Received: 21 July 2021 | Revised: 24 February 2022 | Accepted: 4 March 2022

DOI: 10.1111/dom.14690

ORIGINAL ARTICLE

WILEY

Previously unrecognized risk factors for severe hypoglycaemia requiring emergency medical care in insulin-treated type 2 diabetes: Results from a real-world nested case-control study

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Funding information
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Abstract

Aim: Several risk factors for severe hypoglycaemia (SH) are associated with insulin-treated diabetes. This study explored potential risk factors in adults with insulin-treated type 2 diabetes mellitus (T2DM).

Materials and Methods: In this case-control study, adults with T2DM initiating insulin were identified in the IQVIA PharMetrics® Plus database. The index date was the date of the first SH event (cases). Using incidence-density sampling, controls were selected from those who had been exposed 'at risk' of SH for the same amount of time as each case. After exact-matching on the well-established factors, previously unreported risk factors were evaluated through conditional logistic regression.

Results: In 3153 case-control pairs, pregnancy [odds ratios (OR) = 3.20, $p = .0003$], alcohol abuse (OR = 2.43, $p < .0001$), short-/rapid-acting insulin (OR = 2.22/1.47, $p < .0001$), cancer (OR = 1.87, $p < .0001$), dementia/Alzheimer's disease (OR = 1.73, $p = .0175$), peripheral vascular disease (OR = 1.59, $p < .0001$), antipsychotics (OR = 1.59; $p = .0059$), anxiolytics (OR = 1.51, $p = .0012$), paralysis/hemiplegia/paraplegia (OR = 1.51, $p = .0416$), hepatitis (OR = 1.50, $p = .0303$), congestive heart failure (OR = 1.47, $p = .0002$), adrenergic-corticosteroid combinations (OR = 1.45, $p = .0165$), β-adrenoceptor agonists (OR = 1.40, $p = .0225$), opioids (OR = 1.38, $p < .0001$), corticosteroids (OR = 1.35, $p = .0159$), cardiac arrhythmia (OR = 1.29. $p = .0065$), smoking (OR = 1.28, $p = .005$), Charlson Comorbidity Index score 2 (OR = 1.28, $p = .0026$), 3 (OR = 1.41, $p = .0016$) or ≥4 (OR = 1.57, $p = .0002$), liver/gallbladder/pancreatic disease (OR = 1.26, $p = .0182$) and hypertension (OR = 1.19, $p = .0164$) were independently associated with SH.

Conclusions: Although all people with insulin-treated diabetes are at risk of SH, these results have identified some previously unrecognized risk factors and sub-groups of

insulin-treated adults with T2DM at greater risk. Scrutiny of current therapies and comorbidities are advised as well as additional glucose monitoring and education, when identifying and managing SH in vulnerable populations.

KEYWORDS
insulin therapy, risk factors, severe hypoglycaemia, type 2 diabetes mellitus

1 | INTRODUCTION

With progressive pancreatic β-cell failure, many people with type 2 diabetes mellitus (T2DM) will eventually require insulin, either alone or in combination with other glucose-lowering agents.[1] A common adverse side effect of insulin therapy is hypoglycaemia.[2] Its causes and risk factors are well established, particularly in type 1 diabetes (T1DM), and hypoglycaemia is an important and potentially preventable cause of morbidity, mortality, substantial socio-economic costs, diminished productivity and reduced quality of life.[3,4] In particular, severe hypoglycaemia (SH), characterized by incapacitating cognitive impairment and defined by necessitating assistance for recovery,[5] is a marker of high absolute risk of cardiovascular morbidity and mortality in people with T2DM.[6] Fear of SH is a significant barrier to optimizing glycaemic control in T2DM, both for patients, whose motivation to adhere to intensive regimens is diminished, and for health care providers, who are often reluctant to initiate or intensify treatment.[7,8] By identifying the potential risk factors in people with insulin-treated T2DM and introducing measures to minimize SH, it may be possible to overcome this barrier and deliver better glycaemic control.[3,4]

While the role of insulin and insulin secretagogues, such as the sulphonylureas, in provoking SH is well recognized,[2,4] the range of potential factors that are associated with an increased risk of SH has received less attention in adults with T2DM than in those with T1DM.[9] Established risk factors in T2DM include a preceding history of SH, older age, longer duration of diabetes, renal impairment and chronic kidney disease (CKD), cognitive impairment, cardiovascular disease, depression, cardiac failure and impaired awareness of hypoglycaemia.[2,4,10] In addition, the risk of SH is known to rise with increasing duration of insulin treatment.[11] Karter et al. developed a hypoglycaemia risk stratification tool in T2DM that uses six predictors, namely a history of hypoglycaemia-related health care utilization, insulin use, sulphonylurea use, emergency department use, renal dialysis or CKD stage 4 or 5, and age.[10] These predictors can be applied in clinical practice to identify patients at higher risk.[4] However, as other patient-related and treatment characteristics have been described that are associated with increased risk of hypoglycaemia,[12-16] further real-world investigation of these and other unidentified factors is warranted.

The present study aimed to identify factors associated with increased risk of SH that resulted in emergency medical treatment in insulin-treated T2DM in addition to those already established, by using data derived from a large administrative health care claims database in the USA.

2 | MATERIALS AND METHODS

2.1 | Study design

A retrospective, nested, case-control study was performed within a cohort of insulin-treated adults with T2DM from the IQVIA PharMetrics® Plus claims database.[17] PharMetrics Plus is one of the largest databases of adjudicated medical and pharmacy claims in the USA, covering 90% of hospitals and 80% of doctors across all 50 States.[17] In addition to standard fields such as inpatient and outpatient diagnoses and procedures, retail and mail order prescription records, PharMetrics Plus contains detailed information on pharmacy and medical benefits, inpatient stay and provider details. Amounts charged by providers and amounts allowed and paid by health plans are available for all services rendered, along with dates of service for all claims. Other data elements include demographic variables, payer type, and start and stop dates of health-plan enrolment.

An overview of the study design and patient selection methods is shown in Figure 1. The study protocol was pre-registered with the European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP, study no. EUPAS31111) before study execution.[18] As this study used anonymized information, the requirement for patient informed consent was waived by the New England Institutional Review Board (WO 1-9936-1).

2.2 | Population selection criteria

All people with at least one insulin prescription claim between 1 July 2012 and 31 December 2018 were identified within the data source. The first insulin claim during this period was defined as the cohort entry date. Insulin users were included in the analysis if they had a diagnosis of T2DM and had not filled an insulin prescription in the preceding 6 months (i.e. new starters). Claimants were also required to be ≥18 years at the cohort entry date and to have at least 6 months of continuous health plan enrolment before the cohort entry date, with both medical and pharmacy benefits. Those with a record indicative of diabetes other than T2DM (i.e. T1DM, gestational, non-clinical or secondary diabetes) during the study period were excluded. People who underwent bariatric surgery were also excluded because of its effect on metabolic control. Finally, to ensure good data quality, all people with a missing or invalid year of birth and payer type, who were of unknown sex or

region, or who were covered by an invalid medical insurer, were excluded from analysis.

2.3 | Cases and controls identification

To identify cases and controls, adults treated with insulin were followed from the cohort entry date until either the earliest occurrence of SH, or insulin treatment discontinuation, or the end of continuous health plan enrolment, or the end of the study period. Discontinuation of insulin treatment was defined as having no insulin prescriptions for >90 days from the end of the treatment coverage of the previous claim.[19]

During the follow-up period all claimants were assumed to be 'at risk' of SH. Cases were identified by occurrence of SH while on insulin treatment, with the date of the first SH event being the index date. To account for any potential deviations from the prescribed treatment schedule, patients were considered to be on insulin treatment for up to 30 days after the supply of the last insulin claim was recorded. International Classification of Diseases (ICD) ninth and tenth revision codes

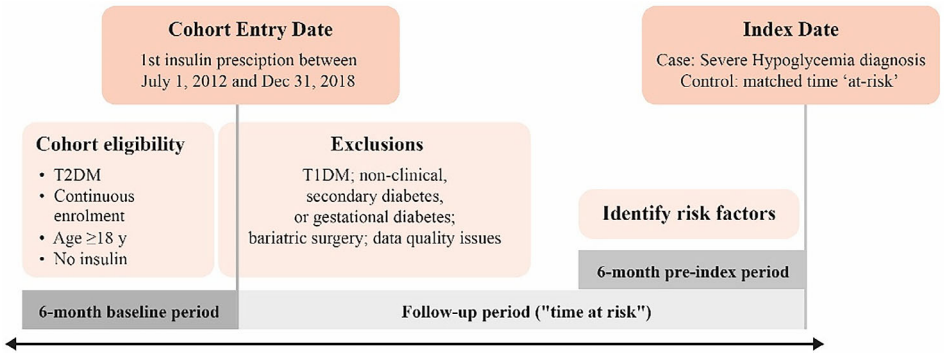

FIGURE 1 Overview of the study design and patient eligibility criteria. T1DM, type 1 diabetes

TABLE 1 Univariate comparisons of baseline characteristics between patients experiencing severe hypoglycaemia while on insulin (cases) and matched controls

Characteristics	Cases $N = 3153$	Controls $N = 3153$	*p* value
Age[a]			
Median (minimum, maximum)	57 (18, 84)	57 (19, 84)	.7800
Sex			.0083
Male	1638 (52.0)	1744 (55.3)	
Time 'at risk' for severe hypoglycaemia (months)[b]			
Mean ± SD	11.2 ± 13.8	11.2 ± 13.8	NA
Median	5.6	5.6	NA
Index date			<.0001
Pre-Oct 2015	794 (25.2)	1293 (41.0)	
Oct 2015 and later	2359 (74.8)	1860 (59.0)	
Lifestyle variables			
Alcohol abuse[c]	138 (4.4)	35 (1.1)	<.0001
Smoking or history of smoking	639 (20.3)	327 (10.4)	<.0001
Pregnancy status			
Pregnancy 2-6 months pre index	58 (1.8)	19 (0.6)	<.0001
Pregnancy 1 month pre index (current)	59 (1.9)	15 (0.5)	<.0001
History of severe hypoglycaemia[a]	196 (6.2)	196 (6.2)	NA

Note: Index date was the date of the first severe hypoglycaemia event. Data are n (%). Matching variables included: age (5-year increments), sulphonylurea use and severe hypoglycaemia episodes in the 6 months before the index (yes/no), and renal disease in the 2-6 months and in the month before the index (yes/no).

[a]Matching variables.

[b]Controls matched to cases on time 'at risk' using incidence density sampling.

[c]Included claims indicative of both acute and chronic abuse.

were used to identify diagnoses of SH in both inpatient and outpatient settings, based on the algorithm proposed by Karter et al. (Table S1).[20,21] Controls were identified using incidence-density sampling, whereby one control was randomly selected for each identified case from the pool of people who had not experienced SH and who had been exposed to at least the same amount of time 'at risk' as the case. Controls could become cases if they subsequently experienced SH.

2.4 | Factors potentially associated with severe hypoglycaemia

Factors that were evaluated for their association with SH in the present study included the established predictors that were used in the risk stratification tool by Karter et al.[10] and were available in the PharMetrics Plus database, namely previous SH, sulphonylurea use, renal disease (including CKD and renal failure/dialysis) and older age, as well as other characteristics including demographics, insurance type, lifestyle habits, comorbidities and co-medications that have seldom been studied in previous published reports (-Table S2).[12-15] A 6-month period preceding the index date was used to evaluate any potential association (Figure 1). For medication use, the measurement period was divided into 1-month and 2-6-month intervals preceding the index date, to evaluate the effect of 'current' (1 month) versus 'long-term' (2-6 months) exposure. Some patients with long-term exposure may also have exposure within 1-month before the index date. Similarly, comorbidities such as cognitive disorders (defined as anxiety, dementia,

TABLE 2 Univariate comparisons of pre-index comorbidities between patients experiencing severe hypoglycaemia while on insulin (cases) and matched controls

	Cases	Controls	
	N = 3153	*N* = 3153	*p* value
Comorbidities			
Anxiety	430 (13.6)	274 (8.7)	<.0001
Asthma	288 (9.1)	153 (4.9)	<.0001
Cancer 2-6 months pre index	396 (12.6)	250 (7.9)	<.0001
Cancer 1 month pre index (current)	309 (9.8)	113 (3.6)	<.0001
Cardiac arrhythmia	623 (19.8)	366 (11.6)	<.0001
Chronic pain/fibromyalgia	463 (14.7)	255 (8.1)	<.0001
Congestive heart failure	529 (16.8)	295 (9.4)	<.0001
Chronic obstructive pulmonary disease	323 (10.2)	127 (4.0)	<.0001
Dementia/Alzheimer's disease	105 (3.3)	44 (1.4)	<.0001
Depression	548 (17.4)	360 (11.4)	<.0001
Hepatitis	139 (4.4)	56 (1.8)	<.0001
Hypertension	2433 (77.2)	2218 (70.4)	<.0001
Liver/gallbladder/pancreatic disease	537 (17.0)	275 (8.7)	<.0001
Myocardial infarction/coronary heart disease	709 (22.5)	480 (15.2)	<.0001
Osteoarthritis	1104 (35.0)	872 (27.7)	<.0001
Paralysis/hemiplegia/paraplegia	132 (4.2)	45 (1.4)	<.0001
Peripheral vascular disease	400 (12.7)	213 (6.8)	<.0001
Renal disease[a,b] 2-6 months pre index	644 (20.4)	644 (20.4)	NA
Renal disease[a,b] 1 month pre index (current)	412 (13.1)	412 (13.1)	NA
Charlson comorbidity index group			<.0001
0	37 (1.2)	87 (2.8)	
1	757 (24.0)	1152 (36.5)	
2	690 (21.9)	735 (23.3)	
3	395 (12.5)	332 (10.5)	
≥4	1274 (40.4)	847 (26.9)	

Note: Index date was the date of the first severe hypoglycaemia event. Data are n (%) unless otherwise stated. Matching variables included: age (5-year increments), sulphonylurea use and severe hypoglycaemia episodes in the 6 months before the index (yes/no), and renal disease in the 2-6 months and in the month before the index (yes/no).

Abbreviation: NA, not applicable.

[a]Matching variables.

[b]Including chronic kidney disease and renal failure/dialysis.

TABLE 3 Univariate comparisons of current and long-term medication use between patients experiencing severe hypoglycaemia while on insulin (cases) and matched controls

Drug use	Cases $N = 3153$	Controls $N = 3153$	p value
Current medication use (1 month preceding the index date)			
Insulin type			
Rapid-acting insulin	1188 (37.7)	840 (26.6)	<.0001
Short-acting insulin	162 (5.1)	72 (2.3)	<.0001
Non-insulin glucose-lowering medications	1711 (54.3)	1953 (61.9)	<.0001
Third-generation β blockers	426 (13.5)	309 (9.8)	<.0001
Opioids	858 (27.2)	508 (16.1)	<.0001
Anxiolytics	281 (8.9)	143 (4.5)	<.0001
Antipsychotics	207 (6.6)	67 (2.1)	<.0001
Corticosteroids	310 (9.8)	148 (4.7)	<.0001
Sympathomimetics	369 (11.7)	197 (6.3)	<.0001
β-Adrenoceptor agonists	269 (8.5)	140 (4.4)	<.0001
Adrenergic corticosteroid combinations	185 (5.9)	95 (3.0)	<.0001
Long-term medication use (2-6 months preceding the index date)			
Insulin type			
Rapid-acting insulin	1113 (35.3)	821 (26.0)	<.0001
Short-acting insulin	141 (4.5)	66 (2.1)	<.0001
Non-insulin glucose-lowering medications	1939 (61.5)	2131 (67.6)	<.0001
Third-generation β-blockers	435 (13.8)	325 (10.3)	<.0001
Opioids	1246 (39.5)	898 (28.5)	<.0001
Anxiolytics	396 (12.6)	237 (7.5)	<.0001
Antipsychotics	237 (7.5)	88 (2.8)	<.0001
Corticosteroids	468 (14.8)	294 (9.3)	<.0001
Sympathomimetics			
β-Adrenoceptor agonists	386 (12.2)	278 (8.8)	<.0001
Adrenergic-corticosteroid combinations	220 (7.0)	107 (3.4)	<.0001

Note: Index date was the date of the first severe hypoglycaemia event. Data are n (%). Matching variables included: age (5-year increments), sulphonylurea use and severe hypoglycaemia episodes in the 6 months before the index (yes/no), and renal disease in the 2-6 months and in the month before the index (yes/no).

depression, or schizophrenia), renal disease, cancer (any type) and pregnancy (past or ongoing) were evaluated in the 1 month and in the 2-6 months preceding the index date to assess the effect of 'current' versus 'long-term' events.

2.5 | Matching

To evaluate the importance of newly identified risk factors independently from those used by Karter et al.,[10] before the analyses were made each control was exact-matched to its case on age (5-year increments), sulphonylurea use, and SH episodes in the 6 months before index (yes/no), and renal disease in the 2-6 months and in the month before index (yes/no). A sensitivity analysis without exact-matching on the established risk factors was also performed to confirm the role of the established risk factors in the prediction.

2.6 | Statistical analyses

All analyses were conducted using SAS version 9.4 (SAS Institute Inc., Cary, NC, USA). Univariate comparisons of patient characteristics between matched cases and controls were carried out via McNemar's/Stuart-Maxwell tests and paired t-test (matched samples). Variables with $p < .1$ and a standardized mean difference ≥15% were selected for initial inclusion into a conditional logistic regression model used to identify associations with SH. A backward elimination procedure was applied to keep only statistically significant ($p < .05$) covariates in the model. For each variable, results are reported as odds

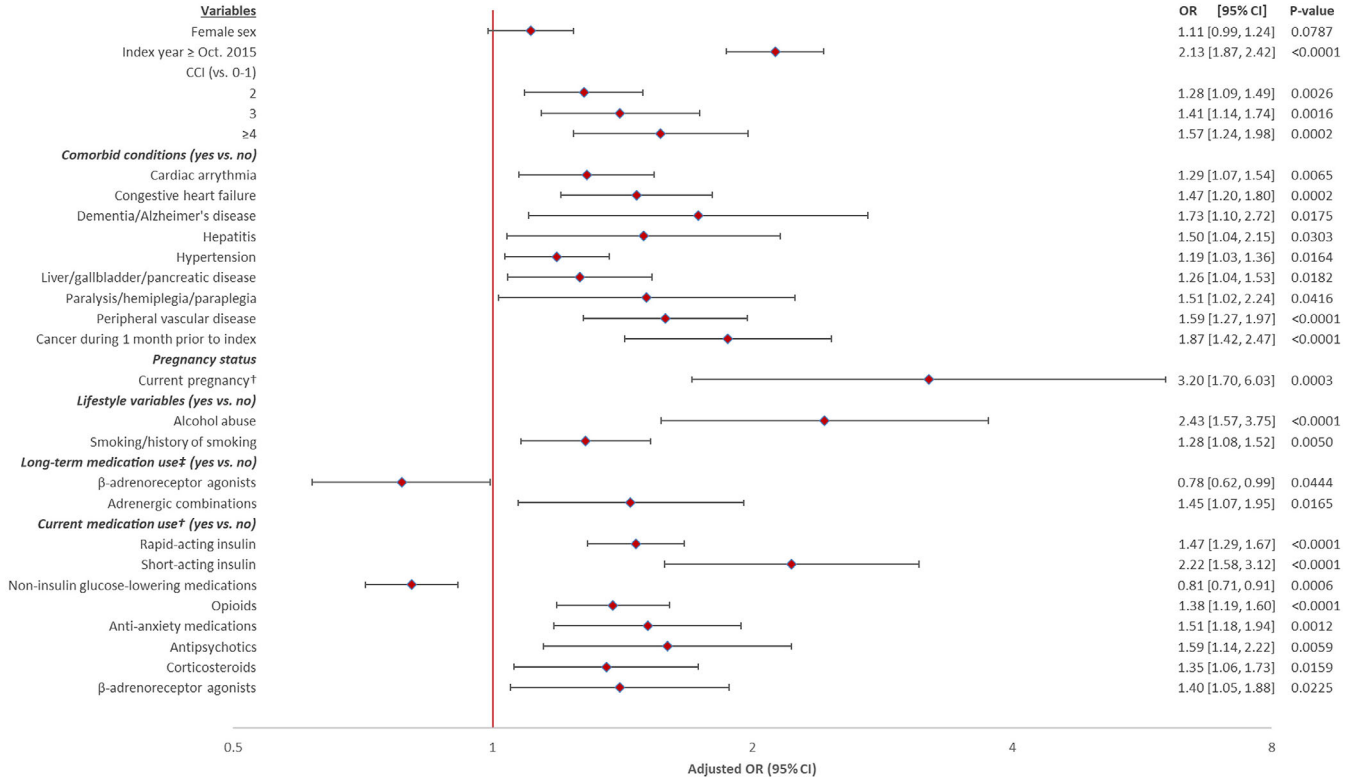

FIGURE 2 Factors associated with higher odds of severe hypoglycaemia. Results from the final conditional logistic regression model in matched cases and controls—Final conditional logistic regression model. †Current is defined as 1 month preceding the index date (first severe hypoglycaemia event); ‡long-term use is defined as exposure to medications in the previous 2-6 months; alcohol abuse included both acute and chronic abuse. Matching variables included: age (5-year increments), sulphonylurea use, and severe hypoglycaemia episodes in the 6 months before the index (yes/no), and renal disease in the 2-6 months and in the month before the index (yes/no). CCI, Charlson Comorbidity Index; CI, confidence interval; OR, odds ratio

ratios (ORs) and 95% confidence intervals adjusted for all the other variables in the model. Statistical significance for risk factors was assessed with $p < .05$ in the final model. Variables with clinical relevance were included into the final model irrespective of their statistical significance.

3 | RESULTS

3.1 | Baseline characteristics and medication use before hypoglycaemia

In total, 3207 eligible adults were identified as cases (Figure S1 shows attrition of overall patients at risk who were identified as cases). Incidence density and exact matching led to 3153 case-control pairs, aged between 18 and 84 years and with mean ± SD time 'at risk' before the first SH event of 11.2 ± 13.8 months (Table 1).

Through univariate analyses, 37 variables with a $p < .1$ and a standardized mean difference ≥15% were selected from the initial list of potential risk factors (Table S2, bolded variables). In addition, sex, dementia/Alzheimer's disease and pregnancy were retained regardless of their apparent effect on hypoglycaemia, based on their clinical importance to glycaemic control in T2DM. The demographics, clinical characteristics and medication use of cases and matched controls based on these selected variables are shown in Tables 1-3.

3.2 | Factors associated with increased risk of severe hypoglycaemia

The backward selection process produced a final list of 24 variables that were retained for their association with SH in the final model. However, even though not significant, the variable, 'sex', was included into the final model for its clinical relevance. For exact-matched cases and controls ($N = 3153$ case-control pairs), recent or ongoing pregnancy, alcohol abuse, smoking and history of smoking, and having a higher Charlson Comorbidity Index (CCI) score or specific comorbidities (i.e. cardiac arrhythmia, congestive heart failure, dementia/Alzheimer's disease, hepatitis, hypertension, liver/gallbladder/pancreas disease, paralysis/hemiplegia/paraplegia, peripheral vascular disease, and/or current cancer) were all significantly and independently associated with increased odds of SH (Figure 2). Being diagnosed on October 1, 2015, or later, that is after the introduction of the ICD-10 coding system, was associated with twice the odds of experiencing SH (OR = 2.13, $p < .0001$) (Figure 2).

With regard to insulin type and co-medication use, current exposure to short- and rapid-acting insulin, opioids, anxiolytics, antipsychotics, corticosteroids and β-adrenoceptor agonists, and the long-term use of adrenergic-corticosteroid combinations, were all associated with increased odds of SH. Conversely, long-term use of β-adrenoceptor agonists and current use of non-insulin glucose-lowering medications were associated with lower odds of SH (Figure 2). With respect to medication use, the statistical model showed that current exposure to medications was more strongly associated with increased risk of SH than long-term use of medication (Figure 2).

In the sensitivity analysis where cases and controls were not exact-matched ($N = 3207$ in each group), adjustment for the established risk factors produced similar results as the matched analysis. Furthermore, previous SH (OR: 23.63, $p < .0001$), age ≥75 years versus 26-49 years (OR: 2.49, $p < .0001$), current use of sulphonylureas (OR: 1.33, $p = .0219$) and current renal disease (OR: 1.93, $p = .0001$), all of which are established risk factors of SH, were significantly associated with increased odds in the present model (Table S4).

4 | DISCUSSION

This large retrospective, nested, case-control study of over 6000 cases and controls with insulin-treated T2DM has identified several factors that appear to be associated with an increased risk of SH. Although SH is defined as an event that necessitates assistance for recovery,[5] the present study utilized SH events that had resulted in emergency medical care being required, using a validated algorithm.[20,21] Events that were treated outside of the health care system were therefore not included. A previous study that examined the difference between self-reported SH events and hypoglycaemia-related emergency department and hospital utilization observed that using the latter alone significantly underestimates the real rate of SH.[22] The results of the present study should be interpreted within this context. To that end, the present study identified various factors that were associated with an increased risk of SH, in addition to the well-recognized association with older age, sulphonylurea use, renal disease and a history of previous SH. Risk factors that were identified included the current use of rapid-/short-acting insulins, indicators of poor health (high comorbidity burden as measured by the CCI), cardiac arrhythmia, congestive heart failure, dementia/Alzheimer's disease, hepatitis, hypertension, liver/gallbladder/pancreas disease, paralysis/hemiplegia/paraplegia, peripheral vascular disease, and cancer and the current use of various medications, namely, opioids, anxiolytics, antipsychotics, corticosteroids, β-adrenoceptor agonists, and adrenergic-corticosteroid combinations. Lifestyle factors (alcohol abuse, smoking) and pregnancy were also identified. Apart from a previous history of SH, which is known to be a powerful predictor of subsequent SH, the association between the additional identified factors (with ORs ranging between 1.2 and 3.2) and SH was as strong as that reported for factors that are well known (ORs ranging between 1.3 and 2.5).

In the present study, the current use of short-acting and rapid-acting insulins was associated with a higher risk of SH and the odds of SH was 2.2 times higher in people using short-acting insulin compared with 1.5 times higher in people using rapid-acting insulin. The larger OR for short-acting insulin compared with rapid-acting insulin provides a signal that using short-acting insulin may pose a greater risk for SH than fast-acting insulin. While this observation is consistent with previous studies,[23] the present study was not designed to make such a comparison. Clinical trials showed the marked increase in SH associated with use of short-acting insulin; however, few studies using real-world data have reported the increased risk when using short-acting compared with rapid-acting insulin. Further research will be needed to verify this finding, but in the meantime people treated with these insulin analogues (rapid-acting and short-acting insulins) should be advised to undertake careful glucose monitoring, be provided with glucagon for the treatment of SH and may benefit from additional education about hypoglycaemia.

Several coexisting comorbidities and current exposure to various medications were associated with an increased risk of SH. These were associations alone and this does not show causality. In the large endpoint trial in T2DM, ADVANCE, SH was strongly associated with increased risks of adverse clinical outcomes that included a range of several unexpected outcomes other than cardiovascular morbidity, involving, for example, respiratory, digestive and skin diseases. While these investigators considered the possibility that SH may contribute to adverse outcomes affecting other systems, they proposed that it was probable that hypoglycaemia represented a marker of vulnerability to experience adverse clinical outcomes.[24] Many of the disease states identified in the present study as being associated with an increased risk of SH, are indicative of serious illness affecting people with T2DM. While each of the factors in the present study were independently associated with an increased risk of hypoglycaemia, taken collectively, they appear to indicate a subgroup of people with serious underlying ill health, who, consequently, are more vulnerable to developing SH. For example, higher CCI scores indicate either the presence of multiple comorbid conditions or the presence of severe comorbidities (such as cancer).

The present observations showed that the odds of SH occurring in people with a CCI score ≥4 were nearly twice as high as those of people with a score of 0 or 1 were. These findings are consistent with those of a cross-sectional French study[25] and a retrospective cohort study in Korea in both of which CCI was reported to be independently associated with hypoglycaemia in people with T2DM.[13] In addition, the present findings are consistent with an observational study in the USA of more than 1 million adults with diabetes, where cardiovascular disease and congestive cardiac failure, as well as CKD, were reported associated with a four- to six-fold higher frequency of SH.[26] Similarly, drugs such as opioids, anxiolytics, antipsychotics, corticosteroids and β-adrenoceptor agonists are frequently prescribed for people who are very unwell, many of whom having serious physical and/or mental conditions, many of which are associated with inadequate diet and who may therefore be more prone to the development of SH. The relationship between the use of these medications and an increased

risk of SH, which was identified in the present study, does not necessarily imply a direct effect of these drugs in causing or promoting SH, as the association may be primarily with the presence of serious illness. However, the association of these medications with an increased risk of SH may be of clinical relevance. The present data suggest that caution should be exercised before advocating intensive insulin treatment for people with T2DM who have serious comorbidities as they may be at greater risk of SH. The fact that the present study shows a stronger association with current, as opposed to longer-term medication use, may also be important, as treatment with insulin is often necessary during the management of acute illness and emphasizes the need for clinicians to be alert to the potential risk of SH in these situations.

Unsatisfactory lifestyle behaviours, such as alcohol abuse and smoking, were associated with an increased risk of SH. Alcohol can suppress hepatic gluconeogenesis, and so interfere with the counter-regulatory response to hypoglycaemia, and it diminishes awareness of hypoglycaemia, which can increase the risk of SH.[27] Excessive alcohol consumption could therefore be a risk factor in people with insulin-treated T2DM. The present study also observed that people who smoke or have a history of smoking have a 30% higher risk of SH compared with non-smokers. A similar association has been reported in smokers with T1DM.[28-30] It has been suggested that smoking may reduce insulin clearance in people with T2DM, leading to hyperinsulinaemia, increased risk of postprandial hypoglycaemia, and poorer metabolic control overall.[31] This might explain the association shown in the present study, which suggests that even though smoking is associated with poor glycaemic control in individuals with diabetes,[31-35] intensive insulin treatment to improve glycaemic control may be hazardous in some smokers. Recently, Jensen and colleagues reached similar conclusions in a risk analysis of adult smokers with T1DM from Europe and North America.[30] While there are physiological reasons for increased risk of SH in patients with these factors, it is also important to note that alcohol abuse and smoking tend to be more prevalent in people with other behavioural risk factors, including poor diet,[36] which can be associated with poor glycaemic control.

Pregnant women with diabetes are encouraged to attain strict glycaemic control to minimize the risk of fetal abnormalities.[37] However, SH is a common clinical problem in pregnant women with diabetes, particularly in T1DM.[38] The present study confirms that a similar risk exists in pregnant women with T2DM. Although the present study cannot confirm causation, this may be a consequence of intensifying insulin treatment to improve glycaemic control during pregnancy.

Cases were identified in the present study using the algorithm developed by Karter et al., which included ICD-9-CM and ICD-10-CM codes depending on whether the SH was recorded before or after the introduction of the 10th revision on 1 October 2015.[10,20,21] The observation that more SH was diagnosed after the transition to ICD-10-CM codes is probably explained by the number of diagnostic codes for hypoglycaemia being increased from 5 to 27 with a renewed focus on coding in general after the transition.

The health care administrative claims database used in this study is a large and representative source of data in the USA.[17] However, these types of data have inherent limitations. Claims data are collected for billing purposes rather than for research, and it is possible that patients in the control group may have experienced hypoglycaemia events that were not recorded as 'severe' as they did not trigger a costed consultation with a health care provider and were managed outside of the health care setting by relatives or others. Medication use in this study was based on pharmacy claims; it is not possible to confirm whether people had actually taken their medications as prescribed. Similarly, it is not possible to determine when, and if, people used insulin after the prescription had been filled. In addition, the results of the present study are limited by the absence of information regarding behavioural, dietary and socio-economic factors that may be associated with SH (e.g. food insecurity, ethnicity, social deprivation and poverty). Finally, as the study sample was composed principally of commercially insured patients of working age, the results are not generalizable to uninsured populations or to people with other types of insurance. Finally, this study used a data-driven approach to identify factors associated with increased risk of hypoglycaemia. Variables showing a strong association with SH may directly cause the condition, or they could be correlated with other unmeasured factors that are correlated with SH. Some risk factors for SH are recognized to have a bidirectional relationship, such as the role of depression in people with T1DM, and in the relationship to cognitive decline in T2DM.[39,40] The exact relationship between the identified risk factors and SH is open to interpretation.

In conclusion, while all people with insulin-treated diabetes are at risk of experiencing hypoglycaemia, the present study has revealed that people with T2DM in poor health, using certain medications and with some lifestyle behaviours are more vulnerable to developing SH. Based on the present observations, clinicians should take a detailed clinical history that includes documentation of comorbid conditions occurring during the previous 6 months and either recent or current medication usage, if they are to identify 'high-risk' patients. Therapeutic regimens and individualized targets may have to be modified in the presence of factors highlighted in the present study. People who have any of these factors may require additional glucose monitoring, be provided with rescue medication and, along with their relatives or caregivers, receive detailed education about hypoglycaemia. This would include how to take preventative measures to reduce the risk, how to recognize the early symptoms of hypoglycaemia to permit early intervention, how to treat non-severe hypoglycaemia and SH and how to avoid its recurrence. Finally, health care providers should exercise caution and balance risk when proposing intensive insulin regimens for smokers/ex-smokers, those with heavy alcohol consumption and pregnant women, in view of the enhanced risk of SH and ensure that these patients receive appropriate education.

ACKNOWLEDGMENTS

The authors thank Jin Wu for providing support with data analysis and statistical services. This study was funded by Eli Lilly and Company.

CONFLICT OF INTEREST

The authors declare the following potential conflicts of interest with respect to the research, authorship and/or publication of this article: HK, CJC and JAS are full time employees of Eli Lilly and Company. CBMcG, JKM, RLW and MG are full-time employees of IQVIA, which is a consulting company that has received consulting fees from Eli Lilly and Company. BMF did not receive an honorarium for any aspect of the manuscript development and submission; he participates in speakers bureaus for Eli Lilly, Novo Nordisk, Abbott and the Worldwide Initiative for Diabetes Education, and in advisory boards with Eli Lilly and Zucara Pharmaceuticals.

AUTHOR CONTRIBUTIONS

Hong Kan, Rolin L. Wade, and Julie Settles contributed to the study concept and plan development. Hong Kan, Julie Settles, Christopher J. Child, Catherine B. McGuiness, Jasjit K. Multani, Rolin L. Wade and Magdaliz Gorritz contributed to the study design. Hong Kan, Catherine B. McGuiness, Jasjit K. Multani, Rolin L. Wade and Magdaliz Gorritz contributed to the data analysis. Brian M. Frier, Hong Kan, Julie Settles, Christopher J. Child, Catherine B. McGuiness, Jasjit K. Multani, Rolin L. Wade and Magdaliz Gorritz contributed to the data interpretation and manuscript preparation. All authors approved the final draft of the manuscript for submission.

PEER REVIEW

The peer review history for this article is available at https://publons.com/publon/10.1111/dom.14690.

DATA AVAILABILITY STATEMENT

Research data are not shared.

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SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

How to cite this article: Settles J, Kan H, Child CJ, et al. Previously unrecognized risk factors for severe hypoglycaemia requiring emergency medical care in insulin-treated type 2 diabetes: Results from a real-world nested case-control study. *Diabetes Obes Metab*. 2022;24(7):1235-1244. doi:10.1111/dom.14690