9-6-2022 10:30 AM

Quantifying and predicting real-world iatrogenic severe hypoglycemia in adults with type 1 or 2 diabetes mellitus (the iNPHORM study, United States)

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A thesis submitted in partial fulfillment of the requirements for the Doctor of Philosophy degree in Epidemiology and Biostatistics

Abstract

Clinical outpatient strategies to accurately predict diabetes-related iatrogenic severe hypoglycemia (SH) are lacking. To redress this gap, we conducted the first-ever prognosis investigation of guideline-defined (Level 3) SH in the United States (US) (iNPHORM).

Chapter 4 details the design and implementation of iNPHORM: a prospective 12-wave panel survey (2020–2021). N=1206 adults with type 1 or insulin- and/or secretagogue-treated type 2 diabetes mellitus (T1DM or T2DM) were recruited from a US-wide, probability-based internet panel. For one-year, we collected monthly data on SH occurrence (frequencies, detection methods, symptoms, causes, and treatments) and related factors (anthropometric, sociodemographic, clinical, environmental/situational, behavioural, and psychosocial).

iNPHORM data were analyzed in Chapter 5 to characterize and quantify Level 3 SH (N=978). Overall, 60% of events were treated outside the healthcare system; <5% required hospitalization (T1DM: 1.6%; T2DM: 4.9%, *p*-value=0.0014, α=0.0083). About one-third of participants experienced ≥1 event(s) over prospective follow-up (T1DM: 44.2% [95% CI: 36.8% to 51.8%]; T2DM: 30.8% [95% CI: 28.7% to 35.1%], *p*-value=0.0404, α=0.0007). The incidence rate was 5.01 (95% CI: 4.15 to 6.05) events per person-year (EPPY) (T1DM: 3.57 [95% CI: 2.49 to 5.11] EPPY; 5.29 [95% CI: 4.26 to 6.57] EPPY).

Chapter 6 describes the development and internal validation of the iNPHORM prognostic model. We modelled one-year recurrent Level 3 SH using Andersen-Gill Cox proportional hazards and penalized regression with multiple imputation (N=986). A range of anthropometric; sociodemographic; and clinical (diabetes-, hypoglycemia-, and general health-related) candidate variables were selected for their relevance and feasibility. The final model demonstrated strong discriminative validity and parsimony (optimism corrected c-statistic: 0.77).

The results of this dissertation promise to enhance real-world SH screening; evidence-based, risk-tailored prevention; and ultimately cost containment.

Keywords: type 1 diabetes mellitus, type 2 diabetes mellitus, hypoglycemia, insulin, secretagogues, prognosis.

Summary for diverse audiences

Certain diabetes medications can make a person's blood sugar drop too low. This condition, known as hypoglycemia, can occur frequently and without warning. Hypoglycemia can trigger symptoms like sweating and shakiness. In very severe cases, events can cause confusion and clumsiness, seizures, coma, and even death. Nevertheless, little is known about who is most likely to get severe hypoglycemia and how often. Such insight could help clinicians deliver better diabetes care that is not only effective but also safe.

For this dissertation, I designed and carried out the first-ever long-term research project on self-reported severe hypoglycemia in the United States, called the iNPHORM study. Over the course of one year, our team at Western University emailed monthly questionnaires to 1206 adult Americans with type 1 or type 2 diabetes mellitus at-risk of hypoglycemia. The questionnaires asked respondents about how often they experienced low blood sugar. We also collected information on various clinical and socio-demographic traits. Based on these data, we analyzed 1) the total number of severe hypoglycemia events, and 2) the factors associated with event occurrence (i.e., predictors).

Our study showed that severe hypoglycemia is alarmingly common among Americans with diabetes. After one year, about a third of participants reported at least one severe hypoglycemia event and had, on average, five events per person-year. In total, 60% of events were treated outside the healthcare system and less than 5% required hospitalization.

To identify the predictors of severe hypoglycemia, we used a statistical method called prediction modelling. Our analysis linked higher severe hypoglycemia risk to a range of different predictors including diabetes type and duration, medication type, age, sex, marital status, race, and general health. The results of iNPHORM will be used to create a tool that can predict severe hypoglycemia risk during routine medical appointments. Clinicians could use this tool to adjust treatment and care so that, in the future, severe hypoglycemia happens less often, or not at all.

Co-authorship statement

All chapters were written by Alexandria Ratzki-Leewing in partial fulfilment of the requirements for Doctor of Philosophy from the Department of Epidemiology and Biostatistics.

Chapters 4, 5, and 6 constitute three original research manuscripts that were produced in collaboration with other scientists and clinicians. Chapter 4 details the iNPHORM protocol, which Ms. Ratzki-Leewing conceived, designed, and implemented. For this international primary investigation, Ms. Ratzki-Leewing planned, coordinated, and led all data collection (over 12 months) via survey panel vendors (Ipsos Interactive Services Ltd.); created all iNPHORM questionnaires and materials (with guidance from Drs. Stewart Harris and Bridget L. Ryan, and support from Susan Webster-Bogaert); engaged in formative and regular consultations with vendor partners (John D. Buchenberger); wrote a research ethics board application (with support from Susan Webster-Bogaert and Natalie H. Au); and cleaned/coded all data (with support from Jason E. Black). Chapters 5 and 6 are based on the iNPHORM dataset, for which Ms. Ratzki-Leewing conceptualized the research questions, and performed all statistical analyses with support from Jason E. Black, and Drs. Guangyong Zou, Neil Klar, and Bridget L. Ryan. Dr. Stewart Harris guided analyses and interpretations of results.

Ms. Ratzki-Leewing's supervisory committee—Drs. Stewart Harris, Neil Klar, and Bridget Ryan—and colleagues were listed as co-authors where they assisted in conceptualizing analyses, interpreting results, and editing manuscripts. Specifically:

Chapter 4 was written with input from the following writing group: Bridget L. Ryan, Guangyong Zou, Susan Webster-Bogaert, Jason E. Black, Kathryn Stirling, Kristina Timcevska, Nadia Khan, John D. Buchenberger, and Stewart B. Harris. Chapter 5 was written with input from the following writing group: Jason E. Black, Anna Kahkoska, Bridget L. Ryan, Neil Klar, Guangyong Zou, Kristina Timcevska, and Stewart B. Harris. Chapter 6 was written with input from the following writing group: Jason E. Black, Bridget L. Ryan, Neil Klar, Guangyong Zou, Susan Webster-Bogaert, Kristina Timcevska, and Stewart B. Harris.

Dedication

To the statistically anomalous who are anything but insignificant.

Acknowledgments

I am ineffably grateful to the community of people whose generous investments and unflagging support facilitated this dissertation.

It is my honour to share in this achievement with you.

To the Mentors among mentors who entrusted to me their knowledge and time:

Dr. Stewart Harris, for years, I have had the privilege of benefiting from your indefatigable tutelage and altruism. In your legacy, I will strive always to make you proud. Dr. Neil Klar, your guidance and care buoyed me to this rite of passage. You encouraged me to be bold. Dr. Bridget Ryan, my role model; your grounding mentorship inspirited me to become the proud, ambitious female academic I am. Dr. Brian Frier, it is upon your shoulders I stand.

To Dr. William Wall, whose heartfelt generosity vitalized this work. Dr. GY Zou whose kinship and wisdom was my compass. Jason E. Black, whose indispensable brilliance and dedication to iNPHORM innervate the words that follow. Kristina Timcevska whose 11th hour editorial prowess was the glue of it all. And to Susan Webster-Bogaert, Natalie Au, and the Diabetes Alliance. Thank you, thank you, thank you.

To my beautiful and perfectly untamed Mom, I love you. Because of you, I am raised and unafraid; this dissertation is my humble tribute to your motherhood. To Aunty Linda, my guardian angel. To Andy and all my brothers and sisters, and their dazzling young ones; to RM, AK^2, NK, L-B, and LM—*My Love is Your Love*. To AC and ST for their unwavering belief in me—*illegitimi non carborundum*—you give me hope.

To my sweet Indy boy.

And, finally, to all iNPHORM participants. It is with deep gratitude and respect that I acknowledge your invaluable contributions. You are the heartbeat of this work.

Funding Statement

The iNPHORM (Investigating Novel Predictions of Hypoglycemia Occurrence Using Real-world Models) study was funded through an investigator-initiated grant from Sanofi Global. Sanofi was not involved in the design of the study; collection, analysis, and interpretation of data; writing of any reports; nor decisions to publish or present results.

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List of abbreviations

A1C or HbA1C	glycated hemoglobin (not an acronym)
ACCORD	Action to Control Cardiovascular Risk in Diabetes
ADA	American Diabetes Association
ADVANCE	Action in Diabetes and Vascular Disease: Preterax and Diamicron - MR Controlled Evaluation
BG	blood glucose
BGAT	Blood Glucose Awareness Training
BMI	body mass index
CDC	Centers for Disease Control and Prevention
CI	confidence interval
CIR	cumulative incidence ratio
cm	centimeter
CRASH	Conversations and Reactions Around Severe Hypoglycemia
CSII	continuous subcutaneous insulin infusion
CV	cardiovascular
CVD	cardiovascular disease
DAFNE	Dose Adjustment For Normal Eating
DAFNE-HART	Dose Adjustment For Normal Eating - Hypoglycemia Awareness Restoration Training
DCCT	Diabetes Control and Complications Trial
DEVOTE	Degludec Versus Insulin Glargine in Subjects with Type 2 Diabetes at High Risk of Cardiovascular Events
DPP-4	dipeptidyl peptidase-4
EASD	European Association for the Study of Diabetes
ED	emergency department
eGFR	estimated glomerular filtration rate
EHR	electronic health record
EMR	electronic medical record
EMS	emergency medical services
EPPY	events per person-year
EPP30	events per 30 person days
ER	emergency room
ES	Endocrine Society
FDA	Food and Drug Administration
FoH	Fear of hypoglycemia
Fo*Hyper*	Fear of hyperglycemia
g	grams
GLP-1	glucagon-like peptide 1

HAAF	Hypoglycaemia Associated Autonomic Failure
HAATT	Hypoglycemia Anticipation, Awareness and Treatment Training
HARPdoc	Hypoglycaemia Awareness Restoration Programme despite optimised self-care
HART	Hypoglycemia Awareness Restoration Training
HAT	Hypoglycemia Assessment Tool
HCL	hybrid closed loop
HFS-II	Hypoglycemia Fear Survey-II
IAH	impaired awareness of hypoglycemia
ICD-10	International Classification of Diseases, 10th revision
ICD-9	International Classification of Diseases, 9th revision
IHSG	International Hypoglycaemia Study Group
IIS	Ipsos Interactive Services Ltd.
IM	intramuscular
InHypo-DM	UnderstandINg the impact of HYPOglycemia on Diabetes Management: A Survey of Perspectives and Practices
iNPHORM	Investigating Novel Predictions of Hypoglycemia Occurrence Using Real-world Models
IP	incidence proportion
IPA	index prediction accuracy
IQR	interquartile range
IR	incidence density
IRR	incidence rate ratio
IV	intravenous
LASSO	Least Absolute Shrinkage and Selection Operator
MI	myocardial infarction
mg	milligrams
mg/dL	milligrams per decilitre
mmHG	millimeters of mercury
mmol/L	millimoles per litre
NHANES	National Health and Nutrition Examination Survey
NLP	natural language processing
NPH	Neutral Protamine Hagedorn
NSDH	non-severe daytime hypoglycemia
NSH	non-severe hypoglycemia
NSNH	non-severe nocturnal hypoglycemia
ORIGIN	Outcome Reduction with Initial Glargine Intervention
PG	plasma glucose
PROBAST	Prediction model Risk Of Bias Assessment Tool
PROM	patient-reported outcome measure

QoL	quality of life
QTc	corrected QT interval
RCT	randomized controlled trial
ROB	risk of bias
rt-C/FGM	real-time continuous or flash glucose monitoring
SD	standard deviation
SDH	severe daytime hypoglycemia
SE	standard error
SGLT2	sodium-glucose cotransporter-2
SH	severe hypoglycemia
SNH	severe nocturnal hypoglycemia
SMBG	self-monitoring blood glucose
T1DM	type 1 diabetes mellitus
T2DM	type 2 diabetes mellitus
UKPDS	United Kingdom Prospective Diabetes Study
US	United States
USD	United States Dollars
VADT	Veterans Affairs Diabetes Trial
VADT	Veterans Affairs Diabetes Trial follow-up study

Chapter 1

1 Introduction and aims

Chapter 1 provides an overview of diabetes-related iatrogenic severe hypoglycemia (SH) risk and management in the United States (US), as well as the aims, conceptual framework, delimitations, and structure of this dissertation.

1.1 General overview of dissertation

The past quarter-century has seen rapid pharmacological and technological advances that have helped people with diabetes prevent or delay long-term micro- and macrovascular disease. And yet, iatrogenic hypoglycemia remains, as Philip E. Cryer described in his 1994 American Diabetes Association (ADA) Banting Lecture, "…the limiting factor in the glycemic management of diabetes."(1)

In severe cases, hypoglycemia can impose catastrophic consequences, exacerbating the risk of serious physical and psychosocial morbidity (2–7), and death (8). While multiple interventions have been devised to reduce SH risk in outpatient settings, poor understanding on how best to target them in practice has inhibited modern diabetes care. Prognostic models offer a powerful opportunity to identify individual-level risk and potentiate patient-centered diabetes care. Today, some longer-term SH risk models exist in the US; though, all depend on pre-existing datasets limited by insufficient generalizability, and gaps in information. Primary, prospective research is needed to properly quantify the true US epidemiology of events based on current guideline diagnostics. A prognostic model derived from such data could enhance clinical decision-making that optimizes type 1 and 2 diabetes mellitus (T1DM, T2DM) outcomes.

1.2 Aims

For my doctoral research, I designed and conducted the iNPHORM (Investigating Novel Predictions of Hypoglycemia Occurrence Using Real-world Models) study: the first prospective, prognosis investigation of long-term hypoglycemia risk in the US (2020-2021).

A screener, baseline, and 12 monthly self-assessments were administered online to a clinically varied cohort of American adults (≥18 years old) with T1DM (taking insulin) or T2DM (taking insulin and/or secretagogues) (N=1206). Participants were recruited from a probability-based internet panel designed to reflect the general US public. Survey items elicited information on anthropometric, sociodemographic, clinical, environmental/situational, behavioural, and psychosocial variables, as well as on hypoglycemia frequencies, detection methods, symptoms, causes, and treatments.

The purpose of this dissertation was threefold:

> *Aim 1: To design and implement iNPHORM.* Aim 1 details the study protocol.
>
> *Aim 2: To determine the real-world incidence of severe hypoglycemia.* Aim 2 uses longitudinal iNPHORM data to assess one-year self-reported SH incidence proportions (IPs) and incidence rates (IRs), as well as treatment modes/contexts.
>
> *Aim 3: To estimate and predict real-world severe hypoglycemia risk.* Aim 3 uses longitudinal data from iNPHORM to develop and internally validate a pragmatic one-year model of recurrent SH for use in real-world, outpatient contexts.

1.3 Conceptual framework

The contained work falls within the purview of clinical epidemiology and real-world evidence generation. According to the US Food and Drug Administration (FDA) (9), real-world data relate to patient health status and/or the delivery of healthcare. Sources include claims and billing activities, registries, electronic health records (EHRs), and community surveys—the basis of this

thesis. Herein, I use ‘real-world’ in the same way other scientists might use *in vivo* or *in vitro*: while inadequate as stand-alone descriptors of research design, such terms supply valuable lenses through which to conceptualize and critique the scope, purpose, and methods of inquiry.

1.4 Delimitations and structure

This integrated thesis focuses on outpatient, community-based SH occurrence and risk prediction in the US. It includes six chapters: one has been published and two have been formatted as publishable manuscripts. Chapters 2 and 3 jointly introduce the reader to the characteristics and burden of iatrogenic SH and current gaps in management. Chapter 4 describes the design and implementation protocol of the iNPHORM study (published manuscript). Chapter 5 reports on the iNPHORM longitudinal cohort and quantifies the one-year incidence of SH—overall, by diabetes type, and by healthcare use (unpublished manuscript). Chapter 6 describes the development and internal validation of a real-world, one-year risk prediction model for recurrent SH using novel and traditional risk factors (unpublished manuscript). The dissertation concludes with a summary of results, and discussion of the study’s strengths, limitations, and significance.

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Chapter 2

2 Hypoglycemia: The crux of diabetes

The risk of hypoglycemia creates a challenging (1,2) and uncertain (3–5) terrain for effective diabetes management. Chapter 2 summarizes the evidence on diabetes frequency in the US, and current clinical and pharmacologic approaches to glycemic control. The barrier of iatrogenic SH is introduced, followed by an in-depth literature review of SH pathophysiology; physical, psychosocial, and economic implications; and epidemiology.

2.1 Background on diabetes

2.1.1 Considerable and rising burden of diabetes

Diabetes—a chronic disease of hyperglycemia associated with metabolic syndrome (6)—is a leading cause of death and disability in the US. In 2020, case counts reached 28.5 million: a 23% rise from 2019.(7) Prevalence is projected to increase 40% by 2030 and a further 50% by 2060.(8) Type 1 and 2 diabetes mellitus are the two major subtypes of diabetes, distinguished mainly by differences in underlying pathophysiology and treatment.

An estimated 5.7% of Americans with diagnosed diabetes live with T1DM (formerly known as insulin-dependent or juvenile-onset diabetes).(9) The disease is caused by absolute insulin deficiency rooted in the autoimmune destruction of insulin-producing pancreatic β-cells. Diagnosed individuals, therefore, require exogenous insulin to survive.(10) Roughly three-quarters of the time, the disease is identified in children or young adults; though, it can manifest later in life.(11) For reasons that are unclear, the rate of diagnosis continues to climb in the US, independent of improved detection. Possible mechanisms include changes in environmental exposures, diet in early life, and viral infections.(12)

Type 2 diabetes mellitus (formerly known as non-insulin dependent or adult-onset diabetes (10)) is by far the more common diabetes subtype, accounting for 91% of all American cases. Usually, the disease is detected in middle to late adulthood,(10) typified by progressive insulin resistance and relative (as opposed to absolute) insulin deficiency. Lifestyle intervention is normally indicated during the early stages of diagnosis, followed by oral antihyperglycemic therapy as pancreatic insulin secretion declines. Research suggests that secretagogues constitute 93.5% of all prescribed oral therapies in the US,(13) likely owing to their low cost and high availability.(14) Nevertheless, gradual β-cell exhaustion and weight gain (15) decrease the durability of these agents over time and, as a result, add-on treatment, such as insulin, are generally required (approximately seven years from oral therapy initiation.(16–18) Today, roughly 75% of people with T2DM use secretagogues and/or insulin.(13,19,20) As the US population ages (21) and as rates of obesity climb (22), the prevalence of pharmacologically treated T2DM—and with it the problem of hypoglycemia—is only expected to grow.(23–25)

2.1.2 Intensive glycemic control preëmpts vascular complications

Type 1 and 2 diabetes mellitus are defined by their associations with hyperglycemia-specific microvascular complications (e.g., visual disabilities, renal failure, sensory loss, and neuropathy, which can lead to amputation (26)) and cardiovascular disease (CVD)—especially among individuals with longer disease durations.(27) Premature mortality can occur secondary to microvascular impairment; however, CVD remains the primary cause of diabetes-related death.(8) In 2020, diabetes ranked as the eighth leading cause of US mortality.(7)

Epidemiologic studies from the 1950s (28,29), correlating long-term vascular complications with elevated glucose concentrations, first catalyzed the pursuit of near-euglycemia in diabetes. The case for glucocentric disease management was bolstered in the 1990s by two large randomized controlled trials (RCTs): the Diabetes Control and Complications Trial (DCCT) in T1DM,(30) and the UK Prospective Diabetes Study (UKPDS) in T2DM.(31) Both trials conclusively demonstrated an inverse, log-linear relationship between early manifestations of microvascular complications and increased glycemic control.(31–34)

In the DCCT, intensive therapy (fasting target plasma glucose [PG] of 3.9 mmol/L [70 mg/dL] to 6.7 mmol/L [120 mg/dL]) resulted in a 60% reduction in the development or progression of retinopathy, nephropathy, and neuropathy over 6.5 years compared to standard care. A similar effect trended in the UKPDS, where ten-year rates of microvascular complications were 37% lower in the intervention (fasting target PG of <6 mmol/L [106 mg/dL]) versus control arm. Declines in CVD risk were also achieved. A nine-year post-DCCT follow-up,(35) revealed a statistically significant 42% to 57% reduction in nonfatal myocardial infarction (MI), stroke, or cardiovascular (CV)-death following intensive therapy. In the UKPDS, each 1% reduction in A1C was associated with a 21% decrease in the risk of any end point, including myocardial infarction or diabetes-related death.(36)

Impelled by these results, diabetes clinical practice guidelines (37–40) recommended that most adults with T1DM or T2DM strive for near-euglycemic A1C[1] targets of <6.5–7%. This threshold was extrapolated from trial results that demonstrated improved outcomes in patients with a mean A1C of 7% versus 9% (DCCT) (35) or 7.9% (UKPDS).(31,32)

2.1.3 The barrier of hypoglycemia

"If it was not for the barrier of hypoglycaemia [sic], people with diabetes mellitus could have normal HbA1C values throughout a lifetime of diabetes." (Cryer P., 26, p.937)

Severe hypoglycemia[2] remains the most inimical barrier to insulin- and/or secretagogue-treated diabetes.(30,34,42) In the short term, events can cause disabling neuroglycopenia,(43)

[1] Glycosylated hemoglobin is typically measured by the hemoglobin A1C fraction: the amount of glucose irreversibly bound to the hemoglobin molecule during the lifetime of the erythrocyte. As the average lifespan of an erythrocyte and its hemoglobin molecule is 120 days, the A1C fraction provides a useful indicator of an individual's average glucose level over the past three months.

[2] Iatrogenic hypoglycemia refers to acute low blood glucose resulting from the use of insulin or secretagogues: two mainstay diabetes medications. It can occur repeatedly, without warning, and any time of the day/night. Event severity tends to correspond with depth of cerebral dysfunction; as such, SH often necessitates external aid for recovery (See §2.2.2 Clinical definitions).

accidents,(44–47) coma,(48) seizures,(49,50) and defective counter-regulation and, in the long term, contribute to neuro- and cardiologic damage,(51–53) and premature mortality.(54–60) Due to fear of SH (61)—which itself can impair daily functioning,(62–64) quality of life (QoL),(65) and relationships (66–69)—many people with diabetes deliberately maintain glucose levels above recommended targets.(70) Collectively, these effects impose substantial human and economic costs.(54,55,71–78)

Trials over the past decade indicate that intensive glycemic control with insulin and/or secretagogues induces more than a 150–300% increase in SH risk (Table 2.1).(79–82) Participants in the DCCT assigned to intensive versus standard therapy reported 3-fold the annual rate of SH.(30,42) Intensive glucose-lowering was also associated with increased SH risk in the Action to Control Cardiovascular Risk in Diabetes (ACCORD);(56) Action in Diabetes and Vascular Disease: Preterax and Diamicron MR Controlled Evaluation (ADVANCE),(57) Veterans Affairs Diabetes trial (VADT),(60) and UKPDS.(34,83) In the CV Outcome Reduction with an Initial Glargine Intervention (ORIGIN) trial (median follow-up duration: 6.2 years),(84) intensive sulphonylurea or insulin use resulted in 2 and 4.5 times the number of SH, respectively (30,42); events were defined as requiring third-party aid with either a PG level of 2.0 mmol/L (36 mg/dL) or prompt recovery after glucose or glucagon administration.(30,42) Several observational studies have reported analogous relative risks (2–3-fold for sulphonylureas and 3–4-fold for insulin when comparing intensive to standard therapy).(85–87)

Thus, at the crux of diabetes management lies the trade-off between preventing long-term complications and accepting the harms associated with SH.

Table 2.1: Relative risks of severe hypoglycemia in landmark diabetes trials comparing intensive versus standard therapy

Trial	Type of diabetes	Study duration, years	Intervention	Risk	Relative risk (95% CI)
DCCT, 1993 (30)	T1DM	6.5	Intensive	459/711 (64.6%)	1.85 (1.65 to 2.07)*
			Standard	255/730 (34.9%)	
UKPDS, 1998 (31,34)	T2DM	10	Intensive	33/3071 (1.1%)	1.53 (0.71 to 3.30)
			Standard	8/1138 (0.7%)	
ACCORD, 2008 (79)	T2DM	3.5	Intensive	830/5128 (16.2%)	3.18 (2.78 to 3.63)*
			Standard	261/5123 (5.1%)	
ADVANCE, 2008 (57)	T2DM	5	Intensive	150/5571 (2.7%)	1.85 (1.42 to 2.42)*
			Standard	81/5569 (1.5%)	
VADT, 2009 (60)	T2DM	5.6	Intensive	76/892 (8.5%)	2.74 (1.79 to 4.18)*
			Standard	28/899 (3.1%)	

*Statistically significant at α=0.05; T1DM, type 1 diabetes mellitus; T2DM, type 2 diabetes mellitus; DCCT, Diabetes Control and Complications Trial; UKPDS, United Kingdom Prospective Diabetes Study; ACCORD, Action to Control Cardiovascular Risk in Diabetes; ADVANCE, Action in Diabetes and Vascular Disease: Preterax and Diamicron MR Controlled Evaluation; VADT, Veterans Affairs Diabetes Trial; CI, confidence interval.

2.2 Background on severe hypoglycemia

2.2.1 Pathophysiology

Hypoglycemia occurs when the rate of endogenous glucose uptake into systemic circulation exceeds that of glucose entry (hepatic or gastrointestinal). When blood glucose (BG) levels drop below physiologic conditions, endogenous insulin secretion from β-cells is suppressed, and a cascade of counterregulatory hormones (namely glucagon and catecholamines) sets off to restabilize BG.

In people with diabetes, who are taking secretagogues or exogenous insulin therapies, plasma insulin concentrations are largely unregulatable. Defective insulin autoregulation (i.e., pancreatic islet dysfunction); absolute or relative iatrogenic hyperinsulinemia; and deficient or absent physiologic defenses, catalyze the risk for hypoglycemia. Early in the disease trajectory, physiological responses, initiated by stress pathways, protect against iatrogenic hypoglycemia. However, with increasing diabetes duration (in both T1DM and advanced T2DM), progressive insulin deficiency impairs crosstalk between α- and β-cells, dysregulating the release of glucagon and consequent glycogenolysis from the liver.(88)

As a backstop to declining glucagon responses, the sympathoadrenal nervous system activates to defend the brain from hypoglycemia. One of its functions is to release catecholamines (epinephrine and norepinephrine), which not only trigger rapid hepatic glycogenolysis, but also the mobilization of precursors that feed into the process of gluconeogenesis.(89) Catecholamine release, in addition to acetylcholine (a neurotransmitter in the parasympathetic nervous symptom), produces autonomic symptoms (e.g., tremulousness, palpitations, anxiety, sweating, and hunger). Thus, inhibition of this hierarchical counterregulatory response—following antecedent hypoglycemia, for example—is implicated in impaired awareness of hypoglycemia (IAH, § 2.2.4.1 Physiological consequences).

At BG levels below 3.0 mmol/L (54 mg/dL)[3], neuroglycopenia can arise (e.g., dizziness, light headedness, confusion, disorientation, mental obtundation, seizures, unconsciousness and coma).(43) Left untreated, such events can be fatal.

2.2.2 Clinical definitions

In a 2017 joint position statement, the International Hypoglycaemia Study Group (IHSG) and American Diabetes Association (ADA) recommended a new classification scheme for reporting and evaluating diabetes-related hypoglycemia.(90) Their proposed three-level nomenclature (Table 2.2) has been adopted by most major diabetes organizations around the world, including the European Association for the Study of Diabetes (EASD), the International Society for Paediatric and Adolescent Diabetes,(91) the European Medicines Agency, and an international expert panel on continuous glucose monitoring.(92)

Level 1 ‘non-severe’ (<3.9 [70 mg/dL] to 3.0 mmol/L [54 mg/dL]) and Level 2 ‘clinically serious’ (<3.0 mmol/L [54 mg/dL]) hypoglycemia capture events that are self-treatable. Conversely, Level 3 (‘severe’ hypoglycemia) constitutes self-reported[4] low BG concentrations necessitating assistance for recovery (90,95). Of note, the IHSG/ADA does not specify a glucose cut-off for Level 3 SH: 1) PG measurements are generally unavailable during hypoglycemic crises, 2) thresholds for symptom onset are idiosyncratic anyway,(96–100) and 3) neurological recovery following BG normalization innately proves the event was caused by low glucose.(90,95,101)

Daytime and nocturnal (a.k.a. nighttime) hypoglycemia normally refer to events occurring while awake and asleep, respectively; although, in some cases (e.g., in treat-to-target trials) nocturnal events are defined by a clock-based method (e.g., occurring between 12 a.m. and 8 a.m. (102,103)).

[3] This threshold may vary with recent hyperglycemia or antecedent hypoglycemia.

[4] Given the saliency of SH,(93) recall up to one year has shown to be robust with an estimated 90% accuracy.(94)

Table 2.2: Levels of hypoglycemia according to the International Hypoglycaemia Study Group and the American Diabetes Association[5]

Classification	Glucose criteria	Description	Treatment modality
Level 1 "Non-severe hypoglycemia"	<3.9 mmol/L (70 mg/dL) to 3.0 mmol/L (54 mg/dL)	Highly relevant as an alert level. Events may be asymptomatic. May trigger therapeutic modification.	Able to self-treat.
Level 2 "Major, serious, or clinically relevant hypoglycemia"	<3.0 mmol/L (54 mg/dL)	Sufficiently low BG to indicate serious, clinically important hypoglycemia. These events are associated with impaired cognition, cardiac arrhythmias predicting mortality, IAH, increased risk of SH, and economic burden.	Able to self-treat.
Level 3 "Severe hypoglycemia"	No threshold specified	A medical emergency. Altered mental and/or physical functioning. High clinical relevance.	***Not*** able to self-treat. External assistance often required for recovery.

BG, blood glucose; IAH, impaired awareness of hypoglycemia; SH, severe hypoglycemia.

[5] Given the US focus of this dissertation, hypoglycemia classifications will follow IHSG/ADA recommendations. It is, however, recognized that different definitions have been endorsed elsewhere (e.g., Diabetes Canada Practice Guidelines).(104)

2.2.3 Treatment of severe hypoglycemia

The treatment of hypoglycemia—which depends on event severity and duration—is represented by a spectrum of increasing therapeutic complexity: self-administered oral carbohydrates on one end, and parenteral therapy on the other (Table 2.3).(105)

Table 2.3: Treatment of Hypoglycemia. Adapted from MacCuish AC (106)

Duration of hypoglycemia	Administrator	Treatment
Minutes	Patient	• Oral carbohydrate (>15 g)
Hours	Caregiver (e.g., family/friend/colleague)	• Oral carbohydrate (liquid or solid) • 1 mg intramuscular or nasal glucagon*
	Primary healthcare setting	• 1 mg intramuscular or intravenous glucagon* • 25 g intravenous glucose
	Hospital setting	• 25 g intravenous glucose • 1 mg intravenous glucagon*

*Treatment should be followed by oral carbohydrate (20–40 g) after consciousness regained

For individuals who are conscious and able to swallow, first-line treatment consists of 15–20 g of fast-acting oral glucose[6], followed by 20–40 g if BG levels fail to normalize within 15 minutes. In cases of more serious neuroglycopenia, third-party administration of carbohydrates may be required to recover clinical status.

[6] Any form of carbohydrate that contains glucose will increase BG; however, pure glucose is preferred when treating hypoglycemia. Food sources that contain fat may delay and subsequently prolong the acute glycemic response. Moreover, ingested protein during hypoglycemia has shown to increase insulin response in people with T2DM, without increasing PG concentrations.(40,107)

When oral ingestion is unsafe (e.g., due to stupor or unconsciousness), emergency glucagon is indicated[7].(40) Various formulations are available, including traditional intramuscular (IM) injections as well as, more recently, rescue pens/syringes (using a stable liquid solution) and a dry powder nasal spray. Glucagon is the only non-oral rescue therapy administrable outside professional care contexts; nonetheless, national dispensation rates remain low.(68,109)

Injectable intravenous (IV) or IM glucose provides a third-line option when glucagon is unavailable; contraindicated (110–112) (e.g., for people with known hypersensitivity or pheochromocytoma); ineffectively administered; or unsuccessful (e.g., in states of starvation, adrenal insufficiency, or chronic hypoglycemia).(104,113) Given the potential for rebound hyperglycemia and localized tissue damage,(114) IV/IM glucose is administrable only by medically trained professionals in prehospital or hospital settings.

Generally, glucagon is used to treat SH in people with T1DM, whereas IV glucose is more commonly used in T2DM.(115) Glucagon may be considered for T2DM individuals with advanced disease or receiving intensive insulin therapy (115); however, for those taking secretagogues (without insulin), glucagon is less useful as it stimulates insulin secretion through glycogenolysis.(116)

2.2.4 Physical, psychosocial, and economic consequences

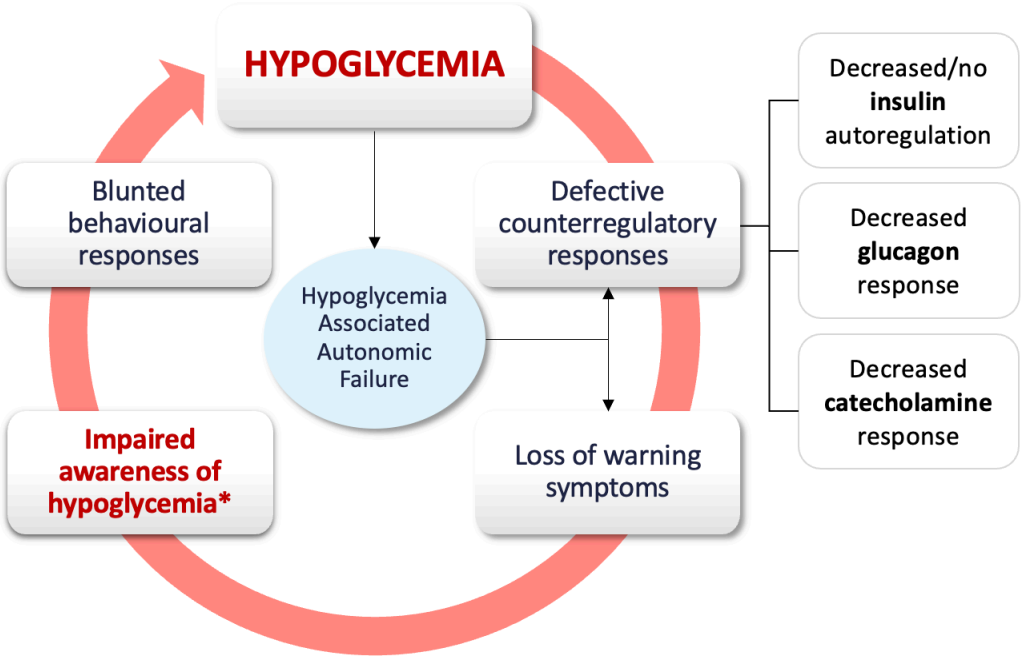
2.2.4.1 Physical consequences

Symptoms of hypoglycemia can be distressing and even debilitating. Because events can cause neuroglycopenia and cognitive dysfunction, accidents resulting in personal injury are a common sequela (e.g., falls with fractures, joint injuries, or head trauma).(44–47) In addition, events can induce coma (48) or epileptiform seizures, as well as cardiac arrhythmias, sudden death, and permanent changes in regional cerebral blood flow (a marker of transient ischemic attacks and

[7] Glucagon raises BG concentrations by increasing hepatic glucose production, first by glycogenolysis and then by gluconeogenesis. By way of comparison, among individuals without diabetes, secretion of glucagon from α-cells is inhibited by insulin, which signals the liver to stop producing endogenous glucose.(108)

hemiplegia).(49,50) Studies have correlated SH with an increased risk of dementia (51–53); possible mechanisms include neuronal damage (117,118) or death,(118) brain insulin resistance,(119) and oxidative stress from hyperinsulinemia.(120)

Repeated instances of hypoglycemia can lead to IAH, a syndrome marked by the loss of adrenergic responses and a diminished ability to perceive and, thus, correct incipient low BG. Prior hypoglycemia has shown to excessively activate nicotinic acetylcholine receptors (121) that suppress catecholamine secretion during subsequent episodes.(122–124) The result is an attenuation and delay of symptomatic warning signs to hypoglycemia. Cryer et al. referred to this phenomenon as Hypoglycaemia Associated Autonomic Failure (HAAF), and attributed it to a centrally mediated failure in counter-regulation.(125) Studies have since demonstrated reduced IAH following scrupulous avoidance of hypoglycemia without restoration of normal counter-regulatory responses.(41,126–128) Thus, both conditions uniquely contribute to a cyclical pathology of elevated recurrent hypoglycemia risk (Figure 2.1).



*Based on clinical evaluation (Gold method,(129) Clarke method,(130) Pedersen-Bjergaard method(131))

Figure 2.1: Cyclical pathology of recurrent hypoglycemia

At the same time, frequent catecholamine responses can aggravate myocardial contractility and output (132) with potential consequent effects on ischemic heart disease.(133) Studies have linked sympathoadrenal activation to lengthened differential parasympathetic and sympathetic activation,(134–136) as well as corrected QT interval (QTc) prolongation (137) that can eventuate ventricular tachycardia.(49,138,139)

The foregoing pathways could explain the observed relationships between SH and adverse CV and fatal outcomes. Meta-analyses and other large clinical studies associate event exposure with 2–3.4 times the risk of CV-related and all-cause mortality compared to non-exposure.(54–60) In 2008, ACCORD was terminated early due to 54 excess deaths in the intensive treatment arm; post hoc analyses revealed that trial participants reporting one or more versus no SH event(s) experienced a 41% increase in the rate of death and vascular complications.(72) The DCCT, VADT-F, and ADVANCE reported equivalent results.(35,57,140)

Nevertheless, debate persists over whether SH is a cause or marker of morbidity and frailty.

2.2.4.2 Psychosocial consequences

Hypoglycemia can also constrain psychological well-being and daily functioning (e.g., sleep quality, occupational pursuits, leisure activities, and driving).(61–64) Emotional distress, depressive symptoms, and diabetes-specific QoL have been variably associated with the risk and occurrence of hypoglycemia. Although, convincing data link events to increased fear of hypo- (FoH) (141,142) and hyperglycemia (FoHyper).(143–145)

Despite the well-known benefits of optimal glycemic control, many with diabetes develop an extreme FoH that—besides impairing overall QoL (65)—withers effective self-management.(146) In a study by Leiter et al., 35–44% of participants with T1DM and 11–47% with T2DM modified their insulin dose to avoid SH; over-compensatory eating (146) and reduced exercise were further documented.(147) Fear of hypoglycemia has shown to directly correlate with event history (both frequency and severity).(148–150) Other predictors include female sex,(151) lower mean daily BG levels,(148) and higher glycemic variability.(148)

Of opposing concern is FoHyper (152) whereby symptoms of hyperglycemia (143) (e.g., fatigue and irritability) or risk of long-term diabetes complications are perceived to outweigh the hazards of low BG.(153) It follows that, like FoH, FoHyper can motivate avoidant self-management behaviours.(154) Wang and colleagues revealed that when BG levels are low, 68% of individuals "do nothing", while only 30% achieve normal glucose levels 30 minutes from onset.(155,156) Gonder-Frederick and colleagues observed a greater prevalence FoHyper among pump users, drivers who had been in two or more versus one or less motor vehicle accident(s), and women.(144,145)

People with diabetes often depend on their significant others to help moderate and normalize the disruptive effects of hypoglycemia (157,158); however, this can result in a transference of psychological burden and distress. In the Canada-wide InHypo-DM (UnderstandINg the impact of HYPOglycemia on Diabetes Management: A Survey of Perspectives and Practices) study, 87% of significant others of people with diabetes claimed they would forgo aspects of their lives to help manage hypoglycemia (69) and, in the TALK-HYPO study, 43% experienced negative emotional reactions because of it (e.g., worry and anxiety).(67) Some caregivers recruited in the Dose Adjustment For Normal Eating - Hypoglycemia Awareness Restoration Training (DAFNE-HART) study reported experiencing physical and emotional abuse when helping treat events due to the cognitive changes that can arise from low BG.(66) Ultimately, these consequences can strain social dynamics and imperil relationships that are most important.(159)

2.2.4.3 Economic consequences

In the US, SH accounts for a quarter of all adverse drug event-related hospitalization.(78) In 2014, the number of hypoglycemic-related emergency department (ED) visits surpassed hyperglycemic-related visits, culminating in annual direct expenditures of $1.8 to $5.9 billion (USD).(160) Emergency services, clinic visits, and use of at-home and professional diabetes supplies impose further economic strain, as do the numerous indirect costs incurred by patients and their nonpaid caregivers (e.g., pain and suffering, lost productivity, and resources).(161,162) Cumulatively, acute morbidities resulting from hypoglycemia can reduce overall well-being and generate downstream expenses for long-term monitoring and care.

2.2.5 Epidemiology

2.2.5.1 Crude frequency

Research on SH frequency gained traction in the 1980s; although, the earliest data date back to 1928.(163) For much of the 20th century, epidemiologic studies on SH were restricted to T1DM cohorts.(164) Interest shifted to T2DM when the burgeoning use of secretagogues and insulin raised concerns about hypoglycemia in this numerically larger disease group.(165)

While considerable evidence now affirms the right skewed distribution of SH[8] (166–168), methodological limitations and heterogeneity continue to confound understandings of population event frequency.

Data from trials

Historically, information on SH frequency[9] came from RCTs. The landmark DCCT (30) (1982–1993) investigated intensive versus standard human insulin therapy in a cohort of 1441 participants aged 13–39 years with T1DM.(30) Mean follow-up was 6.5 years. Over a third (36%) reported experiencing one or more event. Rates ranged from 0.2 (standard arm) to 0.62 (intensive arm) events per person-year [EPPY].(30,169) Based on a 30-year observational follow-up (Epidemiology of Diabetes Interventions and Complications [EDIC],(170) 1994–present), rates fell in the former DCCT intensive arm (0.37 EPPY) but rose in the standard arm (0.41 EPPY).(171) A review of 13 T1DM RCTs using equivalent eligibility criteria reported an overall comparable SH rate of 0.4 (min, max: 0.1, 0.8) EPPY.(172)

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[8] Most people with diabetes will experience a few SH events in their lifetime; however, some will experience several. Events are typically reported as incidence rates and/or as cumulative incidences. Medians are sometimes provided as a supplemental measure of dispersion; however, given the positively skewed distribution of most SH data, median values are typically zero and, thus, compared to incidence calculations, relatively non-informative.

[9] Note, most trials define SH as an acute episode of low BG requiring external aid for recovery; though, often an auxiliary criterion of BG <3.9 mmol/L (70 mg/dL) or <2.8 mmol/L (50 mg/dL) is specified.

The UKPDS (1977–1991) monitored 4209 T2DM participants with no significant micro- or macrovascular disease.(34,83) Interventional treatment consisted of metformin, sulphonylureas (chlorpropamide or glibenclamide), and/or insulin to achieve a fasting PG <6 mmol/L (108 mg/dL). Standard treatment comprised diet alone with a fasting target PG <15 mmol/L (270 mg/dL).(31,34) Over the first ten years, the annual mean proportions of one or more SH events were 1.0% with chlorpropamide, 1.4% glibenclamide, and 1.8% with insulin.(31) The CV outcome ORIGIN trial (N=12537; 2003–2011), also conducted in people with T2DM, compared intensive insulin glargine therapy (target fasting PG ≤5.3 mmol/L [95 mg/dL]) to standard treatment in older adults with prediabetes or a recent diagnosis.(173) The rate of SH was 0.01 and 0.0031 EPPY in the insulin glargine and standard treatment group, respectively.(173)

Trial results axiomatically depend on the characteristics of the participant sample. In the DCCT (30) people without a history of recurrent SH (defined as two or more events per year) or IAH were excluded, and in ORIGIN (173) and UKPDS (34,83) enrollment was restricted to those with newly diagnosed T2DM[10]. In the latter trial, insulin therapy was initiated after only a three-month run-in following diagnosis.(34,83)

Comparatively, the SWITCH 1 trial (2014–2016) of insulin degludec versus glargine U-100 therapy comprised 501 people with T1DM and at least one hypoglycemia risk factor (one or more SH in the past year; estimated glomerular filtration rate [eGFR] of 30–59 mL/min/1.73 m^2; IAH; diabetes duration >15 years; or one or more BG level ≤3.9 mmol/L [70 mg/dL] in the past 12 weeks). Annual rates in this trial well-exceed those in the DCCT, ranging from 0.87 in the insulin degludec arm to 1.05 in the glargine U-100 arm during the full treatment period.(174) When only individuals prone to recurrent SH are permitted to enrol, incidences increase even further. Across four such trials, Pedersen-Bjergaard and Thorsteinsson (172) calculated a median preintervention SH rate and yearly IP of 6.1 (min, max: 3.6, 8.9) EPPY and 86% (min, max: 77, 100%), respectively.(175–178)

[10] People with newly diagnosed T2DM poorly represent the typical insulin-taking person as counterregulatory defenses that protect against SH are still intact at diagnosis. For this reason, insulin is not considered a first-line T2DM treatment.

Likewise, T2DM trials with broader sample boundaries report higher frequencies than UKPDS and ORIGIN. The ACCORD trial (56) (2001; 2003–2005) enrolled a T2DM cohort of 10251 individuals with A1C values ≥7.5% and either 1) CVD; or 2) among people 55–79 years old, atherosclerosis, albuminuria, left ventricular hypertrophy, or two or more CVD risk factors (i.e., dyslipidemia, hypertension, current status as a smoker, or obesity). The annual IP was 3.1% for intensive therapy (target A1C <6.0%) and 1.0% for standard therapy (target A1C 7.0–7.9%).(56) Equivalent estimates are reported in ADVANCE (2008) (57), the VADT (2000–2008) (60), and other pragmatic RCTs.(179–187) Nevertheless, landmark T2DM trials have shown to represent only 3.5% (PROactive trial) to 35.7% (ADVANCE) of the general diabetes population.(188–190)

Issues of poor generalizability are compounded by unrealistically frequent and rigorous follow-ups, dependence on protocol versus real-world treatment regimens, and over selection of motivated and well-off participants. Because of these factors, RCTs are liable to underestimate true SH burden.(191)

Data from observational studies

Over the past decade, growing demands for Phase IV pharmacoepidemiologic research on hypoglycemia sparked an upsurge of observational inquiry. At the same time, expanding access to administrative claims and electronic health records (EHRs) carved new latitudes in population health surveillance.(192) In one of the largest SH claims studies to date, McCoy et al. (193) analyzed ~3.7 million patient records to quantify dysglycemia necessitating hospital use. Based on candidate codes from the International Classification of Diseases - Ninth Revision (ICD-9)[11], the authors were able to show consistently higher rates of hypo- versus hyperglycemia related emergencies from 2009 to 2018 (0.0096 [95% CI: 0.0094–0.0098] versus 0.0057 [95% CI: 0.0056–0.0059] EPPY, respectively [2018 rates]).

[11] Based on the validated Ginde et al. algorithm (194) for classifying SH requiring emergency room (ER) medical treatment using ICD-9-CM codes (250.3, 250.8, 251.0, 251.1, 251.2, 270.3, 775.0, 775.6, and 962.3). The positive predictive value was 89% in any position, and 93% in the primary position.

Yet, no matter the promise of increased sample representivity, health records reflect only the small fraction of events resulting in healthcare use.(195) Forty years ago, Potter et al. (196) famously analogized hospital-based hypoglycemia to the "tip of an iceberg". Extending beyond analyses of diagnostic codes alone, some researchers have explored free-text clinical notes using natural language processing (NLP)[12]. In a 2022 systematic review of T1DM and T2DM,(197) the yearly IP of SH was 12.4% for ICD-9/10[13] codes versus 25.1% for NLP algorithms and 32.2% when combined. Nonetheless, while an improvement, NLP still fails to capture events treated by emergency medical services (EMS) (198) and, moreover, compensate for the high documented prevalence of patient non-disclosure and provider under-recognition (see § 3.2.1 Routine Clinical Practice).(199–201)

The 2017 IHSG/ADA guidelines drew attention to the fundamental importance of self-report as a viable (94) and clinically relevant (90,95–101) metric for SH. Prior to this publication, no consistent, standardized classifications of hypoglycemia were used in clinical research. Swinnen et al. (202) illustrates a strong positive correlation between glucose thresholds and apparent number of events (Figure 2.2).(203) Building on these findings, a more recent evaluation revealed 4–15 times the annual rate of SH when events were classified as requiring third-party (i.e., according to Level 3 nomenclature) versus parenteral aid, specifically.(172)

In a review of 24 observational studies, Level 3 SH rates were as high as 5.8 EPPY in T1DM and 2.5 EPPY in T2DM.(191) Still, these estimates may underestimate true, real-world event frequencies, as most stem from cross-sectional research.(204) Of the relatively few prospective studies that exist,(24,129,168,204–210) only one took place in the US (duration: 41.2 [standard deviation {SD}: 8.6] weeks).(168) This investigation by Murata et al. (168) included 344 individuals (mean age: 65.5 [SD: 9.7] years; 97% men) with stable insulin treated T2DM (Neutral Protamine Hagedorn [NPH]). It is dubious these results generalize to the modern

[12] Natural language processing is a statistical technique belonging to the subfields of linguistics, computer sciences, and artificial intelligence that facilitates analyses of natural language data, including contextual nuances. Generally, its purpose is to extract and organize information contained in the target dataset.

[13] In October 2015, the Centers for Medicare & Medicaid Services mandated use of ICD-10 codes.

management of Americans with T2DM let alone T1DM. Clearly, improved insight into Level 3 SH is needed to understand real-world event burden.

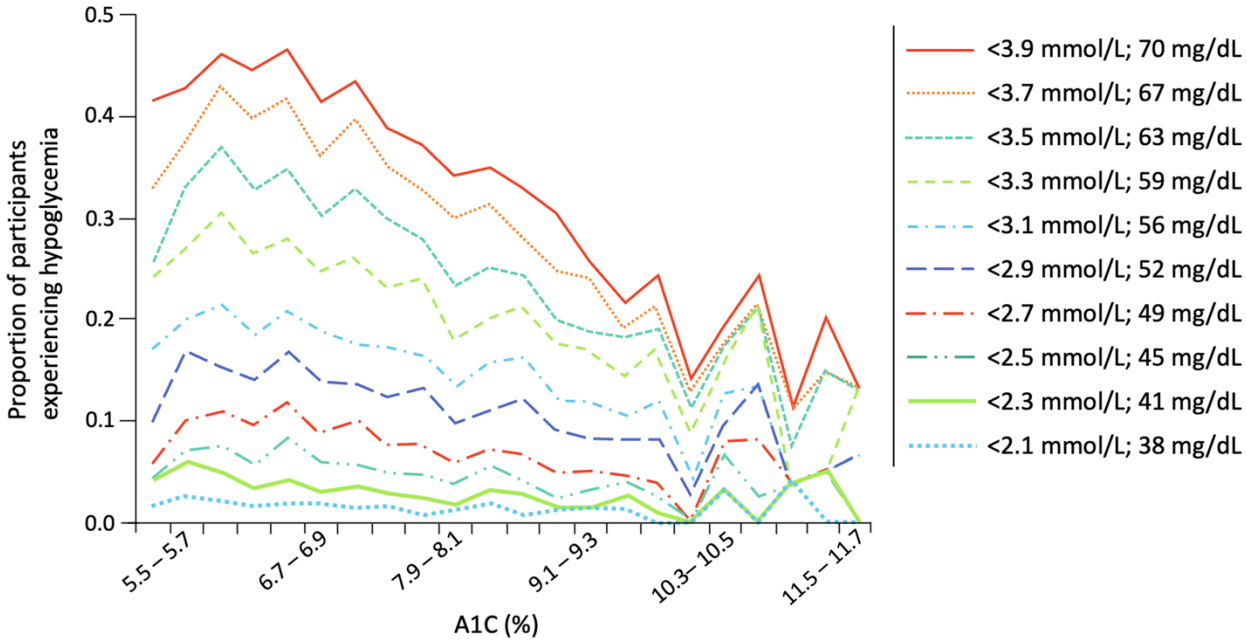

Figure 2.2: Proportion of patients experiencing one or more hypoglycemia event(s) during a 12-week period for a range of predefined cut-off points. Adapted from Swinnen et al. (203)

2.2.5.2 Major epidemiologic correlates

Besides intensive glycemic control, several SH risk factors have been identified.(211) The most commonly cited ones are described below. Evidence from studies of Level 3 hypoglycemia is provided whenever appropriate and available.

Age and cognitive function

Adrenergic responses to hypoglycemia decrease with age,(212) causing alterations in the threshold for autonomic and neuroglycopenic symptoms that trigger self-treatment.(213) Consequently, older age may diminish an individual's ability recognize and treat

hypoglycemia.(212,213) The elderly, particularly those with reduced cognition and dementia,(51,52,214) are especially vulnerable to SH. Cognitive impairment may lead to inappropriate self-management behaviour that further increases hypoglycemia risk.(215)

Duration of diabetes and therapy

Longer diabetes duration is associated with a progressive decline in β-cell functioning and counter-regulatory responses, increasing the risk of hypoglycemia.(216) The UK Hypoglycaemia Study Group showed that people with T2DM taking insulin for less than five years experienced equivalent event frequencies as those on sulphonylureas; however, rates rose on par with T1DM estimates (disease duration: <5 years) when insulin therapy surpassed five years.(24,217) Among those with T1DM, insulin duration of more than 15 years versus less than five years tripled the risk of hypoglycemia.(24)

A1C, glycemic variability, and time in range

Several diabetes trials report an inverse relationship between A1C and SH (30,31,56,56,57,60); but a post hoc analysis of ACCORD indicates that tight as well as poor glycemic control (in contrast with optimal control) aggravates event risk.(218) Lipska et al. also documented a J-shaped relationship in a large, US population-based survey.(219)

The potential for SH occurrence despite elevated A1C values, signals a susceptibility to both hyper- and hypoglycemia. Recent analyses have attributed this finding to steady increases in glycemic variability (BG fluctuations around the mean glucose value from peaks to nadirs).(220–223) In one longitudinal investigation (2014–2020), SH correlated with a 3–4-fold risk of emergent hyperglycemia .(224) The clear relevance of glycemic variability to diabetes control, buttressed by enhanced glucose monitoring (real-time continuous/flash glucose monitoring [rt-C/FGM] devices), has fueled the promulgation of ‘time in range’ as a complement metric to A1C.(225)

History of severe hypoglycemia

In the Fremantle Diabetes Study (1998–2006), hypoglycemia-related hospital- (with or without admission) or EMS-based care was 6 times as likely in people with a prior episode.(85) Similar trends are reported in the US, where, between 2004 and 2008, the odds of a successive SH-related ED visit among individuals with a previous SH-related hospitalization was 9.5 times that of individuals with no previous SH-related hospitalization.(86)

Impaired awareness of hypoglycemia

Research suggests that 50% of people with T1DM (129) and 28% with insulin- and/or secretagogue-treated T2DM (226) have difficulty recognizing the warning signs of hypoglycemia. These individuals face 3–20 times the risk of SH compared to patients with preserved hypoglycemia awareness during standard treatment.(94,129,130,166,227)

Renal function

Renal impairment can impede clearance of insulin and secretagogue metabolites as well as affect gluconeogenesis and glycogenesis. According to the US National Health and Nutrition Examination Survey (NHANES) (2011–2012), 19% of Americans with diabetes (T1DM or T2DM) have an eGFR <60 mL/min/1.73 m^2,(228) while over 50% have diagnosed kidney disease (eGFR <60 mL/min/1.73 m^2 or albuminuria ≥3 mg/mmol [≥30 mg/g]). Research has linked elevated versus normal serum creatinine to 5 times the annual rate of SH in people with T1DM.(229) In T2DM, the 8-year risk of SH was 2–3 times as high in people with an eGFR <60 mL/min/1.73 m^2 compared to those with an eGFR >60 mL/min/1.73 m^2.(85)

Self-management behaviour

Diabetes self-management explains >60% of the variance in hypoglycemia occurrence.(230) Events are most commonly attributed to delayed, irregular, or insufficient carbohydrate intake (25–29%); skipped meals or snacks (20–50%); unplanned or excessive physical activity (12–

16%); incorrect medication use (i.e., excess dosing) (5–10%); stress (13%); and illness (3–4%).(187,231,232) Alcohol consumption can also inhibit gluconeogenesis and increase the risk of hypoglycemia, as can the use of concomitant medications that suppress or stimulate appetite.(233)

Socioeconomic status

Studies indicate that diabetes-related SH is more common in people with low income,(234) minimal formal education and health literacy,(235) and food insecurity.(236–238) Disparities in wealth and economic opportunities are also speculated to underpin the higher observed event frequencies in Black versus white populations with diabetes.(239)

2.3 Summary

Severe hypoglycemia—the most common and, arguably, dangerous adverse effect of insulin and/or secretagogues—is the greatest barrier to diabetes control. This chapter reviewed the pathophysiology, treatment, consequences, and epidemiology of iatrogenic SH, amid rising diabetes rates in the US. The next chapter discusses current SH management approaches, barriers to prevention, and the purpose of this dissertation.

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Chapter 3

3 Thesis rationale

Prevention of iatrogenic SH is incontrovertibly safer and more effective than treatment; yet this appears little appreciated in real-world practice. Chapter 3 discusses current approaches to, gaps in, and opportunities for improved SH risk management. It concludes with a précis on the motivation of this doctoral thesis, from clinical needs to research priorities.

3.1 Current approaches to managing severe hypoglycemia

In the US, diabetes performance measures predicate mainly on whether patients achieve A1Cs above or below 8%. However, this 'diabetes-out-of-control' catchall is ill-suited to evaluating the individualized quality and safety of care and, worse, may actually disincentivize best practice. For example, research indicates that people with low complexity (e.g., younger, healthier adults (1)) are more often undertreated, despite inappropriately high A1Cs (7–8%),(2–4) while people with high complexity (e.g., older adults (5)) are more often overtreated, despite risks of hypoglycemia.(2,3,6–14)

Growing attention on the adverse effects of SH has led to calls for a re-evaluation of A1C as the sole metric of diabetes control. Practice guidelines now advocate for the use of tailored therapeutic goals (ideally A1C values <7%) that purposefully counterbalance hypoglycemia risk.(15–19) A workgroup by the ADA and the Endocrine Society (ES) created a framework for managing outpatient hypoglycemia risk with focus on routine event inquiry and documentation.(20) Recommendations by major diabetes organizations are reinforced by initiatives like the National Action Plan for Adverse Drug Event Prevention, which lists diabetes-related iatrogenic hypoglycemia as a high-priority target.(21) The Patient Protection and Affordable Care Act also brought patient-reported metrics to the forefront of chronic diabetes management,(22) challenging traditional glucocentric modalities.

Multiple clinical strategies have been proposed to mitigate hypoglycemia risk (Table 3.1). In addition to proactive deintensification (8,12,23,24) and simplification,(11,25) providers may consider relaxing A1C targets,(19) prescribing agents with little to no hypoglycemia risk, and leveraging adjuvant technologies (continuous subcutaneous insulin infusion [CSII], rt-C/FGM, and hybrid closed-loop [HCL] insulin pumps). Non-therapeutic approaches include IAH screening,(26–29) multi-disciplinary care provision,(30) engagement of significant others,(31) and structured psychoeducational programs. Human islet cell transplantation may be indicated for patients who are refractory to medication.

Table 3.1: Summary of current approaches to reduce hypoglycemia

Intervention	Description
Therapeutic deintensification	Therapeutic deintensification, including reduction or removal or medications should be evaluated routinely, especially in older adults and patients with comorbidity or high clinical complexity.(8,11,24,32–34) In this population, intensive glucose-lowering therapy not only confers higher risks of hypoglycemia, but it also returns less benefit.(10,33,34)
Therapeutic simplification	Therapeutic simplification premises on the two principals of Ockham's Razor—Parsimony and Plurality—and has been likened to a reverse form of clinical inertia.(35,36) Broadly, the practice involves decreasing the complexity and, therefore, burden of treatment, while maintaining good glycemic control, efficacy, and safety.(37–39) Approaches can include reductions in the number and type of medications, doses, glucose checks, or carbohydrate calculations.(17) It can also entail treatment modifications that prioritize individuals' self-management skills, preferences, or means.(40) Simplification has shown to moderate hypoglycemia risk in patients who are older, clinically complex, or on polytherapeutic regimens.(25,41)
Relaxed A1C targets	The 2021 ADA Standards of Medical Care in Diabetes (19) recommends an A1C value of <7% if it can be achieved without significant hypoglycemia.

	The guidelines caution providers in using aggressive near-normal A1C targets in patients at-risk of severe or frequent events. For these individuals, higher glycemic goals should be considered. The ADA also advises short-term relaxations of glycemic targets in people with IAH, as scrupulous avoidance of hypoglycemia has shown to restore symptom detection.
Preferential use of agents that obviate or lessen hypoglycemia	If logical and feasible, changes in glucose-lowering therapies to those that confer little to no hypoglycemia risk may be the most effective preventive approach. For example, second generation basal insulin analogues have similar glycemic efficacy as first-generation basal insulins; however, their longer durations of action and smoother pharmacokinetic/ pharmacodynamic profiles confer reduced risks of hypoglycemia.(42) For patients not requiring insulin but oral therapy, metformin, GLP-1 receptor agonists, DPP-4 inhibitors, and SGLT2 inhibitors could be considered (depending on kidney function (43)), as none of these agents induce iatrogenic hypoglycemia.
CSII pump	Also known as insulin pump therapy, CSII involves the subcutaneous administration of insulin through the abdominal wall; the dose is determined by levels of capillary glucose. Use of CSII has been associated with better glycemic control,(44–49) fewer SH events,(45,47,48,50,51) and reductions in total daily insulin doses compared to multiple daily injections.(45,49) It can be used by people with T1DM or T2DM.
rt-C/FGM	Continuous glucose monitoring is a wearable tool that allows people to view their glucose readings 24 hours a day. The device functions by measuring interstitial glucose every one to five minutes via a small electrode. Readings are collected automatically (real-time [rt]-CGM) or by manual scan of the sensor (intermittent [i]-CGM, also known as FGM). Real-time continuous or flash glucose monitoring technology can be essential to refining therapy and detecting incipient low BG. Particular benefit has been observed in patients prone to glycemic variability, SH,

	IAH, or severe insulin deficiency.(19,52–54) Devices can be used by people with T1DM or T2DM.
HCL insulin pump	An HCL pump, also known as an artificial pancreas, comprises an insulin pump and a computer-programmed rt-CGM that facilitates automated insulin delivery, including basal adjustments and corrective boluses. People with either T1DM or T2DM can benefit from this technology. The primary goal of the HCL pump is to maintain glucose levels within a target range by minimizing the rate of hypo- and hyperglycemic excursions. Manual programming is still required with meals (hence, "hybrid"). Studies show that, compared to sensor-augmented pump therapy, use of HCL pumps increases time in range (55–58) and decreases A1C (55,59). Future directions in closed-loop technologies are aimed at advanced generations of fully automated and multi-hormone (e.g., insulin infusion + glucagon boluses) systems.(60)
IAH screening	Impaired awareness of hypoglycemia is a potent predictor of SH.(26,27,61,62) Restoration and maintenance of hypoglycemia awareness is, thus, crucial. At least three validated, point-of-care questionnaires have been developed to assess IAH: the Gold method,(26) the Clarke method,(27) and the Pedersen-Bjergaard method.(29) Self-identified IAH has shown to agree with clinical evaluation.(27)
Multidisciplinary care provision	Coördination of a multidisciplinary care team (e.g., physicians, nurses, pharmacists, dieticians, mental health professionals, and certified diabetes educators) may facilitate improved diabetes management and reduced risks of hypoglycemia.(63–65)
Significant other engagement	Significant others of people with diabetes can function as an important source of information on hypoglycemia. When asked by clinicians, they usually report higher event frequencies than people with diabetes.(66) Strategic collaboration between care providers and significant others could reduce the burden and risk of hypoglycemia.(31) It may also help

	facilitate improved A1Cs and self-management behaviours among people with diabetes.(67)
Structured psychoeducational programs	BGAT-2 (68,69): An eight-weekly program that fosters enhanced internal (e.g., physical symptomatic cues, cognitive skills, mood changes) and external (e.g., timing/dose of previous insulin, food intake, exercise) cues to identify and anticipate the signs of dysglycemia. Documented effects include improved detection of hypo- and hyperglycemic excursions.(68,70,71) HAATT (72): An eight-session T1DM structured program on hypoglycemia detection. The program was associated with significant and sustained improvements in detection and reduction of SH.(72,73) DAFNE (74,75): A structured five-day program for people with T1DM that focuses on insulin to carbohydrate adjustments and use of home BG monitoring. The intervention improved overall glycemic control, reduced hypoglycemia, and increased QoL.(76) DAFNE-HART (77): A six-week program using motivational interviewing and cognitive behavioral therapy to help attendees identify hypoglycemia cues, its consequences, and IAH. The program significantly improved IAH after 12-months. HARPdoc (78): A six-week structured session for people with T1DM. The program builds on the DAFNE-HART curriculum to specifically address hypoglycemia avoidance. The intervention proved to alter unhelpful health beliefs around hypoglycemia and barriers to avoiding future events. HypoCOMPaSS (79): Half-day education session focused on reducing hypoglycemia episodes. Following the program, IAH and incidence of SH decreased significantly, as did, fear of hypoglycemia; treatment satisfaction improved. HyPOS (75): Structured T1DM program delivered over five-weekly 90-min sessions that focused specifically on hypoglycemia (rather than general

	diabetes) management and education. The program demonstrated significant benefit on IAH, hypoglycemia detection, treatment with reductions in the number mild events.
Islet cell transplantation	Pancreatic islet transplantation, also known as pancreatic islet allotransplantation, involves extracting an adequate number of pancreatic islets from a donor pancreas and infusing them into a recipient's liver. In addition to long-term insulin independence, transplantation has shown to produce marked reductions in SH.(80) Currently, clinical islet transplantation is reserved for patients with T1DM.

T1DM, type 1 diabetes mellitus; T2DM, type 2 diabetes mellitus; SH, severe hypoglycemia; ADA, American Diabetes Association; BG; blood glucose; BGAT-2, Blood Glucose Awareness Training-2; CSII, continuous subcutaneous insulin infusion; DAFNE, Dose Adjustment for Normal Eating; HART, Hypoglycemia Awareness Restoration Training; DPP-4 inhibitors, dipeptidyl peptidase-4 inhibitors; GLP-1 receptor agonists, glucagon-like peptide 1 receptor agonists; HAATT, Hypoglycemia Anticipation, Awareness and Treatment Training; HARPdoc, Hypoglycaemia Awareness Restoration Programme despite optimised self-care; HCL, hybrid closed loop; HypoCOMPaSS, Recovery of Hypoglycemia Awareness in Long-Standing Type 1 Diabetes; IAH, impaired awareness of hypoglycemia; QoL, quality of life; rt-C/FGM, real-time continuous or flash glucose monitoring; SGLT2 inhibitors, sodium-glucose transport protein 2 inhibitors.

3.2 Elusive pathways to prevention

Despite the plethora of interventions to reduce hypoglycemia risk, no valid methods exist to target them in practice. This gap could explain why, in the US, SH frequencies remain persistently high.(81–83)

3.2.1 Routine clinical practice

Modern management of hypoglycemia continues to rely on providers' subjective impressions of patients' recounted event histories. However, patient underreporting and provider under-recognition can occlude the elicitation of SH during routine encounters. In the Conversations and Reactions Around Severe Hypoglycemia Study (CRASH) Canadian study, 45% (T1DM: 49%; T2DM: 39%) of people with diabetes did not discuss their most recent SH with their providers.

Commonly cited reasons for SH nondisclosure include apathy/indifference, fear of provider judgment or legal ramifications (e.g., loss of license); impact on employment; discomfort/desire for privacy; and IAH.(19,84–90)

Studies also indicate that 10–16% of people with T1DM and 13–26% with T2DM are not asked about hypoglycemia during consultations.(91,92) Of the conversations that are had, most are facilitated by family medicine practitioners.(93) Lack of germane quality metrics, competing priorities, unfamiliarity with guidelines, and ethical dilemmas around license revocation (94) could impede routine clinical surveillance. Furthermore, selective information processing (95,96) and biased judgments may effectively minimize (97,98) providers' perceptions of SH risk and occurrence, especially regarding certain patient groups (e.g., secretagogue-users and older people with cognitive impairment).(95)

Research is needed to better characterize not only the prevalence but also per-person density of clinically unapparent SH. An exploratory sub-analysis of the InHypo-DM study found that participants with partial versus complete disclosure experienced twice the number of events.(99) Even so, the fallout of under-reported and -recognized hypoglycemia is significant, not least is the perpetuation of otherwise preventable SH.

3.2.2 Prognostic research

Questions of prognosis are of principal concern to preventing Level 3 SH.(100) In 2013, the ADA and ES published a call-to-action for improved clinical scrutiny of patients at-risk of hypoglycemia. Today, the diabetes literature is replete with studies on SH risk factors; however, for many clinicians, a self-perceived lack of knowledge and time to appraise scientific articles impedes the translation of evidence in daily practice.(101,102)

By relating multiple individual-level predictors to the probability of an outcome occurring within a specific time period,(103–108) prognostic modelling[14] offers an efficient link between

[14] Also referred to as risk/clinical prediction modelling or predictive modelling. The term 'model' (as in 'prediction model') is also sometimes interchanged with index or rule, or risk score.

research, and its clinical application. Generally, predictor values are combined and converted into an estimate of the absolute risk of experiencing some endpoint, although risk grouping can be used to produce relative risk scores.(104,109,110) Nevertheless, the primary aim of prognostic models is to inform accurate prognoses where a level of clinical uncertainty exists. Prominent examples include Framingham Risk Score (outcome: ten-year CVD risk),(111) Nottingham Prognostic Index (outcome: five-year survival following surgery for breast cancer),(112) and CHADS score (outcome: one-year risk of stroke).(113)

In the context of predicting Level 3 SH, profound population heterogeneity—further complicated by the frequent lack of empirical evidence and clinical inertia(114)—obfuscate routine surveillance. This challenges even the "basic" task of identifying individuals at highest risk, and hence most in need of intervention.(107) A user-friendly prognostic model to predict future SH would help simplify routine practice while enhancing event screening; evidence-based, risk-tailored prevention; and ultimately cost containment.(115–118) In a 2020 report, ADA's Chief Scientific and Medical Officer pushed for the increased development and dissemination of decision-support tools, touting their ability to enrich shared decision-making and individualized care plans that co-mitigate hypo- and hyperglycemia.(119) Gabbay's proposed mission aligns with escalating appeals for values-based reimbursement in the US.(120,121)

3.2.2.1 Current models to predict severe hypoglycemia

In 2022, Wu et al. published a systematic review and meta-analysis on prognostic prediction models for hypoglycemia in diabetes.(122) Their search yielded 22 models (across 16 studies). Thirteen models (across nine studies) pertained to outpatient SH risk, of which nine were derived in a T2DM sample,(123–128) three in a combined T2DM and T1DM sample,(129,130) and one in T1DM sample (131). The most common predictors of SH risk were age, insulin use, body mass index (BMI), history of hypoglycemia, and A1C. Prediction horizons ranged from three months (123) to five years (127) or hospitalization (131).

For each study included in the review, Wu et al. evaluated risk of bias (ROB) and applicability using the Prediction model Risk Of Bias Assessment Tool (PROBAST).(132) The authors uncovered a high and ubiquitous ROB for the domain of Analysis, largely precipitated by absent

statistical methods for overfitting (e.g., shrinkage) and calibration. For this reason, they recommended against the clinical use of any current hypoglycemia prediction model.(122)

Impact of data source on studies of prognosis

Notably, all extant prognostic models stem from trial repositories (124,127,131) or routine care registries (123,125,126,128–130), including an additional six that were not identified by Wu et al. (Table 3.2).

Table 3.2: Primary characteristics of prognostic models for severe hypoglycemia not reviewed by Wu et al.

	Choi et al.(133)
Publication year	2021
Country	Korea
Study design	Retrospective cohort study
Study cohort	Adults (eligible age: N/S) with T2DM enrolled in the Korean National Health Insurance Service database
Type of diabetes	T2DM
Data years	10.4 years
Data source	The Korean National Health Insurance Service database
Setting	Hospital
Sample size (development)	1260
Type of hypoglycemia	SH resulting in hospitalization
Hypoglycemia measure	N/S
Prediction horizon	1 year
Type of model	Cox proportional hazards regression model

Repeated events	Yes
Predictor selection	Identified via literature review
Candidate predictors	Adapted from Han et al.(126)
Final predictors	Age; Sex; Smoking status; Alcohol drinking status; Body mass index; Exercise; Previous SH; Use of insulin; Multiple oral hypoglycemic agents; Hypertension; Chronic kidney disease; Duration of diabetes; Fasting plasma glucose (mmol/L); Charlson Comorbidity Index c-statistic: 0.871
Time-varying covariates	N/S
Type of validation	N/S
	Weiner et al.(134)
Publication year	2020
Country	US
Study design	Model development: Retrospective cohort study Implementation: Randomized naturalistic study
Study cohort	Primary care clinicians belonging to Eskenazi Health electronic healthcare record system. Risk tool was displayed for all outpatients who were 21 years old prescribed 1: acarbose, acetohexamide, alogliptin, canagliflozin, chlorpropamide, colesevelam, dapagliflozin, exenatide, glibenclamide, glimepiride, glipizide, glyburide, insulin, linagliptin, liraglutide, meglitol, metformin, nateglinide, pioglitazone, pramlintide, repaglinide, rosiglitazone, saxagliptin, sitagliptin, tolazamide, or voglibose
Type of diabetes	T1DM and T2DM
Data years	9 months (2016)
Data source	Eskenazi Health

Setting	Integrated health care delivery system
Sample size (development)	Patients (N=3350) visited 123 intervention primary care providers; 3395 patients visited 220 control primary care providers.
Type of hypoglycemia	SH
Hypoglycemia measure	Outpatient PG <3.9 mmol/L (70 mg/dL), identified through laboratory reports, ICD codes or natural language processing (NLP)
Prediction horizon	2-years
Type of model	Logistic regression
Repeated events	No
Predictor selection	N/S
Candidate predictors	Demographic data from medical records of patients seen at the Indiana Network for Patient Care
Final predictors	Eating disorder, infection within 30 days, insulin other than long-acting insulin, previous HG within 12 months, Black, diabetic neuropathy, Medicaid recipient, alcohol use, chronic heart failure, no antibiotics, antibiotics with a sulphonylurea, dementia or falls, A1C 6.5%, serum calcium, long-acting insulin plus sulphonylurea within 90 days, Hispanic, and 75 years old c-statistic: N/S
Time-varying covariates	N/S
Type of validation	N/S
	Raghavan et al.(135)
Publication year	2020
Country	US
Study design	Retrospective cohort study

Study cohort	US veterans with diabetes and angiographic assessment of CVD
Type of diabetes	N/S
Data years	2005–2018
Data source	Electronic health records
Setting	N/S
Sample size (development)	128893
Type of hypoglycemia	SH
Hypoglycemia measure	Based on a previously validated (N/S) algorithm that uses diagnosis codes and glucose measurements
Prediction horizon	2-years
Type of model	Supervised machine learning using adaptive elastic net
Repeated events	Yes
Predictor selection	Multivariable adaptive regression splines
Candidate predictors	33 potential predictors, including demographics, diabetes-related variables, comorbidities, and CVD risk factors
Final predictors	Number of SH-related ED visits or hospitalizations in the prior 2 years; >2 ED visits in the last year; not using insulin; sulphonylurea use; age of 77 or greater; chronic kidney disease; peripheral arterial disease; congestive heart failure; obstructive coronary artery disease; dialysis use; cognitive impairment; total number of comorbidities; statin use; beta-blocker use; ACE-inhibitor use; number of total diabetes medications; A1C; diabetes duration; BMI; family history of coronary artery disease c-statistic (external): 0.729
Time-varying covariates	N/S

Type of validation	Internal and external
	Mueller et al.(136)
Publication year	2020
Country	US
Study design	Retrospective cohort study
Eligibility	Adults (18 years old at index date) with T2DM with 1) 1 medical claim (ICD-9 codes 250.x0, 250.x2; ICD-10 code E11) anytime during patients' available claims history; 2) 1 prescription claim for a qualifying antidiabetic medication anytime during patients' available claims history; and continuously enrolled with a medical and pharmacy benefit during the 12-month pre-index and 12-month post-index periods
Type of diabetes	T2DM
Data years	2014–2017
Data source	Optum Clinformatics Data Mart
Setting	Integrated health care delivery system
Sample size (development)	453487
Type of hypoglycemia	SH and NSH (combined)
Hypoglycemia measure	Medical claim with ICD-9 and -10 hypoglycemia diagnosis codes or at least one BG of 3.9 mmol/L (≤70 mg/dL)
Prediction horizon	1-year
Type of model	Reverse Engineering and Forward Simulation
Repeated events	No
Predictor selection	Reverse Engineering and Forward Simulation was used for all modeling. Each model was an ensemble consisting of 128 generalized linear models that was constructed using Markov chain Monte Carlo sampling of the full Bayesian posterior distribution of models

Candidate predictors	Pertained to demographics, diagnoses, pharmaceutical use, procedures, laboratory data, and healthcare use
Final predictors	388 predictors were selected including 13 demographic variables, 89 diagnosis variables, 180 pharmacy variables, 68 procedure variables, 30 laboratory variables and 8 utilisation variables c-statistic: 0.77
Time-varying covariates	N/S
Type of validation	Internal
	Bosnyak et al.(137)
Publication year	2019
Country	US
Study design	Retrospective cohort study
Study cohort	Individuals (eligible age: N/S) with a confirmed diagnosis of T2DM (1 ICD-9 or 10 diagnosis codes [ICD-9: 250.x0; 250.x2; ICD-10: E11]); 1 antidiabetic medication at any time during the study; and <10 basal insulin treatments
Type of diabetes	T2DM
Data years	2007–2017
Data source	Optum longitudinal clinical repository
Setting	Integrated health care delivery system
Sample size (development)	831456
Type of hypoglycemia	SH and NSH (combined)
Hypoglycemia measure	ICD-9 and -10 hypoglycemia diagnostic codes, glucose levels 3.9 mmol/L (70 mg/dL), administration of intramuscular glucagon, or through natural language processing

Prediction horizon	1 year
Type of model	Poisson regression
Repeated events	Yes
Predictor selection	Clustered covariates: most common clusters were included in the final model; lasso was then used to select the final variables
Candidate predictors	Manually created predictors (e.g., demographics, socioeconomics, comorbidities, diabetes complications and disease status, medication use) were identified via literature review based on their relevance to T2DM hypoglycemia and cost. Automatically created predictors were then identified via algorithm based on clinical relevance.
Final predictors	N/S
Time-varying covariates	N/S
Type of validation	Internal
	Shao et al.(138)
Publication year	2018
Country	US
Study design	Retrospective cohort study
Study cohort	ACCORD trial participants: Adults (40–79 years old) with diagnosed T2DM; for individuals 40 years old, history of CVD; for individuals 55 years old, considered at high risk for experiencing a CVD event due to existing CVD, subclinical disease, or 2 CVD risk factors
Type of diabetes	T2DM
Data years	2001–2007
Data source	Action to Control Cardiovascular Risk in Diabetes (ACCORD)
Setting	Clinical trial
Sample size (development)	10251

Type of hypoglycemia	SH
Hypoglycemia measure	Symptomatic SH requiring assistance with either a documented BG concentration of <2.8 mmol/L (50 mg/dL) or recovery with carbohydrate treatment. Assessed by the ACCORD staff at each trial visit.
Prediction horizon	1 year
Type of model	Poisson regression
Repeated events	Yes
Predictor selection	Backwards selection
Candidate predictors	Identified via literature review. Explanatory variables were categorized into 3 groups: biomedical factors, demographic characteristics, and complications
Final predictors	Age; A1C; diabetes duration; race c-statistic: N/S
Time-varying covariates	Yes
Type of validation	Internal and external

N/S, not specified; US, United States; T1DM, type 1 diabetes mellitus; T2DM, type 2 diabetes mellitus; SH, severe hypoglycemia; ACCORD, Action to Control Cardiovascular Risk in Diabetes; ACE, angiotensin-converting enzyme; BG, blood glucose; BMI, body mass index; CVD, cardiovascular disease; ICD, International Classification of Diseases; NSH, non-severe hypoglycemia; PG, plasma glucose.

Risk of bias increases for models that use existing data. Moreover, their applicability wanes to the extent that the original sample differs from the reidentified target population.(139) However, in their systematic review, Wu et al. only cursorily discuss the impacts of underlying data sources on SH prognoses.(122)

Because trial repositories often exclude specific subgroups, they are apt to produce biased estimates that alter the performance of secondary prognostic models in novel contexts. Typically

bound by restricted eligibility criteria, these data sources can produce narrower predictor distributions, which, in turn, attenuate discriminative ability.(140–143) Real-world applicability is also likely to depreciate. For example, the DCCT, analyzed by Lagani et al. (131), excluded individuals with a history of recurrent hypoglycemia and IAH. The ACCORD trial, used by Chow and colleagues,(127,138) provided only a marginally more pragmatic sampling frame, representing 11.4% of the general population.(144)

The breadth of information in care registries usually exceeds trials, but a lack of standardized data collection (145,146) can instigate inappropriate sample selection (e.g., due to misdiagnoses or incomplete/outdated charting). Of course, systematic errors in defining the eligible population are also possible. In prognostic model studies by Karter et al.,(128,147) 45% of the development sample comprised individuals not on an insulin or secretagogue regimen—i.e., nearly half of participants had a zero-probability of experiencing iatrogenic SH over follow-up. That these individuals were counted towards the risk set likely inflated predictive performance.(139)

In addition to the sampling pool, repurposed sources variously affect the quantity, frequency, and types of predictors available for analysis. As with data on participant factors, trial records usually contain fewer predictor variables than registries, challenging their viability to address secondary prognostic questions. Moreover, issues of applicability are raised by the frequent use of specialized measurement techniques in RCTs (e.g., serum creatinine and urinary albumin creatinine ratio (127)). Randomized treatment (e.g., intensive insulin therapy) may further induce a misrepresentation of outcome distributions in trial samples versus real-world populations; although, secondary prognostic studies rarely take this into account.(138)

In contrast, scopious healthcare records—designed for clinical purposes rather than research per se—are more susceptible to errors in data collection and measurement. System-level evolutions in healthcare or documentation may also obsolete the applicability of models derived from older datasets. For example, several US models were validated using ICD-9 codes,(128,129) as opposed to ICD-10, which is now mandated practice.

Finally, and most crucially, secondary prognostic studies are at-risk of outcome misclassification. In a 2016 review, Elliot et al. (148) concluded that, on average, experimental versus observational research underestimates real-world event frequencies. This finding was

attributed to intensified follow-up in RCTs, preferential enrolment of younger/healthier patients, and glucose-defined SH (e.g., PG <2.8 mmol/L [50 mg/dL]). Elaborating on this review, Pedersen-Bjergaard and Thorsteinsson (66) analyzed 55 articles to explore how variations in sample characteristics and SH definitions influence reported incidences. Like Elliot et al., the authors noted lower frequencies in trials than observational studies—but with one important caveat: When defined as requiring parenteral versus third-party aid, SH rates fell by ~25%, irrespective of sample representativity. In other words, observational studies yield higher incidences than trials, *except* when derived from care registries; in this case, estimates are lower.

Backdropped by potential differential outcome verification,(139) partial SH determination can distort prognostic coefficients and intercepts/baseline hazards.(139,149) An evaluation by Ransohoff et al., related spectrum bias (i.e., restricting events to speciously "definite" cases) to an underrepresentation of originated cases and inflated validity diagnostics.(150)

Along the same vein, over a quarter (n=5/19) of prognostic studies (123,125,130,134,136) modelled SH as a dichotomous (typically, zero versus one or more events) rather than count response; however, forfeiting information on the variability of event occurrence among cases introduces estimation and interpretive problems.(151) Certainly, identifying and targeting this disproportionately vulnerable subgroup (which could not be achieved with purely binary approaches given the right-skewed distribution of SH (152–154)) would lead to a comparatively maximized interventional benefit, with minimized economic expenditures.

3.3 Clinical needs and research priorities

Diabetes care paradigms must prioritize the optimization of hypoglycemia outcomes—particularly SH—for which mainstay insulin and secretagogue therapies are inherently antagonistic. A thorough review of the literature reveals two major research directives:

1. *Level 3 event capture is needed to form a representative and valid understanding of SH burden in the US.*

Descriptive epidemiologic evidence is an essential precursor to sound clinical and public health decision-making, still little is known about the true, real-world incidence of SH in the US (see § 2.2.5 Epidemiology). The paucity of patient engagement and integration of person-focused endpoints conflicts with IHSG/ADA guidelines and recommendations by the PROGnosis RESearch Strategy.(100) Above all, it may extenuate the true, real-world burden of SH and thereby suppress vigilant clinical prevention.

2. *A prognostic model study on Level 3 risk in diverse, outpatient populations could remedy elusive interventional targets and potentiate preventive action.*

Heightened awareness of the hidden dangers of insulin and secretagogues is an urgent imperative for standard professional practice. Indeed, optimized glycemic management is unattainable without effectively counterbalancing patient safety—to this end, clinicians are the linchpin.

While the number of published risk models on SH is increasing, there is a hazard in moving too quickly to use these models without due consideration of their limitations. In particular, an overdependence on sub-optimal data sources arguably misrepresents information necessary to make informed decisions on SH management—particularly in primary care settings where most people with diabetes are managed.(107)

Prospective research that overcomes the pitfalls of routine clinical surveillance is needed to characterize recurrent Level 3 events, and the predictors thereof. Synthesizing these data into an easy-to-use, point-of-care prognostic model could engender more effective and efficient patient-provider conversations about hypoglycemia (across levels of healthcare), informed decision-making, and, ultimately, interventions that meet the unique circumstances, needs, and preferences of people with diabetes.(120,121)

3.4 Summary

Gaps in SH-prognosis pose an impasse to the delivery of personalized diabetes care that is as effective as it is safe. The next chapter details the design and implementation of the iNPHORM study: the first prospective risk assessment of Level 3 SH in the US.

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Chapter 4

4 Design and implementation of iNPHORM

Prognostic studies that employ a prospective, longitudinal cohort design confer the lowest ROB and highest potential for applicability,(1) particularly when the observation period spans the targeted prediction horizon.(2) Nevertheless, all extant prognostic models for iatrogenic SH stem from existing sources subject to bias and poor generalizability. Redressing this gap, we conducted the iNPHORM panel survey.

Chapter 4 describes the design and setting of this study, as well as participant selection, sampling and data collection procedures, variables and measures, ethical considerations, and, finally, data management and analysis plan. The content of this chapter and all related materials were published in the *Journal of Medical Internet Research (JMIR) Research Protocols*[15].

iNPHORM was funded through an investigator-initiated grant from Sanofi Global (contract executed with Sanofi Canada, April 11, 2019). Before recruitment, we obtained ethics approval from the Western University health sciences research ethics board (Project ID: 112986; December 17, 2019) (Appendices 1 to 3) and registered the study with ClinicalTrials.gov (NCT04219514; January 7, 2020) (Appendix 4).

[15] Ratzki-Leewing A, Ryan BL, Zou GY, Webster-Bogaert S, Black JE, Stirling K, et al. Predicting Real-world Hypoglycemia Risk in American Adults With Type 1 or 2 Diabetes Mellitus Prescribed Insulin and/or Secretagogues: Protocol for a Prospective, 12-Wave Internet-Based Panel Survey With Email Support (the iNPHORM [Investigating Novel Predictions of Hypoglycemia Occurrence Using Real-world Models] Study). JMIR Res Protoc. 2022;11(2):e33726. doi: 10.2196/33726. Note: Tables, figures, references, and appendices have been renumbered/reconfigured to align with the format and organization of this dissertation.

4.1 Manuscript title

Predicting real-world hypoglycemia risk in American adults with type 1 or 2 diabetes mellitus prescribed insulin and/or secretagogues: Protocol for a prospective, 12-wave internet-based panel survey with email support (the iNPHORM [Investigating Novel Predictions of Hypoglycemia Occurrence Using Real-world Models] Study)

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4.4 Keywords

adverse event; diabetes; hypoglycemia; insulin; internet survey; model; nonsevere hypoglycemia; protocol; real-world; risk; risk model; risk prediction; secretagogue; severe hypoglycemia; survey; symptom; type 1 diabetes mellitus; type 2 diabetes mellitus.

4.5 Background

Although prognostic models can complement clinical decision-making and risk-tailored interventions,(3–7) their performance depends heavily on the attributes of their underlying data sources.(8) The prognostic literature on diabetes-related hypoglycemia—a potentially lethal (9,10) and costly (11–13) side effect of insulin and/or secretagogues—has been dominated by analyses of pre-existing trial (14) or administrative databases (15). However, these sources poorly represent high-risk diabetes populations,(16–20) underestimate up to 95% of hypoglycemia events,(16,21,22) and limit substantive evidence on potential predictors (23).

Prospective, web-based survey data, especially when collected anonymously,(24) can reveal robust indications of hypoglycemia burden (25–28) routinely unmeasured or uncapturable by other research methods.(22) Such insight could help rectify extant evidence gaps, leading to more valid, real-world event prognostication (29) and, ultimately, targeted, cost-effective strategies that support hypoglycemia prevention in broad clinical contexts.

In 2020, our team launched iNPHORM (Investigating Novel Predictions of Hypoglycemia Occurrence Using Real-world Models)—the first prospective (one-year) survey of hypoglycemia risk in the American public with T1DM and T2DM prescribed insulin and/or secretagogues. The results of this study will culminate in real-world hypoglycemia prognostic models that are readily compatible with and complementary to routine practice. Here, we detail the design and implementation protocol of iNPHORM. The paper has been structured according to established guidelines (30,31) and the Checklist for Reporting Results of Internet E-Surveys guidelines (32).

4.5.1 Objectives of the iNPHORM study research

4.5.1.1 Co-primary objectives

The primary objectives are as follows:

1. To determine the real-world incidence of self-reported one-year SH and 30-day non-severe daytime and nocturnal hypoglycemia (NSDH and NSNH) among American adults with T1DM or T2DM prescribed insulin and/or insulin secretagogues

2. To develop and internally validate real-world hypoglycemia risk prediction models for one-year SH, 30-day NSDH, and 30-day NSNH, which will be converted into a user-friendly, clinic-based tool

4.5.1.2 Secondary objective

The secondary objective is to assess treatment-related causes of hypoglycemia among American adults with T1DM or T2DM prescribed insulin and/or insulin secretagogues.

4.6 Methods

4.6.1 Study design and setting

iNPHORM is an internet-based panel survey that was conducted across the US. Repeated self-assessed measures were taken over 12 monthly interwave intervals via web-based questionnaires. Prospective longitudinality allowed us to 1) obtain data not reliably collected retrospectively or cross-sectionally (e.g., variability in totals/averages or low-salience events), 2) assess within-person changes or stability masked by aggregate statistics, and 3) narrow the standard error (SE) between measurements.

4.6.2 Participants and sample size

Participants were recruited via the web from an established, closed, probability-based internet panel. The internet panel comprised five vendor samples of the US public consenting to receive survey notifications by email (sample frame). Vendor partners used random probability sampling and, when necessary, validity checks, quotas, and multidimensional calibration. These approaches helped maintain fair and representative (geodemographic, attitudinal, and behavioral)

sampling within communities.(33) The internet panel comprised >65,000 Americans with self-reported T1DM (N=10,000 approximately) and T2DM (N=58,000 approximately).

Internet panelists could enroll if they were 1) aged 18 to 90 years, 2) living in the US (past year), 3) self-reporting a diagnosis of T1DM or T2DM,(34) and 4) using insulin, secretagogues, or both insulin and secretagogues (past year). Individuals were ineligible if they were unable to read and understand English, possessed insufficient computer and internet literacy, or were participating in a concurrent trial. Those who were pregnant (at screening or in the prior year) and/or those with gestational diabetes were excluded, given their distinct pathogenesis and clinical management.

On the basis of recent conservative techniques,(35,36) N≥521 respondents would be required to produce a 25-factor prognostic model for SH (the rarest event type) with sufficient precision and minimal overfitting with ≤0.05 expected optimism (Appendix 5).(36,37) Anticipating a degree of right censoring,(37,38) we inflated our target sample to 1250 enrollees.

4.6.3 Sampling, recruitment, and data collection

Figure 4.1 summarizes participant sampling, recruitment, and data collection.

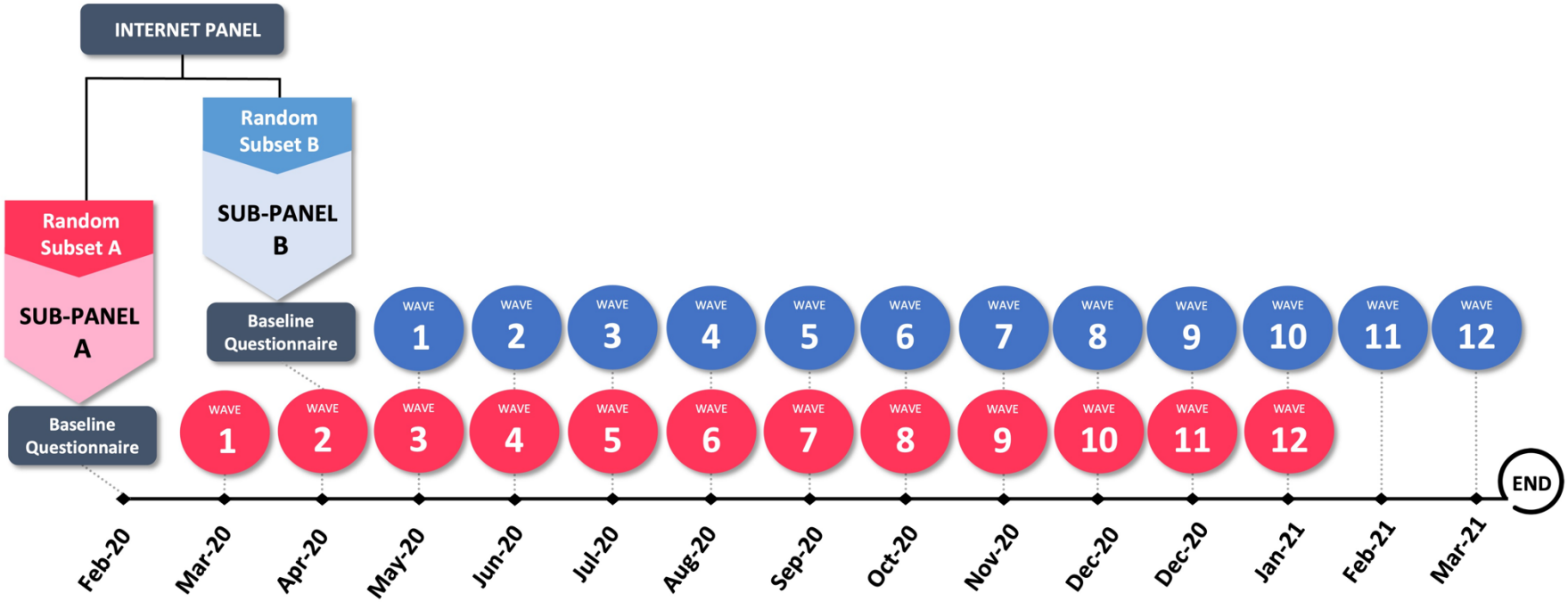

Figure 4.1: Schematic of participant sampling, recruitment, and data collection

A total of two subpanels (*A* and *B*) were recruited into the prospective, 12-wave iNPHORM study using convenience sampling. First, vendor partners emailed a generally worded study invitation to a randomly selected subset of the internet panel (subset A). Those interested were emailed a link to a screener. To enroll, eligible respondents were required to provide consent (see § 4.6.10 Ethical Considerations), complete a baseline questionnaire (accessible by the emailed link), and register with iNPHORM using a confirmed, valid email address and unique username/password. Enrollees were hosted and monitored by Ipsos Interactive Services Ltd. (IIS),(39) a global leader in diabetes insights and patient-centered, real-world survey conduct.

Links to the screener and baseline questionnaires remained active until we reached 1250 enrollees (i.e., *subpanel A*). Participants in *subpanel A* who failed to complete the first wave follow-up questionnaire were withdrawn and systematically refreshed with new eligible recruits (i.e., *subpanel B*). *Subpanel B* was sampled and enrolled in the same way as *subpanel A* but from a different, randomly selected subset (subset B) of the contemporaneous internet panel. Screener and baseline links remained active for approximately two weeks or until a 1:1 ratio of *subpanel B* to *subpanel A* Wave One dropouts was achieved (whichever came first). Collectively, individuals in *subpanel A* who completed the first follow-up questionnaire and all those in *subpanel B* comprised the *iNPHORM longitudinal panel*.

Quota sampling ensured prespecified minimum parameters of the *iNPHORM longitudinal panel*. We required that ≥10% of participants report T1DM, ≥5% are aged ≥75 years, and ≥10% are female/male. Among T2DM respondents, we specified a ≥10% representation for insulin (without secretagogues), secretagogues (without insulin), and a combination of insulin and secretagogue users each.

We followed the *iNPHORM longitudinal panel* for 12 months. The calendar schedule between subpanels was identical; however, systematic refreshment caused follow-up waves to offset by two months (*subpanel A*: February 2020 to January 2021; *subpanel B*: April 2020 to March 2021). At each wave, IIS emailed participants an individualized link to a closed, fully automated questionnaire that involved no face-to-face contact. The link could only be accessed by the email recipient using his/her *iNPHORM longitudinal panel* username/password. Links were active for

seven days from distribution (activation window). The responses were synchronously stored on the IIS platform. Completed questionnaires could not be re-accessed or modified.

4.6.4 Notifications, precontacts, and reminders

Personalized notifications, precontacts, and reminders were emailed automatically by IIS. Each notification contained the questionnaire link, the deadline for submission, and details on remuneration (see § 4.6.5 Incentivization Scheme). Notifications also included the date of the participant's last completed questionnaire, as well as their last reported use/type of antihyperglycemic(s) and glucose monitoring device(s).

To boost completion rates,(40,41) a precontact alerting participants of an upcoming questionnaire was emailed seven days before the notification. After the notification, individuals were sent two reminder emails on days four and six of the seven-day activation window. Reminders contained the same information as the corresponding notification emails.

4.6.5 Incentivization scheme

Figure 4.2 summarizes participant honoraria.

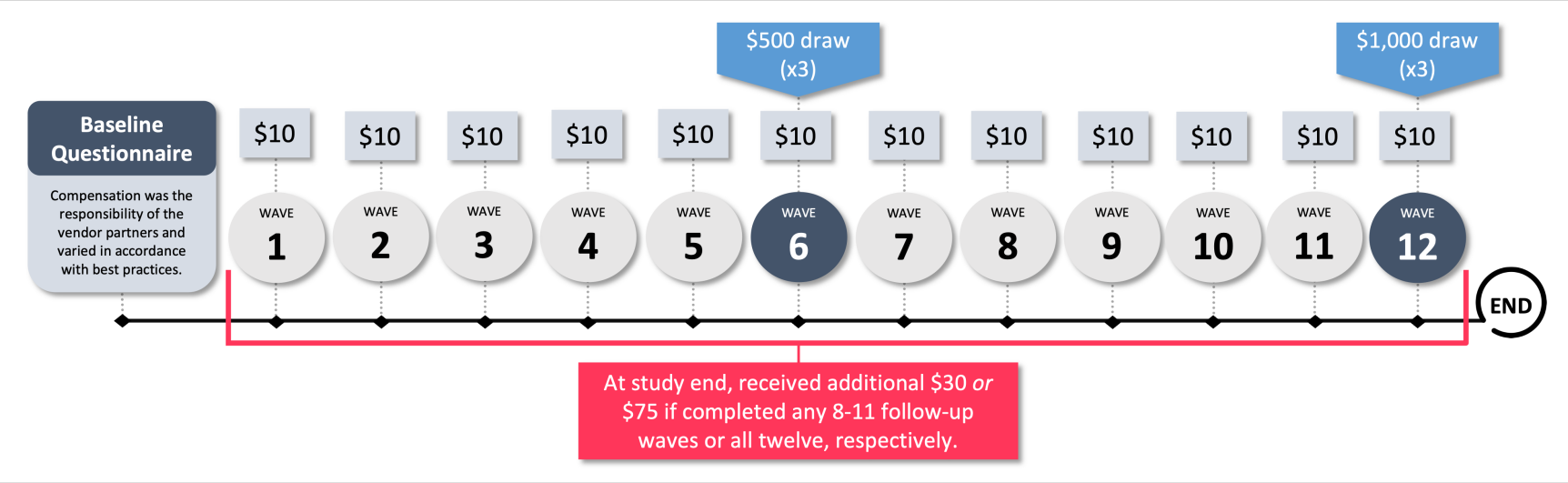

Figure 4.2: Incentivization scheme

A thank you message and link to a $10 USD e-gift card was emailed after each submitted follow-up. At the end of the study, participants received an additional e-gift card of $30 USD if they completed any eight to eleven waves or $75 USD if they completed all 12 waves. Wave Six and 12 responders were entered to win one of three randomly selected $500 USD or $1000 USD e-gift cards, respectively.

Incentive amounts balanced our desired response rates against ethical standards of reciprocity.(42) For internet-based surveys, monetary versus other inducements can decrease volunteer bias (37,38) and respondent refusals.(43–45) Lottery incentivization has been shown to act much like cash incentives with a value effect equal to the lottery prize divided by the sample size.(46)

4.6.6 Questionnaire development procedures

Western University scientists (AR-L, BLR, and SBH) developed questionnaires in consultation with the literature and pre-existing surveys. Questionnaires were designed in English for use on diverse internet-equipped devices (e.g., computers, phones, and tablets). The content was crafted parsimoniously to lessen panel fatigue, conditioning, satisficing, social desirability bias, and demand characteristics.(40) Double-barreled questions, clinical jargon, and value-laden or complex/ambiguous language were avoided. We also ensured that the items were mutually exclusive, exhaustive, and specified an appropriate and consistent level of detail. Key questions were prioritized early; conversely, all sensitive items—justified and respectfully crafted (e.g., income was categorized)—were interspersed to encourage respondent honesty.(47) We did not randomize/alternate items within or between questionnaires or participants. When applicable, items addressed the causal ordering of sequence, timing, and duration.(48) Recall intervals balanced the observation probability against the timing of questionnaire completion.

Established design principles were adopted to minimize burden and sustain engagement. Clearly worded preambles signaled topic changes and explained the importance of respondent honesty and vigilance.(41,49) To mitigate comprehension bias, concise instructions and definitions were provided in text and on mouseover.(49) In addition, efforts were taken to enhance accessible

visual appeal, navigation, and user convenience. Adaptive questioning streamlined transitions between items and decreased the complexity and length (i.e., number of screens) of the web interface questionnaires. For ease of completion, straightforward response options (via radio buttons, checkboxes, drop-down lists, and open-text fields) were presented, and only one item appeared per screen. Questionnaires could be accessed, delayed, and/or paused ad libitum up until submission or the activation window closed (whichever came first). Percentage-based progress bars on each screen supplied visual feedback on completion.

Quality assurance methods were applied to reinforce data integrity. Calibration questions (50) were incorporated in the screener to detect straight lining, verify item comprehension, and avert nonsensical free text (51); unsatisfactory answers precluded participant enrollment. In-built logic checks supported data accuracy.(51) For example, questions were prespecified with single- or multi-responses, and ‘not applicable’, ‘prefer not to say’, and ‘I don’t know’ were delimited as exclusive options. Missing responses were immediately flagged. To bypass a question, individuals had to type “OPT OUT” in a pop-up response box, helping discriminate intentional nonresponse from inadvertent omissions/straight lining. At the start of every questionnaire, respondents were reminded to retrieve any documents/materials that could facilitate response accuracy (e.g., medication lists/containers and glucose monitoring logs/graphs).

During follow-up, IIS monitored bugs, downtimes, and other unexpected events that could have affected the study design. At any point, participants could email IIS Technical Support (email address was included in all iNPHORM communications).

4.6.7 Pretesting and piloting

iNPHORM researchers and colleagues performed extensive pretesting of detailed mock-up and programmed study materials to redress issues of content, display, adaptive questioning, and implementation. Before their dissemination, programmed questionnaires, notifications, and reminders were piloted via in-depth semi-structured interviews with three participants who were screened and sampled purposively from a subset different than subsets A and B of the internet panel. Of the three participants, one (33%) participant had T1DM; the other two (67%) had T2DM (one [50%] was prescribed secretagogues without insulin, and one [50%] a combination

of insulin and secretagogues). A trained IIS moderator (JDB) interviewed participants simultaneously by phone and a computer-assisted personal interview platform using an interview guide developed by the Western University research team.

Qualitative feedback was collected on content, formatting, flow, usability, and technical functionality. Pilot data were also gathered on sample variability, item response rate, and time to completion. Behaviors signaling design issues were documented (e.g., instances where the respondent hesitated or requested to change an answer).(40) Interviews took 60 to 90 minutes. The study materials were emended based on respondents' feedback. Pilot participants were remunerated $300 USD (e-gift card); they were not permitted to enroll in the panel survey.

Once finalized and in field, no changes were made to questionnaires except for the addition of a COVID-19 sub-questionnaire (see § 4.6.8.5 COVID-19 sub-questionnaire). Dynamic components were obviated to preserve study replicability.

4.6.8 Prognostic factors and related hypoglycemia and COVID-19

4.6.8.1 Overview

Across the screener, baseline, and follow-up questionnaires, web-based self-assessed data were collected on a broad scope of hypoglycemia-related anthropometric, demographic, situational or environmental, lifestyle (Appendix 6), and clinical (Appendix 7 (52–55)) prognostic factors. Follow-up questionnaires also contained items related to COVID-19 (Appendix 8; see § 4.6.9 Definitions and Measures of Hypoglycemia, for methods of hypoglycemia-specific data capture).

4.6.8.2 Screener

The pilot screener took an average of 9.6 (SD: 4.73; minimum six and maximum 15) minutes to complete. Data were collected on age, sex assigned at birth, self-identified gender, residence, concurrent trial involvement, diabetes type, pregnancy status, and insulin and/or secretagogue use (e.g., administration mode [when applicable], dose, and duration). Response options for

medication type were arranged by class, save second-generation basal insulin analogs, which were listed by brand (Toujeo SoloSTAR, Toujeo Max SoloStar, Tresiba FlexTouch U-100, and Tresiba FlexTouch U-200). Screener data were retained for all consenting individuals.

4.6.8.3 Baseline questionnaire

On average, pilot respondents completed the baseline questionnaire in 47.3 (SD: 13.65; minimum 38 and maximum 63) minutes. Information was elicited on anthropometric, demographic, situational or environmental, and lifestyle factors (e.g., levels of aerobic/anaerobic activity and cigarette, alcohol, and recreational drug use). Numerous clinical data were also collected on diabetes duration, diabetes self-management behaviors, diabetes complications (e.g., chronic kidney disease), general health status (e.g., chronic multi-morbidities and use of dialysis), and health-related QoL.

To simplify future population-based comparisons and statistical weighting, we devised items with reference to existing population-based surveys by the US Census Bureau (2020) (56) and the Centers for Disease Control and Prevention (CDC) (i.e., NHANES [2019-2020],(57) Behavioral Risk Factor Surveillance System [2020],(58) and National Health Interview Survey [2020] (59)). We also embedded several validated questionnaires (e.g., Veterans RAND-12,(52,55) Self-Rated Health,(53) and Brief Health Literacy Screening Tool (54)).

4.6.8.4 Follow-up questionnaire

Follow-ups (except Wave Six see § 4.6.9 Definitions and Measures of Hypoglycemia) were on average piloted in 10.8 (SD: 5.30; minimum seven and maximum 14.5) minutes. Items assessed mutable clinical variables (e.g., medication regimen, hemoglobin A1c, and continuous/flash glucose monitoring). Employment status, household income, and health insurance were re-evaluated at Waves four, eight, and 12.

4.6.8.5 COVID-19 sub-questionnaire

Pandemic-related items were added after study commencement in response to the escalating severity of the COVID-19 pandemic. Beginning with *subpanel A* Wave Two (April 21 to April 28, 2020), each follow-up contained a 25-item COVID-19 sub-questionnaire that assessed self-reported infection status (per CDC community case definitions [April 2020]; (60)) and the impact of the pandemic situation on socioeconomic, clinical, and psychosocial aspects of diabetes management.(61)

4.6.9 Definitions and measures of hypoglycemia

At baseline and at each follow-up (Appendix 9 (62–65)]), web-based self-assessed data were collected on SH, NSDH, and NSNH; definitions consistent with the 2019 ADA Standards of Medical Care in Diabetes (66) were provided in all questionnaires (Table 4.1).

Table 4.1: Hypoglycemia definitions provided to participants by severity and timing

Type of hypoglycemia	Definition
Severe	"When you are *physically unable* to treat your hypoglycemia by yourself, it is considered an SH event. You may be severely disorientated, unable to swallow, or unconscious. As a result, you are likely to need the help of another person to recover. This person may need to administer glucagon or a glucose injection to treat your SH event. Emergency medical services may be called, and hospitalization may be required. Severe events can arise when your low blood glucose is left untreated and continues to drop. The early signs and symptoms of SH typically include blurred vision, difficulty concentrating, confused thinking, slurred speech, numbness, and/or drowsiness. If your blood glucose stays low for too long, it can result in seizures, comas, and in rare cases, death. Consequently, SH is a medical emergency."

Mild/moderate (also known as non-severe)	"When you are *physically able* to treat your hypoglycemia by yourself, it is considered a Mild/Moderate Hypoglycemia event. Treatment can include taking a glucose or sucrose tablet, drinking a glass of juice, or eating some food. Mild/moderate hypoglycemia events can be identified by symptoms such as shakiness, sweatiness or chills, irritability, feeling nervous or anxious, hunger, weakness, mild confusion, forgetfulness, fast heartbeat, feeling dizzy, and color draining from the skin. Mild/moderate hypoglycemia events can be identified from these symptoms or by a measured blood glucose level taken from an [SMBG] meter or [rt-C/FGM] device. You are still conscious and able to swallow."
Daytime	"Daytime events (mild/moderate or severe) occur while you are awake."
Nocturnal	"Nocturnal events (mild/moderate or severe) occur while you are sleeping or attempting to sleep. In addition to the symptoms described above, nocturnal hypoglycemia can be marked by symptoms such as vivid dreams/nightmares, restless sleep, morning headaches, night sweats, tiredness, irritability/confusion upon waking, convulsions, and talking/shouting while sleeping."

SH, severe hypoglycemia; SMBG, self-monitoring blood glucose; rt-C/FGM, real-time continuous or flash glucose monitoring

In line with past research,(62,67–69) we specified interwaves of ≤1 year for SH and ≤30 days for NSH. At baseline, participants were asked to report on their SDH/SNH in the past year and NSDH/NSNH in the past 30 days. To prevent overlapping recall intervals during follow-up, data on NSDH and NSNH were captured 'within the past 30 days' (if the last scheduled questionnaire was not completed) or 'since the last time an iNPHORM survey was completed' (if the last scheduled questionnaire was completed). Given its relative infrequency and saliency, SDH and SNH data were captured 'since the last time an iNPHORM survey was completed'.

Besides hypoglycemia frequency, closed- and open-ended items assessed event detection methods (e.g., symptoms and/or blood glucose), symptom severity (e.g., unconsciousness), causes (e.g., excess insulin and/or secretagogue use, insufficient carbohydrate intake, and excess physical activity), treatments, hypoglycemia-specific self-management behaviors/social support, and experiences with continuous/flash glucose monitoring. We also investigated the type of

assistance required for SH recovery (e.g., treatment by family/friend and health care use). Each month, modified Clarke (63) and Gold (64) scores evaluated impaired hypoglycemia awareness. At Wave 6, we administered the Hypoglycemia Fear Survey II (65) and the InHypo-DM Person with Diabetes Questionnaire (62).

4.6.10 Ethical considerations

iNPHORM was funded by an investigator-initiated grant from Sanofi Global (contract executed with Sanofi Canada, April 11, 2019). Before recruitment, we obtained ethics approval from the Western University health sciences research ethics board (December 17, 2019) and registered the study with ClinicalTrials.gov (NCT04219514; January 7, 2020). The COVID-19 sub-questionnaire was approved as an ethics amendment before fielding.

A letter of information was emailed to all eligible respondents (Appendices 10 and 11). The letter named Western University as the responsible academic institution and Sanofi Canada as the funding agency. It also outlined the study's purpose, nature and expectations of participation (e.g., content of surveys, time commitment, follow-up frequency, and incentivization), risks and benefits, participant rights (e.g., refusals/withdrawals), and confidentiality/privacy measures (e.g., data storage, retention, sharing, and reporting). Contacts were provided for IIS, faculty coprincipal investigator (SBH), Western University research team, and the Office of Human Research Ethics at Western University. Conflicts of interest for SBH have been declared. Consent was obtained via the web. Individuals were advised to read the letter of information before clicking on ''I agree to participate' or 'I do not agree to participate'.

Participation was voluntary. Enrollees could withdraw at any time by informing the IIS interviewer (pilot participants only), clicking an unsubscribe button provided in each email, or by emailing IIS directly. Privacy breaches and technical problems were monitored by IIS. Personally identifiable data (e.g., phone numbers [pilot participants only], email addresses, and full birthdates) were encrypted automatically by the IIS platform and kept confidential from IIS and research personnel. IIS transferred deidentified data files to the Western University research team using a secure file transfer protocol on a password-protected network drive. All deidentified data will be stored for seven years on a password-protected network drive at the Department of

Family Medicine at Western University and on encrypted password-protected external drives; storage devices will be erased after this time. The iNPHORM assessments and data are owned by Western University.

Complying with US FDA post market safety reporting regulations (70), we emailed Sanofi United States and Novo Nordisk United States monthly pharmacovigilance reports of severe adverse events among Toujeo and Tresiba users, respectively. The reports were anonymized.

4.6.11 Planned statistical analysis

4.6.11.1 Overview

Unique IDs, randomly assigned by IIS at the study outset, were used to tether the participants' data across waves. Closed-ended responses were directly precoded, and a data dictionary and map have been developed. Repair rules addressing impossible, implausible, and discordant values will be documented in iNPHORM's metadata (e.g., erroneous responses will be classified as missing or cross-checked against valid responses). Both the raw and repaired data sets will be retained.

4.6.11.2 Describing the iNPHORM sample

Recruitment and completion rate

The recruitment rate will be calculated as the ratio of consenting individuals to enrollees. The average total completion rates for the *iNPHORM longitudinal panel* will be computed as the ratio of the observed number of completed waves to the maximum expected number (12 waves per participant). To evaluate the success of our completion rate against our predetermined sample size (N=521; see § 4.6.2 Participants and Sample Size), the observed number of waves for which SH information was available will be compared against the maximum expected number of completed follow-ups.

Completeness rate

All data were stored in real time for analysis, even if the questionnaire was incomplete (e.g., prematurely terminated). The completeness rate will be assessed after data cleaning and repair. Missing values will be coded as unit, block, item (because of skip logic), or residual (because of 'not applicable', 'prefer not to say', 'I don't know' or 'opt out') nonresponses. Missing data will be handled using multiple imputation by chained equations.(71)

Participant Characteristics

Categorical variables will be summarized as frequencies and percentages, and continuous variables as means and SDs (parametric) or medians and interquartile ranges (IQRs) (nonparametric).

4.6.11.3 Hypoglycemia incidence (Co-primary Objective 1)

Crude SH, NSDH, and NSNH IPs and IRs with 95% confidence intervals (CIs) for overdispersed count data will be reported overall and by diabetes type, medication regimen, mode of detection (symptoms and/or blood glucose), symptom severity (unconsciousness), and health care use. Incidence density calculations will account for observation durations as an offset for zero-risk and/or unobserved periods.

4.6.11.4 Prognostic model construction (Co-primary Objective 2)

Overview

The following procedures comply with current guidelines (72,73) and the Transparent Reporting of a Multivariable Prediction Model for Individual Prognosis or Diagnosis statement (74,75). Analyses will be performed on baseline respondents who submitted ≥1 follow-up questionnaire. To pre-empt statistical power loss and selection bias, all baseline and follow-up data on this

cohort will be examined.(76) Iterative proportional fitting (raking) (40) to correct for nonresponse and unequal selection probability will be investigated.

Model Development

Prognostic models will be developed for SH, NSDH, and NSNH. Daytime and nocturnal severe events will be combined, given their nonspecific relevance and to ensure sufficient precision. Severe hypoglycemia will be modeled over one year using the Andersen-Gill Cox proportional hazards regression for recurrent events.(36) Non-severe daytime and nocturnal hypoglycemia will be modeled over 30 days using negative binomial regression. Observation duration will be included as an offset variable and generalized estimating equations will account for within-person dependence.

Candidate prognostic factors will be selected a priori based on biological plausibility, previous literature, data quality, measurement reliability, and multicollinearity. Intrinsic, extrinsic, nonmodifiable, and modifiable predictors (including frequency of previous SH and NSH) will be considered. To minimize overfitting (77,78) and improve parsimony, model parameters will be estimated using machine learning penalized regression with Lasso (least absolute shrinkage and selection operator).(79) Regression splines and fractional polynomials will assess the potential for nonlinearity and nonmonotonicity.(80) Interaction and subgroup analyses will be performed where suggested by external evidence (4); sensitivity analyses will test the robustness of the findings. Informative censoring will be explored using inverse probability of censoring weighted estimation.(81,82)

Internal Validation

Bootstrapping will be used to determine the optimism-corrected performance of each final model.(76,79,83) Discrimination will be evaluated using receiver operating characteristic curves and c-statistics.(84) Calibration will be assessed visually (e.g., via graphical plots) and quantified using the calibration slope, the Hosmer-Lemeshow goodness-of-fit test, and the Grønnesby and Borgan test for survival data.(85–87)

Pragmatic Tool Creation

Models will be converted into a user-friendly, clinic-based tool to complement real-world practice. Back-end computations of patients' prognostic factors will provide point-of-care assessments for one-year SH and/or 30-day NSDH/NSNH. To aid interpretation, risk estimates will also be categorized (e.g., low, moderate, high, and very high).

The tool will be streamlined for easy integration in clinicians' existing electronic medical records (EMRs) and compatible with prepopulated EMRs and manually inputted data. A standalone internet application and paper-based nomogram will be developed for when EMR integration is not possible. Real-time imputation will be explored.(88)

4.6.11.5 Treatment-related causes of hypoglycemia (Secondary Objective)

Differential effects of antihyperglycemic regimens on hypoglycemia rates will be tested using causal analytic techniques (e.g., directed acyclic graphs, parallel and serial mediation, and time-dependent confounding). The results may help in identifying new and useful associations that can improve model performance or otherwise real-world event detection and management.(89)

4.7 Results

4.7.1 Overview

iNPHORM commenced in February 2020 and concluded in March 2021. No bugs, downtimes, privacy breaches, or other unexpected events were reported/detected. Herein, we present the recruitment and completion rates (Figure 4.3). Analyses of participant characteristics and hypoglycemia incidence and prognostication are currently underway, with published results anticipated by fall 2022. Future studies will investigate the distributions of participant discontinuance (37) and systematically report on quality metrics, including missing values and data cleaning statistics, follow-up completeness,(90) degree of coverage/sampling bias, and process outcomes (e.g., average time-to-completion).

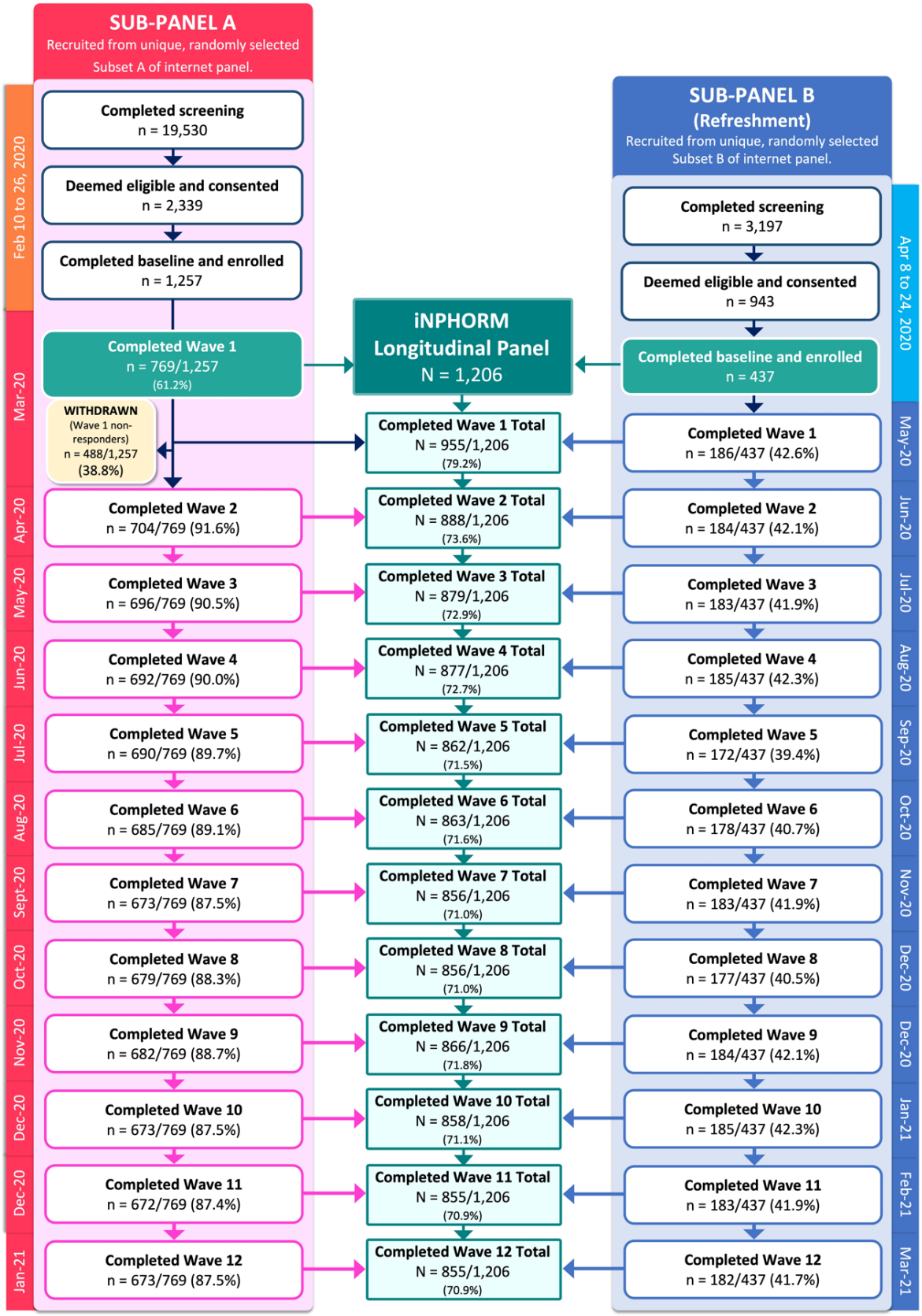

Figure 4.3: Recruitment and completion rates

4.7.2 Recruitment rate

From February 10 to February 25, 2020, 2339 individuals consented to participate in iNPHORM; of these individuals, 1257 (53.74%) completed all actions to enroll (i.e., *subpanel A*). Individuals in *subpanel A* who failed to complete Wave One were withdrawn (488/1257, 38.82%) and systematically refreshed with *subpanel B*. From April 7 to April 23, 3197 individuals consented, of whom 437 (13.67%) were enrolled. Thus, as of April 2020, 1206 participants comprised the *iNPHORM longitudinal panel*.

4.7.3 Completion rate

The average total completion rate across the *iNPHORM longitudinal panel* was 72.4% (Appendix 12). Given our use of systematic refreshment, *subpanel A* exhibited a higher completion rate than *subpanel B* (89.8% vs 41.6%, respectively). Dropout was highest at Wave One, with completion rates stabilizing thereafter. Across respondents, 71.89% (867/1206) completed ≥8 follow-ups, with 55.22% (666/1206) completing all 12 (Table 4.2). We observed minimal loss to follow-up (i.e., individuals who discontinued participation until the end of the study). Most (855/1206, 70.9%) completed Wave 12 (Table 4.3). Compared with our target sample size (N=521), we calculated a completion rate of 179% (Appendix 13).

Table 4.2: Number of questionnaires completed, overall and by diabetes type (N=1206)

Number questionnaires completed*	Respondents, n (%)		
	Total	T1DM† (n=194)	T2DM‡ (n=1012)
Baseline only§	193 (16)	29 (14.9)	164 (16.2)
1-7	146 (12.1)	20 (10.2)	126 (12.5)
8-11	201 (16.7)	35 (18.2)	166 (16.4)
All 12	666 (55.2)	110 (56.7)	556 (54.9)

*Questionnaires completed could be non-consecutive.

[†]T1DM: type 1 diabetes mellitus.
[‡]T2DM: type 2 diabetes mellitus.
[§]Only *subpanel B* respondents; *subpanel A* respondents were removed upon Wave 1 noncompletion.

Table 4.3: Number of respondents lost to follow-up after each wave, overall and by diabetes type (N=1206)

	Respondents lost to follow-up after each wave, n (%)		
Wave[*]	Total	T1DM[†] (n=194)	T2DM[‡] (n=1012)
Baseline[§]	193 (16)	29 (14.9)	164 (16.2)
Wave 1	33 (2.7)	8 (4.1)	25 (2.5)
Wave 2	17 (1.4)	2 (1)	15 (1.5)
Wave 3	10 (0.8)	1 (0.5)	9 (0.9)
Wave 4	14 (1.2)	0 (0)	14 (1.4)
Wave 5	7 (0.6)	0 (0)	7 (0.7)
Wave 6	5 (0.4)	3 (1.6)	2 (0.2)
Wave 7	8 (0.7)	0 (0)	8 (0.8)
Wave 8	6 (0.5)	1 (0.5)	5 (0.5)
Wave 9	8 (0.7)	1 (0.5)	7 (0.7)
Wave 10	12 (1)	0 (0)	12 (1.2)
Wave 11	38 (3.2)	9 (4.6)	29 (2.9)
Wave 12[‖]	855 (70.9)	140 (72.2)	715 (70.7)

[*]Last wave responded to; after this wave, the respondent was considered lost to follow-up.
[†]T1DM, type 1 diabetes mellitus.
[‡]T2DM, type 2 diabetes mellitus.
[§]Only *subpanel B* respondents; *subpanel A* respondents were removed upon Wave 1 noncompletion.
[‖]No data were collected past Wave 12.

4.8 Discussion

4.8.1 Principal findings

The real-world iNPHORM study is the first primary research investigation focused on quantifying and predicting prospective self-reported hypoglycemia in the US. A general cohort of adult Americans with self-reported T1DM or insulin- and/or secretagogue-treated T2DM was recruited between February and April 2020 and followed for one year. The sample size was achieved using a one-time systematic refreshment and quota sampling. The use of an established probability-based internet panel, push factors (precontacts, reminders, and incentives), and easy-to-complete questionnaires shored up high participation rates. Sample characteristics, quality metrics, and hypoglycemia incidence and prognostication will be published by fall 2022.

4.8.2 Study strengths

Poor generalizability has been an ongoing problem in prognostic hypoglycemia research.(91) To promote real-word representativeness and population inferencing, iNPHORM participants were recruited from random subsets of a well-established, probability-based internet panel. Community-based adults across a wide age range with either T1DM or T2DM, irrespective of past hypoglycemia, were eligible to enroll, as were people prescribed secretagogues, an often underappreciated cause of events.(92) Backstopped by quota sampling, our use of broad eligibility criteria stands in juxtaposition to most prognostic models,(93) especially those based on pre-existing trial data, which focus on inpatient (20–23) or younger, healthier (e.g., no SH history or IAH) (16,19) populations.

Data were collected over 12 one-month intervals, balancing the probability of observing events against participants' abilities to recall them accurately. Frequent and long-term data capture enabled us to obtain maximally valid self-reported information on not only hypoglycemia occurrence but also a range of important, preselected factors commonly unavailable in secondary sources.(94) The longitudinal, prospective nature of our study contrasts the typically short, retrospective follow-ups of other prediction models (mode duration 24 hours–3 months).(14,95–

98) Buttressed by a sufficiently large sample size and completion rate >70%, iNPHORM will facilitate assessments of time-varying predictors, lagged dependent variables, and low-salience events (e.g., NSH) with minimal false negatives, extrapolation bias, and statistical power loss.(99)

Our self-report study yields pertinent insights into the routinely uncaptured burden of hypoglycemia. Past prognostic hypoglycemia research has relied heavily on administrative, insurance-based claims records; however, these sources poorly represent events occurring outside the health care system. Recent evidence suggests that only 5% of SH require hospitalization, and as many as 50% are treated at home by family/friends.(21,22) Moreover, NSH, by definition self-treated,(100) is scarcely, if ever, documented. Patient nondisclosure and provider under-recognition further constrain the real-world applicability of epidemiological data gleaned from clinical encounters. Studies indicate that 65% and 85% of people with diabetes deliberately underreport their SH (101) and NSH (102), respectively, whereas 57% are seldom asked about hypoglycemia by their providers.(101) Not surprisingly, anonymous versus onymous hypoglycemia reporting has been associated with 2–3-fold higher rates.(24)

iNPHORM builds on the methodological and economic advantages of real-time, web-based self-report to acquire instantaneous and representative (27,28) data within large samples (103). Indeed, web-based questionnaires have been lauded for democratizing and potentiating self-report research. Currently, >90% of Americans use the internet.(104) iNPHORM data were collected via user-friendly, self-administered questionnaires completable on diverse internet-equipped devices at the participants' convenience. Very little personal information was requested, and participants were made aware in the letter of information that their data would be deidentified before analysis. By forgoing dependence on health care codes and records, we could obtain real-world, granular information on SH (regardless of health care use) and NSH—events rarely reported in the literature, despite their clinical significance.

4.8.3 Limitations and strategies to mitigate them

Certain limitations and safeguards warrant elaboration. Notwithstanding efforts to promote generalizability, selection biases could have arisen because of the non-representativeness of the

internet panel demography and/or of respondents/responses.(38,105,106) This concern affects correlative estimates less; however, it could distort the validity of summary statistics.(107) For this reason, post hoc statistical weighting will be explored.(107) Biases resulting from English language restriction, lack of technological literacy, having limited to no internet access, and survivorship cannot be discounted. Furthermore, although volunteer bias will be assessed during follow-up, baseline self-selection is not calculable (it was unethical to retain data on otherwise eligible invited panelists who did not complete the screener).

Another related limitation is the risk of attrition bias. To mitigate loss to follow-up, ostensibly unmotivated respondents in *subpanel A* were identified and removed at Wave One via logic testing and noncompletion. One-time systematic refreshment, especially during the first interwave when attrition is highest, has been shown to reduce panel stagnation while improving study feasibility and analytic validity.(40) To prevent further biases, *subpanel B* was recruited from a contemporaneous subgroup of the same frame population as *subpanel A*. Push factors were used to sustain participation.(37) Remuneration coincided with the widely recognized Tailored Design Method by Dillman.(108) Cash amounts were vetted and approved by the Western University health sciences research ethics board before study commencement and outlined in the letter of information. Token incentives were strategized to facilitate revenue-neutral participation (e.g., reasonably compensate individuals for their time and help overcome access barriers), reducing volunteer bias (37,38) and respondent dropout (43–45).

Although web-based (vs postal or telephone) surveys have shown to promote item completeness and accuracy,(25,26) they are not immune to recall bias. Research indicates that 90% (65) of patients correctly recall past-year SH; however, past-month NSH recall ranges from 48% to 75% (69). To reduce differential misclassification bias, standardized, accessibly worded instructions and definitions were provided in each questionnaire. Furthermore, sensitive items were carefully crafted and positioned to encourage respondent honesty.(47) Technical constraints on the IIS platform precluded participants from reviewing or changing the submitted items. In addition, as mechanisms for deterring multiple participant identities, individuals could not re-access/resubmit questionnaires, and authentication by email plus log-in was required. To foster confident and accurate responses, we provided individuals as much time as needed to reflect on items and/or

review personal clinical documentation/materials. Each notification also contained information on the participants' last completed questionnaire.

Before fielding, the assessments underwent pretesting and piloting to promote content usability and accuracy. A total of three individuals participated in the pilot process; this sample size aligned with established best practices at IIS while permitting parsimonious representativity and feasibility. Nevertheless, a larger pilot sample size may have yielded further meaningful feedback. Finally, despite the proven validity/reliability and/or widespread use of many iNPHORM items, no validated self-reported hypoglycemia measures exist. To attenuate instrumentation effects in our study,(109) hypoglycemia definitions and classifications followed the 2019 ADA standards,(66) and recall periods echoed peer-reviewed conventions.(62,67–69) Frequent and recurrent hypoglycemia-related information was amassed across extensive, detailed, and standardized items formulated to promote scientific replicability and future outgrowth. The validity of iNPHORM is further fortified by high completion rates (110) and numerous design principles and quality assurance methods that reinforce data accuracy and integrity.

4.9 Conclusions

iNPHORM promises important forward strides in real-world hypoglycemia detection and prevention. This protocol highlights the powerful application of an internet-based panel survey to assess long-term hypoglycemia risk in a large, community-based cohort of adult Americans with T1DM or insulin- and/or secretagogue-treated T2DM. To date, descriptive and prognostic hypoglycemia estimates have stemmed mainly from cross-sectional and short-term retrospective analyses of pre-existing databases subject to untenable bias. Pairing the importance of longitudinal, prospective self-reported hypoglycemia data with the advantages of web-based survey modes, iNPHORM aims to clarify putative epidemiological understandings and reveal opportune insights into point-of-care decision-making, research priorities, and effective interventional precision.(111–113)

4.10 Acknowledgments

The iNPHORM study was funded through an investigator-initiated grant from Sanofi Canada. Neither Sanofi Global nor Sanofi Canada was involved in the study design; collection, analysis, and interpretation of data; writing of the report; or the decision to submit the paper for publication. All authors confirm their independence from funders and that they had full access to the study data (including statistical reports and tables). They take responsibility for the integrity of the data and the accuracy of the data analysis.

4.11 Conflicts of interest

AR-L received grants from Sanofi and Eli Lilly, paid fees for presentations, and is a consultant at Novo Nordisk and Eli Lilly. SBH is a consultant at, received grants from, and is in the member advisory boards of Sanofi, Eli Lilly, Novo Nordisk, Janssen, AstraZeneca, Abbott, and Boehringer Ingelheim and is involved in clinical studies at Eli Lilly, Novo Nordisk, AstraZeneca, and Boehringer Ingelheim. SBH also received grants from Juvenile Diabetes Research Foundation, Lawson, and the Canadian Institutes of Health and Research. The authors are distinct from the developers/sponsors of the iNPHORM (Investigating Novel Predictions of Hypoglycemia Occurrence Using Real-world Models) questionnaires.

4.12 Summary

Chapter 4 describes the design and implementation of the iNPHORM 12-wave panel survey: the first prognostic hypoglycemia investigation to employ a primary, prospective design (study duration: February 2020 to March 2021). The sample comprised a general online cohort of adult Americans with T1DM or insulin- and/or secretagogue-treated T2DM. Compared to our target sample size (N=521), we achieved a completion rate of 179%. Chapter 5 analyzes data from the *iNPHORM longitudinal panel* to quantify the crude incidence of Level 3 SH in the US.

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Chapter 5

5 Quantifying severe hypoglycemia

Descriptive epidemiologic evidence is foundational to questions of etiology and prognosis and, moreover, to the design and implementation of sound health interventions. Nevertheless, little is known about the true, real-world incidence of SH in the US. The current evidence base leans heavily on routine care registries; however, these sources discount events treated outside the healthcare system. The IHSG/ADA case definitions for SH (i.e., Level 3 hypoglycemia) holds a lens to the often-uncaptured burden of severe events. To date, virtually no US-based epidemiologic studies have investigated this endpoint.

Chapter 5 characterizes and quantifies the IPs and IRs of Level 3 SH overall, by diabetes type, and mode of recovery (e.g., hospital-, non-transport EMS-, 'at home'-treated) using long-term, ambidirectional data from the iNPHORM study. This manuscript, which has been formatted for *Diabetes, Obesity, and Metabolism*, describes the study design, participants and data collection, instruments, statistical analysis, and results. It concludes with a summary of key findings and discussion of the study's significance, strengths, and limitations.

5.1 Manuscript title

Incidence of Level 3 severe hypoglycemia in a real-world cohort of Americans with type 1 or 2 diabetes mellitus: Results of the one-year, prospective iNPHORM study (2020-2021)

Short running title: Real-world severe hypoglycemia, iNPHORM

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5.4 Keywords

adverse event; diabetes; hypoglycemia; insulin; secretagogue; internet survey; real-world; severe hypoglycemia; type 1 diabetes mellitus; type 2 diabetes mellitus

5.5 Introduction

As the rate and prevalence of diabetes increases, so too does the use of insulin and/or secretagogues and ensuing problem of hypoglycemia.(1) Iatrogenic SH accounts for a significant portion of diabetes-related morbidity and mortality. Accurate and precise data on SH incidence are, thus, imperative to guide prognostic hypotheses and preventive strategies.

The IHSG defines SH as a Level 3 event requiring either non-professional or professional aid for recovery.(2–4) This reporting "gold" standard has been endorsed by nearly all major diabetes clinical practice guidelines, including the ADA. Nevertheless, US epidemiologic research into Level 3 hypoglycemia remains sparse, outdated, and, furthermore, limited by a lack of sample generalizability, as well as long-term and prospective follow-up. Instead, burgeoning analyses of registries and routine care records dominate the SH evidence base. Such studies—despite often enrolling impressively large, longitudinal cohorts—are liable to underestimate the true population frequency of SH by discounting events treated outside the healthcare system.

To form a more representative and complete understanding of SH epidemiology in the US, we conducted the 12-monthly, prospective iNPHORM study: the first primary epidemiologic investigation of adults with diabetes at-risk of iatrogenic hypoglycemia. Because patient underreporting and provider under-recognition can limit accurate SH elicitation in practice,(5–11) we obtained participant information using anonymously-completed, self-administered questionnaires. Leveraging these data, we aimed to characterize US Level 3 SH occurrence—first, in terms of event recovery mode/context(s) (e.g., treatment by a healthcare provider [HCP] versus non-HCP); and second, as one-year IRs and IPs.

5.6 Materials and methods

5.6.1 Study design

iNPHORM is a US-wide, 12-wave ambidirectional panel survey that included a 12-month retrospective lookback at baseline, and 12 consecutive months of prospective data collection.

Complete details on the design and conduct of iNPHORM are published elsewhere.(12) The current article complies with 'The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) Statement: guidelines for reporting observational studies'.(13)

5.6.2 Participants and data collection

Individuals living in the US (past year); 18–90 years old; with a self-reported diagnosis of T1DM (past year) or T2DM taking insulin, secretagogues, or both (past year) were recruited from a well-established, probability-based internet panel (~68,000 members with diabetes). We excluded people who were concurrently involved in a trial or pregnant (at screening or past year). The internet panel was designed to reflect the general US public; validity checks, quotas, and multidimensional calibration were used to maintain fair and representative—geodemographic, attitudinal, and behavioral—sampling.(14)

A random subset of the internet panel was invited via email to participate in iNPHORM. To enrol, eligible screener respondents had to provide consent, complete a baseline questionnaire, and register to receive 12 monthly follow-ups. Recruitment continued until we reached 1250 enrollees (i.e., *subpanel A*). Members of *subpanel A* not completing the first follow-up were withdrawn and systematically refreshed with new participants (i.e., *subpanel B*). No other post-enrolment exclusions were performed.

Individuals in *subpanel A* who completed Wave 1, plus all those in *subpanel B*, comprised the *iNPHORM Longitudinal Panel*. Precontacts, reminders, and cash incentives were used to promote retention. Participants and data collection were managed by IIS.(15) Individuals in *subpanel A* were followed from February 2020 to January 2021, and individuals in *subpanel B* from April 2020 and March 2021. Wave responses were tracked by a random, unique ID assigned at enrolment.

5.6.3 Instruments

Questionnaires were constructed in English by A.R.-L., B.L.R., and S.B.H. for completion on internet-equipped devices (e.g., computer, phone, tablet); they were pretested and piloted prior to

roll-out. Follow-ups were scheduled monthly to promote response accuracy while mitigating participant fatigue. At screening, we collected data on sex assigned at birth, diabetes type, and medication regimen (responses were retained for all consenting individuals) and, at baseline, various anthropometric, sociodemographic, and clinical variables. Information on SH, eligibility status, medications, A1C, and use of rt-C/FGM was obtained at every wave. Participants had seven days to complete each follow-up.

5.6.4 Outcome measure

Per the IHSG and ADA guidelines, we operationalized SH as a Level 3 low BG concentration, irrespective of glycemic threshold, requiring external non-professional or professional aid for recovery.(3) Event frequencies were assessed at baseline (past year) and each follow-up ('since the last time an iNPHORM survey was completed'). For reported SH event(s), we also captured information on mode/context(s) of recovery (e.g., hospitalization, ED or non-transport EMS, or non-HCP treatment). The response option 'I recovered on my own without any kind of treatment' was provided, as was 'Other', and 'Unknown treatment'. Participants could bypass questions by typing "OPT OUT" in a response box.

5.6.5 Sample size

A target sample size of 958 respondents was calculated to meet the primary objective of iNPHORM. We inflated this value to N=1250 to allow for a degree of participant discontinuance over follow-up. Additional information on sample size is available in the study protocol.(12)

5.6.6 Statistical analysis

The ambidirectional nature of iNPHORM enabled us to collect participant data one-year retrospectively (12-month lookback from baseline) as well as one-year prospectively (12 monthly follow-ups). Data obtained over these two observation windows were compared to explore the potential impacts of different data collection methods and periods on SH estimates.

All analyses were performed on respondents who completed one or more follow-up(s). Retention was calculated as the ratio of the observed versus maximum number of completed follow-ups. Sample characteristics were reported as frequencies and percentages for categorical variables, and as means and SDs or medians and IQRs for continuous variables. Event frequencies were compared overall, as well as by period of observation, diabetes type, and recovery mode/context.

For inclusion in the population denominator, individuals had to possess a non-zero SH probability. As such, prospective data pertaining to periods of participant ineligibility were omitted (e.g., reports of no insulin or secretagogue use). To ensure our risk set was consistently specified across observation periods, we right censored anyone who became pregnant or moved outside of the US during follow-up.

Cases (i.e., those who experienced one or more SH event[s]) were identified from the denominator population. Incidence proportions (percentage with one or more SH event[s]) and rates (EPPY) were calculated alongside Wilson's and negative binomial confidence intervals, respectively. Incidences were computed overall and by recovery mode/context; any variability between observation periods and diabetes type was assessed using z-tests and Wald tests, respectively, with relative differences assessed as cumulative incidence ratios (CIRs) and incidence rate ratios (IRRs).

Retrospectively, IPs spanned the full year preceding baseline; whereas, prospectively, they spanned the length of follow-up (less than or equal to one year). We evaluated differences in sample characteristics between subgroups reporting zero versus one or more SH event(s), retrospectively versus prospectively, using z-tests, Wilcoxon rank-sum tests, and chi-square tests for mean, median, and categorical variables, respectively. Unlike IPs, IRs could be annualized; as such, both prospective and retrospective estimates spanned a complete year. The numerator of the IR constituted the sum of all, including recurrent, events. We used the point estimate from an intercept only negative binomial regression model to determine IRs; values were offset for non-zero SH probability.

All significance tests were based on a two-sided Bonferroni-adjusted α-level for a family-wise error rate of $\alpha=0.05$.

5.6.7 Ethical considerations

Prior to recruitment, we obtained ethics approval from the Western University Health Sciences Research Ethics Board (Project ID: 112986; December 17, 2019) and registered iNPHORM with ClinicalTrials.gov (NCT04219514; January 7, 2020). Individuals had to consent to enrol and could withdraw at any time. Personally identifiable data (e.g., email addresses) were collected strictly to monitor participants over follow-up; all questionnaires were completed anonymously. Only deidentified data were transferred by IIS to Western University.

5.7 Results

5.7.1 Characterizing the iNPHORM cohort

5.7.1.1 iNPHORM Longitudinal Panel

Of the 1206 enrolled in the *iNPHORM longitudinal panel*, we excluded 221 participants who did not complete one or more follow-up(s), and seven without baseline SH information (Table 5.1). Therefore, 978 individuals were analyzed in this study (mean age: 51 [SD: 14.3] years; male: 49.6%; T1DM: 17%). The retention rate was 86.2% (85.5% completed eight or more follow-ups with 66.1% completing all 12) and less than 15% were lost to follow-up (Appendix 14). The average prospective observation period was 9.62 (SD: 3.15) months (T1DM: 10.15 [SD: 2.84] months; T2DM: 9.51 [SD: 3.20] months; *p*-value=0.02).

Table 5.1: Baseline descriptive statistics of *iNPHORM longitudinal panel*

Table 5.1a: Anthropometric and sociodemographic characteristics

Characteristic	Overall (n=978)	T1DM (n=163)	T2DM (n=815)
Age (years), mean (SD)			
	50.97 (14.29)	44.61 (13.82)	52.24 (14.05)
Sex assigned at birth, n (%)			
Male	485 (49.59)	56 (34.36)	429 (52.64)
Female	493 (50.41)	107 (65.64)	386 (47.36)
BMI (kg/m2), median (IQR)			
	30.35 (12.05)	26.34 (7.13)	31.45 (12.42)
Marital status, n (%)			
Married	615 (62.88)	94 (57.67)	521 (63.93)
Divorced, separated, widowed	162 (16.56)	25 (15.34)	137 (16.81)
Never married	200 (20.45)	44 (26.99)	156 (19.14)
Missing/unknown	1 (0.10)	0 (0)	1 (0.12)
Race, n (%)			
White alone	776 (79.35)	148 (90.80)	628 (77.06)
Part-white multiracial	37 (3.78)	3 (1.84)	34 (4.17)
Non-white	143 (14.62)	10 (6.13)	133 (16.32)
Missing/unknown	22 (2.25)	2 (1.23)	20 (2.45)
Education, n (%)			
High school, some high school, or Grade 8	170 (17.38)	30 (18.40)	140 (17.18)

College degree or some college	627 (64.11)	105 (64.42)	522 (64.05)
Degree beyond first college degree	181 (18.51)	28 (17.18)	153 (18.77)
Employment, n (%)			
Full-time	427 (43.66)	72 (44.17)	355 (43.56)
Part-time	81 (8.28)	21 (12.88)	60 (7.36)
Unemployed, retired, or student	470 (48.06)	70 (42.94)	400 (49.08)
Annual household income (gross), n (%)			
<$25,000	167 (17.08)	22 (13.50)	145 (17.79)
$25,000 to $54,999	266 (27.20)	39 (23.93)	227 (27.85)
$55,000 to $84,999	211 (21.57)	53 (32.52)	158 (19.39)
$85,000 to $114,999	149 (15.24)	24 (14.72)	125 (15.34)
$115,000 to $144,999	64 (6.54)	7 (4.29)	57 (6.99)
≥$145,000	112 (11.45)	14 (8.59)	98 (12.02)
Missing/unknown	9 (0.92)	4 (2.45)	5 (0.61)
Insurance, n (%)			
Private insurance plan	420 (42.94)	88 (53.99)	332 (40.74)
Government-assistance plan	319 (32.62)	47 (28.83)	272 (33.37)
Multiple insurance plans and other insurance plans	221 (22.60)	23 (14.11)	198 (24.29)
Out-of-pocket (i.e., no insurance coverage)	18 (1.84)	5 (3.07)	13 (1.60)

T1DM, type 1 diabetes mellitus; T2DM, type 2 diabetes mellitus; SD, standard deviation; IQR, interquartile range; BMI, body mass index.

Table 5.1b: Clinical characteristics

Characteristic	Overall (n=978)	T1DM (n=163)	T2DM (n=815)
Duration of diabetes, median (IQR)			
	12 (14)	26 (20)	11 (13)
Medication regimen, n (%)			
Insulin without secretagogues	475 (48.57)	163 (100.00)	312 (38.28)
Secretagogues without insulin	312 (31.90)	0 (0)	312 (38.28)
Insulin with secretagogues	191 (19.53)	0 (0)	191 (23.44)
Duration of insulin use (years)*, median (IQR)			
	6.67 (12.08)	25.58 (22.08)	5.00 (7.50)
Missing/unknown, n (%)	1 (0.001)	1 (0.01)	0
Duration of secretagogue use (years)*, median (IQR)			
	4.50 (5.75)	-	4.50 (5.75)
Missing/unknown, n (%)	10 (0.01)	-	10 (0.01)
Most recent A1C, n (%)			
≤7%	323 (33.03)	58 (35.58)	265 (32.52)
7.1-8%	337 (34.46)	60 (36.81)	277 (33.99)
8.1-9%	161 (16.46)	23 (14.11)	138 (16.93)
≥9.1%	95 (9.71)	20 (12.27)	75 (9.20)
Missing/unknown	62 (6.34)	2 (1.23)	60 (7.36)
Impaired Awareness of Hypoglycemia, n (%)			
No	226 (23.11)	47 (28.82)	179 (21.96)
Yes	649 (66.36)	116 (71.17)	533 (65.40)

Missing/unknown	103 (10.53)	0	103 (12.64)
Number of diabetes complications[†], n (%)			
0	402 (41.10)	50 (30.67)	352 (43.19)
1	242 (24.74)	42 (25.77)	200 (24.54)
2	111 (11.35)	21 (12.88)	90 (11.04)
3	69 (7.06)	20 (12.27)	49 (6.01)
4	29 (2.97)	8 (4.91)	21 (2.58)
5 or greater	57 (5.83)	16 (9.81)	41 (5.03)
Missing/unknown	68 (6.95)	6 (3.68)	62 (7.61)
Number of comorbidities[‡], n (%)			
0	171 (17.48)	42 (25.77)	129 (15.83)
1	166 (16.97)	32 (19.63)	134 (16.44)
2	181 (18.51)	26 (15.95)	155 (19.02)
3	132 (13.50)	18 (11.04)	114 (13.99)
4	125 (12.78)	19 (11.66)	106 (13.01)
5 or greater	148 (15.14)	19 (11.66)	129 (15.83)
Missing/unknown	55 (5.62)	7 (4.29)	48 (5.89)
rt-C/FGM use, n (%)			
No	766 (78.32)	82 (50.31)	684 (83.93)
Yes	208 (21.27)	80 (49.08)	128 (15.71)
Missing/unknown	4 (0.41)	1 (0.61)	3 (0.37)

T1DM, type 1 diabetes mellitus; T2DM, type 2 diabetes mellitus; IQR, interquartile range; rt-C/FGM, real-time continuous or flash glucose monitoring.
-: Not applicable
[*]Among those treated.
[†]Diabetes complications included amputation, diabetic ketoacidosis, foot damage, gastroparesis, hyperosmolar coma, nephropathy, neuropathy, and retinopathy.

‡Comorbidities included bone, joint, or muscle problems; cancer; cardiovascular disease; chronic kidney disease; chronic liver failure; eating disorders; gastrointestinal disease; HIV/AIDS; hypertension; mental health conditions; neurological disorders; and stroke.

5.7.1.2 Subset reporting one or more severe hypoglycemia event(s)

Table 5.2 profiles participants reporting one or more SH event(s) (461/978 [47.14%]). Half were female (230/461) and 76.36% (352/461) self-identified as white. Most (381/461 [82.65%]) respondents had at least some college education and nearly all had health insurance (455/461 [98.70%]). The mean age was 46.82 (SD: 14.06) years. Close to 80% (362/461) self-reported a T2DM diagnosis. People with T1DM (99/461 [21.48%]) were on average younger (45.02 [SD: 13.60] years) than those with T2DM (47.31 [SD: 14.17] years); they also reported a longer median diabetes duration (T1DM: 27 [IQR: 22] years; T2DM: 10 [IQR: 12] years). All T1DM participants reported using insulin (without secretagogues). Among T2DM respondents, 23.48% (85/362) were on insulin without secretagogues, 24.31% (88/362) on secretagogues without insulin, and 52.21% (189/362) insulin with secretagogues. Appendix 15 statistically compares sample characteristics for participants reporting zero versus one or more prospective event(s).

Table 5.2: Sample characteristics of individuals reporting one or more SH event(s) by observation period

Table 5.2a: Anthropometric and sociodemographic characteristics

	Retro. or Prosp.			Retro.			Prosp.			Retro. versus Prosp.
	Overall (n=461)	T1DM (n=99)	T2DM (n=362)	Overall (n=324)	T1DM (n=74)	T2DM (n=250)	Overall (n=331)	T1DM (n=72)	T2DM (n=259)	Overall *p*-value*
Age, mean (SD)										0.421
	46.82 (14.06)	45.02 (13.60)	47.31 (14.17)	45.02 (13.35)	44.43 (12.52)	45.19 (13.60)	45.88 (13.97)	44.78 (13.83)	46.18 (14.02)	
Sex assigned at birth, n (%)										0.453
Male	231 (50.11)	36 (36.36)	195 (53.87)	172 (53.09)	24 (32.43)	148 (59.20)	166 (50.15)	30 (41.67)	136 (52.51)	
Female	230 (49.89)	63 (63.64)	167 (46.13)	152 (46.91)	50 (67.57)	102 (40.80)	165 (49.85)	42 (58.33)	123 (47.49)	
BMI (kg/m^2), median (IQR)										0.8132
	28.41 (9.97)	25.74 (6.96)	29.41 (10.55)	28.16 (9.30)	26.05 (7.10)	28.77 (9.97)	27.95 (10.35)	24.89 (5.76)	29.53 (11.06)	

Marital status, n (%)										0.349
Married	296 (64.21)	61 (61.62)	235 (64.92)	220 (67.90)	46 (62.16)	174 (69.60)	211 (63.75)	42 (58.33)	169 (65.25)	
Divorced, separated, widowed	74 (16.05)	17 (17.17)	57 (15.75)	43 (13.27)	12 (16.22)	31 (12.40)	57 (17.22)	14 (19.44)	43 (16.60)	
Never married	91 (19.74)	21 (21.21)	70 (19.34)	61 (18.83)	16 (21.62)	45 (18.00)	63 (19.03)	16 (22.22)	47 (18.15)	
Missing/unknown	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	
Race, n (%)										0.561
White alone	352 (76.36)	89 (89.90)	263 (72.65)	253 (78.09)	67 (90.54)	186 (74.40)	256 (77.34)	63 (87.50)	193 (74.52)	
Part-white multiracial	16 (3.47)	1 (1.01)	15 (4.14)	9 (2.78)	1 (1.35)	8 (3.20)	14 (4.23)	1 (1.39)	13 (5.02)	
Non-white	79 (17.14)	7 (7.07)	72 (19.89)	52 (16.05)	5 (6.76)	47 (18.80)	49 (14.80)	6 (8.33)	43 (16.60)	
Missing/unknown	14 (3.04)	2 (2.02)	12 (3.31)	10 (3.09)	1 (1.35)	9 (3.60)	12 (3.63)	2 (2.78)	10 (3.86)	
Education, n (%)										0.078

High school, some high school, or Grade 8	80 (17.35)	21 (21.21)	59 (16.30)	45 (13.89)	16 (21.62)	29 (11.60)	68 (20.54)	19 (26.39)	49 (18.92)	
College degree or some college	302 (65.51)	64 (64.65)	238 (65.75)	220 (67.90)	47 (63.51)	173 (69.20)	209 (63.14)	46 (63.89)	163 (62.93)	
Degree beyond 1st college degree	79 (17.14)	14 (14.14)	65 (17.96)	59 (18.21)	11 (14.86)	48 (19.20)	54 (16.31)	7 (9.72)	47 (18.15)	
Employment, n (%)										0.1983
Full-time	239 (51.84)	40 (40.40)	199 (54.97)	187 (57.72)	30 (40.54)	157 (62.80)	168 (50.76)	28 (38.89)	140 (54.05)	
Part-time	50 (10.85)	16 (16.16)	34 (9.39)	35 (10.80)	10 (13.51)	25 (10.00)	40 (12.08)	12 (16.67)	28 (10.81)	
Unemployed, retired, or student	172 (37.31)	43 (43.43)	129 (35.64)	102 (31.48)	34 (45.95)	68 (27.20)	123 (37.16)	32 (44.44)	91 (35.14)	
Annual household income (gross), n (%)										0.3902
<$25,000	75 (16.27)	14 (14.14)	61 (16.85)	40 (12.35)	9 (12.16)	31 (12.40)	60 (18.13)	13 (18.06)	47 (18.15)	
$25,000 to $54,999	122 (26.46)	26 (26.26)	96 (26.52)	86 (26.54)	21 (28.38)	65 (26.00)	87 (26.28)	20 (27.78)	67 (25.87)	

$55,000 to $84,999	84 (18.22)	29 (29.29)	55 (15.19)	61 (18.83)	22 (29.73)	39 (15.60)	57 (17.22)	20 (27.78)	37 (14.29)	
$85,000 to $114,999	67 (14.53)	14 (14.14)	53 (14.64)	49 (15.12)	9 (12.16)	40 (16.00)	40 (12.08)	8 (11.11)	32 (12.36)	
$115,000 to $144,999	34 (7.38)	5 (5.05)	29 (8.01)	23 (7.10)	4 (5.41)	19 (7.60)	25 (7.55)	2 (2.78)	23 (8.88)	
≥$145,000	74 (16.05)	7 (7.07)	67 (18.51)	61 (18.83)	6 (8.11)	55 (22.00)	57 (17.22)	5 (6.94)	52 (20.08)	
Missing/unknown	5 (1.08)	4 (4.04)	1 (0.28)	4 (1.23)	3 (4.05)	1 (0.40)	5 (1.51)	4 (5.56)	1 (0.39)	
Insurance, n (%)										0.120
Private insurance plan	166 (36.01)	40 (40.40)	126 (34.81)	157 (48.46)	37 (50.00)	120 (48.00)	103 (31.12)	25 (34.72)	78 (30.12)	
Government-assistance plan	136 (29.50)	33 (33.33)	103 (28.45)	89 (27.47)	27 (36.49)	62 (24.80)	102 (30.82)	25 (34.72)	77 (29.73)	
Multiple insurance plans and other insurance plans	153 (33.19)	22 (22.22)	131 (36.19)	72 (22.22)	6 (8.11)	66 (26.40)	122 (36.86)	19 (26.39)	103 (39.77)	
Out-of-pocket (i.e., no insurance coverage)	6 (1.30)	4 (4.04)	2 (0.55)	6 (1.85)	4 (5.41)	2 (0.80)	4 (1.21)	3 (4.17)	1 (0.39)	

T1DM, type 1 diabetes mellitus; T2DM, type 2 diabetes mellitus; SD, standard deviation; IQR, interquartile range; BMI, body mass index; Prosp, prospective observation period (up to one year); Retro, retrospective observation period (past year).

*Means and proportions compared using *z*-tests; medians using Wilcoxon rank-sum test; and categories using chi-square tests.

Table 5.2b: Clinical characteristics

	Retro. or Prosp.			Retro.			Prosp.			Retro. vs. Prosp.
	Overall (n=461)	T1DM (n=99)	T2DM (n=362)	Overall (n=324)	T1DM (n=74)	T2DM (n=250)	Overall (n=331)	T1DM (n=72)	T2DM (n=259)	Overall *p*-value*
Diabetes duration, median (IQR)										0.702
	12 (16)	27 (22)	10 (12)	12 (16)	26 (18)	9 (12)	12 (16.5)	28.5 (21)	10 (13)	
Medication regimen, n (%)										0.866
Insulin without secretagogues	184 (39.91)	99 (100)	85 (23.48)	164 (50.62)	74 (100)	90 (36.00)	129 (38.97)	72 (100)	57 (22.01)	
Secretagogues without insulin	88 (19.09)	0 (0)	88 (24.31)	67 (20.68)	0 (0)	67 (26.80)	53 (16.01)	0 (0)	53 (20.46)	
Insulin with secretagogues	189 (41.00)	0 (0)	189 (52.21)	93 (28.70)	0 (0)	93 (37.20)	149 (45.02)	0 (0)	149 (57.53)	
Duration of insulin use (years), median (IQR)										
	6.13 (12.58)	25.46 (24.75)	4.46 (7.08)	5.50 (12.5)	25.17 (23.92)	4.17 (6.17)	5.75 (12.67)	25.92 (25.29)	4.00 (7.00)	0.751
Duration of secretagogue use (years), median (IQR)										

	3.58 (4.25)	-	3.58 (4.25)	3.42 (3.50)	-	3.42 (3.50)	3.50 (4.33)	-	3.50 (4.33)	0.2699
A1C, n (%)										0.346
Less than or equal to 7%	73 (15.84)	28 (28.28)	45 (12.43)	80 (24.69)	25 (33.78)	55 (22.00)	48 (14.50)	18 (25.00)	30 (11.58)	
7.1% to 8%	142 (30.80)	31 (31.31)	111 (30.66)	113 (34.88)	26 (35.14)	87 (34.80)	96 (29.00)	23 (31.94)	73 (28.19)	
8.1% to 9%	114 (24.73)	19 (19.19)	95 (26.24)	73 (22.53)	12 (16.22)	61 (24.40)	79 (23.87)	12 (16.67)	67 (25.87)	
Greater than or equal to 9.1%	90 (19.52)	15 (15.15)	75 (20.72)	40 (12.35)	10 (13.51)	30 (12.00)	78 (23.56)	13 (18.06)	65 (25.10)	
Missing/unknown	42 (9.11)	6 (6.06)	36 (9.94)	18 (5.56)	1 (1.35)	17 (6.80)	30 (9.06)	6 (8.33)	24 (9.27)	
IAH, n (%)										0.633
No	106 (22.99)	28 (28.28)	78 (21.55)	72 (22.22)	21 (28.38)	51 (20.40)	67 (20.24)	19 (26.39)	48 (18.53)	
Yes	344 (74.62)	71 (71.72)	273 (75.41)	250 (77.16)	53 (71.62)	197 (78.80)	255 (77.04)	53 (73.61)	202 (77.99)	

Missing/unknown	11 (2.39)	0	11 (3.04)	2 (0.62)	0	2 (0.80)	9 (2.72)	0	9 (3.47)	
Number of diabetes complications[†], n (%)										0.342
0	162 (35.14)	24 (24.24)	138 (38.12)	114 (35.19)	16 (21.62)	98 (39.20)	106 (32.02)	16 (22.22)	90 (34.75)	
1	113 (24.51)	26 (26.26)	87 (24.03)	70 (21.60)	20 (27.03)	50 (20.00)	81 (24.47)	18 (25.00)	63 (24.32)	
2	54 (11.71)	11 (11.11)	43 (11.88)	43 (13.27)	10 (13.51)	33 (13.20)	40 (12.08)	7 (9.72)	33 (12.74)	
3	43 (9.33)	16 (16.16)	27 (7.46)	32 (9.88)	13 (17.57)	19 (7.60)	35 (10.57)	13 (18.06)	22 (8.49)	
4	23 (4.99)	5 (5.05)	18 (4.97)	18 (5.56)	4 (5.41)	14 (5.60)	21 (6.34)	4 (5.56)	17 (6.56)	
5 or greater	37 (8.02)	13 (13.13)	24 (6.63)	26 (8.02)	8 (10.81)	18 (7.20)	32 (9.67)	11 (15.28)	21 (8.11)	
Missing/unknown	29 (6.29)	4 (4.04)	25 (6.91)	21 (6.48)	3 (4.05)	18 (7.20)	16 (4.83)	3 (4.17)	13 (5.02)	
Number of comorbidities[‡], n (%)										0.843

0	93 (20.17)	24 (24.24)	69 (19.06)	63 (19.44)	16 (21.62)	47 (18.80)	69 (20.85)	19 (26.39)	50 (19.31)	
1	68 (14.75)	15 (15.15)	53 (14.64)	49 (15.12)	11 (14.86)	38 (15.20)	42 (12.69)	10 (13.89)	32 (12.36)	
2	79 (17.14)	14 (14.14)	65 (17.96)	57 (17.59)	13 (17.57)	44 (17.60)	52 (15.71)	10 (13.89)	42 (16.22)	
3	55 (11.93)	13 (13.13)	42 (11.60)	32 (9.88)	7 (9.46)	25 (10.00)	45 (13.60)	12 (16.67)	33 (12.74)	
4	60 (13.02)	17 (17.17)	43 (11.88)	43 (13.27)	14 (18.92)	29 (11.60)	41 (12.39)	13 (18.06)	28 (10.81)	
5 or greater	77 (16.70)	13 (13.13)	64 (17.68)	120 (37.04)	10 (13.51)	50 (20.00)	63 (19.03)	6 (8.33)	57 (22.01)	
Missing/unknown	29 (6.29)	3 (3.03)	26 (7.18)	20 (6.17)	3 (4.05)	17 (6.80)	19 (5.74)	2 (2.78)	17 (6.56)	
rt-C/FGM use, n (%)										0.799
No	173 (37.53)	38 (38.38)	135 (37.29)	207 (63.89)	40 (54.05)	167 (66.80)	110 (33.23)	27 (37.50)	83 (32.05)	
Yes	274 (59.44)	59 (59.60)	215 (59.39)	115 (35.49)	33 (44.59)	82 (32.80)	210 (63.44)	43 (59.72)	167 (64.48)	

Missing/unknown	14 (3.04)	2 (2.02)	12 (3.31)	2 (0.62)	1 (1.35)	1 (0.40)	11 (3.32)	2 (2.78)	9 (3.47)	

T1DM, type 1 diabetes mellitus; T2DM, type 2 diabetes mellitus; IQR, interquartile range; rt-C/FGM: real-time continuous or flash glucose monitoring; IAH, impaired awareness of hypoglycemia; Prosp, prospective; Retro, retrospective.

*Means and proportions compared using *z*-tests; medians using Wilcoxon rank-sum test; and categories using chi-square tests.

†Diabetes complications included amputation, ketoacidosis, foot damage, gastroparesis, hyperosmolar, nephropathy, neuropathy, and retinopathy.

‡Comorbidities included bone, joint, or muscle problems; cancer; cardiovascular disease; chronic kidney disease; chronic liver failure; eating disorders; gastrointestinal disease; HIV/AIDS; hypertension; mental health conditions; neurological disorders; and stroke.

5.7.2 Quantifying severe hypoglycemia

5.7.2.1 Severe hypoglycemia by recovery mode/context

Table 5.3 summarizes the distribution of SH by treatment mode/context. Prospectively, over 60% (2523/4007) of events were treated outside the healthcare system by a non-HCP (T1DM: 309/443 [69.8%]; T2DM: 2214/3564 [62.1%], *p*-value=0.0017, α=0.0016). In general, 9.2% (367/4007) resulted in hospital services with 4.6% (183/4007) requiring admission (T1DM: 7/443 [1.6%] versus T2DM: 176/3564 [4.9%], *p*-value=0.0014, α=0.0016).

Among T2DM respondents, the fraction of SH requiring non-transport EMS or ED care (no admission) was 4.9 (*p*-value<0.0001, α=0.0016) and 4.4 (*p*-value=0.0002, α=0.0016) times that reported by T1DM respondents, respectively. The percentage of SH requiring no external aid (i.e., resulting in spontaneous recovery) was also 50% higher in T2DM (216/3564 [6.0%]) than T1DM (17/443 [3.8 %]) diabetes, but statistically non-significant (*p*-value=0.0621, α=0.0016). For 10% of SH (388/4007), the recovery mode/context was unspecified (T2DM: 296/3564 [8.31%] versus T1DM: 92/443 [20.77%], *p*-value<0.0001, α=0.0016).

Table 5.3: Retrospective and prospective SH frequencies by treatment mode/context (overall and by diabetes type)

	Overall (n=978)			T1DM (n=163)			T2DM (n=815)			T1DM vs T2DM	
	Retro.	Prosp.	*p*-value*	Retro.	Prosp.	*p*-value*	Retro.	Prosp.	*p*-value*	Retro. *p*-value*	Prosp. *p*-value*
Total number of SH events											
	2354	4007	-	750	443	-	1604	3564	-	-	-
Treated outside hospital by non-HCP (e.g., family or friend), n (%)											
	1207 (51.27)	2523 (62.96)	<0.0001†	432 (57.60)	309 (69.75)	<0.0001†	775 (48.32)	2214 (62.12)	<0.0001†	<0.0001†	0.0017
Treated outside hospital by HCP (e.g., non-transport EMS), n (%)											
	234 (9.94)	486 (12.13)	0.0078	11 (1.47)	12 (2.71)	0.1317	223 (13.90)	474 (13.30)	0.5571	<0.0001†	<0.0001†
Treated in ED *without* hospital admission, n (%)											
	130 (5.52)	184 (4.59)	0.0981	2 (0.27)	5 (1.13)	0.0596	128 (7.98)	179 (5.02)	<0.0001†	<0.0001†	0.0002†
Treated in ED *with* hospital admission, n (%)											

	61 (2.59)	183 (4.57)	0.0001*	4 (0.53)	7 (1.58)	0.068	57 (3.55)	176 (4.94)	0.0265	<0.0001†	0.0014†
No external aid (i.e., spontaneously recovered), n (%)											
	150 (6.37)	232 (5.79)	0.3453	28 (3.73)	17 (3.84)	0.9273	122 (7.61)	215 (6.03)	0.0340	0.0003	0.0621
Other/Unknown, n (%)											
	572 (24.30)	388 (9.68)	<0.0001†	273 (36.40)	92 (20.77)	<0.0001†	299 (18.64)	296 (8.31)	<0.0001†	<0.0001†	<0.0001†

T1DM, type 1 diabetes mellitus; T2DM, type 2 diabetes mellitus; SH, severe hypoglycemia; HCP, healthcare provider; EMS, emergency medical services; ED, emergency department; Prosp, prospective observation period (up to one year); Retro, retrospective observation period (past year).

*z-tests were used to compare proportions.

†Significant based on a Bonferroni-adjusted $\alpha=0.0016$, giving a family-wise error rate of $\alpha=0.05$.

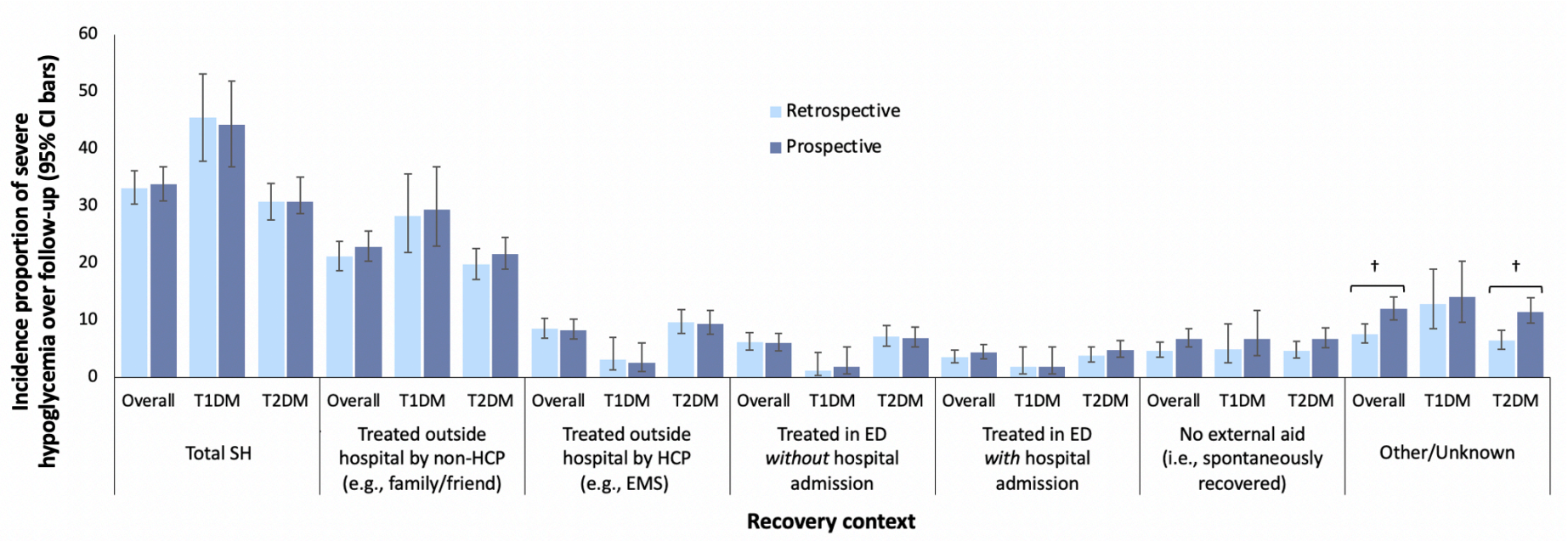
5.7.2.2 Incidence of severe hypoglycemia

Events were right-skewed (Appendix 16). Retrospectively, 110 people (11%) had five or more events, corresponding to 1981 or 84% of all SH (T1DM: 13.5% had 89% of events; T2DM: 11% had 82% of events). Prospectively, 128 (13%) had five or more events, corresponding to 3634 or 91% of all SH (T1DM: 12% had 78% of events; T2DM: 13% had 92% of events).

Retrospective and prospective IPs are reported in Figure 5.1 and IRs in Figure 5.2, for total SH, as well as by recovery mode/context and diabetes type. During the prospective phase, 33.1% (95% CI: 30.9% to 36.9%) of participants had one or more SH event(s). No significant differences between T1DM and T2DM emerged for retrospective and prospective IPs, overall or by specified recovery modes/contexts. Annual retrospective IPs—subdivided by diabetes type and recovery/mode context—were statistically on par with corresponding prospective values.

The IR for total SH was 5.01 (95% CI: 4.15 to 6.05) EPPY, prospectively, and 2.41 (95% CI: 2.01 to 2.88) EPPY, retrospectively (IRR: 2.08 [95% CI: 1.61 to 2.70], p-value<0.0001, α=0.0007). We observed significantly greater overall prospective versus retrospective IRs for SH treated outside the care system by a non-HCP (IRR: 2.40 [95% CI: 1.74 to 3.32], p-value <0.0001, α=0.0007); by non-transport EMS (IRR: 2.57 [95% CI: 1.60 to 4.13], p-value<0.0001, α=0.0007); and in hospital with admission (IRR: 3.83 [95% CI: 1.98 to 7.43], p-value<0.0001, α=0.0007).

People with T2DM reported significantly higher prospective versus retrospective IRs for total SH (IRR: 2.69 [95% CI: 2.00 to 3.61], p-value<0.0001, α=0.0007); as well as for events treated outside the care system by a non-HCP (IRR: 3.26 [95% CI: 2.27 to 4.68], p-value<0.0001, α=0.0007); by non-transport EMS (IRR: 2.64 [95% CI: 1.62 to 4.30], p-value<0.0001, α=0.0007); and in hospital with admission (IRR: 3.93 [95% CI: 1.97 to 7.86], p-value=0.0001, α=0.0007). No significant differences between retrospective and prospective IRs arose for T1DM. Retrospectively, the IR for total SH was significantly greater in T1DM than T2DM (IRR: 2.34 [95% CI: 1.47 to 3.73], p-value=0.0004, α=0.0007); but not significantly lower, prospectively (IRR: 0.68 [95% CI: 0.41 to 1.13], p-value=0.1352, α=0.0007). Throughout follow-up, more people with T2DM than T1DM reported SH treated by non-transport EMS (IRR: 8.57 [95% CI: 2.93 to 25.00], p-value<0.0001, α=0.0007)

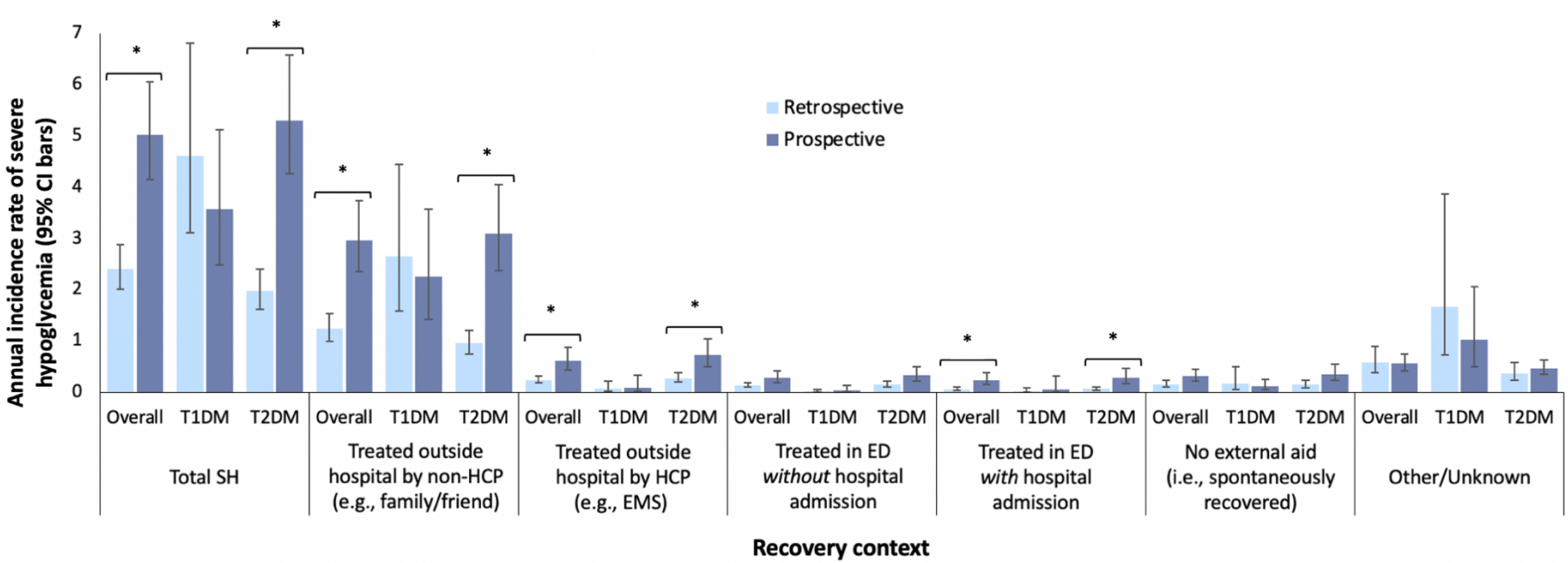


	Overall (n=978)			T1DM (n=163)			T2DM (n=815)			T1DM versus T2DM	
	Retro. (95% CI)	Prosp. (95% CI)	*p*-value‡	Retro. (95% CI)	Prosp. (95% CI)	*p*-value‡	Retro. (95% CI)	Prosp. (95% CI)	*p*-value‡	Retro. *p*-value‡	Prosp. *p*-value‡
Total SH	33.1 (30.3 to 36.1)	33.8 (30.9 to 36.9)	0.7146	45.4 (37.9 to 53.1)	44.2 (36.8 to 51.8)	0.8725	30.7 (27.6 to 33.9)	30.8 (28.7 to 35.1)	0.6266	0.0003†	0.0404
Treated outside hospital by non-HCP (e.g., family/friend)	21.2 (18.7 to 23.8)	22.9 (20.4 to 25.6)	0.3994	28.2 (21.9 to 35.6)	29.4 (23.0 to 36.9)	0.8349	19.8 (17.2 to 22.6)	21.6 (18.9 to 24.5)	0.4004	0.0157	0.0294

Treated outside hospital by HCP (e.g., non-transport EMS)	8.5 (6.9 to 10.4)	8.3 (6.7 to 10.2)	0.8331	3.1 (1.3 to 7.0)	2.5 (1.0 to 6.1)	0.7293	9.6 (7.7 to 11.8)	9.4 (7.6 to 11.7)	0.8947	0.0065†	0.0031
Treated in ED *without* hospital admission	6.1 (4.8 to 7.8)	6.0 (4.7 to 7.7)	0.8929	1.2 (0.3 to 4.4)	1.8 (0.6 to 5.3)	0.6584	7.1 (5.5 to 9.1)	6.9 (5.3 to 8.8)	0.8145	0.0042†	0.0138
Treated in ED *with* hospital admission	3.5 (2.5 to 4.8)	4.3 (3.2 to 5.8)	0.3661	1.8 (0.6 to 5.3)	1.8 (0.6 to 5.3)	0.9940	3.8 (2.7 to 5.3)	4.8 (3.5 to 6.5)	0.3445	0.2121	0.0906
No external aid (i.e., spontaneously recovered)	4.7 (3.5 to 6.2)	6.7 (5.3 to 8.5)	0.0460	4.9 (2.5 to 9.4)	6.7 (3.8 to 11.7)	0.4883	4.7 (3.4 to 6.3)	6.7 (5.2 to 8.7)	0.0608	0.8927	0.9999
Other/Unknown	7.5 (6.0 to 9.3)	12.0 (10.1 to 14.1)	0.0004†	12.9 (8.6 to 18.9)	14.1 (9.6 to 20.3)	0.6471	6.4 (4.9 to 8.3)	11.5 (9.5 to 13.9)	0.0002†	0.0039	0.3553

T1DM, type 1 diabetes mellitus; T2DM, type 2 diabetes mellitus; SH, severe hypoglycemia; HCP, healthcare provider; EMS, emergency medical services; ED, emergency department; Prosp, prospective observation period (up to one year); Retro, retrospective observation period (past year); CI, confidence interval.
*Retrospective incidence proportions were observed over 1 year; prospective incidence proportions were observed over follow-up for each respondent.
†Significant based on a Bonferroni-adjusted $\alpha=0.0007$, giving a family-wise error rate of $\alpha=0.05$.
‡*z*-tests were used to compare proportions.

Figure 5.1: Retrospective and prospective incidence proportions of SH*, overall and by diabetes type



	Overall (n=978)			T1DM (n=163)			T2DM (n=815)			T1DM versus T2DM	
	Retro. (95% CI)	Prosp. (95% CI)	*p*-value†	Retro. (95% CI)	Prosp. (95% CI)	*p*-value†	Retro. (95% CI)	Prosp. (95% CI)	*p*-value†	Retro. *p*-value†	Prosp. *p*-value†
Total SH	2.41 (2.01 to 2.88)	5.01 (4.15 to 6.05)	<0.0001*	4.60 (3.11 to 6.81)	3.57 (2.49 to 5.11)	0.3447	1.97 (1.61 to 2.40)	5.29 (4.26 to 6.57)	<0.0001*	0.0004*	0.1352
Treated outside hospital by non-HCP (e.g., family/friend)	1.23 (0.99 to 1.54)	2.96 (2.35 to 3.74)	<0.0001*	2.65 (1.58 to 4.44)	2.25 (1.42 to 3.57)	0.6324	0.95 (0.75 to 1.21)	3.10 (2.37 to 4.04)	<0.0001*	0.0005*	0.3216

Treated outside hospital by HCP (e.g., non-transport EMS)	0.24 (0.18 to 0.32)	0.61 (0.43 to 0.88)	0.0001*	0.07 (0.02 to 0.22)	0.08 (0.02 to 0.34)	0.8286	0.27 (0.20 to 0.38)	0.72 (0.50 to 1.04)	<0.0001*	0.0036	<0.0001*
Treated in ED *without* hospital admission	0.13 (0.10 to 0.19)	0.28 (0.19 to 0.42)	0.0064	0.01 (0.003 to 0.05)	0.04 (0.01 to 0.14)	0.3141	0.16 (0.11 to 0.22)	0.33 (0.22 to 0.50)	0.0078	0.0015	0.0008
Treated in ED *with* hospital admission	0.06 (0.04 to 0.10)	0.24 (0.15 to 0.39)	<0.0001*	0.02 (0.007 to 0.09)	0.06 (0.01 to 0.32)	0.4335	0.07 (0.04 to 0.11)	0.28 (0.17 to 0.46)	<0.0001*	0.1281	0.0337
No external aid (i.e., spontaneously recovered)	0.15 (0.10 to 0.24)	0.31 (0.22 to 0.45)	0.0126	0.17 (0.06 to 0.49)	0.12 (0.06 to 0.25)	0.5994	0.15 (0.09 to 0.24)	0.35 (0.23 to 0.54)	0.0069	0.8161	0.0502
Other/Unknown	0.58 (0.39 to 0.89)	0.56 (0.42 to 0.74)	0.8977	1.67 (0.73 to 3.86)	1.02 (0.50 to 2.05)	0.3698	0.37 (0.23 to 0.58)	0.47 (0.35 to 0.63)	0.3055	0.0050	0.0387

T1DM, type 1 diabetes mellitus; T2DM, type 2 diabetes mellitus; SH, severe hypoglycemia; HCP, healthcare provider; EMS, emergency medical services; ED, emergency department; Prosp, prospective observation period (up to one year); Retro, retrospective observation period (past year); CI, confidence interval.
*Significant based on a Bonferroni-adjusted $\alpha=0.0007$, giving a family-wise error rate of $\alpha=0.05$.
†Wald tests were used to compare rates.

Figure 5.2: Retrospective and prospective incidence rates of SH, overall and by diabetes type

5.8 Discussion

Previous epidemiologic data on iatrogenic SH are inadequate to quantify its true frequency. Consequently, we conducted the US-wide iNPHORM study: a real-world, longitudinal survey of Level 3 hypoglycemia. Participant responses were collected anonymously, one-year retrospectively and 12-months prospectively, from a clinically varied, community-based cohort of US residents with T1DM or insulin- and/or secretagogue-treated T2DM (N=978). Individuals were sampled from a probability-based internet panel designed to represent the general US public. Self-reports were returned for eight-plus months by 86% of participants, surpassing retention rates documented in other mailed and online hypoglycemia surveys.(11,16–18)

5.9 Severe hypoglycemia by recovery mode/context

Most current SH surveillance stems from administrative claims and medical records; but, as we show, up to 80% of events are treated outside the healthcare system (10% by non-transport EMS and 70% by non-professional aid [e.g., a family or friend]). Aligning with past research, only 10% of reported SH in our study required a hospital visit, of which <5% resulted in admission. Healthcare-related SH was also significantly more common among T2DM than T1DM respondents, echoing observations by Donnelly et al.(18) Such findings bear important implications for health and economic outcomes.(19,20)

Of note, 4% and 6% of people with T1DM and T2DM, respectively, experienced SH that resolved by spontaneous recovery. Thus, whether the definition of Level 3 SH needs to be revised warrants further research; in its current form, severe events where individuals recovered without the assistance of a third-party risk being misclassified as non-severe.

5.10 Incidence of severe hypoglycemia

Akin to other global surveys of the same duration,(18,21–24) a third of iNPHORM respondents reported one or more past-year SH event(s) at baseline. As expected, IPs were statistically significantly higher in people with T1DM versus T2DM. Nonetheless, this magnitude of difference attenuated over prospective follow-up (*p*-value=0.0404, α=0.0007), countering the longstanding assumption that SH is less common in T2DM than T1DM.(25) Incidence proportions calculated prospectively were markedly equable to past-year baseline estimates, a trend that corroborates former evidence on the durability of annual SH recall of one or a cluster of events.(26)

The baseline IR for total SH fell within range of previous retrospective estimates.(22,27–29) In a manner, such congruity substantiates the credibility of our results and signifies a degree of parity between the distribution of our sample and those of other real-world, retrospective analyses. Nevertheless—despite a virtually unchanged case cohort—the overall IR at study end doubled that reported at baseline (5.01 [95% CI: 4.15 to 6.05] versus 2.41 [95% CI: 2.01 to 2.88] EPPY [*p*-value<0.0001, α=0.0007], respectively).

Variability in recall interval length from baseline to study end may have contributed to the rate difference between observation periods. Remember that, prospectively, SH was captured as often as each month, whereas at baseline, events were captured over the past year. Survey design research clearly correlates enhanced absolute recall performance with decreased recall interval length.(26,30,31) While this contention bolsters the validity of our prospective results, it raises concerns around the utility of a 12-month lookback to estimate SH rates—especially among people with T2DM for whom IRs may be underestimated by 63%.

As with IPs, it is often presumed that SH IRs are lower in T2DM than T1DM; however, analogous to other non-US research (e.g., the InHypo-DM (22) study and Hypoglycemia Assessment Tool program (27)), we identified statistically comparable annual IRs by diabetes type during the prospective phase (*p*-value=0.1352, α=0.0007). A range of factors may underpin this finding including the high percentage of combination insulin-secretagogue users,(33) as well as the relatively long median duration of insulin or secretagogue use in T2DM (approximately 5

years).(16,32) According to the UK Hypoglycaemia Study,(16) people with T2DM taking insulin for >5 years, experience equivalent SH rates as those with T1DM for <5 years.

We also revealed considerably higher prospective IRs for T2DM versus T1DM SH requiring healthcare use, perhaps reflecting the low documented dispensation of glucagon among T2DM Americans.(20,34,35) Moreover, compared to exogenous insulin,(36,37) secretagogues can induce more profound cognitive dysfunction and SH prolongation leading to parenteral therapy and extended in-hospital stays.(38)

Additionally, as we describe in an earlier iNPHORM publication,(39) many participants experienced gaps in routine care because of pandemic, which initially flared in the US around study commencement. Notably, compared to our T1DM cohort, those with T2DM reported increased difficulties testing their blood glucose, monitoring hypoglycemia, and accessing social support to help mitigate event occurrence. Such disruptions may have exacerbated hypoglycemia occurrence among T2DM cases during study follow-up. From March 2020 to study end, 12% of our T1DM cohort reported 78% of all SH, while approximately the same percentage with T2DM reported 92% of events. Conversely, during the year preceding baseline—that is, during the months prior to the pandemic—we observed a steadier distribution of SH by diabetes type.

Our prospective estimates surpass those reported elsewhere in the literature; although, the dearth of prospective research on Level 3 SH inhibits meaningful comparisons of our work. We identified only one other US investigation (N=344; duration: 41.2 [SD: 8.6] weeks), and it enrolled a chiefly male T2DM cohort on stable NPH insulin.(40) Similarly, global prospective data are lacking. Of the ten germane articles we identified, (16,18,23,24,27,40–44) most focused on small, homogeneous, and clinic-based samples. However, given the well-established right-skew of SH,(40,45,46) under- or overrepresentation of certain groups is liable to impose extreme effects on apparent frequencies.(45)

Short observation windows also dominate the prospective evidence base (≤4-weeks). Khunti et al. conducted the largest international study on Level 3 SH (US excluded). However, in their analysis, rates were annualized from only one-month of follow-up.(27) Extrapolation bias can arise when conclusions are drawn beyond the time period of study and, in the case of hypoglycemia, underestimate true event frequency. Clark and Sugrue showed that uncontrolled

Hawthorne effects are strongest during and up to the first eight-weeks of participant monitoring.(47) Contextualizing their findings, the incidence of SH may increase by eight-tenths or more of an SD from just the first to second month of follow-up.

Thus, by methodically emulating real-world US diabetes populations and practice patterns over time, iNPHORM stands to provide the truest representation of event burden to date.

5.11 Study strengths and limitations

Participants were selected using home-based (as opposed to clinic-based) sampling to derive a study population optimally reflective of the general outpatient community with diabetes. Online recruitment of a large, probability-based internet panel—augmented by systematic refreshment (48) and push factors—facilitated sample reach and representativeness. The use of broad eligibility criteria contrasts earlier investigations, which exclude individuals on the basis of insulin dependency and medication regimen,(23,40) diabetes type,(18,21,24) or hypoglycemia risk.(49) Nevertheless, volunteer and survivorship bias cannot be discounted.(50,51) Coverage error due to an overrepresentation of technology-abled Americans may also have distorted results; though, US internet penetration rates are now over 90%.(52) Lastly, we could not objectively verify diabetes diagnoses, A1Cs, prescriptions, or SH-related healthcare use.

To mitigate reporting and ascertainment bias,(5–8,53–55) while also promoting response honesty,(56,57) we collected anonymized data via self-administered questionnaires. Long-term prospective follow-up was instrumental to garner accurate information and reduce false negatives compared to cross-sectional or short-term cohort investigations. Monthly follow-up helped fortify episodic memory (by continually calling events to participants' minds(58)), while curbing the number of SH needing to be remembered. Each questionnaire contained clear case definitions to preëmpt misclassification (e.g., encoding a non-severe event as severe), as well as context-specific cues to enhance recollection of both SH frequencies and type of treatment.(30)

Still, panel conditioning could have influenced the magnitude and direction of reported estimates. Availability bias—conceivably modulated by variability in recall intervals—may also

have led to differential reporting. For example, the higher incidences of healthcare-related SH among T2DM respondents could have increased the distinctiveness, meaning, and, thereby, retrieval of events,(30) as compared to those with T1DM. To protect against erroneous responding, participants could forgo completing any item. Likewise, we included 'Other', and 'Unknown' as possible response options, when appropriate.

Lastly, because IPs inherently discount zero-risk or unobserved periods, it is possible our estimates diverge from true population parameters. On the other hand, IRs allowed us to factor time to event, differences in follow-up duration, and changes in exposure or eligibility status; although, we had to assume constant SH probability for each recall period. Adjusted incidences to understand the causal factors of SH were beyond the scope of this descriptive study and will be analyzed in subsequent articles.

5.12 Final remarks

To our knowledge, iNPHORM is the first prospective, long-term analysis of Level 3 SH incidence in the US. Leveraging online, self-assessment, we demonstrate that routine care registries grossly underestimate complete, real-world SH burden.

In total, SH events were disturbingly common. Across iNPHORM participants, 33% reported having ≥1 SH, and the rate was 5 EPPY. Strikingly, besides the number of EMS encounters, we found no statistical differences in SH frequencies by diabetes type. Our finding emphasizes the importance of prioritizing clinical hypoglycemia prevention, not only in people with T1DM but also T2DM. Based on our results, 91% of Level 3 events may be prevented with the scrupulous management of only 13% of insulin and/or secretagogue users. Future iNPHORM prognosis studies will focus on ways to identify this "13%" in diverse outpatient practice.

The wealth of registry-based analyses in the US has left a paradoxical poverty of valid epidemiologic data on real-world hypoglycemia. Backfilling this gap, our investigation affords ground-breaking insight into the true frequency of Level 3 SH. We contend such data are essential to the bedrock of sound clinical intervention and public health decision-making.

5.13 Acknowledgments

iNPHORM was funded by an investigator-initiated grant from Sanofi Canada. Sanofi played no part in the study design; collection, analysis, and interpretation of data; writing of the report; or the decision to submit this manuscript for publication. All authors take responsibility for the integrity of the data and the accuracy of the data analysis. The authors are distinct from those at IIS who programmed iNPHORM questionnaires.

5.14 Conflicts of interest

AR-L received grants from Sanofi; paid presentation fees from Eli Lilly, Sanofi, and Novo Nordisk; and consultant fees from Eli Lilly and Novo Nordisk. JEB, ARK, BLR, GZ, NK, SWB, and KT have no conflicts of interest to report. SBH received grants from Sanofi, Eli Lilly, Novo Nordisk, Janssen, AstraZeneca, Abbott, Boehringer Ingelheim, Juvenile Diabetes Research Foundation, Lawson, and the Canadian Institutes of Health and Research; as well as consultant and advisory board fees from Sanofi, Eli Lilly, Novo Nordisk, Janssen, AstraZeneca, Abbott, and Boehringer Ingelheim. SBH is involved in clinical trials sponsored by Eli Lilly, Novo Nordisk, AstraZeneca, and Boehringer Ingelheim.

5.15 Summary

Using longitudinal data from the iNPHORM study, Chapter 5 characterizes and quantifies the frequency of real-world iatrogenic SH in an unselected cohort of adult Americans with T1DM and T2DM taking insulin and/or secretagogues. Annualized IRs and IPs over follow-up are reported. To our knowledge, this is the first long-term, prospective analysis of Level 3 SH epidemiology in the US. Chapter 6 describes how iNPHORM data were analyzed to develop and internally validate a robust, clinically practical one-year risk model for recurrent SH.

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Chapter 6

6 Predicting severe hypoglycemia

Chapter 6 describes the development and internal validation of a prognostic model for one-year recurrent SH risk using long-term, primary data from the US-wide iNPHORM panel survey. The contents of this chapter, along with its related materials, have been prepared as an original manuscript for submission to *Diabetes Care*.

6.1 Manuscript title

Development and validation of a real-world model to predict one-year, recurrent Level 3 severe hypoglycemia risk in Americans with diabetes (the iNPHORM study)

Running title: Predicting severe hypoglycemia risk (iNPHORM)

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6.4 Keywords

diabetes; type 1 diabetes mellitus; type 2 diabetes mellitus; adverse event; hypoglycemia; severe hypoglycemia; insulin; secretagogue; internet survey; model; prediction; real-world; risk; risk model; risk prediction; prognostic prediction model; decision support; survival analysis

6.5 Twitter summary

Some #diabetes meds can cause severe #hypoglycemia: a low blood sugar event that can be fatal.

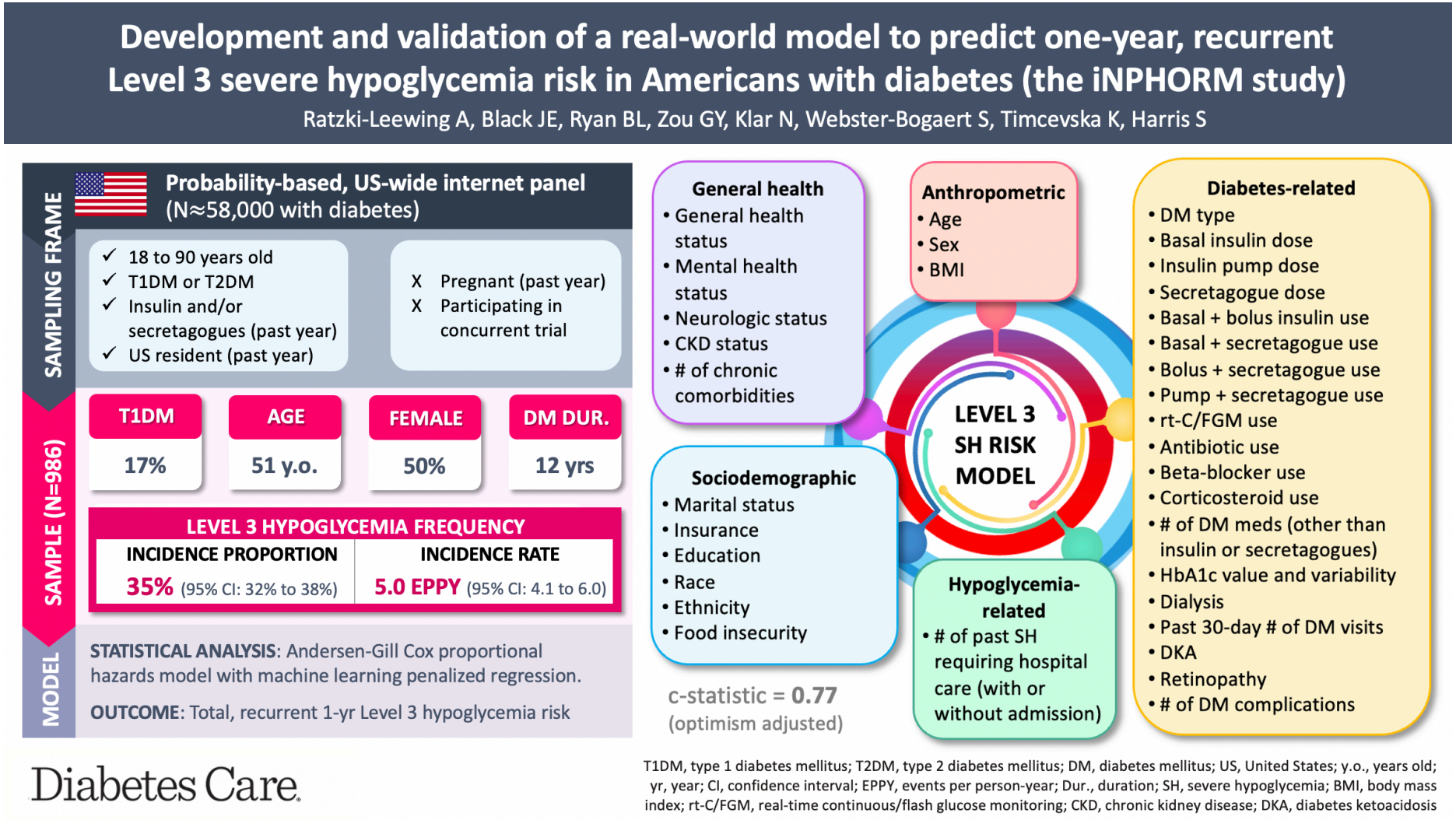
In the USA 🇺🇸, rates of #hypoglycaemia keep going ⤴️ and ⤴️

As #providers, we CAN & MUST do better at preventing lows.

But HOW?

Check out our latest #iNPHORM article 👇

6.6 Visual abstract



T1DM, type 1 diabetes mellitus; T2DM, type 2 diabetes mellitus; DM, diabetes mellitus; US, United States; y.o., years old; yr, year; CI, confidence interval; EPPY, events per person-year; Dur., duration; SH, severe hypoglycemia; BMI, body mass index; rt-C/FGM, real-time continuous/flash glucose monitoring; CKD, chronic kidney disease; DKA, diabetes ketoacidosis

6.7 Introduction

At the heart of diabetes management is not just achieving glycemic control, but ensuring it is done safely. Severe hypoglycemia is the most dangerous adverse event of insulin and/or secretagogues. Yet, despite a growing therapeutic armamentarium, secular trends suggest unabated and even rising event rates. In the US, hypoglycemia-related emergencies already exceed hyperglycemia-related emergencies by >50% (1) and, among older adults, is a leading adverse drug event requiring hospital care.(2) Direct US expenditures for SH hospitalization have reached $5.8 billion (USD) per annum.(3) This figure is compounded by myriad indirect costs and expenses for non-hospital resources, lost productivity (among people with diabetes and their caregivers), treatment inertia, and other downstream sequelae.(4)

Multiple clinical strategies can decrease SH risk; however, approaches to target these interventions in outpatient practice lack precision and nuance.(5) A systematic method to identify patients at elevated SH risk could streamline and potentiate preventive efforts. Nevertheless, most hypoglycemia research focuses on targets of intervention (i.e., causal factors), rather than populations to target (i.e., groups needing intervention). Prognostic modelling is a well-established technique for estimating future event probability. While, in the US, several SH models exist, all derive from secondary sources limited by poor representativeness and data gaps that can discount the ~96% (6) of events not requiring healthcare.

Real-world, prospective self-reported data—specifically collected via self-administered questionnaires—are essential to generate a felicitous model that duly complements modern diabetes management. First, self-report is necessary to accurately assess Level 3 SH: the current diagnostic gold standard set by the IHSG and the ADA.(7) Second, primary research supports the comprehensive capture of real-world participant information over time, including patient-reported outcome measures (PROMs) and other variables commonly absent in pre-existing datasets.

From 2020 to 2021, we conducted a 12-month, population-based survey of a large internet panel designed to represent the American public. Analyzing these data, we aimed to develop and

internally validate a pragmatic one-year model of recurrent SH for real-world, outpatient contexts. This is the first prognostic investigation of SH to draw on primary evidence, and the only in the US to comply with established hypoglycemia reporting standards.

6.8 Research design and methods

6.8.1 Study design

iNPHORM was a US-wide, 12-wave panel survey of adults with T1DM or T2DM taking insulin and/or secretagogues. We constructed the iNPHORM prognostic model according to the Transparent Reporting of a Multivariable Prediction Model for Individual Prognosis or Diagnosis statement (8) and recommendations by the Prognosis Research Strategy Group.(9) The present article complies with STrengthening the Reporting of OBservational studies in Epidemiology (STROBE) guidelines.(10)

6.8.2 Sampling and data collection

Participants were recruited from a well-established, probability-based internet panel designed to represent the US public.(11) American residents (past year), 18 to 90 years old, with a self-reported diagnosis of type 1 or 2 diabetes and taking insulin, secretagogues, or both (past year) could enrol. Those involved in a concurrent interventional study or pregnant (at screening or past year) were ineligible. We calculated a sample size of N=958 to produce a risk model with 46 predictors (Appendix 17); this target was inflated to N=1250 to accommodate participant discontinuance.(12)

A random subset of the internet panel was emailed an invitation to participate; those interested clicked a button to receive a link to a screening questionnaire. To enrol, eligible respondents had to provide consent, complete a baseline questionnaire, and register to receive 12-monthly follow-ups. Recruitment continued until we reached 1250 enrollees (i.e., *subpanel A*). Those in *subpanel A* who did not complete the first follow-up were withdrawn and systematically refreshed with

new participants (i.e., *subpanel B*). *Subpanel B* was sampled and enrolled in the same way as *subpanel A* but from a different, random subset of the internet panel.

Each subpanel was monitored for 12 months (*subpanel A*: February 2020 to January 2021; *subpanel B*: April 2020 to March 2021). Collectively, individuals in *subpanel A* who completed Wave 1, and all those in *subpanel B* comprised the *iNPHORM longitudinal panel*. Push factors (i.e., precontacts, reminders, and honoraria) were distributed to promote retention. Participants and data collection were managed by IIS.(11) Wave responses were tethered by a random, unique ID assigned at enrolment.

6.8.3 Instruments and measures

iNPHORM questionnaires were constructed by A.R.-L., B.L.R., and S.B.H. for completion in English on internet-equipped devices (e.g., computer, phone, tablet). Web automation facilitated visual appeal, accessibility, and navigation. Materials were pretested and piloted prior to roll-out.

Self-reported sex assigned at birth (female, male, other) and gender (female, male, self-identify in another way, prefer not to disclose); diabetes type; and insulin and/or secretagogue regimen were measured at screening—these responses were retained for consenting individuals. At baseline, anthropometric and sociodemographic variables were captured. Self-assessed questions of race (multi response option items) and ethnicity were based on definitions and categories used by the US Census Bureau (2020) and the CDC. Lifestyle/behavioural and clinical variables were also evaluated, as well as SH frequency, mode/context of recovery (e.g., hospitalization), IAH, and use of rt-C/FGM. Monthly, we collected data on SH frequency, eligibility, and other mutable factors (e.g., medications, A1C, and rt-C/FGM use). Follow-up questionnaires had to be submitted within seven days of their distribution date.

6.8.3.1 Severe hypoglycemia

Each month, we measured SH frequencies since the last time an iNPHORM survey was completed. Conforming to IHSG/ADA guidelines, we defined SH as a ‘Level 3’ low BG event—independent of a glycemic threshold—requiring professional or nonprofessional aid for

recovery.(7) Events could have occurred while awake (daytime) or sleeping/trying to sleep (nocturnal).

6.8.3.2 Candidate prognostic factors

Our aim was to delineate the best set of predictors that collectively explained individual-level SH probability. Nonmodifiable and modifiable candidate factors were selected in consultation with experts and the literature, including previous SH models. Whenever possible, we integrated survey items by the US Census Bureau (2020), the CDC, and validated PROMs.

To increase model usability, we only included factors that, in future uses, could be assessed via 1) EHR data (if available) or, at least, 2) patient self-report. Variables considered expensive or impractical to collect (e.g., biological samples or biospecimens) were down prioritized or ruled out. Candidate factors were categorized according to how easily they could be ascertained in practice. Group 1 consisted of variables likely stored in an EHR (Appendix 18); Group 2, variables not likely stored in an EHR but easily obtainable via verbal self-report (Appendix 19); and Group 3, variables not likely stored in an EHR and obtainable only via self-administered questionnaires (Appendix 20). Groups 1; {1,2}; and {1,2,3} were tested sequentially.

6.8.4 Statistical analysis

6.8.4.1 Cohort characteristics

Analyses were performed on respondents who completed one or more follow-up(s). We calculated retention rates as the ratio of the observed versus maximum number of completed follow-ups for 1) our final sample size and 2) target sample size (N=958). The average length of follow-up and lost-to-follow-up were assessed; we addressed predictor missingness using multiple imputation with chained equations.

Sample characteristics were reported as frequencies and percentages for categorical variables, and as means and SDs or medians and IQRs for continuous variables. Crude IPs were calculated

alongside Wilson's CIs for binomial proportions, and IRs alongside negative binomial CIs given the known overdispersed distribution of SH.(13) As participants could become ineligible throughout follow-up, rates were offset for observation periods of zero-risk defined as: 1) no insulin or secretagogue use, 2) pregnancy (right censored), 3) concurrent trial involvement, and/or 4) non-US residence (right censored). Incidence estimates were computed overall and by diabetes type.

6.8.4.2 Model construction

Development

Three models were developed consecutively: Model 1 tested candidate variable Group 1, Model 2 tested {1,2}, and Model 3, {1,2,3}. One-year SH risk was computed for combined daytime and nocturnal events to improve precision and decrease misclassification bias. Adjusting for time-dependent covariates, within-person dependence, and right censoring, we used Andersen and Gill's Cox proportional hazards regression for recurrent events.(14) Zero-risk periods were subtracted from total time-at-risk. Multiple imputation accounted for interval censoring.(15)

Penalized regression minimized dimensionality and overfitting. Candidate variables contributing little to no information were biased to zero and dropped from the model using LASSO machine learning. Factors with parameter estimates greater than zero, regardless of *p*-value, were retained in the final model. Corresponding 95% CIs were calculated from 200 cluster bootstrapping procedures (16) within each multiply imputed dataset [m=10]). We tested linearity assumptions for all continuous variables and two- and three-way interactions between basal, bolus, and secretagogue use.

Validation

Cluster bootstrap resampling was used to test the reproducibility and optimism-corrected performance of our models. First, the apparent performances of Models 1, 2, and 3 were evaluated for each multiply imputed dataset. All model estimation steps were executed on a

bootstrapped sample drawn from this imputed cohort. An optimism estimate equal to the difference between the bootstrapped sample and the imputed cohort was calculated to measure performance. This process was repeated 200 times to yield a stable optimism estimate, which when subtracted from the apparent performance, approximates the optimism-corrected performance. We gauged discrimination using the Harell's c-statistic (per convention: >0.7='good'; >0.8='excellent').

6.8.5 Ethical considerations

Before recruitment, we obtained ethics approval from the Western University Health Sciences Research Ethics Board (Project ID: 112986; December 17, 2019). Individuals were asked to read a Letter of Information prior to enrolling. Personally identifiable data (e.g., email addresses) were collected to monitor participants over follow-up; only deidentified data were transferred by IIS to Western University.

6.8.6 Data and resource availability

Complete details regarding the design and implementation of iNPHORM can be found in the study protocol (12) and on ClinicalTrials.gov (NCT04219514; January 7, 2020). The dataset generated during and analyzed in the current study are available from the corresponding authors upon reasonable request.

6.9 Results

6.9.1 Cohort characteristics

See Appendix 21 for a flow diagram of sample recruitment and participation. Of the *iNPHORM longitudinal panel* (N=1206), 986 (81.8%) completed one or more follow-up(s). Compared to our final sample size, the retention rate was 86.2% (85.6% completed ≥8 follow-ups with 66.1% completing all 12); compared to our target sample size, it was 97.4%. The average prospective

observation period was 9.74 (SD: 3.19) months, and less than 25% of participants were lost to follow-up. Missingness is summarized in Appendix 22.

Sample characteristics are reported in Table 6.1. The mean age was 51 (SD: 14.3) years, 50.4% were female (49.6% male), and 83% had type 2 diabetes. Overall, the median diabetes duration was 12 (IQR: 14) years. All individuals with type 1 diabetes reported taking insulin (without secretagogues); among type 2 diabetes participants, 38% were on insulin (without secretagogues), 38% on secretagogues (without insulin), and 24% on insulin plus secretagogues. About a quarter (26%) reported an A1C value ≥8.1% (65 mmol/mol).

Table 6.2 summarizes SH frequencies, overall and by diabetes type. The IP during follow-up was 35.1% (95% CI: 32.2% to 38.1%), while the rate was 4.97 (95% CI: 4.13 to 5.99) events per person-year. Appendix 23 graphs the probability of event-free survival over follow-up for each sequential SH event; Appendix 24 describes the distribution of event occurrence.

Table 6.1: Sample characteristics, overall and by diabetes type

Table 6.1a. Anthropometric and sociodemographic

Characteristic	Overall (n=986)	T1DM (n=164)	T2DM (n=822)
Age, mean (SD)			
	51 (14.3)	44.8 (14)	52.2 (14.1)
Sex assigned at birth, n (%)			
Male	489 (49.6)	57 (34.8)	432 (52.6)
Female	497 (50.4)	107 (65.2)	390 (47.5)
BMI (kg/m^2), median (IQR)			
	30.37 (12)	26.36 (6.9)	31.52 (12.4)
Missing/unknown	6 (0.6)	0	6 (0.7)

Marital status, n (%)			
Partnered	620 (62.9)	95 (57.9)	525 (63.9)
Divorced, separated, widowed	162 (16.4)	25 (15.2)	137 (16.7)
Never married	203 (20.6)	44 (26.8)	159 (19.3)
Missing/unknown	1 (0.1)	0	1 (0.1)
Highest education achieved, n (%)			
Grade 8, some high school, or high school diploma	172 (17.4)	30 (18.3)	142 (17.3)
College degree or some college	632 (64.1)	105 (64)	527 (64.1)
Degree beyond first college degree	182 (18.5)	29 (17.7)	153 (18.6)
Annual household income (gross), n (%)			
<$25,000	168 (17)	22 (13.4)	146 (17.8)
$25,000 to $54,999	269 (27.3)	39 (23.8)	230 (28)
$55,000 to $84,999	212 (21.5)	53 (32.3)	159 (19.3)
$85,000 to $114,999	150 (15.2)	24 (14.6)	126 (15.3)
$115,000 to $144,999	65 (6.6)	7 (4.3)	58 (7.1)
≥$145,000	113 (11.5)	15 (9.2)	98 (11.9)
Missing/unknown	9 (0.9)	4 (2.4)	5 (0.6)
Health insurance, n (%)			
Private insurance plan	423 (42.9)	88 (53.7)	335 (40.8)
Government-assistance plan	320 (32.5)	47 (28.7)	273 (33.2)
Multiple/other insurance plans	225 (22.8)	24 (14.6)	201 (24.5)
Out-of-pocket (i.e., no coverage)	18 (1.8)	5 (3.1)	13 (1.6)
Race, n (%)			
White alone	784 (79.5)	149 (90.9)	635 (77.3)

Part-white multiracial	37 (3.8)	3 (1.8)	34 (4.1)
Non-white	143 (14.5)	10 (6.1)	133 (16.2)
Missing/unknown	22 (2.2)	2 (1.2)	20 (2.4)
Ethnicity, n (%)			
Hispanic, Latino/a, or Spanish	68 (6.9)	6 (3.7)	62 (7.5)
Not Hispanic, Latino/a, or Spanish	918 (93.1)	158 (96.3)	760 (92.5)
Missing/unknown	0	0	0
Experiencing food insecurity, n (%)			
Yes	198 (20.1)	30 (18.3)	168 (20.4)
No	788 (79.9)	134 (81.7)	654 (79.6)
Missing/unknown	0	0	0
Requires assistance with health materials, n (%)			
I always need help	18 (1.8)	2 (1.2)	16 (2)
I often need help	42 (4.3)	4 (2.4)	38 (4.6)
I sometimes need help	92 (9.3)	12 (7.3)	80 (9.7)
I rarely need help	217 (22.0)	37 (22.6)	180 (21.9)
I never need help	617 (62.6)	109 (66.5)	508 (61.8)

T1DM, type 1 diabetes mellitus; T2DM, type 2 diabetes mellitus; SD, standard deviation; BMI, body mass index; IQR: interquartile range.

Table 6.1b. Diabetes status and management

Characteristic	Overall (n=986)	T1DM (n=164)	T2DM (n=822)
Diabetes type, n (%)			
T1DM	164 (16.6)	164 (100)	0

T2DM	822 (83.4)	0	822 (100)
Diabetes duration, median (IQR)			
	12 (14)	26 (21)	11 (12)
Missing/unknown	9 (0.9)	1 (0.6)	8 (1)
Number of diabetes visits (past 30 days), n (IQR)			
	4 (2)	4 (2)	4 (2)
Missing/unknown	0	0	0
Most recent A1C value, n (%)			
Less than or equal to 7%	326 (33.2)	59 (35.9)	267 (32.5)
7.1% to 8%	337 (34.3)	60 (36.6)	277 (33.7)
8.1% to 9%	163 (16.5)	23 (14)	140 (17)
Greater than or equal to 9.1%	95 (9.6)	20 (12.2)	75 (9.1)
Missing/unknown	65 (6.6)	2 (1.2)	63 (7.7)
Variability of A1C (index of variation), median (IQR)			
	0 (0.30)	0 (0.25)	0 (0.30)
Basal insulin use, n (%)			
	438 (44.4)	89 (54.3)	349 (42.5)
Basal insulin dose (units)*, median (IQR)			
	40 (55)	28 (32)	46 (56)
Bolus insulin use, n (%)			
	312 (31.6)	85 (51.8)	227 (27.6)
Bolus insulin dose (units)*, median (IQR)			
	30 (48)	25 (25)	30 (60)
Insulin pump use, n (%)			

	193 (19.6)	71 (43.3)	122 (14.8)
Insulin pump dose (units)*, median (IQR)			
	22 (51)	45 (40)	4.5 (24)
Duration of insulin use (years), median (IQR)			
	6.58 (12.08)	25.58 (22.16)	5.00 (7.50)
Secretagogue use, n (%)			
	510 (51.7)	0	510 (62)
Secretagogue dose (mg)*, median (IQR)			
Short-acting sulphonylurea	10 (15)	-	10 (15)
Intermediate-acting sulphonylurea	5 (17)	-	5 (17)
Long-acting sulphonylurea	5 (7)	-	5 (7)
Meglitinide	12 (96)	-	12 (96)
Combination secretagogues†	500 (955)	-	500 (955)
Duration of secretagogue use (years), median (IQR)			
	4.50 (5.75)	-	4.50 (5.75)
Basal and bolus insulin use, n (%)			
	272 (27.6)	81 (49.4)	191 (23.2)
Basal insulin and secretagogue use, n (%)			
	101 (10.2)	0	101 (12.3)
Bolus insulin and secretagogue use, n (%)			
	55 (5.6)	0	55 (6.7)
Basal and bolus insulin and secretagogue use, n (%)			
	43 (4.4)	0	43 (5.2)
Insulin pump and secretagogue use, n (%)			

	82 (8.3)	0	82 (10)
Number of diabetes medications (other than insulin or secretagogues), n (%)			
0	358 (36.3)	143 (87.2)	215 (26.2)
1	424 (43)	17 (10.4)	407 (49.5)
2	151 (15.3)	4 (2.4)	147 (17.9)
3	36 (3.7)	0	36 (4.4)
4 or more	14 (1.4)	0	14 (1.7)
Missing/unknown	3 (0.3)	0	3 (0.4)
rt-C/FGM device use, n (%)			
	211 (21.4)	81 (49.4)	130 (15.8)
Missing/unknown	5 (0.5)	1 (0.6)	4 (0.5)
Received diabetes training, n (%)			
	534 (54.2)	122 (74.4)	412 (50.1)
Missing/unknown	0	0	0

T1DM, type 1 diabetes mellitus; T2DM, type 2 diabetes mellitus; IQR, interquartile range; rt-C/FGM, continuous/flash glucose monitoring.
*Among those treated using the medication.
†Combination secretagogues: Meglitinide and Biguanide Fixed-Dose Combination or Sulphonylurea and Biguanide Fixed-Dose Combination.
-: Not applicable.

Table 6.1c. Hypoglycemia-related

Characteristic	Overall (n=986)	T1DM (n=164)	T2DM (n=822)
Number of past severe hypoglycemia requiring ED visit or hospitalization, n (%)			
0	906 (91.9)	158 (96.3)	748 (91)
1	32 (3.3)	4 (2.4)	28 (3.4)

2	17 (1.7)	1 (0.6)	16 (2.0)
3	9 (0.9)	0	9 (1.1)
4	3 (0.3)	0	3 (0.4)
5 or more	12 (1.2)	0	12 (1.5)
Missing/unknown	7 (0.7)	1 (0.6)	6 (0.73)
Hypoglycemia awareness, n (%)			
Always aware	229 (23.2)	47 (28.7)	182 (22.1)
Often, sometimes, rarely, never aware	652 (66.1)	117 (71.3)	535 (65.1)
Missing/unknown	105 (10.7)	0	105 (12.8)
Fear of hypoglycemia (Total HFS-II score*), median (IQR)			
	59 (38)	68 (34.5)	57 (37)
Missing/unknown	150 (15.2)	20 (12.2)	130 (15.8)

T1DM, type 1 diabetes mellitus; T2DM, type 2 diabetes mellitus; IQR, interquartile range; HFS-II, Hypoglycemia Fear Survey-II.
*Assessed at Wave 6.

Table 6.1d. Diabetes complications and comorbidities

Characteristic	Overall (n=986)	T1DM (n=164)	T2DM (n=822)
Diabetic ketoacidosis, n (%)			
	137 (13.9)	62 (37.8)	75 (9.1)
Missing/unknown	22 (2.2)	0	22 (2.7)
Amputation of toes, feet, legs, n (%)			
	109 (11.1)	13 (7.9)	96 (11.7)
Missing/unknown	2 (0.2)	0	2 (0.2)
Retinopathy, n (%)			

	197 (20)	60 (36.6)	137 (16.7)
Missing/unknown	16 (1.6)	2 (1.2)	14 (1.7)
Number of other diabetes complications, n (%)			
0	465 (47.2)	85 (51.8)	380 (46.2)
1	271 (27.5)	32 (19.5)	239 (29.1)
2	122 (12.4)	24 (14.6)	98 (11.9)
3	45 (4.6)	12 (7.3)	33 (4)
4	11 (1.1)	3 (1.8)	8 (1)
5	17 (1.7)	3 (1.8)	14 (1.7)
Missing/unknown	55 (5.6)	5 (3.1)	50 (6.1)
Mental health condition, n (%)			
	330 (33.5)	58 (35.4)	272 (33.1)
Missing/unknown	12 (1.2)	0	12 (1.5)
Chronic kidney disease, n (%)			
	107 (10.9)	17 (10.4)	90 (11)
Missing/unknown	11 (1.1)	0	11 (1.3)
Neurologic disorder, n (%)			
	55 (5.6)	11 (6.7)	44 (5.4)
Missing/unknown	8 (0.8)	0	8 (1)
Number of other comorbidities, n (%)			
0	197 (20)	50 (30.5)	147 (17.9)
1	206 (20.9)	41 (25)	165 (20.1)
2	216 (21.9)	20 (12.2)	196 (23.8)
3	147 (14.9)	25 (15.2)	122 (14.8)

4	93 (9.4)	13 (7.9)	80 (9.7)
5 or more	78 (7.9)	8 (4.9)	70 (8.5)
Missing/unknown	49 (5)	7 (4.3)	42 (5.1)

T1DM, type 1 diabetes mellitus; T2DM, type 2 diabetes mellitus

Table 6.1e. Lifestyle-related

Characteristic	Overall (n=986)	T1DM (n=164)	T2DM (n=822)
Alcohol use, n (%)			
Never	149 (15.1)	15 (9.2)	134 (16.3)
In the past but not currently	421 (42.7)	62 (37.8)	359 (43.7)
Less than once a month but at least once per year	106 (10.8)	20 (12.2)	86 (10.5)
1 to 4 times per month	180 (18.3)	45 (27.4)	135 (16.4)
2 to 6 times per week	98 (9.9)	18 (11)	80 (9.7)
Everyday	31 (3.1)	3 (1.8)	28 (3.4)
Missing/unknown	1 (0.1)	1 (0.6)	0
Binge drinking frequency (past 30 days), n (%)			
0 times	856 (86.8)	150 (91.5)	706 (85.9)
1 time	40 (4.1)	7 (4.3)	33 (4)
2 or 3 times	57 (5.8)	5 (3.1)	52 (6.3)
4 or 5 times	20 (2)	0	20 (2.4)
More than 5 times	12 (1.2)	1 (0.6)	11 (1.3)
Missing/unknown	1 (0.1)	1 (0.6)	0
Smoking status, n (%)			

Never used tobacco or other nicotine products	429 (43.5)	88 (53.7)	341 (41.5)
Previously used tobacco or other nicotine products	344 (34.9)	40 (24.4)	304 (37)
Currently uses tobacco or other nicotine products	212 (21.5)	35 (21.3)	177 (21.5)
Missing/unknown	1 (0.1)	1 (0.6)	0
Recreational drug use, n (%)			
Never	676 (68.6)	114 (69.5)	562 (68.4)
In the past but not currently	226 (22.9)	38 (23.2)	188 (22.9)
Less than once a month but at least once per year	7 (0.7)	0	7 (0.9)
1 to 4 times per month	11 (1.1)	1 (0.6)	10 (1.2)
2 to 6 times per week	34 (3.5)	7 (4.3)	27 (3.3)
Everyday	29 (2.9)	4 (2.4)	25 (3)
Missing/unknown	3 (0.3)	0	3 (0.4)
Aerobic exercise, n (%)			
Never	262 (26.6)	26 (15.9)	236 (28.7)
Less than once a month but at least once per year	143 (14.5)	20 (12.2)	123 (15)
1 to 4 times per month	213 (21.6)	41 (25)	172 (20.9)
2 to 6 times per week	310 (31.4)	67 (40.9)	243 (29.6)
Everyday	57 (5.8)	9 (5.5)	48 (5.8)
Missing/unknown	1 (0.1)	1 (0.6)	0
Anaerobic exercise, n (%)			

Never	385 (39.1)	42 (25.6)	343 (41.7)
Less than once a month but at least once per year	147 (14.9)	28 (17.1)	119 (14.5)
1 to 4 times per month	227 (23)	48 (29.3)	179 (21.8)
2 to 6 times per week	189 (19.2)	40 (24.4)	149 (18.1)
Everyday	37 (3.8)	5 (3.1)	32 (4)
Missing/unknown	1 (0.1)	1 (0.6)	0

T1DM, type 1 diabetes mellitus; T2DM, type 2 diabetes mellitus

Table 6.1f. General health

Characteristic	Overall (n=986)	T1DM (n=164)	T2DM (n=822)
Antibiotic use, n (%)			
	77 (7.8)	5 (3.1)	72 (8.8)
Missing/unknown	7 (0.7)	1 (0.6)	6 (0.7)
Beta-blocker use, n (%)			
	211 (21.4)	19 (11.6)	192 (23.4)
Missing/unknown	18 (1.8)	1 (0.6)	17 (2.1)
Corticosteroid use, n (%)			
	77 (7.8)	3 (1.8)	74 (9)
Missing/unknown	6 (0.6)	1 (0.6)	5 (0.6)
Self-rated health, n (%)			
Excellent	44 (4.5)	8 (4.9)	32 (4.4)
Very good	176 (17.9)	49 (29.9)	127 (15.5)
Good	413 (41.9)	53 (32.3)	360 (43.8)

Fair	275 (27.9)	42 (25.6)	233 (28.4)
Poor	78 (7.9)	12 (7.3)	66 (8)
Quality of life (VR-12), median (IQR)			
	67.1 (34.2)	77.7 (29)	65 (34.2)
Missing/unknown	0	0	0

T1DM, type 1 diabetes mellitus; T2DM, type 2 diabetes mellitus; IQR, interquartile range; VR-12, Veterans RAND 12 Item Health Survey.

Table 6.2: Incidence proportions and rates of total (combined daytime and nocturnal) severe hypoglycemia, overall and by diabetes type

	Incidence proportion	Annualized rate
	New events over follow-up* (95% CI)	Events per person-year (95% CI)
Total severe hypoglycemia		
Overall (n=986)	0.35 (0.32 to 0.38)	4.97 (4.13 to 5.99)
T1DM (n=164)	0.45 (0.37 to 0.52)	3.54 (2.48 to 5.06)
T2DM (n=822)	0.33 (0.30 to 0.37)	5.25 (4.23 to 6.51)

T1DM, type 1 diabetes mellitus; T2DM, type 2 diabetes mellitus; CI, confidence interval.
* Incidence proportions do not account for zero-risk or unobserved periods.

6.9.2 Prognostic model

Table 6.3 reports estimated beta coefficients and biased hazard ratios for candidate factors included in each model. The optimism adjusted c-statistic for Model 1 was 0.755. Performance increased in Model 2 (c-statistic: 0.774) and incrementally again in Model 3 (c-statistic: 0.794). The optimism estimate for all models was small (<0.02). Interaction terms for basal/bolus insulin plus secretagogues were selected in each model. We found no non-linear associations. All

models displayed strong calibration, as evidenced by the close approximation of predicted to observed risks (Figure 6.1). Only slight miscalibration was exhibited for Models 2 and 3 among participants with moderate (between 0.2 and 0.4) predicted risks.

For each model, the log cumulative baseline hazard as a function of day of follow-up was approximated by a fractional polynomial function (Appendix 25). For a given individual, annual SH risk can be estimated by their prognostic information and log cumulative baseline hazard at one-year (365 days).

Table 6.3: Beta coefficients and biased hazard ratios estimated by LASSO

	Model 1		Model 2		Model 3	
	Beta coefficient (95% CI)	Biased hazard ratio (95% CI)	Beta coefficient (95% CI)	Biased hazard ratio (95% CI)	Beta coefficient (95% CI)	Biased hazard ratio (95% CI)
Age (10-year increments)	-0.029 (-0.039 to -0.019)	0.971 (0.962 to 0.981)	-0.028 (-0.040 to -0.017)	0.972 (0.961 to 0.983)	-0.017 (-0.027 to -0.005)	0.983 (0.973 to 0.995)
Female sex	-0.067 (-0.279 to 0.153)	0.935 (0.756 to 1.160)	-0.062 (-0.265 to 0.120)	0.940 (0.767 to 1.130)	-0.056 (-0.276 to 0.169)	0.946 (0.759 to 1.180)
BMI (kg/m^2)	-0.012 (-0.028 to 0.000)	0.988 (0.973 to 1.000)	-0.010 (-0.024 to 0.000)	0.990 (0.976 to 1.000)	-0.002 (-0.017 to 0.007)	0.999 (0.983 to 1.010)
Basal insulin use	-	-	-	-	-	-
Basal insulin dose (units)	-0.003 (-0.006 to 0.000)	0.997 (0.994 to 1.000)	-0.003 (-0.006 to 0.000)	0.997 (0.994 to 1.000)	-0.003 (-0.006 to 0.000)	0.997 (0.994 to 1.000)
Bolus insulin use	0.025 (-0.035 to 0.358)	1.020 (0.966 to 1.430)	-	-	-	-
Bolus insulin dose (units)	-	-	-	-	-	-
Insulin pump use	0.091	1.100	-	-	-0.001	0.999

	(0.000 to 0.527)	(1.000 to 1.690)			(-0.281 to 0.236)	(0.755 to 1.270)
Insulin pump dose (units)	-0.002 (-0.010 to 0.001)	0.998 (0.990 to 1.000)	-0.004 (-0.011 to 0.000)	0.996 (0.989 to 1.000)	-0.003 (-0.010 to 0.000)	0.997 (0.990 to 1.000)
Secretagogue use	-0.007 (-0.260 to 0.154)	0.993 (0.771 to 1.170)	-	-	-	-
Secretagogue dose (mg)	0.034 (0.000 to 0.115)	1.030 (1.000 to 1.120)	0.028 (-0.008 to 0.104)	1.030 (0.992 to 1.110)	0.024 (-0.011 to 0.119)	1.020 (0.989 to 1.130)
Basal and bolus insulin use	-	-	-0.002 (-0.304 to 0.026)	0.998 (0.738 to 1.030)	-0.011 (-0.389 to 0.060)	0.989 (0.678 to 1.060)
Basal insulin and secretagogue use	0.207 (0.000 to 0.632)	1.230 (1.000 to 1.880)	0.275 (0.000 to 0.652)	1.320 (1.000 to 1.920)	0.332 (0.000 to 0.702)	1.390 (1.000 to 2.020)
Bolus insulin and secretagogue use	0.010 (-0.137 to 0.823)	1.010 (0.872 to 2.280)	0.069 (-0.003 to 0.737)	1.070 (0.997 to 2.090)	0.074 (-0.061 to 0.505)	1.080 (0.941 to 1.660)
Basal and bolus insulin and secretagogue use	-0.002 (-0.909 to 0.180)	0.998 (0.403 to 1.200)	-	-	-	-
Insulin pump and secretagogue use	0.248 (-0.064 to 0.623)	1.280 (0.938 to 1.860)	0.147 (-0.143 to 0.513)	1.160 (0.867 to 1.670)	-0.008 (-0.402 to 0.232)	0.992 (0.669 to 1.260)

Antibiotic use	0.352 (0.000 to 0.644)	1.420 (1.000 to 1.900)	0.265 (0.000 to 0.516)	1.300 (1.000 to 1.670)	0.292 (0.000 to 0.590)	1.340 (1.000 to 1.800)
Beta-blocker use	0.292 (0.071 to 0.464)	1.340 (1.070 to 1.590)	0.178 (0.000 to 0.389)	1.200 (1.000 to 1.470)	0.175 (0.000 to 0.367)	1.190 (1.000 to 1.440)
Corticosteroid use	0.289 (0.028 to 0.510)	1.340 (1.030 to 1.670)	0.209 (0.000 to 0.420)	1.230 (1.000 to 1.520)	0.120 (-0.099 to 0.323)	1.130 (0.906 to 1.380)
Number of diabetes medications (other than insulin or secretagogues)	-0.118 (-0.233 to -0.005)	0.888 (0.792 to 0.995)	-0.083 (-0.193 to 0.000)	0.921 (0.825 to 1.000)	-0.088 (-0.200 to 0.001)	0.915 (0.819 to 1.000)
A1C						
Less than or equal to 7%	-	-	-	-	0.023 (-0.062 to 0.207)	1.020 (0.940 to 1.230)
7.1% to 8%	-	-	0.014 (-0.050 to 0.161)	1.010 (0.951 to 1.170)	-	-
8.1% to 9%	-0.002 (-0.166 to 0.122)	0.998 (0.847 to 1.130)	-0.009 (-0.173 to 0.099)	0.991 (0.841 to 1.100)	-0.048 (-0.208 to 0.091)	0.953 (0.812 to 1.100)
Greater than or equal to 9.1%	-0.022 (-0.292 to 0.191)	0.979 (0.747 to 1.210)	-0.111 (-0.380 to 0.059)	0.895 (0.684 to 1.060)	-0.107 (-0.379 to 0.068)	0.899 (0.684 to 1.070)

Variability of A1C (index of variation)	0.441 (0.000 to 0.979)	1.550 (1.000 to 2.660)	0.185 (-0.131 to 0.690)	1.200 (0.877 to 1.990)	0.089 (-0.317 to 0.589)	1.090 (0.728 to 1.800)
Number of past severe hypoglycemia events resulting in emergency department use or hospitalization	0.037 (0.019 to 0.077)	1.040 (1.020 to 1.080)	0.037 (0.015 to 0.089)	1.040 (1.020 to 1.090)	0.049 (0.026 to 0.095)	1.050 (1.030 to 1.100)
Currently treated using dialysis	0.735 (0.398 to 1.130)	2.090 (1.490 to 3.090)	0.320 (0.000 to 0.662)	1.380 (1.000 to 1.940)	0.079 (-0.171 to 0.438)	1.080 (0.843 to 1.550)
Number of diabetes visits (past 30 days)	0.182 (0.125 to 0.252)	1.200 (1.130 to 1.290)	0.121 (0.064 to 0.184)	1.130 (1.070 to 1.200)	0.084 (0.025 to 0.145)	1.090 (1.030 to 1.160)
T1DM v. T2DM			-0.183 (-0.557 to 0.000)	0.833 (0.573 to 1.000)	-0.303 (-0.678 to 0.000)	0.739 (0.507 to 1.000)
Duration of diabetes (years)			-	-	-0.001 (-0.015 to 0.007)	0.999 (0.985 to 1.010)
rt-C/FGM device use			0.454 (0.206 to 0.734)	1.570 (1.230 to 2.080)	0.348 (0.113 to 0.640)	1.420 (1.120 to 1.900)
IAH			-	-	-0.003	0.997

			(-0.148 to 0.138)	(0.862 to 1.150)
Mental health condition	0.137 (-0.017 to 0.369)	1.150 (0.984 to 1.450)	0.018 (-0.219 to 0.217)	1.020 (0.803 to 1.240)
Chronic kidney disease	0.170 (-0.023 to 0.483)	1.190 (0.977 to 1.620)	0.089 (-0.137 to 0.402)	1.090 (0.872 to 1.500)
Neurologic disorder	-0.154 (-0.443 to 0.034)	0.857 (0.642 to 1.030)	-0.191 (-0.494 to 0.052)	0.826 (0.610 to 1.050)
Number of other comorbidities	0.027 (-0.017 to 0.074)	1.030 (0.983 to 1.080)	0.018 (-0.037 to 0.064)	1.020 (0.964 to 1.070)
Diabetic ketoacidosis	0.017 (-0.313 to 0.325)	1.020 (0.731 to 1.380)	0.059 (-0.288 to 0.372)	1.060 (0.750 to 1.450)
Amputation of toes, feet, or legs	-	-	-0.002 (-0.387 to 0.292)	0.998 (0.679 to 1.340)
Retinopathy	0.219 (-0.091 to 0.627)	1.240 (0.913 to 1.870)	0.190 (-0.108 to 0.588)	1.210 (0.897 to 1.800)
Number of other diabetes complications	0.115 (0.000 to 0.219)	1.120 (1.000 to 1.250)	0.101 (0.000 to 0.200)	1.110 (1.000 to 1.220)

Marital status, n (%)				
Partnered	-	-	-	-
Divorced, separated, widowed	0.174 (0.000 to 0.488)	1.190 (1.000 to 1.630)	0.209 (-0.009 to 0.500)	1.230 (0.991 to 1.650)
Never married	-0.020 (-0.321 to 0.000)	0.980 (0.725 to 1.000)	-0.018 (-0.320 to 0.026)	0.982 (0.726 to 1.030)
Highest education achieved				
High school, some high school, or Grade 8	0.230 (0.000 to 0.519)	1.260 (1.000 to 1.680)	0.142 (0.000 to 0.493)	1.150 (1.000 to 1.640)
College degree or some college	-0.116 (-0.393 to 0.000)	0.890 (0.675 to 1.000)	-0.178 (-0.398 to 0.000)	0.837 (0.672 to 1.000)
Degree beyond first college degree	-	-	-	-
Income ($15000 increments)	-	-	-0.007 (-0.052 to 0.032)	0.993 (0.950 to 1.030)
Insurance coverage				
Private insurance plan	-0.095 (-0.384 to 0.000)	0.909 (0.681 to 1.000)	-0.030 (-0.297 to 0.073)	0.970 (0.743 to 1.080)

Government-assistance plan	-	-	-	-
Multiple insurance plans and other insurance plans	0.161 (0.000 to 0.422)	1.180 (1.000 to 1.520)	0.136 (-0.028 to 0.365)	1.150 (0.973 to 1.440)
Out-of-pocket (i.e., no insurance coverage)	0.182 (-1.200 to 0.966)	1.200 (0.302 to 2.630)	0.022 (-1.250 to 0.817)	1.020 (0.286 to 2.260)
Race				
Only White	-0.010 (-0.314 to 0.129)	0.990 (0.731 to 1.140)	-0.009 (-0.365 to 0.045)	0.991 (0.695 to 1.050)
Multiracial (White and non-White)	-	-	-0.020 (-0.515 to 0.414)	0.980 (0.598 to 1.510)
Non-white or multiracial (non-White)	0.057 (-0.125 to 0.340)	1.060 (0.882 to 1.410)	0.197 (-0.033 to 0.478)	1.220 (0.967 to 1.610)
Ethnicity				
Hispanic, Latino/a, or Spanish origin	-0.001 (-0.447 to 0.308)	0.999 (0.640 to 1.360)	-0.124 (-0.591 to 0.240)	0.884 (0.554 to 1.270)
Experiencing food insecurity	0.480 (0.240 to 0.752)	1.620 (1.270 to 2.120)	0.264 (0.000 to 0.565)	1.300 (1.000 to 1.760)

Received diabetes education	-	-	-0.066 (-0.313 to 0.115)	0.936 (0.731 to 1.120)
General health status	-0.123 (-0.230 to -0.008)	0.884 (0.795 to 0.992)	-0.113 (-0.232 to 0.000)	0.894 (0.793 to 1.000)
Health literacy			-	-
Alcohol use			-0.090 (-0.195 to 0.000)	0.914 (0.823 to 1.000)
Binge drinking behaviour			0.168 (0.017 to 0.326)	1.180 (1.020 to 1.380)
Smoking status			0.103 (-0.032 to 0.264)	1.110 (0.969 to 1.300)
Recreational drug use			-0.039 (-0.132 to 0.058)	0.962 (0.877 to 1.060)
Aerobic exercise			0.099 (0.000 to 0.204)	1.100 (1.000 to 1.230)
Anaerobic exercise			-0.074 (-0.168 to 0.000)	0.929 (0.845 to 1.000)

Fear of hypoglycemia			0.016 (0.011 to 0.022)	1.020 (1.010 to 1.020)
Quality of life			-0.002 (-0.009 to 0.003)	0.998 (0.991 to 1.000)
c-statistic	0.764	0.792	0.812	
Optimism estimate	0.009	0.018	0.018	
Optimism adjusted c-statistic	0.755	0.774	0.794	

T1DM, type 1 diabetes mellitus; T2DM, type 2 diabetes mellitus; CI, confidence interval; BMI, body mass index; mg, milligrams; rt-C/FGM, continuous or flash glucose monitoring; IAH, impaired awareness of hypoglycemia; HFS-II, Hypoglycemia Fear Survey-II; VR-12, Veterans RAND 12 Item Health Survey.

-: Candidate predictor was not selected by LASSO

Figure 6.1a: Model 1

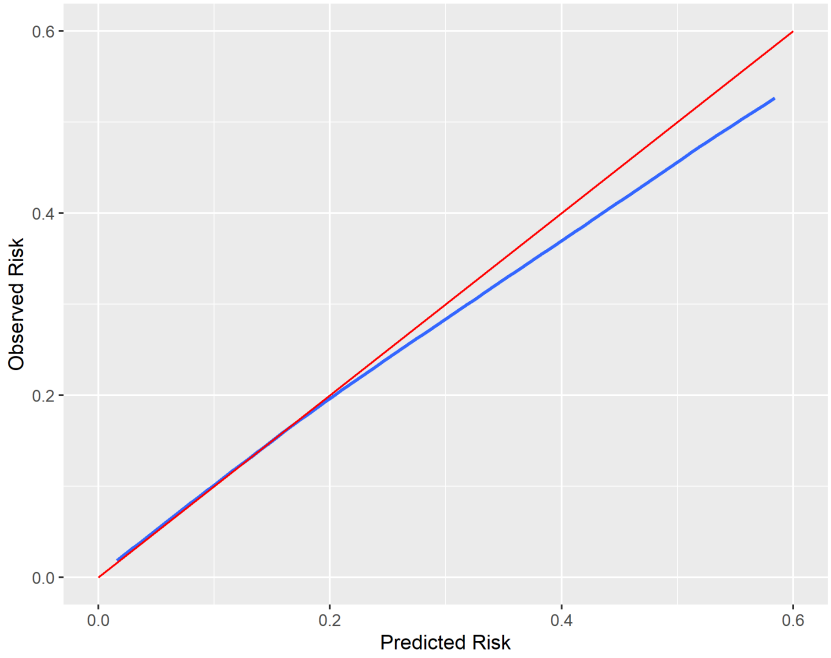


Figure 6.1b: Model 2

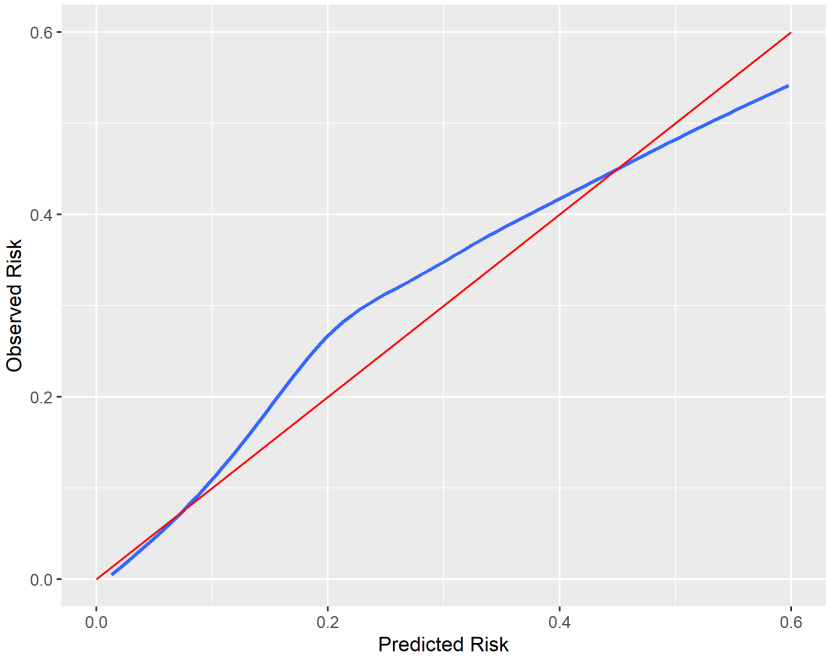


Figure 6.1c: Model 3

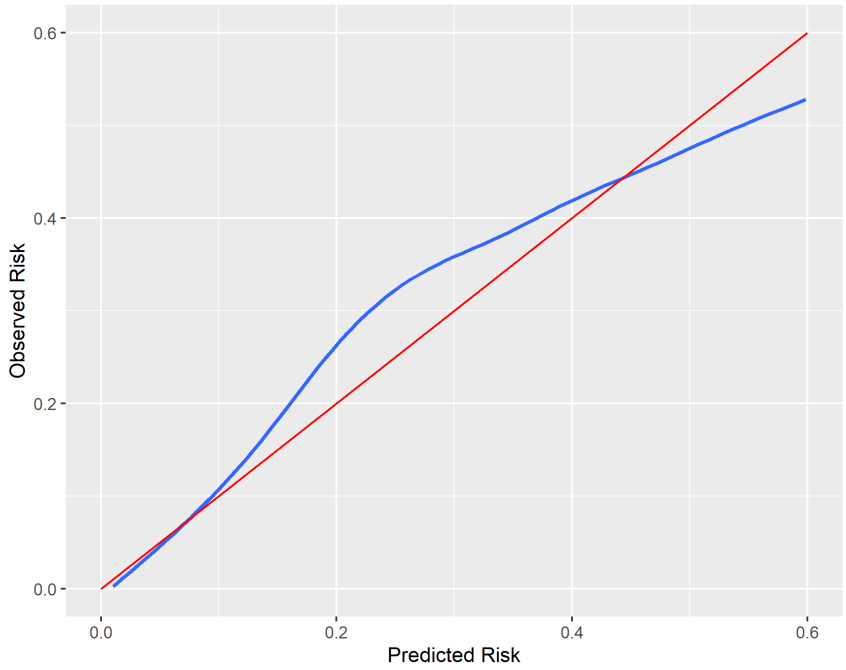


Figure 6.1: Calibration plots displaying agreement between predicted and observed risks

6.10 Conclusions

6.10.1 Principal findings

The iNPHORM study leveraged longitudinal, primary data from a real-world cohort of US residents with diabetes (N=986) to develop and internally validate a pragmatic, one-year risk model of recurrent SH, compatible with outpatient practice. Coinciding with other epidemiologic studies,(17,18) we observed high crude incidences of SH across both diabetes types.

On balance, Model 2 demonstrated ideal discriminative validity and parsimony. The model corroborated associations between SH risk and several demographic variables previously reported in the prognostic literature: age,(19–25) sex,(20,25) marital status,(24) race,(19,20,22–25) ethnicity,(22,25) and highest education achieved (19). Additionally, many clinical variables echoed themes of earlier models: BMI (19,21–25); diabetes type (22) and duration (19–21,24,25); insulin use (basal and/or bolus) and dose (units) (26); secretagogue use and dose (mg)

(25); polypharmacy (21,22,25) (including beta-blocker use (21)); A1C and A1C variability (25); number of past SH resulting in healthcare (19,21–25); comorbidity status (i.e., kidney function),(19,21–23,25) mental health status,(22,23,25) neurologic disorder status (21,23,25)); as well as diabetes-related complication type (i.e., diabetic ketoacidosis,(23,24) amputation,(25) retinopathy (22,24,25)) and number (20,21,23–26).

Numerous novel predictors were identified. Unlike former models,(19–26) combination insulin-secretagogue therapy emerged as a salient predictor. Likewise, we observed unique associations for insulin pump use, rt-C/FGM use, food insecurity, antibiotic and/or corticosteroid use, IAH, insurance coverage, structured diabetes education, and general health status.

The optimism estimate of Model 2 was negligible, indicating a low risk of overfitting. Furthermore, while penalized regression has shown to temper internal performance,(27) we report a strong concordance index equivalent to prior models. Overall, calibration plots demonstrated strong agreement between estimated and actual risks, though Models 2 and 3 overestimated risks slightly among moderate-risk participants. It must be emphasized, however, that these statistics measure model fit, and not systematic errors in participant selection, data collection, or outcome ascertainment. For predictions to be clinically applicable, their accuracy should garner the confidence of the end-user. This requires cautious appraisal of the model's design, limitations, and potential real-world utility. We elaborate on this next.

6.10.2 Contributions to the literature

To our knowledge, iNPHORM is the first primary, prognostic investigation on SH. Other longer-term SH risk models have been developed for outpatient care in the US, but all depend on pre-existing datasets prone to ascertainment bias (such that participants poorly reflect cases in the population). Lagani et al. (24) produced models from the DCCT, and Chow (19) and colleagues (20) from the ACCORD repositories. Karter and colleagues used health service records.(21–23,25,26)

For all its efficiencies, secondary research demands that investigators relinquish control over many key study aspects. To begin, pre-existing sources leave aside variables possibly relevant to

modelling SH risk. Repurposed trial registries, for instance, while supplying high-quality physiologic and disease-specific data, are constrained by narrow questions and designs; metrics may also be too complicated or intensive to practically replicate. Health service records, on the other hand, generally designed for clinical and not research purposes per se, often contain only medical and laboratory data documented over inconsistently timed visits. As a result, records can lack pertinent and accurate detail, especially on events occurring outside the health system. In a recent article, we showed that only 3.8% and 6.4% of SH require hospitalization or ED care, respectively.(6)

Conduct of a panel survey furnished choice over not just what but also how SH-related data were captured in our study. All variables were selected a priori for their clinical relevance; when possible, we adopted previously validated survey items and PROMs. To optimize model precision and predictive power, we only considered variables feasibly (e.g., compatibility with routine methods for collecting clinical information) and reliably obtainable during patient-provider interactions. Numerous nonmodifiable, or otherwise stable, predictors deemed useful in guiding treatment decisions were measured (e.g., age may affect an individual's probability of responding to a certain therapeutic modality). As well, we frequently and regularly evaluated several mutable factors potentially modifiable on the causal pathway of SH occurrence.

Monthly scheduled interwaves over one-year reduced recall and extrapolation errors, while enabling investigation of SH recurrence, contrary to index occurrence like earlier analyses.(23) It further facilitated predictions across a time window sufficient to accommodate preventive action. Distinctively, we defined SH per IHSG/ADA guidelines, encapsulating events requiring and not requiring healthcare. Web-based, self-administered questionnaires were especially critical to this end, helping motivate complete (28) and honest responding.(29) According to data from the InHypo-DM program, 66% of people with diabetes under-report their SH to providers (e.g., due to fear of driver's license revocation, apathy, or sub-optimal medical enquiry); these individuals, compared to those with full SH disclosure, experienced 2.5 times the annual number of events.(30) Mirroring these findings, Pedersen-Bjergaard et al., found 2-3-fold higher SH rates with anonymous, versus onymous, reporting.(31)

Validation studies have substantiated questionnaire-based self-reported SH. One investigation reported a 90% recall accuracy for past-year events.(32) Additionally, McCoy and colleagues revealed strong criterion validity for the effects of self-reported SH on all-cause mortality (33) and quality of life (34). The DCCT and ACCORD trial defined SH using self-report; although, conflicting with current IHSG/ADA reporting standards, each stipulated an auxiliary criterion of blood glucose <2.8mmol/L (50 mg/dL). As advised by guidelines, glucose-defined SH is rarely appropriate: 1) glycemic thresholds for symptom onset vary across patients, and 2) neurologic recovery post-BG normalization typically supplies proof that hypoglycemia occurred.(35)

Adverse effects of selection factors compound information biases in earlier models. Consider risk estimates based on data from the DCCT (24)—a trial that excluded people with a history of SH and IAH. Health service records may afford more inclusive samples, but their real-world representativeness is limited by variance in functionality (e.g., EHR versus claims), setting (fee-for-service versus non-profit), and region. Moreover, arbitrary sample boundaries (e.g., by T1DM (24) and T2DM (19,20,23,25,26), or age group (20,24)) can inhibit transportability.

Ideally, prognostic analyses would apply to the patient profile routinely seen in practice. That is, SH prediction should be possible among all individuals at risk (i.e., any person with T1DM or T2DM taking insulin and/or secretagogues) for all SH events (i.e., requiring and not requiring healthcare). Thus, we employed broad eligibility criteria to align the iNPHORM sample with our target population. Use of a probability-based internet panel plus online survey modes buttressed participant reach and engagement, maximizing our capacity to attain real-world representativeness. The Pew Research Center reports a 90% internet penetration in the US.(36)

6.10.3 Clinical significance

Managing insulin- and/or secretagogue-treated diabetes is a Pyrrhic game of seesaw. On one end, is the imperative to achieve optimal glycemic control. On the other, is the inescapable burden to avoid SH. Various interventions have proven to reduce events in outpatient settings, such as personalized glycemic goals and therapeutic simplification,(5) as well as use of adjuvant technologies.(37) Except, until now, a valid, risk-tailored approach to target these interventions effectively and efficiently was lacking.

Current diabetes practice usually involves a review of patients' SH histories to forecast event probabilities and need for preventive action. Given that records and laboratory data alone are often inadequate, this process can lean heavily on subjective clinical impressions of patients' recounted experiences. However, deliberate SH non-disclosure, coupled by provider under-recognition and exiguous clinical documentation, undermine the validity of medical encounters to apprehend true SH risk. In fact, most all events may go unappreciated by the clinician and, ultimately, unmanaged—in spite of their preventability.

iNPHORM uncovers new insight into the risk of Level 3 SH: the gold standard metric that is not only medically and epidemiologically significant, but also patient important. Earlier risk assessments restricted to "definite" healthcare events—at the expense of the whole spectrum of SH—can underrepresent originated cases and artefactually inflate validity diagnostics.(38) Various biases may, furthermore, lead to inappropriate definitions of the eligible population.

It has been claimed that hospital-based SH constitutes the most severe form of hypoglycemia.(39) However, we argue that it is neither scientifically substantiated, commonsensical, nor ethical to presume that clinically unapparent SH events are less physically or psychosocially harmful to patients than those documented in health records. Behavioural theorists (40) might even contend that SH-related healthcare is more a function of structural- and personal-level forces—e.g., whether an individual has rescue therapy on-hand, a person close by to administer it, or access to medical care—than depth of cerebral dysfunction.

Conversion of the iNPHORM risk equation into a clinic-based tool is on the horizon. In view of this, we designed our model for straightforward implementation in diverse, care contexts. Virtually no restrictions on the target patient population were imposed. A maximally parsimonious model was devised based on low-cost inputs measurable at point-of-care. Simplifying uptake, we prioritized variables normally found in pre-existing health records; nevertheless, in the absence of health records, verbal patient report alone could suffice. Traditional and novel predictors were considered, and modifiable factors were integrated to signal specific patient needs. Finally, because Level 3 SH is optimally quantified using self-administered questionnaires (as compared to verbal report), we excluded it as a potential predictor in our model. Instead, we assessed history of SH-related healthcare (i.e., hospitalization

or ED care); while this variable as an outcome measure is inadequate, as a predictor it is relatively precise and easy to obtain. In this way—no matter how forthcoming the patient or discerning the provider—our model promises to produce a full and accurate depiction of individuals' SH risks.

6.10.4 Limitations and strategies to mitigate them

To foster representativeness, participants were sampled from random subsets of a probability-based source population—systematic refreshment, push factors, and online survey modes bolstered retention. Nevertheless, selection (due to differential panel membership, enrolment, and questionnaire completion) and coverage (due to English-language restriction and poor web literacy/access) biases cannot be discounted. Immortal time bias (e.g., whereby eligibility predicates on survival of previous SH) was not found to appreciably influence our results.

To minimize misclassification bias, we standardized questionnaires; incorporated validated metrics; gave participants seven days to review items and clinical records (e.g., glucose logs) before responding; and, to promote honest responses, requested little personally identifiable data. Still, residual information biases may have attenuated or inflated SH frequency estimates. Notwithstanding, compared to earlier models, we provide a more prudent (even overcautious) assessment of SH risk.

Our risk equation is intended for use in adults living in the US with either T1DM or T2DM who have been taking insulin and/or secretagogues for at least one year. In the case of all prognostic analyses, we caution readers against over-interpreting individual parameter estimates as targets of intervention: predictors are not necessarily causal factors. Model 3 was largely exploratory given that the sample size required to assess Group {1,2,3} exceeded the number of participants in our study. Finally, it is possible that self-reported versus clinically documented data of the same variable may systematically differ. Model assumptions will be detailed in a supplementary statistical analysis protocol. Future research is needed to test the external validity of our model, and its impact on real-world practice and health outcomes.

6.10.5 Final remarks

The ability to predict in whom and how often insulin- and/or secretagogue-induced SH will occur is essential to optimize both the effectiveness and safety of outpatient diabetes care. Prognostic models can enhance SH risk detection and personalized intervention. In the US, several risk assessments exist; however, major methodological shortcomings deter confidence in their accuracy and real-world utility.

This article describes the first primary prognostic analysis of one-year, recurrent Level 3 SH risk defined according to IHSG/ADA guidelines. Our simple yet robust model operates purely on pre-existing EHR data and/or verbal patient report. By shedding crucial light on the insidious burden of events routinely unapparent in conventional practice, we hope to enrich clinical awareness and interventional decision-making. Indeed, each prevented case of SH bears the hope of improving individual well-being and economic costs.

6.11 Acknowledgments

The iNPHORM study was funded through an investigator-initiated grant from Sanofi Canada. Neither Sanofi Global nor Sanofi Canada was involved in the study design; collection, analysis, and interpretation of data; writing of the report; or the decision to submit the paper for publication. All authors confirm their independence from funders and that they had full access to the study data (including statistical reports and tables). They take responsibility for the integrity of the data and the accuracy of the data analysis.

6.12 Conflicts of interest

AR-L received grants and paid fees for presentations from Sanofi and Eli Lilly, and was a consultant at Novo Nordisk and Eli Lilly. SBH is a consultant at, received grants from, and is in the member advisory boards of Sanofi, Eli Lilly, Novo Nordisk, Janssen, AstraZeneca, Abbott, and Boehringer Ingelheim and is involved in clinical studies at Eli Lilly, Novo Nordisk,

AstraZeneca, and Boehringer Ingelheim. SBH also received grants from Juvenile Diabetes Research Foundation, Lawson, and the Canadian Institutes of Health and Research. JEB, BLR, GZ, NK, SW-B, and KT have no conflicts of interest to report. The authors are distinct from the developers/sponsors of the iNPHORM (Investigating Novel Predictions of Hypoglycemia Occurrence Using Real-world Models) questionnaires.

6.13 Authorship contribution

AR-L planned the study, contributed to the discussion, researched data, and wrote the manuscript. JEB researched the data and reviewed/edited the manuscript. BLR, GZ, NK, and SBH contributed to the discussion and reviewed/edited the manuscript. SW-B and KT reviewed/edited the manuscript. All authors reviewed and approved the final version of the manuscript. AR-L is the guarantor of this work and, as such, had full access to all study data (anonymized) and takes responsibility for the integrity of the data and the accuracy of the data analysis.

6.14 Summary

Chapter 6 describes the development and internal validation of a one-year prognostic prediction model for recurrent Level 3 SH in adult Americans with T1DM or T2DM using insulin and/or secretagogues. Our model was designed for relevance and practical implementation in diverse, real-world care contexts. Chapter 7 summarizes, critiques, and conceptualizes the entirety of all contained works and postulates on the future of hypoglycemia research in America and abroad.

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Chapter 7

7 Evaluation and synthesis

The burden of SH is avoidable, but the burden to prevent it is not. This dissertation sought to quantify and predict the true, real-world incidence and risk of iatrogenic Level 3 SH among adults in the US with diabetes taking insulin and/or secretagogues. Specifically, chapter 4 details the protocol of the prospective, longitudinal iNPHORM study. Drawing on these data, chapter 5 characterizes and quantifies the frequency of Level 3 SH, and chapter 6 describes the development and internal validation of a one-year risk model. This final chapter summarizes key findings, proposes future research directions, and concludes with a discussion on the significance of this thesis to general understandings of hypoglycemia.

7.1 Summary of key findings

7.1.1 Designing and implementing iNPHORM

To characterize the epidemiology of Level 3 SH, we undertook a population-based, one-year, US-based panel survey. The primary objectives were to 1) measure real-world Level 3 SH and NSH incidence (daytime and nocturnal) in American adults with T1DM or T1DM prescribed insulin and/or secretagogues, and 2) develop and internally validate prognostic models for SH, NSDH, and NSNH.

Residents of the US (past year), 18 to 90 years old, with T1DM or insulin- and/or secretagogue-treated T2DM (past year) were conveniently sampled from two random subsets of a large, probability-based internet panel designed to represent the general public. We excluded people who were pregnant (at the time of screening or within the previous year) or involved in a concurrent interventional study.

To enrol, individuals had to complete an online screening questionnaire and then, if deemed eligible and after providing consent, a baseline questionnaire. Thereafter, each participant received 12 consecutive follow-ups, which were disseminated on a pre-scheduled calendar basis. Items assessed a range of information related to hypoglycemia occurrence (e.g., severity, timing, frequency, recovery mode) and related factors (anthropometric, sociodemographic, clinical, behavioural, and psychosocial). Strategically timed notifications, reminders, and incentives were emailed over follow-up to mitigate attrition. All study materials were pretested and piloted via semi-structured interviews prior to fielding.

Recruitment and data collection spanned February 2020 to March 2021 (ethics approval was obtained on December 17, 2019). N=1694 completed the screener and baseline questionnaire; n=1206 (71.19%) were followed for 12 months. Relative to our target sample size (N=521), we achieved a participation rate of 179%.

To our knowledge, this is the first hypoglycemia prognostic study in the US to leverage prospective, longitudinal self-report.

7.1.2 Characterizing and quantifying Level 3 severe hypoglycemia

Severe hypoglycemia is the most important iatrogenic diabetes complication; yet in the US, its real-world frequency remains unknown. Addressing this gap, we collected primary, longitudinal data—including 12 months of prospective follow-up—to 1) characterize (i.e., by recovery mode/context) and 2) quantify the IRs and IPs of guideline-defined (‘Level 3’) SH.

iNPHORM is a US-wide, 12-wave ambidirectional panel survey (2020–2021). Adults (18–90 years old) with T1DM or insulin- and/or secretagogue-treated T2DM were recruited from a probability-based internet panel. Participants completing one or more follow-up questionnaire(s) were analyzed.

Among 978 respondents (T1DM: 17%; age: 51 [SD: 14.3] years; male: 49.6%), 60% of SH events did not result in healthcare use and <5% required hospitalization. Prospectively, one-third of individuals reported ≥1 event(s) (T1DM: 44.2% [95% CI: 36.8%–51.8%]; T2DM: 30.8%

[95% CI: 28.7%–35.1%], p-value=0.0404, α=0.0007); and the IR was 5.01 (95% CI: 4.15–6.05) EPPY (T1DM: 3.57 [95% CI: 2.49–5.11] EPPY; T2DM: 5.29 [95% CI: 4.26–6.57] EPPY). Healthcare-related SH was more common in T2DM than T1DM. In total, >90% of events were experienced by <15% of participants.

iNPHORM is the first long-term and, moreover, prospective investigation of US Level 3 hypoglycemia epidemiology. Our results underscore the importance of participant-reported data to ascertain the complete spectrum of population SH burden. Events were alarmingly frequent and concentrated in a small subsample.

7.1.3 Modelling Level 3 severe hypoglycemia risk

Building on the foregoing research, we developed and internally validated a real-world prognostic model for Level 3 SH compatible with outpatient care. Again, data were analyzed from the subset completing one or more follow-up(s). One-year recurrent SH risk was modelled using Andersen-Gill Cox proportional hazards and penalized regression with multiple imputation. Candidate variables were selected for their clinical relevance and feasibility.

A total of 986 participants (T1DM: 17%; male: 49.6%; age: 51 [SD:14.3]) were analyzed. Across follow-up, 35.1% (95% CI: 32.2% to 38.1%) reported one or more SH, and the annual event rate was 4.97 (95% CI: 4.13 to 5.99). Our final model demonstrated strong discriminative validity and parsimony (optimism corrected c-statistic: 0.77). We identified numerous anthropometric predictors (e.g., age, and body mass index); sociodemographic predictors (e.g., marital status, race, ethnicity, insurance coverage, education, food insecurity); and clinical predictors (e.g., diabetes type; number, type, and dose of diabetes medications; real-time continuous/flash glucose monitoring use; A1C value and variability; number of past SH requiring hospital care; type and number of comorbidities and complications; number of diabetes healthcare visits [past 30-days]; general health status).

Implementation of our model could potentiate risk-tailored strategies that reduce real-world SH occurrence and overall diabetes burden.

7.2 Overarching limitations

The limitations of each study are appraised in their respective chapters (see § 4.83, 5.83, and 6.84). However, regarding the composite work, certain shortcomings warrant elaboration.

First, to achieve bias reduction, iNPHORM participants were drawn from a panel that was developed using probability-based sampling techniques and modified quotas. Design approaches to balance the participant pool are in most, if not all, cases superior to statistical weighting during analysis.(1) Nonetheless, as individuals were still required to opt-in to the web panel, we cannot discount the potential for self-selection (2) or nonresponse (3) bias.

Period effects of COVID-19 are also expected to have impacted prospective results (e.g., via retention/attrition bias or increasing the true probability of SH). Thus, the extent to which our results generalize, or will generalize, "post"-outbreak is unclear. Exploratory temporal analyses of SH trends in relation to pandemic waves are currently underway.

Third, self-administered questionnaires were strategically implemented to promote participant reach, engagement, and honesty. However, while self-report is a conceivably effective, and arguably ideal, method to elicit information on Level 3 SH and related experiences, no validated instruments exist. Furthermore, we could not collect data on actual healthcare utilization to corroborate reported hospital/EMS-related SH events, nor could we verify self-reported health metrics (e.g., c-peptide confirmed diabetes diagnosis, A1C, prescriptions) with objective clinical or laboratory data. Resulting misclassification may have distorted crude estimates, leading to spurious associations.

7.3 Overarching strengths

Notwithstanding its limitations, iNPHORM is bolstered by numerous strengths.

First and foremost, this study represents the first global attempt to prognosticate Level 3 SH risk. As such, the investigation draws critical awareness to Level 3 SH as a pressing health concern that requires reformative clinical action. Chapters 4, 5, and 6 each address key research gaps (see

§ 4.8.3, 5.11, and 6.10.4, respectively) and, collectively, endeavour to remediate critical barriers to SH prevention.

The novel execution of a long-term, prospective study on Level 3 SH in the US enabled unprecedented insight into population-based event burden. Primary data collection permitted tailored and thorough measurement of prespecified variables relevant to the primary research aims. As well, it facilitated a recall structure designed to reduce error (e.g., short intervals over a long duration). Repeated observations over a one-year period helped clarify temporal sequencing, including analyses of mutable factors, and their impacts on SH incidence. These advantages are underlined by high retention and completion rates throughout follow-up.

Third, data were collected from a community-based sample selected independent of healthcare system affiliation or use. Broad eligibility criteria supported the real-world representivity of results and, in turn, applicability to the general US population with diabetes.

Last, the iNPHORM risk model integrates diverse, clinically relevant variables, flexibly compatible with routine practice. Shrinkage techniques were used to develop a parsimonious model, while avoiding overly-confident estimates that can result from conventional selection techniques (e.g., backward elimination or forward selection).(4) Additionally, parameters were estimated using multivariable regression to enhance feasible application in real-world practice settings. Internal validation demonstrates a projected success in similar populations.

7.4 Proposed future studies

7.4.1 Evolution of the iNPHORM risk model

Implementation of the iNPHORM model could help overcome the myriad pitfalls and deficiencies of current prognostic modalities, ushering improved risk-tailored intervention and glycemic outcomes. To this end, prospective validation in similar and different populations/contexts will be conducted to ensure reproducibility and generalizability. Testing its feasibility and acceptability (e.g., clinical benefit, ease-of-use, compatibility with existing workflow, and integration at point-of-care) is imperative, though, far from trivial. This next

phase of iNPHORM will involve a collaborative undertaking by clinicians, implementation scientists, and trialists.

7.4.2 Continuity of the broader iNPHORM research program

The iNPHORM dataset presents an opportunity for future research outgrowth focused on SH-related questions previously unaddressed in the literature. Such analyses could uncover new and important pathways to improved diabetes care and, ultimately, population-based hypoglycemia reduction in the US. Leveraging iNPHORM, future studies could investigate:

1. The determinants of total Level 3 SH.
2. The determinants of healthcare-related SH.
3. The long-term risk of SH among 2nd generation versus other generation basal insulin analogue users.
4. The effect of rt-C/FGM on long-term SH rates in T1DM and T2DM. A subgroup analysis could test the effect in older-aged individuals.
5. The long-term rates and determinants of IAH.

7.5 Significance and closing remarks

"The physician must be able to tell the antecedent, know the present, and foretell the future—must mediate these things, and two special objects in view with regard to disease, namely, to do good or to do no harm."

(Hippocrates, *Of the Epidemics* (5))

Tight glycemic control can mitigate diabetes-related micro- and macrovascular complications. However, among individuals on an insulin or secretagogue regimen, glycemic optimization is limited by the distressing and potentially lethal barrier of iatrogenic SH. Epidemiologic and trial

data suggest that intensive versus standard glucose-lowering therapy increases the risk of SH by 3–4-fold. (6–9) (10–12) Because of this, some people with diabetes, as well as their care providers, deliberately maintain BG levels above therapeutic targets.(13,14)

Historically, understandings of SH frequency stemmed from landmark diabetes trials. However, highly controlled conditions and strict eligibility criteria that preference younger and healthier participants (e.g., without history of SH or IAH) (15) hamper the generalizability of these investigations. Reviews by Elliot (16) and colleagues (17) found that compared to observational studies, trials produce significantly lower incidence estimates. This, in part, galvanized an increased focus on real-world evidence generation in hypoglycemia. Today, most SH surveillance predicates on administrative claims of health records, likely owing to their ease of access, large populations, and scopious data capture. A recent registry analysis included over 3.5 million patient records.(18)

But seemingly lost in the race for bigger data, was a stack of 20th century papers cautioning against the sole use of hospital records to quantify population-based SH burden.(17,19,20) (17,21,22) It was not until 2017 that the IHSG/ADA released a position statement formally advising that SH (referred to as Level 3 hypoglycemia) be defined as any low BG requiring professional or non-professional aid for recovery.

Nevertheless, the uptake of these guidelines in research remains slow, shadowed by the yet ever-growing body of registry-based studies. In a powerful evidence synthesis, Pedersen-Bjergaard and Thorsteinsson (17) showed that observational studies that define SH as requiring parenteral therapy (i.e., registries) versus third-party assistance (i.e., Level 3) produce even lower incidence estimates than trials that actively exclude people at-risk of hypoglycemia.

Arguably, this knowledge gap has undermined the prioritization of SH prevention and, furthermore, counteracted whatever efforts have or are being made to practice safe glycemic management. Still, hypoglycemia is not recognized by the Healthcare Effectiveness Data and Information Set as a pertinent metric of quality care. And, still, US event incidence remains woefully unabated.

This dissertation offers evidence to redress the long unanswered questions surrounding real-world SH burden and prognosis. Moreover, it aims to supply readers with an understanding that is clinically actionable. As the first prognostic study in the world on Level 3 SH, iNPHORM breaks ground toward a new diabetes care paradigm that rightly embodies the quintessence of *primum non nocere*.

7.6 References

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Appendices

Appendix 1: Letter of approval from the Western University Health Science Research Board

Western Research

Date: 17 December 2019

To: Dr. Stewart Harris

Project ID: 112986

Study Title: INVESTIGATING NOVEL PREDICTIONS OF HYPOGLYCEMIA OCCURRENCE USING REAL-WORLD MODELS (iNPHORM)

Application Type: HSREB Initial Application

Review Type: Delegated

Full Board Reporting Date: 14Janurary2020

Date Approval Issued: 17/Dec/2019 08:41

REB Approval Expiry Date: 17/Dec/2020

Dear Dr. Stewart Harris

The Western University Health Science Research Ethics Board (HSREB) has reviewed and approved the above mentioned study as described in the WREM application form, as of the HSREB Initial Approval Date noted above. This research study is to be conducted by the investigator noted above. All other required institutional approvals must also be obtained prior to the conduct of the study.

Documents Approved:

Document Name	Document Type	Document Date	Document Version
Appendix 1-A PILOT Pilot_Letter of Information Consent	Written Consent/Assent	12/Dec/2019	
Appendix 1-B COHORT Letter of Information Consent	Written Consent/Assent	12/Dec/2019	
Appendix 2-A iNPHORM Screening Questionnaire	Online Survey	11/Nov/2019	
Appendix 2-B iNPHORM Baseline Questionnaire	Online Survey	21/Nov/2019	
Appendix 2-C iNPHORM Follow-up Questionnaire	Online Survey	21/Nov/2019	
Appendix 2-D iNPHORM Follow-up Questionnaire MO6	Online Survey	21/Nov/2019	
Appendix 2-E Feedback Questionnaire-Data Collection Form	Interview Guide	12/Dec/2019	
Appendix 2-E Feedback Questionnaire-Data Collection Form	Other Data Collection Instruments	12/Dec/2019	
Appendix 2-F1 iNPHORM Screening Questionnaire ANNOTATED Feedback Q	Other Data Collection Instruments	21/Nov/2019	
Appendix 2-F2 iNPHORM Baseline Questionnaire ANNOTATED Feedback Q	Other Data Collection Instruments	21/Nov/2019	
Appendix 2-F3 iNPHORM Follow-up Questionnaire ANNOTATED Feedback Q	Other Data Collection Instruments	21/Nov/2019	
Appendix 2-F4 iNPHORM Follow-up Questionnaire MO6 ANNOTATED Feedback Q	Other Data Collection Instruments	21/Nov/2019	
Appendix 2-G Pilot Screening Questionnaire	Online Survey	12/Dec/2019	
Appendix 3-A PILOT - Electronic Invite Email	Email Script	30/Oct/2019	
Appendix 3-A PILOT - Electronic Invite Email	Other Data Collection Instruments	30/Oct/2019	
Appendix 3-B PILOT Screener Eligible Message	Other Data Collection Instruments	16/Sep/2019	
Appendix 3-C PILOT Screener Ineligible Message	Other Data Collection Instruments	16/Sep/2019	
Appendix 3-D PILOT Consent Declined Exit Message	Other Data Collection Instruments	29/Jul/2019	

Appendix 3-E PILOT Consent confirmation Message	Other Data Collection Instruments	16/Sep/2019
Appendix 3-F PILOT Interview Confirmation Email	Other Data Collection Instruments	12/Dec/2019
Appendix 3-G PILOT Interview Declined Email	Other Data Collection Instruments	16/Sep/2019
Appendix 3-H PILOT Reminder Email	Other Data Collection Instruments	21/Nov/2019
Appendix 3-I PILOT Telephone Script-schedule	Other Data Collection Instruments	16/Sep/2019
Appendix 3-J PILOT Notification of Incentive Email	Other Data Collection Instruments	16/Sep/2019
Appendix 3-K PILOT Opt-Out Withdrawal Instructions	Other Data Collection Instruments	29/Jul/2019
Appendix 4-B COHORT Screener Eligible message	Other Data Collection Instruments	21/Nov/2019
Appendix 4-C COHORT Screener Ineligible Message	Other Data Collection Instruments	12/Sep/2019
Appendix 4-D COHORT Consent Given Message	Other Data Collection Instruments	19/Nov/2019
Appendix 4-D-A COHORT Community Consent Message	Other Data Collection Instruments	22/Nov/2019
Appendix 4-D-B COHORT Terms & Conditions Statement	Other Data Collection Instruments	18/Nov/2019
Appendix 4-D-C COHORT Privacy Policy	Other Data Collection Instruments	18/Nov/2019
Appendix 4-E COHORT Consent Declined Message	Other Data Collection Instruments	15/Jul/2019
Appendix 4-F COHORT Baseline Q Completion Message	Other Data Collection Instruments	21/Nov/2019
Appendix 4-F COHORT Baseline Q Completion Message	Other Data Collection Instruments	12/Dec/2019
Appendix 4-G COHORT Baseline Q Break Message	Other Data Collection Instruments	30/Sep/2019
Appendix 4-H COHORT Link to Baseline Q Email	Other Data Collection Instruments	21/Sep/2019
Appendix 4-I COHORT Expiry Baseline Q1 Message	Other Data Collection Instruments	12/Sep/2019
Appendix 4-J COHORT FollowUp Q Heads Up Email	Other Data Collection Instruments	12/Sep/2019
Appendix 4-K COHORT FollowUp Q Notification Email	Other Data Collection Instruments	07/Oct/2019
Appendix 4-L COHORT FollowUp Q Completion Message	Other Data Collection Instruments	12/Sep/2019
Appendix 4-M COHORT FQ Reminder Email	Other Data Collection Instruments	07/Oct/2019
Appendix 4-N COHORT FQ Notification Incentive	Other Data Collection Instruments	01/Oct/2019
Appendix 4-O COHORT Survey Link Expiry Message	Other Data Collection Instruments	12/Sep/2019
Appendix 4-P COHORT Notification Replacement	Other Data Collection Instruments	16/Jul/2019
Appendix 4-Q COHORT FQ6 Heads Up Email	Other Data Collection Instruments	12/Sep/2019
Appendix 4-R COHORT FQ6 Notification Email	Other Data Collection Instruments	07/Oct/2019
Appendix 4-S COHORT FQ6 Reminder Email	Other Data Collection Instruments	07/Oct/2019
Appendix 4-T COHORT FQ6 Completion Message	Other Data Collection	12/Sep/2019

	Instruments	
Appendix 4-U COHORT Notification Draw1 Win	Other Data Collection Instruments	01/Oct/2019
Appendix 4-V COHORT FQ12 Heads Up Email	Other Data Collection Instruments	16/Sep/2019
Appendix 4-W COHORT FQ12 Notification Email	Other Data Collection Instruments	07/Oct/2019
Appendix 4-X COHORT FQ12 Reminder Email	Other Data Collection Instruments	07/Oct/2019
Appendix 4-Y COHORT FQ12 and study completion	Other Data Collection Instruments	16/Sep/2019
Appendix 4-Z COHORT FQ12 Expiry Message	Other Data Collection Instruments	16/Sep/2019
Appendix 4-Z-A COHORT 30 USD Honorarium Email	Other Data Collection Instruments	01/Oct/2019
Appendix 4-Z-B COHORT 75 USD Honorarium Email	Other Data Collection Instruments	01/Oct/2019
Appendix 4-Z-C COHORT Notification Draw2 Win	Other Data Collection Instruments	01/Oct/2019
Appendix 4-Z-D COHORT Registration WebPage	Other Data Collection Instruments	03/Sep/2019
Appendix 4-Z-E COHORT Withdrawal Page	Other Data Collection Instruments	12/Sep/2019
Appendix 4-Z-F COHORT FollowUp Q1 Heads Up Email	Other Data Collection Instruments	12/Dec/2019
Appendix 5 - Cohort Data Collection Timeline	Other Data Collection Instruments	23/Oct/2019
Appendix 6-A PV REPORT - defining criteria	Other Data Collection Instruments	30/Oct/2019
Appendix 6-B PV Report Template	Other Data Collection Instruments	12/Dec/2019
iNPHORM Study Protocol	Protocol	12/Dec/2019

No deviations from, or changes to, the protocol or WREM application should be initiated without prior written approval of an appropriate amendment from Western HSREB , except when necessary to eliminate immediate hazard(s) to study participants or when the change(s) involves only administrative or logistical aspects of the trial.

REB members involved in the research project do not participate in the review, discussion or decision.

The Western University HSREB operates in compliance with, and is constituted in accordance with, the requirements of the TriCouncil Policy Statement: Ethical Conduct for Research Involving Humans (TCPS 2); the International Conference on Harmonisation Good Clinical Practice Consolidated Guideline (ICH GCP); Part C, Division 5 of the Food and Drug Regulations; Part 4 of the Natural Health Products Regulations; Part 3 of the Medical Devices Regulations and the provisions of the Ontario Personal Health Information Protection Act (PHIPA 2004) and its applicable regulations. The HSREB is registered with the U.S. Department of Health & Human Services under the IRB registration number IRB 00000940.

Please do not hesitate to contact us if you have any questions.

Sincerely,

Nicola Geoghegan-Morphet, Ethics Officer on behalf of Dr. Philip Jones, HSREB Vice-Chair

Note: This correspondence includes an electronic signature (validation and approval via an online system that is compliant with all regulations).

Appendix 2: Continuing ethics review - Letter of approval from the Western University Health Science

Western Research

Date: 9 December 2020

To: Dr. Stewart Harris

Project ID: 112986

Study Title: INVESTIGATING NOVEL PREDICTIONS OF HYPOGLYCEMIA OCCURRENCE USING REAL-WORLD MODELS (iNPHORM)

Application Type: Continuing Ethics Review (CER) Form

Review Type: Delegated

REB Meeting Date: 12/Jan/2021

Date Approval Issued: 09/Dec/2020

REB Approval Expiry Date: 17/Dec/2021

Dear Dr. Stewart Harris,

The Western University Research Ethics Board has reviewed the application. This study, including all currently approved documents, has been re-approved until the expiry date noted above.

REB members involved in the research project do not participate in the review, discussion or decision.

Western University REB operates in compliance with, and is constituted in accordance with, the requirements of the TriCouncil Policy Statement: Ethical Conduct for Research Involving Humans (TCPS 2); the International Conference on Harmonisation Good Clinical Practice Consolidated Guideline (ICH GCP); Part C, Division 5 of the Food and Drug Regulations; Part 4 of the Natural Health Products Regulations; Part 3 of the Medical Devices Regulations and the provisions of the Ontario Personal Health Information Protection Act (PHIPA 2004) and its applicable regulations. The REB is registered with the U.S. Department of Health & Human Services under the IRB registration number IRB 00000940.

Please do not hesitate to contact us if you have any questions.

Sincerely,

The Office of Human Research Ethics

Note: This correspondence includes an electronic signature (validation and approval via an online system that is compliant with all regulations).

Appendix 3: Study closure - Letter of approval from the Western University Health Science

Western Research

Date: 3 December 2021

To: Dr. Stewart Harris

Project ID: 112986

Study Title: iNPHORM

Study Sponsor:

Application Type: Study Closure Form

Review Type: Delegated

Date Acknowledgement Issued: 03/Dec/2021

Dear Dr. Stewart Harris,

The Western University Research Ethics Board has reviewed the application, and the closure of this study is acknowledged. The REB file on this study is now officially closed.

Thank you for using the Western Research Ethics Manager System (WREM).

Sincerely,

The Office of Human Research Ethics

Note: This correspondence includes an electronic signature (validation and approval via an online system that is compliant with all regulations).

Appendix 4: Investigating Novel Predictions of Hypoglycemia Occurrence in Real-world Models (iNPHORM) - Tracking Information ClinicalTrials.gov

First Submitted Date	December 19, 2019
First Posted Date	January 7, 2020
Last Update Posted Date	April 13, 2021
Actual Study Start Date	February 10, 2020
Actual Primary Completion Date	March 30, 2021 (Final data collection date for primary outcome measure)
Current Primary Outcome Measures (Submitted: January 7, 2020)	• Incidence proportions and densities of severe hypoglycemia, non-severe daytime hypoglycemia, and non-severe nighttime hypoglycemia [Time Frame: Up to 12 months prospectively] • Self-reported through questionnaires • Risk scores for severe hypoglycemia, non-severe daytime hypoglycemia, non-severe nighttime hypoglycemia [Time Frame: Up to 12 months prospectively] • Investigating Novel Predictions of Hypoglycemia Occurrence Using Real-World Models (iNPHORM) Hypoglycemia Risk Score: Risk scores using the probabilities (0-100%) from our validated multivariable prediction models will be calculated to reflect the degree of risk due to the candidate variables (low to high-risk scores will denote low to high risks of hypoglycemia occurrence, respectively). Any selected ranges of predicted probabilities used as boundaries for risk stratification will be justified. Details relevant to the calculation of subject-specific risks will be reported, including

	the intercepts and betas from the logistic regression models and nomograms.
Original Primary Outcome Measures (Submitted: January 2, 2020)	• Incidence proportions and densities of severe hypoglycemia, non-severe daytime hypoglycemia, and non-severe nighttime hypoglycemia [Time Frame: Up to 12 months prospectively] Self-reported through questionnaires • Risk scores for severe hypoglycemia, non-severe daytime hypoglycemia, non-severe nighttime hypoglycemia [Time Frame: Up to 12 months prospectively] Derived from data captured through questionnaires
Change History	Complete list of historical versions of study NCT04219514 on ClinicalTrials.gov Archive Site
Current Secondary Outcome Measures (Submitted: January 2, 2020)	Exploratory causal estimates of different treatment regimens an hypoglycemia rates [Time Frame: Up to 12 months prospectively] Derived from data captured through questionnaires
Original Secondary Outcome Measures	*Same as current*
Current Other Pre-specified Outcome Measures	*Not Provided*
Original Other Pre-specified Outcome Measures	*Not Provided*
Descriptive Information	
Brief Title	Investigating Novel Predictions of Hypoglycemia Occurrence in Real-world Models

Official Title	Investigating Novel Predictions of Hypoglycemia Occurrence in Real-world Models
Brief Summary	Hypoglycemia is the most common diabetes-related adverse event. However, it is often under-reported to healthcare providers by patients and simultaneously, not often asked about by healthcare providers. As a result, little is known about how often hypoglycemia occurs and consequently, which individuals with diabetes will experience such events. The aims of this study are to determine the real- world occurrence of hypoglycemia and develop/validate real-world risk prediction models for hypoglycemia. These risk prediction models will generate a risk score that indicates an individual's risk for hypoglycemia given their socio-demographic, clinical, and/or behaviour-related characteristics. They can be used to promote clinician awareness around patients' hypoglycemia risks, guide point-of-care and patient decision-making with regard to treatment changes, inform the development and conduct of population-based interventions, and lead to tailored, cost-effective management strategies.
Detailed Description	The overarching purpose of the proposed investigation is to develop and validate three real-world risk prediction models for: 1) severe hypoglycemia, 2) non-severe daytime hypoglycemia, and 3) non-severe nighttime hypoglycemia, that are applicable to the general population with diabetes (Type 1 and Type 2). These prediction models, which will produce risk scores, will be generated using long-term, prospective data on the frequency and multidimensional risk factors of real-world hypoglycemia. Self-reported hypoglycemia data - a pragmatic and significant patient-important outcome in the clinical management of diabetes - will collected in a non-clinical setting as they are crucial to determining the true distributional

	burden of events and impactful avenues for prevention, especially given the known epidemiological challenges of existent data collection strategies (e.g., via RCT- or registry-based designs). The use of real-world data will also enhance the generalizability and thus, clinical value of hypoglycemia risk prediction models. The study will employ an ambidirectional (one-year retrospective and one-year prospective) observational cohort design such that multiple exposures (i.e., risk factors) will be collected and evaluated in relation to the occurrence of an outcome (hypoglycemia events). Participants will be enrolled into a prospective, observational cohort referred to as the 'Diabetes iNPHORM Community'. Data will be collected through online questionnaires administered at baseline (to collect retrospective data) and each month of the one-year prospective period. A pilot test will be conducted prior to the enrollment of participants into the Diabetes iNPHORM Community. The purpose of this pilot test is to test the usability of the online question platform, flow and format of the questionnaires, and the readability of the questions. Participants will be recruited into the pilot test and the observational cohort of the study from a pre-existing online panel representative of the general public that has been developed and managed by Ipsos Interactive Services (IIS), a global leader in survey conduct. All individuals in the pre-existing online panel provided profile information and consented to be approached by IIS and its subsidiary partners to complete surveys. For this study, individuals approached to participate in the pilot tests will not subsequently be invited to participate in the observational cohort.
Study Type	Observational

Study Design	Observational Model: Cohort Time Perspective: Other
Target Follow-Up Duration	*Not Provided*
Biospecimen	*Not Provided*
Sampling Method	Non-Probability Sample
Study Population	Participants will be recruited into the pilot test and the observational cohort of the study from a pre-existing online panel representative of the general public developed and managed by Ipsos Interactive Services (IIS), a global leader in survey conduct. Within the USA, IIS and its subsidiary partners manage a nationwide panel of 65,000+ people with diabetes (~10,000 with T1DM and ~58,000 with T2DM); this panel will serve as the sampling frame for the current investigation. All individuals in the pre-existing online panel provided profile information and consented to be approached by IIS and its subsidiary partners to complete surveys. For this study, individuals approached to participate in the pilot tests will not subsequently be invited to participate in the observational cohort.
Condition	• Hypoglycemia • Diabetes Mellitus, Type 2 • Diabetes Mellitus, Type 1
Intervention	*Not Provided*
Study Groups/Cohorts	*Not Provided*
Publications *	• Ratzki-Leewing A, Ryan BL, Zou G, Webster-Bogaert S, Black JE, Stirling K, Timcevska K, Khan N,

Buchenberger JD, Harris SB. Predicting Real-world Hypoglycemia Risk in American Adults With Type 1 or 2 Diabetes Mellitus Prescribed Insulin and/or Secretagogues: Protocol for a Prospective, 12-Wave Internet-Based Panel Survey With Email Support (the iNPHORM [Investigating Novel Predictions of Hypoglycemia Occurrence Using Real-world Models] Study). JMIR Res Protoc. 2022 Feb 11;11(2):e33726. doi: 10.2196/33726.

- Ratzki-Leewing AA, Ryan BL, Buchenberger JD, Dickens JW, Black JE, Harris SB. COVID-19 hinterland: surveilling the self-reported impacts of the pandemic on diabetes management in the USA (cross-sectional results of the iNPHORM study). BMJ Open. 2021 Sep 2;11(9):e049782. doi: 10.1136/bmjopen-2021-049782.

* Includes publications given by the data provider as well as publications identified by ClinicalTrials.gov Identifier (NCT Number) in Medline.

Recruitment Information

Recruitment Status	Completed
Actual Enrollment (Submitted: May 19, 2020)	1206
Original Estimated Enrollment (Submitted: January 2, 2020)	1250

Actual Study Completion Date	March 30, 2021
Actual Primary Completion Date	March 30, 2021 (Final data collection date for primary outcome measure)
Eligibility Criteria	Inclusion Criteria: • Self-reported diagnosis of T1DM or T2DM • Use of insulin and/or secretagogues for at least one year at the time of enrolment • Living in the United States of America for at least one year at the time of enrolment Exclusion Criteria: • Unable to read and understand English • Currently pregnant or pregnant within the previous year • Currently participating in an interventional clinical trial or research study
Sex/Gender	Sexes Eligible for Study: All
Ages	18 Years to 90 Years (Adult, Older Adult)
Accepts Healthy Volunteers	No
Contacts	*Contact information is only displayed when the study is recruiting subjects*
Listed Location Countries	United States

Removed Location Countries	

Administrative Information			
NCT Number	NCT04219514		
Other Study ID Numbers	112986		
Has Data Monitoring Committee	No		
U.S. FDA-regulated Product	Studies a U.S. FDA-regulated Device Product:	No	
IPD Sharing Statement	Plan to Share IPD:	No	
Responsible Party	Stewart Harris, Western University, Canada		
Study Sponsor	Stewart Harris		
Collaborators	Sanofi		
Investigators	Principal Investigator:	Stewart Harris, MD MPH	Western University
	Principal Investigator:	Alexandria Ratzki-Leewing, PhD(c) MSc	Western University
PRS Account	Western University, Canada		
Verification Date	April 2021		

Appendix 5: Estimated sample size for overall iNPHORM study

This method determines the sample size required to ensure a small expected optimism in the apparent $R^2_{Nagelkerke}$ (i.e., $R^2_{cs}/\max(R^2_{cs})$). First, the shrinkage factor that corresponds to an expected optimism of δ (0.05) in $R^2_{Nagelkerke}$ is calculated using the above calculated $\max(R^2_{cs})$ and an anticipated R^2_{cs} of 0.2:

$$S = \frac{R^2_{cs}}{R^2_{cs} + \delta \times \max(R^2_{cs})}$$
$$S = \frac{0.2}{0.2 + 0.05 \times 0.84} = 0.83$$

Given 25 predictors, the required number of participants to ensure a small expected optimism can be estimated:

$$n = \frac{P}{(S-1)\ln\left(1 - \frac{R^2_{cs}}{S}\right)}$$
$$n = \frac{25}{(0.83-1)\ln\left(1 - \frac{0.2}{0.83}\right)} \cong 521 \text{ participants}$$

Appendix 6: Anthropometric, demographic, situational or environmental, and lifestyle variables

Appendix 6i. Anthropometric variables

Prognostic variable	Questionnaire	Recall time frame	Response type	Measurement unit(s)/ Response categories*	Data type
Height	Baseline	Current	Fill-in response	Feet and inches	Continuous
Weight	Baseline	Current	Fill-in response	Pounds	Continuous
Body mass index	Baseline	Current	Calculated	kg/m^2	Continuous

*Response categories may differ from actual questionnaire.

Appendix 6ii. Demographic variables

Prognostic variable	Questionnaire	Recall time frame	Response type	Measurement unit(s)/ Response categories*	Data type
Living in the US	Screener and all waves	Current	Single response	Yes; No; Don't know	Categorical
US residence	Screener	Current	Drop-down response	State/Territory	Categorical

Stationed at military base	Screener	Current	Single response	Yes; No	Categorical
Age	Screener	Current	Calculated	Years	Continuous
Sex	Screener	Assigned at birth	Single response	Male; Female; Other	Categorical
Gender	Screener	Current	Single response	Male; Female; Identify in another way; Prefer not to disclose	Categorical
Race	Baseline	Current	Multi response	White; Black or African American; Asian; Hispanic, Latino/a, or Spanish origin; Native Hawaiian or other Pacific Islander; American Indian or Alaska Native; Other Additional options if selected 'Asian' or 'Native Hawaiian or other Pacific Islander'	Categorical
Ethnicity	Baseline	Current	Single response	Mexican, Mexican American, Chicano; Puerto Rican; Cuban; Another Hispanic, Latino/a, or Spanish origin (for example: Salvadoran, Dominican, Colombian, Guatemalan, Spaniard, Ecuadorian, etc.); Not of Hispanic, Latino/a, or Spanish origin	Categorical

Marital Status	Baseline	Current	Single response	Married; Divorced; Widowed; Domestic partnership; Separated; Never married	Categorical
Highest level of education	Baseline	Current	Single response	No schooling completed; Grades 1 through 8; Grades 9 through 12, no diploma; Regular high school diploma or GED/alternative credential; College degree or some college; Degree beyond completing first college Bachelor's degree Additional options if selected 'College degree or some college' or 'Degree beyond completing first college Bachelor's degree	Categorical
Served on active duty in the USA Armed Forces	Baseline	Lifetime	Single response	Yes; No	Categorical
Employment status	Baseline, Waves 4, 8, and 12	Current	Single response	Working full-time, including self-employment (25 hours per week or more); Working part-time, including self-employment (less than 25 hours per week); Temporarily laid off; Temporarily unemployed due to a health-related	Categorical

				reason; Unemployed and looking for work; Unemployed and not looking for work; Unable to work due to disability; Going to school; Looking after house/family; Retired	
Duration of employment status	Baseline	Past 12+ months	Single response	For less than 1 month; For 1 month but less than 3 months; For 3 months but less than 6 months; For 6 months but less than 9 months; For 9 months but less than 12 months; For 12 months or longer	Categorical
Number of people in household	Baseline	Current	Single response	1; 2; 3; 4; 5; 6; 7; 8; 9; 10 or more	Categorical
Sources of income (each source must contribute 10% to total household income)	Baseline	Current	Multi response	Wages, salaries, commissions, bonuses, and tips; Income from self-employment; Dividends and interest; Worker's compensation, including Family Medical Leave Act; Employment based retirement program; Military retirement, including VA payments; Social security or other government benefits, not for disability; Social security benefits or other government benefits, specifically for	Categorical

				disability; Child support or alimony; Other (for example: rental income, scholarships)	
Total household income (before taxes and deductions)	Baseline	Past 12 months	Single response	Less than $10,000; $10,000 to less than $25,000; $25,000 to less than $40,000; $40,000 to less than $55,000; $55,000 to less than $70,000; $70,000 to less than $85,000; $85,000 to less than $100,000; $100,000 to less than $115,000; $115,000 to less than $130,000; $130,000 to less than $145,000; $145,000 to less than $160,000; $160,000 to less than $175,000; $175,000 to less than $200,000; $200,000 or more	Categorical
Change in total household income	Waves 4, 8, and 12	Past 4 months	Single response	No longer has a household income; Household income has decreased significantly (decreased by more than half but still has some income); Household income has decreased some (decreased by less than half); Household income is the same; Household income has increased some (increased by less than half);	Categorical

				Household income has increased significantly (increased by more than half)	
Health insurance coverage	Baseline	Current	Single response matrix	Insurance through a current or former employer or union (of participant or family member) that is not a high deductible plan; Insurance purchased directly from an insurance company that is not a high deductible plan; High deductible plan; Medicare; Medicaid, Medical Assistance, or any kind of government-assistance plan; TRICARE; Veterans Affairs; Native American; Health Service; Any other type of health insurance/coverage plan	Categorical
	Waves 4, 8, and 12	Current	Single response matrix 'Yes' / 'No' / 'Don't know' response categories provided for each option	Insurance through a current or former employer or union (of participant or family member) that is not a high deductible plan; Insurance purchased directly from an insurance company that is not a high deductible plan; High deductible plan; Medicare; Medicaid, Medical Assistance, or any kind of government-assistance plan; TRICARE; Veterans Affairs; Native	Categorical

				American Health Service; Consolidated Omnibus Budget Reconciliation Act (COBRA) insurance Any other type of health insurance/coverage plan	
Insurance coverage (other)	Baseline	Current	Fill-in response	Free-form text	String
Duration of insurance coverage	Baseline	Past 12 months	Single response	For less than 1 month; For 1 month but less than 3 months; For 3 months but less than 6 months; For 6 months but less than 9 months; For 9 months but less than 12 months; For 12 months	Categorical
Care received as part of a Health Maintenance Organization (HMO)	Baseline	Current	Single response	Yes; No; Don't know	Categorical
Co-pay assistance	Baseline	Current	Single response	Yes; No; Don't know	Categorical
Healthcare affordability (cost prohibitive)	Baseline	Past 12 months	Single response matrix	Prescription medicine(s); A treatment, such as surgery or other procedure; A medical device or medical equipment; A medical test; An appointment with a	Categorical

			'Yes'/ 'No' / 'N/A' response categories provided for each option	primary care doctor ; An appointment with a specialist; An appointment with a healthcare provider other than a primary care doctor or specialist; Mental healthcare or counseling; Treatment or counseling for alcohol or drug use	
Food insecurity	Baseline	Past 12 months	Single response	Yes; No	Categorical

*Response categories may differ from actual questionnaire.

Appendix 6iii. Situational/environmental variables

Prognostic variable	Questionnaire	Recall time frame	Response type	Measurement unit(s)/ Response categories*	Data type
Geographic area	Baseline	Current	Single response	Urban; Suburban; Rural	Categorical
Living arrangement	Baseline	Current	Multi response	Lives alone; Lives with a spouse or partner; Lives with minor children; Lives with other adult family members; Lives with other people; Lives with pet(s)	Categorical

Neighborhood characteristics	Baseline	Current	Single response matrix 'Poor' / 'Fair' / 'Good' / 'Very Good' / 'Excellent' response categories provided for each option	Overall rating of neighborhood as a place to live; Availability of places to buy healthy food; Ability to get around without driving a car; Availability of recreational facilities, such as parks and playgrounds; Safety from crime and violence; Overall cost of living	5-point Likert
Healthcare proximity (services located close enough to home)	Baseline	Current	Single response matrix 'Yes' / 'No' / 'Don't know' response categories provided for each option	A primary care doctor; A specialist; A healthcare provider other than a primary care doctor or specialist; A pharmacy; A hospital	Categorical

*Response categories may differ from actual questionnaire.

Appendix 6iv. Lifestyle variables

Prognostic variable	Questionnaire	Recall time frame	Response type	Measurement unit(s)/ Response categories*	Data type
Tobacco use	Baseline	Lifetime	Single response	Never; In the past but not currently; Currently	Categorical
Recency of tobacco use	Baseline	Past 12+ months	Single response	Within the past 12 months; 12 months ago, or longer	Categorical
Frequency of tobacco use	Baseline	Current	Single response	Less than once a month but at least once per year; 1 to 4 times per month; 2 to 6 times per week; Everyday	Categorical
Alcohol consumption	Baseline	Lifetime	Single response	Never; In the past but not currently; Currently	Categorical
Recency of alcohol consumption	Baseline	Past 12+ months	Single response	Within the past 12 months; 12 months ago, or longer	Categorical
Frequency of alcohol consumption	Baseline	Current	Single response	Less than once a month but at least once per year; 1 to 4 times per month; 2 to 6 times per week; Everyday	Categorical
Binge drinking behaviour	Baseline	Past 30 days	Single response	0 times; 1 time; 2 or 3 times; 4 or 5 times; More than 5 times	Categorical

Recreational drug use	Baseline	Lifetime	Single response	Never; In the past but not currently; Currently	Categorical
Recency of recreational drug use	Baseline	Past 12+ months	Single response	Within the past 12 months; 12 months ago, or longer	Categorical
Frequency of recreational drug use	Baseline	Current	Single response	Less than once a month but at least once per year; 1 to 4 times per month; 2 to 6 times per week; Everyday	Categorical
Aerobic physical activity	Baseline	Past 12 months	Single response	Never; Less than once a month but at least once per year; 1 to 4 times per month; 2 to 6 times per week; Everyday	Categorical
Anaerobic physical activity	Baseline	Past 12 months	Single response	Never; Less than once a month but at least once per year; 1 to 4 times per month; 2 to 6 times per week; Everyday	Categorical

*Response categories may differ from actual questionnaire.

Appendix 7: Clinical variables

Appendix 7i. Diabetes-related variables

Prognostic variable	Questionnaire	Recall time frame	Response type	Measurement unit(s)/ Response categories*	Data type
Type of diabetes	Screener	Current	Single response	Type 1 diabetes; Type 2 diabetes; Diabetes while pregnant; Don't know; No	Categorical
	Baseline (verifier)	Current	Single response	Type 1 diabetes; Type 2 diabetes	Categorical
Duration of diabetes	Baseline	Current	Calculated	Years	Continuous
A1C value	Baseline	Most recent	Single response	Less than or equal to 7%; 7.1% to 8%; 8.1% to 9%; Greater than or equal to 9.1%; Don't know	Categorical
	All waves	Since last iNPHORM survey was completed	(as listed above)	(as listed above)	(as listed above)
Time since A1C test (If *within* past 12 months)	Baseline	Past 12 month	Single response	Less than 1 month ago; Between 1 month and 3 months ago; Between 3 months and 6 months ago; Between 6 months and 9	Categorical

				months ago; Between 9 months and 12 months ago	
Time since A1C test (If *beyond* past 12 months)	Baseline	Past 12+ month	Calculated	Years	Continuous
	All waves	Since last iNPHORM survey was completed	Calculated	Months	Continuous
Diabetes-related complication	Baseline	Lifetime	Single response matrix 'Yes' / 'No' / 'Don't know' response categories provided for each option	Amputation of toes, feet, or legs; Diabetes ketoacidosis; Foot damage; Gastroparesis; Hyperosmolar hyperglycemic nonketotic coma; Nephropathy; Neuropathy; Retinopathy	Categorical
	All waves	Since last iNPHORM	(as listed above)	(as listed above)	(as listed above)

		survey was completed			
Referral to kidney specialist	Baseline	Past 12 months	Single response	Yes; No	Categorical
	All waves	Since last iNPHORM survey was completed	(as listed above)	(as listed above)	(as listed above)
Dialysis	Baseline	Past 12 months	Single response	Never; In the past but not currently; Currently	Categorical
	All waves	Current	Single response	Yes; No	Categorical
Indicated for dialysis	Baseline and all waves	Lifetime	Single response	Yes; No	Categorical

A1C, Hemoglobin A1c

*Response categories may differ from actual questionnaires

Appendix 7ii. Diabetes medication-related variables

Prognostic variable	Questionnaire	Recall time frame	Response type	Measurement unit(s)/ Response categories*	Data type
Insulin pump use	Screener and all waves	Current	Single response	Yes; No; Don't know	Categorical
Insulin use by type	Screener and all waves	Current	Multi response	Insulin Glargine U300; Insulin Degludec; Basal Insulin (including intermediate and long-acting); Bolus/Prandial (a.k.a. mealtime) Insulin (including rapid- and short-acting); Premixed Insulin; Fixed-Ratio Combination Insulin; Not currently taking any of these insulins	Categorical
Insulin dose for each insulin type/pump	Screener and all waves	Yesterday	Fill-in response	Total daily units	Discrete
Insulin duration for each insulin type/pump	Screener	Past 12+ months	Single response	For less than 1 month; For 1 month but less than 3 months; For 3 months but less than 6 months; For 6 months but less than 9 months; For 9 months but less than 12 months; For 12 months or longer; Don't know	Categorical

	All waves	Since last iNPHORM survey was completed or longer	Single response	Taking insulin type/pump last iNPHORM survey was competed; Started taking insulin type/pump since the last time iNPHORM survey complete	Categorical
Insulin duration for each insulin type/pump (If started taking insulin type/pump since the last time iNPHORM survey was completed	All waves	Since last iNPHORM survey was completed	Calculated	Months	Continuous
Duration of insulin use (in general)	Screener	Lifetime	Single response	For less than 12 months; For 12 months or longer	Categorical
Duration of insulin use (in general) (If used for 12 months or longer)	Baseline	Lifetime	Calculated	Years	Continuous
Secretagogue use by type	Screener and all waves	Current	Multi response	Short-Acting Sulphonylurea; Intermediate-Acting Sulphonylurea; Long-Acting	Categorical

				Sulphonylurea; Meglitinide; Meglitinide and Biguanide Fixed-Dose Combination OR Sulphonylurea and Biguanide Fixed-Dose Combination; Not currently taking any of these secretagogues	
Secretagogue dose for each secretagogue type	Screener and all waves	Yesterday	Fill-in response	Total daily milligrams	Discrete
Secretagogue duration for each secretagogue type	Screener	Past 12+ months	Single response	For less than 1 month; For 1 month but less than 3 months; For 3 months but less than 6 months; For 6 months but less than 9 months; For 9 months but less than 12 months; For 12 months or longer; Don't know	Categorical
	All waves	Since last iNPHORM survey was completed or longer	Single response	Taking secretagogue type the last time iNPHORM survey was completed; Started taking secretagogue type since the last time iNPHORM survey was completed	Categorical
Secretagogue duration for each secretagogue type (If started taking	All waves	Since last iNPHORM survey was completed	Calculated	Months	Continuous

secretagogue type since the last time iNPHORM survey was completed)					
Duration of secretagogue use (in general)	Screener	Lifetime	Single response	For less than 12 months; For 12 months or longer	Categorical
Duration of secretagogue use (in general) (If used for 12 months or longer	Screener	Lifetime	Calculated	Years	Continuous
Insulin and/or secretagogue medication adherence	Baseline	Past 12 months	Single response matrix 'Never' / 'Rarely' / 'Sometimes' / 'Often' / 'Always' response categories provided for each option	Forgot to take insulin and/or secretagogue dose; cut back on insulin and/or secretagogue dose without telling healthcare provider to avoid hypoglycemia; cut back on insulin and/or secretagogue dose without telling healthcare provider to avoid side effects other than hypoglycemia; did not take insulin and/or secretagogue dose at all to avoid hypoglycemia; did not take insulin and/or secretagogue dose at all to avoid side effects other than hypoglycemia; cut back on insulin and/or secretagogue dose without telling	5-point Likert

				healthcare provider because felt blood glucose was under control; did not take insulin and/or secretagogue dose at all because felt blood glucose was under control	
Use of diabetes medications (other than insulin and secretagogues) by type	Baseline and all waves	Current	Multi response	Biguanide; Alpha-Glucosidase Inhibitor; Amylin Analog; Bile Acid Sequestrant; GLP-1 Receptor Agonist; Dipeptidyl Peptidase-4 (DPP-4) Inhibitor; DPP-4 Inhibitor and Biguanide Fixed-dose Combination OR DPP-4 Inhibitor and Thiazolidinedione Fixed-dose Combination; SGLT2 Inhibitor; SGLT2 Inhibitor and Biguanide Fixed-dose Combination; SGLT2 Inhibitor and DPP-4 Inhibitor Fixed-Dose Combination; Thiazolidinedione; Thiazolidinedione and Biguanide Fixed-Dose Combination; Thiazolidinedione and Sulphonylurea Fixed-Dose Combination; Not currently taking any of these diabetes medication	Categorical

A1C, Hemoglobin A1c

*Response categories may differ from actual questionnaires

Appendix 7iii. Diabetes management-related variables

Prognostic variable	Questionnaire	Recall time frame	Response type	Measurement unit(s)/ Response categories*	Data type
Visits with healthcare provider where diabetes was discussed	Baseline	Past 12 months	Single response	0; 1; 2; 3; 4; 5; 6; 7; 8; 9; 10; 11; 12; More than 12 visits	Categorical
	All waves	Since last iNPHORM survey was completed	Single response	0; 1; 2; 3; 4; 5; 6; More than 6 visits	Categorical
Visits with healthcare provider where hypoglycemia was discussed	Baseline	Past 12 months	Single response	Every visit; Most visits; Some visits; Only a few visits; No visits	5-point Likert
	All waves	Since last iNPHORM survey was completed	(as listed above)	(as listed above)	(as listed above)

Use of blood glucose monitoring device	Baseline	Current	Single response matrix 'Yes' / 'No' / 'Don't know' response categories provided for each option	Self-monitoring blood glucose meter Continuous or flash glucose monitoring device	Categorical
Use of a continuous or flash glucose monitoring device	All waves	Current	Single response	Yes; No; Don't know	Categorical
Frequency of blood glucose testing if using self-monitoring blood glucose meter	Baseline	Past 12 months	Single response	Three or more times a day; Twice a day; Once a day; 2 to 6 times per week; 1 to 4 times per month; Less than once per month; Did not check blood glucose levels using a self-monitoring blood glucose meter	Categorical
Time of routine blood glucose testing if using	Baseline	Current	Single response matrix	Upon awakening and before first meal; Around mealtimes; Right before bed; Before	Categorical/ String

self-monitoring blood glucose meter			'Yes' / 'No' response categories provided for each option	taking diabetes medications; At another time (Free-form-text)	
Circumstances of routine blood glucose testing if using self-monitoring blood glucose meter	Baseline	Current	Single response matrix 'Yes' / 'No' / 'N/A' response categories provided for each option	During or after experiencing a *hypo*glycemia event; During or after experiencing a *hyper*glycemia event; A change in diabetes medication routine; A change in work schedule Engaging in physical activity; Traveling when driver; Traveling when not the driver; Variation in food intake; Experiencing a short-term illness; Other (Free-form-text)	Categorical/ String
Duration of continuous or flash glucose monitoring device use	Baseline	Past 12+ months	Single response	Less than 1 month ago; Between 1 month and 3 months ago; Between 3 months and 6 months ago; Between 6 months and 9 months ago; Between 9 months and 12 months ago; More than 12 months ago	Categorical
	All waves	Since last iNPHORM survey was	Single response	Using a continuous or flash glucose monitoring device the last time I completed an iNPHORM survey; I started using a	Categorical

		completed or longer		continuous or flash glucose monitoring device since the last time I completed an iNPHORM survey; Don't know	
Duration of continuous or flash glucose monitoring device use (If started using a continuous or flash glucose monitoring device since the last time an iNPHORM survey was completed)	All waves	Since last iNPHORM survey was completed	Calculated	Months	Continuous
Structured diabetes education	Baseline	Lifetime	Single response	Yes; No	Categorical
Health literacy[†]	Baseline	Current	Single response	Modified BRIEF: Health Literacy Screening Tool (1); 3-item survey	5-point Likert
Sick day plan	Baseline	Lifetime	Single response	Yes; No	Categorical
Use sick day plan	Baseline	Pro re nata	Single response	Always; Often; Sometimes; Rarely; Never	5-point Likert

A1C, Hemoglobin A1c
*Response categories may differ from actual questionnaires
†Patient-reported outcome

Appendix 7iv. General health-related variables

Prognostic variable	Questionnaire	Recall time frame	Response type	Measurement unit(s)/ Response categories*	Data type
Pregnancy	Screener	Current or Past 12 months	Single response	Yes; No; Don't know	Categorical
	All waves	Current	(as listed above)	(as listed above)	(as listed above)
Enrolled in interventional clinical trial or research study	Screener and all waves	Current	Single response	Yes; No; Don't know	Categorical
Health-related quality of life†	Baseline	Past 4 weeks	Single response	VR-12 © (2,3); 12-item survey	3-, 5-, and 6-point Likert
Self-rated health†	Baseline	Current	Single response	Self-rated health; 1-item survey (4)	5-point Likert

Chronic co-morbidity	Baseline	Lifetime	Single response matrix 'Yes' / 'No' / 'Don't know' response categories provided for each option	Bone, joint, or muscle problem; Cancer; Cardiovascular condition; Chronic kidney disease; Chronic liver failure or liver disease; Eating disorder; Gastrointestinal disease; HIV/AIDS; Hypertension; Mental health condition; Neurological disorder; Physical impairment; Respiratory condition; Stroke or transient ischemic attack	Categorical
Number of prescriptions medications for chronic co-morbidity	Baseline	Current	Fill-in response	Number of prescription medications	Discrete
Chronic condition that impacts hypoglycemia management	Baseline	Current	Single response	Yes; No	Categorical
Use of corticosteroids	Baseline	Current	Single response	Yes; No; Don't know	Categorical
Duration of corticosteroids	Baseline	Past 12+ months	Single response	For less than 1 month; For 1 month but less than 3 months; For 3 months but less than 6 months; For 6 months but less than 9	Categorical

				months; For 9 months but less than 12 months; For 12 months or longer	
Use of beta-blockers	Baseline	Current	Single response	Yes; No; Don't know	Categorical
Duration of beta-blockers	Baseline	Past 12+ months	Single response	For less than 1 month; For 1 month but less than 3 months; For 3 months but less than 6 months; For 6 months but less than 9 months; For 9 months but less than 12 months; For 12 months or longer	Categorical
Use of antibiotics	Baseline	Current	Single response	Yes; No; Don't know	Categorical
Duration of antibiotics	Baseline	Past 12+ months	Single response	For less than 1 month; For 1 month but less than 3 months; For 3 months but less than 6 months; For 6 months but less than 9 months; For 9 months but less than 12 months; For 12 months or longer	Categorical
Use of corticosteroids, beta-blockers, antibiotics	All waves	Current	Multi response	Corticosteroids; beta-blockers; Antibiotics	Categorical
Duration of corticosteroids	All waves	Since last iNPHORM survey was	Single response	Taking medication type the last time completed an iNPHORM survey; Started	Categorical

		completed or longer		taking medication type since the last time completed an iNPHORM survey	
Duration of corticosteroids (If started corticosteroids since the last time an iNPHORM survey was completed)	All waves	Since last iNPHORM survey was completed	Calculated	Months	Continuous
Duration of beta-blockers	All waves	Since last iNPHORM survey was completed or longer	Single response	Taking medication type the last time completed an iNPHORM survey; Started taking medication type since the last time completed an iNPHORM survey	Categorical
Duration of beta-blockers (If started beta-blockers since the last time an iNPHORM survey was completed)	All waves	Since last iNPHORM survey was completed	Calculated	Months	Continuous
Duration of antibiotics	All waves	Since last iNPHORM survey was	Single response	Taking medication type the last time completed an iNPHORM survey; Started	Categorical

		completed or longer		taking medication type since the last time completed an iNPHORM survey	
Duration of antibiotics (If started antibiotics since the last time an iNPHORM survey was completed)	All waves	Since last iNPHORM survey was completed	Calculated	Months	Continuous

A1C, Hemoglobin A1c
*Response categories may differ from actual questionnaires
†Patient-reported outcome

Appendix 8: COVID-19-related variables*

Appendix 8i. COVID-19 infection status

Prognostic variable	Questionnaire	Recall time frame	Response type	Measurement unit(s)/ Response categories†	Data type
COVID-19 symptoms and epidemiologic exposure	Sub-panel A: Waves 2-12 Sub-panel B: Waves 1-12	Since last iNPHORM survey was completed	Single response matrix 'Yes' / 'No' response categories provided for each option	Cough, difficulty breathing, and/or fever (over 100 degrees Fahrenheit); Symptoms typical of COVID-19 such as sore throat, headache, tiredness, or muscle aches and pains; Had close contact with someone who has been tested and is confirmed to have COVID-19; Had close contact with someone who has been tested for COVID-19 and does not know the results of the test yet; Had close contact with someone who is ill with cough and/or fever that travelled outside of the US prior to feeling ill; Travelled outside of the US	Categorical
COVID-19 diagnosis	Sub-panel A: Waves 2-12	Since last iNPHORM survey was completed	Single response	Confirmed by a test from a healthcare professional; Suspected but not confirmed by a test from a healthcare professional; Neither confirmed nor suspected	Categorical

	Sub-panel B: Waves 1-12				

*The COVID-19 sub-questionnaire was administered first to Sub-panel A at Wave 2 (April 2020)
†Response categories may differ from actual questionnaire

Appendix 8ii. Community containment because of COVID-19 infection/situation

Prognostic variable	Questionnaire	Recall time frame	Response type	Measurement unit(s)/ Response categories†	Data type
Social/physical distancing or shelter-in-place	Sub-panel A: Waves 2-12 Sub-panel B: Waves 1-12	Since last iNPHORM survey was completed	Single response	Always; Often; Sometimes; Rarely; Never	5-point Liker
Self-quarantine or self-isolation	Sub-panel A: Waves 2-12 Sub-panel B: Waves 1-12	Since last iNPHORM survey was completed	Single response	Currently in self-quarantine/self-isolation; Previously in self-quarantine/self-isolation; Not been in self-quarantine/self-isolation	Categorical

*The COVID-19 sub-questionnaire was administered first to Sub-panel A at Wave 2 (April 2020)
†Response categories may differ from actual questionnaire

Appendix 8iii. Impact of COVID-19 situation on financial well-being

Prognostic variable	Questionnaire	Recall time frame	Response type	Measurement unit(s)/ Response categories[†]	Data type
Impact of COVID-19 situation on employment status, total household income, or health insurance income	Waves 4, 8, and 12	Current/Past 4 month	Single response matrix 'Yes' / 'No' response categories provided for each option	Current employment status has been impacted; Total household income within the past 4 months has been impacted; Current health insurance coverage has been impacted	Categorical
Impact of COVID-19 situation on economic well-being in general	Waves 4, 8, and 12	Past 4 months	Fill-in response	Free-form-text	String

[*]The COVID-19 sub-questionnaire was administered first to Sub-panel A at Wave 2 (April 2020)
[†]Response categories may differ from actual questionnaire

Appendix 8iv. Impact of COVID-19 situation on diabetes management and outcomes

Prognostic variable	Questionnaire	Recall time frame	Response type	Measurement unit(s)/ Response categories[†]	Data type
Impact of COVID-19 situation on various aspects glycemic management	Sub-panel A: Waves 2-12 Sub-panel B: Waves 1-12	Since last iNPHORM survey was completed	Single response matrix '...has been much harder '/ '...has been somewhat harder' / '...has not been impacted' / '... has been somewhat easier' / '...has been much easier' response	Affording rent and other living expenses...; Affording diabetes medication(s)...; Affording test strips and/or sensors...; Retrieving diabetes medication(s) from the pharmacy...; Ensuring enough food to avoid hypoglycemia...; Testing/monitoring blood glucose...; Staying as physically active as usual...; Consulting with healthcare provider(s) about diabetes...;Remembering to take diabetes medication(s) as prescribed...; Monitoring risk of hypoglycemia regularly...; Having enough social support to help manage hypoglycemia...; Feeling in control of hypoglycemia...	5-point Likert

			categories provided for each option		
Impact of COVID-19 situation on drug rationing to preserve medical supplies	Sub-panel A: Waves 2-12 Sub-panel B: Waves 1-12	Since last iNPHORM survey was completed	Single response	Yes; No	Categorical
Impact of COVID-19 situation on drug rationing to avoid hypoglycemia	Sub-panel A: Waves 2-12 Sub-panel B: Waves 1-12	Since last iNPHORM survey was completed	Single response	Yes; No	Categorical
Impact of COVID-19 situation on hypoglycemia frequency	Sub-panel A: Waves 2-12 Sub-panel B: Waves 1-12	Since last iNPHORM survey was completed	Single response	Experienced far more hypoglycemia events; Experienced somewhat more hypoglycemia events; Number of hypoglycemia events has not been impacted; Experienced somewhat fewer hypoglycemia events; Experienced far fewer hypoglycemia events	5-point Likert
Impact of COVID-19 situation on diabetes	Sub-panel A: Waves 2-12	Since last iNPHORM	Fill-in response	Free-form-text	String

management and outcomes	Sub-panel B: Waves 1-12	survey was completed

*The COVID-19 sub-questionnaire was administered first to Sub-panel A at Wave 2 (April 2020)
†Response categories may differ from actual questionnaire

Appendix 9: Hypoglycemia-related variables

Appendix 9i. Hypoglycemia symptoms

Prognostic variable	Questionnaire	Recall time frame	Response type	Measurement unit(s)/ Response categories*	Data type
Symptomology	Baseline	Current	Multi response	Aura; Mood swings; Fatigue; Shakiness; Dizziness; Headache; Sudden hunger; Food cravings; Cravings for sweets; Mental confusion; Depression; Nervousness; Heart palpitations; Blurred vision; Phobias; Cold hands or feet; Outbursts of temper; Crying; Insomnia; Loss of consciousness; Other; None; Don't know	Categorical
	All waves	Since last iNPHORM survey was completed	(as listed above)	(as listed above)	(as listed above)
Impaired awareness of hypoglycemia†	Baseline	Current	Single response	Modified Clarke method; 8-item survey (5)	Categorical
	All waves	Current/Since last iNPHORM	(as listed above)	(as listed above)	(as listed above)

		survey was completed			
	Wave 6	Current	Single response	Gold method; 1-item survey (6)	Categorical

*Response categories may differ from actual questionnaire
†Patient-reported outcome

Appendix 9ii. Non-severe hypoglycemia: nature, frequency, and treatment

Prognostic variable	Questionnaire	Recall time frame	Response type	Measurement unit(s)/ Response categories*	Data type
Total frequency of non-severe hypoglycemia (Question asked separately for daytime non-severe and nocturnal non-severe hypoglycemia)	Baseline	Past 30 days	Fill-in response	Frequency	Discrete
	All waves	Past 30 days or since last iNPHORM	(as listed above)	(as listed above)	(as listed above)

		survey was completed			
Identification of non-severe hypoglycemia (Question asked separately for daytime non-severe and nocturnal non-severe hypoglycemia)	Baseline	Past 30 days	Fill-in single response matrix	Frequencies reported for events identified by: Symptoms without a measured blood glucose value; Measured blood glucose value without symptoms; Both symptoms and a measured blood glucose value; Don't know	Discrete
	All waves	Past 30 days or since last iNPHORM survey was completed	(as listed above)	(as listed above)	(as listed above)
Cause of non-severe hypoglycemia (Question asked separately for daytime non-severe and nocturnal	Baseline	Past 30 days	Multi response	Variation in food intake; Exercise; Incorrect insulin and/or secretagogue use; Other (Free-form-text option); Don't know	Categorical /String

non-severe hypoglycemia)					
	All waves	Past 30 days or since last iNPHORM survey was completed	(as listed above)	(as listed above)	(as listed above)
Methods used to treat non-severe hypoglycemia (Question asked separately for daytime non-severe and nocturnal non-severe hypoglycemia)	Baseline	Past 30 days	Multi response	Juice or a soft drink; Glucose or sucrose taken orally; Candies; A snack; A meal; Other (Free-form-text option); None (Recovered without treatment); Don't know	Categorical /String
	All waves	Past 30 days or since last iNPHORM survey was completed	(as listed above)	(as listed above)	(as listed above)

Use of second treatment because unable to treat non-severe hypoglycemia effectively (Question asked separately for daytime non-severe and nocturnal non-severe hypoglycemia)	Baseline	Past 30 days	Single response	Never, Rarely; Sometimes; Often; Always	5-point Likert
	All waves	Past 30 days or since last iNPHORM survey was completed	(as listed above)	(as listed above)	(as listed above)
Blood glucose level when non-severe hypoglycemia is experienced	Baseline	Current	Fill-in response	mg/dl or less	Continuous
	All waves	Past 30 days or since last iNPHORM	(as listed above)	(as listed above)	(as listed above)

		survey was completed			

*Response categories may differ from actual questionnaire

Appendix 9iii. Severe hypoglycemia: nature, frequency, and treatment

Prognostic variable	Questionnaire	Recall time frame	Response type	Measurement unit(s)/ Response categories*	Data type
Total frequency of severe hypoglycemia (Question asked separately for daytime severe and nocturnal severe hypoglycemia)	Baseline	Past 12 months	Fill-in response	Frequency	Discrete
	All waves	Since last iNPHORM survey was completed	(as listed above)	(as listed above)	(as listed above)

Treatment location of severe hypoglycemia (Question asked separately for daytime severe and nocturnal severe hypoglycemia)	Baseline	Past 12 months	Fill-in single response matrix	Frequencies reported for each of the following: Treated outside of a hospital by a person who is not a healthcare provider; Treated outside of a hospital by a paramedic, doctor, or other healthcare provider; Treated in the emergency department of a hospital. No hospital admission; Treated in the emergency department of a hospital. Hospital admission; Recovered spontaneously; Treated in another way; Don't know	Discrete
	All waves	Since last iNPHORM survey was completed	(as listed above)	(as listed above)	(as listed above)
Frequency of unconsciousness due to severe hypoglycemia (Question asked separately for daytime	Baseline	Past 12 months	Fill-in response	Frequency	Discrete

severe and nocturnal severe hypoglycemia)					
	All waves	Since last iNPHORM survey was completed	(as listed above)	(as listed above)	(as listed above)
Cause of severe hypoglycemia (Question asked separately for daytime severe and nocturnal severe hypoglycemia)	Baseline	Past 12 months	Multi response	Variation in food intake (for example: missed or delayed meals, less carbohydrate intake, etc.); Exercise; Incorrect insulin and/or secretagogue use; Other (Free-form-text option); Don't know	Categorical /String
	All waves	Since last iNPHORM survey was completed	(as listed above)	(as listed above)	(as listed above)
Treatment of severe hypoglycemia (Question asked separately for daytime	Baseline	Past 12 months	Multi response	Glucagon injection; Glucagon nasal spray; Glucose injection; Glucose or sucrose taken orally; Other (Free-form-text option); Don't know	Categorical /String

severe and nocturnal severe hypoglycemia)					
	All waves	Since last iNPHORM survey was completed	(as listed above)	(as listed above)	(as listed above)

*Response categories may differ from actual questionnaire

Appendix 9iv. Hypoglycemia management

Prognostic variable	Questionnaire	Recall time frame	Response type	Measurement unit(s)/ Response categories*	Data type
Self-management behaviour	Baseline	Current	Single response matrix 'Never' / 'Rarely' / 'Sometimes' / 'Often' / 'Always' response categories	Adjust diabetes medications that have been recommended by a healthcare provider to avoid hypoglycemia.; Adjust diabetes medications that have *not* been recommended by a healthcare provider to avoid hypoglycemia.; Monitor risk of hypoglycemia regularly.; Take measures to avoid hypoglycemia when exercising.; Monitor food/carbohydrate intake to avoid hypoglycemia.; Treat hypoglycemia with	5-point Likert

			provided for each option	the appropriate amount of food/carbohydrates.; Check blood glucose level 15 minutes after treating a hypoglycemia event to ensure no longer low.; Keep glucagon on-hand for emergency.	
Hypoglycemia detection because of continuous or flash glucose monitoring device	Baseline	Current	Single response	Detect a higher number of hypoglycemia events while using a continuous or flash glucose monitoring device; Detect the same number of hypoglycemia events while using a continuous or flash glucose monitoring device; Detect a lower number of hypoglycemia events while using a continuous or flash glucose monitoring device; N/A	3-point Likert
	All waves (If started using continuous or flash glucose monitoring device since	Since last iNPHORM survey was completed	(as listed above)	(as listed above)	(as listed above)

	the last iNPHORM survey was completed)				
Social support to help manage hypoglycemia	Baseline	Current	Single response	Yes; No	Categorical
Describe relationship type with social support	Baseline	Current	Fill-in response	Free-form-text	String
Social support lives with respondent	Baseline	Current	Single response	Yes; No	Categorical
Social support's level of commitment	Baseline	Current	Single response	Far too much; Too much; The right amount; Too little; Far too little	5-point Likert
Social support knows how to administer glucagon	Baseline	Current	Single response	Yes; No	Categorical
Fear of hypoglycemia†	Wave 6	Past 6 months	Single response	Hypoglycemia Fear Survey II (HFS-II) (7); 33-item survey	5-point Likert
Modifiable factors of hypoglycemia self-management behaviour†	Wave 6	Current	Single response	InHypo-DM Person with Diabetes Questionnaire (8); 61-item survey	5-point Likert

*Response categories may differ from actual questionnaire
†Patient-reported outcome

Appendix 10: Letter of information and consent emailed to prospective participants of the iNPHORM (Investigating Novel Predictions of Hypoglycemia Occurrence Using Real-world Models) pilot study

Please save/print this letter for your reference before moving to the consent section

Introduction:

Low blood sugar (also known as hypoglycemia) is the most common adverse event of insulin and secretagogue use in people with diabetes. It can result in distressing and sometimes severe physical and social consequences. A better understanding of who is at greatest risk of diabetes-related hypoglycemia, and why, is needed.

The purpose of the iNPHORM study is 1) to understand how often people with diabetes have hypoglycemia; and 2) to build a tool that healthcare providers can use to predict the chance that a given person with diabetes will have hypoglycemia in the future.

The purpose of the **testing phase** of the iNPHORM study is to evaluate the surveys that will be used.

You are invited to participate in the **testing phase** of the iNPHORM study because you are: 1) an existing member of a survey panel consenting to be contacted for research surveys; and 2) have been prescribed insulin or secretagogues to treat your diabetes. The testing phase will take 2 weeks to complete.

What will be requested of me as a participant?

If you choose to participate, your role will be to test and provide your feedback on surveys that have been developed for the iNPHORM study at an online/telephone testing session where an interviewer will ask you questions about the length, clarity, and overall design of the surveys.

You will be asked to complete and provide feedback on:

A survey that will be used to screen people to determine whether they are qualified to participate. This is the same qualification screening survey that you just completed.

A survey that will be used to gather initial information on participants. The survey includes questions about yourself, your general health, diabetes health, medication use, and experience(s) with hypoglycemia.

In addition, you might be asked to review or complete and provide feedback on:

A short survey that will be sent out on a monthly basis to gather updated health information. The survey includes questions about your health, diabetes, medication use, and experience(s) with hypoglycemia.

An email that will notify the iNPHORM participant of the next survey

OR

A survey that will be used to gather information on 1) how hypoglycemia affects emotions; 2) thoughts, feelings, beliefs, and actions around hypoglycemia management; and 3) updated health information including questions health, diabetes, medication use, experience(s) with hypoglycemia.

An email that will notify the iNPHORM participant of the next survey

What will happen during this study?

If, after reading this letter, you consent to participate you will receive a confirmation message. There will be only three people with diabetes involved in this testing phase therefore once three individuals have agreed to participate, no more participants will be enrolled into this study. It is possible that you may submit your information but not be enrolled into this study. If this is the case you will receive a second email informing you that enrollment is full.

Once enrolled, you will receive an email confirming the date of your testing session and how to access the session. You will also receive reminders before the session.

The testing session will be hosted over an online screen-sharing platform and by telephone by a staff person from Ipsos Healthcare who will observe you completing the surveys and obtain your feedback on them. The testing session will take 60- 90 minutes.

Your responses to the original qualification screening survey will be used as part of this study.

To thank you for your time and effort in completing the testing session, you'll receive a $300 honorarium credited to your OpinionSite portal.

What will be the risks and benefits of participating?

You may not directly benefit from participating in this study but your responses will help improve the design of the surveys for future use. There are no major risks associated with participating in this study however, you may be reminded of stressful circumstances when describing your experience(s) with hypoglycemia in these surveys. There is a very minimal risk of privacy breach of the Ipsos servers for the personal identifying data (your phone number, full birthdate) collected as part of the study.

What are my rights as a participant?

Your participation is completely voluntary. You may refuse to answer any survey questions you do not want to answer, or any interview questions by saying "pass".

You do not waive any legal rights by consenting to this study. You have the right withdraw from the study at any time by:

Unsubscribing - clicking on the unsubscribe link at the bottom of any email communication, or

Emailing the moderator at [redacted], or

Telling your interviewer during the interview

By withdrawing, your survey responses and interview responses collected before you leave the study will still be used to improve the surveys. No new information will be collected without your permission.

How will my confidentiality be maintained?

All of your responses will be kept strictly confidential. You will be given a unique participant ID number when you enroll in this study. Your survey responses and interview responses will only be linked to your participant ID number.

OpinionSite will send your responses to the qualification screening survey and your personal identifiers (phone number, full birthdate) to Ipsos so you can be personally addressed in the testing session. After the testing session the data gathered will be de-identified, meaning Ipsos will remove the personal identifying data prior to sending it to Dr. Stewart Harris at Western University. Only members of Dr. Harris's research team will have access to the data. As your data is de-identified, you will not be named in any reports, publications, or presentations.

OpinionSite will archive your responses to the qualification screening survey for 5 years. Ipsos will archive your survey responses and your personal identifying data for 7 years. The research team at Western University will keep your de-identified survey responses for 7 years.

Who do I contact with my questions?

If you have any questions about the OpinionSite survey platform or how the study operates from a technical standpoint, please email [redacted].

If you have any questions or concerns about the content of the research study, please contact Susan Webster-Bogaert from Dr. Stewart Harris's Research Team (telephone [redacted] email: [redacted]).

If you have any questions about your rights as a participant or the conduct of this study, you may contact the Office of Human Research Ethics at Western University (toll-free telephone #: [redacted] or email: [redacted]). The Office of Human Research Ethics is a group of people who oversee the ethical conduct of research studies. They are not part of the research team or OpinionSite or Ipsos. Everything that you discuss will be kept confidential.

Please save/print this letter for your reference before moving to the consent section.

You may also email [redacted] for a copy of this letter.

[After reading the Letter of Information, the participants will click on a “Next” button that will direct them to a separate webpage to obtain consent]

I have reviewed the Letter of Information and understand my role. I know that I may leave the study at any time.

- ☐ I agree to participate
- ☐ I do not agree to participate

Appendix 11: Letter of information and consent emailed to prospective participants of the iNPHORM (Investigating Novel Predictions of Hypoglycemia Occurrence Using Real-world Models) longitudinal study

Study Title	Investigating Novel Predictions of Hypoglycemia Occurrence using Real-World Models - the **iNPHORM** Study
Principal Investigator	Dr. Stewart Harris, Professor Department of Family Medicine at Western University, London, Ontario, Canada [redacted]
Funder	Sanofi Canada
Conflict of Interest	Dr. Harris receives consulting fees from Sanofi for participating in advisory boards, symposiums, and clinical trials.

Please save or print this letter for your reference before moving to the consent section

Introduction:

Low blood sugar (also known as hypoglycemia) is the most common adverse event of insulin and secretagogue use in people with diabetes. It can result in distressing and sometimes severe physical and social consequences. A better understanding of who is at greatest risk of diabetes-related hypoglycemia, and why, is needed.

The purpose of the iNPHORM study is: 1) to understand how often people with diabetes have hypoglycemia; and 2) to build a tool that healthcare providers can use to predict the chance that a given person with diabetes will have hypoglycemia in the future.

You are invited to participate in the iNPHORM study because you are: 1) an existing member of a survey panel consenting to be contacted for research surveys; and 2) have been prescribed insulin or secretagogues to treat your diabetes. There will be at least 1250 people with diabetes from all over the United States of America involved in this 16-month survey study.

What will be requested of me as a participant?

If you choose to participate, you will be involved for 12 months and be asked to:

Complete an initial survey to share some information about yourself, your general health, diabetes health, medication use, and experience(s) with hypoglycemia. This survey will take approximately 30 minutes to complete.

Join the iNPHORM Diabetes Community, so you can be contacted each month for the next 12 months to complete surveys for the iNPHORM study. This community will not put you in contact with other participants.

Complete a series of short, 10 minute, monthly surveys sharing updates about your health and experience(s) with hypoglycemia.

Complete a longer 30 minute survey at 6 months sharing

how hypoglycemia affects your emotions

your thoughts, feelings, beliefs, and actions around hypoglycemia management

an update of your health and experience(s) with hypoglycemia.

What will happen during this study?

If, after reading this letter, you consent to participate you will then start the process to join the iNPHORM Diabetes Community by reading and agreeing to abide by Ipsos' community Terms and Conditions and Privacy Policy.

Next you will be directed to the initial survey. You will be able to save your place while filling out the survey. To do this you will click the *Need a break?* checkbox and then you will be asked to enter your email address. You will be emailed a link to your saved survey. Note however that the number of participants is limited to 1250 and you will be only enrolled in the study after the initial survey is complete and you have joined the iNPHORM Diabetes Community.

Once you submit the initial survey you will be directed to enter and confirm your email address to continue the process of joining the iNPHORM Diabetes Community.

You will be directed to a registration webpage where you will be asked to provide some information. Please only provide: 1) a username, 2) a password, 3) your time zone, and 4) your first name, so emails can be addressed to you personally. Please leave all other boxes blank.

Each month, you will receive an email to notify you that the survey will be sent in a week. Seven days later, you will receive an email containing a link to the survey. The link will be active for 7 days. You will receive two reminder emails if you have not completed the survey.

For the **first** monthly survey, if you do not complete the survey within the 7 days, **you will be withdrawn from the study.**

For all other months if you do not complete a survey within the 7 days, you will still have the opportunity to fill out a survey the next month.

Note if you consent to participate, your responses to the qualification screening survey will also be used as part of this study.

Are participants paid to be in this study?

Participants are not paid to be in the study however honorarium gift-cards are offered to thank you for your time and effort.

For completing the initial survey, you will receive the honorarium as shown in the email by the site that invited you to participate.

For completing each monthly survey, you will receive a $10 honorarium giftcard. At the end of the year, if you complete 8-11 monthly surveys, you'll receive an additional $30 honorarium giftcard; if you complete all 12 monthly surveys, you'll receive a $75 honorarium giftcard.

In addition, there will be two draws:

For completing the 6th monthly survey, you will be entered into a draw where three winners will be randomly selected to receive a $500 honorarium giftcard each.

For completing the 12th (also the last) monthly survey, you will be entered into a draw where three winners will be randomly selected to receive a $1000 honorarium giftcard each.

What will be the risks and benefits of participating?

You may not directly benefit from participating in this study but your responses may guide improvements to future diabetes management strategies.

There are no major risks associated with participating in this study. However, you may be reminded of stressful circumstances when describing your experience(s) with hypoglycemia in the surveys. There is a very minimal risk of privacy breach of the Ipsos servers for any personal identifying data collected in this study as part of registration or completing the surveys (name, date of birth, email address).

What are my rights as a participant?

Your participation is voluntary. You may decide not to be in this study, or to be in the study now and then change your mind later. You may refuse to answer any question you do not want to answer.

You do not waive any legal rights by consenting to this study. You have the right to withdraw from the study at any time by:

Unsubscribing - clicking on the unsubscribe link at the bottom of any email communication, or

Emailing the moderator at [redacted]

If you decide to withdraw or if you are withdrawn because you did not complete the first monthly survey, you will be removed from the iNPHORM Diabetes Community but all past survey responses including the qualification screening survey will still be used as part of this study.

How will my confidentiality be maintained?

All of your responses will be kept strictly confidential. You will be given a unique participant ID number when you join the iNPHORM Diabetes Community. Your survey responses will only be linked to your participant ID number.

Your survey data will be de-identified, meaning Ipsos will remove any personal identifying data collected in this study as part of registration or completing the surveys (name, email address, and full birthdate). This survey data will be sent to Dr. Stewart Harris at Western University. Only members of Dr. Harris's research team will have access to the data. As the data sent to Western University are de-identified, you will not be named in any reports, publications, or presentations that may result from this research study.

Dr. Harris is required to share information on severe hypoglycemia events and other significant health events with drug manufacturers. For respondents prescribed *Toujeo® SoloSTAR®* or *Toujeo® Max SoloStar®* anonymized data will be sent to Sanofi and for those prescribed *Tresiba® FlexTouch® U-100* or *Tresiba® FlexTouch® U- 200* anonymized data will be sent to Novo Nordisk.

Ipsos will store your survey responses for 7 years. The research team at Western University will keep the de-identified survey data for 7 years.

Who do I contact with my questions?

If you have any questions about the Ipsos survey platform or how the study operates from a technical standpoint, please email [redacted].

If you have any questions or concerns about the content of the research study, please contact Susan Webster-Bogaert from Dr. Stewart Harris's Research Team (telephone [redacted] email: [redacted]).

If you have any questions about your rights as a participant or the conduct of this study, you may contact the Office of Human Research Ethics at Western University (toll-free telephone #: [redacted] or email: [redacted]). The Office of Human Research Ethics is a group of people who oversee the ethical conduct of research studies. They are not part of the research team or Ipsos. Everything that you discuss will be kept confidential.

Please save or print this letter for your reference before moving to the consent section.

You may also email [redacted] for a copy of this letter.

[After reading the Letter of Information, the participants will click on a "Next" button that will direct them to a separate webpage with the following consent question.]

I have reviewed the Letter of Information and understand that the study includes completing an initial survey plus 12 surveys over 12 months. I know that I may leave the study at any time.

- ☐ I agree to participate
- ☐ I do not agree to participate

Appendix 12: Calculation of average total completion rate

Average total completion rate was calculated by comparing the observed number of completed follow-up questionnaires to the maximum expected number (i.e., completion of all follow-up questionnaires by all individuals):

$$= \left(\frac{\text{Actual number of follow-up questionnaires completed}}{\text{Expected number of follow-up questionnaires completed under complete follow-up}}\right) * 100\%$$

$$= \left[\frac{\text{10,470 follow up questionnaires}}{\text{(1,206 individuals*12 months)}}\right] * 100\%$$

$$= \left(\frac{10{,}470}{14{,}472}\right) * 100\%$$

$$= 72.4\%$$

Appendix 13: Calculation of average total completion rate against estimated required sample size (N=521)

Recall that iNPHORM follow-up questionnaires assessed individuals' number of severe hypoglycemia events since their last completed questionnaire and, as such, complete information on severe hypoglycemia events is available for all individuals up until their last completed questionnaire (after this point, they were considered "right-censored"). Participants were considered under observation for severe hypoglycemia events from baseline until their last completed questionnaire. Therefore, our completion rate as compared to our estimated required sample size (N=521) was calculated as follows:

$$= \left(\frac{\text{Observed sum of person-months for severe hypoglycemia}}{\text{Expected sum of person-months for severe hypoglycemia under complete follow-up for estimated required sample size}}\right) * 100\%$$

$$= \left[\frac{11{,}192 \text{ person-months}}{(521 \text{ individuals} * 12 \text{ months})}\right] * 100\%$$

$$= \left(\frac{11{,}192}{6{,}252}\right) * 100\%$$

$$= 179.0\%$$

Appendix 14: Number of respondents lost to follow-up after each wave, overall and by diabetes type (N=978)

	Respondents lost to follow-up after each wave, n (%)		
Wave*	Total (n=978)	T1DM† (n=163)	T2DM‡ (n=815)
Wave 1	31 (3.17)	8 (4.91)	23 (2.82)
Wave 2	17 (1.74)	2 (1.23)	15 (1.84)
Wave 3	10 (1.02)	1 (0.61)	9 (1.10)
Wave 4	14 (1.43)	0	14 (1.72)
Wave 5	7 (0.72)	0	7 (0.86)
Wave 6	5 (0.51)	3 (1.84)	2 (0.25)
Wave 7	8 (0.82)	0	8 (0.98)
Wave 8	5 (0.51)	1 (0.61)	4 (0.49)
Wave 9	8 (0.82)	1 (0.61)	7 (0.86)
Wave 10	11 (1.12)	0	11 (1.35)
Wave 11	35 (3.58)	9 (5.52)	26 (3.19)
Wave 12†	827 (84.56)	138 (84.66)	689 (84.54)

T1DM, type 1 diabetes mellitus; T2DM, type 2 diabetes mellitus.
*Last wave responded to; after this wave, the respondent was considered lost to follow-up.
†No data were collected past Wave 12.

Appendix 15: Comparison of sample distributions for participants (overall and by diabetes type) reporting zero versus ≥1 severe hypoglycemia, overall and by observation period

Appendix 15i: Anthropometric and sociodemographic characteristics

	Zero prospective SH			≥1 prospective SH			Zero vs ≥1 prospective SH		
	Overall (n=647)	T1DM (n=91)	T2DM (n=556)	Overall (n=331)	T1DM (n=72)	T2DM (n=259)	Overall *p*-value*	T1DM *p*-value*	T2DM *p*-value*
Age, mean (SD)							<0.0001†	0.8891	<0.0001†
	53.58 (13.76)	44.47 (13.89)	55.07 (13.16)	45.88 (13.97)	44.78 (13.83)	46.18 (14.02)			
Sex assigned at birth, n (%)							0.8024	0.0813	0.9601
Male	319 (49.30)	26 (28.57)	293 (52.70)	166 (50.15)	30 (41.67)	136 (52.51)			
Female	328 (50.70)	65 (71.43)	263 (47.30)	165 (49.85)	42 (58.33)	123 (47.49)			
Race, n (%)							0.8048	0.5256	0.6627
White alone	520 (80.37)	85 (93.41)	435 (78.24)	256 (77.34)	63 (87.50)	193 (74.52)			

Part-white multiracial	23 (3.55)	2 (2.20)	21 (3.78)	14 (4.23)	1 (1.39)	13 (5.02)			
Non-white	94 (14.53)	4 (4.40)	90 (16.19)	49 (14.80)	6 (8.33)	43 (16.60)			
Missing/unknown	10 (1.55)	0	10 (1.80)	12 (3.63)	2 (2.78)	10 (3.86)			
Education, n (%)							0.1194	0.1326	0.6627
High school, some high school, or Grade 8	102 (15.77)	11 (12.09)	91 (16.37)	68 (20.54)	19 (26.39)	49 (18.92)			
College degree or some college	418 (64.61)	59 (64.84)	359 (64.57)	209 (63.14)	46 (63.89)	163 (62.93)			
Degree beyond 1st college degree	127 (19.63)	21 (23.08)	106 (19.06)	54 (16.31)	7 (9.72)	47 (18.15)			
Insurance, n (%)							0.2591	0.1094	0.0765
Private insurance plan	288 (44.51)	56 (61.54)	232 (41.73)	132 (39.88)	32 (44.44)	100 (38.61)			
Government-assistance plan	208 (32.15)	20 (21.98)	188 (33.81)	111 (33.53)	27 (37.50)	84 (32.43)			

Multiple insurance plans and other insurance plans	137 (21.17)	13 (14.29)	124 (22.30)	84 (25.38)	10 (13.89)	74 (28.57)			
Out-of-pocket (i.e., no insurance coverage)	14 (2.16)	2 (2.20)	12 (2.16)	4 (1.21)	3 (4.17)	1 (0.39)			
Marital status, n (%)							0.7120	0.2842	0.8567
Partnered	404 (62.44)	52 (57.14)	352 (63.31)	211 (63.75)	42 (58.33)	169 (65.25)			
Divorced, separated, widowed	105 (16.23)	11 (12.09)	94 (16.91)	57 (17.22)	14 (19.44)	43 (16.60)			
Never married	137 (21.17)	28 (30.77)	109 (19.60)	63 (19.03)	16 (22.22)	47 (18.15)			
Missing/unknown	1 (0.15)	0 (0)	1 (0.18)	0 (0)	0 (0)	0 (0)			
Employment, n (%)							<0.0001†	0.3142	<0.0001†
Full time	259 (40.03)	44 (48.35)	215 (38.67)	168 (50.76)	28 (38.89)	140 (54.05)			
Part time	41 (6.34)	9 (9.89)	32 (5.76)	40 (12.08)	12 (16.67)	28 (10.81)			
Student/retired/ unemployed	347 (53.63)	38 (41.76)	309 (55.58)	123 (37.16)	32 (44.44)	91 (35.14)			

Annual household income (gross), n (%)							0.0003[†]	0.3229	<0.0001[†]
<$25,000	107 (16.54)	9 (9.89)	98 (17.63)	60 (18.13)	13 (18.06)	47 (18.15)			
$25,000 to $54,999	179 (27.67)	19 (20.88)	160 (28.78)	87 (26.28)	20 (27.78)	67 (25.87)			
$55,000 to $84,999	154 (23.80)	33 (36.26)	121 (21.76)	57 (17.22)	20 (27.78)	37 (14.29)			
$85,000 to $114,999	109 (16.85)	16 (17.58)	93 (16.73)	40 (12.08)	8 (11.11)	32 (12.36)			
$115,000 to $144,999	39 (6.03)	5 (5.49)	34 (6.12)	25 (7.55)	2 (2.78)	23 (8.88)			
≥$145,000	55 (8.50)	9 (9.89)	46 (8.27)	57 (17.22)	5 (6.94)	52 (20.08)			
Missing/unknown	4 (0.62)	0 (0)	4 (0.72)	5 (1.51)	4 (5.56)	1 (0.39)			

T1DM: type 1 diabetes mellitus; T2DM: type 2 diabetes mellitus; SD: standard deviation.

[*] *z*-tests were used to compare means and proportions; chi-square tests were used to compare categories.

[†] Significant based on α=0.0010 significance level, to give an α=0.05 family-wise error rate.

Appendix 15ii: Clinical characteristics

	Zero prospective SH			≥1 prospective SH			Zero vs ≥1 prospective SH		
	Overall (n=647)	T1DM (n=91)	T2DM (n=556)	Overall (n=331)	T1DM (n=72)	T2DM (n=259)	Overall *p*-value*	T1DM *p*-value*	T2DM *p*-value*
BMI (kg/m^2), median (IQR)							<0.0001†	0.0204	<0.0001†
	31.56 (11.65)	27.39 (9.34)	32.28 (11.52)	27.95 (10.35)	24.89 (5.76)	29.53 (11.06)			
Diabetes duration, median (IQR)							0.5197	0.8767	0.6014
	12 (14)	25 (20)	11 (13)	12 (16.5)	28.5 (21)	10 (13)			
Medication use, n (%)							<0.0001†	-	<0.0001†
Insulin without secretagogues	305 (47.14)	91 (100)	214 (38.49)	170 (51.36)	72 (100)	98 (37.84)			
Secretagogues without insulin	249 (38.49)	0 (0)	249 (44.78)	63 (19.03)	0 (0)	63 (24.32)			
Insulin with secretagogues	93 (14.37)	0 (0)	93 (16.73)	98 (29.61)	0 (0)	98 (37.84)			
Duration of insulin use (years), median (IQR)							0.1795	0.5967	0.0242

	8.00 (11.75)	25.58 (20.92)	5.50 (7.25)	5.75 (12.67)	25.92 (25.29)	4.00 (7.00)			
Duration of secretagogue use (years), median (IQR)							0.0234	-	0.0234
	5.00 (7.42)	-	5.00 (7.42)	3.50 (4.33)	-	3.50 (4.33)			
A1C, n (%)							<0.0001†	0.2207	<0.0001†
Less than or equal to 7%	242 (37.40)	35 (38.46)	207 (37.23)	81 (24.47)	23 (31.94)	58 (22.39)			
7.1% to 8%	224 (34.62)	32 (35.16)	192 (34.53)	113 (34.14)	28 (38.89)	85 (32.82)			
8.1% to 9%	102 (15.77)	16 (17.58)	86 (15.47)	59 (17.82)	7 (9.72)	52 (20.08)			
Greater than or equal to 9.1%	42 (6.49)	8 (8.79)	34 (6.12)	53 (16.01)	12 (16.67)	41 (15.83)			
Missing/unknown	37 (5.72)	0 (0)	37 (6.65)	25 (7.55)	2 (2.78)	23 (8.88)			
IAH, n (%)							0.0096	0.5427	0.0071
No	159 (24.57)	28 (30.77)	131 (23.56)	67 (20.24)	19 (26.39)	48 (18.53)			

Yes	394 (60.90)	63 (69.23)	331 (59.53)	255 (77.04)	53 (73.61)	202 (77.99)			
Missing/unknown	94 (14.53)	0	94 (16.91)	9 (2.72)	0	9 (3.47)			
One or more complications[‡], n (%)							<0.0001[†]	0.0606	0.0004[†]
No	307 (47.45)	34 (37.36)	273 (49.10)	110 (33.23)	17 (23.61)	93 (35.91)			
Yes	340 (52.55)	57 (62.64)	283 (50.90)	221 (66.77)	55 (76.39)	166 (64.09)			
Missing/unknown	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)			
Reported one or more past-year severe hypoglycemia event at baseline, n (%)							<0.0001[†]	<0.0001[†]	<0.0001[†]
No	517 (79.91)	64 (70.33)	453 (81.47)	137 (41.39)	25 (34.72)	112 (43.24)			
Yes	130 (20.09)	27 (29.67)	103 (18.53)	194 (58.61)	47 (65.28)	147 (56.76)			
One or more comorbidities[§], n (%)							0.0380	0.8727	0.0476
No	104 (16.07)	23 (25.27)	81 (14.57)	71 (21.45)	19 (26.39)	52 (20.08)			

	Yes	543 (83.93)	68 (74.73)	475 (85.43)	260 (78.55)	53 (73.61)	207 (79.92)		
	Missing/unknown	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)		
rt-C/FGM use, n (%)								<0.0001[†]	0.9845	<0.0001[†]
	No	552 (85.32)	46 (50.55)	506 (91.01)	214 (64.65)	36 (50.00)	178 (68.73)		
	Yes	94 (14.53)	45 (49.45)	49 (8.81)	114 (34.44)	35 (48.61)	79 (30.50)		
	Missing/unknown	1 (0.15)	0 (0)	1 (0.18)	3 (0.91)	1 (1.39)	2 (0.77)		

T1DM, type 1 diabetes mellitus; T2DM, type 2 diabetes mellitus; SD, standard deviation; IQR, interquartile range; BMI, body mass index; rt-C/FGM, real-time continuous or flash glucose monitoring; IAH, impaired awareness of hypoglycemia.

[*]Wilcoxon rank-sum tests were used to compare medians; chi-square tests were used to compare categories.

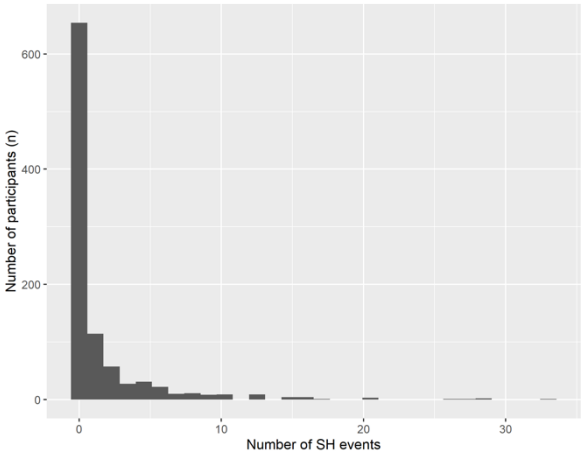
[†]Significant based on α=0.0010 significance level, to give an α=0.05 family-wise error rate.

[‡]Diabetes complications included amputation, ketoacidosis, foot damage, gastroparesis, hyperosmolar, nephropathy, neuropathy, and retinopathy.

[§]Comorbidities included bone, joint, or muscle problems; cancer; cardiovascular disease; chronic kidney disease; chronic liver failure; eating disorders; gastrointestinal disease; HIV/AIDS; hypertension; mental health conditions; neurological disorders; and stroke.

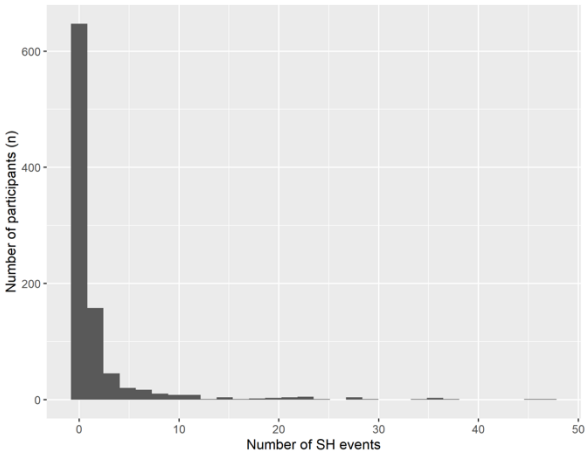
Appendix 16: Number of severe hypoglycemia by observation period, overall and by diabetes type

(a) Retrospective period, overall



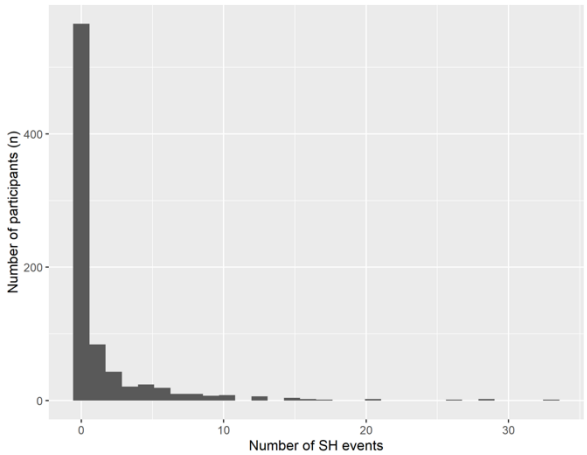
n=9 with >50 retrospective SH not displayed

(b) Prospective period, overall



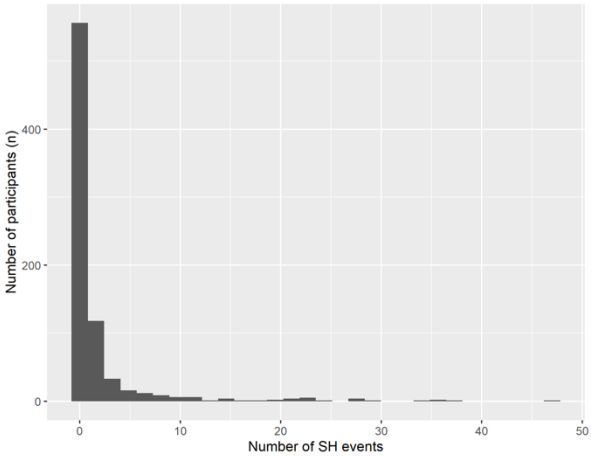
n=32 with >50 prospective SH not displayed

(c) Retrospective period, T1DM



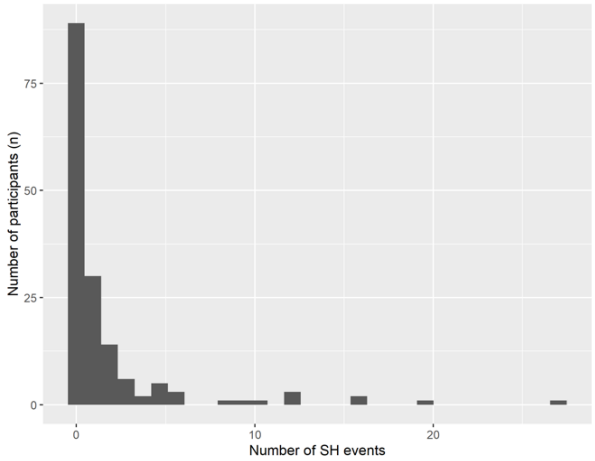
n=4 with >50 retrospective SH not displayed

(d) Prospective period, T1DM



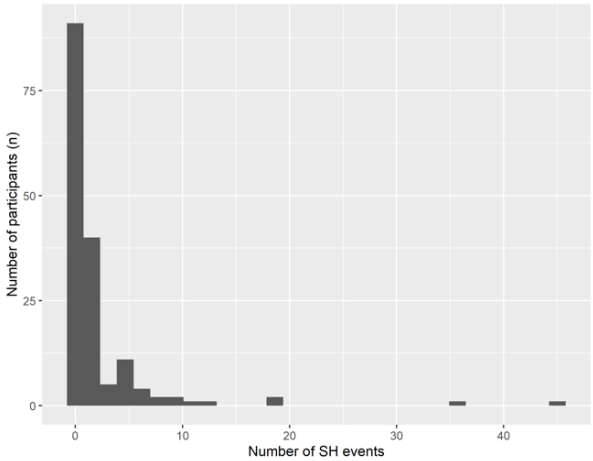
n=2 with >50 prospective SH not displayed

(e) Retrospective period, T2DM



n=5 with >50 retrospective SH not displayed

(f) Prospective period, T2DM



n=30 with >50 prospective SH not displayed

T1DM, type 1 diabetes mellitus; T2DM, type 2 diabetes mellitus; SH, severe hypoglycemia

Appendix 17: Sample size calculation for severe hypoglycemia risk prediction model

This method determines the sample size required to ensure a small expected optimism in the apparent $R^2_{Nagelkerke}$ (i.e., $R^2_{cs}/\max(R^2_{cs})$). First, the shrinkage factor that corresponds to an expected optimism of δ (0.05) in $R^2_{Nagelkerke}$ is calculated using the above calculated $\max(R^2_{cs})$ and an anticipated R^2_{cs} of 0.2:

$$S = \frac{R^2_{cs}}{R^2_{cs} + \delta \times \max(R^2_{cs})}$$
$$S = \frac{0.2}{0.2 + 0.05 \times 0.84} = 0.83$$

Given 46 predictors, the required number of participants to ensure a small expected optimism can be estimated:

$$n = \frac{P}{(S-1)\ln\left(1 - \frac{R^2_{cs}}{S}\right)}$$
$$n = \frac{46}{(0.83-1)\ln\left(1 - \frac{0.2}{0.83}\right)} \cong 958 \text{ participants}$$

Appendix 18: Group 1: Candidate prognostic variables likely stored in an electronic health record

Prognostic variable	Recall period	Original measurement unit(s)/response categories	Transformed unit(s) /grouped response categories	Data type	Time-varying
Age (9–25)	Baseline	Years	Years	Continuous	No
Sex (9,10,14,16,17,22)	Assigned at birth	Male; Female; Other	Male; Female	Categorical	No
BMI (9,11–17,26)	Baseline	Pounds (weight) and inches (height)	kg/m^2	Continuous	No
Basal insulin use (27,28)	Current	Insulin Glargine U300; Insulin Degludec; Basal Insulin (including intermediate and long-acting); Premixed Insulin; Fixed-Ratio Combination Insulin	Yes; No	Categorical	Yes
Basal insulin dose	Current	Units of insulin	Units of insulin	Discrete	Yes
Bolus insulin use (29)	Current	Bolus/Prandial (a.k.a. mealtime) Insulin (including rapid- and short-acting); Premixed Insulin	Yes; No	Categorical	Yes
Bolus insulin dose	Current	Units of insulin	Units of insulin	Discrete	Yes

Basal and bolus insulin use	Current	Insulin Glargine U300; Insulin Degludec; Basal Insulin (including intermediate and long-acting); Bolus/Prandial (a.k.a. mealtime) Insulin (including rapid- and short-acting); Premixed Insulin; Fixed-Ratio Combination Insulin	Yes ([Insulin Glargine U300; Insulin Degludec; Basal Insulin (including intermediate and long-acting); Premixed Insulin; Fixed-Ratio Combination Insulin] AND (Bolus/Prandial (a.k.a. mealtime) Insulin (including rapid- and short-acting))	Categorical	Yes
Insulin pump use	Current	Yes; No; I don't know	Yes; No	Categorical	Yes
Insulin pump dose	Current	Units of insulin	Units of insulin	Discrete	Yes
Secretagogue use (25)	Current	Short-Acting Sulphonylurea; Intermediate-Acting Sulphonylurea; Long-Acting Sulphonylurea; Meglitinide; Meglitinide and Biguanide Fixed-Dose Combination OR Sulphonylurea and Biguanide Fixed-Dose Combination; Not currently taking any of these secretagogues	Yes (Short-Acting Sulphonylurea OR Intermediate-Acting Sulphonylurea OR Long-Acting Sulphonylurea OR Meglitinide OR Meglitinide and Biguanide Fixed-Dose Combination OR Sulphonylurea and Biguanide Fixed-Dose Combination); No	Categorical	Yes

Secretagogue dose	Current	Milligrams	Log transformed and divided by standard deviation to sum across medications		Yes
Basal insulin and secretagogue use (Interaction term)	Current	Insulin Glargine U300; Insulin Degludec; Basal Insulin (including intermediate and long-acting); Premixed Insulin; Fixed-Ratio Combination Insulin; Short-Acting Sulphonylurea; Intermediate-Acting Sulphonylurea; Long-Acting Sulphonylurea; Meglitinide; Meglitinide and Biguanide Fixed-Dose Combination OR Sulphonylurea and Biguanide Fixed-Dose Combination	Yes ([Insulin Glargine U300 OR Insulin Degludec OR Basal Insulin (including intermediate and long-acting) OR Premixed Insulin OR Fixed-Ratio Combination Insulin] AND [Short-Acting Sulphonylurea OR Intermediate-Acting Sulphonylurea OR Long-Acting Sulphonylurea OR Meglitinide OR Meglitinide and Biguanide Fixed-Dose Combination OR Sulphonylurea and Biguanide Fixed-Dose Combination]); No	Categorical	Yes
Bolus insulin and secretagogue use (Interaction term)	Current	Bolus/Prandial (a.k.a. mealtime) Insulin (including rapid- and short-acting); Premixed Insulin; Short-Acting Sulphonylurea; Intermediate-Acting	Yes ([Bolus/Prandial (a.k.a. mealtime) Insulin (including rapid- and short-acting) OR Premixed Insulin] AND [Short-Acting Sulphonylurea OR	Categorical	Yes

		Sulphonylurea; Long-Acting Sulphonylurea; Meglitinide; Meglitinide and Biguanide Fixed-Dose Combination OR Sulphonylurea and Biguanide Fixed-Dose Combination	Intermediate-Acting Sulphonylurea OR Long-Acting Sulphonylurea OR Meglitinide OR Meglitinide and Biguanide Fixed-Dose Combination OR Sulphonylurea and Biguanide Fixed-Dose Combination]); No		
Basal and bolus insulin and secretagogue use (Interaction term)	Current	Insulin Glargine U300; Insulin Degludec; Basal Insulin (including intermediate and long-acting); Bolus/Prandial (a.k.a. mealtime) Insulin (including rapid- and short-acting); Premixed Insulin; Fixed-Ratio Combination Insulin; Short-Acting Sulphonylurea; Intermediate-Acting Sulphonylurea; Long-Acting Sulphonylurea; Meglitinide; Meglitinide and Biguanide Fixed-Dose Combination OR	Yes ([Insulin Glargine U300 OR Insulin Degludec OR Basal Insulin (including intermediate and long-acting) OR Premixed Insulin OR Fixed-Ratio Combination Insulin] AND [Bolus/Prandial (a.k.a. mealtime) Insulin (including rapid- and short-acting) OR Premixed Insulin] AND [Short-Acting Sulphonylurea OR Intermediate-Acting Sulphonylurea OR Long-Acting Sulphonylurea OR Meglitinide OR Meglitinide and Biguanide	Categorical	Yes

		Sulphonylurea and Biguanide Fixed-Dose Combination	Fixed-Dose Combination OR Sulphonylurea and Biguanide Fixed-Dose Combination]); No		
Insulin pump and secretagogue use (Interaction term)	Current	Insulin pump; Short-Acting Sulphonylurea; Intermediate-Acting Sulphonylurea; Long-Acting Sulphonylurea; Meglitinide; Meglitinide and Biguanide Fixed-Dose Combination OR Sulphonylurea and Biguanide Fixed-Dose Combination	Yes ([Insulin pump] AND [Short-Acting Sulphonylurea OR Intermediate-Acting Sulphonylurea OR Long-Acting Sulphonylurea OR Meglitinide OR Meglitinide and Biguanide Fixed-Dose Combination OR Sulphonylurea and Biguanide Fixed-Dose Combination]); No	Categorical	Yes
Antibiotic use (30)	Current	Yes; No; Don't know	Yes; No	Categorical	Yes
Beta-blocker use (11)	Current	Yes; No; Don't know	Yes; No	Categorical	Yes
Corticosteroid use	Current	Yes; No; Don't know	Yes; No	Categorical	Yes
Number of diabetes medications (other than insulin or secretagogues) (11,12,14,16,24,31,32)	Current	Biguanide; Alpha-Glucosidase Inhibitor; Amylin Analog; Bile Acid Sequestrant; GLP-1 Receptor Agonist; Dipeptidyl Peptidase-4 (DPP-4) Inhibitor;	Number of diabetes medications	Ordinal	Yes

		DPP-4 Inhibitor and Biguanide Fixed-dose Combination OR DPP-4 Inhibitor and Thiazolidinedione Fixed-dose Combination; SGLT2 Inhibitor; SGLT2 Inhibitor and Biguanide Fixed-dose Combination; SGLT2 Inhibitor and DPP-4 Inhibitor Fixed-Dose Combination; Thiazolidinedione; Thiazolidinedione and Biguanide Fixed-Dose Combination; Thiazolidinedione and Sulphonylurea Fixed-Dose Combination; Not currently taking any of these diabetes medications			
A1C (9–16,18,20–22,25,31–34)	Most recent	Less than or equal to 7%; 7.1% to 8%; 8.1% to 9%; Greater than or equal to 9.1%; Don't know	Less than or equal to 7%; 7.1% to 8%; 8.1% to 9%; Greater than or equal to 9.1%	Categorical	Yes
Variability of A1C during 1 year before baseline (14,16)	Over follow-up	Index of variation	Index of variation	Continuous	No

Number of previous severe hypoglycemia events requiring emergency department use or hospitalization (9,11–17,19,20,22,24,25,31,33)	Past year, up to 2 years	Number of events	Number of events	Discrete	Yes
Dialysis (11,14,16)	Current	Never received or required dialysis; previously received dialysis, but not currently receiving; not currently receiving dialysis, but may require in the future; currently receiving dialysis	Not currently receiving dialysis; Currently receiving dialysis	Categorical	Yes
Number of diabetes visits (11,14,16,35)	Current	Number of visits (past month)	Number of visits (past month)	Discrete	

BMI, body mass index

Appendix 19: Group 2: Candidate prognostic variables not likely stored in an electronic health record but easily obtainable via verbal self-report

Prognostic variable	Recall period	Original measurement unit(s)/response categories	Transformed unit(s) /grouped response categories	Data type	Time-varying
Diabetes type (12,33)	Baseline	T1DM; T2DM	T1DM; T2DM	Categorical	No
Duration of diabetes (9–11,14–17,22–24,31)	Baseline	Years	Years	Continuous	No
rt-C/FGM use (36)	Current	Yes; No	Yes; No	Categorical	Yes
IAH (21,22,25,31,33)	Current	*The extent the respondent can tell by their symptoms that their blood glucose is low:* Never; Rarely; Sometimes; Often; Always	Unaware (Never OR Rarely OR Sometimes OR Often); Aware (Always)	Categorical	Yes
Mental health condition (e.g., anxiety, depression, schizophrenia, bipolar, post-traumatic stress disorder, addiction) (12–14,16)	Baseline	Yes; No	Yes; No	Categorical	No

Chronic kidney disease (11,13,14,16–18,25,31,32)	Baseline	Yes; No	Yes; No	Categorical	No
Neurologic disorder (e.g., dementia, epilepsy, Parkinson's diseases) (11,13,14,16,18,23,25,31,32)	Baseline	Yes; No	Yes; No	Categorical	No
Number of other comorbidities (11,13–17,26,27)	Baseline	Bone, joint, or muscle problem; Cancer; Cardiovascular condition; Chronic liver failure or liver disease; Eating disorder (e.g., anorexia nervosa, bulimia nervosa, binge eating disorder); Gastrointestinal disease (e.g., Inflammatory Bowel Disease [IBD] such as Crohn's or ulcerative colitis); HIV/AIDS; Hypertension; Physical impairment; Respiratory condition; Stroke or transient ischemic attack	Number of comorbidities	Discrete	No
Diabetic ketoacidosis (13,15)	Current	Yes; No	Yes; No	Categorical	Yes

Amputation of toes, feet, legs (14,16)	Current	Yes; No	Yes; No	Categorical	Yes
Retinopathy (12,14–16)	Current	Yes; No	Yes; No	Categorical	Yes
Number of other diabetes complications (10,15,27)	Current	Foot damage (Charcot foot, foot ulcers); Gastroparesis; Hyperosmolar hyperglycemic nonketotic coma; Nephropathy; Neuropathy (e.g., numbness/tingling in hands or feet)	Number of complications	Discrete	Yes
Marital status (15)	Baseline	Married; Divorced; Widowed; Domestic partnership; Separated; Never married	Married or domestic partnership; Divorced, separated, or widowed; Never married	Categorical	No
Highest education achieved (9)	Baseline	No schooling completed; Grades 1 through 8; Grades 9 through 12, NO DIPLOMA; Regular high school diploma or GED/alternative credential; College degree or some college;	No schooling completed; Grades 1 through 8; Grades 9 through 12, NO DIPLOMA; Regular high school diploma or GED/alternative credential; College degree or some college;	Ordinal	No

		Degree beyond completing first college Bachelor's degree	Degree beyond completing first college Bachelor's degree		
Income (13,25)	Baseline	Less than $10,000; $10,000 to less than $25,000; $25,000 to less than $40,000; $40,000 to less than $55,000; $55,000 to less than $70,000; $70,000 to less than $85,000; $85,000 to less than $100,000; $100,000 to less than $115,000; $115,000 to less than $130,000; $130,000 to less than $145,000; $145,000 to less than $160,000; $160,000 to less than $175,000; $175,000 to less than $200,000; $200,000 or more	Less than $10,000; $10,000 to less than $25,000; $25,000 to less than $40,000; $40,000 to less than $55,000; $55,000 to less than $70,000; $70,000 to less than $85,000; $85,000 to less than $100,000; $100,000 to less than $115,000; $115,000 to less than $130,000; $130,000 to less than $145,000; $145,000 to less than $160,000; $160,000 to less than $175,000; $175,000 to less than $200,000; $200,000 or more	Ordinal	No
Insurance coverage (19,23)	Current	Insurance through a current or former employer or union (of participant or family member) that is not a high deductible plan; Insurance purchased directly from an insurance	Private insurance plan (Insurance through a current or former employer or union (of participant or family member) that is not a high deductible plan OR Insurance purchased	Categorical	Yes

		company that is not a high deductible plan; High deductible plan; Medicare; Medicaid, Medical Assistance, or any kind of government-assistance plan; TRICARE; Veterans Affairs; Native American Health Service; Consolidated Omnibus Budget Reconciliation Act (COBRA) insurance; Any other type of health insurance/coverage plan	directly from an insurance company that is not a high deductible plan OR High deductible plan); Government-assistance plan (Medicare OR Medicaid, Medical Assistance, or any kind of government-assistance plan OR TRICARE OR Veterans Affairs OR Native American Health Service OR Consolidated Omnibus Budget Reconciliation Act (COBRA) insurance); Multiple insurance plans and other insurance plans ([Private insurance plan AND Government-assistance plan] OR Any other type of health insurance/coverage plan); Out-of-pocket (i.e., no insurance coverage)

Race (9,10,12–16,18,19,23)	Current	White; Black or African American; Asian; Hispanic, Latino/a, or Spanish origin; Native Hawaiian or other Pacific Islander; American Indian or Alaska Native; Other	Only White; White and Non-White (Black or African American OR Asian OR Hispanic, Latino/a, or Spanish origin OR Native Hawaiian or other Pacific Islander OR American Indian or Alaska Native OR Other); Only non-White or multiracial (Black or African American OR Asian OR Hispanic, Latino/a, or Spanish origin OR Native Hawaiian or other Pacific Islander OR American Indian or Alaska Native OR Other)	Categorical	No
Ethnicity (12,14,16)	Current	Hispanic, Latino/a, or Spanish origin	Yes; No	Categorical	No
Food insecurity (25,31)	Current	Whether the respondent reduced the size of or skipped a meal due to cost Yes; No	Yes; No	Categorical	No

Diabetes education (20,31)	Current	Whether the respondent has ever taken a course or class with a trained educator to learn about how to manage their diabetes Yes; No	Yes; No	Categorical	No
Self-rated health (4)	Baseline	Excellent; very good; good; fair; poor	Excellent; very good; good; fair; poor	Ordinal	No

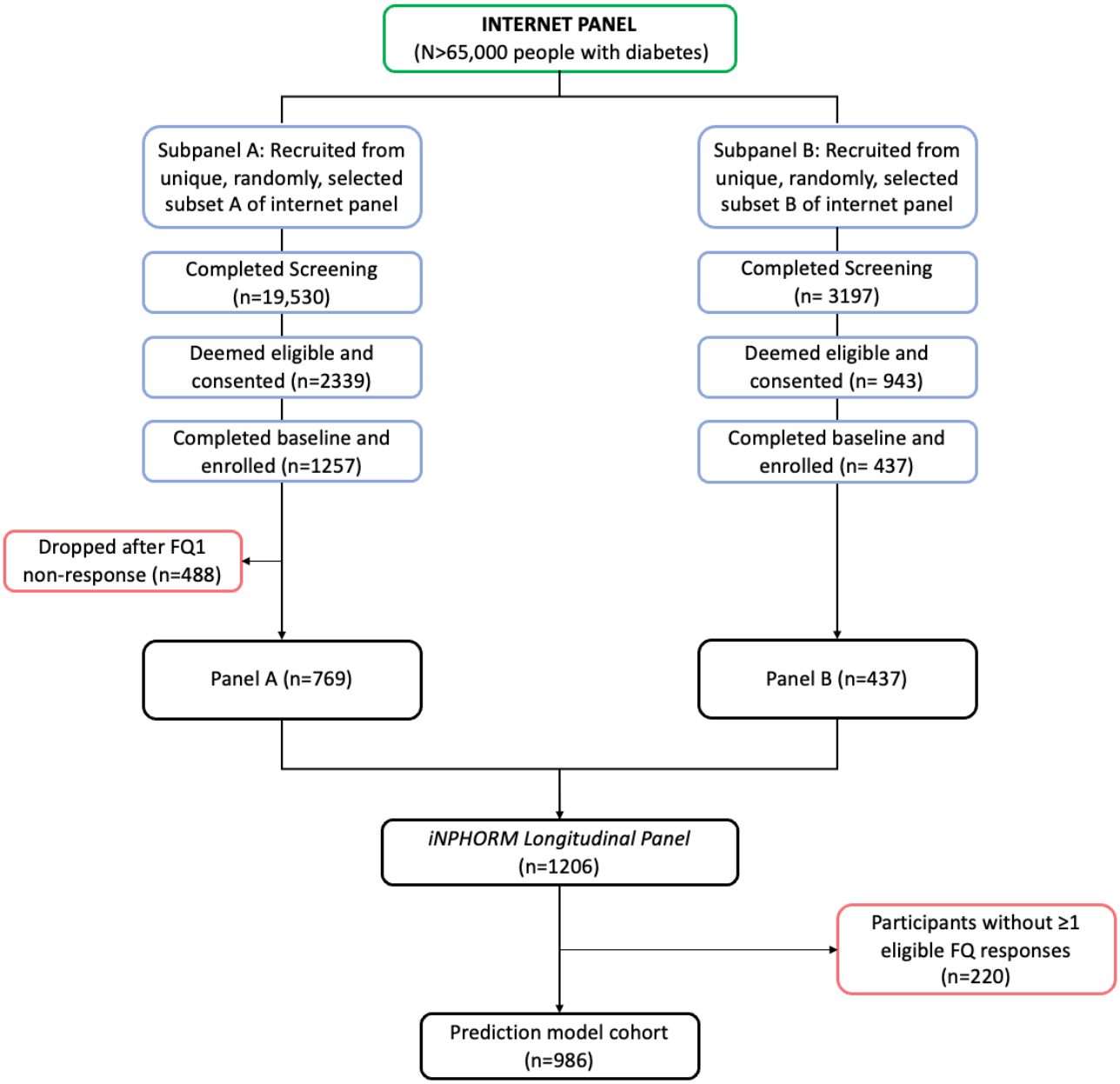
T1DM, type 1 diabetes mellitus; T2DM, type 2 diabetes mellitus; rt-C/FGM, real-time continuous or flash glucose monitoring; IAH, impaired awareness of hypoglycemia

Appendix 20: Group 3: Candidate prognostic variables not likely stored in an electronic health record and obtainable only via self-administered questionnaires

Prognostic variable	Recall period	Original measurement unit(s)/response categories	Transformed unit(s) /grouped response categories	Data type	Time-varying
Health literacy (25,31)	Current	Modified BRIEF: Health Literacy Screening Tool(1) 3-item survey	Composite score of Modified BRIEF: Health Literacy Screening Tool(1) 3-item survey	Continuous	No
Alcohol use (9,13,15,17–19,33)	Current	Never; In the past but not currently; Less than once a month but at least once per year; 1 to 4 times per month; 2 to 6 times per week; Everyday	Never; In the past but not currently; Less than once a month but at least once per year; 1 to 4 times per month; 2 to 6 times per week; Everyday	Ordinal	No
Binge drinking behaviour (17)	Current	0 times; 1 time; 2 or 3 times; 4 or 5 times; More than 5 times	0 times; 1 time; 2 or 3 times; 4 or 5 times; More than 5 times	Ordinal	No
Smoking status (14–16,26)	Current	Never used tobacco or other nicotine products; Previously used tobacco or other nicotine products; Currently uses	Never used tobacco or other nicotine products; Previously used tobacco or other nicotine products; Currently uses	Ordinal	No

		tobacco or other nicotine products	tobacco or other nicotine products		
Recreational drug use (37)	Current	Never; In the past but not currently; Less than once a month but at least once per year; 1 to 4 times per month; 2 to 6 times per week; Everyday	Never; In the past but not currently; Less than once a month but at least once per year; 1 to 4 times per month; 2 to 6 times per week; Everyday	Ordinal	No
Aerobic exercise (17,18,21,33)	Current	Never; Less than once a month but at least once per year; 1 to 4 times per month; 2 to 6 times per week; Everyday	Never; Less than once a month but at least once per year; 1 to 4 times per month; 2 to 6 times per week; Everyday	Ordinal	No
Anaerobic exercise (38)	Current	Never; Less than once a month but at least once per year; 1 to 4 times per month; 2 to 6 times per week; Everyday	Never; Less than once a month but at least once per year; 1 to 4 times per month; 2 to 6 times per week; Everyday	Ordinal	No
Fear of hypoglycemia (7)	Month 6	Hypoglycemia Fear Survey-II (HFS-II) score	Hypoglycemia Fear Survey-II (HFS-II) score	Continuous	No
Quality of life (39)	Baseline	Veterans RAND 12 Item Health Survey (VR-12)	Veterans RAND 12 Item Health Survey (VR-12)	Continuous	No

Appendix 21: Overview of sample recruitment and participation



Appendix 23: Missing data table for iNPHORM risk model

Characteristic	Base-line n=986	Wave 1 n=929	Wave 2 n=869	Wave 3 n=858	Wave 4 n=855	Wave 5 n=840	Wave 6 n=841	Wave 7 n=833	Wave 8 n=832	Wave 9 n=844	Wave 10 n=835	Wave 11 n=833	Wave 12 n=834
Age, mean (SD)	0 (0)	-	-	-	-	-	-	-	-	-	-	-	-
Sex assigned at birth, n (%)	0 (0)	-	-	-	-	-	-	-	-	-	-	-	-
BMI (kg/m^2), median (IQR)	12 (1.22)	-	-	-	-	-	-	-	-	-	-	-	-
Basal insulin use, n (%)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Basal insulin dose (units)*, median (IQR)	7 (0.71)	1 (0.11)	0 (0)	0 (0)	3 (0.35)	0 (0)	0 (0)	0 (0)	1 (0.12)	1 (0.12)	4 (0.48)	3 (0.36)	0 (0)
Bolus insulin use, n (%)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Bolus insulin dose (units)*, median (IQR)	13 (1.32)	1 (0.11)	0 (0)	1 (0.12)	0 (0)	1 (0.12)	0 (0)	0 (0)	0 (0)	0 (0)	2 (0.24)	1 (0.12)	0 (0)
Insulin pump use, n (%)	0 (0)	1 (0.11)	2 (0.23)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (0.12)	0 (0)	0 (0)	0 (0)
Insulin pump dose (units)*, median (IQR)	2 (0)	2 (0.22)	2 (0.23)	1 (0.12)	0 (0)	1 (0.12)	2 (0.24)	3 (0.36)	3 (0.36)	5 (0.59)	2 (0.24)	3 (0.36)	2 (0.24)

Secretagogue use, n (%)	0 (0)	1 (0.11)	1 (0.12)	4 (0.47)	2 (0.23)	2 (0.24)	2 (0.24)	1 (0.12)	2 (0.24)	2 (0.24)	2 (0.24)	3 (0.36)	5 (0.6)
Secretagogue dose (mg)*, median (IQR)	18 (1.83)	24 (2.58)	23 (2.65)	26 (3.03)	25 (2.92)	25 (2.98)	23 (2.73)	26 (3.12)	23 (2.76)	29 (3.44)	31 (3.71)	20 (2.4)	29 (3.48)
Basal and bolus insulin use, n (%)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Basal insulin and secretagogue use, n (%)	0 (0)	0 (0)	0 (0)	2 (0.23)	1 (0.12)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Bolus insulin and secretagogue use, n (%)	0 (0)	0 (0)	0 (0)	1 (0.12)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (0.12)
Basal and bolus insulin and secretagogue use, n (%)	0 (0)	0 (0)	0 (0)	1 (0.12)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Insulin pump and secretagogue use, n (%)	0 (0)	1 (0.11)	2 (0.23)	0 (0)	0 (0)	1 (0.12)	1 (0.12)	0 (0)	0 (0)	2 (0.24)	0 (0)	2 (0.24)	1 (0.12)
Antibiotic use, n (%)	7 (0.71)	0 (0)	1 (0.12)	2 (0.23)	1 (0.12)	1 (0.12)	2 (0.24)	1 (0.12)	2 (0.24)	2 (0.24)	3 (0.36)	3 (0.36)	2 (0.24)
Beta-blocker use, n (%)	18 (1.83)	0 (0)	1 (0.12)	2 (0.23)	1 (0.12)	1 (0.12)	2 (0.24)	1 (0.12)	2 (0.24)	2 (0.24)	3 (0.36)	3 (0.36)	2 (0.24)
Corticosteroid use, n (%)	6 (0.61)	0 (0)	1 (0.12)	2 (0.23)	1 (0.12)	1 (0.12)	2 (0.24)	1 (0.12)	2 (0.24)	2 (0.24)	3 (0.36)	3 (0.36)	2 (0.24)

Number of diabetes medications, n (%)	3 (0.3)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Most recent A1C value, n (%)	65 (6.59)	49 (5.27)	41 (4.72)	43 (5.01)	44 (5.15)	48 (5.71)	44 (5.23)	46 (5.52)	42 (5.05)	40 (4.74)	41 (4.91)	38 (4.56)	34 (4.08)
Number of past severe hypoglycemia events resulting in emergency department use or hospitalization, n (%)	7 (0.71)	7 (0.75)	8 (0.92)	12 (1.4)	14 (1.64)	14 (1.67)	14 (1.66)	15 (1.8)	17 (2.04)	21 (2.49)	22 (2.63)	23 (2.76)	24 (2.88)
Currently treated using dialysis, n (%)	0 (0)	0 (0)	2 (0.23)	4 (0.47)	1 (0.12)	1 (0.12)	1 (0.12)	1 (0.12)	1 (0.12)	1 (0.12)	2 (0.24)	1 (0.12)	2 (0.24)
Number of diabetes visits, n (IQR)	0 (0)	1 (0.11)	2 (0.23)	3 (0.35)	1 (0.12)	0 (0)	1 (0.12)	1 (0.12)	1 (0.12)	1 (0.12)	2 (0.24)	1 (0.12)	2 (0.24)
Diabetes type, n (%)	0 (0)	-	-	-	-	-	-	-	-	-	-	-	-
Diabetes duration, median (IQR)	9 (0.91)	-	-	-	-	-	-	-	-	-	-	-	-
CGM device use, n (%)	5 (0.51)	4 (0.43)	3 (0.35)	6 (0.7)	1 (0.12)	2 (0.24)	3 (0.36)	3 (0.36)	1 (0.12)	4 (0.47)	2 (0.24)	3 (0.36)	2 (0.24)

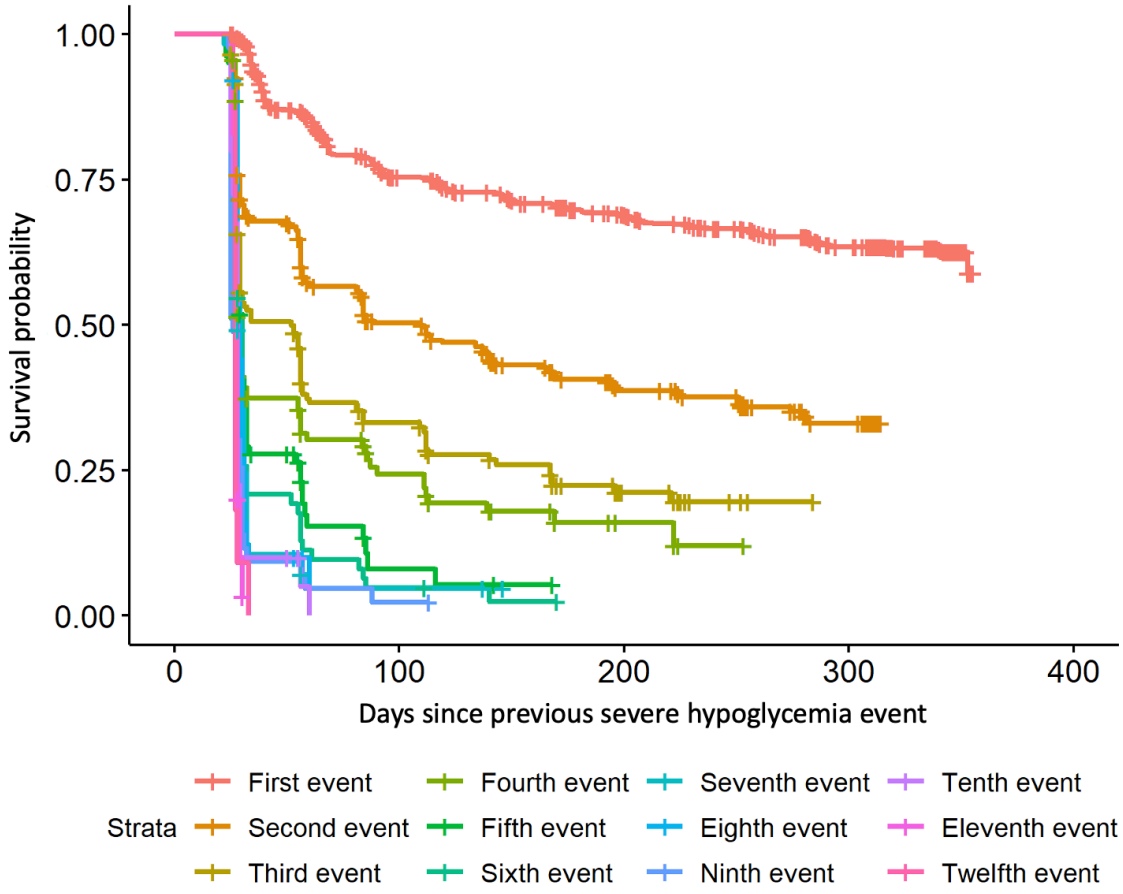
Hypoglycemia awareness, n (%)	105 (10.65)	1 (0.11)	4 (0.46)	8 (0.93)	3 (0.35)	4 (0.48)	2 (0.24)	3 (0.36)	3 (0.36)	4 (0.47)	5 (0.6)	6 (0.72)	6 (0.72)
Mental health condition, n (%)	12 (1.22)	-	-	-	-	-	-	-	-	-	-	-	-
Chronic kidney disease, n (%)	11 (1.12)	-	-	-	-	-	-	-	-	-	-	-	-
Neurologic disorder, n (%)	8 (0.81)	-	-	-	-	-	-	-	-	-	-	-	-
Number of other comorbidities, n (%)	49 (4.97)	-	-	-	-	-	-	-	-	-	-	-	-
Diabetic ketoacidosis, n (%)	22 (2.23)	13 (1.4)	13 (1.5)	10 (1.17)	6 (0.7)	11 (1.31)	11 (1.31)	16 (1.92)	9 (1.08)	13 (1.54)	11 (1.32)	10 (1.2)	8 (0.96)
Amputation of toes, feet, legs, n (%)	2 (0.2)	9 (0.97)	5 (0.58)	8 (0.93)	4 (0.47)	6 (0.71)	3 (0.36)	8 (0.96)	3 (0.36)	5 (0.59)	7 (0.84)	7 (0.84)	3 (0.36)
Retinopathy, n (%)	16 (1.62)	12 (1.29)	13 (1.5)	14 (1.63)	16 (1.87)	12 (1.43)	14 (1.66)	12 (1.44)	12 (1.44)	9 (1.07)	13 (1.56)	14 (1.68)	14 (1.68)
Number of other diabetes complications, n (%)	55 (5.58)	34 (3.66)	32 (3.68)	33 (3.85)	34 (3.98)	31 (3.69)	32 (3.8)	31 (3.72)	26 (3.13)	32 (3.79)	30 (3.59)	21 (2.52)	25 (3)
Marital status, n (%)	1 (0.1)	-	-	-	-	-	-	-	-	-	-	-	-

Highest education achieved, n (%)	0 (0)	-	-	-	-	-	-	-	-	-	-	-	-
Household income, n (%)	9 (0.91)	-	-	-	-	-	-	-	-	-	-	-	-
Health insurance, n (%)	0 (0)	-	-	-	43 (5.03)	-	-	-	45 (5.41)	-	-	-	36 (4.32)
Race, n (%)	22 (2.23)	-	-	-	-	-	-	-	-	-	-	-	-
Ethnicity, n (%)	0 (0)	-	-	-	-	-	-	-	-	-	-	-	-
Experiencing food insecurity, n (%)	0 (0)	-	-	-	-	-	-	-	-	-	-	-	-
Received diabetes training, n (%)	0 (0)	-	-	-	-	-	-	-	-	-	-	-	-
General health status, n (%)	0 (0)	-	-	-	-	-	-	-	-	-	-	-	-
Requires assistance with health materials, n (%)	0 (0)	-	-	-	-	-	-	-	-	-	-	-	-
Alcohol use, n (%)	1 (0.1)	-	-	-	-	-	-	-	-	-	-	-	-
Binge drinking frequency, n (%)	1 (0.1)	-	-	-	-	-	-	-	-	-	-	-	-

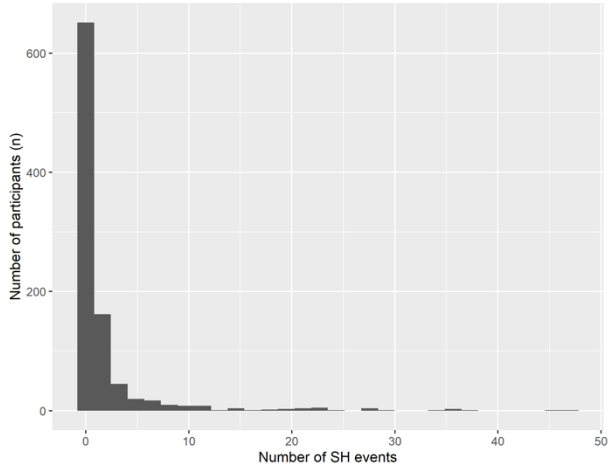
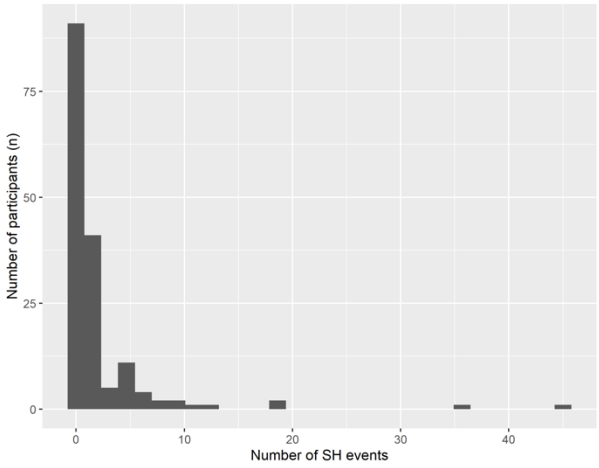
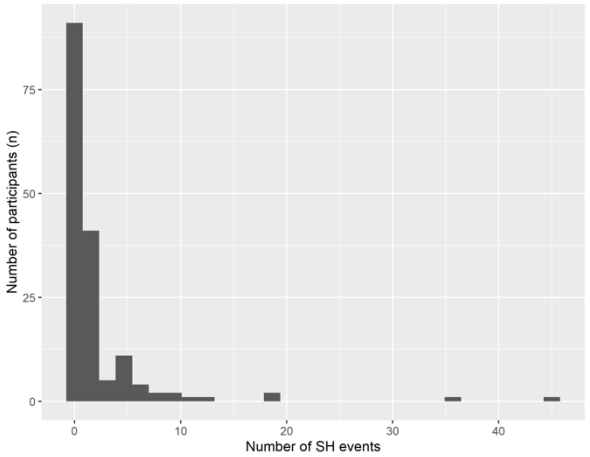
Smoking status, n (%)	1 (0.1)	-	-	-	-	-	-	-	-	-	-	-	-	-
Recreational drug use, n (%)	3 (0.3)	-	-	-	-	-	-	-	-	-	-	-	-	-
Aerobic exercise, n (%)	1 (0.1)	-	-	-	-	-	-	-	-	-	-	-	-	-
Anaerobic exercise, n (%)	1 (0.1)	-	-	-	-	-	-	-	-	-	-	-	-	-
Fear of hypoglycemia (Total HFS-II score), median (IQR)	-	-	-	-	-	-	150 (17.8)	-	-	-	-	-	-	-
Quality of life (VR-12), median (IQR)	0 (0)	-	-	-	-	-	-	-	-	-	-	-	-	-

SD, standard deviation; BMI, body mass index; IQR, interquartile range; rt-C/FGM, real-time continuous or flash glucose monitoring; HFS-II, Hypoglycemia Fear Survey-II; VR-12, Veterans RAND 12 Item Health Survey.
-: Not applicable.

Appendix 24: Probability of event-free survival over follow-up for each sequential severe hypoglycemia event



Appendix 25: Distribution of severe hypoglycemia event occurrence, overall and by diabetes type

Overall	Type 1 diabetes mellitus	Type 2 diabetes mellitus
		
*32 participants with greater than 50 severe hypoglycemia prospective events not displayed	*2 participants with greater than 50 severe hypoglycemia prospective events not displayed	*30 participants with greater than 50 severe hypoglycemia prospective events not displayed

Appendix 26: Using risk prediction models to determine risk of severe hypoglycemia

To determine the risk of severe hypoglycemia for patient *i*, $\hat{F}(t; \mathrm{x}_i)$ at some number of days, t, the log cumulative baseline hazard is combined with the patient's prognostic index, which considers all prognostic factors included in the model (40):

$$\hat{F}(t; \mathrm{x}_i) = 1 - \hat{S}_0^{\exp(\mathrm{PI}_i)}$$

Where $\hat{S}_0$ is the baseline survival function, which is determined from the log baseline cumulative hazard function, $\log H_0(t) = \log(-\log S_0(t))$; time is represented in days, t; and PI_i is the prognostic index for patient *i* based on their prognostic index PI_i.

For each model, the log baseline cumulative hazard, $\log H_0(t)$, was approximated by a fractional polynomial function of follow-up day, t:

$$\text{Model 1: } \log H_0(t) = -9.517 + 1.162 \log(t) + 0.00000001542\ (t)^3$$

$$\text{Model 2: } \log H_0(t) = -9.779 + 1.166 \log(t) + 0.00000001554 (t)^3$$

$$\text{Model 3: } \log H_0(t) = -9.988 + 1.164 \log(t) + 0.00000001558 (t)^3$$

The prognostic index for patient *i* is determined by their prognostic factors and model-specific parameter estimates: $\mathrm{PI}_i = \beta \mathrm{x}_i$, when β is a vector of the model-specific parameter estimates and x_i is a vector of prognostic factors for patient *i*.

The β estimates for each model are reported below. For a given individual, their one-year SH risk is estimated by their prognostic information and log cumulative baseline hazard at 1 year (365 days).

	Model 1	Model 2	Model 3
	Estimated coefficient (95% CI)	Estimated coefficient (95% CI)	Estimated coefficient (95% CI)
Age (10-year increments)	-0.029 (-0.039 to -0.019)	-0.028 (-0.040 to -0.017)	-0.017 (-0.027 to -0.005)
Female sex	-0.067 (-0.279 to 0.153)	-0.062 (-0.265 to 0.120)	-0.056 (-0.276 to 0.169)
BMI (kg/m^2)	-0.012 (-0.028 to 0.000)	-0.010 (-0.024 to 0.000)	-0.002 (-0.017 to 0.007)
Basal insulin use	-	-	-
Basal insulin dose (units)	-0.003 (-0.006 to 0.000)	-0.003 (-0.006 to 0.000)	-0.003 (-0.006 to 0.000)
Bolus insulin use	0.025 (-0.035 to 0.358)	-	-
Bolus insulin dose (units)	-	-	-
Insulin pump use	0.091 (0.000 to 0.527)	-	-0.001 (-0.281 to 0.236)
Insulin pump dose (units)	-0.002 (-0.010 to 0.001)	-0.004 (-0.011 to 0.000)	-0.003 (-0.010 to 0.000)
Secretagogue use	-0.007 (-0.260 to 0.154)	-	-

Secretagogue dose (mg)	0.034 (0.000 to 0.115)	0.028 (-0.008 to 0.104)	0.024 (-0.011 to 0.119)
Basal and bolus insulin use	-	-0.002 (-0.304 to 0.026)	-0.011 (-0.389 to 0.060)
Basal insulin and secretagogue use	0.207 (0.000 to 0.632)	0.275 (0.000 to 0.652)	0.332 (0.000 to 0.702)
Bolus insulin and secretagogue use	0.010 (-0.137 to 0.823)	0.069 (-0.003 to 0.737)	0.074 (-0.061 to 0.505)
Basal and bolus insulin and secretagogue use	-0.002 (-0.909 to 0.180)	-	-
Insulin pump and secretagogue use	0.248 (-0.064 to 0.623)	0.147 (-0.143 to 0.513)	-0.008 (-0.402 to 0.232)
Antibiotic use	0.352 (0.000 to 0.644)	0.265 (0.000 to 0.516)	0.292 (0.000 to 0.590)
Beta-blocker use	0.292 (0.071 to 0.464)	0.178 (0.000 to 0.389)	0.175 (0.000 to 0.367)
Corticosteroid use	0.289 (0.028 to 0.510)	0.209 (0.000 to 0.420)	0.120 (-0.099 to 0.323)
Number of diabetes medications (other than insulin or secretagogues)	-0.118 (-0.233 to -0.005)	-0.083 (-0.193 to 0.000)	-0.088 (-0.200 to 0.001)
A1C			
Less than or equal to 7%	-	-	0.023 (-0.062 to 0.207)
7.1% to 8%	-	0.014	-

		(-0.050 to 0.161)	
8.1% to 9%	-0.002 (-0.166 to 0.122)	-0.009 (-0.173 to 0.099)	-0.048 (-0.208 to 0.091)
Greater than or equal to 9.1%	-0.022 (-0.292 to 0.191)	-0.111 (-0.380 to 0.059)	-0.107 (-0.379 to 0.068)
Variability of A1C (index of variation)	0.441 (0.000 to 0.979)	0.185 (-0.131 to 0.690)	0.089 (-0.317 to 0.589)
Number of past severe hypoglycemia events resulting in emergency department use or hospitalization	0.037 (0.019 to 0.077)	0.037 (0.015 to 0.089)	0.049 (0.026 to 0.095)
Currently treated using dialysis	0.735 (0.398 to 1.130)	0.320 (0.000 to 0.662)	0.079 (-0.171 to 0.438)
Number of diabetes visits (past 30 days)	0.182 (0.125 to 0.252)	0.121 (0.064 to 0.184)	0.084 (0.025 to 0.145)
T2DM vs. T1DM		-0.183 (-0.557 to 0.000)	-0.303 (-0.678 to 0.000)
Duration of diabetes (years)		-	-0.001 (-0.015 to 0.007)
rt-C/FGM device use		0.454 (0.206 to 0.734)	0.348 (0.113 to 0.640)
IAH		-	-0.003 (-0.148 to 0.138)
Mental health condition		0.137 (-0.017 to 0.369)	0.018 (-0.219 to 0.217)

Chronic kidney disease	0.170 (-0.023 to 0.483)	0.089 (-0.137 to 0.402)
Neurologic disorder	-0.154 (-0.443 to 0.034)	-0.191 (-0.494 to 0.052)
Number of other comorbidities	0.027 (-0.017 to 0.074)	0.018 (-0.037 to 0.064)
Diabetic ketoacidosis	0.017 (-0.313 to 0.325)	0.059 (-0.288 to 0.372)
Amputation of toes, feet, or legs	-	-0.002 (-0.387 to 0.292)
Retinopathy	0.219 (-0.091 to 0.627)	0.190 (-0.108 to 0.588)
Number of other diabetes complications	0.115 (0.000 to 0.219)	0.101 (0.000 to 0.200)
Marital status, n (%)		
Partnered	-	-
Divorced, separated, widowed	0.174 (0.000 to 0.488)	0.209 (-0.009 to 0.500)
Never married	-0.020 (-0.321 to 0.000)	-0.018 (-0.320 to 0.026)
Highest education achieved		
High school, some high school, or Grade 8	0.230 (0.000 to 0.519)	0.142 (0.000 to 0.493)
College degree or some college	-0.116	-0.178

	(-0.393 to 0.000)	(-0.398 to 0.000)
Degree beyond first college degree	-	-
Income ($15000 increments)	-	-0.007 (-0.052 to 0.032)
Insurance coverage		
Private insurance plan	-0.095 (-0.384 to 0.000)	-0.030 (-0.297 to 0.073)
Government-assistance plan	-	-
Multiple insurance plans and other insurance plans	0.161 (0.000 to 0.422)	0.136 (-0.028 to 0.365)
Out-of-pocket (i.e., no insurance coverage)	0.182 (-1.200 to 0.966)	0.022 (-1.250 to 0.817)
Race		
Only White	-0.010 (-0.314 to 0.129)	-0.009 (-0.365 to 0.045)
Multiracial (White and non-White)	-	-0.020 (-0.515 to 0.414)
Non-white or multiracial (non-White)	0.057 (-0.125 to 0.340)	0.197 (-0.033 to 0.478)
Ethnicity		
Hispanic, Latino/a, or Spanish origin	-0.001 (-0.447 to 0.308)	-0.124 (-0.591 to 0.240)
Experiencing food insecurity	0.480 (0.240 to 0.752)	0.264 (0.000 to 0.565)

Received diabetes education	-	-0.066 (-0.313 to 0.115)
General health status	-0.123 (-0.230 to -0.008)	-0.113 (-0.232 to 0.000)
Health literacy		-
Alcohol use		-0.090 (-0.195 to 0.000)
Binge drinking behaviour		0.168 (0.017 to 0.326)
Smoking status		0.103 (-0.032 to 0.264)
Recreational drug use		-0.039 (-0.132 to 0.058)
Aerobic exercise		0.099 (0.000 to 0.204)
Anaerobic exercise		-0.074 (-0.168 to 0.000)
Fear of hypoglycemia		0.016 (0.011 to 0.022)
Quality of life		-0.002 (-0.009 to 0.003)

T1DM, type 1 diabetes mellitus; T2DM, type 2 diabetes mellitus; IAH, impaired awareness of hypoglycemia; BMI, body mass index; rt-C/FGM, real-time continuous or flash glucose monitoring; HFS-II, Hypoglycemia Fear Survey-II; VR-12, Veterans RAND 12 Item Health Survey; CI, confidence interval.
-: Candidate predictor was not selected by LASSO

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Curriculum Vitae

Selected works

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Post-secondary Education Degrees

Western University
London, Ontario, Canada
2006-2011, Hons. BHSc

Western University
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McMaster University
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2012-2015, MSc

Western University
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2014-2022, PhD

Graduate Honours and Awards

Province of Ontario Graduate Scholarship
2016 – 2017; 2018 – 2019

Queen Elizabeth II Graduate Scholarship in Science & Technology (PhD)
2017 – 2018

National Institutes of Health Grant
2015

Western University Vice President of Research Support Grant,
2014 – 2015

Grants

1. An extension of the iNPHORM study that includes the production of and publication five manuscripts as well as related knowledge exchange materials and resources. (2022 – 2023). PIs: Ratzki-Leewing A, Harris S. Investigator Sponsored Study, Sanofi Global: $96,970.00 (CAD)

2. An investigation of the impacts of COVID-19 on diabetes management in the US. Data are used from the iNPHORM study. (2021) PIs: Ratzki-Leewing A, Harris S. Investigator Sponsored Study, Sanofi Global: $49,816 (CAD)

3. A 1-year prospective survey investigation to understand hypoglycemia risk stratification in a real-world, population-based cohort of American adults with diabetes taking insulin and/or secretagogues. (2019 – 2021).

PIs: Ratzki-Leewing A, Harris S. Investigator Sponsored Study, Sanofi Global: $1.3 million (CAD)

4. A national population-based research study to ascertain the real-world burden of hypoglycemia among at-risk people with diabetes, their significant others, and diabetes care providers. (2014 – 2017). PIs: Harris S. Role: Co-Investigator (1 of 4) Investigator Sponsored Study, Sanofi Canada: $533,792 (CAD)

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Invited Symposia

1. Ratzki-Leewing A. Health disparities, risk of hypoglycemia, and treatment options: Hypoglycemia risk and events in the US – Geographic distribution. The American Diabetes Association's 82nd Scientific Sessions. New Orleans, LA. Jun 5th, 2022

2. Ratzki-Leewing A. Metrics and connected solutions for diabetes care in an evolving era: Remaining barriers and current outcomes in a changing world. 15th International Conference on Advanced Technologies & Treatments for Diabetes. Barcelona, ES. Mar 10th, 2022.

3. Ratzki-Leewing A, Harris S. 100 years of hypoglycemia. Diabetes Update Day. Virtual Meeting. Nov 10th, 2021

4. Ratzki-Leewing A, Harris S. The real-world burden and cost of diabetes: Results from the iNPHORM study. The 57th Annual Meeting of the European Association for the Study of Diabetes (EASD). Virtual Meeting. Sept 30th, 2021

5. Ratzki-Leewing A. Spotlight on hypoglycemia in type 2 diabetes: Misconceptions debunked. Practical Diabetes Forum 2020. Virtual Meeting. Sept 12th, 2020

6. Ratzki-Leewing A, Harris S. Hypoglycemia: Is it a problem? Evidence-Based Management of the Diabetes Epidemic. Hamilton, CA. Nov 13th, 2019

7. Ratzki-Leewing A, Harris S. Hypoglycemia: Is it a problem? Diabetes Update Day. London, CA. Nov 13th, 2019

8. Ratzki-Leewing A, Harris S. Hypoglycemia: Is it a problem? 2019 Diabetes Canada/CSEM Professional Conference. Winnipeg, CA. Oct 2nd-5th, 2019

9. Ratzki-Leewing A, Harris S. Family members: The forgotten players in the diabetes care team (The TALK-HYPO Study). The 55th Annual Meeting of the European Association for the Study of Diabetes (EASD). Barcelona, ES. Sept 16th-20th, 2019