.
22. Petersen RC, Caracciolo B, Brayne C, Gauthier S, Jelic V, Fratiglioni L. Mild cognitive impairment: A concept in evolution. *J Intern Med*. 2014;275(3):214-228.
23. Nasreddine ZS, Phillips NA, Bedirian V, et al. The Montreal Cognitive Assessment, MoCA : A Brief Screening Tool for Mild Cognitive Impairment. *J Am Geriatr Soc*. 2005;53:695-699.
24. Julayanont P, Nasreddine ZS. Chapter 7: Montreal Cognitive Assessment (MoCA): Concept and Clinical Review. In: *Cognitive Screening Instruments*.; 2016:139-195.
25. Larner AJ. Screening utility of the Montreal Cognitive Assessment (MoCA): in place of – or as well as – the MMSE? *Int Psychogeriatrics*. 2012;24(3):391-396.
26. Kirkman MS, Briscoe VJ, Clark N, et al. Diabetes in older adults: a consensus report. *J Am Geriatr Soc*. 2012;60(12):2342-2356.
27. Abdul-Ghani M, Defronzo RA, Prato S Del, Chilton R, Singh R, Ryder REJ. Cardiovascular Disease and Type 2 Diabetes: Has the Dawn of a New Era Arrived? *Diabetes Care*. 2017;40:813-820.
28. Applebaum KM, Malloy EJ, Eisen EA. Left Truncation, Susceptibility, and Bias in Occupational Cohort Studies. *Epidemiology*. 2011;22(4):599-606.
29. Schisterman EF, Cole SR, Ye A, Platt RW. Accuracy Loss Due to Selection Bias in Cohort Studies with Left Truncation. *Paediatr Perinat Epidemiol*. 2013;27:491-502.
30. Brookmeyer R, Gail MH. Biases in prevalent cohorts. *Biometrics*. 1987;739-749.

31. Bergenstal R. Glycemic Variability and Diabetes Complications: Does It Matter? Simply Put, There Are Better Glycemic Markers! *Diabetes Care*. 2015;38(8):1610-1614.
32. Hypoglycaemia International Study Group. Minimizing Hypoglycemia in Diabetes. *Diabetes Care*. 2015;38(8):1583-1591.
33. Klimontov VV, Myakina NE. Glucose variability indices predict the episodes of nocturnal hypoglycemia in elderly type 2 diabetic patients treated with insulin. *Diabetes Metab Syndr Clin Res Rev*. 2016. 10.1016/j.dsx.2016.08.023 Accessed April 19, 2017.
34. Kovatchev B, Cobelli C. Glucose Variability: Timing, Risk Analysis, and Relationship to Hypoglycemia in Diabetes. *Diabetes Care*. 2016;39:502-510.
35. Hirsch IB. Glycemic Variability and Diabetes Complications: Does It Matter? Of Course It Does! *Diabetes Care*. 2015;38:1610-1614.
36. Munshi MN, Slyne C, Segal AR, Saul N, Lyons C, Weinger K. Simplification of Insulin Regimen in Older Adults and Risk of Hypoglycemia. *JAMA Intern Med*. 2016;176(7):1023-1025.
37. 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.
38. Leese GP, Wang J, Broomhall J, et al. Frequency of Severe Hypoglycemia Requiring Emergency Treatment in Type 1 and Type 2 Diabetes. *Diabetes Care*. 2003;26(4):1176-1180.
39. Vimalananda VG, Desotto K, Chen T, et al. A Quality Improvement Program to Reduce Potential Overtreatment of Diabetes Among Veterans at High Risk of Hypoglycemia. *Diabetes Spectr*. 2017;(8):1-6.

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Master of Science in Public Health, Epidemiology
Member of Delta Omega (Public Health Honorary Society)

May 2009 — ***Amherst College***
Bachelor of Arts, Music
Rite with Distinction

WORK EXPERIENCE

2015 – present — Johns Hopkins Bloomberg School of Public Health
Research Assistant to Professor Elizabeth Selvin, PhD, MPH, Department of Epidemiology

- Conducted analyses of diabetes incidence rates in ARIC and NHANES using Stata; created figures for talks and publication
- Designed and help implement protocol for peripheral neuropathy exam at ARIC Visit 6; conducted interim quality control analyses

2013 – 2014

California Department of Public Health
California-EIS Fellow, Chronic Disease Control Branch

- Conducted analysis in SAS to examine racial differences in hospital admission after an emergency department visit for diabetes
- Identified data sources appropriate for evaluation of diabetes prevention programs and diabetes self-management programs
- Provided epidemiologic support to program managers

Summer 2013

Children's Healthcare of Atlanta
Research Assistant to Jean Welsh, PhD, MPH, RN

- Conducted analyses in SAS and wrote manuscript on sugar consumption in the National Growth and Health Study

2012 – 2013

Centers for Disease Control and Prevention
Research Associate, Division of Heart Disease and Stroke Prevention

- Used GIS to geo-code locations of clinics and to create county-level maps of mortality rates, clinic locations, and socio-demographic characteristics
- Conducted analyses in SUDAAN of weighted Nielsen Market-Scan database of sodium purchased in grocery stores
- Maintained SAS database on social determinants of health

Summer 2012

University of California San Francisco
Research Assistant

- Utilized SAS to clean and analyze medical and pharmacy claims to determine the efficacy of a stepped-wedge design clinical trial of a telephonic intervention to improve diabetes control

2012 – 2013

Emory University Rollins School of Public Health
Research Assistant to Professor William McClellan, MD, MPH, Department of Epidemiology

- Submitted documentation for IRB approval of data analysis
- Investigated correlation between measures of kidney function (eGFR and ACR) and measures of obesity (BMI and waist circumference) in the REGARDS study using SAS

2010 – 2011

Medical Forefronts Financial Services
Associate

- Created protocols for integration of vendors' services, resulting in an 8% increase in monthly revenue

HONORS AND AWARDS

Sept 2015 – present	Cardiovascular Disease Epidemiology T32 Training Grant
May 2017	The Dorothy and Arthur Samet Student Support Fund in Epidemiology
March 2017	Spring Student Assembly Conference Fund
February 2017	Department of Epidemiology Student Support Travel Fund
March 2016	American Heart Association Epidemiology Council Early Career Travel Award
May 2009	The Psi Upsilon Prize for preeminence in scholarship, leadership, athletics, and character

PUBLICATIONS

Lee AK, Warren BW, Lee CJ, McEvoy JW, Matsushita K, Huang ES, Sharrett AR, Coresh J, Selvin E. The Association of Severe Hypoglycemia with Incident Cardiovascular Events and Mortality in Adults with Type 2 Diabetes (under review at *Diabetes Care*)

Lee AK, Lee CJ, Huang ES, Sharrett AR, Coresh J, Selvin E. Risk Factors for Severe Hypoglycemia in Black and White Older Adults with Diabetes: the Atherosclerosis Risk in Communities (ARIC) Study (in press, *Diabetes Care*)

Selvin E, Wang D, **Lee AK**, Bergenstal RM, Coresh J. Trends in Undiagnosed Diabetes in U.S. Adults Using a Confirmatory Definition (in press, *Annals of Internal Medicine*)

Warren B, Rawlings AM, **Lee AK**, Grams M, Coresh J, Selvin E. Increases in Biomarkers of Hyperglycemia with Age in the Atherosclerosis Risk in Communities Study. *Diabetes Care* 2017;40(8):e96-e97. PMID: 28507023

Lee AK, McEvoy JW, Hoogeveen RC, Ballantyne CM, Selvin E. History of Severe Hypoglycemia and Elevated High Sensitivity Cardiac Troponin T in Older Adults with Diabetes: the Atherosclerosis Risk in Communities (ARIC) Study. *Journal of the American College of Cardiology.* 2016;68(12):1370-1371. PMID: 27634129

Lee AK, Chowdhury R, Welsh JA. Sugars and adiposity: the long-term effects of consuming added and naturally occurring sugars in foods and in beverages. *Obesity Science & Practice*. 2015;1(1):41-49. PMID: 27774248

Lee AK, Schieb LJ, Yuan K, Maalouf J, Gillespie C, Cogswell ME. Sodium Content in Packaged Foods by Census Division in the United States, 2009. *Preventing Chronic Disease*. 2015;12:E43. PMID: 25837256

Quan, J, **Lee AK**, Handley MA, Ratanawongsa N, Sarkar U, Tseng S, Pfiefer K, Schillinger D. Automated Telephone Self-Management Support for Diabetes in a Low-Income Health Plan: A Healthcare Utilization and Cost Analysis. *Population Health Management*. 2015;18(6):412-20. PMID: 26102298

Lee AK, Binongo JNG, Chowdhury R, Stein AD, Gazmararian JA, Vos MB, Welsh JA. Consumption of Less Than 10% of Total Energy from Added Sugars is Associated with Increasing HDL in Females during Adolescence: A Longitudinal Analysis. *Journal of the American Heart Association*. 2014;3(1):e000615. PMID: 24572253

PRESENTATIONS

June 2017	Severe Hypoglycemia and Frailty in Older Adults with Diabetes Moderated Poster presentation at the American Diabetes Association Conference 2017, San Diego, California
June 2017	Large Weight Loss, Cardiovascular Disease, and Mortality: The ADVANCE Trial. Moderated Poster presentation at the American Diabetes Association Conference 2017, San Diego, California
March 2017	Association of Severe Hypoglycemia with Cardiovascular Diseases and All-Cause Mortality in Older Adults with Diabetes. Oral presentation at American Heart Association Epi/Lifestyle Conference 2017, Portland, Oregon
March 2017	Risk Factors for Severe Hypoglycemia in Black and White Older Adults with Diabetes. Poster presentation at American Heart Association Epi/Lifestyle Conference 2017, Portland, Oregon
October 2016	Risk Factors for Severe Hypoglycemia in Black and White Older Adults with Diabetes. Oral presentation at Welch Center Research in Progress, Johns Hopkins Bloomberg School of Public Health, Baltimore, Maryland
June 2016	Racial Differences in Potential Overuse of Glucose-lowering Medication Use among Older Adults. Moderated Poster presentation at American Diabetes Association Conference 2016, New Orleans, Louisiana
April 2016	Racial Differences in Potential Overuse of Glucose-lowering Medication Use among Older Adults. Research on Aging Showcase & Poster Competition, Johns Hopkins Bloomberg School of Public Health, Baltimore, Maryland 2nd prize in graduate student category

March 2016	Severe Hypoglycemia and Prevalence of Cognitive Impairment in Older Adults with Diabetes. Moderated Poster presentation at the American Heart Association Epi/Lifestyle Conference 2016, Phoenix, Arizona
February 2016	Hypoglycemia and Cognitive Function in Older Adults with Diabetes. Oral presentation at Welch Center Research in Progress, Johns Hopkins Bloomberg School of Public Health, Baltimore, Maryland
January 2016	Differences in Potential Overuse of Glucose-lowering Medication Use among Older Adults. Delta Omega poster competition, Johns Hopkins Bloomberg School of Public Health, Baltimore, Maryland
November 2015	Severe Hypoglycemia and Prevalence of Cognitive Impairment in Older Adults with Diabetes. Centennial poster presentation, Johns Hopkins Bloomberg School of Public Health, Baltimore, Maryland
March 2014	Increased Intake of Non-Dairy Sugars in Foods as well as Beverages is Positively Associated with Annual Increases in Waist Circumference Among Overweight and Obese Adolescent Girls. Moderated Poster presentation at the American Heart Association Epi/Lifestyle Conference 2014, San Francisco, California
November 2013	Added Sugars Consumed in Beverages Are Associated with Larger Waist Circumference among Adolescent Females in the NGHS Cohort. Poster presentation at The Obesity Society Conference 2013, Atlanta, Georgia

TEACHING

Fall 2015	Teaching Assistant, Epidemiologic Methods I Johns Hopkins Bloomberg School of Public Health
Sept 2015 – May 2016	Course Coordinator, Welch Center Journal Club Johns Hopkins Bloomberg School of Public Health

MENTORING

June 2016 – present	Caroline Liu, Johns Hopkins undergraduate student
Fall 2016	Nidhi Madan, Johns Hopkins MPH student

PROFESSIONAL ACTIVITIES

2014 – present	Member of American Heart Association, Council of Epidemiology
Nov 2016 – July 2017	Coordinator of the Atherosclerosis Risk in Communities (ARIC) Study Neurocognitive Analysis Workgroup
2015 – present	Member of the Atherosclerosis Risk in Communities (ARIC) Study Neurocognitive Analysis Workgroup
2015 – present	Member of the Atherosclerosis Risk in Communities (ARIC) Study CMS Surveillance Workgroup

EDITORIAL ACTIVITIES

December 2015	Reviewed article for *Neurology*
May 2017	Reviewed article for *JAMA*