UNDERSTANDING HYPOGLYCEMIA FROM POPULATION, INDIVIDUAL, AND BEHAVIORAL PERSPECTIVES

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ABSTRACT

Victor W. Zhong: Understanding hypoglycemia from population, individual, and behavioral perspectives
(Under the direction of Elizabeth J. Mayer-Davis)

Hypoglycemia (blood glucose <70 mg/dL) is a major barrier for achieving normoglycemia in diabetes. Three critical gaps are: i) limited data exist on describing longitudinal incidence of severe hypoglycemia both in patients with type 1 diabetes (T1D) and type 2 diabetes (T2D); ii) the relationship of HbA1c level with risk of severe hypoglycemia in patients with T1D or T2D remains controversial; iii) how usual dietary intake impacts on risk of hypoglycemia in patients with T1D is unclear.

To address first two gaps, we used primary and secondary care data from the Clinical Practice Research Datalink and Hospital Episode Statistics in England. Temporal trends of hypoglycemia requiring hospitalization in adults with T1D (N=23,251) or T2D (N=241,829) from 1998 to 2013 were estimated using joinpoint regression model. By analyzing 1:6 case-control matched dataset using conditional logistic regression models, we investigated the association between HbA1c level and risk of hypoglycemia hospitalization in adults with incident T1D (N=5,776) or T2D (N=163,237). To address the third gap, we applied logistic regression models to identify dietary predictors of non-severe hypoglycemia in 98 T1D adolescents who wore continuous glucose monitor for one week and had two days of 24-hour dietary recalls.

Between 1998 and 2013 in England, the incidence of hypoglycemia hospitalizations

increased both in adults with T1D and T2D. In adults with T1D, compared to HbA1c 7-7.9%, higher HbA1c level was associated with lower risk of hypoglycemia hospitalization while lower HbA1c level did not increase the risk. In adults with T2D, both lower and higher HbA1c level increased hypoglycemia hospitalization risk (i.e., U-shape). In adolescents with T1D, lower risk of daytime non-severe hypoglycemia was related to higher glycemic index of the diet or higher intake of monounsaturated or polyunsaturated fat. Higher intake of soluble fiber or protein was associated with higher risk of daytime and nocturnal non-severe hypoglycemia. Adjusting for insulin dose per kilogram eliminated all these associations.

Practical approaches for hypoglycemia management are urgently needed to reduce the fast growing hypoglycemia burden in England. Applying appropriate HbA1c treatment targets and appropriately matching insulin dose and injection time to freely consumed meals may reduce hypoglycemia risk.

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LIST OF ABBREVIATIONS

ACCORD	Action to Control Cardiovascular Risk in Diabetes
ADA	American Diabetes Association
ADVANCE	Action in Diabetes and Vascular Disease
BMI	body mass index
CDC	Center for Disease Control
CGM	continuous glucose monitor
CI	confidence interval
CPRD	Clinical Practice Research Datalink
DCCT	Diabetes Control and Complications Trial
DPP-4	dipeptidyl peptidase-4
DPV	Diabetes Patienten Verlaufsdokumentation
FL3X	Flexible Lifestyles
GI	glycemic index
GL	glycemic load
GLP-1	glucagon-like peptide-1
HES	Hospital Episode Statistics
ICD-10	international classification of diseases, 10th revision
IRR	incidence rate ratio
ISPAD	International Society for Pediatric and Adolescent Diabetes
MUFA	monounsaturated fat
NCHS	National Center for Health Statistics
NDSR	Nutrient Data System for Research software
NIDDK	National Institute of Diabetes and Digestive and Kidney Diseases
NIH	National Institute of Health
NORC	Nutrition Obesity Research Center
OAD	oral anti-diabetic drug
OR	odds ratio

PDPAR	Previous Day Physical Activity Recall
PUFA	polyunsaturated fat
QOF	Quality and Outcomes Framework
SFA	saturated fat
SGLT-2	sodium-glucose co-transporter-2
UK	United Kingdom
UNC	University of North Carolina
US	United States
UTS	Up To Standard
VADT	Veterans' Administration Diabetes Trial

CHAPTER 1. INTRODUCTION

Background

Hypoglycemia (blood glucose ≤70 mg/dL) is common and can affect up to 60% of patients with type 1 diabetes and 20% of patients with type 2 diabetes within a month. Severe hypoglycemia requires external assistance for recovery and can be fatal. Approximately 88-98% of hypoglycemic events are non-severe that can result in poor quality of life. In spite of tremendous progress in diabetes care in the past few decades, hypoglycemia remains a major barrier that prevents patients with diabetes from maintaining euglycemia, in part due to the following three critical gaps.

First, data that describe longitudinal incidence of hypoglycemia in people with type 1 or type 2 diabetes from a population perspective are limited. During the past few decades, several new anti-diabetic medications for type 2 diabetes have been introduced including inhibitors of dipeptidyl peptidase-4 (DPP-4), inhibitors of sodium-glucose co-transporter-2 (SGLT-2), and glucagon-like peptide-1 (GLP-1) agonists. They are associated with low hypoglycemia risk. Also, new insulin products and new technologies (e.g., insulin pump, continuous glucose monitor (CGM)) may assist in improving glycemic control, particularly for type 1 diabetes. Importantly, diabetes treatment guidelines have recently evolved from emphasizing hyperglycemia management towards recommending individualized glycemic targets to balance long-term glycemic benefits and short-term hypoglycemia risk. It is not known if these changes have led to a reduction in hypoglycemia risk in diabetes, and if the trends of hypoglycemia differ by diabetes type. Second, according to current diabetes guidelines, deciding a person's HbA1c

treatment target may need to consider this individual's hypoglycemia risk factors including age, diabetes duration, comorbidities, current use of anti-diabetic drug(s), life expectancy, and history of hypoglycemia. However, the association between HbA1c level and risk of hypoglycemia remains unclear. It is not known if the association differs by diabetes type or patient hypoglycemia risk factors. Finally, dietary intake is a major determinant of blood glucose concentrations. Current nutrition guidelines have specific recommendations for treating hypoglycemia; glucose, sucrose or any form of carbohydrates are to be immediately administered. However, information regarding whether or how usual dietary intake influences risk of hypoglycemia is limited.

Available data allowed us to study the first two gaps in adults and the third gap in adolescents. To address the first two gaps, we used primary care data from the Clinical Practice Research Datalink (CPRD) in the United Kingdom (UK) and secondary care data from the Hospital Episode Statistics (HES) in England. The CPRD currently includes over 15 million patient records, drawn from more than 680 practices nationwide. The HES is a data warehouse storing records of all patients admitted to National Health Service hospitals in England. The CPRD and HES can be linked via an independent third-party. The large population from the CPRD and HES allowed us to evaluate longitudinal trends of severe hypoglycemia for both type 1 and type 2 diabetes from a population perspective. It also offered an opportunity to determine the relationship between HbA1c level and risk of severe hypoglycemia by diabetes type and evaluate important effect modifications. To address the third gap, we used baseline data from a subset of 258 adolescents with type 1 diabetes from the Flexible Lifestyles (FL3X) randomized trial (ClinicalTrials.gov identifier: NCT01286350), which is a 18-month efficacy study with the primary goal of improving glycemic outcomes and quality of life in adolescents with type 1

diabetes. Participants wore CGM for one week during which two 24-hour dietary and physical activity recalls were collected.

Research Aims

Aim 1. To describe incidence and trends in hypoglycemia hospitalizations in adults with type 1 or type 2 diabetes from 1998 to 2013 in England.

In Aim 1, the goal is to characterize incidence and longitudinal trends of hypoglycemia requiring hospitalization among adults with type 1 or type 2 diabetes between 1998 and 2013, both overall and according to key patient characteristics including age, gender, diabetes duration, and current anti-diabetic medication (for type 2 diabetes only).

We hypothesize that annual incidence rates increase first and then decrease due to the recent negative findings on the cardiovascular benefits of more aggressive glycemic control therapy in 2008-2009. The slope may vary by diabetes type, demographics, duration of diabetes or current anti-diabetic medication.

Aim 2. To determine the relationship between HbA1c level and risk of hypoglycemia hospitalization in adults with type 1 or type 2 diabetes.

In this aim, the primary goal is to determine the association between recently measured HbA1c level and risk of hypoglycemia hospitalization. HbA1c is a widely used marker of chronic glycemia, reflecting average blood glucose levels over a 2- to 3-month period of time. We define HbA1c measured within 3 months of hypoglycemia hospitalization as recent HbA1c, which is more relevant to hypoglycemia as an acute complication of diabetes than earlier HbA1c measurements. Also, we aim to determine whether the association between recently measured

HbA1c level and risk of hypoglycemia hospitalization is modified by age, gender, diabetes duration, weight status, comorbidities, and current anti-diabetic medication.

Aim 3. To determine the association between usual dietary intake and risk of non-severe hypoglycemia in adolescents with type 1 diabetes.

We use averaged intake from two 24-hour dietary recalls to represent usual dietary intake in the CGM-wearing week at baseline. Due to different etiology between daytime and nocturnal hypoglycemia and different dietary behaviors between daytime and nighttime, we study daytime hypoglycemia and nocturnal hypoglycemia separately.

We hypothesize that higher intake of fat or protein reduces risk of both daytime and nocturnal non-severe hypoglycemia. A diet low in glycemic index (GI) or high in fiber increases the risk of both daytime and nocturnal non-severe hypoglycemia.

CHAPTER 2: LITERATURE REVIEW

A. Overview on diabetes and hypoglycemia

Section 1. Diabetes

Considerable and fast-increasing diabetes burden

The International Diabetes Federation reported a diabetes prevalence of 8.3% in adults worldwide in 2013, representing 382 million people.[1] In less than 25 years, the number of people with diabetes will rise to more than 592 million. Just within 5 years in the United States (US), the estimated total economic cost of diagnosed diabetes increased from $174 billion in 2007[2] to $245 billion in 2012.[3] By 2050, one in three US adults is predicted to have diabetes.[4] In the UK, there were 2.6 million people with diagnosed diabetes in 2009 and this number may be increased to more than 4 million by 2025.[5] The burden of diabetes has also been increasing at a fearsome pace in many developing countries. A national study in 2010 revealed that the prevalence of diabetes was 11.6% in Chinese adults.[6] In India, the number of diabetes doubled between 1995 and 2005.[7] There were about 61.3 million patients with type 2 diabetes in 2011 and the predicted number is about 101.2 million by 2030 in India.[1, 7] Undoubtedly, the diabetes pandemic poses enormous public health and economic challenges globally, currently and into the future.

Importance of distinction between type 1 and type 2 diabetes

Type 1 and type 2 diabetes are two major types of diabetes.[8] Both can occur in people of any age. They are two very different diseases, although increased blood glucose is a major common symptom. Type 1 diabetes, previously known as insulin-dependent diabetes or juvenile-

onset diabetes, accounts for about 5-10% of those with diabetes. Type 1 diabetes is generally caused by a cellular-mediated autoimmune destruction of the beta-cells in pancreas.[8] Type 1 diabetes is commonly diagnosed in children or young adults with about 75% of the cases diagnosed in individuals <18 years of age.[9] Patients need insulin every day to control blood glucose. The prevalence of type 1 diabetes has been increasing, but the reasons are not clear;[1] possible reasons are changes in environmental risk factors, diet in early life, and viral infections.

About 90-95% of all diabetes are type 2 diabetes, previously known as non-insulin-dependent diabetes or adult-onset diabetes.[8] Individuals with type 2 diabetes have insulin resistance and usually relative (rather than absolute compared to type 1 diabetes) insulin deficiency. Many patients can manage diabetes through lifestyle change alone in early stages. Monotherapy or a combination of oral anti-diabetic drugs may suffice as the disease progresses. As capacity of the pancreas to secrete adequate insulin declines over time, patients commonly need insulin, specifically among the elderly or advanced type 2 patients.[10] Most of type 2 patients are diagnosed during middle adulthood or older.[8] However, recently and although still rare, the prevalence of type 2 diabetes has been increasing in children and adolescents, particularly among non-white racial and ethnic populations, likely related to the increasing prevalence of obesity.[11]

Because of the different etiology and treatment strategies explained above between type 1 and type 2 diabetes, risk of hypoglycemia is generally higher in type 1 than type 2 diabetes.[12] However, hypoglycemia risk is also high in the elderly patients with type 2 diabetes or type 2 patients treated with insulin, sulfonylureas or glinide.[12, 13]

Diabetes in children and adults

The previous section described that in children, type 1 diabetes is the predominant type of diabetes while type 2 diabetes is the predominant type in adults. Further, the diabetes treatment strategies may be different between children and adults, and between type 1 and type 2 diabetes.[9, 14] Diabetes in children has a number of unique features including insulin sensitivity/resistance influenced by physical growth and sexual maturation, capability of self-care, supervision in the child care and school environment, neurological vulnerability to hypo- and hyperglycemia, and neurocognitive impact of diabetic ketoacidosis.[9] A general glycemic goal with HbA1c <7.5% is recommended for children of all ages.[9] In adults, a general glycemic target of <7.0% is recommended, although more or less stringent goal may be applied to specific individuals.[15] Therefore, diabetes research should be clear about study population (pediatric versus adult, or both) and the type of diabetes of interest. In terms of the risk of hypoglycemia, children are more vulnerable, because of the challenges presented by inaccurate insulin dosing, variable eating patterns, erratic activity and the child's capacity to detect hypoglycemia.[12]

Section 2. Hypoglycemia

Definition of hypoglycemia, severe and non-severe hypoglycemia

A blood glucose of <70 mg/dL is recommended by the American Diabetes Association (ADA) and The Endocrine Society to define hypoglycemia.[12] Hypoglycemia occurs more often in individuals with type 1 diabetes compared to type 2 diabetes. In type 2 diabetes, most episodes of hypoglycemia happen to elderly patients or patients treated with insulin, sulfonylureas or glinide.[12, 13] Hypoglycemia can be severe or non-severe (i.e., mild or moderate). Severe hypoglycemia is defined as a low blood glucose event requiring assistance of another person to

actively administer carbohydrates, glucagon, or take other corrective actions.[12] Hypoglycemia leading to emergency department visit or hospital admission is also considered as severe hypoglycemia.[16, 17] Hypoglycemia that is not severe enough of requiring external help or emergency department visit or hospital admission is termed non-severe hypoglycemia.

Impacts and consequences of hypoglycemia

Despite the great advance in the knowledge of diabetes management and related technology, optimal glycemic control has not been satisfactorily achieved in many patients with diabetes. A primary limiting factor is hypoglycemia.[18] Severe hypoglycemia has been independently associated with an increased risk of cardiovascular disease,[19] dementia,[20] cancer,[21] and death.[22, 23] Furthermore, a recent meta-analysis of 13 randomized trials suggests that the harms associated with severe hypoglycemic events could even negate the benefits of intensive glucose reduction.[24]

Mild and moderate hypoglycemia, accounting for 88-98% of the total hypoglycemia episodes,[25] can as well decrease quality of life of patients with diabetes and may increase mortality.[26] Management of non-severe hypoglycemia accounts for up to 13% of all out-of-pocket costs related to diabetes.[27] A survey of people with diabetes in the US, UK, Germany, and France found that, over a 1-month period, mean losses in workplace productivity were estimated to range from $15.26–93.47 per non-severe hypoglycemia episode, representing 8.3 to 15.9 hours of lost work time per month.[28]

Further, fear of hypoglycemia causes exaggerated avoidance behavior and consequently suboptimum insulin therapy and poor glycemic control.[25] Fear of hypoglycemia may cause

patients to decline participation in physical activity, thus limiting these patients' receipt of the many benefits of physical activity.[29, 30]

Hypoglycemia in children needs particular attention. Children are most vulnerable to the adverse consequences of hypoglycemia, because their brains are still developing.[12] They are at high risk of brain dysfunction and neurological sequelae of hypoglycemia. Repeated episodes of severe hypoglycemia may even cause permanent damage to the brain with structural changes in the white and gray matter of developing brains.[31]

Section 3. Advances in diabetes management in the previous two decades

Two decades ago, the Diabetes Control and Complications Trial (DCCT),[32] demonstrated the convincing microvascular benefits of tight glycemic control. In years following the DCCT study, controlling HbA1c under 6.5-7.0% for individuals with diabetes was the common clinical practice,[33, 34] and a near-normal HbA1c <6% can also be considered based on individual assessment.[35] With a few exceptions,[13, 33] most diabetes guidelines did not place much emphasis, until very recently, on adjusting glycemic targets through evaluating individual's hypoglycemia risk factors including prior history of severe hypoglycemia, advanced age, limited life expectancy, and comorbidities.[14, 15, 36] Although more stringent glycemic control improves HbA1c and reduces various macrovascular and microvascular complications, it increases risk of severe hypoglycemia.[37-39] A meta-analysis of 13 randomized trials suggests that the harm associated with severe hypoglycemia could even negate the benefit of intensive glucose reduction.[24] Further, three large clinical trials published in 2008-2009 provide persuasive evidence that applying intensive therapy to all patients with diabetes may not gain macrovascular benefits.[40-42] Instead, it may be associated with a broad range of potential harms and death

followed by increased risk of severe hypoglycemia.[43, 44] Accordingly, most current guidelines suggest that individualized glycemic targets may be more appropriate to balance hyper- and hypoglycemia risk.[14, 15]

Further, in the past few decades, several new anti-diabetic drugs have been introduced including DPP-4 inhibitors, SGLT-2 inhibitors, and GLP-1 agonists. All of these drugs do not usually cause hypoglycemia unless combined with therapies that can cause hypoglycemia.[45, 46] Also, new insulin products, improved insulin delivery methods and dosing algorithm, and continuous glucose monitoring are likely to help patients with diabetes to better control blood glucose within a reasonable range.[47-49] Additionally, standards for diabetes self-management and education have been established.[50] All these critical changes in the previous few decades may contribute to improvement of diabetes control including reduction of hypoglycemia risk in patients with type 1 and type 2 diabetes.

B. Previous studies related to describing trends of severe hypoglycemia

Evidence in the US

Three studies reported temporal trends of severe hypoglycemia in people with diabetes without differentiating between type 1 and type 2 diabetes (Table 2).[51-53] Only one study investigated trends of severe hypoglycemia specifically in adults with type 2 diabetes.[54] Trends in type 1 diabetes have not been studied. Lipska et al.[51] reported trends of hospital admissions for hypoglycemia among Medicare beneficiaries between 1999 and 2011. Limitations of this investigation included not accounting for diabetes prevalence, difficulty in defining the denominator, and no differentiation between type 1 and type 2 diabetes. Further, these results could not be generalized to the US population ≤64 years of age. Ginde et al.[52] used the National

Table 2. Selected studies reporting on trends of hypoglycemia

First author	Location	Period	Data source	Population	Outcome	Main findings
Lipska KJ,[54] Diabetes Care. 2016	US	2006-2013	OptumLabs Data Warehouse	Adults with type 2 diabetes	Hypoglycemia requiring emergency room visit or hospital admission or observation stay	The overall rate of severe hypoglycemia remains largely unchanged.
Wang J,[53] PLoS One. 2015	US	2006-2011	Nationwide Emergency Department Sample	Adults with diabetes	Emergency department visit for hypoglycemia	Hypoglycemia rates have declined for all adults but persons aged 18-44 years.
Lipska KJ,[51] JAMA Intern Med. 2014	US	1999-2011	Inpatient National Claims History files from the Centers for Medicare and Medicaid Services	Elderly adults	Hypoglycemia requiring hospital admission	Admissions for hypoglycemia increased until 2007, and declined subsequently, but remained above the baseline (1999) levels.
Ginde AA,[52] Diabetes Care. 2008	US	1993-2005	National Hospital Ambulatory Medical Care Survey	All people with diabetes	Emergency department visits for hypoglycemia	While the total number of visits for hypoglycemia increased during the study period, the rate per diabetic population or emergency department visits did not change significantly.
Zaccardi F,[55] Lancet Diabetes Endocrinol. 2016	England	2005-2014	Hospital Episode Statistics	All people	Hypoglycemia requiring hospital admission	Over 10 years, hospital admissions in England for hypoglycemia increased by 39% in absolute terms and by 14% considering the general increase in hospitalization; however, accounting for

						diabetes prevalence, there was a reduction of admission rates.
Clemens KK,[56] PLoS One. 2015	Ontario, Canada	2002-2013	Linked health care databases	Elderly adults with diabetes	Emergency room visit or inpatient admission for hypoglycemia	Although the absolute number of treated patients with a hypoglycemia encounter increased until mid-2006 and then decreased, the overall percentage with an encounter declined over the study period.
Booth GL,[57] Diabetes Care. 2005	Ontario, Canada	1994-1999	Ontario Diabetes Database and hospital discharge abstracts prepared by the Canadian Institute for Health Information	Adults with diabetes	Hypoglycemia requiring hospital admission	Rates of hospitalization for hypoglycemic emergencies decreased by 76.9%.
Chen YJ,[58] Prim Care Diabetes. 2015	Taiwan	2000-2010	National Health Insurance Research Database	Middle-aged or elderly adults with type 2 diabetes	Emergency department visit for hypoglycemia	Within a 10-year period, there was a substantial increase in the rates of hypoglycemia-related emergency department visits from type 2 diabetic patients in Taiwan.
Lombardo F,[59] PLoS One. 2013	Italy	2001-2010	National Hospital Discharge Database	All people with diabetes	Hypoglycemic coma	Decreased rate of hypoglycemic coma.

Hospital Ambulatory Medical Care Survey to characterize national trends in hypoglycemia admitted to emergency department between 1993 and 2005. Although Ginde et al. analyzed a representative sample of all US non-institutional general and short-stay hospitals, diabetes type-specific trends were not available. Additionally, data presented pertained to emergency department visits, not individual patients. According to Wang et al.,[53] rates of emergency department visits for hypoglycemia declined for all adults but persons aged 18-44 years from 2006 to 2011. Again they did not distinguish between type 1 and type 2 diabetes and reported visit-level estimates only. Using claims data, Lipska et al.[54] found that the overall rate of hypoglycemia requiring emergency department visit or hospital admission or observation stay remained largely unchanged between 2006 and 2013 in adults with type 2 diabetes. However, these were privately insured patients and may not be representative of all patients with type 2 diabetes.

Evidence in other countries

Recently, using the HES database, Zaccardi et al.[55] reported a 10-year trends (2005-2014) in hospital admissions for hypoglycemia in England. The hospital admission rate for hypoglycemia increased by 14% in England, but the hospital admission rate showed a reduction after accounting for prevalence of diabetes. Still, Zaccardi et al. did not investigate the trends by diabetes type. A study in Taiwan assessed hypoglycemia trend specifically in adults with type 2 diabetes; Chen et al.[58] reported an increasing trend in the incidence of hypoglycemia-related emergency department visits from 2000 to 2010. However Chen et al. excluded patients younger than 45 years old. A nationwide study in Italy reported temporal trend in hospitalization for hypoglycemic coma between 2001 and 2010, but other specified and unspecified severe

hypoglycemia was not evaluated.[59] Two studies from Ontario, Canada reported decreased rates of hypoglycemia leading to emergency room or hospitalization.[56, 57] All these last three studies were not able to describe diabetes type-specific trend.

In summary, the primary limitation of the current literature is without being able to provide estimates of diabetes type-specific hypoglycemia trend from a population perspective, both overall and by subgroups such as use of anti-diabetic medication. Thus, clear clinical messages could not be given such as who are at increased/decreased risk of hypoglycemia over time, which subgroups have the greatest increase/decrease in hypoglycemia risk, and which subgroups have the highest/lowest hypoglycemia burden.

C. HbA1c level and severe hypoglycemia

The goal of diabetes treatment is to control blood glucose and prevent complications and HbA1c is the main treatment target. Improved HbA1c over time prevents or delays microvascular complications—retinopathy, nephropathy, and neuropathy—in patients with type 1 diabetes[32] or type 2 diabetes;[60, 61] and may reduce macrovascular events.[32, 60, 61] As explained above, current diabetes guidelines recommend personalized glycemic targets to balance long-term glycemic benefits and short-term hypoglycemia risk.[14, 15, 62, 63] More specifically, deciding an individual's HbA1c treatment goal needs to consider this person's hypoglycemia risk factors including age, diabetes duration, comorbidities, current use of anti-diabetic drug(s), life expectancy, and history of hypoglycemia. However, the association between HbA1c level and risk of severe hypoglycemia remains unclear.

HbA1c level and severe hypoglycemia in patients with type 1 diabetes

Evidence from the DCCT and other studies in the previous decades have revealed an inverse association between HbA1c and risk of severe hypoglycemia in adults[32] and children with T1D [64-66]. However, recent studies reported no association between HbA1c and the incidence of severe hypoglycemia [67-70]. A trend analysis on a large cohort of patients with type 1 diabetes from the Diabetes Patienten Verlaufsdokumentation (DPV) Initiative found that the previous strong association of HbA1c level between 6.0% - 7.9% with severe hypoglycemia has considerably decreased from 1995 to 2012.[71] Therefore, the HbA1c-hypogliycemia relationship remains unclear in type 1 diabetes.

HbA1c level and severe hypoglycemia in patients with type 2 diabetes

In patients with type 2 diabetes, a number of large randomized clinical trials provides persuasive evidence that near normal or good glycemic control increased risk of severe hypoglycemia.[40-42] However, post hoc analyses of the Action to Control Cardiovascular Risk in Diabetes study reported that the risk of severe hypoglycemia was increased among participants with poorer glycemic control compared to those with more desirable HbA1c, irrespective of assigned treatment group.[72] A cross-sectional survey on patients from an integrated health care system in the US found a U-shape relationship between HbA1c and risk of severe hypoglycemia [73]. However, this relationship has not been confirmed in other large cohorts of patients with T2D from the usual care setting.

In both type 1 and type 2 diabetes, the majority of investigations mentioned above did not evaluate possible critical interactions between HbA1c and important patient characteristics that are related to hypoglycemia vulnerability including age, diabetes duration, comorbidities, and

specific glucose-lowering medications. Further, HbA1c measured within 2-3 months of hypoglycemic events may be more relevant to the acute event of severe hypoglycemia. However, previous studies used "baseline" HbA1c values measured more than three months or even years before,[38, 72-75] which may be less predictive of severe hypoglycemia and more likely to be confounded given the big time gap in between.

D. Dietary intake and hypoglycemia in children

Lacking nutrition recommendations for hypoglycemia prevention

Hypoglycemia is the consequence of a mismatch between insulin dose, food consumed, and recent exercise.[31] Hypoglycemia is manageable though behavioral intervention.[30] As a major determinant of blood glucose, nutrition therapy plays a key role in managing hypoglycemia in diabetes.[76] Current recommendations from the ADA[77] and International Society for Pediatric and Adolescent Diabetes (ISPAD)[30] suggest using glucose, sucrose or any form of carbohydrate to treat hypoglycemia. However, specific dietary recommendations for preventing hypoglycemia are limited, particularly for children. Evidence from adults with type 2 diabetes may not be applicable to children with type 1 diabetes. For example, a position statement from the ADA presents nutrition therapy recommendations for adults with type 2 diabetes, in which protein is not recommended to either treat or prevent hypoglycemia.[76] The reason is that ingested protein appears to increase insulin secretion in type 2 diabetes without increasing blood glucose concentrations and thus may increase hypoglycemia risk.[78, 79] However, the glycemic effect of protein is likely to be different between type 1 and type 2 diabetes, because pancreas of patients with type 1 diabetes has minimal insulin secretion capability, although residual insulin secretion in youth with type 1 diabetes may be relevant.[80, 81] In fact, a clinical trial conducted by Smart et

al.[82] found that high protein diet substantially reduced the risk of hypoglycemia in children with type 1 diabetes when consumed with carbohydrate.

Carbohydrate, protein, fat, and hypoglycemia

The majority of the literature in children with type 1 diabetes focuses on postprandial glycemic excursions following experimental meals with different macronutrients composition in clinical trial settings. Hypoglycemia is rarely studied as a primary outcome. Available data, though very limited in children, suggest that quality of carbohydrate matters for prevention of hypoglycemia. Published studies consistently reported that higher fiber intake was associated with lower postprandial blood glucose.[83, 84] Lafrance et al.[83] found that high-fiber diet did not increase the risk of hypoglycemia, although lower mean blood glucose was seen with high-fiber diet compared to low-fiber diet, in well-controlled patients with type 1 diabetes on intensive insulin therapy. Convincing evidence has shown that low GI foods and meals produce lower glycemic responses in people with diabetes.[83, 85-87] However, the relationship between the GI and risk of hypoglycemia is inconsistent. Opposite results were reported, possibly due to the very different definition of high- and low-GI diet in these studies and different length of blood glucose monitoring.[83, 86, 87]

Expanding evidence suggests that carbohydrate does not fully explain postprandial glycemic excursions.[82, 88, 89] Fat and protein, when consumed with carbohydrate, can cause sustained late high postprandial blood glucose up to or over 5 hours.[90] And protein and fat may have an additive impact on blood glucose independent of carbohydrate.[82] However, none of previous studies differentiated fat type. Therefore, it is not known if saturated fat and unsaturated fat have similar glycemic effect. The effect of protein on blood glucose excursions is

complicated. Protein may have very different effects when consumed with and without carbohydrate. Paterson et al.[91] examined the effect of protein only (without intake of carbohydrate and fat) and found that consuming 12.5–50 grams of protein did not influence blood glucose, although consuming 75-100 grams of protein significantly increased glucose concentrations, causing an increase in glucose concentrations similar to that of consuming 20 grams of carbohydrate without injecting insulin.

Differential effects of dietary intake on daytime and nocturnal hypoglycemia

The effects of dietary intake on daytime and nocturnal hypoglycemia may be different. Current insulin preparations do not adequately mimic normal physiologic patterns of insulin secretion[92] and sleep attenuates counter-regulatory responses to hypoglycemia.[93] Further, dietary intake and exercise[94] as two major determinants of blood glucose occur mainly in the daytime. A clinical trial conducted in children with type 1 diabetes found no differences in the mean blood glucose and hypoglycemia risk in the night between consuming a low-GI and a high-GI diet, although the mean blood glucose was lower and hypoglycemia risk was higher in the daytime.[86] However, these findings have not been confirmed in an outpatient setting. Further, it is not known if differential effects on the risk of daytime and nocturnal hypoglycemia exist for major macronutrients.

In summary, the majority of above studies are clinical trials. Few investigations have studied the effect of usual dietary intake on the risk of hypoglycemia in free-living youth with diabetes, which associates typical dietary patterns with day-to-day glycemic control.[84] Further, most studies have not studied hypoglycemia as the primary outcome. We do not know if dietary intake predictive of postprandial blood glucose is also associated with occurrence of

hypoglycemia. In addition, it may be important to differentiate between daytime and nocturnal hypoglycemia for studying dietary effects on blood glucose excursions. To address these gaps, our project will investigate the effect of usual dietary intake on the risk of daytime and nocturnal hypoglycemia in free-living adolescents with type 1 diabetes.

CHAPTER 3. INCIDENCE AND TEMPORAL TRENDS IN HYPOGLYCEMIA HOSPITALIZATIONS IN ADULTS WITH TYPE 1 AND TYPE 2 DIABETES IN ENGLAND, 1998 TO 2013: A RETROSPECTIVE COHORT STUDY

Introduction

Severe hypoglycemia frequently occurs in people with type 1 diabetes and can also occur in individuals with type 2 diabetes, particularly among elderly people or those treated with insulin or sulfonylureas.[12] In the two decades following the DCCT,[32] diabetes treatment guidelines have evolved from emphasizing hyperglycemia management with achieving HbA1c <6.5-7.0% towards recommending individualized glycemic targets to balance long-term glycemic benefits and hypoglycemia risk.[14, 15] For example, less stringent HbA1c goals (e.g., <8.0%) may be appropriate for patients with a history of severe hypoglycemia, limited life expectancy, extensive comorbid conditions, or long duration of diabetes. Conversely, more stringent HbA1c goals (e.g. <6.5%) may be applied to individuals with short duration of diabetes, few comorbidities, long life expectancy, or treated with lifestyle or metformin only.[14, 15] Particularly, the argument for individualization of glycemic targets was further supported by evidence from three recent clinical trials – the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial,[40] the Action in Diabetes and Vascular Disease (ADVANCE) trial,[41] and the Veterans' Administration Diabetes Trial[42] (VADT) – that consistently reported no macrovascular benefits of intensive therapy, but revealed a broad range of potential harms and death followed by increased risk of severe hypoglycemia.[43, 44]

It is not clear whether changes in clinical practice guidelines that resulted from this evidence base have led to a change in severe hypoglycemia risk in adults with diabetes. The majority of published studies quantified frequencies of severe hypoglycemia using cross-sectional[13, 16, 95] or clinical trial data[96] and thus are not appropriate for assessing temporal trends from a population perspective. A few studies on trends in hypoglycemia incidence are available, but they are limited to middle-age and/or elderly adults,[51, 58] visit-level estimates,[52] or a short-term early trend in 1994-1998.[57] Further, the epidemiology of severe hypoglycemia differs considerably by diabetes type,[12] yet most studies do not distinguish between type 1 and type 2 diabetes.[51, 52, 59, 97]

In the present study, we aimed to study hypoglycemia that requires hospital admission, which is a most severe form of hypoglycemia and associated with considerable morbidity, mortality, healthcare resources use, and expenditure.[98] The main goal was to characterize incidence and longitudinal trends of hypoglycemia hospitalizations among adults with type 1 and type 2 diabetes between 1998 and 2013, both overall and according to key patient characteristics. Data for analyses were from the CPRD and HES from the UK.

Methods

Two data sources: the CPRD and HES

Established in 1987, the CPRD included 684 practices from England, Scotland, Wales and Northern Ireland and contained over 15 million patient records as of January 2015. Patients in the CPRD are representative of age, gender and geographic regions of the UK.[99] The CPRD contains detailed longitudinal primary care information including, but not limited to, demographics, clinical diagnoses, prescriptions, laboratory test results and hospital referrals.

Clinical entries in the CPRD are coded using Read codes, which is a hierarchical clinical coding system used in General Practice in the UK.[100]

The HES is a data warehouse storing records of all patients admitted to National Health Service hospitals in England (not Northern Ireland, Scotland or Wales). Patient-level data from consenting CPRD practices are linked to the HES data via a trusted third party.[99] The HES data utilized for the current study included admitted patient care information from April 1, 1997 to March 31, 2014. ICD-10 codes (international classification of diseases, 10th revision) are used within the HES, which were mandated for use in the UK starting in 1995.

Hypoglycemia hospitalizations were identified from the HES. All other information including diabetes diagnosis, demographics and anti-diabetic drug prescriptions were extracted from the CPRD.

Definition of type 1 and type 2 diabetes

As of March 31, 2014, 384 of the 684 CPRD practices were linked to the HES data and thus were included in our study, accounting for approximately 60% of the entire CPRD population. Patients with ≥1 diabetes related Read code were first identified.[101] Patients were next excluded if they had any record of secondary diabetes, maturity onset diabetes of young, latent autoimmune diabetes in adults, malnutrition related diabetes, or considered not to be of research standard by the CPRD team.

Criteria to identify diabetes cases and type were adopted from relevant CPRD literature with modifications to reflect specific differentiation between type 1 and type 2 diabetes.[102-104] Among those with at least one diabetes related code, type 1 diabetes was identified if one of the following three criteria was met: (i) ≥1 type 1 code and use of insulin only; (ii) ≥1 type 1 code

and use of insulin only on the diagnosis date and oral anti-diabetic drug (OAD), if any, was introduced 6 months later; (iii) ≥2 insulin prescriptions only and ≥1 unspecified diabetes code. Type 2 diabetes was defined as any of the following: (i) ≥2 type 2 codes and 0 type 1 code, regardless of drug use; (ii) ≥1 type 2 code and 0 type 1 code and OAD only; (iii) ≥1 type 2 code and 0 type 1 code and on OAD and insulin, but oral drug prescribed no later than insulin; (iv) ≥2 classes of OAD; (v) ≥2 prescriptions of a non-insulin non-metformin diabetes related drug only. OAD included metformin, sulfonylureas, glinide, thiazolidinediones, DPP-4 inhibitors, SGLT-2 inhibitors, GLP-1 agonists, and acarbose.

Study period and definition of hypoglycemia hospitalization

The study period was between January 1, 1998 and December 31, 2013 when full-year HES data were available. The follow-up started at the maximum date of January 1 1998, first date of diabetes visit, patient registration, Up To Standard (UTS) date or 18 years old. UTS is the date at which the practice data is deemed to be of research quality.[99] Follow-up ended at the minimum date of December 31 2013, death, transfer out or last data collection for the practice. Hypoglycemia (E16.0, E16.1 and E16.2) listed as primary diagnosis for hospitalization during the follow-up period was identified.

Statistical analysis

All analyses were performed separately for adults with type 1 diabetes and type 2 diabetes. Treatment guidelines for type 2 diabetes vary according to individual's hypoglycemia risk factors, such as age, current anti-diabetic medications, number of comorbidities, duration of diabetes, history of severe hypoglycemia, and life expectancy.[14, 15] Therefore, separate analyses

were performed in young and middle-aged adults (18-64 years) with type 2 diabetes and elderly adults (≥65 years) with type 2 diabetes.

Incidence rate Incidence rates of hypoglycemia hospitalizations were calculated by dividing the total number of hypoglycemia hospitalizations by total accumulated person-years with diabetes within each year between 1998 and 2013. All episodes of hypoglycemia hospitalizations from a patient during the follow-up period specified above were included. The accumulated person-years for a patient was obtained by subtracting the follow-up start date from the follow-up end date, which was then divided by 365.25.

Stratified incidence rates were also computed. For adults with type 1 diabetes, incidence rates were calculated by age (18-44, 45-64, 65-79, ≥80 years), gender (male or female), diabetes duration (0-4, 5-9, 10-14, ≥15 years). For young and middle-aged adults with type 2 diabetes, incidence rates were calculated by age (18-44, 45-64 years), gender, diabetes duration (0-9, ≥10 years) and current use of anti-diabetic drugs (insulin with/without OAD, sulfonylureas with/without other OAD, and "other"). For elderly adults with type 2 diabetes, incidence rates were calculated by age (65-79, ≥80 years), gender, diabetes duration (0-4, 5-9, 10-14, ≥15 years), and current use of anti-diabetic drugs (insulin only, insulin and OAD, sulfonylureas only, sulfonylureas and other OAD, and "other"). All rates were reported per 1000 person-years.

Trend analysis We applied joinpoint regression models to quantify temporal trends for both overall and stratified incidence rates.[105] Each joinpoint (i.e., specific year) denoted a statistically significant change in trend. We fitted a heteroscedastic and uncorrelated error joinpoint regression model, and allowed a maximum of 3 joinpoints. A grid search was employed to identify locations of joinpoint(s). We selected the best fitting model by conducting a series of permutation tests based on 4,500 Monte Carlo replicates, using a Bonferroni correction

for multiple testing.[106] Parameters in the model were estimated using weighted least squares with weights proportional to the inverse of the variance of the incidence rate at each year. Annual percentage change and 95% CI were estimated.

Negative binomial model We fitted a negative binomial regression model with the number of hospitalizations as the outcome and the logarithm of person-years as the offset to determine risk factors and change in the incidence rate of hypoglycemia hospitalizations by year. Using year 1998 as the reference year, we included 15 dummy year variables, representing subsequent years from 1999 to 2013, age (18-44, 45-64, 65-79, ≥80 years), gender, duration of diabetes (0-4, 5-9, 10-14, ≥15 years) and current use of anti-diabetic drugs (for type 2 diabetes only: self-management alone without using insulin or any OAD, metformin only, sulfonylureas only, sulfonylureas and other OAD, insulin only, insulin and OAD, and "other"). Incidence rate ratio (IRR) and 95% CI were estimated.

Additional analyses Using identical methodologies described above, the incidence rates and trends in first hypoglycemia hospitalization were also studied, among adults with incident type 1 and type 2 diabetes between 1998 and 2013. Patients with incident type 1 and type 2 diabetes between January 1, 1998 and December 31, 2013 were identified as those with the first diabetes visit date >365 days after registration.[102]

SAS (version 9.4, SAS Institute Inc.) and Joinpoint software were used to perform analyses.[105] Statistical significance was indicated by a two sided *P* value <0.05.

Patient involvement

No patients were involved in setting the research question or the outcome measures, nor were they involved in developing plans for design or implementation of the study. There are no

plans to involve patients in the dissemination of results, nor will we disseminate results directly to patients.

Results

Among 23,251 adults with type 1 diabetes (Figure 3.1), 1,591 hypoglycemia hospitalizations occurred during 121,262.34 follow-up years (Table 3.1). Among 241,829 adults with type 2 diabetes, 553 episodes of hypoglycemia hospitalizations were documented during 560,685.97 person-years of follow-up among young and middle-aged adults while 3,185 episodes were documented during 784,131.67 person-years of follow-up among elderly adults.

Type 1 diabetes

During the study period, the overall incidence rate was 13.12 hospitalizations for hypoglycemia per 1000 person-years (Table 3.1). The incidence rate was 9.57 and 14.80 hospitalizations for hypoglycemia per 1000 person-years in 1998 and 2013, respectively. Elderly adults (≥65 years) and those with the longest duration of diabetes (≥15 years) had higher incidence rates of hypoglycemia hospitalizations compared to those with younger age and shorter diabetes duration, respectively.

From 1998 to 2013, the incidence rate of hypoglycemia hospitalizations increased 3.74% (95% CI, 1.70 to 5.83%, P=0.001) annually in all patients with type 1 diabetes (Table 3.2, Figure 3.2A). This increasing trend was seen in all age groups (Figure 3.2B) and in males and females (Figure 3.2C). However, the increasing trend was found only in those with the longest diabetes duration; the incidence rate increased 4.97% annually (2.66 to 7.33%, P=0.0004) (Figure 3.2D).

Young and middle-aged adults with type 2 diabetes

During the study period, the overall incidence rate was 0.99 hospitalizations for hypoglycemia per 1000 person-years (Table 3.1). The incidence rate was 0.73 and 1.19 hospitalizations for hypoglycemia per 1000 person-years in 1998 and 2013, respectively. The incidence rate was the highest among insulin users. It was also considerably higher among those with long diabetes duration (≥10 years) or older age (45-64 years) compared to those with shorter diabetes duration and younger age, respectively.

Overall, from 1998 to 2013, the incidence rate increased 4.12% (0.61 to 7.75%, P=0.02) annually (Table 3.3, Figure 3.3A). This increasing trend was similar between young (18-44 years) and middle-aged adults (45-64 years) (Figure 3.3C), between males and females (Figure 3.3E), and between short duration <10 years and long duration ≥10 years (Figure 3.3G), respectively. The incidence rate was increasing among current insulin users; the incidence rate increased 5.76% annually (1.11 to 10.64%, P=0.02), but not current sulfonylureas users and "other" users (Figure 3.3I).

Elderly adults with type 2 diabetes

During the study period, the overall incidence rate was 4.06 hospitalizations for hypoglycemia per 1000 person-years (Table 3.1). The incidence rate was 1.12 and 3.52 hospitalizations for hypoglycemia per 1000 person-years in 1998 and 2013, respectively. The incidence rate was high among those who were currently taking insulin, the oldest (≥80 years), having the longest duration of diabetes (≥15 years) or currently taking sulfonylureas.

Overall, the incidence rate increased 8.59% (5.76 to 11.50%, P<0.0001) annually from 1998 to 2009, and decreased 8.05% (-14.48 to -1.13%, P=0.03) annually from 2009 to 2013

(Table 3.4, Figure 3.3B). This non-linear trend was observed among two subgroups of age (65-79 years and ≥80 years, Figure 3.3D), and both gender groups (Figure 3.3F). The trend differed by diabetes duration (Figure 3.3H). The incidence rate did not change among those with the shortest duration (0-4 years). A non-linear trend was seen in the remaining three groups with longer duration. The temporal trend differed by current use of anti-diabetic drug(s) (Figure 3.3J). There was a linear increasing trend in all groups except users of both insulin and OAD among whom a decline in the incidence rate was observed since 2009. Removing current insulin and OAD users or two groups with long diabetes duration (10-14 years and ≥15 years) from the analyses did not change the overall trend change in year 2009 (data not shown).

Risk factors

Adults with type 1 diabetes had higher risk of hypoglycemia hospitalization than adults with type 2 diabetes (adjusted IRR 5.61, 95% CI 5.06 to 6.21, Table 3.5). Older age, female gender and long diabetes duration ≥15 years were risk factors for hypoglycemia hospitalization in adults with type 1 diabetes. In adults with type 2 diabetes, older age, diabetes duration ≥10 years, current insulin, and sulfonylureas use were risk factors. The risk of hypoglycemia hospitalization increased substantially when adults with type 2 diabetes were ≥80 years old, current insulin or sulfonylureas users. Current metformin use was associated with lower risk of hypoglycemia hospitalization compared to self-management (i.e. currently not taking any anti-diabetic drug). Compared to the year 1998, the incidence rate of hypoglycemia hospitalizations in 2013 increased both in adults with type 1 diabetes (adjusted IRR 1.67, 1.14 to 2.43) and type 2 diabetes (2.68, 1.71 to 4.20).

First hypoglycemia hospitalization only

Among 3,266 adults with incident type 1 diabetes, 87 episodes of first hypoglycemia hospitalization were recorded during 14,479.82 person-years of follow-up. Among 135,517 adults with incident type 2 diabetes, 799 episodes of first hypoglycemia hospitalization occurred during 752,500.99 person-years of follow-up. In adults with incident type 1 diabetes, the overall incidence rate of first hypoglycemia hospitalization was 6.01 hospitalizations per 1000 person-years and did not change from 1998 to 2013. In young and middle-aged adults with incident type 2 diabetes, the overall incidence rate was 0.48 hospitalizations/1000 person-years and it increased 5.76% (0.72 to 11.05%, *P*=0.03) annually from 1998 to 2013. In elderly adults with incident type 2 diabetes, the overall incidence rate was 1.53 hospitalizations for hypoglycemia per 1000 person-years. The incidence rate decreased 6.87% (-11.98 to -1.46%, *P*=0.02) annually since 2009 and no statistically significant trend was seen before 2009.

Discussion

Principle findings

In England, the incidence rate of hypoglycemia hospitalizations increased in adults with type 1 diabetes from 1998 to 2013. This increasing trend was seen in all age groups, both genders and those with the longest diabetes duration. In young and middle-aged adults with type 2 diabetes, the incidence rate of hypoglycemia hospitalizations also increased during the entire study period. The increasing trend was observed in all subgroups; however, current insulin users exhibited the greatest increase. In elderly adults with type 2 diabetes, after a sharp increase in years prior to 2009, a decline in the incidence rate of hypoglycemia hospitalizations was observed between 2009 and 2013. Nonetheless, the incidence rate in 2013 was still over 2.5

times that observed in 1998. This non-linear trend among the elderly with type 2 diabetes was seen in two age subgroups, both genders, in patients with ≥5 years of diabetes duration, and among current insulin and OAD users. The growing burden of hypoglycemia hospitalizations calls for effective approaches to reduce severe hypoglycemia risk in adults with diabetes in England.

Type 1 diabetes

We are not aware of any investigation of temporal trends in severe hypoglycemia incidence specifically among adults with type 1 diabetes in recent decades. Our study provided initial evidence of a steady increase in the incidence rate of hypoglycemia hospitalizations in adults with type 1 diabetes in England. Major causes of insulin-related hypoglycemia are excessive insulin dose, ill-timed dosing or administration of wrong insulin product (e.g., short-, intermediate-, or long-acting insulin).[13] In adults with type 1 diabetes in England, more attention may be given to appropriate meal-planning, correct insulin dosing and adjustment, and use of the correct insulin product, in order to reverse the rising trends of hypoglycemia hospitalizations.

Type 2 diabetes

In adults with type 2 diabetes, notable differences in temporal trends were found between young and middle-aged adults (i.e., linear increasing trend) and elderly adults (i.e., non-linear trend), suggesting that age played a crucial role in diabetes management. The increasing trend of hypoglycemia hospitalizations in young and middle-aged adults may be driven by the convincing microvascular benefits of tight glycemic control[32] and diabetes guidelines that individuals with short diabetes duration, few comorbidities, and long life expectancy can be treated with more

stringent glycemic control.[15, 107] The former reason may also explain the rapidly increasing incidence rate of hypoglycemia hospitalizations in elderly adults with type 2 diabetes before 2009. The decline in the incidence rate of hypoglycemia hospitalizations starting in 2009 in elderly adults with type 2 diabetes may be driven by physicians who may have recently started to treat a proportion of elderly adults with type 2 diabetes with less stringent glycemic control who were vulnerable to hypoglycemia. First, well-publicized negative results in 2008-2009 from the three trials (ACCORD,[40] ADVANCE,[41] and VADT[42]) suggested that elderly adults may not gain macrovascular benefits from aggressive glycemic control; rather, intensive therapy was associated with increased risk of severe hypoglycemia and may increase mortality. Second, with a few exceptions,[13, 33] most diabetes guidelines did not emphasize, until very recently, on adjusting glycemic targets through evaluating individual's hypoglycemia risk factors.[14, 15, 36] Subset analyses of ACCORD, ADVANCE and VADT trial data also supported that deciding an individual's HbA1c goal may need to consider this patient's characteristics such as advanced age, long diabetes duration, and advanced atherosclerosis; applying stringent glycemic control to all patients with type 2 diabetes was not advisable.[108]

Lipska et al.[51] had the same hypothesis that the decreasing trend may be driven by the persuasive findings from the three trials.[40-42] Lipska et al.'s study was conducted among US Medicare beneficiaries ≥65 years old. The hospital admission rate for hypoglycemia decreased slightly since 2007 among the entire sample. The decline occurred earlier in 2004 when only Medicare beneficiaries with diabetes were analyzed, but diabetes-type specific trend was not reported. Only one study assessed long-term severe hypoglycemia trend specifically in adults with type 2 diabetes. Chen et al.[58] reported an increasing trend of hypoglycemia-related emergency department visits from 2000 to 2010 among adults with type 2 diabetes ≥45 years old

in Taiwan. The incidence rate increased 4.88 fold (95% CI 3.94 to 6.05) which was similar to 3.66 fold (2.35 to 5.71) from our study from 1998 to 2009.

Subgroup analyses in adults with type 2 diabetes revealed important differences in trends by current use of anti-diabetic medications. In young and middle-aged adults with type 2 diabetes, the incidence rate of hypoglycemia hospitalizations was considerably higher among current insulin users than patients who were currently taking other anti-diabetic drug(s). Furthermore, the annual increase rate was also the greatest among current insulin users. Similarly, in elderly adults with type 2 diabetes, subgroups (e.g., current insulin or sulfonylureas users) with markedly high incidence rate of hypoglycemia hospitalizations also had large annual increase in trends, contributing to hypoglycemia burden substantially. Although the incidence rate of hypoglycemia hospitalizations dropped down in current insulin and OAD users since 2009, the incidence rate in 2013 was still much higher than that observed in 1998. In addition, removing them from analyses did not change the overall non-linear trend (data not shown), suggesting that the declining trend was not determined by the subgroup who were currently taking insulin and OAD.

Clinical implications

Hypoglycemia requiring hospital admission only represents <10% of total severe hypoglycemia defined as an event requiring assistance of another person[71] and approximately 25% of emergency department visits for hypoglycemia.[52] However, treating hypoglycemic episodes resulting in hospital admission is expensive and associated with significant use of healthcare resources.[98] A CPRD study reported a mean cost of £1034 and a mean hospital stay of over 5 days per admission for hypoglycemia; no difference was found between type 1 and type 2

diabetes.[98] Other studies found substantially higher cost per hypoglycemia related hospitalization.[109] Our data revealed increased incidence rate of hypoglycemia hospitalizations in England in adults with type 1 and type 2 diabetes. Reducing the burden of hypoglycemia hospitalizations in England is urgent, and medically and economically critical. Of note, although the risk of severe hypoglycemia is much lower in type 2 than type 1 diabetes, the number of people having type 2 diabetes is about 10 fold more;[110] thus, both diabetes types contribute significant hypoglycemia burden.

Hypoglycemia is a multifactorial problem, but it is preventable in most cases.[12] Further, preventing hypoglycemia does not mean to sacrifice optimal glycemic control; both can be accomplished safely.[111] Approaches known to effectively reduce the risk of hypoglycemia include patient education, dietary and exercise modifications, medication adjustment, careful glucose monitoring by the patient, and conscientious surveillance by the clinician.[12] However, choosing appropriate strategies for patients with diabetes should consider each individual's specific barriers of hypoglycemia, hypoglycemia risk factors, and long-term health goals.[12, 14, 15, 111]

Strengths and limitations

Our study provided informative longitudinal trend data following the DCCT study in the incidence rate of hypoglycemia hospitalizations in adults with type 1 and type 2 diabetes. However, several limitations should be noted. First, misclassification of diabetes and diabetes type is a common problem by using electronic health data. We employed conservative definitions to differentiate between type 1 and type 2 diabetes compared to other CPRD studies,[102-104] which may have reduced misclassification error. Second, we only studied

hypoglycemia requiring hospital admission. Our data may not be applied to severe hypoglycemia not leading to hospitalization. Third, the Quality and Outcomes Framework (QOF) financial incentive scheme was introduced in 2004 to the UK primary care clinical systems and the diabetes type-specific Read codes were used since 2006 rather than the high level general Read code for diabetes.[112] They have resulted in more complete data recorded in the CPRD and facilitated the distinction between diabetes types. A study reported slightly increased prevalence of type 2 diabetes and decreased diagnosis age post the QOF period;[113] adjusting these changes might even demonstrate larger change in trends, but that is outside the scope of this work. Of note, we did not observe any significant change in hypoglycemia trend around 2004-2006. Finally, the first recorded diabetes visit date in the CPRD was used as an approximate for diabetes diagnosis date which may have underestimated duration of diabetes.

Conclusions

In conclusion, hypoglycemia that requires hospitalization has been a rapidly growing burden to the healthcare system in England. The incidence rate of hypoglycemia hospitalizations increased from 1998 to 2013 in adults with type 1 diabetes, and young and middle-aged adults with type 2 diabetes. Although a decline since 2009 was seen in elderly adults with type 2 diabetes, the incidence rate of hypoglycemia hospitalizations in 2013 was still much higher than in 1998. Practical approaches for hypoglycemia management to reverse the increasing trend of hypoglycemia hospitalizations in England are critically needed. Studies that are able to investigate longitudinal trends of severe hypoglycemia not resulting in hospital admission are encouraged.

Table 3.1. Observed incidence rates of hypoglycemia hospitalizations per 1000 person years in adults with type 1 and type 2 diabetes, in all years combined and by each single year*

	All years	1998	1999	2000	2001	2002	2003	2004	2005
Type 1 diabetes									
Overall									
Number of hospitalizations	1,591	38	60	51	66	65	76	97	119
Incidence rate	13.12	9.57	12.10	8.40	9.80	8.80	9.87	12.25	14.69
Subgroups									
Age group									
18-44 years	9.02	5.91	6.33	5.51	6.49	5.63	4.51	10.99	11.09
45-64 years	10.94	5.99	11.03	7.28	7.62	7.66	8.96	4.53	11.89
65-79 years	21.47	20.13	19.16	15.99	13.00	11.52	19.94	24.30	22.94
≥80 years	48.69	25.29	48.33	15.51	39.91	35.48	35.97	36.33	46.79
Gender									
Male	12.05	8.31	10.57	7.14	10.79	8.22	9.61	12.57	12.58
Female	14.60	11.27	14.15	10.12	8.45	9.59	10.22	11.80	17.60
Diabetes duration									
0-4 years	10.22	9.79	9.21	5.03	7.05	7.13	10.86	8.64	15.17
5-9 years	8.79	7.75	7.52	9.56	13.12	4.67	4.75	9.36	11.13
10-14 years	11.83	9.30	18.45	8.78	8.60	12.05	10.04	12.55	12.78
≥15 years	15.36	10.26	12.88	9.00	10.17	9.46	10.83	13.94	15.97
Type 2 Diabetes									
<65 years old									
Overall									
Number of hospitalizations	553	7	13	9	9	7	22	28	43
Incidence rate	0.99	0.73	1.03	0.54	0.44	0.28	0.77	0.86	1.19
Subgroups									
Age group									
18-44 years	0.73	0	0.63	0	0.36	0.29	0.77	0.22	0.98
45-64 years	1.03	0.84	1.09	0.62	0.46	0.28	0.77	0.97	1.23
Gender									
Male	0.94	0.87	1.06	0.60	0.58	0.34	0.59	0.83	0.89
Female	1.05	0.53	0.99	0.45	0.25	0.2	1.05	0.92	1.64
Diabetes duration									
0-9 years	0.70	0.62	0.57	0.22	0.41	0.24	0.50	0.73	0.79
≥10 years	2.24	1.36	3.52	2.16	0.60	0.51	2.22	1.57	3.34
Current anti-diabetic drugs									
Insulin with/without oral drug(s)	4.33	3.72	4.87	1.22	1.28	1.04	3.07	2.99	4.88
Sulfonylureas with/without other oral drug(s)	0.64	0.66	0.68	0.66	0.35	0.31	0.49	0.65	1.08
Other§	0.21	0	0.20	0.15	0.24	0	0.22	0.31	0.11
Type 2 Diabetes									
≥65 years old									
Overall									
Number of hospitalizations	3,185	15	42	53	88	120	136	158	204
Incidence rate	4.06	1.12	2.34	2.20	3.00	3.40	3.35	3.45	4.02

Subgroups									
Age group									
65-79 years	2.62	0.79	1.61	1.77	2.10	2.32	1.99	1.86	2.57
≥80 years	7.78	2.16	4.68	3.51	5.65	6.51	7.29	7.98	8.06
Gender									
Male	3.81	0.90	2.57	1.99	2.30	3.30	2.95	2.61	3.54
Female	4.34	1.33	2.11	2.41	3.71	3.50	3.77	4.33	4.51
Diabetes duration									
0-4 years	1.41	0.53	0.95	1.19	1.77	1.96	1.51	1.09	1.71
5-9 years	2.57	1.35	2.40	2.50	2.92	3.80	3.01	3.68	3.37
10-14 years	5.63	2.70	4.11	3.92	5.19	4.69	5.65	5.21	4.97
≥15 years	11.47	0.66	4.90	2.58	4.49	5.91	7.69	9.02	11.51
Current anti-diabetic drugs									
Sulfonylureas only	5.10	1.09	2.34	2.50	2.36	4.76	5.50	4.35	4.33
Sulfonylureas + other oral drug(s)	4.63	0.87	1.89	2.67	4.16	3.35	2.94	4.70	5.45
Insulin only	19.70	7.20	10.47	7.87	7.63	13.39	16.95	11.08	14.98
Insulin + oral drug(s)	12.09	3.63	9.13	5.88	10.36	8.50	7.04	8.69	10.52
Other†	0.40	0.23	0.51	0	0.30	0.30	0.30	0.35	0.51

Table 3.1. Continued

	2006	2007	2008	2009	2010	2011	2012	2013
Type 1 diabetes								
Overall								
Number of hospitalizations	118	115	132	130	168	112	121	123
Incidence rate	14.19	13.41	15.20	14.78	19.21	13.10	14.34	14.80
Subgroups								
Age group								
18-44 years	9.75	11.55	10.31	9.71	13.31	8.23	11.62	7.68
45-64 years	12.46	10.02	9.96	14.86	18.28	10.13	10.99	15.88
65-79 years	22.77	18.10	33.74	25.02	24.76	30.64	21.11	22.00
≥80 years	51.72	49.44	64.94	48.34	88.2	49.39	59.73	86.31
Gender								
Male	12.67	13.49	13.69	12.24	17.01	12.59	12.03	14.07
Female	16.27	13.31	17.29	18.36	22.30	13.81	17.53	15.81
Diabetes duration								
0-4 years	11.36	13.20	12.86	6.83	13.77	8.63	10.72	12.45
5-9 years	11.12	4.56	9.31	11.80	11.20	6.59	10.97	6.66
10-14 years	14.78	12.83	16.29	10.09	11.33	8.71	13.53	10.49
≥15 years	15.54	15.95	16.99	18.39	24.17	16.69	16.09	18.54
Type 2 Diabetes								
<65 years old								
Overall								
Number of hospitalizations	35	33	57	64	63	49	53	61
Incidence rate	0.88	0.76	1.24	1.33	1.26	0.97	1.05	1.19
Subgroups								
Age group								
18-44 years	0.72	0.99	0.63	0.75	1.02	1.00	0.86	0.70
45-64 years	0.90	0.73	1.34	1.42	1.29	0.96	1.08	1.27
Gender								
Male	0.72	0.86	1.39	1.28	1.27	0.66	1.03	1.18
Female	1.11	0.63	1.02	1.39	1.24	1.42	1.08	1.21
Diabetes duration								
0-9 years	0.75	0.50	1.00	1.01	0.97	0.73	0.59	0.69
≥10 years	1.56	2.09	2.36	2.74	2.44	1.85	2.57	2.80
Current anti-diabetic drugs								
Insulin with/without oral drug(s)	3.85	3.24	6.00	6.10	5.52	3.61	4.99	6.30
Sulfonylureas with/without other oral drug(s)	0.51	0.48	0.75	0.63	0.87	0.94	0.55	0.44
Other§	0.18	0.17	0.08	0.30	0.25	0.25	0.25	0.27
Type 2 Diabetes								
≥65 years old								
Overall								
Number of hospitalizations	225	251	327	346	329	316	324	251
Incidence rate	4.06	4.19	5.17	5.18	4.78	4.51	4.53	3.52
Subgroups								
Age group								
65-79 years	2.66	2.89	3.12	3.66	2.91	2.91	2.97	2.25

≥80 years	7.81	7.59	10.31	8.93	9.24	8.23	8.16	6.45
Gender								
Male	3.92	4.24	4.73	4.83	4.16	4.55	4.41	3.57
Female	4.21	4.15	5.63	5.56	5.46	4.47	4.67	3.47
Diabetes duration								
0-4 years	1.65	1.33	1.40	1.99	1.39	1.10	0.88	1.20
5-9 years	2.52	3.02	2.52	3.12	2.43	1.79	1.92	1.57
10-14 years	5.43	6.62	8.82	7.06	6.97	5.25	5.05	4.07
≥15 years	12.57	11.36	15.55	13.99	13.25	14.25	13.76	9.31
Current anti-diabetic drugs								
Sulfonylureas only	5.74	4.46	7.76	10.68	9.21	6.05	7.71	6.65
Sulfonylureas + other oral drug(s)	4.20	4.81	5.98	5.61	5.19	5.09	4.49	5.33
Insulin only	20.02	16.44	25.08	23.80	27.95	23.55	29.25	20.01
Insulin + oral drug(s)	12.35	14.41	14.57	16.02	12.21	15.04	13.71	9.19
Other†	0.34	0.61	0.59	0.29	0.50	0.40	0.41	0.24

*Cell counts <5 were not reported with specific values.

† Included self-management alone (i.e., not currently taking any anti-diabetic drug), oral anti-diabetic drug monotherapy (excluding sulfonylureas) or combinations of any anti-diabetic drugs (excluding insulin and sulfonylureas).

Table 3.2. Trends of hypoglycemia hospitalizations in adults with type 1 diabetes

	Period	Annual percent change (95% confidence interval)	*P* value
Overall	1998-2013	3.74 (1.70 to 5.83)	0.001
Age group			
18-44 years	1998-2013	3.91 (0.42 to 7.52)	0.03
45-64 years	1998-2013	5.12 (1.65 to 8.70)	0.01
65-79 years	1998-2013	3.48 (0.59 to 6.46)	0.02
≥80 years	1998-2013	6.71 (3.52 to 9.99)	0.0004
Gender			
Male	1998-2013	3.36 (1.41 to 5.34)	0.002
Female	1998-2013	4.13 (1.43 to 6.89)	0.005
Diabetes duration			
0-4 years	1998-2013	2.67 (-0.77 to 6.22)	0.12
5-9 years	1998-2013	0.47 (-3.38 to 4.47)	0.80
10-14 years	1998-2013	-0.14 (-2.97 to 2.76)	0.92
≥15 years	1998-2013	4.97 (2.66 to 7.33)	0.0004

Table 3.3. Trends of hypoglycemia hospitalizations in young and middle-aged adults with type 2 diabetes

	Period	Annual percent change (95% confidence interval)	*P* value
Overall	1998-2013	4.12 (0.61 to 7.75)	0.02
Age group			
18-44 years	1998-2013	4.23 (-0.99 to 9.73)	0.11
45-64 years	1998-2013	3.90 (0.18 to 7.76)	0.04
Gender			
Male	1998-2013	4.04 (0.04 to 8.21)	0.048
Female	1998-2013	3.77 (-1.01 to 8.77)	0.11
Diabetes duration			
<10 years	1998-2013	3.53 (-0.98 to 8.25)	0.12
≥10 years	1998-2013	1.82 (-2.22 to 6.04)	0.36
Current status of anti-diabetic drug use			
Insulin with/without oral drug (s)	1998-2013	5.76 (1.11 to 10.64)	0.02
Sulfonylureas with/without other oral drug (s)	1998-2013	1.42 (-2.87 to 5.90)	0.50
Other*	1998-2013	2.93 (-2.08 to 8.20)	0.23

* Included self-management alone (i.e., not currently taking any anti-diabetic drug), oral anti-diabetic drug monotherapy (excluding sulfonylureas) or combinations of any anti-diabetic drugs (excluding insulin and sulfonylureas).

Table 3.4. Trends of hypoglycemia hospitalizations in elderly adults with type 2 diabetes*

	Trend 1		Trend 2		Trend 3	
	Period	APC (95% CI)	Period	APC (95% CI)	Period	APC (95% CI)
Overall	1998-2009	8.59 (5.76 to 11.50)	2009-2013	-8.05 (-14.48 to -1.13)		
Age group						
65-79 years	1998-2009	8.28 (4.96 to 11.71)	2009-2013	-8.13 (-16.11 to 0.61)		
≥80 years	1998-2008	8.86 (4.02 to 13.93)	2008-2013	-6.41 (-12.45 to 0.06)		
Gender						
Male	1998-2009	9.00 (5.33 to 12.79)	2009-2013	-6.13 (-14.30 to 2.83)		
Female	1998-2009	8.18 (4.41 to 12.08)	2009-2013	-9.92 (-18.50 to -0.43)		
Diabetes duration						
0-4 years	1998-2013	-1.38 (-4.87 to 2.23)				
5-9 years	1998-2002	24.29 (-5.62 to 63.67)	2002-2013	-6.51 (-9.54 to -3.38)		
10-14 years	1998-2005	3.12 (-3.19 to 9.85)	2005-2008	17.90 (-9.17 to 53.03)	2008-2013	-12.95 (-17.16 to -8.52)
≥15 years	1998-2008	16.60 (8.21 to 25.64)	2008-2013	-6.32 (-13.67 to 1.66)		
Current anti-diabetic drug use						
Sulfonylureas only	1998-2013	9.42 (5.11 to 13.91)				
Sulfonylureas + other OAD	1998-2013	3.74 (0.86 to 6.71)				
Insulin only	1998-2013	7.62 (4.34 to 11.01)				
Insulin + OAD	1998-2009	9.50 (3.98 to 15.30)	2009-2013	-8.71 (-19.92 to 4.06)		
Other*	1998-2013	-0.39 (-5.29 to 4.77)				

Abbreviation: APC, annual percent change; CI, confidence interval; OAD, oral anti-diabetic drug.

* Included self-management alone (i.e., not currently taking any anti-diabetic drug), oral anti-diabetic drug monotherapy (excluding sulfonylureas) or combinations of any anti-diabetic drugs (excluding insulin and sulfonylureas).

Table 3.5. Risk factors for hypoglycemia hospitalizations

	Type 1 diabetes		Type 2 diabetes	
	Crude IRR (95% CI)	Adjusted* IRR (95% CI)	Crude IRR (95% CI)	Adjusted† IRR (95% CI)
Overall (type 1 versus type 2)	4.58 (3.96 to 5.30)	5.61 (5.06 to 6.21)	Reference	Reference
Year				
1998	Reference	Reference	Reference	Reference
2009			5.21 (2.86 to 9.48)	3.66 (2.35 to 5.71)
2013	1.77 (1.01 to 3.13)	1.67 (1.14 to 2.43)	3.45 (1.89 to 6.30)	2.68 (1.71 to 4.20)
Age group				
18-44 years	Reference	Reference	Reference	Reference
45-64 years	1.21 (1.02 to 1.42)	1.13 (0.98 to 1.30)	2.01 (1.43 to 2.81)	1.32 (0.99 to 1.75)
65-79 years	2.46 (2.08 to 2.91)	2.35 (2.03 to 2.72)	4.53 (3.27 to 6.27)	2.92 (2.22 to 3.84)
≥80 years	5.28 (4.42 to 6.32)	5.21 (4.45 to 6.10)	11.93 (8.61 to 16.54)	8.58 (6.51 to 11.31)
Gender				
Male	Reference	Reference	Reference	Reference
Female	1.21 (1.01 to 1.46)	1.11 (1.00 to 1.23)	1.04 (0.90 to 1.21)	1.07 (0.99 to 1.16)
Diabetes duration				
0-4 years	Reference	Reference	Reference	Reference
5-9 years	0.74 (0.55 to 1.01)	0.84 (0.68 to 1.05)	1.24 (1.01 to 1.53)	0.95 (0.84 to 1.08)
10-14 years	1.06 (0.80 to 1.42)	1.14 (0.93 to 1.40)	2.12 (1.73 to 2.61)	1.27 (1.12 to 1.43)
≥15 years	1.67 (1.29 to 2.16)	1.31 (1.11 to 1.54)	3.29 (2.69 to 4.04)	1.66 (1.47 to 1.87)
Current anti-diabetic drugs				
Self-management alone‡			Reference	Reference
Metformin only			0.31 (0.21 to 0.45)	0.42 (0.30 to 0.59)
Sulfonylureas only			7.87 (6.06 to 10.21)	7.44 (6.03 to 9.17)
Sulfonylureas + other oral drug(s)			6.43 (5.01 to 8.25)	6.59 (5.40 to 8.04)
Insulin only			23.45 (18.21 to 30.19)	26.46 (21.53 to 32.51)
Insulin + any oral drug(s)			15.73 (12.25 to 20.21)	18.11 (14.80 to 22.17)
Other§			0.82 (0.53 to 1.27)	1.36 (0.92 to 2.02)

Abbreviation: CI, confidence interval; IRR, incidence rate ratio.

* Adjusted for age (18-44, 45-64, 65-79, ≥80 years), gender (male or female), duration of diabetes (0-4, 5-9, 10-14, ≥15 years) and categorical year, as relevant.

† Adjusted for age (18-44, 45-64, 65-79, ≥80 years), gender (male or female), duration of diabetes (0-4, 5-9, 10-14, ≥15 years), anti-diabetic drug classes as shown in the table and categorical year, as relevant.

‡ Diabetes managed by lifestyle and not currently taking any anti-diabetic drug.

§ Oral anti-diabetic drug monotherapy (excluding metformin and sulfonylureas) or combinations of any anti-diabetic drugs (excluding insulin, metformin and sulfonylureas).

Figure 3.1. Flow chart of identification of type 1 and type 2 diabetes

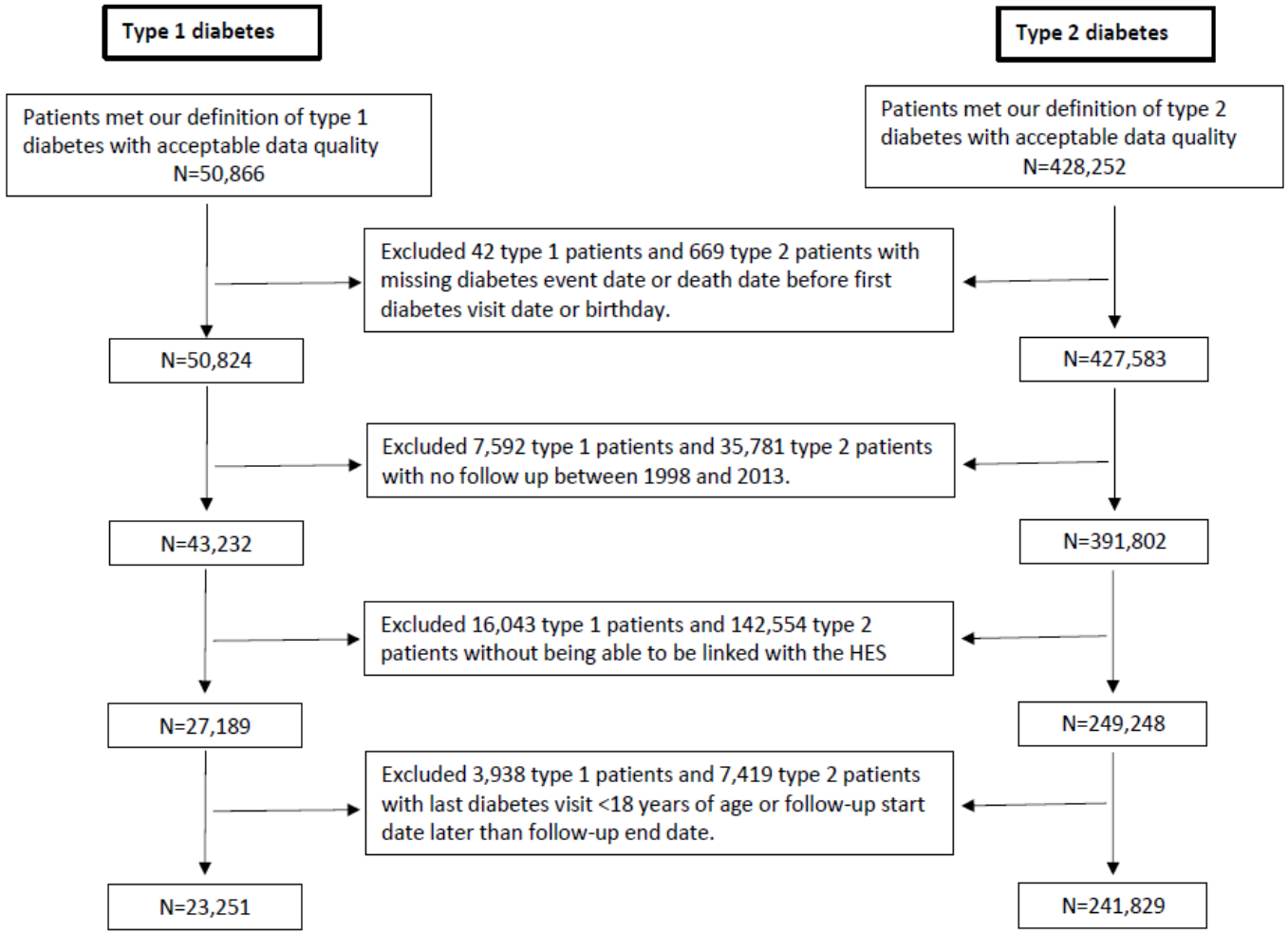


Figure 3.2. Incidence rate of hypoglycemia hospitalizations in adults with type 1 diabetes in the total sample (2A), and by age (2B), gender (2C) and diabetes duration (2D)

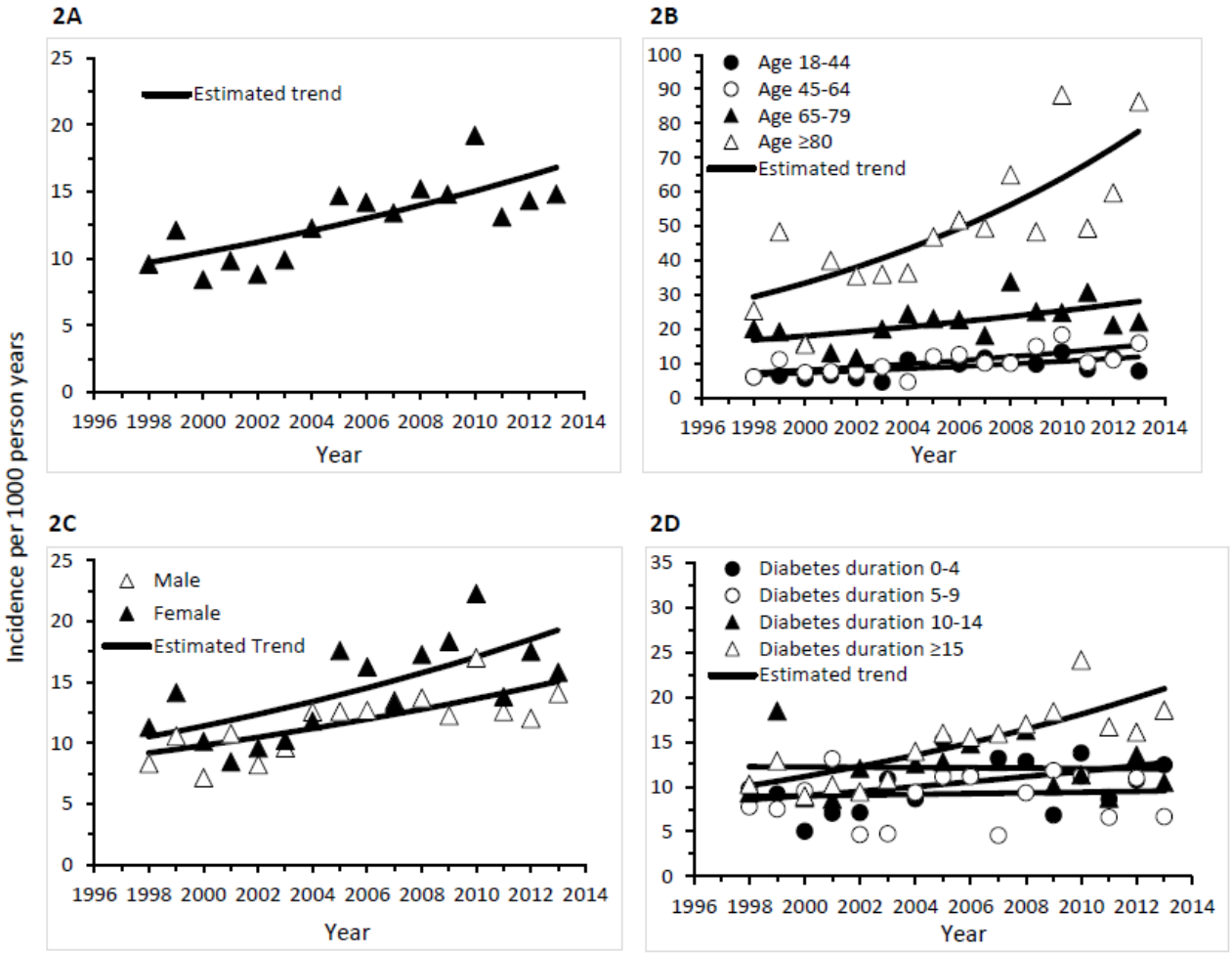
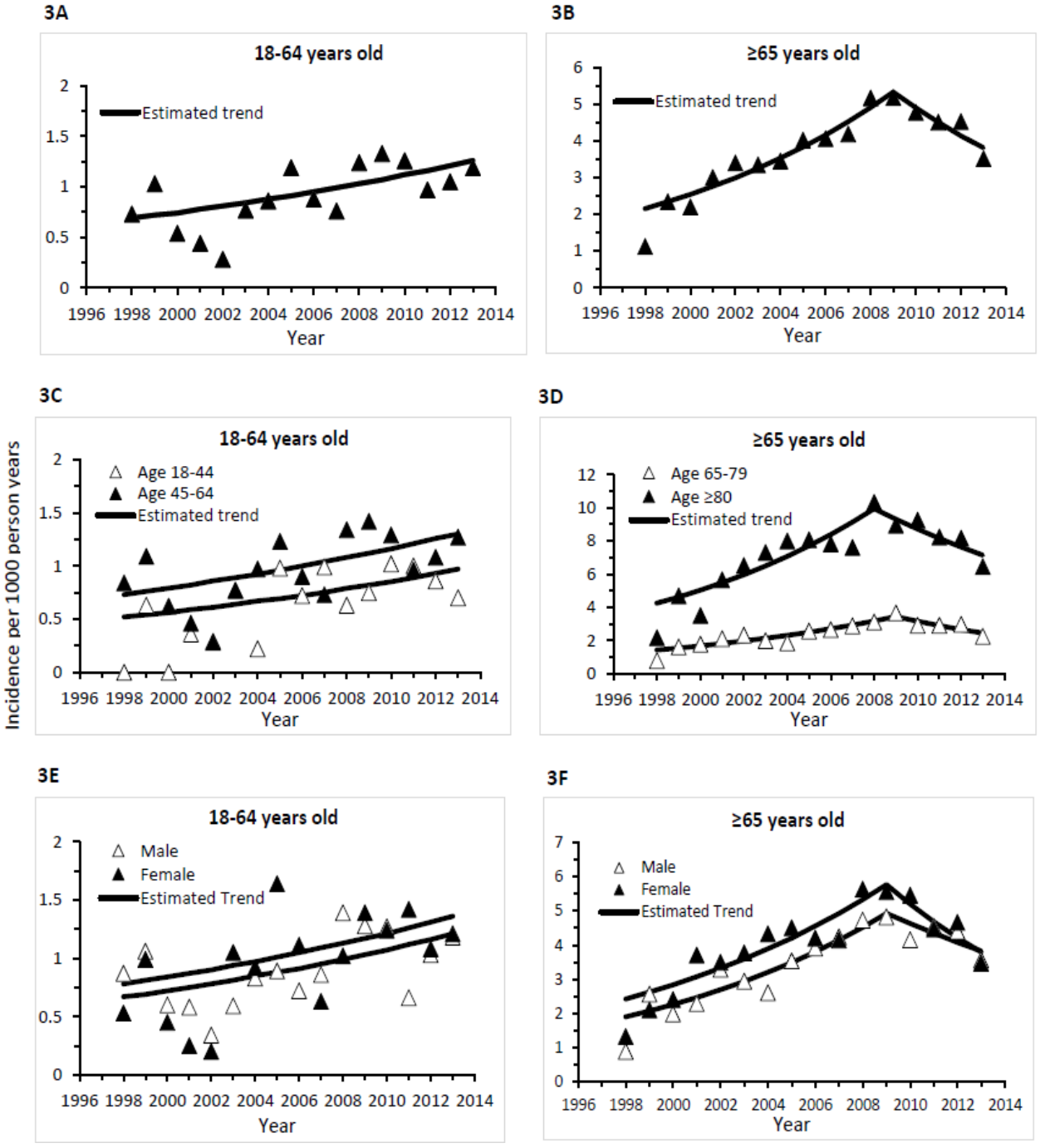
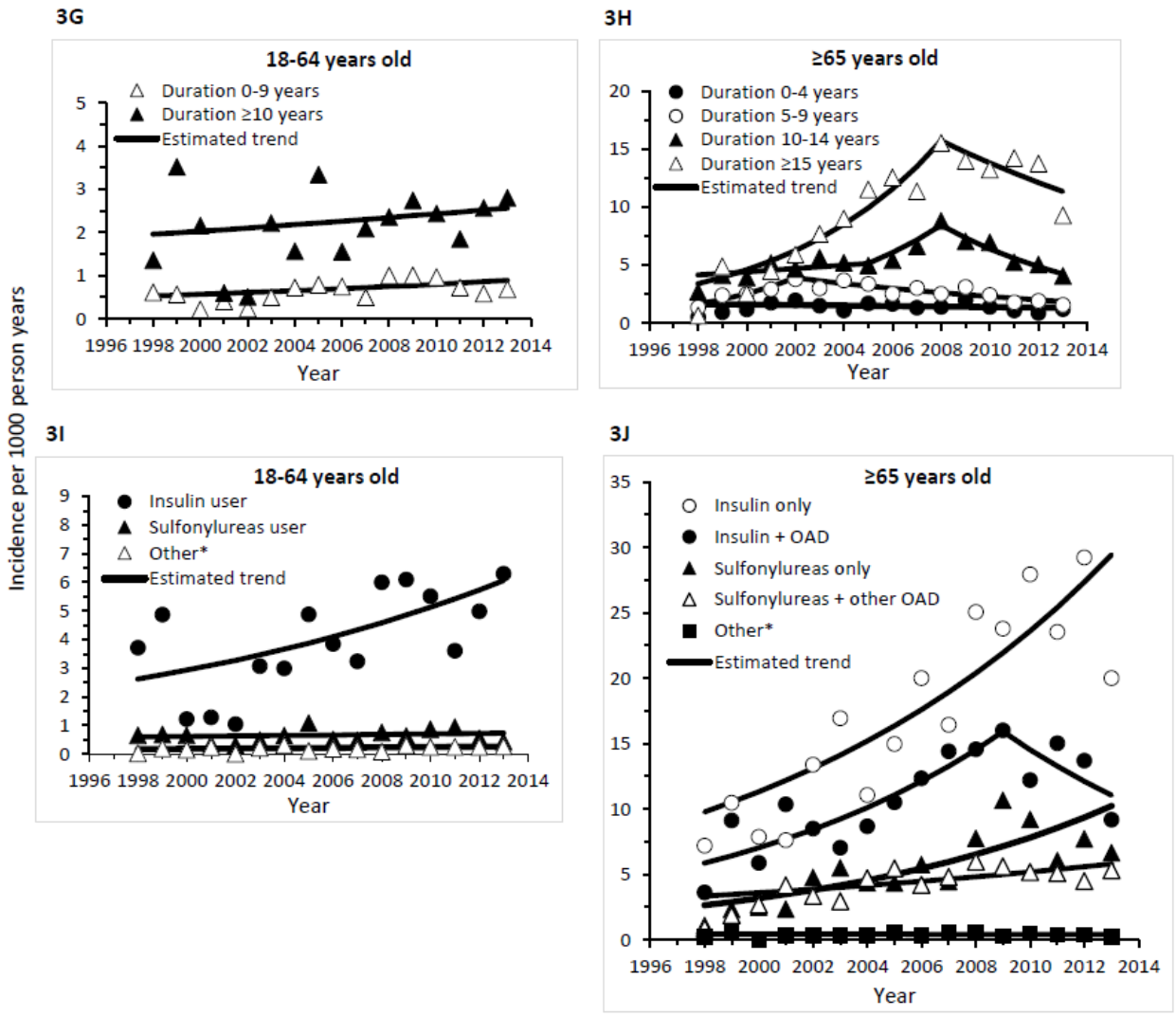


Figure 3.3. Incidence rate of hypoglycemia hospitalizations in young and middle-aged (3A) and elderly adults (3B) with type 2 diabetes in the total sample, and by age (3C and 3D), gender (3E and 3F), diabetes duration (3G and 3H), and current use of anti-diabetic drugs (3I and 3J)





* "Other" included self-management alone (i.e., currently not taking any anti-diabetic drug), oral anti-diabetic drug monotherapy (excluding sulfonylureas) or combinations of any anti-diabetic drugs (excluding insulin and sulfonylureas).

CHAPTER 4. RECENT HBA1C LEVEL AND RISK OF HYPOGLYCEMIA HOSPITALIZATION IN ADULTS WITH TYPE 1 AND TYPE 2 DIABETES: A NESTED CASE-CONTROL STUDY

Introduction

Major diabetes guidelines recommend personalized glycemic management for type 1 diabetes and type 2 diabetes to balance long-term glycemic benefits and short-term hypoglycemia risk.[14, 15, 62, 63] Deciding HbA1c treatment target may need to evaluate individual's hypoglycemia risk factors including age, diabetes duration, comorbidities, current use of anti-diabetic drug(s), life expectancy and history of hypoglycemia. However, the association between HbA1c level and risk of severe hypoglycemia remains unclear. In adults with type 1 diabetes, earlier studies including the DCCT[38] found an inverse association. More recent studies identified a U-shape relationship[74] or that the previous strong inverse association was considerably attenuated with time.[71] In adults with type 2 diabetes, aggressive glycemic control increased the risk of severe hypoglycemia.[114] However, post hoc analyses of the ACCORD trial[72] and other studies[73] found that the risk of severe hypoglycemia was also higher among patients with poor glycemic control.

For investigating the association between HbA1c level and risk of severe hypoglycemia, studies that specifically utilize HbA1c measurements obtained close to the time of severe hypoglycemia are rare. Existing studies used "baseline" HbA1c value measured more than three months or even years before, or updated average HbA1c,[38, 72-75] which may be less predictive of the acute event of severe hypoglycemia. Additionally, the majority of investigations did not

evaluate possible critical interactions between HbA1c level and important patient characteristics that are related to hypoglycemia vulnerability including age, diabetes duration, comorbidities, and specific glucose-lowering medications.[14, 15, 62, 63, 115]

To address these gaps, we analyzed linked primary and secondary care data from the CPRD and HES from the UK. The primary goal was to determine the association between recently measured HbA1c level and risk of hypoglycemia hospitalization in adults with type 1 and type 2 diabetes. Also, we aimed to determine whether the association was modified by age, gender, diabetes duration, weight status, comorbidities, and current anti-diabetic medications.

Methods

The study protocol (15_259RA) was approved by the Independent Scientific Advisory Committee for Medicines and Healthcare Products Regulatory Agency in the UK.

Data sources

Established in 1987, the CPRD is a primary care database that comprises anonymous electronic medical records from 684 practices from England, Scotland, Wales and Northern Ireland as of January 2015.[99] It contained >15 million patient records who were representative of age, gender and geographic regions of the UK. The HES stores patient-level information on every hospital admission to National Health Service hospitals in England only. The CPRD and HES can be linked via a trusted third party.[99] 384 of 684 CPRD practices that can be linked to the HES data between April 1, 1997 and March 31, 2014 comprised our study population. Hypoglycemia hospitalizations were extracted from the HES while all other data were obtained from the CPRD.

Definition of incident type 1 and type 2 diabetes

Criteria to identify diabetes cases and type were adopted from relevant CPRD literature with modifications to reflect specific differentiation between type 1 and type 2 diabetes.[102-104] Among those with at least one diabetes related code, type 1 diabetes was identified if one of the following three criteria was met: (i) ≥1 type 1 code and use of insulin only; (ii) ≥1 type 1 code and use of insulin only on the diagnosis date and OAD, if any, was introduced 6 months later; (iii) ≥2 insulin prescriptions only and ≥1 unspecified diabetes code. Type 2 diabetes was defined as any of the following: (i) ≥2 type 2 codes and 0 type 1 code, regardless of drug use; (ii) ≥1 type 2 code and 0 type 1 code and OAD only; (iii) ≥1 type 2 code and 0 type 1 code and on OAD and insulin, but oral drug prescribed no later than insulin; (iv) ≥2 classes of OAD; (v) ≥2 prescriptions of a non-insulin non-metformin diabetes related drug only. OAD included metformin, sulfonylureas, glinide, thiazolidinediones, DPP-4 inhibitors, SGLT-2 inhibitors, GLP-1 agonists, and acarbose. Patients were excluded if they had non-research quality data determined by the CPRD team or had a record of secondary diabetes, maturity onset diabetes of young, latent autoimmune diabetes in adults, and malnutrition related diabetes. Patients with incident type 1 and type 2 diabetes were those with first diabetes visit >365 days after registration.[102]

Follow-up period and definition of hypoglycemia hospitalization

The start of follow-up was defined using the latest among the following dates: April 1, 1997, first diabetes visit date, registration date, the UTS date, or date of turning 18 years old. UTS is the date at which the practice data is deemed to be of research quality.[99] Follow-up ended on the earliest of the following dates: March 31, 2014, death date, transfer-out date, last data

collection date, or date of having hypoglycemia (E16.0, E16.1 and E16.2) as primary diagnosis for hospitalization.

HbA1c and covariates

The HbA1c value most proximal to but within 90 days of hypoglycemia hospitalization was the exposure (termed recent HbA1c level). We extracted data on age, gender, smoking status, body mass index (BMI), insulin and OAD prescriptions, antihypertensive drug prescriptions (including alpha-blockers, beta-blockers, calcium channel blockers, angiotensin II receptor blockers, angiotensin-converting enzyme inhibitors, renin inhibitors, diuretics, and nitrates), specific diseases that may cause hypoglycemia (including insulinoma, chronic pancreatitis, pancreatic adenoma, pituitary adenoma, cystic fibrosis, hypopituitarism, adrenal insufficiency, and Addison's disease), and Charlson comorbidity score calculated according to the Khan et al.'s approach.[116]Relevant codes for these variables are available upon request.

Nested-case control design

Cases were patients with diabetes who were admitted to hospital due to hypoglycemia. For each case, the index date was the date of hospital admission for hypoglycemia. Up to 6 controls were randomly selected from the case's risk set after matching. Controls were those who had no previous hypoglycemia hospitalization at the risk set date (i.e., index date for controls). Cases and matched controls had equal duration of diabetes in days at the respective index date. For type 1 adults, cases and controls were matched on age (18-44 or ≥45 years), gender (male or female), weight status (normal/underweight or overweight/obese), Charlson score (≤2 or ≥3), and having HbA1c within 90 days of the index date. For type 2 adults, cases and controls were

matched on age (18-64, 65-79, ≥80 years), gender, weight status (normal/underweight, overweight and obese), Charlson score (≤3, 4-5, ≥6), current insulin use (yes/no), current sulphonylureas use (yes/no), and having HbA1c within 90 days of the index date.

Statistical analysis

We performed Wilcoxon-Mann Whitney, χ^2, and Fisher's exact tests to compare cases and controls. Recent HbA1c level was divided into the following categories: <6%, 6-6.9%, 7.0-7.9% (reference), 8-8.9%, ≥9%. ORs and 95% CIs were estimated from conditional logistic regression models. To minimize residual confounding, we sequentially adjusted for matching variables (age, Charlson score, BMI in continuous instead of categorical form), number of years of registration, smoking status (non-smoker, current smoker, ex-smoker, and unknown), current use of antihypertensive drugs (yes/no), and specific diseases causing hypoglycemia as described (yes/no), and current use of metformin (yes/no) or other OAD excluding metformin and sulfonylureas (yes/no) (for type 2 diabetes only). The interaction between recent HbA1c level and risk of hypoglycemia hospitalization by each of the matching variables was tested by adding an interaction term in the fully adjusted model. If *P* value was <0.1, subgroup analyses were performed. In a subset of the study sample with ≥3 HbA1c results prior to hypoglycemia hospitalization, we included HbA1c variability (quantified as standard deviation) as an additional covariate in the fully adjusted model. All analyses were performed separately for type 1 and type 2 diabetes using SAS (version 9.4, SAS Institute Inc., Cary, NC).

Results

Characteristics of cases and controls

In adults with type 1 diabetes, 143 cases of hypoglycemia hospitalization were matched to 817 controls (Table 4.1); cases were more likely to have specific diseases that may cause hypoglycemia compared to controls. In adults with type 2 diabetes, 1,007 cases were matched to 5,842 controls (Table 4.2). Cases had slightly lower HbA1c level, slightly older age and greater Charlson score, lower prevalence of current metformin use, GLP-1 agonists use, and other OAD use, and higher prevalence of specific diseases compared to controls. All other characteristics were similar between cases and controls.

Recent HbA1c level and risk of hypoglycemia hospitalization

In adults with type 1 diabetes

Overall, compared to HbA1c 7-7.9%, higher HbA1c level was associated with lower risk of hypoglycemia hospitalization (Figure 4.1); the OR (95% CI) was 0.48 (0.27-0.85) for HbA1c 8-8.9% and 0.69 (0.42-1.11) for HbA1c ≥9.0%. HbA1c level <7.0% did not increase the risk of hypoglycemia hospitalization. The association between HbA1c level and risk of hypoglycemia hospitalization was modified by weight status (P=0.04, Figure 4.2). In overweight/obese adults with type 1 diabetes, HbA1c <6.0% tended to increase the risk of hypoglycemia hospitalization (OR, 2.82; 95% CI, 0.94-8.44), compared to HbA1c 7-7.9%. higher HbA1c level was related to lower risk of hypoglycemia hospitalization. HbA1c level was not associated with hypoglycemia hospitalization in normal weight or underweight adults with type 1 diabetes. No interaction was observed between HbA1c level and risk of hypoglycemia hospitalization by age, gender, diabetes duration or comorbidities (P≥0.1); results were not shown.

In adults with type 2 diabetes

Overall, a U-shape relationship between HbA1c level and risk of hypoglycemia hospitalization was identified (Figure 4.1). Specifically, compared to HbA1c 7-7.9%, lower HbA1c level was associated with greater risk of hypoglycemia hospitalization; the OR (95% CI) was 2.40 (1.87-3.08) for HbA1c <6.0% and 1.54 (1.28-1.86) for HbA1c 6-6.9%. The risk of hypoglycemia hospitalization was also higher with HbA1c ≥9.0% (OR, 1.36; 95% CI, 1.09-1.70).

No effect modification for the association between HbA1c level and risk of hypoglycemia hospitalization by age, diabetes duration, weight status or comorbidities was found ($P \geq 0.1$); results were not shown. No clinically meaningful difference was discovered by gender, although the *P* value for interaction was 0.07 (Figure 4.3). Current use of insulin or sulfonylureas modified the association ($P < 0.0001$, Figure 4.4). Among adults with T2D who were not currently taking insulin and sulfonylureas, HbA1c 8-8.9% and ≥9.0% were associated with 88% (OR, 1.88; 95% CI, 1.11-3.17) and 248% (OR, 3.48; 95% CI, 1.98-6.13) higher risk of hypoglycemia hospitalization, respectively, compared to HbA1c 7-7.9%. No association was found with HbA1c <7.0%. Conversely, among current insulin users or sulfonylureas users, HbA1c <7.0% substantially increased the risk of hypoglycemia hospitalization. HbA1c ≥9.0% was associated with increased risk in current insulin users, not current sulfonylureas users.

Inclusion of HbA1c variability as an additional covariate

Results were not affected by adjusting for HbA1c variability in type 1 diabetes while additional adjustment for HbA1c variability in type 2 diabetes attenuated the association between recent HbA1c level and risk of hypoglycemia hospitalization for HbA1c ≥9.0% group only, with

OR (95% CI) from 1.36 (1.09-1.70) to 1.14 (0.90-1.44) (Table 4.3). The attenuation was mainly caused by those not currently taking insulin and sulfonylureas, with OR (95% CI) from 3.48 (1.98-6.13, Figure 4.4) to 2.01 (1.01-3.98). 84.4% of the type 1 sample and 94.9% of the type 2 sample were included for this analysis.

Discussion

In this investigation using a large cohort of adults with incident type 1 and type 2 diabetes from England, the relationship of recent HbA1c level with risk of hypoglycemia hospitalization differed markedly between type 1 and type 2 diabetes. For adults with type 1 diabetes, compared to HbA1c 7-7.9%, risk of hypoglycemia hospitalization was lower with worse glycemic control (HbA1c ≥8.0%) while having better glycemic control (HbA1c <7.0%) did not increase the risk. For adults with type 2 diabetes, a U-shape relationship was discovered. Compared to HbA1c 7-7.9%, better (HbA1c <7.0%) and worst glycemic control (HbA1c ≥9.0%) were associated with higher risk of hypoglycemia hospitalization. Further, the association differed by weights status in type 1 diabetes and current use of anti-diabetic medications in type 2 diabetes. These results supported personalized glycemic targets to reduce hypoglycemia risk.

The differences observed in the association of recent HbA1c level with risk of hypoglycemia hospitalization between type 1 and type 2 diabetes were likely a result of different treatment regimen utilized. Type 1 patients require lifelong exogenous insulin while the majority of type 2 patients do not, which also determines higher incidence of severe hypoglycemia in type 1 diabetes than type 2 diabetes.[12] A few studies evaluated the association between HbA1c level and risk of severe hypoglycemia in samples involving adults with type 1 diabetes; the findings were inconsistent. Earlier studies including the DCCT reported an inverse association,[38, 117] or no

association.[118] A recent study from the DPV Initiative found that the previous strong association was substantially attenuated recently and HbA1c became a minor predictor of severe hypoglycemia.[71] Our population with type 1 diabetes was about 15 years or older on average compared to populations examined in these studies.[38, 71, 117, 118] However, heterogeneity in age may not explain the inconsistencies, because the association between HbA1c level and risk of hypoglycemia hospitalization did not differ by age based on our analyses. Notably, the age distribution from a recently published study from the T1D Exchange Clinic Registry was similar to patients in our study; however, results revealed a U-shape relationship with the lowest risk of severe hypoglycemia in HbA1c 7-7.5% group.[74]

The U-shape relationship between recent HbA1c level and risk of hypoglycemia hospitalization found in our study in adults with type 2 diabetes was similar to the Lipska et al.'s study, but they reported weaker associations.[73] Lipska et al. used HbA1c measured between 1 and 2 years prior to hypoglycemic event as the exposure. They reported that only HbA1c <6.0% (OR, 1.25; 95% CI, 0.99-1.57) but not HbA1c 6-6.9% increased the risk of severe hypoglycemia compared to HbA1c 7-7.9%. The stronger association identified from our study was possibly due to using HbA1c measured in 3 months rather than an earlier time. The former may be more closely related to hypoglycemia as an acute complication. In line with the ACCORD study[72] and the Lipska et al.'s study, we found that poor glycemic control was associated with increased risk of hypoglycemia hospitalization. The main previously proposed explanation was that the increased risk of severe hypoglycemia was driven by a proportion of patients with type 2 diabetes who have persistently high HbA1c and are resistant to intensive anti-hyperglycemic treatment with stronger drugs or higher doses.[38, 72, 73] Another possible explanation may be that those with poorest glycemic control had greatest HbA1c variability, because HbA1c variability

has been positively associated with risk of severe hypoglycemia.[75] In our study, from the lowest to highest HbA1c category, the mean HbA1c standard deviation was 0.94, 0.92, 1.01, 1.12, 1.38, respectively (*P* for trend <0.0001; data not shown). Adjusting for HbA1c variability attenuated the association considerably in the poorest glycemic control group (HbA1c ≥9.0%). However, HbA1c variability did not explain the increased risk of hypoglycemia with low HbA1c (HbA1c <7.0%).

Interaction analyses from our study revealed critical subgroup findings. For type 1 diabetes, HbA1c <6.0% potentially increased the risk of hypoglycemia hospitalization only among overweight/obese adults. Overweight/obese individuals are likely to be more insulin resistant.[119] Thus, more intensive insulin regimens may be used, which may increase hypoglycemia risk. However, we could not rule out it as a chance finding. For type 2 diabetes, the association between recent HbA1c level and risk of hypoglycemia hospitalization differed according to current use of insulin or sulfonylureas. The interpretation of the association in subgroups by medication should take into account the background incidence of hypoglycemia hospitalization within each subgroup. In our data, the incidence of hypoglycemia hospitalization per 1000 persons-years was 0.21, 2.47, 6.67 and 7.62, respectively, among those who were not currently taking insulin and sulfonylureas, current sulfonylureas users, current insulin users, and current both users (data not shown in table). Among adults with type 2 diabetes who were not currently taking insulin and sulfonylureas, HbA1c 8-8.9% and ≥9.0% increased the risk of hypoglycemia hospitalization by 88% and 248%, respectively. Even after adjusting for HbA1c variability, HbA1c ≥9.0% still significantly increased the risk by approximately 100%. This implied that more stringent glycemic control may be appropriate for type 2 adults who were self-managed alone or currently taking anti-diabetic drugs other than insulin and sulfonylureas.

Conversely, the risk of hypoglycemia hospitalization was substantially increased with low HbA1c level among current insulin or sulfonylureas users who also had considerably high background incidence of severe hypoglycemia. This implied that less stringent glycemic control may be appropriate for adults with type 2 diabetes who were currently on insulin or sulfonylureas, for reducing individual's risk of severe hypoglycemia and hypoglycemia burden to associated healthcare system.

Our study was unique because it was the only study using HbA1c measured specifically within 3 months of hypoglycemic event. Further, we compared the association of recent HbA1c level with risk of hypoglycemia hospitalization between type 1 and type 2 diabetes, both overall and by subgroups. However, limitations should be noted. Firstly, the study outcome was a selective sample of all hypoglycemia hospitalizations due to restrictions of requiring availability of recent HbA1c and case-control matching. The included and excluded hypoglycemia hospitalizations were not different in patients with type 1 diabetes (Supplemental Table 4.1), but differed in patients with type 2 diabetes (Supplemental Table 4.2). Secondly, misclassification of diabetes type may be possible. However, we used conservative definitions to differentiate diabetes type and identify incident diabetes compared to other CPRD studies,[102, 120, 121] which minimized misclassification error. Thirdly, the data completeness in the CPRD and diabetes coding methodology were improved due to the introduction of the Quality of Framework financial incentive scheme in 2004 and the diabetes type-specific Read codes in 2006.[112] However, the association between recent HbA1c level and risk of hypoglycemia hospitalization remained similarly when only investigating the sample from more recent years after 2006 (P=0.86, data not shown). Fourthly, our study was not designed to study absolute risk differences. Translating OR estimates should be in the context of background incidence of severe

hypoglycemia in specific population subgroups. Finally, though treatment intensification is an important risk factor of severe hypoglycemia and associated with HbA1c,[38, 114] it was not accounted in the current analyses.

In conclusion, the association of recent HbA1c level with risk of hypoglycemia hospitalization differed substantially between adults with type 1 and type 2 diabetes. Different HbA1c targets may be applied to individuals with diabetes for hypoglycemia management according to diabetes type and patient characteristics including weight status in type 1 diabetes and current use of insulin or sulfonylureas in type 2 diabetes. Future studies are encouraged that have both recently measured HbA1c and detailed information on intensification of treatment with time and are also able to study interactions among recent HbA1c level, intensive therapy, and patient characteristics.

Table 4.1. Characteristics of cases with hypoglycemia hospitalization and matched controls in adults with type 1 diabetes

	Cases (N=143) %	Control (N=817) %	*P* value
Recent HbA1c level	8.26 ± 1.83	8.46 ± 1.76	0.08
Category of recent HbA1c level			0.07
<6%	6.99	5.39	
6-6.9%	18.18	13.34	
7-7.9%	26.57	21.30	
8-8.9%	16.78	26.32	
≥9%	31.47	33.66	
Matching variables			
Age, years	51.42 ± 21.35	48.66 ± 19.55	0.16
Age groups			0.93
18-44 years	41.96	42.35	
≥45 years	58.04	57.65	
Male	56.64	55.69	0.83
Duration of diabetes, years	16.64 ± 12.40	15.39 ± 11.07	0.41
Duration of diabetes category			0.55
0-14 years	53.85	56.55	
≥15 years	46.15	43.45	
BMI	25.13 ± 4.64	25.51 ± 4.47	0.08
Weight status			0.74
Normal/underweight	53.15	51.65	
Overweight/obese	46.85	48.35	
Charlson comorbidity score	2.83 ± 2.08	2.55 ± 1.71	0.23
Comorbidity category			0.77
Charlson score ≤2	51.05	52.39	
Charlson score ≥3	48.95	47.61	
Other confounders			
Number of years of registration	30.30 ± 16.17	28.15 ± 14.84	0.16
Smoking status			0.26
Non-smoker	28.67	31.70	
Current smoker	25.87	18.73	
Ex-smoker	16.78	17.50	
Unknown	28.67	32.07	
Current use of antihypertensive drugs[a]	46.15	43.57	0.57
Specific diseases causing hypoglycemia[b]	4.90	1.71	**0.02**

P values <0.05 were in bold.

Plus/minus values were means and standard deviations. All other values were percentages.

[a] Included alpha-blockers, beta-blockers, calcium channel blockers, angiotensin II receptor blockers, angiotensin-converting enzyme inhibitors, renin inhibitors, diuretics, and nitrates.

[b] Included insulinoma, chronic pancreatitis, pancreatic adenoma, pituitary adenoma, cystic fibrosis, hypopituitarism, adrenal insufficiency, and Addison's disease.

Table 4.2. Characteristics of cases with hypoglycemia hospitalization and matched controls in adults with type 2 diabetes

	Cases (N=1,007) %	Control (N=5,842) %	*P* value
Recent HbA1c level	7.52 ± 1.75	7.67 ± 1.52	**<0.0001**
Category of recent HbA1c level			**<0.0001**
<6%	13.60	7.39	
6-6.9%	32.37	27.85	
7-7.9%	23.34	30.74	
8-8.9%	13.01	17.63	
≥9%	17.68	16.38	
Matching variables			
Age, years	74.74 ± 11.79	74.15 ± 11.32	**0.02**
Age groups			0.98
18-64 years	17.28	17.36	
65-79 years	41.91	42.14	
≥80 years	40.81	40.50	
Male	54.02	54.25	0.90
Duration of diabetes, years	11.54 ± 6.68	11.22 ± 6.28	0.36
Duration of diabetes categories			0.71
0-7 years	31.78	32.20	
8-13 years	35.15	36.03	
≥14 years	33.07	31.77	
BMI	28.55 ± 6.71	28.64 ± 6.20	0.25
Weight status			0.84
Normal	31.78	30.90	
Overweight	34.36	34.53	
Obese	33.86	34.58	
Current insulin use	41.71	41.00	0.67
Current sulfonylureas use	41.21	41.25	0.98
Charlson score	4.31 ± 2.22	4.12 ± 2.23	**0.01**
Comorbidity category			0.82
Charlson score ≤3	40.42	41.10	
Charlson score =4,5	31.08	31.34	
Charlson score ≥6	28.50	27.56	
Other confounders			
Number of years of registration	30.51 ± 17.47	30.17 ± 16.55	0.97
Smoking status			0.09
Non-smoker	33.86	36.49	
Current smoker	11.52	9.21	
Ex-smoker	33.37	32.93	
Unknown	21.25	21.36	
Current metformin use	43.69	56.85	**<0.0001**
Current glinide use	0.50	0.65	0.57
Current thiazolidinediones use	6.06	7.22	0.18
Current DPP4 inhibitor use	2.78	3.08	0.61
Current GLP1 agonist use	<0.50	1.01	**0.03**
Current acarbose use	0.79	0.77	0.94
Current other oral drug use[a]	9.43	12.12	**0.01**

Current use of antihypertensive drugs[b]	88.08	86.13	0.10
Specific diseases causing hypoglycemia[c]	1.79	1.03	**0.04**

Abbreviations: DPP4, inhibitors of dipeptidyl peptidase 4; GLP-1; glucagon-like peptide-1 agonists.

Plus/minus values were means and standard deviations. All other values were percentages.

The cells with count <5 were not provided with specific value/percentage.

P values <0.05 were in bold.

[a] Included glinide, thiazolidinediones, DPP4 inhibitors, GLP-1 agonists, inhibitors of sodium-glucose co-transporter 2, and acarbose.

[b] Included alpha-blockers, beta-blockers, calcium channel blockers, angiotensin II receptor blockers, angiotensin-converting enzyme inhibitors, renin inhibitors, diuretics, and nitrates.

[c] Included insulinoma, chronic pancreatitis, pancreatic adenoma, pituitary adenoma, cystic fibrosis, hypopituitarism, adrenal insufficiency, and Addison's disease.

Table 4.3. Recent HbA1c level and risk of hypoglycemia hospitalization in adults with type 1 and type 2 diabetes, accounting for HbA1c variability[a]

	Cases / controls (N)	Category of recent HbA1c level, odds ratio (95% confidence interval)					*P* for interaction[b]
		<6%	6-6.9%	7-7.9%	8-8.9%	≥9%	
Type 1 diabetes							
Total							
Model 1[c]	143/817	1.01 (0.44-2.32)	1.03 (0.58-1.83)	Ref	**0.48 (0.27-0.85)**	0.69 (0.42-1.11)	
Model 2[d]	121/689	1.12 (0.44-2.82)	1.36 (0.73-2.54)	Ref	**0.44 (0.23-0.82)**	0.62 (0.35-1.09)	
Subgroups							
Overweight/obese							0.16
Yes	58/341	3.17 (0.85-11.84)	1.10 (0.43-2.81)	Ref	**0.31 (0.12-0.76)**	0.63 (0.29-1.37)	
No	63/348	0.33 (0.05-2.03)	1.85 (0.72-4.72)	Ref	0.70 (0.27-1.81)	0.73 (0.30-1.77)	
Type 2 diabetes							
Total							
Model 3[e]	1,007/5,842	**2.40 (1.87-3.08)**	**1.54 (1.28-1.86)**	Ref	0.95 (0.75-1.20)	**1.36 (1.09-1.70)**	
Model 4[f]	957/5,542	**2.26 (1.73-2.94)**	**1.53 (1.26-1.86)**	Ref	0.91 (0.71-1.15)	1.14 (0.90-1.44)	
Subgroups							
Gender							0.12
Male	519/3,013	**2.07 (1.44-2.98)**	**1.78 (1.37-2.31)**	Ref	0.83 (0.60-1.17)	1.06 (0.77-1.47)	
Female	438/2,529	**2.47 (1.67-3.65)**	1.26 (0.94-1.69)	Ref	0.99 (0.70-1.40)	1.24 (0.89-1.73)	
Status of current insulin and sulfonylureas use							**<0.0001**
Not on insulin and sulfonylureas[g]	222/1,258	1.36 (0.80-2.31)	0.95 (0.62-1.47)	Ref	1.36 (0.75-2.49)	**2.01 (1.01-3.98)**	
Sulfonylureas use only	326/1,959	**3.13 (2.11-4.66)**	**1.65 (1.22-2.23)**	Ref	0.67 (0.43-1.06)	0.59 (0.34-1.01)	
Insulin use only	342/1,980	**2.33 (1.31-4.14)**	**2.00 (1.40-2.85)**	Ref	0.98 (0.68-1.41)	1.37 (0.99-1.91)	
Both	67/345	3.29 (0.64-16.88)	**2.63 (1.10-6.27)**	Ref	1.16 (0.46-2.96)	1.33 (0.58-3.06)	

Values in bold were significant (i.e. P <0.05)

[a] Only show fully-adjusted results for subgroup analyses (i.e., with HbA1c standard deviation and number of HbA1c test results included).

[b] *P* value was from the interaction term between HbA1c categorical variable and each of the stratification variables in the fully adjusted model.

[c] Model 1 included HbA1c categories, age in years, gender, BMI, Charlson score, duration of diabetes, years of registration, smoking status (non-smoker, current smoker, ex-smoker and unknown), current use of antihypertensive drugs (y/n), and specific diseases (y/n).

[d] Model 2: Model 1 + HbA1c standard deviation calculated from all previous HbA1c results prior to hypoglycemia hospitalization, and number of

HbA1c test results.

[e] Model 3 included HbA1c categories, age in years, gender, BMI, Charlson score, duration of diabetes, current insulin user (y/n), current sulfonylureas user (y/n), years of registration, smoking status (non-smoker, current smoker, ex-smoker and unknown), current use of antihypertensive drugs (y/n), specific diseases (y/n), current metformin user (y/n), and current other anti-diabetic drug user (y/n).

[f] Model 4: Model 3 + HbA1c standard deviation calculated from all previous HbA1c results prior to hypoglycemia hospitalization, and number of HbA1c test results.

[g] Included self-management alone (i.e., by lifestyle only) or currently taking anti-diabetic drug(s) other than insulin and sulfonylureas.

Figure 4.1. Association between recent HbA1c level and risk of hypoglycemia hospitalization among adults with type 1 and type 2 diabetes in the total sample

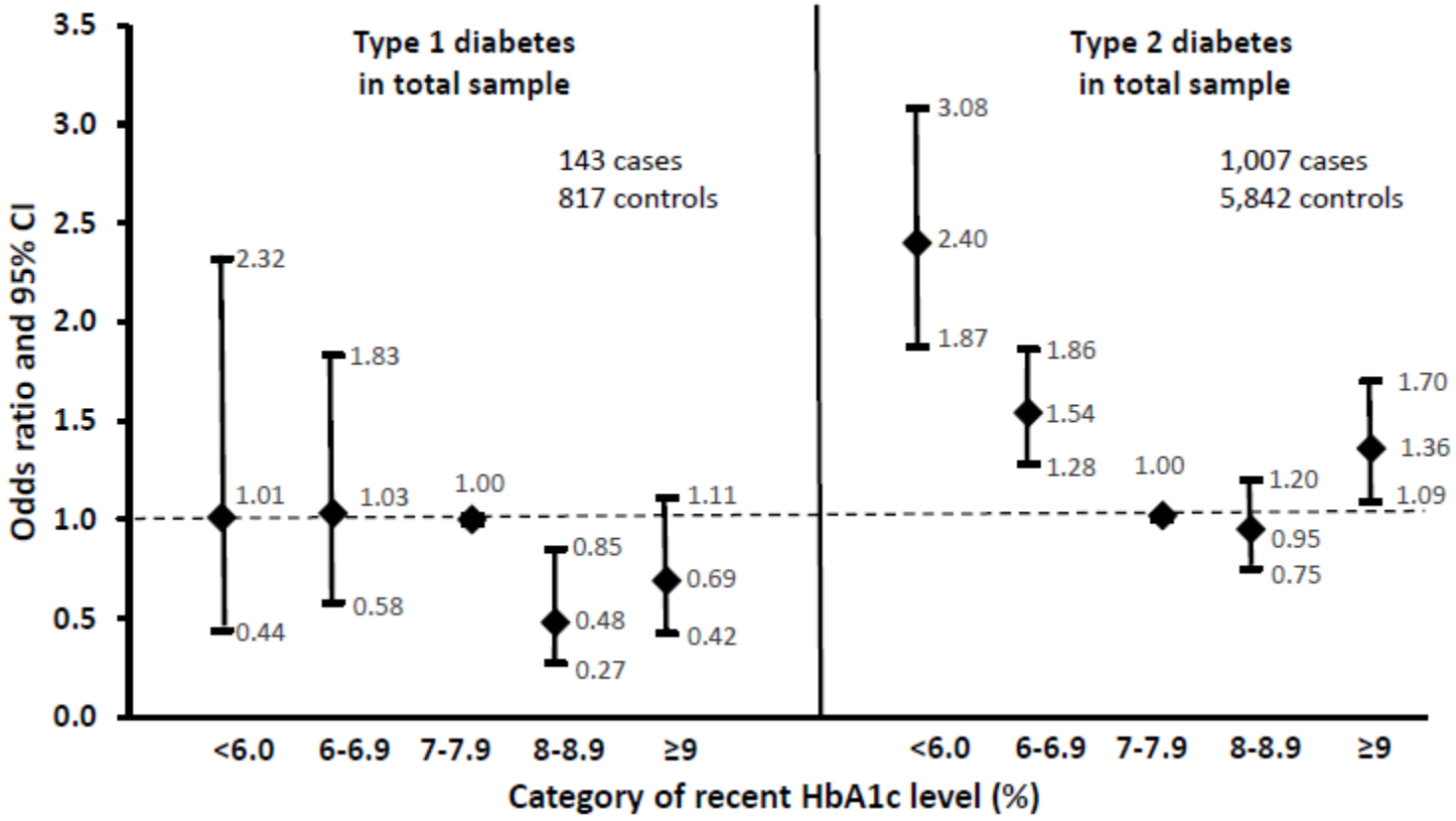


Figure 4.2. Association between recent HbA1c level and risk of hypoglycemia hospitalization among adults with type 1 diabetes, by weight status

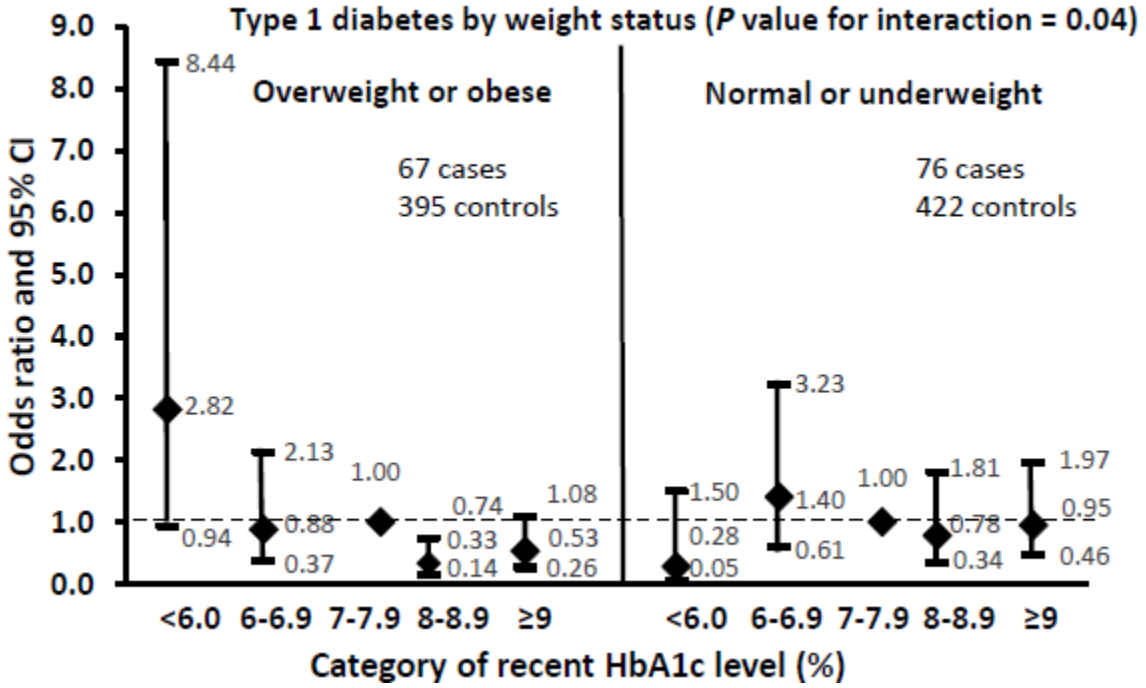


Figure 4.3. Association between recent HbA1c level and risk of hypoglycemia hospitalization among adults with type 2 diabetes, by gender

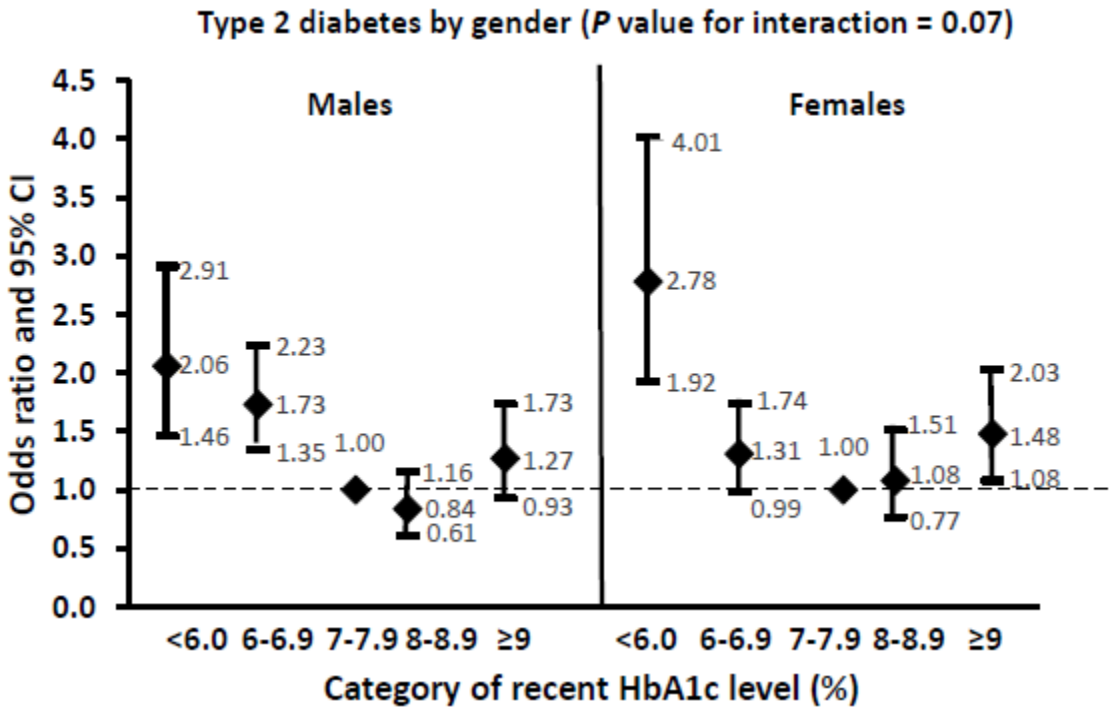


Figure 4.4. Association between recent HbA1c level and risk of hypoglycemia hospitalization among adults with type 2 diabetes, by anti-diabetic medication

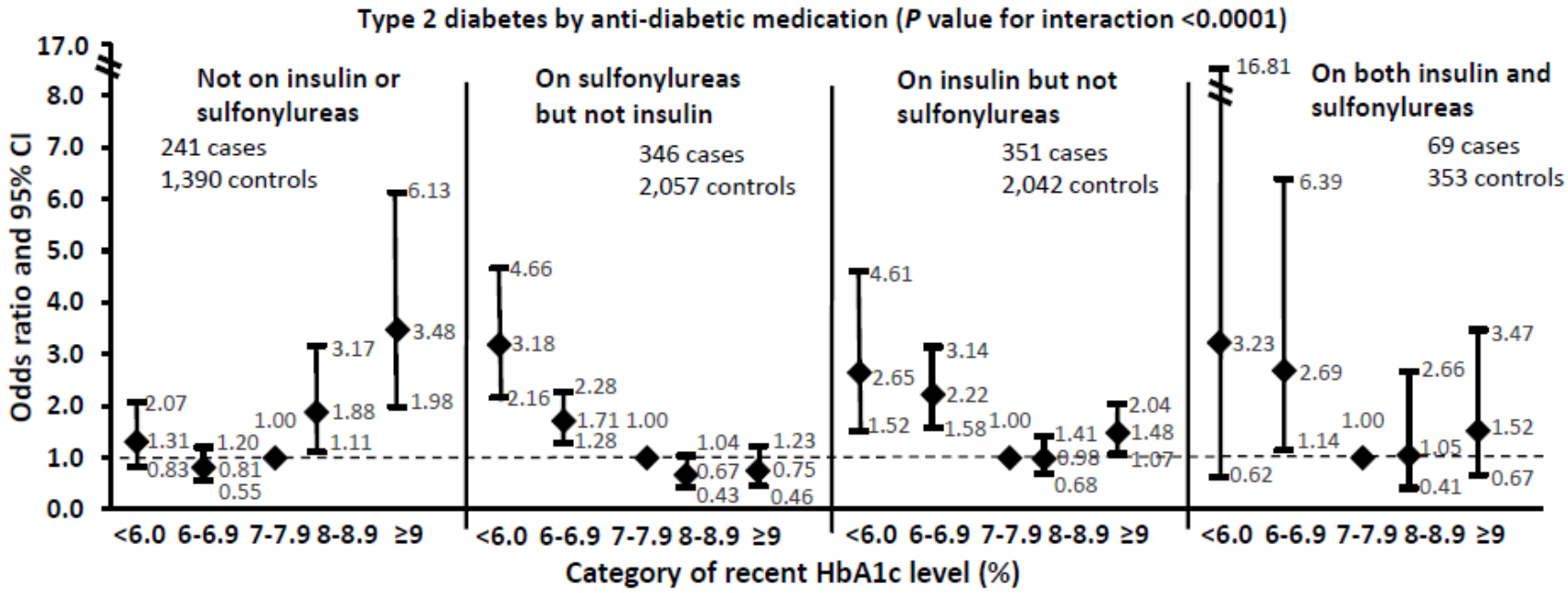


Figure legend for Figure 4.1-4.4

The displayed results were estimated from conditional logistic regression in fully adjusted models (reference: HbA1c 7-7.9%). In type 1 diabetes, the fully adjusted model included HbA1c categories, age in years, gender, BMI, Charlson score, duration of diabetes, number of years of registration, smoking status (non-smoker, current smoker, ex-smoker and unknown), current use of antihypertensive drugs (yes/no), and specific diseases causing hypoglycemia (yes/no). In type 2 diabetes, the fully adjusted model additionally included current insulin use (yes/no), current sulfonylureas use (yes/no), current metformin use (yes/no), and current use of other oral anti-diabetic drug excluding metformin and sulfonylureas (yes/no). For both types in subgroup analyses, the stratification variable was not included in the fully adjusted model. *P* value was from the interaction term between HbA1c categorical variable and each of the stratification variables in the fully adjusted model.

Supplemental Table 4.1. Characteristics of cases of hypoglycemia hospitalization included and excluded in adults with type 1 diabetes

	Excluded (N=168) %	Included (N=143) %	*P* value
Age, years	53.83 ± 22.64	51.42 ± 21.35	0.33
Male	53.57	56.64	0.59
Duration of diabetes, years	14.84 ± 11.42	16.64 ± 12.40	0.23
BMI	24.75 ± 5.15	25.13 ± 4.64	0.34
Charlson score	2.87 ± 2.11	2.83 ± 2.08	0.99
Years of registration	29.34 ± 15.93	30.30 ± 16.17	0.64
Smoking status			0.26
Non-smoker	31.70	28.67	
Current smoker	18.73	25.87	
Ex-smoker	17.50	16.78	
Unknown	32.07	28.67	
Current use of antihypertensive drugs[a]	47.62	46.15	0.81
Specific diseases causing hypoglycemia[b]	6.55	4.90	0.53

Plus/minus values were means and standard deviations. All other values were percentages.

[a] Included alpha-blockers, beta-blockers, calcium channel blockers, angiotensin II receptor blockers, angiotensin-converting enzyme inhibitors, renin inhibitors, diuretics, and nitrates.

[b] Include insulinoma, chronic pancreatitis, pancreatic adenoma, pituitary adenoma, cystic fibrosis, hypopituitarism, adrenal insufficiency, and Addison's disease.

Supplemental Table 4.2. Characteristics of cases of hypoglycemia hospitalization included and excluded in adults with type 2 diabetes

	Excluded (N=731) %	Included (N=1,007) %	*P* value
Age, years	77.89 ± 10.50	74.74 ± 11.79	**<0.0001**
Male	45.83	54.02	**0.0007**
Duration of diabetes, years	10.98 ± 7.22	11.54 ± 6.68	**0.03**
BMI	28.27 ± 9.19	28.55 ± 6.71	0.06
Charlson score	4.32 ± 2.34	4.31 ± 2.22	0.76
Years of registration	29.93 ± 16.64	30.51 ± 17.47	0.64
Smoking status			**<0.0001**
Non-smoker	25.99	33.86	
Current smoker	8.62	11.52	
Ex-smoker	24.62	33.37	
Unknown	40.77	21.25	
Current use of antihypertensive drugs[a]	85.64	88.08	0.15
Specific diseases causing hypoglycemia[b]	2.33	1.79	0.43
Current insulin use	31.46	41.71	**<0.0001**
Current sulfonylureas use	41.72	41.21	0.83
Current metformin use	29.96	43.69	**<0.0001**
Current other oral drug use[c]	4.38	9.43	**<0.0001**

Plus/minus values were means and standard deviations. All other values were percentages.

P values <0.05 were in bold.

[a] Included alpha-blockers, beta-blockers, calcium channel blockers, angiotensin II receptor blockers, angiotensin-converting enzyme inhibitors, renin inhibitors, diuretics, and nitrates.

[b] Included insulinoma, chronic pancreatitis, pancreatic adenoma, pituitary adenoma, cystic fibrosis, hypopituitarism, adrenal insufficiency, and Addison's disease.

[c] Included glinide, thiazolidinediones, inhibitors of dipeptidyl peptidase-4, glucagon-like peptide-1 agonists, inhibitors of sodium-glucose co-transporter-2, and acarbose.

CHAPTER 5. USUAL DIETARY INTAKE AND RISK OF NON-SEVERE HYPOGLYCEMIA IN ADOLESCENTS WITH TYPE 1 DIABETES

Introduction

Hypoglycemia occurs frequently in people with type 1 diabetes with an incidence of over 1-2 episodes per week per patient.[122] Hypoglycemia is preventable and nutrition therapy plays a pivotal role in this.[76] Current nutrition guidelines are very specific in terms of how to treat hypoglycemia when it occurs;[30] glucose, sucrose or any form of carbohydrates are to be immediately administered. However, information regarding whether or how usual dietary intake influences risk of hypoglycemia is limited, particularly for children with diabetes. Medical nutrition therapy for adults may not be applicable to children or even conflicts with the evidence rising from pediatric populations.[76, 82] Further, the literature has primarily focused on postprandial glycemic excursions following experimental meals in clinical trial settings, which is directly related to acute dietary effect on blood glucose after consuming test meals.[82, 89, 123] Yet, to our knowledge, no study has examined the effect of usual dietary intake on the risk of hypoglycemia measured by CGM in free-living youth with type 1 diabetes, which associates typical dietary patterns with day-to-day glycemic control.

Youth with type 1 diabetes are particularly vulnerable to hypoglycemia due to unpredictable food consumption, erratic activity, and problems with accurate insulin dosing and detecting hypoglycemia.[30, 62] Their brains are still developing and central nervous systems are not yet mature, which put them at high risk of cognitive dysfunction and neurological sequelae of hypoglycemia.[12, 124] If untreated, mild or moderate hypoglycemia can develop into severe

hypoglycemia, resulting in seizure, coma, and death.[30] Repeated episodes of severe hypoglycemia may even cause permanent damage to the brain with structural changes in the white and gray matter of developing brains.[31]

The present study focused on non-severe (i.e., mild or moderate) hypoglycemia, which is a low blood glucose event <70 mg/dL but does not require external assistance for recovery. Non-severe hypoglycemia accounts for 88-98% of all hypoglycemic events in patients with diabetes.[25] We aimed to determine the association between usual dietary intake and risk of developing non-severe hypoglycemia in a one-week period in a sample of adolescents with type 1 diabetes who participated in the FL3X randomized clinical trial (ClinicalTrials.gov identifier: NCT01286350). The primary goal of the FL3X trial is to improve glycemic control and quality of life in adolescents with type 1 diabetes through an evidence-based flexible lifestyle intervention.

Methods

Participants

Study participants were a subset of 258 adolescents with type 1 diabetes from the FL3X trial who also participated in the ancillary study: *Measures of Hypoglycemia and Glycemic Variability Using Continuous Glucose Monitoring*. Eligible participants were aged 13-16 years at study entry who had HbA1c 8-13% and duration of diabetes >1 year. Participants were enrolled from two sites: Barbara Davis Center for Childhood Diabetes in Colorado and Cincinnati Children's Hospital Medical Center in Ohio, coordinated by the University of North Carolina (UNC) at Chapel Hill. Written informed consent was obtained from parents or legal guardians.

The study protocol was approved by the Institutional Review Boards at each participating site. For the current study, data were collected during one week period of time at baseline.

Measuring blood glucose using CGM

At the baseline visit, the iPro2 CGM system (Medtronic Inc.) with the Enlite sensor was inserted into the abdominal subcutaneous adipose tissue. Participants were carefully instructed on the use and maintenance of the CGM system and were advised to calibrate the sensor before eating and before bed with iPro2 compatible glucometer (OneTouch Ultra2). The Enlite sensor measured interstitial glucose level every five minutes within a range 40–400 mg/dL. On the last day of the CGM wear week, participants were reminded to send the devices back, using the pre-paid box/envelope given at the end of the study visit in the first day. The CGM data were downloaded with CareLink iPro System and uploaded to the CGM data coordinating center for data processing. CGM readings were blinded to study participants. No alarms for hypoglycemia or hyperglycemia or any communication from the device were available to participants.

24-hour dietary and physical activity recalls

Telephone-administered 24-hour dietary recalls were administered to participants (ideally one weekday and one weekend day) to ascertain dietary intake. Interviews were conducted by trained and certified interviewers from the UNC NIH/NIDDK Nutrition Obesity Research Center (NORC) staff (P30DK056350), using the Nutrient Data System for Research software (NDSR Version 2014, Nutrition Coordinating Center, University of Minnesota, Minneapolis, MN) and the multiple pass interviewing method.[125, 126]

The validated Previous Day Physical Activity Recall (PDPAR)[127, 128]divided the day into half-hour time blocks and queried the dominant activity and the approximate intensity of that activity for that period. The activity intensity level was grouped into light (slow breathing, little or no movement), moderate (normal breathing and some movement), hard (increased breathing and moderate movement), and vary hard (hard breathing and quick movement).The PDPAR was under the direction of the UNC NORC and administered concurrent with the 24-hour dietary recalls.

Other data

Self-reported data were collected using standardized questionnaires including age, gender, race, highest parental education, duration of diabetes, insulin delivery method, and insulin dose. Weight, height, and HbA1c level were measured or assayed according to standardized protocols. BMI was calculated as weight (kg)/height squared (m^2) and converted to a BMI z score using the Center for Disease Control/National Center for Health Statistics (CDC/NCHS) 2000 reference curves.[129]

Statistical analysis

No severe hypoglycemic events were reported during the study week. Non-severe hypoglycemic events were defined as having CGM readings <70 mg/dL for 10 minutes or more.[130, 131] They were further categorized into daytime and nocturnal non-severe hypoglycemia. This distinction is important because current insulin preparations do not adequately mimic normal physiologic patterns of insulin secretion[92] and sleep attenuates counter-regulatory responses to hypoglycemia.[93] Further, dietary intake and exercise[94] as two major determinants of

blood glucose occur mainly in the daytime. Accordingly, dietary intake is likely to influence differently on hypoglycemia risk between day and night. Hypoglycemia that occurred between 11:00 PM and 7:00 AM was defined as nocturnal hypoglycemia.[130]

Usual daily dietary intake in the study week was averaged from two 24-hour dietary recalls. Macronutrients of interest were total carbohydrate, total protein, animal protein, plant protein, total fat, saturated fat (SFA), MUFA, PUFA, ratio of MUFA to SFA (MUFA/SFA), and ratio of PUFA to SFA (PUFA/SFA). Total fiber, soluble fiber, insoluble fiber, GI, and GL were also studied. Patients with no dietary recall, one recall only, and two recalls were compared. Further, for those with two dietary recalls, patient characteristics and average daily dietary intake were compared among four groups of participants: no hypoglycemia, daytime hypoglycemia only, nocturnal hypoglycemia only, and both daytime and nocturnal hypoglycemia. Differences were evaluated by the Wilcoxon-Mann-Whitney test for two-group comparison and Kruskal-Wallis test for comparison of three or four groups.

Among those with two dietary recalls, logistic regression models were used to identify dietary predictors of daytime hypoglycemia (those with ≥1 episode of daytime hypoglycemia versus those without, regardless of nocturnal hypoglycemia), and nocturnal hypoglycemia (those with ≥1 episode of nocturnal hypoglycemia versus those without, regardless of daytime hypoglycemia). ORs and 95% CIs were estimated. All adjusted models included total calories, CGM wear time, and average number of meals per day. Other covariates were also adjusted if associated *P* value was ≤0.2, including age, gender, race (white, non-white), highest parental education (four-year college or more, some college or less), duration of diabetes, BMI z score, hours with vigorous or moderate physical activity per day, hours with electronic media time or

TV time per day, and HbA1c. Finally, insulin delivery method (pump versus multiple daily injection) and insulin dose per kilogram were added to the fully adjusted model.

Results

Patient characteristics

Among 258 adolescent participants from the FL3X trial at baseline, 128 had no dietary recall; 32 had only one recall while 98 had two recalls (Table 5.1). Participants with no dietary recalls had approximately 0.3% higher HbA1c compared to those with two recalls (P=0.06). Participants with one recall had higher animal protein intake and slightly lower plant protein intake (P=0.04). No difference was found in all other patient characteristics and dietary variables.

Among 98 participants who had two 24-hour dietary recalls, 17 of them had no non-severe hypoglycemia during the study week and 55 developed both daytime and nocturnal non-severe hypoglycemia (Table 5.2). Participants with non-severe hypoglycemia were not different from those without in terms of age, gender, race, diabetes duration, BMI z score, insulin delivery method, insulin dose per kilogram, parental education, and physical activity. However, lower HbA1c level was seen in participants with non-severe hypoglycemia. Regarding dietary intake, descriptively, total fiber including both soluble fiber and insoluble fiber intake were higher in participants with non-severe hypoglycemia than those without. Conversely, the GI of the diet was higher in participants without non-severe hypoglycemia. Participants with both daytime and nocturnal non-severe hypoglycemia had lower MUFA intake compared to participants with only daytime or nocturnal non-severe hypoglycemia or without non-severe hypoglycemia.

Usual dietary intake and risk of daytime non-severe hypoglycemia

Fully adjusted models show that total carbohydrate and the GL were not associated with risk of daytime non-severe hypoglycemia (Figure 5.1A, Table 5.3). Every five units higher in the GI of the diet was associated with 68% lower risk of daytime non-severe hypoglycemia (OR, 0.32; 95% CI 0.14-0.73). Intake of soluble fiber, not total fiber, was positively related to the risk of daytime non-severe hypoglycemia (Figure 5.1B); the OR (95% CI) for every five grams more intake of soluble fiber with risk of daytime non-severe hypoglycemia was 7.86 (0.98-62.19). Higher total protein intake by 10 grams per day was associated with higher risk of daytime non-severe hypoglycemia (OR, 1.47; 95% CI 1.00-2.17; Figure 5.1C). No meaningful difference between animal and plant protein was found. However, type of fat was important. Intake of total fat or SFA was not related to risk of daytime non-severe hypoglycemia while consumption of unsaturated fat was protective (Figure 5.1D). Consuming five grams more MUFA (OR, 0.55; 95% CI 0.30-1.00) and PUFA (OR, 0.47; 95% CI 0.24-0.90) per day were associated with lower risk of daytime non-severe hypoglycemia. An inverse association of MUFA/SFA ratio and PUFA/SFA ratio with risk of daytime non-severe hypoglycemia was also found. Adjusting for insulin delivery method did not change results. However, after accounting for insulin dose per kilogram, all associations disappeared except for PUFA/SFA ratio.

Usual dietary intake and risk of nocturnal non-severe hypoglycemia

Total carbohydrate, the GI, and the GL of the diet were not associated with risk of nocturnal non-severe hypoglycemia (Table 5.4, Figure 5.2A), according results from the fully adjusted model. Similar to daytime non-severe hypoglycemia, soluble fiber intake per 5 grams was positively associated with risk of nocturnal non-severe hypoglycemia (OR 8.57, 95% CI

1.33-55.07; Figure 5.2B). Higher total protein intake by 10 grams was associated with higher risk of nocturnal non-severe hypoglycemia (OR 1.36, 95% CI 0.99-1.86; Figure 5.2C). Dietary fat intake was not related to risk of nocturnal non-severe hypoglycemia, including both saturated and unsaturated fat (Figure 5.2D). Adjusting for insulin delivery method did not change results. After accounting for insulin dose per kilogram, the positive association of soluble fiber and total protein with risk of nocturnal non-severe hypoglycemia was no longer statistically significant. Unexpectedly, PUFA/SFA ratio was negatively associated with risk of nocturnal non-severe hypoglycemia.

Discussion

In adolescents with type 1 diabetes, non-severe hypoglycemia was common. Over 80% of the study participants developed non-severe hypoglycemia within a week. Higher intake of soluble fiber and protein was associated with higher risk of both daytime and nocturnal non-severe hypoglycemia. The risk of daytime non-severe hypoglycemia was lower with eating higher GI diet or with higher MUFA and PUFA intake. Insulin delivery method did not influence these associations. After accounting for insulin dose per kilogram, none of these associations remained, except for the inverse association with PUFA/SFA ratio. Our findings suggest that even though diet-hypoglycemia associations were explained by insulin dose per kilogram, hypoglycemia was still very common. How to inject correct dose of insulin at correct time to match freely consumed meals to reduce clinically unfavorable events such as hypoglycemia remains challenging.

Our analyses revealed that total amount of carbohydrate intake was not a predictor of non-severe hypoglycemia in adolescents with type 1 diabetes, but quality of carbohydrate

(soluble fiber and GI) was related to risk of non-severe hypoglycemia. We found that higher intake of soluble fiber, not total fiber, was associated with increased risk of daytime non-severe hypoglycemia. Previous literature demonstrated that the reduction of postprandial glucose responses after carbohydrate-rich meals was mainly driven by soluble fiber, not insoluble fiber, via hindering macronutrient absorption and slowing gastric emptying.[132] However, none of the published studies in type 1 diabetes populations in the CGM context differentiated the two types of fiber. Nonetheless, Maahs et al.[84] reported that every one gram increase in total dietary fiber intake was associated with 2.4 to 6.5 mg/dL lower postprandial blood glucose up to 4 hours, in free-living adolescents with type 1 diabetes. Maahs et al. did not examine the association of dietary fiber with risk of hypoglycemia. Lafrance et al.[83] found that high-fiber diet decreased mean blood glucose, but did not increase the incidence of hypoglycemia. However, Lafrance et al. conducted their study in well-controlled patients with type 1 diabetes on intensive insulin therapy in a clinical trial setting. Further, the fiber content in the test breakfast of Lafrance et al.'s study was approximately 50 grams/1000 kcal, which was substantially higher than that in our study. Therefore, their results may not be comparable to our study findings.

Another important trait of carbohydrate quality is the GI. An inverse association between the GI and risk of daytime non-severe hypoglycemia was identified from our analyses. Discerning the independent effect of the GI from fiber is usually difficult,[76] because foods rich in fiber generally have a low GI, although not all foods with a low GI necessarily have a high fiber content.[133] However, the negative GI-hypoglycemia relationship remained in our data even after adjusting for fiber or other major macronutrients (data not shown). Previous studies consistently reported that low-GI foods or diet lowered mean blood glucose concentrations and reduced peak glucose excursion compared to high-GI foods or diet in people with type 1 diabetes.[83, 85-87]

However, the relationship between the GI and hypoglycemia risk was much less consistent. Nansel et al.[86] found increased incidence of hypoglycemia with low-GI diet in children with type 1 diabetes while other studies did not evaluate hypoglycemia risk[85] or reported no difference between low- and high-GI diet regarding hypoglycemia risk.[83, 87] Notably, these studies used various definitions of low- and high-GI diet, monitored different length of blood glucose, and assigned test meals at different timing. All these may have led to inconsistent findings regarding the relationship between the GI and hypoglycemia risk. Nonetheless, existing evidence indicates that consistent consumption of a low-GI diet may reduce insulin requirement and improve average blood glucose.[86, 90] If usual carbohydrate-to-insulin ratio is used, the risk of hypoglycemia may be increased with consuming low-GI diet in type 1 diabetes.

Our finding that higher protein intake was associated with higher risk of non-severe hypoglycemia is in line with the current nutrition recommendations for managing adults with diabetes,[76] which does not recommend protein for treating or preventing hypoglycemia. Ingested protein appears to increase insulin secretion without increasing blood glucose concentrations in type 2 diabetes and thus may increase hypoglycemia risk.[78, 79] However, the glycemic effect of protein is likely to be different between type 1 and type 2 diabetes given the minimal capacity to secrete insulin in type 1 diabetes, although residual insulin secretion in youth with type 1 diabetes may be relevant.[80, 81] A review of experimental studies in type 1 diabetes led by Bell et al.[90] stated that protein tends to increase glucose concentrations in the late postprandial period. Also, a randomized trial in youth with type 1 diabetes reported that protein had a protective effect on the development of hypoglycemia in the 5-h postprandial period when comparing a diet containing 40 grams of protein to the other diet including only 5 grams of protein, holding fat and carbohydrate constant.[82] This protective effect may not exist in free-living people with type

1 diabetes consuming different amount of protein with different amount of other macronutrients throughout the day, because the glycemic effect of protein depends on the amount of protein and carbohydrate within a meal.[90] However, we did not find an interaction between carbohydrate and protein in relation to hypoglycemia risk (data not shown). Another reason that may explain the positive association between protein intake and risk of non-severe hypoglycemia is that meal-related insulin dosing may not only consider carbohydrate but also fat/protein.[90] Currently, specific insulin dosing guidelines account only for carbohydrate,[134] yet individual experience commonly leads to adjustments for meals high in fat or protein. Thus, some study participants may bolus more insulin than needed for high-protein meals, resulting in greater hypoglycemia risk.

Our data also revealed that fat quality mattered in terms of managing hypoglycemia in adolescents with type 1 diabetes. We found that higher MUFA and PUFA intake, not total fat and saturated fat, were associated with lower risk of daytime non-severe hypoglycemia. To our knowledge, we did not find any diet and CGM study that distinguished fat types. Rather, dietary fat as a whole was considered. Studies from Wolpert et al.,[135] Smart et al.[82] and other investigators[136, 137] demonstrated that meals containing carbohydrate and that are also high in dietary fat can cause sustained late high postprandial blood glucose up to or over 5 hours. The relevant mechanisms are delayed gastric emptying, impaired insulin sensitivity, and enhanced hepatic glucose production.[138] If individuals with type 1 diabetes do not adjust insulin dose for dietary fat, they may be more likely to have hyperglycemia instead of hypoglycemia. However, these findings from previous studies could not explain the difference between saturated and unsaturated fat. In a randomized trial conducted among obese adults with type 2 diabetes, a low carbohydrate diet that was high in unsaturated fat and low in saturated fat reduced glucose

variability measured by 48-hour CGM. Stabilizing glucose may reflect reduction of both hyper- and hypoglycemia. However, adjusting for glucose variability did not change the present results (data not shown). Also, the differential effect on insulin resistance between saturated and unsaturated fat does not apply here; unsaturated fat causes less profound insulin resistance than saturated fat.[139] Future work is needed to confirm our findings and propose mechanistic explanations.

Another notable finding from our study is that dietary intake was a stronger predictor of non-severe hypoglycemia in the daytime than nighttime. Similarly, an early large study on type 1 children by Beregszàszi et al.[140] did not find a difference in food consumption in the daytime between participants with nocturnal hypoglycemia and those without. The GI-hypoglycemia relationship of our study was consistent with the Nansel et al.'s study.[86] They also reported no differences in the mean blood glucose and hypoglycemia risk in the night between consuming a low-GI and a high-GI diet in type 1 children, although the mean blood glucose was lower and hypoglycemia risk was higher in the daytime.[86] Probably, the main reason is that the failure of insulin replacement to mimic normal insulin secretion of pancreas causes a mismatch between nighttime insulin requirements and blood glucose, leading to nocturnal hypoglycemia.[92, 141] In our study, only higher intake of protein or soluble fiber was associated with increased risk of nocturnal non-severe hypoglycemia.

The dietary associations with hypoglycemia were explained by insulin dose per kilogram statistically, but hypoglycemia still occurred in over 80% of our study sample. An important missing piece here may be the timing of insulin injection. The injection time depends on blood glucose concentration, meal composition, exercise, and type of insulin.[142] Different types of insulin have disparate pharmacokinetic properties with different onset, peak, and duration, which

further complicates insulin dosing.[143] We do not know if the high risk of hypoglycemia was in part a consequence of incorrect timing of insulin administration since we did not collect relevant data. Further, inappropriate insulin dose may still be related. Explaining the identified diet-hypoglycemia associations is not equal to correct insulin dose delivered. That current guidelines rely primarily on carbohydrate counting,[134] is not sufficient.[90] Optimal actual amount and delivery pattern of insulin for meals high in fat or protein or varying in the GI are not yet fully understood.

Our study is the largest investigation so far that examined the association of usual dietary intake with risk of non-severe hypoglycemia in CGM-wearing adolescents with type 1 diabetes. However, there are a few important limitations. First, participants with two dietary recalls are a selective sample from all participants in the FL3X trial. However, they are not different from the FL3X trial participants in all variables except for slightly higher HbA1c (P=0.06). Second, participants are not representative of all youth with type 1 diabetes because of requiring HbA1c 8-13% and duration of diabetes >1 year for inclusion. They are a group of patients with poor glycemic control. Third, two days of 24-hour recalls may not capture usual dietary intake, and reporting bias may occur. However, participants were interviewed using multi-pass method on two unannounced non-consecutive days, which may have reduced the bias. Fourth, although our study is the largest study of dietary intake in the CGM setting, the sample size is still not large, which precludes assessment of potential interactions among nutrients and effect modifications by baseline glycemic status, diabetes duration, and pubertal status. Fifth, we did not consider the severity of hypoglycemia which is related to duration of low blood glucose <70 mg/dL and the lowest glucose concentration within a hypoglycemic episode. Finally, the definition of nocturnal

hypoglycemia is arbitrary, although 11PM-7AM threshold is commonly used in the literature.[130, 144]

In conclusion, different nutrients from usual dietary intake had different estimated effects on the occurrence of non-severe hypoglycemia in free-living adolescents with type 1 diabetes. Also, usual dietary intake was differentially associated with risk of non-severe hypoglycemia between daytime and nighttime. Our findings suggest that protein intake may be positively associated with risk of non-severe hypoglycemia and quality of carbohydrate and fat may be critical to reduce risk of non-severe hypoglycemia. Insulin dose per kilogram accounted for the dietary effects on hypoglycemia statistically; thus incorrect timing of insulin injection may be a key for frequent hypoglycemic events observed in adolescents with type 1 diabetes. Future studies that have information on every insulin dosing activity with accurate insulin dose and timing recorded are required to better understand the relationship among diet, insulin timing and dose, and risk of hypoglycemia.

Table 5.1. Patient characteristics according to number of 24-dietary recalls available during the baseline visit

	No recall (N=128)	one recall (N=32)	Two recalls (N=98)	*P**
Characteristics, % or mean ± SD				
Age, years	14.99 ± 1.16	14.69 ± 1.02	14.77 ± 1.15	0.26
Male	51.56	43.75	51.02	0.72
White	84.38	81.25	90.82	0.25
Diabetes duration, years	6.57 ± 3.84	5.73 ± 3.34	6.28 ± 3.79	0.53
HbA1c, %	9.79 ± 1.28	9.58 ± 0.95	9.40 ± 1.15	0.06
BMI z score	0.67 ± 0.96	0.64 ± 0.99	0.64 ± 0.94	0.79
On insulin pump	70.08	68.75	72.16	0.91
Insulin dose per kilogram, unit	0.98 ± 0.33	0.93 ± 0.33	1.00 ± 0.31	0.90
Parental education with 4-year college or more	59.38	53.13	65.31	0.42
Exercise level				
Vigorous, hours/day	0.75 ± 0.76	0.96 ± 1.29	0.89 ± 1.09	0.94
Moderate, hours/day	3.17 ± 1.99	2.52 ± 1.77	2.54 ± 1.74	0.69
Electronic media time, hours/day	2.79 ± 3.07	1.96 ± 1.60	2.81 ± 2.14	0.19
Television, hours/day	2.04 ± 2.03	1.44 ± 1.45	1.80 ± 1.48	0.35
Average number of daily meals		4.78 ± 1.43	4.86 ± 1.22	0.67
Nutrients, % of total energy				
% calorie from fat		35.21 ± 9.69	35.04 ± 6.04	0.95
% calorie from carbohydrate		47.16 ± 9.96	48.74 ± 7.06	0.50
% calorie from protein		17.61 ± 4.98	16.20 ± 3.88	0.27
% calorie from SFA		12.44 ± 4.15	12.31 ± 3.10	0.83
% calorie from MUFA		11.93 ± 4.32	11.89 ± 2.52	0.89
% calorie from PUFA		7.71 ± 4.61	7.84 ± 2.61	0.32
Nutrients, mean ± SD , grams per 1000 kcal				
Total carbohydrate		120.30 ± 25.67	123.72 ± 18.04	0.54
Total fiber		7.83 ± 3.19	8.43 ± 3.42	0.66
Soluble fiber		2.68 ± 1.59	2.78 ± 1.06	0.20
Insoluble fiber		5.10 ± 2.22	5.59 ± 2.57	0.59
Total protein		43.06 ± 11.71	39.89 ± 9.20	0.31

Animal protein	31.00 ± 11.66	25.96 ± 9.32	**0.04**
Plant protein	12.06 ± 4.53	13.93 ± 4.06	**0.04**
Total fat	39.82 ± 10.85	39.88 ± 6.70	0.89
SFA	14.07 ± 4.67	14.04 ± 3.58	0.79
MUFA	13.48 ± 4.86	13.50 ± 2.80	0.82
PUFA	8.73 ± 5.17	8.93 ± 2.97	0.25
Glycemic load (glucose reference)	68.44 ± 15.61	69.65 ± 11.70	0.53
Glycemic index (glucose reference)	61.31 ± 6.29	60.71 ± 4.28	0.75
MUFA/SFA ratio	1.00 ± 0.33	1.00 ± 0.25	0.73
PUFA/SFA ratio	0.72 ± 0.58	0.74 ± 0.39	0.12

Abbreviation: MUFA, monounsaturated fat; PUFA, polyunsaturated fat; SD, standard deviation; SFA, saturated fat

p values <0.05 were in bold.

*Based on Wilcoxon-Mann-Whitney test for two groups and Kruskal-Wallis test for three groups

Table 5.2. Patient characteristics and average daily dietary intake according to category of non-severe hypoglycemia during one week at baseline visit

	No hypoglycemia (N=17)	Daytime hypoglycemia only (N=15)	Nocturnal hypoglycemia* only (N=11)	Daytime and nocturnal hypoglycemia* (N=55)	*P***
Characteristics, % or mean ± SD					
Age, years	14.12 ± 1.22	14.33 ± 1.11	14.27 ± 1.01	14.33 ± 1.16	0.90
Male	47.06	40.00	63.64	52.73	0.67
White	100.0	93.33	90.91	87.27	0.53
Diabetes duration, years	6.59 ± 3.71	6.29 ± 3.75	8.01 ± 5.13	5.83 ± 3.52	0.55
HbA1c, %	10.21 ± 1.08	9.61 ± 1.07	9.84 ± 1.56	9.01 ± 0.94	**0.001**
BMI z score	1.00 ± 1.03	0.47 ± 1.10	0.40 ± 0.92	0.62 ± 0.87	0.30
On insulin pump	64.71	80.00	63.64	74.07	0.69
Insulin dose per kg, unit	1.03 ± 0.37	1.06 ± 0.37	0.98 ± 0.26	0.98 ± 0.28	0.97
Parental education with 4-year college or more	64.71	60.00	63.64	67.27	0.96
Exercise level					
Vigorous, hours/day	0.91 ± 1.65	0.72 ± 0.82	1.34 ± 1.06	0.83 ± 0.95	0.24
Moderate, hours/day	2.25 ± 2.00	2.20 ± 1.70	3.14 ± 1.70	2.60 ± 1.69	0.24
Electronic media time, hours/day	2.91 ± 2.14	2.43 ± 1.30	2.80 ± 2.01	2.89 ± 2.37	0.99
Television, hours/day	1.31 ± 1.01	2.12 ± 1.13	1.66 ± 1.11	1.90 ± 1.72	0.36
Average number of daily meals	4.71 ± 1.23	4.73 ± 1.56	5.55 ± 1.08	4.81 ± 1.12	0.12
Nutrients, % of total energy					
% calorie from fat	36.87 ± 6.82	34.99 ± 6.27	37.46 ± 6.56	34.01 ± 5.50	0.07
% calorie from carbohydrate	47.79 ± 8.80	49.20 ± 8.76	48.07 ± 8.64	49.05 ± 5.69	0.51
% calorie from protein	15.30 ± 4.41	15.85 ± 3.82	14.43 ± 3.34	16.93 ± 3.74	0.16
% calorie from SFA	12.33 ± 3.61	12.30 ± 3.19	12.49 ± 3.02	12.27 ± 3.02	0.95
% calorie from MUFA	12.67 ± 2.25	11.71 ± 2.36	13.14 ± 2.57	11.45 ± 2.55	**0.04**
% calorie from PUFA	8.91 ± 2.90	7.95 ± 2.51	8.93 ± 2.84	7.25 ± 2.38	0.07
Nutrients, mean ± SD , grams per 1000 kcal					
Total carbohydrate	120.66 ± 22.72	123.51 ± 22.01	123.00 ± 21.07	124.86 ± 14.81	0.49

Total fiber	6.47 ± 1.78	7.98 ± 2.65	8.62 ± 2.62	9.12 ± 3.90	**0.01**
Soluble fiber	2.13 ± 0.50	2.77 ± 1.12	2.70 ± 0.73	2.99 ± 1.16	**0.006**
Insoluble fiber	4.27 ± 1.41	5.18 ± 1.76	5.89 ± 2.02	6.06 ± 2.97	**0.04**
Total protein	37.50 ± 10.10	39.26 ± 8.76	36.96 ± 7.77	41.59 ± 9.09	0.17
Animal protein	24.81 ± 11.51	26.53 ± 9.06	23.23 ± 8.30	26.71 ± 8.95	0.65
Plant protein	12.68 ± 3.06	12.72 ± 2.48	12.73 ± 3.81	14.89 ± 4.52	0.09
Total fat	41.87 ± 7.79	40.09 ± 6.53	42.39 ± 6.72	38.70 ± 6.27	0.09
SFA	14.00 ± 4.35	14.18 ± 3.68	14.04 ± 3.41	14.01 ± 3.43	0.93
MUFA	14.37 ± 2.61	13.36 ± 2.56	14.96 ± 2.64	12.97 ± 2.85	**0.03**
PUFA	10.16 ± 3.40	9.05 ± 2.84	10.14 ± 2.92	8.28 ± 2.75	0.06
Glycemic load (glucose reference)	72.24 ± 15.44	68.03 ± 13.37	69.48 ± 11.77	69.33 ± 10.01	0.84
Glycemic index (glucose reference)	63.48 ± 3.69	59.32 ± 3.61	61.33 ± 4.57	60.10 ± 4.27	**0.01**
MUFA/SFA ratio	1.07 ± 0.22	1.00 ± 0.31	1.11 ± 0.27	0.96 ± 0.24	0.08
PUFA/SFA ratio	0.86 ± 0.43	0.75 ± 0.32	0.83 ± 0.31	0.69 ± 0.41	0.20

Abbreviation: MUFA, monounsaturated fat; PUFA, polyunsaturated fat; SD, standard deviation; SFA, saturated fat

p values <0.05 were in bold.

*10 min or more with low blood glucose <70 mg/dL between 11PM and 7AM defined nocturnal hypoglycemia

**P value from Kruskal-Wallis test.

Table 5.3. Usual dietary intake and risk of daytime non-severe hypoglycemia*

Nutrients	Model 1 Unadjusted	Model 2 Partially adjusted	Model 3 Fully adjusted	Model 4 Adding insulin delivery method	Model 5 Further adding insulin dose/kg
Carbohydrate					
Total carbohydrate, per 10 grams	0.98 (0.93-1.03)	1.11 (0.95-1.29)	1.03 (0.86-1.22)	1.03 (0.86-1.22)	0.93 (0.75-1.17)
Total fiber, per 5 grams	1.07 (0.74-1.53)	1.48 (0.87-2.53)	1.71 (0.86-3.40)	1.73 (0.87-3.47)	1.26 (0.54-2.90)
Soluble fiber. per 5 grams	1.68 (0.53-5.33)	8.44 (1.34-53.28)	7.86 (0.98-63.19)	8.07 (0.98-66.51)	5.02 (0.29-87.96)
Insoluble fiber, per 5 grams	1.03 (0.62-1.69)	1.37 (0.69-2.71)	1.74 (0.68-4.47)	1.76 (0.68-4.57)	1.09 (0.36-3.29)
Glycemic index, per 5 score	**0.44 (0.24-0.79)**	**0.40 (0.21-0.76)**	**0.32 (0.14-0.73)**	**0.32 (0.14-0.74)**	0.35 (0.12-1.04)
Glycemic load, per 10 grams	0.52 (0.22-1.23)	0.69 (0.08-6.19)	0.23 (0.02-3.49)	0.24 (0.02-3.53)	0.04 (<0.001-2.50)
Protein					
Total protein, per 10 grams	0.99 (0.85-1.16)	1.23 (0.91-1.65)	**1.47 (1.00-2.17)**	1.47 (1.00-2.17)	1.34 (0.85-2.12)
Animal protein, per 10 grams	0.99 (0.82-1.20)	1.11 (0.84-1.47)	1.27 (0.91-1.79)	1.28 (0.91-1.80)	1.26 (0.83-1.92)
Plant protein, per 10 grams	0.96 (0.61-1.49)	1.65 (0.78-3.49)	1.86 (0.78-4.42)	1.87 (0.79-4.47)	1.35 (0.40-4.51)
Fat					
Total fat, per 5 grams	**0.94 (0.88-1.00)**	**0.81 (0.66-0.99)**	0.84 (0.67-1.06)	0.84 (0.67-1.06)	1.00 (0.76-1.30)
SFA, per 5 grams	0.93 (0.79-1.09)	1.05 (0.76-1.46)	1.20 (0.80-1.80)	1.20 (0.80-1.81)	1.79 (0.92, 3.48)
MUFA, per 5 grams	**0.80 (0.67-0.97)**	**0.54 (0.33-0.88)**	**0.55 (0.30-1.00)**	**0.55 (0.30-1.00)**	0.93 (0.47-1.83)
PUFA, per 5 grams	**0.68 (0.51-0.92)**	**0.55 (0.34-0.90)**	**0.47 (0.24-0.90)**	**0.47 (0.24-0.90)**	0.55 (0.27-1.11)
MUFA/SFA ratio, per 1 unit	**0.16 (0.03-0.94)**	0.17 (0.03-1.04)	**0.07 (0.01-0.83)**	**0.07 (0.006, 0.83)**	0.16 (0.008-3.29)
PUFA/SFA ratio, per 1 unit	0.41 (0.13-1.26)	0.39 (0.13-1.20)	**0.19 (0.05-0.78)**	**0.19 (0.05-0.78)**	**0.15 (0.03, 0.86)**

Abbreviation. MUFA, monounsaturated fat; PUFA, polyunsaturated fat; SFA, saturated fat.

*Significance results (<0.05) were highlighted in bold, but p value for total protein in the fully adjusted model (Model 3) was 0.0503.

Model 1. Unadjusted.

Model 2. Adjusted for CGM wear time, total energy intake per day, and average number of meals per day.

Model 3. Model 2 + diabetes duration, HbA1c, daily electronic media time in hours, and TV time in hours.

Model 4. Model 3 + insulin delivery method (pump versus multiple daily injection).

Model 5. Model 4 + insulin dose per kilogram.

Table 5.4. Usual dietary intake and risk of nocturnal non-severe hypoglycemia*

Nutrients	Model 1 Unadjusted	Model 2 Partially adjusted	Model 3 Fully adjusted	Model 4 Adding insulin delivery method	Model 5 Further adding insulin dose/kg
Carbohydrate					
Total carbohydrate, per 10 grams	0.96 (0.92-1.01)	0.98 (0.86-1.13)	0.95 (0.82-1.11)	0.94 (0.80-1.10)	0.92 (0.76-1.13)
Total fiber, per 5 grams	1.11 (0.78-1.58)	1.68 (0.98-2.85)	1.73 (0.97-3.08)	1.58 (0.88-2.86)	1.38 (0.67-2.82)
Soluble fiber. per 5 grams	1.47 (0.49-4.38)	**8.43 (1.44-49.46)**	**8.57 (1.33-55.07)**	**7.08 (1.08-46.57)**	5.06 (0.51-50.40)
Insoluble fiber, per 5 grams	1.14 (0.70-1.85)	1.69 (0.85-3.34)	1.76 (0.82-3.75)	1.56 (0.72-3.38)	1.27 (0.51-3.18)
Glycemic index, per 5 score	0.71 (0.42-1.18)	0.79 (0.46-1.36)	0.83 (0.47-1.46)	0.86 (0.48-1.53)	0.57 (0.26-1.24)
Glycemic load, per 10 grams	0.45 (0.19-1.03)	0.37 (0.04-3.07)	0.27 (0.03-2.69)	0.27 (0.03-2.93)	0.10 (0.004-2.66)
Protein					
Total protein, per 10 grams	0.96 (0.82-1.11)	1.24 (0.93-1.66)	1.36 (0.99-1.86)	1.38 (0.99-1.91)	1.35 (0.92-1.98)
Animal protein, per 10 grams	0.95 (0.79-1.13)	1.12 (0.86-1.47)	1.21 (0.91-1.60)	1.23 (0.92-1.64)	1.21 (0.86-1.70)
Plant protein, per 10 grams	0.93 (0.61-1.43)	1.65 (0.81-3.39)	1.66 (0.77-3.54)	1.56 (0.71-3.45)	1.66 (0.59-4.63)
Fat					
Total fat, per 5 grams	0.94 (0.88-1.00)	0.96 (0.80-1.14)	0.97 (0.79-1.18)	0.98 (0.79-1.20)	1.00 (0.78-1.28)
SFA, per 5 grams	0.91 (0.78-1.07)	1.12 (0.81-1.53)	1.18 (0.84-1.67)	1.17 (0.82-1.67)	1.60 (0.93-2.74)
MUFA, per 5 grams	0.85 (0.71-1.02)	0.95 (0.62-1.45)	0.93 (0.57-1.52)	1.00 (0.60-1.68)	1.17 (0.62-2.18)
PUFA, per 5 grams	**0.72 (0.55-0.95)**	0.71 (0.46-1.10)	0.70 (0.44-1.13)	0.71 (0.44-1.16)	0.51 (0.26-1.00)
MUFA/SFA ratio, per 1 unit	0.45 (0.09-2.33)	0.41 (0.07-2.33)	0.30 (0.05-1.96)	0.38 (0.06-2.57)	0.18 (0.02-1.89)
PUFA/SFA ratio, per 1 unit	0.56 (0.19-1.64)	0.51 (0.17-1.54)	0.42 (0.13-1.39)	0.41 (0.12-1.38)	**0.20 (0.04-0.90)**

Abbreviation. MUFA, monounsaturated fat; PUFA, polyunsaturated fat; SFA, saturated fat.

*Significance results (<0.05) were highlighted in bold.

Model 1. Unadjusted.

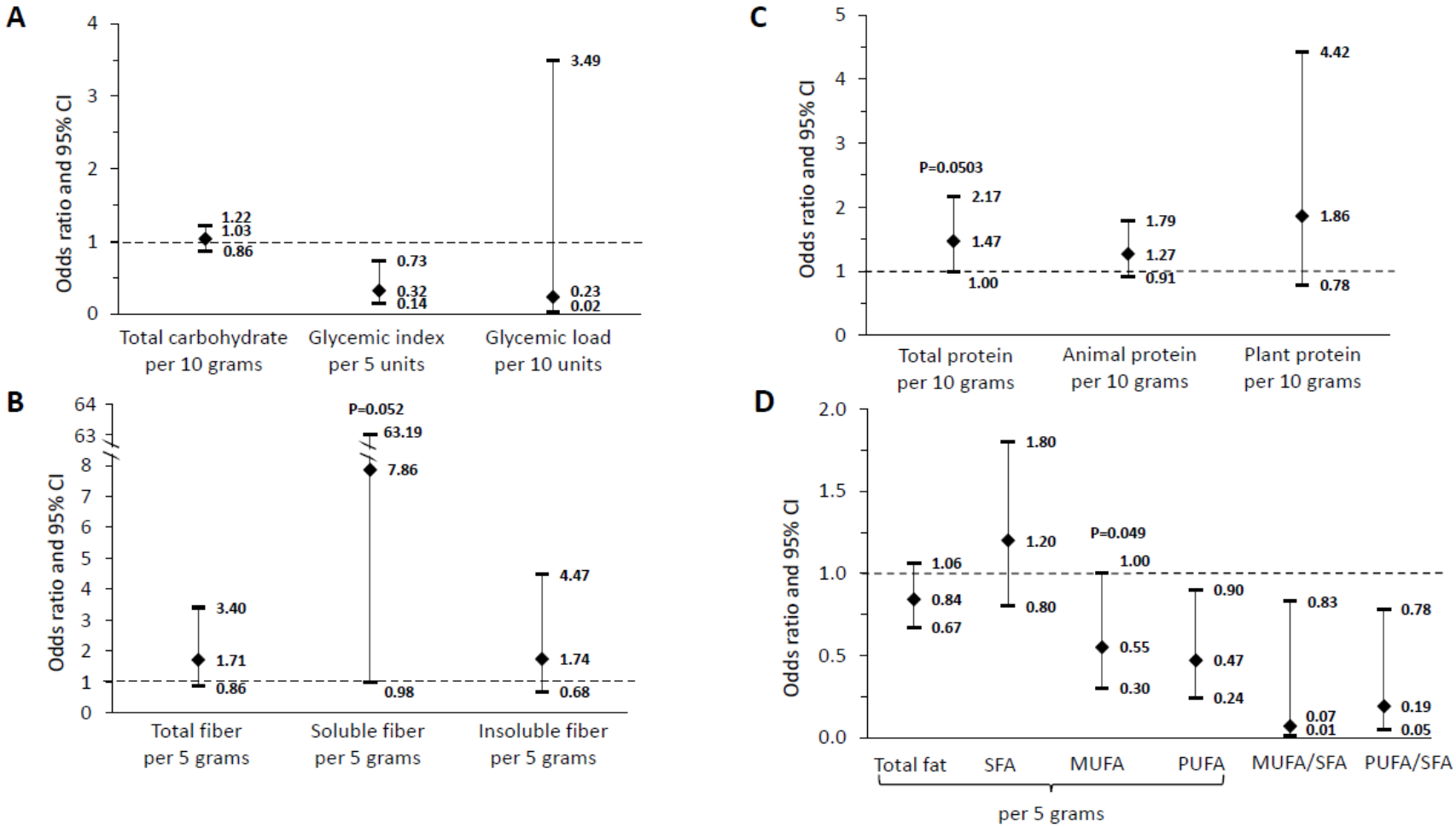
Model 2. Adjusted for CGM wear time, total energy intake per day, and average number of meals per day.

Model 3. Model 2 + diabetes duration, HbA1c, daily electronic media time in hours, and TV time in hours.

Model 4. Model 3 + insulin delivery method (pump versus multiple daily injection).

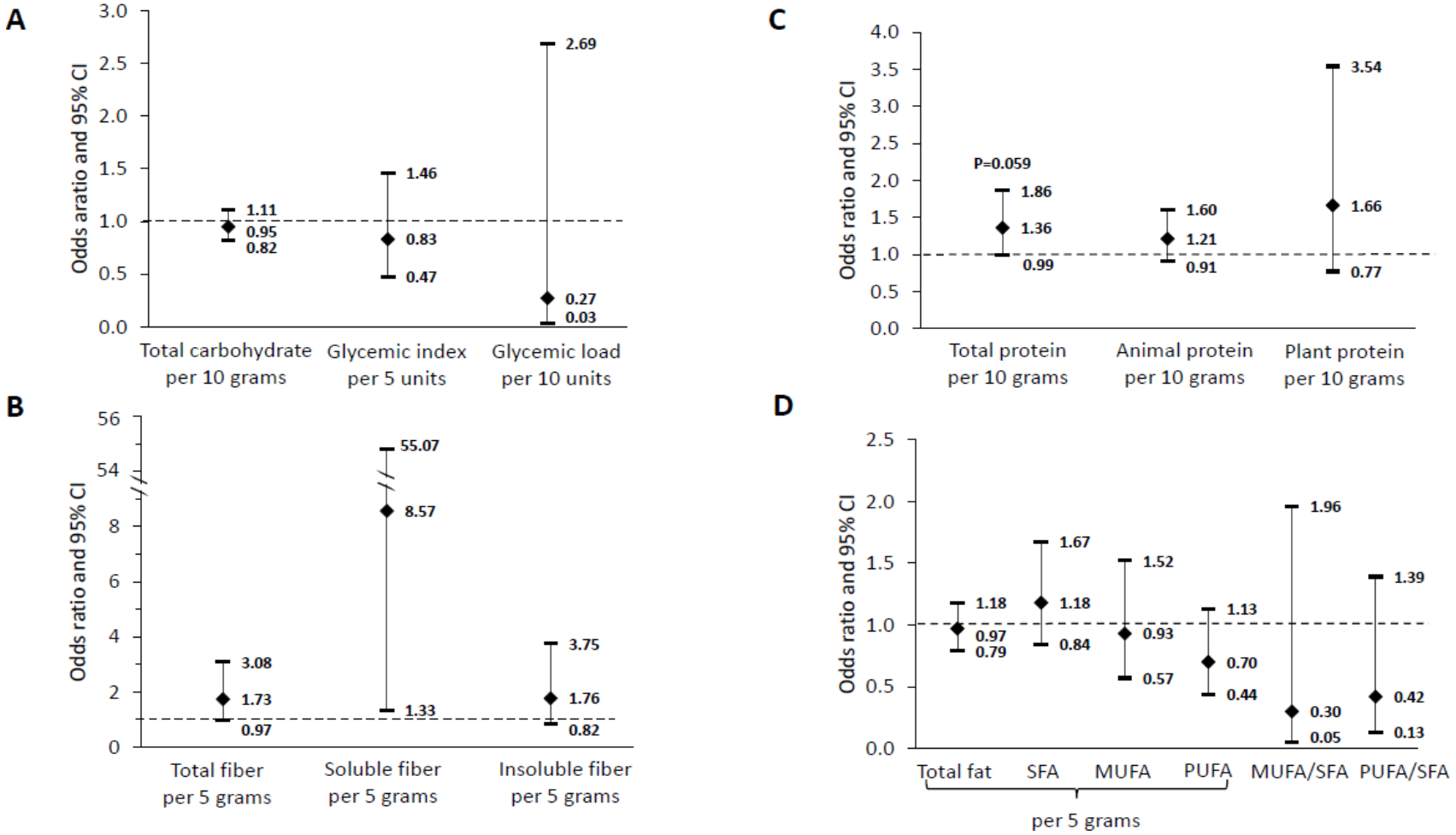
Model 5. Model 4 + insulin dose per kilogram.

Figure 5.1. Daily macronutrients intake and daytime non-severe hypoglycemia



SFA, saturated fat; MUFA, monounsaturated fat; PUFA, polyunsaturated fat. The models were adjusted for CGM wear time, total daily energy intake, average number of daily meals, diabetes duration, HbA1c, daily electronic media and TV time. All associations disappeared after additionally adjusting for insulin dose per kilogram except PUFA/SFA ratio; please refer to Table 5.3 for details.

Figure 5.2. Daily macronutrients intake and nocturnal non-severe hypoglycemia



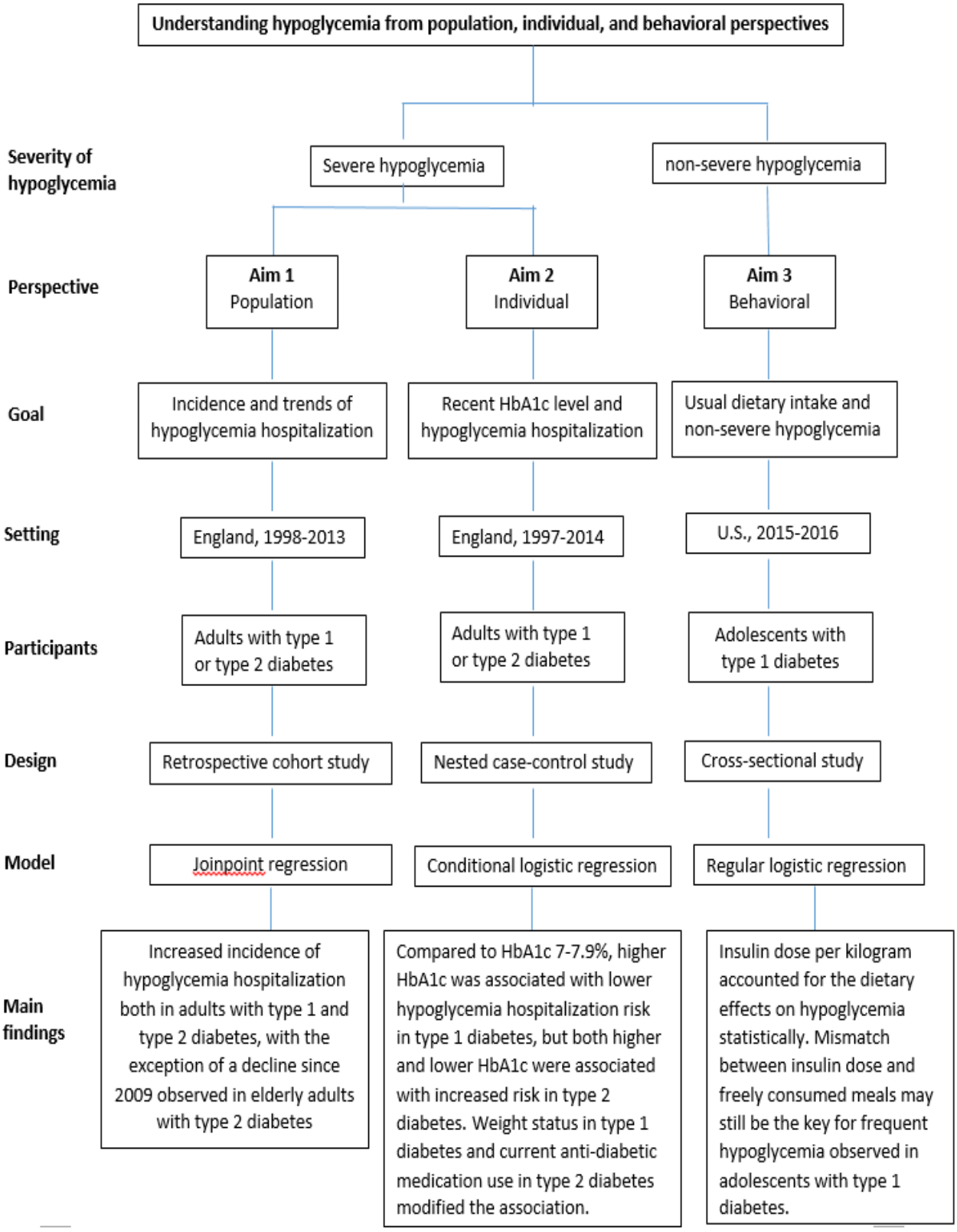
SFA, saturated fat; MUFA, monounsaturated fat; PUFA, polyunsaturated fat. The models were adjusted for CGM wear time, total daily energy intake, average number of meals per day, diabetes duration, HbA1c, daily electronic media and TV time. All associations did not exist after additionally adjusting for insulin dosing except for PUFA/SFA ratio; please refer to Table 5.4 for details.

CHAPTER 6. SYNTHESIS

Overview of findings

Our project improves current understanding on hypoglycemia from population, individual, and behavioral perspectives (Figure 6). For the first time, we reported long-term trends of severe hypoglycemia specifically in adults with type 1 diabetes and compared trends between adults with type 1 and type 2 diabetes from the same source population, covering almost two decades. We are also the first study to investigate HbA1c-hypoglycemia relationship using recently measured HbA1c within 3 months of hypoglycemic events. Importantly, we assessed whether the HbA1c-hypoglycemia association was modified by diabetes type, and a range of hypoglycemia risk factors, which has never been done before. Our study also provided initial data to explain the relationship between usual dietary intake and risk of hypoglycemia in youth with type 1 diabetes. The major findings from each aim are summarized here. At population level explored in Aim 1, we found a rapidly growing burden of hypoglycemia hospitalizations both in adults with type 1 and type 2 diabetes in England, which urgently calls for effective approaches to reduce hypoglycemia in diabetes. Aims 2 and 3 explored two exposures that may ultimately be useful to reduce or prevent hypoglycemia. In Aim 2, we found that recent HbA1c level was associated with risk of hypoglycemia hospitalization differently by diabetes type and other factors like BMI in type 1 diabetes and current anti-diabetic medication use in type 2 diabetes. Our analyses suggested applying individualized glycemic targets to reduce hypoglycemia risk. Finally in Aim 3, we found that the associations between usual dietary intake and risk of non-severe hypoglycemia were accounted by insulin dose per kilogram, but

Figure 6. Dissertation overview



hypoglycemia occurred in >80% of the study sample who were a selective group of adolescents with type 1 diabetes. Injecting insulin at an inappropriate time may be a key reason for the frequent hypoglycemic events seen in our study participants.

We expected a reduced risk of hypoglycemia in recent years due to the following three trends in diabetes management: i) New diabetes drugs including DPP-4 inhibitors, GLP-1 agonists, and SGLT-2 inhibitors have become available and they do not induce hypoglycemia by themselves, unless they are used together with other hypoglycemia-inducing drugs such as insulin or sulfonylureas;[46, 145] ii) Recent shift in diabetes guidelines towards recommending individualized glycemic targets rather than achieving near normal glycemic control in all patients with diabetes would likely to reduce hypoglycemia;[14, 15, 62, 63] iii) new technologies such CGM and insulin pump may help patients with diabetes, in particular type 1 diabetes, to better manage blood glucose.[47, 48] However, our data and other recently published studies show that the risk of hypoglycemia has been increasing.[51, 55, 58] We found that the incidence of hypoglycemia hospitalizations increased in adults with type 1 diabetes and in young and middle-aged adults with type 2 diabetes between 1998 and 2013. A decline in the incidence of hypoglycemia hospitalizations was only seen in elderly adults with type 2 diabetes since 2009 which is coincident with recent changes in diabetes guidelines and the publication of ACCORD,[40] VADT,[42] and ADVANCE[41] trials in 2008-2009 in the New England Journal of Medicine. Although severe hypoglycemia can be fatal and is associated with various poor health outcomes,[19-23] The primary cause of death in people with either type 1 or type 2 diabetes is cardiovascular disease, and cardiovascular disease accounts for the greatest component of health care expenditures in diabetes.[146-148] Also, microvascular complications can have devastating impact on quality of life in patients with diabetes and diabetes is a major cause of blindness,

renal failure, and amputation.[149] Maintaining HbA1c level to a near-normal target is currently the most effective approach to delay the onset and progression of all microvascular complications (i.e., retinopathy, nephropathy, and neuropathy) and to reduce risk of cardiovascular disease and mortality in diabetes.[150] Accordingly, achieving near normal glycemic control , even with intensive therapy, may still be the common practice and the priority. In elderly adults with type 2 diabetes who usually have multiple comorbidities, long diabetes duration, and limited life expectancy, recently, the guidelines started to recommended less stringent glycemic control. Together with the persuasive trials reporting no additional macrovascular benefits by achieving HbA1c lower than the general recommended targets in type 2 diabetes,[40-42] physicians may have recently started to treat a proportion of elderly adults with type 2 diabetes with high hypoglycemia risk with less aggressive therapy. [14, 15, 107] Nonetheless, the risk of hypoglycemia hospitalizations was still high in elderly adults in our study. How to balance between hyper- and hypoglycemia risk is still a major challenge in diabetes.

Setting an appropriate HbA1c target helps reduce risk of severe hypoglycemia in individuals with diabetes and ultimately reduces hypoglycemia burden to associated healthcare systems.[14, 15, 62, 63] We found that, in adults with type 1 diabetes, compared to HbA1c 7-7.9%, higher HbA1c was associated with lower risk of hypoglycemia hospitalization while lower HbA1c was not related to increased hypoglycemia risk. However, in overweight/obese type 1 patients, low HbA1c <6.0% tended to increase the risk of hypoglycemia hospitalization. In adults with type 2 diabetes, the HbA1c-hypoglycemia relationship was U-shaped. Compared to HbA1c 7-7.9%, both lower and higher HbA1c (≥9.0%) were associated with higher risk of hypoglycemia hospitalization. Current use of insulin or sulfonylureas modified the association. Higher HbA1c (≥8.0%) was associated with increased risk of hypoglycemia hospitalization in

adults with type 2 diabetes who were not currently taking insulin or sulfonylureas. Conversely, among current insulin or sulfonylureas users, lower HbA1c (<7.0%) was associated with higher risk of hypoglycemia hospitalization. These findings supported individualized glycemic management according to current diabetes guidelines[14, 15, 62, 63]

Nutrition plays a key role in diabetes management including preventing hypoglycemia.[76] In type 1 diabetes, correctly matching insulin dose to food intake is a key to reduce risk of hypoglycemia.[90] Our analyses confirmed this. In a group of adolescents with type 1 diabetes, we found that the associations between usual dietary intake and risk of non-severe hypoglycemia were fully accounted by insulin dose per kilogram. Of note, the insulin dose used here is the usual daily insulin dose based on self-report, not necessarily the insulin dose administered on the same day of the dietary recall. Current guidelines for insulin dosing primarily based on carbohydrate counting are not sufficient to control risk of hypoglycemia to a low level in most people with type 1 diabetes.[134] Over 80% of our study participants developed non-severe hypoglycemia within a week, although they were patients with poor glycemic control with HbA1c 8-13% at study entry. Since insulin dose per kilogram explained diet-hypoglycemia associations, two other important aspects that were not considered in our analyses are timing of insulin injection and insulin type. The injection time depends on blood glucose concentration, meal composition, exercise, and type of insulin.[142] Different types of insulin have disparate pharmacokinetic properties with different onset, peak, and duration, which further complicates insulin dosing.[143] The high risk of hypoglycemia may be the consequence of incorrect timing of insulin injection and mismatch between insulin pharmacodynamics and postprandial glucose excursions. Although insulin dose per kilogram could explain the diet-hypoglycemia associations, this does not mean that optimal insulin dose was administered by our participants.

Insulin dosing need to consider dietary protein, fat, and possibly the GI. [82, 90, 135] We found that different nutrients (particularly soluble fiber and unsaturated fat) from usual dietary intake had different effects on the occurrence of non-severe hypoglycemia and the effect of dietary intake on risk of non-severe hypoglycemia was different between daytime and nighttime. These findings may contribute to refinement of insulin dosing algorithms in the future. Further, barriers to diabetes self-management also need to be addressed in order for participants to adhere to the recommended insulin therapy, which is also the main goal of the FL3X trial.

Limitations

This research has a number of limitations. The primary limitation is that the selection of study participants by pre-defined inclusion criteria may bias the findings or influence the generalizability of the results. A couple of methodological limitations should be noted. For example, nested-case control design cannot directly study absolute risk differences and true usual dietary intake may not be captured by two 24-hour recalls. Also, confounding bias may be likely due to the missing data on relevant confounders. Further, a few important analyses could not be done due to the insufficient sample size. For example, we are unable to study both the first episode and all episodes of hypoglycemia. Important subgroup analyses or effect modification analyses could not be done. Finally, limitations associated with using longitudinal electronic medical record data need to be discussed.

Selection of study population

Selection of study population exists in all aims which may influence the generalizability of the findings or may bias the results. In Aim 1, the longitudinal trends of hypoglycemia

hospitalizations in adults with type 1 or type 2 diabetes estimated from our study may only be applicable to adult populations with diabetes in England, not the entire UK. Not all CPRD practices are linked to the HES. The CPRD includes practices from England, Scotland, Wales, and Northern Ireland. However, the HES stores patient-level data from all people who have been admitted to National Health Service hospitals in England only.[99] By design for Aim 2, the study sample was limited to only those who had an HbA1c result measured within 90 days of the index date for hypoglycemia cases and controls, based on nested case-control design. This restriction excluded 54% of hypoglycemia hospitalization cases in type 1 diabetes and 42% in type 2 diabetes, which may have resulted in selection bias. In type 1 diabetes, the included and excluded cases were not statistically different (Supplemental Table 4.1). In type 2 diabetes, the excluded cases were different from the included cases who were slightly younger, more likely on insulin and metformin, had higher proportion of males and slightly longer duration of diabetes (Supplemental Table 4.2). The selection bias may have influenced the results in type 2 diabetes. However, the associations in type 2 diabetes are consistent with literature.[72, 73] Further, additional analyses indicate that the association between recent HbA1c level and risk of hypoglycemia hospitalization in type 2 adults is robust. The magnitude and shape of the association remained when using first episode of hypoglycemia hospitalization as the outcome, which results in more loss of study sample (Table 6.1). In Aim 3, the adolescents with type 1 diabetes included in the final analyses (N=98) only account for 38% of the total 258 participants who were enrolled into the FL3X randomized clinical trial. However, the data for current dietary analyses were from an ancillary study of the FL3X trial at baseline in which only 130 participants were administered 24-hour dietary recall. In fact, the demographics and clinical characteristics were not different between final analytical sample (N=98) and FL3X trial participants (N=258), including age,

Table 6.1. Stratification analyses for evaluating association between HbA1c levels and risk of hypoglycemia in the fully adjusted model

	HbA1c, odds ratio (95% confidence interval)					*P* for interaction*
	<6%	6-6.9%	7-7.9%	8-8.9%	>=9%	
Overall	2.72 (1.96, 3.78)	1.46 (1.12, 1.90)	Ref	1.09 (0.76, 1.54)	1.66 (1.21, 2.27)	
Gender						0.02
Male	2.55 (1.62, 4.00)	1.90 (1.35, 2.68)	Ref	1.00 (0.61, 1.65)	1.78 (1.16, 2.73)	
Female	2.92 (1.79, 4.77)	0.94 (0.62, 1.44)	Ref	1.20 (0.73, 1.98)	1.46 (0.91, 2.33)	
Current insulin use						0.01
Yes	3.05 (1.41, 6.55)	2.88 (1.69, 4.93)	Ref	1.30 (0.74, 2.29)	2.74 (1.66, 4.52)	
No	2.46 (1.70, 3.55)	1.17 (0.87, 1.59)	Ref	1.14 (0.72, 1.82)	1.11 (0.70, 1.75)	
Current Sulfonylureas use						<0.0001
Yes	2.80 (1.68, 4.67)	1.87 (1.28, 2.72)	Ref	0.76 (0.44, 1.34)	0.79 (0.46, 1.34)	
No	2.50 (1.62, 3.87)	1.13 (0.78, 1.64)	Ref	1.44 (0.91, 2.29)	2.58 (1.71, 3.90)	

All models adjusted for age in years, gender, BMI, Charlson score, duration of diabetes, current insulin user (y/n), current sulfonylureas user (y/n), years of registration, smoking status (non-smoker, current smoker, ex-smoker and unknown), current use of antihypertensive drugs (y/n), specific diseases (y/n), current metformin user (y/n), and current other anti-diabetic drug user (y/n).

* *P* value was from the interaction term between HbA1c categorical variable and each of the stratification variables in the fully adjusted model.

gender, race, duration of diabetes, parental education, BMI, percent on insulin pump, insulin dose per kilogram, physical activity and HbA1c. Another aspect of selection is related to the inclusion criteria for the FL3X trial participants. Eligible participants were aged 13-16 years at study entry who had HbA1c 8-13% and duration of diabetes >1 year. Thus, our study sample is not representative of all adolescents with type 1 diabetes.

Methodological limitations

Nested-case control design studies relative risk ratio directly, not absolute risk difference. Translating or interpreting results from Aim 2 analyses should consider both the magnitude of the association and the background incidence of hypoglycemia hospitalization. For example, in adults with type 2 diabetes, compared to HbA1c 7-7.9%, HbA1c <6.0% was associated with 218% and 165% higher risk of hypoglycemia hospitalization in current sulfonylureas users and insulin users, respectively. However, the incidence of hypoglycemia hospitalization in current insulin users was 2.7 times that in sulfonylureas users (Table 6.2). Therefore, although the association was slightly stronger in current sulfonylureas users, insulin users contributed more episodes of hypoglycemia hospitalization to associated healthcare systems. Similarly, among type 2 adults who were not currently on insulin and sulfonylureas, HbA1c ≥9.0% was associated with 248% higher risk of hypoglycemia hospitalization compared to HbA1c 7-7.9%. However, the incidence of hypoglycemia hospitalization was about 10% of the incidence in current sulfonylureas users; thus increased risk of severe hypoglycemia in adults who were currently not on insulin and sulfonylureas generated substantially less burden to the healthcare system. Nonetheless, due to the life-threatening but preventable nature of severe hypoglycemia, reducing

Table 6.2. Estimated incidence rate of hypoglycemia hospitalization in adults with type 1 and type 2 diabetes, overall and by subgroups (in type 2 only)

	Number of Cases	Person years	Incidence rate per 1000
Type 1 diabetes, total	311	35,127.75	8.85
Type 2 diabetes, total	1,738	1,002,685.12	1.73
Subgroups			
Status of current insulin and sulfonylureas use*			
Neither	114	553,182.75	0.21
Sulfonylureas use only	825	334,216.33	2.47
Insulin use only	550	82,620.98	6.67
Both	249	32,665.06	7.62

any risk of severe hypoglycemia is important to everyone with diabetes, regardless of population-level impact.

Two days of 24-hour dietary recall may not capture usual dietary intake. In fact, capturing the true usual dietary intake is difficult and a critical challenge to all relevant nutrition studies. Currently available dietary assessment tools all have limitations.[151] Two days of 24-hour dietary recall in two unannounced days may be a best dietary assessment method to capture usual dietary intake in one study week, balancing the accuracy and participant burden. Ideally, dietary intake from one weekday and one weekend day are collected, but this did not happen all the time in our study. Further, with using dietary recalls, reporting bias may be possible. Our study participants were interviewed using multiple pass approach to reduce under-reporting.[125, 126]

Confounding bias

Missing data is a common problem in electronic medical record data. For example, BMI and smoking status had missing data in our study. We categorized these two variables and grouped missing data into a separate category. Therefore, residual confounding is likely. Further, the CPRD lacks information on race, diet, physical activity, and individual-level variable of

social economic status, but they are not considered as the strongest confounders for severe hypoglycemia.

Limitations associated with insufficient sample size

We are unable to study both first episode and all episodes of hypoglycemia. Hypoglycemia is a recurrent event. Previous history of hypoglycemia is a strong independent risk factor for future episodes of hypoglycemia.[115, 117] Further, first episode of severe hypoglycemia and recurrent episodes may represent different etiology and lead to different consequences.[115] For Aim 1, our main focus was to quantify the hypoglycemia burden to the healthcare system in England; thus all episodes of hypoglycemia were considered. However, we also analyzed trends of first hypoglycemia hospitalization in patients with incident diabetes. We found that in adults with incident type 1 diabetes, the risk of hypoglycemia hospitalization did not increase in the previous two decades. The trends in adults with incident type 2 diabetes were consistent with our main analyses; the decline since 2009 was also observed. However, due to the limited cases with hypoglycemia hospitalization, stratified analyses were not possible to assess whether trends of first hypoglycemia hospitalization were similar by important patient characteristics. For Aim 2, although our databases are large, studying first hypoglycemia hospitalization in type 1 diabetes is still not possible. In type 2 diabetes, the U-shaped association including the magnitude of the association remained when only first episode ever of hypoglycemia hospitalization was studied (Table 6.1). For Aim 3, it is unlikely to identify first episode of non-severe hypoglycemia after diabetes diagnosis because it may be asymptomatic.

In the original proposal, we planned to study how hypoglycemia is treated by dietary intake in adolescents with type 1 diabetes. Current recommendations suggest using glucose,

sucrose or any form of carbohydrate to treat hypoglycemia.[30, 77] However, we have very limited information related to how various forms of carbohydrate and other macronutrients either alone or in combination influence recovery of hypoglycemia. We proposed time to event analysis. Time in minutes from food intake to blood glucose rising back to 70 mg/dL or higher was the outcome and nutrients consumed within a meal were exposure. Preliminary analyses found that <60 episodes of hypoglycemia could be used for this purpose. Thus, we focused on how usual dietary intake predicts occurrence of hypoglycemia, not recovery.

Although our study is the largest dietary study in the CGM setting, the sample size is still not large, which precludes assessment of interaction among major macronutrients. Evidence has shown that interactions between protein, fat, and carbohydrate exist.[90] Protein and fat have an additive impact on the delayed postprandial glycemic rise.[82] In spite of the small sample size, we explored the interactions between protein, fat, and carbohydrate, but no interaction was found. Further, the small sample size also precludes evaluation of effect modification for the association of dietary intake with hypoglycemia by baseline glycemic status, diabetes duration, and pubertal status. Previous studies have shown that puberty and duration of diabetes are associated with glycemic control and insulin requirements in children with diabetes, and thus influence hypoglycemia risk.[152] The data collection of the FL3X trial is ongoing. We will have follow-up data at 6 months and 18 months. Assessing of interactions and effect modifications may be possible when full data collection is complete.

Limitations associated with longitudinal electronic health record data

Misclassification of diabetes and diabetes type may be possible by using electronic health record data, although the differentiation between type 1 and type 2 diabetes is also a major

strength of our study. A systematic review highlights a few issues relevant to diabetes classification using medical record data:[153] distinction between diabetes and not diabetes, classification between type 1 and type 2 diabetes, and diagnostic errors/difficulties regarding to differentiate diabetes types other than type 1 and type 2. Our definition was adopted from published CPRD studies but modifications were made to reflect specific differentiation between type 1 and type 2 diabetes.[102-104] For example, we did not use age <35 or 25 years as a criterion to differentiate diabetes type, because the prevalence of type 2 diabetes has been increasing in adolescents and young adults.[154] Also, two, not only one, type 2 diabetes codes were required for diagnosing type 2 diabetes if anti-diabetic medication prescriptions were not available. Further, we excluded patients with any record of secondary diabetes, maturity onset diabetes of young, latent autoimmune diabetes in adults, and malnutrition related diabetes. Accordingly, it is highly unlikely that our findings would be biased by the misclassification of diabetes type.

With the introduction of the QOF since 2004 which is a voluntary incentive scheme for general practitioners,[155] there has been more complete coding and documentation within the CPRD.[99, 156] Further, in April 2006, diabetes type specific Read code for type 1 diabetes (the C10E hierarchy: C10E0 to C10EP) and type 2 diabetes (the C10F hierarchy: C10F0 to C10FQ) were introduced for use, in addition to the higher level general Read code for diabetes (C10 and any codes below it in the hierarchy). The introduction of C10E and C10F facilitates the differentiation of diabetes type, but only using them underestimates prevalence of diabetes.[156] Our case definitions for diabetes utilize both general diabetes codes and type 1 and type 2 codes together with prescriptions of anti-diabetic medication. Therefore, under-ascertainment is less likely. Adjusting for these two changes involves complex modeling and is out of the scope of

this work. Notably, we did not observe any significant change in hypoglycemia trends around 2004-2006.

HbA1c data are not completely recorded in the CPRD although they appear to be widely available for patients with diabetes. From 2003 onward, practices within the CPRD began to use automated approaches to request tests and receive results from laboratories. Test data from this time are likely to be more complete than earlier years when paper-based systems were widely used. We evaluated the effect modification by calendar year for the association between recent HbA1c level and risk of hypoglycemia hospitalization. However, the association did not vary by time.

Other limitations

The form of severe hypoglycemia studied in this research is hypoglycemia requiring hospitalization which only accounts for a small proportion of all severe hypoglycemic events. A study from the DPV Prospective Diabetes Registry reported that hypoglycemia requiring hospitalization accounts for <10% of total severe hypoglycemia defined as low blood glucose event requiring external assistance.[71] By analyzing data from the 1993-2005 National Hospital Ambulatory Medical Care Survey in the US, Ginde et al. found that about 25% of severe hypoglycemia from emergency department visits resulted in hospital admission.[52] Therefore, the results from Aim 1 and 2 analyses may not be generalized to all forms of severe hypoglycemia.

There are multiple dimensions to evaluate hypoglycemia, including occurrence, duration, lowest blood glucose, and timing of occurrence. In Aim 3, we focused on occurrence and timing of occurrence only. We did not consider the severity of hypoglycemia which is related to duration of low blood glucose <70 mg/dL and the lowest glucose concentration within a

hypoglycemic episode. Further, our definition of nocturnal hypoglycemia is arbitrary, although literature commonly defines nocturnal hypoglycemia using 11PM-7AM cutoff.[130, 144]

Strengths

The major strengths of our investigation include distinguishing between type 1 and type 2 diabetes, assessing long-term hypoglycemia trends covering almost two decades, studying HbA1c-hypoglycemia relationship using recently measured HbA1c rather than earlier HbA1c measurements, and assessing usual dietary intake and hypoglycemia risk in an outpatient environment instead of controlled settings.

The primary strength is that we investigated hypoglycemia in type 1 and type 2 diabetes separately in Aim 1 and 2. As explained in Chapter 2, type 1 and type 2 diabetes have very different etiology and require different treatment strategies, resulting in different risk of hypoglycemia. This distinction is critical to obtain results with clear, accurate, and targeted implications. A study led by Zaccardi et al.[55] published in the Lancet Diabetes & Endocrinology in June 2016 reported that the hospital admission rate for hypoglycemia increased between 2005 and 2014 in England, using the HES data. After adjusting for diabetes prevalence, the hospital admission rate showed a reduction since 2010. Zaccardi et al. did not distinguish type 1 and type 2 diabetes. Our analyses found that the trends of hypoglycemia hospitalization differed by diabetes type and the decline was seen only in elderly adults with type 2 diabetes since 2009. Undoubtedly, our results presented a clearer picture of longitudinal trends of hypoglycemia hospitalization in England and had clearer implications. Further, our analyses also suggest differential associations of HbA1c with risk of hypoglycemia hospitalization between type 1 and type 2 diabetes.

To our knowledge, our study is the longest study of trends in severe hypoglycemia in diabetes (1998-2013), which covers most of the time after the publication of major findings from the DCCT study in 1993.[32] The longitudinal hypoglycemia trends we found may be used to evaluate and inform how the major changes in diabetes management and technologies in the previous two decades influenced risk of severe hypoglycemia over time, at least in England.

We used HbA1c measured within 3 months of hypoglycemic events to study the association between HbA1c level and risk of hypoglycemia hospitalization. All published studies used "baseline" HbA1c value measured more than three months or even years before, [38, 72-75] which may be less relevant to the acute event of severe hypoglycemia. This may be the reason that stronger association between HbA1c and risk of severe hypoglycemia in type 2 diabetes was found in our study, although the U-shaped HbA1c-hypoglycemia relationship is consistent with the literature.[72, 73]

The majority of existing data related to dietary intake, postprandial blood glucose, and hypoglycemia are from clinical trials. However, as with any experimental study, the translation of clinical trial findings to an outpatient environment is uncertain. Also, previous literature has primarily focused on postprandial glycemic excursions following one or more pre-designed meals. Data on how nutrients from usual dietary intake impact hypoglycemia risk in an outpatient setting are lacking. Our study filled these gaps and is also the first study to identify soluble fiber and fat quality as two new dietary risk factors of non-severe hypoglycemia in adolescents with type 1 diabetes.

Significance and implication

Reducing the rapidly growing burden of hospital admissions for hypoglycemia in England is urgent. The risk of hypoglycemia hospitalization is high in type 1 diabetes and has steadily increased in the previous two decades. In type 2 diabetes, subgroups (e.g., current insulin or sulfonylureas users) with markedly high incidence of hypoglycemia hospitalizations also have large annual increase in trends. Therefore, the increased hypoglycemia burden is mainly attributed to type 1 diabetes and insulin or sulfonylureas treated type 2 diabetes in adults. Practical approaches for reducing hypoglycemia burden of the healthcare system in England need to primarily target at these patients.

Although all forms of severe hypoglycemia are important, hypoglycemia requiring hospitalization deserves particular attention.[157] Hypoglycemia hospitalization creates considerable burden to related healthcare system and is associated with significant use of healthcare resources. A CPRD study reported a mean direct cost of £1034 and a mean hospital stay of over 5 days per admission for hypoglycemia; no difference was found between type 1 and type 2 diabetes.[98] However, this study is likely to underestimate the cost. A review reported that the mean direct cost was €2807 (total cost €3917) per episode of severe hypoglycemia that requires inpatient care.[157] Accordingly, even small increase in the incidence of hypoglycemia hospitalization would generate substantially more cost. Reducing the burden of hypoglycemia hospitalizations in England is medically and economically urgent.

There may still be an inappropriate impression that the lower frequency of hypoglycemia in patients with type 2 diabetes means that it is of less clinical importance.[158] Although hypoglycemia occurs about 2 to 4 times more often in type 1 diabetes, type 2 diabetes accounts for over 90% of total diabetes cases.[12] In insulin-treated patients with type 2 diabetes,

hypoglycemia is common, too.[51, 159] In fact, it can be potentially more dangerous in patients with advanced type 2 diabetes because they are often older and may have multiple comorbidities. Based on our data, 1,591 hospitalizations for hypoglycemia occurred in adults with type 1 diabetes while 3,738 occurred in adults with type 2 diabetes during the entire study period. Both diabetes types contribute significant hypoglycemia burden.

Although current clinical practice guidelines recommend personalized glycemic targets to maximize benefits and minimize harms (particularly hypoglycemia) of glycemic control therapies,[14, 15] the association of HbA1c level with severe hypoglycemia is controversial. Our study confirmed the U-shaped HbA1c-hypoglycemia relationship in type 2 diabetes. In type 1 diabetes, we found that higher HbA1c is related to lower risk of hypoglycemia, but this does not mean that we should apply less aggressive therapy to patients with type 1 diabetes, because poorly controlled HbA1c is associated with increased microvascular and macrovascular events that are the major cause of mortality and morbidity in diabetes.[32, 160] Deciding an individual's HbA1c target has to appropriately balance long-term glycemic benefits and short-term hypoglycemia risk. Guidelines recommend physicians to consider each patient's hypoglycemia risk factors before prescribing treatment,[14, 15, 62, 63] which is in line with our findings. In addition to diabetes type, obesity status in type 1 diabetes and current anti-diabetic medication in type 2 diabetes are two other factors for consideration.

Our findings suggest that reducing hypoglycemia risk is not possible if correct insulin dose is not correctly injected at correct time to match dietary intake in youth with type 1 diabetes. Current insulin dose calculation primarily based on carbohydrate counting may not sufficiently optimize postprandial glucose and reduce glycemic fluctuations which ultimately lead to hyper- and hypoglycemia.[82, 90, 134] For the first time, we found that soluble fiber is

positively associated while monounsaturated and polyunsaturated fat are negatively associated with risk of hypoglycemia in adolescents with type 1 diabetes. These findings imply that refining future insulin dosing algorithms may also need to consider quality of carbohydrate and fat, but these results need to be confirmed in other studies first. Further, the current recommendation of injecting insulin about 15 minutes before a meal may also need to adjust, because it may not suffice the complexity of insulin dosing. The timing of insulin delivery is influenced by meal composition, blood glucose concentration at insulin injection, previous exercise, and pharmacokinetics of the injected insulin.[142, 143] However, this is a hypothesis based on our findings, since we do not have relevant data on timing of insulin injection.

Hypoglycemia is a major barrier of optimal glycemic control both in type 1 and type 2 diabetes, and in children and adults. However, a large European survey found that during routine appointment, 17% of those with type 1 diabetes and 21–28% with type 2 diabetes reported not being asked about hypoglycemia by their physicians;[25] 65% of people with type 1 diabetes and 50–59% of people with type 2 diabetes who experienced a non-severe hypoglycemic event rarely or never informed their physicians. Physicians and patients should pay more attention and work together to overcome high hypoglycemia risk in diabetes. Although hypoglycemia is a multifactorial problem and is complex, but it is preventable,[12] without the need of sacrificing optimal glycemic control.[111] Approaches known to effectively reduce the risk of hypoglycemia include patient education, dietary and exercise modifications, medication adjustment, careful glucose monitoring by the patient, and conscientious surveillance by the clinician.[12] Our study at least proposed two ideas to reduce hypoglycemia: 1) HbA1c targets need to be individualized; 2) different insulin dosing strategies may need for different nutrients/diet. The amount and quality of major macronutrients are both important. Timing of insulin injection may also be crucial.

Future directions

We are involved in a long battle to overcome hypoglycemia in diabetes. This research provides informative clinical and nutrition data to address three literature gaps and advances current understanding of hypoglycemia from population, individual, and behavioral perspectives. However, future work is critically and urgently needed to carry on, supplement or expand our current investigation.

Continuously monitoring trends of hypoglycemia hospitalization in adults with type 1 and type 2 diabetes in England is needed. This is important, because we will know over time: i) if the increasing trends are reversed in type 1 adults and in young and middle aged adults with type 2 diabetes; ii) if trends of hypoglycemia hospitalization in elderly adults with type 2 diabetes continue to decline. If any clinical practice level or policy level efforts are made to reduce hypoglycemia risk after our findings are published in a peer-reviewed journal, continuous monitoring allows to assess the effectiveness of actions.

Trends of a most severe form of hypoglycemia, hypoglycemia leading to hospitalization, are studied in this research. However, diabetes type-specific trends of severe hypoglycemia resulting in emergency room visits but not being hospitalized have not been studied in a time frame that is sufficiently long enough to cover most of time post the DCCT study. Quantifying incidence and trends of severe hypoglycemia not leading to emergency room visits or hospitalization is difficult using currently available longitudinal electronic health record data. Patients may not tell their physicians all severe hypoglycemic events they experienced and physicians may not record reported events into medical records. Relatively complete recording of severe hypoglycemic events into medical records in the future requires efforts from patients, health professionals, and policy makers.

Our current analyses do not account for daily dose of anti-diabetic medication over time. As explained, the majority of hypoglycemic events are iatrogenic and different medications at different dose are associated with very different risk of hypoglycemia. Current analyses only consider generic types of anti-diabetic medication. We do not know if accounting for daily drug dose modifies hypoglycemia trends and HbA1c-hypogycemia relationship identified from the present study. Future work is encouraged to confirm this.

Current diabetes treatment guidelines broadly recommend less stringent glycemic control to patients who are vulnerable to hypoglycemia. A number of risk factors for hypoglycemia are listed to help define high risk patients for hypoglycemia. Just knowing these factors probably raises physician attention when prescribing intensive treatment, but it is difficult for physicians to decide the optimal glycemic target for each patient. An algorithm that predicts an individual's hypoglycemia risk at different glycemic targets may be useful as a tool for physicians to decide a most appropriate glucose control therapy and for patients as a self-management tool to reduce risk of severe hypoglycemia. Ideally, such a risk prediction algorithm may need to consider patient behavior (e.g., diet, physical activity) as a parameter in addition to demographic, clinical, and therapeutic information.

Convincing evidence has revealed that calculating prandial insulin dose should be based on the complete meal composition. However, we currently do not have simple and easy-to-use insulin algorithms for fat and protein. A number of studies have assessed insulin dosing strategies for different meals including various bolus types, timing of the meal bolus, and methods to calculate the bolus dose.[90] In the short term, to reduce currently high hypoglycemia risk in children with type 1 diabetes, a few insulin dosing algorithms incorporating dietary fat and protein can be designed based on available data and tested for efficacy. Guidelines can be

modified accordingly to improve current recommendations for calculating insulin dose. In the long run, the following questions need to be answered in order to design better insulin dosing algorithm to optimize postprandial glucose concentration:[90] i) Are effects of all types of fat and protein on postprandial blood glucose similar? Our study suggests unsaturated fat, not saturated fat, is negatively associated with hypoglycemia, but more evidence is needed. ii) The inter-person differences of glycemic excursions in response to the same nutrients or diet further complicate designing insulin dosing algorithms. Future studies need to explore if certain phenotypic characteristics can be used as markers to identify individuals who are more nutrient sensitive and require to adjust insulin dose and delivery patterns. iii) Is there a threshold and/or dose response for insulin dose and fat/protein relationship? iv) how carbohydrate, fat, and protein interact with each other to influence postprandial glucose excursions and hypoglycemia risk is not yet fully understood. v) Is injecting insulin about 15 minutes before mealtime a good criterion for all circumstances including different meals and different insulin?

Conclusion

The advance in diabetes management in the past few decades —including the better understanding of the relationship between hypoglycemia and hyperglycemia, availability of new anti-diabetic drugs, and new technologies— has not necessarily contributed to improved control of hypoglycemia. Surprisingly, in Aim 1 at population level, we found that hypoglycemia requiring hospitalization has been an increasing burden in adults with type 1 and type 2 diabetes in England in the previous two decades, with the exception of the decline in elderly adults with type 2 diabetes starting in 2009. We then explored two hypoglycemia prevention strategies. In Aim 2 from individual perspective, our findings suggest that glycemic targets (long-term

glycemic control) need to be individualized to reduce hypoglycemia risk. In Aim 3 from behavioral perspective, optimizing day-to-day blood glucose level (short-term glycemic control) via optimal insulin dosing matching to dietary intake may be critical for preventing hypoglycemia. However, to overcome hypoglycemia as a multifactorial problem, multi-dimensional approaches are needed in addition to the two studied in our project, including patient education, family/social support, and careful self-monitoring of blood glucose. Future hypoglycemia prevention therapies need to consider all these aspects.

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