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Impact of severe hypoglycaemia requiring hospitalization on mortality in people with type 1 diabetes: A national retrospective observational cohort study

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Abstract

Aims: To assess if the risk of all-cause mortality increases in people with type 1 diabetes (T1D) with increasing number of severe hypoglycaemia episodes requiring hospitalization.

Materials and methods: We conducted a national retrospective observational cohort study in people with T1D (diagnosed between 2000 and 2018). Clinical, comorbidity and demographic variables were assessed for impact on mortality for people with no, one, two and three or more episodes of severe hypoglycaemia requiring hospitalization. The time to death (all-cause mortality) from the timepoint of the last episode of severe hypoglycaemia was modelled using a parametric survival model.

Results: A total of 8224 people had a T1D diagnosis in Wales during the study period. The mortality rate (95% confidence interval [CI]) was 6.9 (6.1-7.8) deaths/ 1000 person-years (crude) and 15.31 (13.3-17.63) deaths/ 1000 person-years (age-adjusted) for those with no occurrence of severe hypoglycaemia requiring hospitalization. For those with one episode of severe hypoglycaemia requiring hospitalization the mortality rate (95% CI) was 24.9 (21.0-29.6; crude) and 53.8 (44.6-64.7) deaths/ 1000 person-years (age-adjusted), for those with two episodes of severe hypoglycaemia requiring hospitalization it was 28.0 (23.1-34.0; crude) and 72.8 (59.2-89.5) deaths/ 1000 person-years (age-adjusted), and for those with three or more episodes of severe hypoglycaemia requiring hospitalization it was 33.5 (30.0-37.3; crude) and 86.3 (71.7-103.9) deaths/ 1000 person years (age-adjusted; $P < 0.001$). A parametric survival model showed that having two episodes of severe hypoglycaemia requiring hospitalization was the strongest predictor for time to death (accelerated failure time coefficient 0.073 [95% CI 0.009-0.565]), followed by having one episode of severe hypoglycaemia requiring hospitalization (0.126 [0.036-0.438]) and age at most recent episode of severe hypoglycaemia requiring hospitalization (0.917 [0.885-0.951]).

Othmar Moser and James Rafferty share the first authorship.

Conclusions: The strongest predictor for time to death was having two or more episodes of severe hypoglycaemia requiring hospitalization.

KEYWORDS
mortality, risk prediction, severe hypoglycaemia, type 1 diabetes

1 | INTRODUCTION

Severe hypoglycaemia is defined by the American Diabetes Association Working Group as a severe cognitive impairment accompanied by low blood glucose levels that requires external assistance for recovery.[1] In people with diabetes, hypoglycaemia is a side effect of treatment with glucose-lowering therapies resulting in relative hyperinsulinaemia. In people with type 1 diabetes (T1D), the prevalence of severe hypoglycaemia is approximately 12% to 43%, with an annual incidence of 1.0 to 1.7 episodes per person per year.[2–4] In a long-term study of childhood-onset diabetes, 8% of the causes of death were reported to be hypoglycaemia in people aged <56 years.[5] The relationship between severe hypoglycaemia and mortality is thought to have multiple mechanisms, including increased sympathetic activation, impaired myocardial contractility and cardiac output, accompanied by a rapid decrease in potassium levels, potentially provoking cardiac arrhythmia.[2,6] Furthermore, severe hypoglycaemia may lead to impaired blood flow, endothelial function and tissue perfusion, platelet activation, along with an inflammatory response increasing the risk of intravascular coagulation and thrombosis[6,7] Despite the positive effects of intensive, well-managed insulin therapy on cardiovascular outcomes,[8,9] discussions persist about the relationship between severe hypoglycaemia and mortality.[6,10–17] In people with T1D, various epidemiological studies have linked hypoglycaemia to cardiovascular events and mortality,[18] but it is not currently known if this association is causal.[19–21] In a cohort of individuals with T1D from Denmark/the Netherlands, severe hypoglycaemia was not associated with an increased risk of all-cause mortality and/or cardiovascular mortality.[22] In a population-level study of people in Denmark, it was found there was an increased mortality risk in people experiencing hypoglycaemia, but the authors did not investigate the effect of multiple episodes of hypoglycaemia and did not demonstrate that hypoglycaemia itself was a cause of death.[23] In a study in people with diabetes in the United States, those with self-reported episodes of hypoglycaemia were found to have a 5-year mortality risk that was 3.4 times greater than those who had not had prior hypoglycaemia.[24] Clinical characteristics associated with an increased risk of all-cause mortality were pre-existing macrovascular disease and reduced kidney function; however, the sample size was small, with only 59 deaths in 751 people. Risk factors for severe hypoglycaemia in people with diabetes have been identified, including preceding episodes of hypoglycaemia,[25] having T1D as opposed to other diabetes types, receiving insulin therapy, and having a diagnosis of sepsis.[26] In older adults with long-standing T1D, greater hypoglycaemia unawareness and glucose variability are associated with an increased risk of severe hypoglycaemia.[27] Furthermore, more frequently occurring hypoglycaemic episodes in people with T1D leads to a cumulative effect of hypoglycaemic events, increasing cardiovascular risk.[28] Considering these associations, the question arises if preceding episodes of severe hypoglycaemia are associated with all-cause mortality in people with T1D. Therefore, the aim of this study was to assess whether the number of severe hypoglycaemia episodes in people with T1D is associated with increased risk of all-cause mortality.

2 | MATERIALS AND METHODS

2.1 | Study design and participants

This was a national retrospective observational cohort study. Data were obtained from the Secure Anonymised Information Linkage (SAIL) databank, which is a repository of routinely collected electronic health records for people receiving medical services in Wales, United Kingdom.[29,30] The data held in the SAIL databank and used in this study were from the Welsh Longitudinal General Practice dataset and inpatient hospital records from the Patient Episodes Database for Wales. In addition, the Brecon Cohort, a register of people with T1D diagnosed at the age of 16 years or younger was used to further identify people with T1D in the other data sources to ensure the cohort was as complete as possible.[31] Death certificates were obtained from the Annual District Death Extract. Laboratory and anthropometric data were only available from the Welsh Longitudinal General Practice database, which covers approximately 80% of the population of Wales. The study protocol was reviewed by the independent Information Governance Review Panel of the SAIL databank and approved under the identification code 0779. All people with a diagnosis of T1D at any age between the years 2000 and 2018 across Wales were included in the study. Due to the nature of routinely collected datasets, miscoding and missing data are prevalent and therefore methods should be used to ensure the data are robust. The diagnosis of T1D was confirmed as follows: all persons with a code for diabetes mellitus of any type and one of the following: a prescription of insulin within 6 months of their earliest recorded diagnosis date and prior to any oral antihyperglycaemic medication; a hospital inpatient episode for diabetic ketoacidosis; or a prescription for a medical device used commonly in the management of T1D issued on at least five separate dates within 12 months of initial diagnosis.[32] Medical devices were defined as blood glucose test strips, continuous glucose monitoring (CGM) systems, blood glucometers, insulin pumps, and ketone test strips.

2.2 | Predictors

For those with T1D included in the study, the following data were available and included in the analyses: demographic data, including age at episode of severe hypoglycaemia requiring hospitalization and sex; dates of admission to hospital and the cause of severe hypoglycaemia; clinical data, including glycated haemoglobin (HbA1c), low-density lipoprotein, high-density lipoprotein (HDL), total cholesterol, cholesterol to HDL ratio, microalbuminuria, macroalbuminuria, body mass index (BMI) and smoking status; and comorbidities, including peripheral vascular disease, chronic kidney disease, atrial fibrillation, ischaemic heart disease, diabetic ketoacidosis, heart failure, myocardial infarction and stroke; medications used in the treatment of hypertension including beta-blockers, calcium channel blockers, angiotensin II receptor blockers, angiotensin-converting enzyme inhibitors and statin therapy. For those people without an admission to the hospital for severe hypoglycaemia, a date of admission to hospital was assigned using stochastic imputation. The data on time from diabetes diagnosis to hypoglycaemic episode for people with admissions to hospital with severe hypoglycaemia were examined and fitted to a selection of distribution functions. Parameters of the best fitting distribution were derived from the data and a single random sample was used to assign an imputed index date to each person who did not have an episode of severe hypoglycaemia requiring hospitalization. The clinical variables were included if the event took place within 12 months of the admission to hospital for severe hypoglycaemia, and the comorbidity variables if they occurred at any time prior to the admission to hospital, with the cause of severe hypoglycaemia or the imputed index date for people who did not have an episode of severe hypoglycaemia requiring hospitalization. People were uniquely assigned to groups that had no, one, two, or three or more episodes of severe hypoglycaemia requiring hospitalization during the study period. Severe hypoglycaemia was defined as an episode requiring admission to the hospital, which did not include episodes of severe hypoglycaemia that were treated in a non-hospital setting. General variables included the Welsh Index of Multiple Deprivation (WIMD), which is the Welsh Government's official measure of relative deprivation for small areas in Wales. It identifies areas with the highest concentrations of several different types of deprivation. In our data, WIMD was separated into five quintiles, with the 1st WIMD quintile representing the most deprived and the 5th WIMD quintile the least deprived. WIMD is based on evaluation of eight domains in small geographical areas.

2.3 | Outcomes

Clinical, comorbidity and demographic variables were assessed for their impact on mortality in people with T1D, stratified by the number of severe hypoglycaemia episodes requiring hospitalization: no episode, one episode, two episodes and three or more episodes. The time to death (all-cause mortality) was calculated stratified by the number of severe hypoglycaemia episodes requiring hospitalization. The primary outcome was time to death following an episode of severe hypoglycaemia requiring hospitalization.

2.4 | Statistical analysis

For continuous variables, median and quartiles and for categorical variables, number and percentages were reported. Univariate differences between groups were investigated using Poisson regression, and dispersion was checked by evaluating the ratio of residual deviance to degrees of freedom. Crude mortality rates, and rates adjusted for age were calculated using the standard European population (2013) to adjust mortality rates.[33] A Kaplan-Meier plot was used to illustrate the unadjusted (crude) time from last reported admission for severe hypoglycaemia requiring hospitalization to date of death. A parametric survival model, the output of which is accelerated failure time (AFT) coefficients, was used to model the adjusted time to death from the last occurring episode of severe hypoglycaemia requiring hospitalization. A parametric survival model assumes the effect of covariates are multiplicative on the time scale, whereas they are multiplicative on the hazard scale in proportional hazard models. In AFT models, reporting of time ratios (TRs) is recommended, similarly to the reporting of hazard ratios in proportional hazard models. In this study, the event is death; therefore, a covariate with a TR >1 means the time to death is extended and a TR <1 indicates the covariate shortens time to death. We used routinely collected data for this study and, because we required laboratory and anthropometric tests to have been performed within 12 months of the episode of severe hypoglycaemia requiring hospitalization, we needed a strategy for dealing with higher levels of missing data. We used multiple imputation to construct a dataset where we could compare models before and after adding variables and perform model selection using the imputed dataset. The model distributions assessed were Weibull, Rayleigh, log-logistic, log-normal, exponential and normal distributions, and the best-fitting distribution was chosen using the Akaike information criterion (AIC). Results based on the imputed data are not reported and were only used for model selection. We expected the missing data to be missing at random as the study covers a long period of time and individuals were not excluded according to when they had an episode of severe hypoglycaemia requiring hospitalization. A forward stepwise method was used to construct the model, starting with the minimal base model including variables encoding the number of hypoglycaemic episodes individuals experienced during the study period. Then, each variable in Table 2 was added to the model, with the variable that produced the greatest improvement in AIC retained for future iterations. When adding more variables did not improve the AIC, the process was terminated. The results presented from the final model were fitted using only the original data with no imputed values. A lower AIC is taken to mean a better model fit to the data. All statistical analysis were performed using the R programming language version 4.0.2, the survival package version 3.2-7 was used for survival analysis, the mice package version 3.12.0 for multiple imputation and the poppy package version 0.4.8 for computing standardized rates.

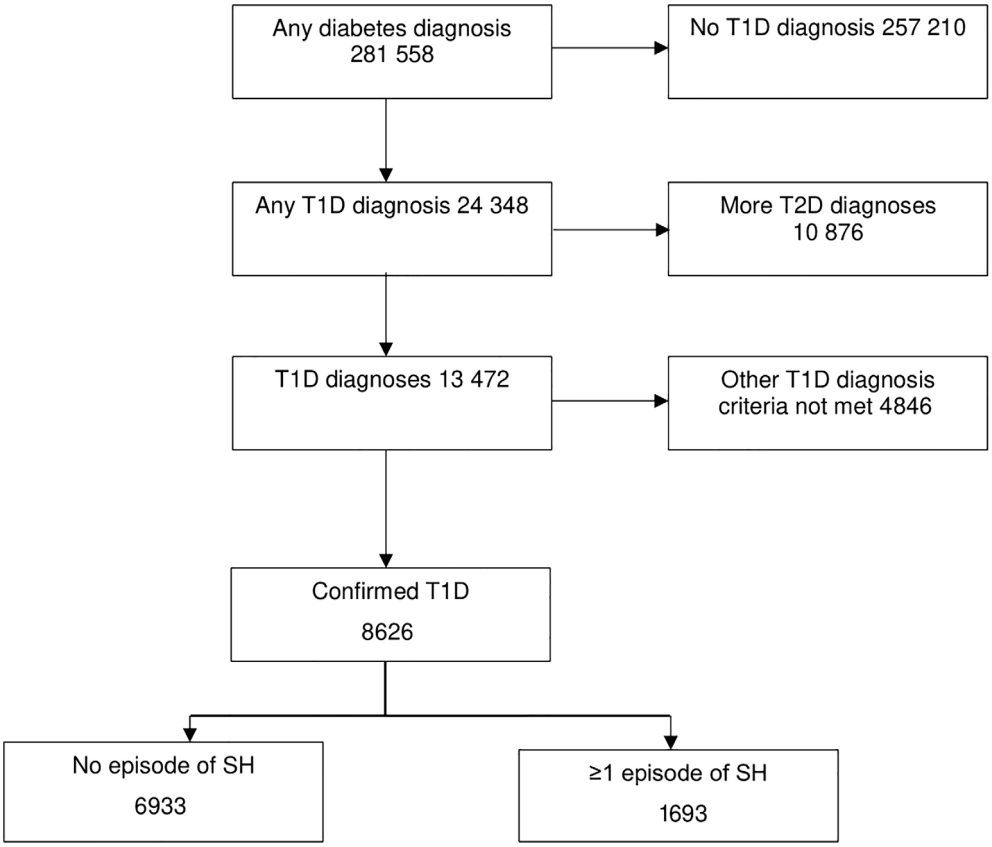

FIGURE 1 Study flow diagram showing the number of people with type 1 diabetes (T1D) eligible for the analyses. SH, severe hypogycaemia

3 | RESULTS

A total of 281 558 people in Wales had a diagnosis of either T1D or type 2 diabetes between 2000 and 2018, of whom 8224 (2.9%) had a confirmed diagnosis of T1D and were included in the analysis (Figure 1). Of those with T1D, the median (interquartile) age was 28.0 (16.9, 45.1) years, 3655 (44.2%) were female, the median HbA1c was 70.5 (58.0, 74.5) mmol/mol (8.6 [7.5, 9.0]%) and 1702 people (20.7%) lived in the most deprived areas (Table 1). The median (IQR) follow-up time from hypoglycaemia episode to endpoint was 4.70 (1.75, 9.32) years and the median (IQR) follow up time from diagnosis to endpoint was 9.77 (4.64, 14.75) years. The median (IQR) time between episodes of severe hypoglycaemia in people who had more than one episode was 183 (37.5, 622.5) days. In those who died, the median (IQR) time from hypoglycaemia episode to death was 229.5 (36.75, 824.75) days. A total of 6632 people (80.6%) had no episodes of severe hypoglycaemia requiring hospitalization, 954 people (11.6%) had one episode, 294 (3.6%) had two episodes, and 344 (4.2%) had three or more episodes. The time from diabetes diagnosis to hypoglycaemia episode was found to follow an exponential distribution, and dates of hypoglycaemia episode were imputed for the group that did not have an episode of hypoglycaemia by randomly sampling from this distribution.

Results from the univariate analysis showed that people who were younger, who had higher HbA1c levels, and lower blood pressure and BMI, those who were female, those who had complications and comorbidities of peripheral vascular disease, amputation, hospitalization for chronic kidney disease, ischaemic heart disease or atrial fibrillation, those who had history of diabetic ketoacidosis and stroke and those who lived in the most and second most deprived areas were more likely to have episodes of severe hypoglycaemia requiring hospitalization. Furthermore, people who were older, who had lower HbA1c levels, higher blood pressure and BMI and complications and comorbidities of micro- and macro-albuminuria, peripheral vascular disease, amputation, atrial fibrillation, ischaemic heart disease and stroke, those who used blood pressure or statin treatment and those living in the most deprived areas were more likely to die (Table 2). The mortality rate (95% confidence interval [CI]) was 6.9 (6.1-7.8) deaths/ 1000 person-years (crude) and 15.3 (13.3-17.6) deaths / 1000 person-years (age-adjusted) for those with no occurrence of severe hypoglycaemia requiring hospitalization. For those with one episode of severe hypoglycaemia requiring hospitalization the mortality rate (95% CI) was 24.9 (21.0-29.6) deaths / 1000 person-years (crude) and 53.8 (44.6-64.7) deaths / 1000 person-years (age-adjusted), for those with two episodes of severe hypoglycaemia requiring hospitalization, it was 28.0 (23.1-34.0) deaths / 1000 person-years (crude) and 72.8 (59.2-89.5) deaths / 1000 person-years (age-adjusted), and for those with three or more episodes of severe hypoglycaemia requiring hospitalization, it was 33.5 (30.0-37.3) deaths / 1000 person-years (crude) and 86.3 (71.7-103.9) deaths / 1000 person-years (age-adjusted; $P < 0.001$, comparing all groups with different numbers of episodes of severe hypoglycaemia requiring hospitalization). Figure 2 shows how the mortality rate following a

TABLE 1 Characteristics of the study cohort, people in Wales with type 1 diabetes from 2000 to 2018 (N = 8626)

Characteristic	
General	
Age, median (IQR) years	28.0 (16.9-45.1)
Sex, n (%)	
Females	3655 (44.2)
Males	4971 (55.8)
Age at diagnosis, median (IQR) years	23.6 (12.6-40.2)
Diabetes duration at SH episode, median (IQR) years	3.3 (1.3-7.0)
BMI, median (IQR) kg/m^2	24.6 (21.7-28.4)
HbA1c, median (IQR)	
mmol/mol	70.5 (58.0-74.5)
%	8.6 (7.5-9.0)
Smokers, n (%)	2780 (33.8)
WIMD[a], n (%)	
1st quintile (most deprived)	1702 (20.7)
2nd quintile	1509 (18.3)
3rd quintile	1439 (17.5)
4th quintile	1209 (14.7)
5th quintile (least deprived)	1220 (14.8)
Clinical data, median (IQR)	
Systolic pressure, mmHg	122 (110-134)
Diastolic pressure, mmHg	73 (67-80)
LDL, mmol/L	1.39 (1.97-3.10)
HDL, mmol/L	1.39 (1.10-1.66)
Total cholesterol, mmol/L	4.54 (3.90-5.30)
Cholesterol to HDL ratio (dimensionless)	3.30 (2.70-4.20)
Comorbidities, n (%)	
Microalbuminuria	110 (1.3)
Macroalbuminuria	6 (0.07)
Peripheral vascular disease	86 (1.0)
Lower limb amputation	56 (0.6)
Percutaneous coronary intervention	31 (0.3)
Hospitalization for chronic kidney disease	40 (0.4)
Atrial fibrillation	114 (1.4)
Ischemic heart disease	271 (3.3)
Diabetic ketoacidosis	2655 (32.3)
Hospitalization for heart failure	95 (1.2)
Myocardial infarction	88 (1.1)
Stroke	74 (0.9)
Medication, n (%)	
Blood pressure medication	1456 (17.7)
Statins	1554 (18.9)

Note: Data are given as mean ± standard deviation or %.

Abbreviations: BMI, body mass index; HbA1c, glycated haemoglobin; HDL, high-density lipoprotein; IQR, interquartile range; LDL, low density lipoprotein; SH, severe hypoglycaemia; WIMD, Welsh Index of Multiple Deprivation.

[a]Remaining number (%) had unknown WIMD. The blood pressure medication category included angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers, beta-blockers and calcium channel blockers.

TABLE 2 Impact of patients' general characteristics, clinical data, laboratory data and medication on number of episodes of severe hypoglycaemia requiring hospitalization and mortality

	No SH episodes		One SH episode		Two SH episodes		Three or more SH episodes		*P* value	
	Alive	Dead	Alive	Dead	Alive	Dead	Alive	Dead	Number SH episodes	Died
Age at most recent SH episode, median (IQR) years			22.54 (13.65-39.01) (n = 830)	60.99 (45.16-77.50) (n = 116)	19.98 (12.39-32.45) (n = 249)	63.61 (49.72-72.02) (n = 45)	24.38 (15.50-33.20) (n = 275)	55.10 (41.86-75.55) (n = 69)	<0.001	<0.001
Male sex, n (%)	3653 (57.25)	138 (54.98)	419 (50.00)	67 (57.76)	114 (45.78)	25 (55.56)	120 (43.64)	50 (72.46)	0.029	0.593
BMI, median (IQR) kg/m^2	24.70 (21.90-28.50) (n = 4838)	26.30 (22.80-30.30) (n = 213)	24.00 (20.85-28.08) (n = 639)	26.00 (22.30-28.90) (n = 93)	23.70 (20.80-27.55) (n = 178)	23.40 (20.42-28.02) (n = 38)	22.90 (20.20-26.82) (n = 208)	23.40 (20.10-26.30) (n = 53)	<0.001	<0.001
HbA1c, median (IQR) mmol/mol	69.40 (57.00-85.00) (n = 4720)	67.50 (55.00-85.75) (n = 114)	74.00 (62.00-92.00) (n = 674)	74.50 (57.80-91.22) (n = 58)	73.00 (64.00-89.00) (n = 200)	68.00 (49.00-82.50) (n = 21)	80.00 (68.75-97.00) (n = 224)	72.85 (62.25-89.75) (n = 38)	<0.001	<0.001
Systolic blood pressure, median (IQR) mmHg	122.00 (111.00-133.00) (n = 5221)	135.50 (122.75-150.00) (n = 226)	120.00 (110.00-130.00) (n = 703)	132.00 (120.00-141.00) (n = 95)	119.00 (109.00-127.50) (n = 203)	130.00 (111.50-142.75) (n = 38)	118.00 (108.00-129.00) (n = 233)	134.00 (120.00-149.00) (n = 55)	<0.001	<0.001
Diastolic blood pressure, median (IQR) mmHg	73.00 (68.00-80.00) (n = 5221)	80.00 (70.00-84.00) (n = 226)	71.00 (64.00-80.00) (n = 703)	77.00 (70.00-83.00) (n = 95)	70.00 (64.00-80.00) (n = 203)	72.50 (64.00-82.25) (n = 38)	70.00 (64.00-79.00) (n = 233)	75.00 (70.00-80.00) (n = 55)	<0.001	<0.001
LDL, median (IQR) mmol/L	2.50 (1.99-3.10) (n = 4040)	2.40 (1.80-3.10) (n = 170)	2.49 (2.00-2.94) (n = 541)	2.38 (1.80-2.80) (n = 75)	2.50 (2.10-3.10) (n = 141)	2.10 (1.60-2.60) (n = 33)	2.60 (2.00-3.10) (n = 178)	2.37 (1.80-3.00) (n = 41)	0.391	0.332
HDL, median (IQR) mmol/L	1.38 (1.10-1.66) (n = 4202)	1.33 (1.05-1.66) (n = 176)	1.40 (1.15-1.70) (n = 558)	1.30 (1.08-1.54) (n = 76)	1.40 (1.20-1.64) (n = 147)	1.40 (1.16-1.64) (n = 34)	1.40 (1.10-1.61) (n = 184)	1.48 (1.18-1.80) (n = 43)	0.688	0.810
Cholesterol, median (IQR) mmol/L	4.59 (3.99-5.30) (n = 4492)	4.60 (3.90-5.40) (n = 203)	4.50 (3.90-5.21) (n = 589)	4.30 (3.80-5.12) (n = 86)	4.80 (4.00-5.32) (n = 163)	4.20 (3.40-4.60) (n = 37)	4.50 (3.75-5.40) (n = 195)	4.48 (4.00-5.10) (n = 49)	0.889	0.482
Cholesterol-HDL ratio, median (IQR)	3.30 (2.70-4.20) (n = 3445)	3.50 (2.70-4.50) (n = 97)	3.30 (2.70-4.10) (n = 457)	3.50 (2.45-4.00) (n = 43)	3.30 (2.51-4.30) (n = 115)	3.40 (2.50-4.43) (n = 20)	3.26 (2.69-4.20) (n = 146)	3.17 (2.65-3.56) (n = 30)	0.097	0.104
Microalbuminuria, n (%)	72 (1.13)	10 (3.98)	8 (0.95)	<5 (<4.31)	<5 (<2.01)	<5 (<11.11)	7 (2.55)	<5 (<7.25)	0.252	<0.001
Macroalbuminuria, n (%)	<5 (<0.08)	<5 (<1.99)	<5 (<0.60)	<5 (<4.31)	<5 (<2.01)	<5 (<11.11)	<5 (<1.82)	<5 (<7.25)	0.055	0.006
Peripheral vascular disease, n (%)	22 (0.34)	11 (4.38)	11 (1.31)	8 (6.90)	5 (2.01)	6 (13.33)	14 (5.09)	9 (13.04)	<0.001	<0.001
Amputation, n (%)	13 (0.20)	7 (2.79)	9 (1.07)	5 (4.31)	<5 (<2.01)	<5 (<11.11)	10 (3.64)	7 (10.14)	<0.001	<0.001
Percutaneous coronary intervention, n (%)	19 (0.30)	6 (2.39)	<5 (<0.60)	<5 (<4.31)	<5 (<2.01)	<5 (<11.11)	<5 (<1.82)	<5 (<7.25)	0.561	0.002
Hospitalization for CKD, n (%)	19 (0.30)	<5 (<1.99)	5 (0.60)	<5 (<4.31)	<5 (<2.01)	<5 (<11.11)	7 (2.55)	<5 (<7.25)	<0.001	0.031
Atrial fibrillation, n (%)	46 (0.72)	20 (7.97)	8 (0.95)	13 (11.21)	<5 (<2.01)	8 (17.78)	8 (2.91)	8 (11.59)	0.022	<0.001
Ischaemic heart disease, n (%)	126 (1.97)	39 (15.54)	32 (3.82)	22 (18.97)	6 (2.41)	11 (24.44)	12 (4.36)	23 (33.33)	<0.001	<0.001
Diabetic ketoacidosis, n (%)	1831 (28.69)	41 (16.33)	360 (42.96)	38 (32.76)	130 (52.21)	18 (40.00)	197 (71.64)	40 (57.97)	<0.001	<0.001
Myocardial infarction, n (%)	42 (0.66)	15 (5.98)	7 (0.84)	6 (5.17)	<5 (<2.01)	<5 (<11.11)	<5 (<1.82)	8 (11.59)	0.059	<0.001
Stroke, n (%)	26 (0.41)	13 (5.18)	9 (1.07)	<5 (<4.31)	<5 (<2.01)	<5 (<11.11)	5 (1.82)	8 (11.59)	<0.001	<0.001
Blood pressure treatment, n (%)	970 (15.20)	138 (54.98)	135 (16.11)	59 (50.86)	41 (16.47)	24 (53.33)	56 (20.36)	33 (47.83)	0.237	<0.001

TABLE 2 (Continued)

	No SH episodes		One SH episode		Two SH episodes		Three or more SH episodes		*P* value	
	Alive	Dead	Alive	Dead	Alive	Dead	Alive	Dead	Number SH episodes	Died
Statin treatment, n (%)	1104 (17.30)	106 (42.23)	152 (18.14)	54 (46.55)	37 (14.86)	18 (40.00)	48 (17.45)	35 (50.72)	0.399	<0.001
WIMD quintile, n (%)										
1st quintile (most deprived)	1200 (22.74)	35 (30.17)	216 (26.57)	35 (30.17)	54 (21.69)	16 (35.56)	90 (33.09)	16 (23.19)	0.006	0.028
2nd quintile	1079 (20.44)	29 (25.00)	180 (22.14)	29 (25.00)	62 (24.90)	12 (26.67)	74 (27.21)	17 (24.64)	0.002	0.106
3rd quintile	1107 (20.97)	21 (18.10)	155 (19.07)	21 (18.10)	58 (23.29)	7 (15.56)	43 (15.81)	12 (17.39)	0.224	0.734
4th quintile	930 (17.62)	20 (17.24)	122 (15.01)	20 (17.24)	43 (17.27)	8 (17.78)	36 (13.24)	16 (23.19)	0.149	0.281
5th quintile (least deprived)	962 (18.23)	11 (9.48)	140 (17.22)	11 (9.48)	32 (12.85)	2 (4.44)	29 (10.66)	8 (11.59)	Comparator	Group

Note: P value, number of SH episodes: the *P* value comparing values for differing number of SH episodes. *P* value, Died: the *P* value comparing values for those who died and those who did not die during the study. Groups with fewer than five individuals are masked due to the data privacy requirements of the SAIL databank.

Abbreviations: CKD, chronic kidney disease; HbA1c, glycated haemoglobin; HDL, high-density lipoprotein; IQR, interquartile range; LDL, low-density lipoprotein; SH, severe hypoglycaemia; WIMD, Welsh Index of Multiple Deprivation.

hospitalization for severe hypoglycaemia varied for people with no, one, two and three or more episodes of severe hypoglycaemia requiring hospitalization.

The fully adjusted parametric survival model contained the following covariates: number of episodes of severe hypoglycaemia requiring hospitalization, sex, age, duration of diabetes, deprivation, HbA1c, use of statins and blood pressure medications, hospitalization for heart failure, chronic kidney disease and diabetic ketoacidosis (Table 3). The survival time for a person with one episode of severe hypoglycaemia requiring hospitalization was 87.4% shorter (TR 0.126) compared with those who did not have an episode of severe hypoglycaemia requiring hospitalization. For those people with two episodes of severe hypoglycaemia requiring hospitalization, the survival time was 92.7% shorter (TR 0.073) compared with those without an episode of severe hypoglycaemia requiring hospitalization. Each additional year of diabetes duration increased the survival time by 25.8% (TR 1.258), while each additional year of age reduced the survival time by 8.3% (TR 0.917), indicating that the people most at risk of death following an episode of severe hypoglycaemia requiring hospitalization were those who were diagnosed with T1D at an older age.

4 | DISCUSSION

This report highlights the elevation in risk of mortality in people with T1D experiencing episodes of severe hypoglycaemia requiring hospitalization. The strongest predictor for time to death, by which we mean the variable with the TR that differed most from 1, was having two or more episodes of severe hypoglycaemia requiring hospitalization. Intriguingly, the parametric survival model showed that even one episode of severe hypoglycaemia requiring hospitalization increased the risk of earlier death compared with having no episodes, and the risk increased further with two episodes of severe hypoglycaemia requiring hospitalization. Having three or more episodes of severe hypoglycaemia requiring hospitalization did not meet our chosen statistical significance threshold, but the trend observed for one and two episodes suggests this was because there were insufficient data to reject the null hypothesis that three or more episodes of severe hypoglycaemia requiring hospitalization was not associated with an increase in mortality. In our study, those who had a higher number of severe hypoglycaemia events requiring hospitalization and who died were older than those with the same number of episodes of severe hypoglycaemia requiring hospitalization and who were alive. However, those who died had a median (IQR) age of 62.4 (48.8, 74.4) years at the occurrence of the last episode of severe hypoglycaemia requiring hospitalization, whereas the general life expectancy in Wales (United Kingdom) is 79.4 years for males and 83.1 years for females. Interestingly, those with three or more episodes of severe hypoglycaemia requiring hospitalization and who died were aged 55.1 (41.9, 75.6) years, which suggests that age per se had only a moderate impact on mortality. Nevertheless, age at the last episode of severe hypoglycaemia requiring hospitalization had an effect on time to death, meaning that, for each additional year, the expected time to

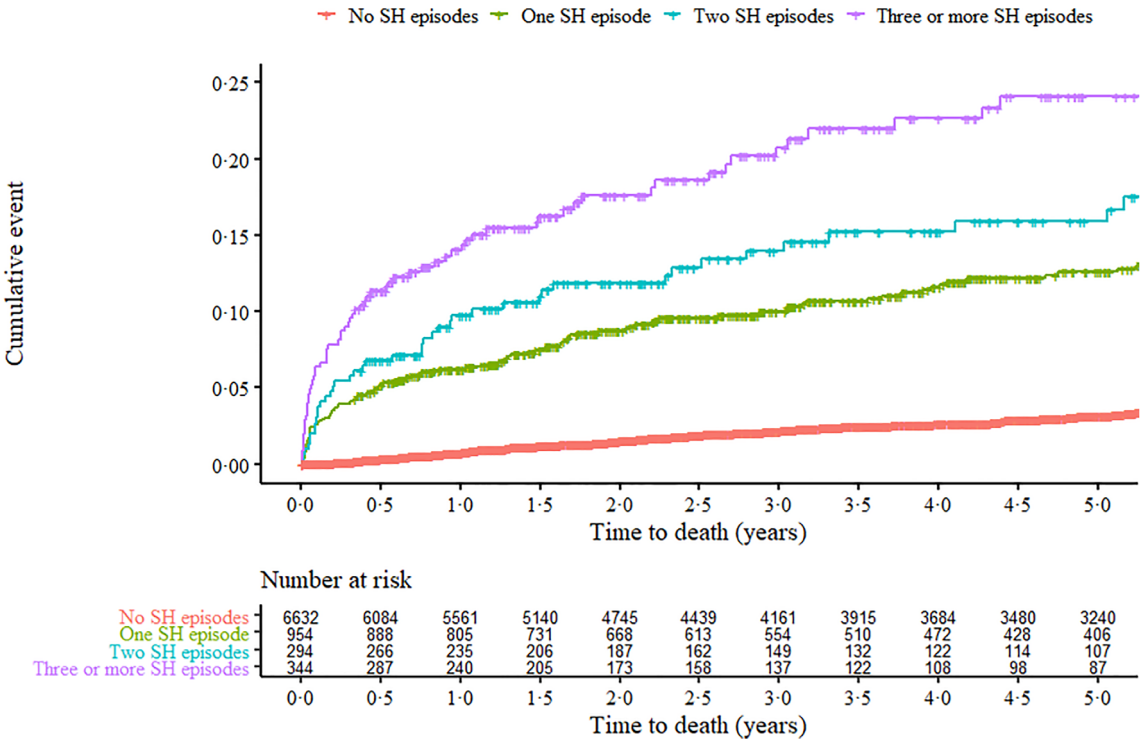

FIGURE 2 Kaplan-Meier mortality probability comparison of those having no episode of severe hypoglycaemia (SH) requiring hospitalization (red line), or one episode (green line), two episodes (turquoise line) and three or more episodes of hypoglycaemia requiring hospitalization (purple line)

death was 8.3% shorter compared to those without an episode of severe hypoglycaemia requiring hospitalization. As shown previously, people with T1D have a substantially increased risk of premature death,[34] which is associated with suboptimal glycaemic management[35] and the presence of acute and chronic complications.[36] In those with a diabetes duration of less than 10 years, acute diabetes complications accounted for 40% of deaths.[36]

In conclusion, our findings indicate an independent association between severe hypoglycaemia requiring hospitalization and mortality in people with T1D. We also note that people who had more episodes of severe hypoglycaemia requiring hospitalization had higher HbA1c levels, which is contrary to the commonly held understanding that imposing lower HbA1c targets on individuals with T1D increases the risk of hypoglycaemic episodes.[37] When assessing the impact of people's demographic characteristics, clinical data, laboratory data and medication, males had a higher number of episodes of severe hypoglycaemia and hence a greater risk of mortality than females.

The inverse relationship between HbA1c levels and time spent in hypoglycaemia is a major hurdle in the management of T1D[38] that often reduces the efficacy of treatments. Taking into account that improving glycaemic management prolongs life expectancy and, coincidently, lowering the number of severe hypoglycaemic events requiring hospitalization improves longevity, current care needs to utilize the advances in diabetes management such as CGM and novel insulin analogues. This notion of CGM being a key tool in minimizing both dangerous hyperglycaemia and hypoglycaemia led to a recent commentary suggesting that we need to move from the HbA1c management era we have been in for almost 30 years to an era in which T1D management is guided by CGM data.[39] In people with the same number of episodes of severe hypoglycaemia requiring hospitalization, those who were alive had lower systolic and diastolic blood pressure when compared with those who died. Interestingly, lower blood pressure was found in those with a higher number of severe hypoglycaemia events requiring hospitalization, which may reflect that some medications could mitigate the effects of hypoglycaemia awareness due to beta-receptor blockade.[40] This finding is also supported by the observation that people who used antihypertensive medication were more prone to hypoglycaemia than those without.

Those who died had a higher BMI than those who remained alive; however, those with a lower BMI had a higher number of episodes of severe hypoglycaemia requiring hospitalization. It is possible that those with a lower BMI might have been more physically active, which could have increased the risk of severe hypoglycaemia requiring hospitalization as shown in a previous study.[41] Albuminuria was found to be more common in those who died and, furthermore, those who had more episodes of severe hypoglycaemia requiring hospitalization had albuminuria more often when compared to those with no episode of severe hypoglycaemia requiring hospitalization. Similar results were found for peripheral vascular disease, amputations, hospitalization for chronic kidney disease, atrial fibrillation, myocardial infarction, and stroke. Interestingly, statin therapy was more often used in those who died, which is

TABLE 3 Accelerated failure time survival model for the time to death for the cohort of people with type 1 diabetes from Wales, from 2000 to 2018

	AFT model	
Variables	**TR (95% CI)**	***P* value**
Number of severe hypoglycaemic episodes		
0	Comparator group	
1	**0.126 (0.036-0.438)**	**0.001**
2	**0.073 (0.009-0.565)**	**0.012**
3+	0.113 (0.007-1.959)	0.134
Diabetes duration	**1.258 (1.079-1.465)**	**0.003**
Sex		
Male	Comparator group	
Female	0.972 (0.370-2.554)	0.954
Age (years) at most recent hypoglycaemic episode	**0.917 (0.885-0.951)**	**<0.001**
WIMD quintile		
1st quintile (most deprived)	0.307 (0.062-1.531)	0.150
2nd quintile	0.720 (0.148-3.506)	0.684
3rd quintile	2.162 (0.317-14.748)	0.431
4th quintile	0.332 (0.061-1.821)	0.204
5th quintile (least deprived)	Comparator group	
HbA1c (mmol/mol)	0.985 (0.966-1.003)	0.108
Systolic blood pressure	1.026 (0.993-1.061)	0.128
Diastolic blood pressure	1.028 (0.972-1.088)	0.328
Use statins		
No	Comparator group	
Yes	0.973 (0.484-1.970)	0.938
Use blood pressure medication		
No	Comparator group	
Yes	0.386 (0.121-1.228)	0.107
Used statin medication		
No	Comparator group	
Yes	0.457 (0.139-1.507)	0.199
Hospitalization for heart failure before SH		
No	Comparator group	
Yes	0.337 (0.054-2.097)	0.244
Hospitalization for CKD before SH		
No	Comparator group	
Yes	2×10^7 (0.000-inf)	0.997
Diabetic ketoacidosis before SH		
No	Comparator group	
Yes	0.660 (0.183-2.377)	0.525

Abbreviations: AFT, accelerated failure time; CI, confidence interval; CKD, chronic kidney disease; HbA1c, glycated haemoglobin; SH, severe hypoglycaemia; TR, time ratio; WIMD, Welsh Index of Multiple Deprivation.

hypothesized to be due to the comorbidities rather than the treatments per se. Among those people who were least deprived there was a lower number of deaths in relation to the number of hypoglycaemia episodes and, in general, a lower risk of severe hypoglycaemia requiring hospitalization.

When assessing the impact of severe hypoglycaemia requiring hospitalization, those with no episodes of severe hypoglycaemia requiring hospitalization had nearly stable mortality curves, which is in contrast to those with one episode of severe hypoglycaemia requiring hospitalization, where the risk for earlier death increased in the period

immediately following the episode of severe hypoglycaemia requiring hospitalization. When stratifying these data based on the number of episodes of severe hypoglycaemia requiring hospitalization, those with more episodes had acutely and chronically increased risk of death. Crude survival probability was found to stabilize approximately 12 months after the episode of severe hypoglycaemia requiring hospitalization. Based on the findings of the Kaplan-Meier analysis, it can be hypothesized that absolute avoidance of severe hypoglycaemia requiring hospitalization is urgently needed in people with T1D to lower the risk of mortality. The focus of therapy management should be based on individualizing education, the use of diabetes technology and physiological insulins. As our data reveal, these interventions should be performed immediately after the occurrence of an episode of severe hypoglycaemia requiring hospitalization.

This study has some limitations. Because we only assessed severe hypoglycaemia episodes requiring hospitalization, those episodes treated outside hospital were not included. The influence of mild hypoglycaemia might have further cumulative effects on our findings but this was not captured by our study. To draw a full picture of the effects of severe hypoglycaemia on mortality, a prospective study utilizing CGM data is required to determine a clear causality instead of association. Large routinely collected healthcare data are limited by coding errors and missing data. However, we attempted to reduce the effects of this by using a robust method to confirm the type of diabetes and used imputation methods to limit the impact of missing data. We were only able to include a snapshot of HbA1c rather than the more appropriate measure of HbA1c exposure over the course of the disease. This is because we aimed to minimize the amount of missing data in the analysis, and HbA1c measurements were only available to us via primary care records. Furthermore, we were only able to determine the presence of an individual in Wales via their registration at a general practice, not by dwelling address or another metric. It is possible that individuals could move out of Wales but remain registered at their previous general practice, which may be more common in people who move often, such as university students. Despite noting this limitation, we feel the scenario is unlikely, because T1D is a disease that requires regular engagement with health services. Additionally, based on our data, we could not assess the mental health and type of insulin therapy (insulin pump therapy vs. insulin pen therapy). Notwithstanding these limitations, this large-scale study performed in people with T1D in the United Kingdom found that an episode of severe hypoglycaemia requiring hospitalization acutely and chronically increases the risk of premature death and this needs to be considered when defining and prescribing treatment for people with T1D.

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CONFLICT OF INTEREST

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PEER REVIEW

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DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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