Ongoing burden and recent trends in severe hospitalised hypoglycaemia events in people with type 1 and type 2 diabetes in Scotland

Berthon, William; McGurnaghan, Stuart J.; Blackbourn, Luke A.K.; Mellor, Joseph; Gibb, Fraser W.; Heller, Simon

Published in:
Diabetes Research and Clinical Practice

DOI:
10.1016/j.diabres.2024.111642

Publication date:
2024

diabetesresearchandclinicalpractice210(2024)111642

Contents lists available at ScienceDirect

Diabetes Research and Clinical Practice

journal homepage: www.journals.elsevier.com/diabetes-research-and-clinical-practice

Ongoing burden and recent trends in severe hospitalised hypoglycaemia events in people with type 1 and type 2 diabetes in Scotland: A nationwide cohort study 2016–2022

William Berthon[a,*], Stuart J. McGurnaghan[b], Luke A.K. Blackbourn[b], Joseph Mellor[a], Fraser W. Gibb[c], Simon Heller[d], Brian Kennon[e], Rory J. McCrimmon[f], Sam Philip[g], Naveed Sattar[h], Paul M. McKeigue[a], Helen M. Colhoun[b,i], On behalf of Scottish Diabetes Research Network Epidemiology Group[j]

[a] Usher Institute, College of Medicine and Veterinary Medicine, The University of Edinburgh, Edinburgh, UK
[b] Institute of Genetics and Cancer, College of Medicine and Veterinary Medicine, The University of Edinburgh, Edinburgh, UK
[c] Edinburgh Centre for Endocrinology & Diabetes, Royal Infirmary of Edinburgh, Edinburgh, UK
[d] Department of Oncology and Metabolism, University of Sheffield, Sheffield, UK
[e] Queen Elizabeth University Hospital, Glasgow, UK
[f] Division of Molecular and Clinical Medicine, University of Dundee, Dundee, UK
[g] JJR Macleod Centre for Diabetes & Endocrinology, Aberdeen Royal Infirmary, Aberdeen, UK
[h] School of Cardiovascular and Metabolic Health, University of Glasgow, Glasgow, UK
[i] Public Health Scotland, Glasgow, UK
[j] on behalf of the Scottish Diabetes Research Network Epidemiology Group, UK

ARTICLE INFO

Keywords:
Type 1 diabetes
Type 2 diabetes
Hypoglycaemia
Hospital admission
Population-based studies
Epidemiology

ABSTRACT

Aims: We examined severe hospitalised hypoglycaemia (SHH) rates in people with type 1 and type 2 diabetes in Scotland during 2016–2022, stratifying by sociodemographics.
Methods: Using the Scottish National diabetes register (SCI-Diabetes), we identified people with type 1 and type 2 diabetes alive anytime during 2016–2022. SHH events were determined through linkage to hospital admission and death registry data. We calculated annual SHH rates overall and by age, sex, and socioeconomic status. Summary estimates of time and stratum effects were obtained by fitting adjusted generalised additive models using R package *mgcv*.
Results: Rates for those under 20 with type 1 diabetes reached their minimum at the 2020–2021 transition, 30% below the study period average. A gradual decline over time also occurred among 20–49-year-olds with type 1 diabetes. Overall, females had 15% higher rates than males with type 2 diabetes (rate ratio 1.15, 95% CI 1.08–1.22). People in the most versus least deprived quintile experienced 2.58 times higher rates (95% CI 2.27–2.93) in type 1 diabetes and 2.33 times higher (95% CI 2.08–2.62) in type 2 diabetes.
Conclusions: Despite advances in care, SHH remains a significant problem in diabetes. Future efforts must address the large socioeconomic disparities in SHH risks.

1. Introduction

Hypoglycaemia represents a significant complication in people with diabetes associated with the loss of quality of life and an increased risk of mortality and morbidity [1–3]. Improving glucose control is a major cornerstone of diabetes management with maintenance of optimal blood glucose whilst avoiding hypoglycaemia being the goal. Most hypoglycaemia is mild and managed out of hospital but the rate of hypoglycaemia severe enough to warrant hospitalisation is an important population level indicator of diabetes management.

Large scale studies in the past twenty years from England, Canada, the USA, Denmark, South Korea and elsewhere found that rates of hospitalised hypoglycaemia peaked around the years 2006–12 then declined in the years thereafter [4–12]. Many of these studies did not

* Corresponding author.
E-mail address: wberthon@ed.ac.uk (W. Berthon).

https://doi.org/10.1016/j.diabres.2024.111642
Received 31 January 2024; Received in revised form 10 March 2024; Accepted 25 March 2024
Available online 27 March 2024

differentiate rates in type 1 and type 2 diabetes or in different age or sociodemographic groups. In the past few years since these reports, there have been several changes in factors important to diabetes care. For type 1 diabetes (T1D), those included the increased adoption of basal bolus therapy, the decreased use of premixed insulins, particularly in younger people with diabetes, the use of novel basal insulins with a flatter basal profile, structured education for informed mealtime bolusing or the increased uptake of devices including insulin pumps and continuous glucose monitoring systems (CGM), used alone or in combination with insulin pumps [13]. For type 2 diabetes (T2D), changes included the availability of novel medication with improved pharmacokinetics for effective glucose control with lower risk of hypoglycaemia like DPP4 inhibitors, GLP-1 agonists and SGLT2 inhibitors, as well as other initiatives such as more structured patient education. We previously reported substantial reductions in HbA1c in those starting intermittently scanned glucose monitoring (or flash GM) after these became freely available in T1D through the national health system in Scotland in 2018 and a reduction in severe hospitalised hypoglycaemia (SHH) in those with a history of SHH [14]. However, some studies have shown that the onset of the COVID-19 pandemic (March 2020) had a major adverse impact on diagnoses, as well as clinic attendance, self-management and monitoring in those with diabetes [15,16], while one study revealed no major changes in glycaemic control in people with T1D using flash glucose monitoring (FGM) [17].

The aim of this study was to examine current rates in SHH in the post-pandemic period in the total population of Scotland with diabetes and recent trends over the period 2016–2022. We examined rates in people with T1D and T2D separately and in age, sex and socioeconomic strata. We aimed to determine the extent to which SHH remains a major challenge in Scotland in this post-pandemic period, whether it affects certain population subgroups more than others and what the net effect of factors influencing SHH has been at population level in recent years. These data are important for identifying those most at risk so that appropriate educational and therapeutic approaches can be implemented and to inform future care models and policy on preventive strategies.

2. Subjects, materials and methods

2.1. Data sources

Pseudonymised data from the Scottish Diabetes Research Network – National Diabetes Dataset (SDRN-NDS) cohort were used for this study. The SDRN-NDS is a comprehensive dataset that contains electronic health records from Scotland's diabetes information system SCI-Diabetes for more than 99 % of individuals with diabetes in Scotland. Additionally, the SDRN-NDS is linked to hospital admissions and discharge data (Scottish Morbidity Record 01 from Public Health Scotland) and mortality data from the National Records of Scotland (NRS). Detailed information regarding the SDRN-NDS and the process of data linkage has been described previously [18].

2.2. Study population

The study period was 1st January 2016 – 31st October 2022. We included in the study population all individuals with T1D alive and those with T2D aged 20 and over and alive at any point during this period. Type of diabetes was that assigned by the clinician provided there was no contradictory evidence in the clinical record using the SDRN-epi type assignation algorithm [18]. An SHH event was defined for individuals in the study population as a hospitalisation or death involving any of the following ICD-10 diagnosis codes as the primary cause, on the hospital discharge summary or death certificate: E16.0 (Drug-induced hypoglycaemia without coma), E16.1 (Other hypoglycaemia), E16.2 (Hypoglycaemia, unspecified) or E15 (Nondiabetic hypoglycaemic coma; there were only 7 such events and we included them as all hypoglycaemia in a person with diabetes could be attributed to diabetes). Additionally, an SHH event was also counted if any of the above codes were listed as a non-primary cause for the hospital admission or death, but the primary diagnosis for that event aligned with a hypoglycaemic episode and was observable in our cohort. The list of selected ICD-10 codes is provided in the Supplementary Materials.

The embarkation or observability status of individuals was defined using attendance of routine observations and receipt of prescriptions during the study period. If individuals became unobservable during the study period, they were censored on the date at which they first became unobservable. Thus, individuals were censored for end of study, end of observability, or death.

2.3. Statistical analyses

Using daily counts of admissions and numbers of people observable in the cohort, we calculated the crude yearly SHH event rate per 1,000 person-years for 2016–2022 in people with T1D and T2D in Scotland, stratified by sex and age bands (T1D: <20, 20–49, ≥ 50; T2D: 20–59, 60–74, ≥ 75). Age bands were based on the age of each person at the midpoint of their observability period. In addition, we conducted further analyses stratified by socioeconomic level using the Scottish Index of Multiple Deprivation 2020 (SIMD, quantiles from 1 to 5, Q1 corresponding to the most deprived individuals) based on the most recent postcode of residence [19]. In addition, an analysis of the electronic dispensing records from the Scottish National Prescribing Information System was performed to obtain the annual prevalence of use of CGM in people with type 1 diabetes from our cohort. To do so, we used the dm+d code "34865511000001109" for Glucose interstitial fluid detection sensor, which includes CGM and flash monitors. We calculated the number of unique individuals with at least one dispensing record with this code during each year from 2017, the year that these devices became available from NHS in Scotland, to 2022.

2.4. Modelling calendar time effect on severe hospitalised hypoglycaemia

To formally estimate the variation in SHH across calendar time and sociodemographic strata, the R package *mgcv* was used to fit a generalised additive model (GAM) [20,21] with Poisson likelihood to the daily counts of SHH events from 1 January 2016 to 31 October 2022. The terms in the model were the intercept, sex, age band, and weekday versus weekend (as an indicator variable) as varying intercepts, a smoothed term for seasonality as a cyclic cubic spline fitted to the week of the hypoglycaemia event (encoded as an integer from 1 to 52), and a smoothed thin-plate spline for calendar time fitted to the calendar date in days. These smoothed terms were separately fitted for each age group. The logarithm of the daily population at risk was used as an offset. Details about the fitting of the model are provided in the Supplementary Materials. The graphical output from the model allows a visualisation of the best fit trend line for SHH event rate over time as a rate ratio (RR) relative to the long-term average. The confidence intervals (CIs) around the trend line can be used to evaluate the significance of rate differences between time points; if the difference is significant, the CIs will not overlap.

All analyses were conducted using R 4.1. No imputation of missing data was required.

3. Results

A total of 36,091 people with T1D (75,968,727 person-days) and 382,065 people with T2D (702,578,888 person-days) from the cohort contributed to the study for the period 2016–2022. There were 2,859 and 4,276 SHH events observed in people with T1D and T2D, respectively. Among these people, 36 of those with T1D and 58 of those with T2D had a selected ICD-10 diagnosis code recorded as cause of death across this period, as explained above (see Materials & Methods). In

individuals with T1D, the number of unique individuals with at least one dispensing record for a glucose monitoring device continuously increased from 61 in 2017 (0.2 % of people observable that year in our cohort) to 12,303 (39.38 %) in 2019, and further to 21,900 (68.73 %) in 2022 (Table S1). Only a small proportion of people with T2D were using a glucose monitoring device during the study period (less than 2 % in 2022 at the highest level).

3.1. SHH rates in those with type 1 diabetes

3.1.1. Variation in SHH over time

The crude annual rates of SHH per 1,000 person-years were at their lowest in 2020, rising again in 2021–2022 though to lower than pre-2020 (Table 1). A GAM adjusted for age band and sex confirmed an overall significant fall ($p < 0.001$).

Fig. 1 shows the age stratum-specific estimate of the calendar time trend (shown by the solid line) and its confidence limits (shown by the coloured ribbon) from the GAM. The younger age band exhibited a steep drop to a low towards late 2020–early 2021 with rates rising somewhat again in 2021 and 2022 but staying below their previous highest value. However, this drop started before the pandemic onset; it was particularly steep during 2019. At the lowest point, SHH rates were approximately 30 % below the long-term average. This represents a fall by about half from the peak observed prior to 2020. The age stratum-specific GAM confirmed significant change over time in the youngest age band ($p < 0.001$). The significant drop is also evidenced by the non-overlapping confidence limits at the 2020–2021 lowest point compared to pre-2020 values (Fig. 1). The GAM suggests a slow downward trend over time for people aged 20–49 and those aged 50 and above (Fig. 1). This slow decrease is significant for the people aged 20–49 ($p \approx 0.013$) but not for the older age band ($p \approx 0.059$).

Over the study period, there were 36 deaths in people with T1D with a selected ICD-10 code on the death certificate as previously detailed, with little variation in the counts per year and, in particular, no substantial increase during the COVID-19 years 2020–21.

3.1.2. Sociodemographic variation in SHH

Table 1 shows highest SHH rates in those aged under 20 and lowest in those aged 20–49. There was no consistent sex difference across the years. The GAM yielded a non-significant 5 % higher rate in females (RR 1.05, 95 % CI 0.97–1.13) across the study period.

Fig. 2 indicates a markedly higher SHH rate in SIMD1 (most deprived quintile) in 2016 and for 2018–2022. The adjusted GAM across all years showed that SIMD1 was associated with SHH rates 2.58 times higher than SIMD5 (95 % CI 2.27–2.93). However, the data suggest that the difference between all quintiles decreased over time, indicating a narrowing of the socioeconomic differential. The crude rate ratio for SIMD1 versus SIMD5 was 2.76 [2.00–3.79] in 2016 and 2.04 [1.42–2.93] in 2022.

3.2. SHH rates in those with type 2 diabetes

3.2.1. Variation in SHH over time

SHH rates in T2D were overall about 15 % of the rates seen in T1D (Table 2). The lowest yearly rates in those with T2D were reached in 2020. An adjusted GAM found significant year-to-year variation ($p < 0.01$) but no consistent downward trend.

Fig. 3 shows that SHH rates in people aged 20–59 fell from an early 2019 peak to a 2020 low that preceded a new rise. At their lowest point, rates were approximately 20 % below the long-term average. This represents a fall by about half from the highest level observed in 2019 and this difference is significant, as shown by the absence of overlapping between the confidence limits for these time points. The age-stratum specific GAM confirmed a significant variation over time compared to the long term average in people aged 20–59 ($p < 0.01$), although the observed fluctuations do not allow concluding in a general trend across the study period. There was no substantial change over time in rates in those aged 60–74 (Fig. 3) and this was confirmed in the GAM ($p \approx 0.593$). Finally, in those aged 75 and higher, an upward trend in rates is suggested between 2016 and late 2018, followed by a downward trend (Fig. 3). The GAM indicates however that variation over time in this group was not significant ($p \approx 0.054$).

Table 1
Severe hospitalised hypoglycaemia event rates in people with type 1 diabetes in Scotland.

Total SHH events/Person-years at risk (Crude SHH event rate per 1,000 person-years)								
Sex	Age	2016	2017	2018	2019	2020	2021	2022
All	All	437/29860.92 (14.63)	455/30020.51 (15.16)	445/30240.19 (14.72)	464/30441.85 (15.24)	343/30685.79 (11.18)	391/30930.47 (12.64)	324/25811.32 (12.55)
	<20	84/2798.75 (30.01)	88/3158.73 (27.86)	96/3542.13 (27.10)	115/3902.78 (29.47)	70/4288.31 (16.32)	74/4741.61 (15.61)	98/4252.93 (23.04)
	20–49	167/15047.70 (11.10)	167/15142.54 (11.03)	152/15249.45 (9.97)	153/15326.87 (9.98)	118/15425.40 (7.65)	156/15494.20 (10.07)	117/12891.55 (9.08)
	≥50	186/12014.48 (15.48)	200/11719.24 (17.07)	197/11448.62 (17.21)	196/11212.19 (17.48)	155/10972.07 (14.13)	161/10694.65 (15.05)	109/8666.83 (12.58)
Females	All	203/13202.21 (15.38)	214/13275.16 (16.12)	209/13403.89 (15.59)	206/13520.27 (15.24)	178/13646.02 (13.04)	178/13751.99 (12.94)	137/11477.28 (11.94)
	<20	36/1367.25 (26.33)	42/1526.71 (27.51)	53/1706.46 (31.06)	59/1879.98 (31.38)	40/2065.58 (19.37)	30/2281.76 (13.15)	47/2045.04 (22.98)
	20–49	74/6506.63 (11.37)	73/6536.77 (11.17)	63/6582.52 (9.57)	64/6617.90 (9.67)	57/6647.52 (8.57)	65/6650.02 (9.77)	44/5526.09 (7.96)
	≥50	93/5328.33 (17.45)	99/5211.68 (19.00)	93/5114.91 (18.18)	83/5022.39 (16.53)	81/4932.92 (16.42)	83/4820.22 (17.22)	46/3906.14 (11.78)
Males	All	234/16658.71 (14.05)	241/16745.35 (14.39)	236/16836.31 (14.02)	258/16921.58 (15.25)	165/17039.77 (9.68)	213/17178.48 (12.40)	187/14334.04 (13.05)
	<20	48/1431.50 (33.53)	46/1632.02 (28.19)	43/1835.67 (23.42)	56/2022.80 (27.68)	30/2222.73 (13.50)	44/2459.85 (17.89)	51/2207.89 (23.10)
	20–49	93/8541.06 (10.89)	94/8605.77 (10.92)	89/8666.93 (10.27)	89/8708.97 (10.22)	61/8777.88 (6.95)	91/8844.19 (10.29)	73/7365.46 (9.91)
	≥50	93/6686.15 (13.91)	101/6507.56 (15.52)	104/6333.70 (16.42)	113/6189.81 (18.26)	74/6039.15 (12.25)	78/5874.43 (13.28)	63/4760.69 (13.23)

Data for year 2022 available until 31 October. Age corresponds to the age at the midpoint of the observability period of people.

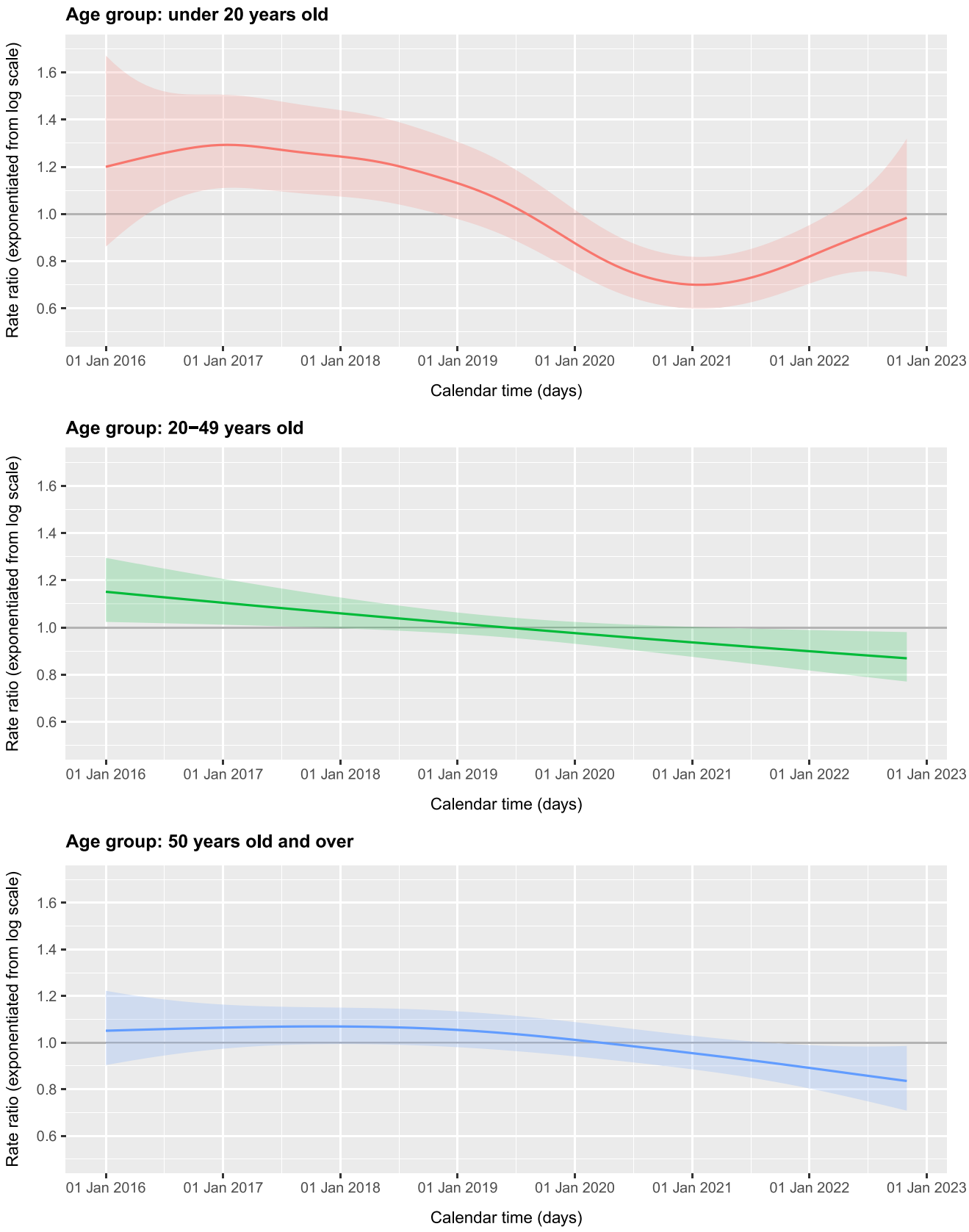

Fig. 1. Smoothed curves showing the relation between daily counts of severe hospitalised hypoglycaemia events and calendar time in people with type 1 diabetes in Scotland, stratified by age. Curves were fitted using a generalised additive model, adjusting for age, sex, seasonality, weekday/weekend, and Scottish Index of Multiple Deprivation (SIMD). Shaded ribbons represent the 95% confidence interval around the fitted curves. A rate ratio of 1.0 corresponds to the 7-year average within each age stratum.

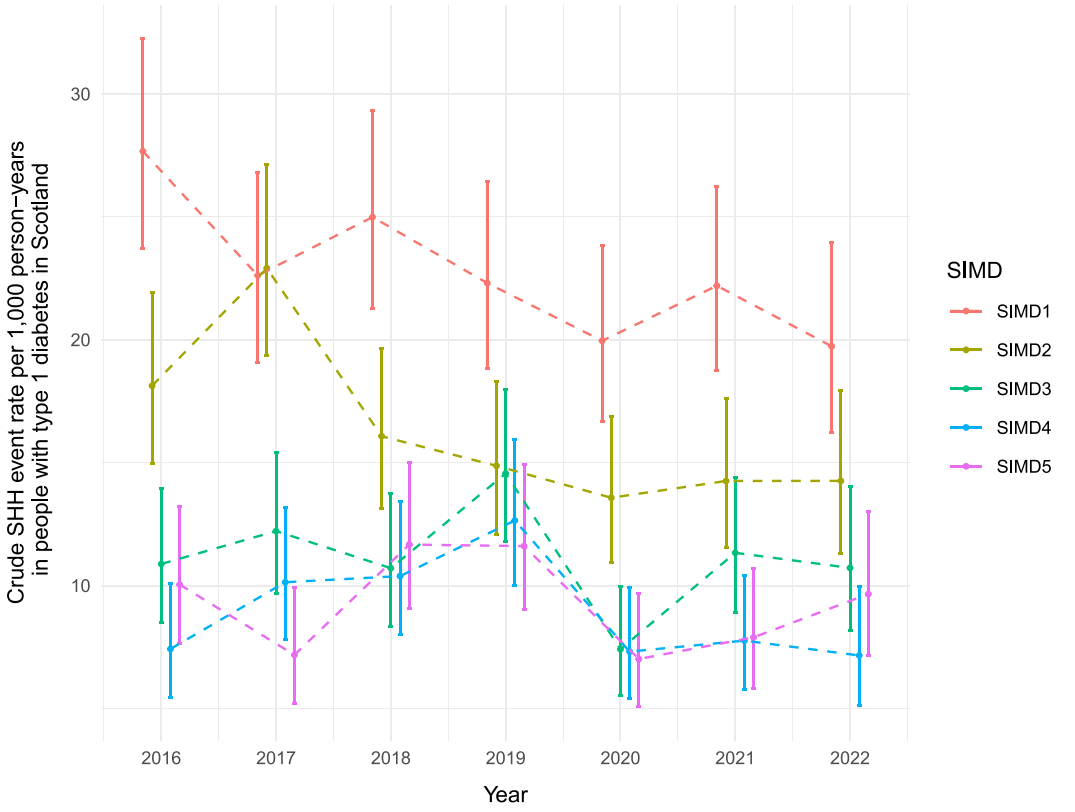

Fig. 2. Crude severe hospitalised hypoglycaemia (SHH) event rates per year (95 % CI) in people with type 1 diabetes in Scotland between 2016 and 2022, stratified by Scottish Index of Multiple Deprivation (SIMD) quintile.

Table 2
Severe hospitalised hypoglycaemia event rates in people with type 2 diabetes in Scotland.

Total SHH events/Person-years at risk (Crude SHH event rate per 1,000 person-years)								
Sex	Age	2016	2017	2018	2019	2020	2021	2022
All	All	644/270132.39 (2.38)	630/275624.88 (2.29)	703/279959.53 (2.51)	680/283840.95 (2.40)	551/286172.57 (1.93)	590/287726.90 (2.05)	478/240098.93 (1.99)
	20–59	69/65657.88 (1.05)	52/71916.75 (0.72)	85/78000.00 (1.09)	97/84023.65 (1.15)	64/89752.50 (0.71)	102/95921.07 (1.06)	67/84062.84 (0.80)
	60–74	219/114002.58 (1.92)	216/117457.53 (1.84)	250/120311.18 (2.08)	238/122675.88 (1.94)	222/124437.09 (1.78)	258/125468.74 (2.06)	217/105163.84 (2.06)
	≥75	356/90471.94 (3.93)	362/86250.60 (4.20)	368/81648.35 (4.51)	345/77141.43 (4.47)	265/71982.99 (3.68)	230/66337.10 (3.47)	194/50872.24 (3.81)
Females	All	336/119666.75 (2.81)	311/121758.95 (2.55)	354/123215.67 (2.87)	333/124604.08 (2.67)	276/125476.61 (2.20)	288/126190.28 (2.28)	235/105375.44 (2.23)
	20–59	43/27885.67 (1.54)	29/30550.66 (0.95)	47/33108.34 (1.42)	46/35635.06 (1.29)	32/38060.81 (0.84)	51/40906.14 (1.25)	32/36075.86 (0.89)
	60–74	94/46026.06 (2.04)	96/47525.63 (2.02)	114/48790.02 (2.34)	94/49889.13 (1.88)	106/50835.84 (2.09)	112/51525.14 (2.17)	91/43386.99 (2.10)
	≥75	199/45755.03 (4.35)	186/43682.65 (4.26)	193/41317.31 (4.67)	193/39079.89 (4.94)	138/36579.95 (3.77)	125/33759.00 (3.70)	112/25912.60 (4.32)
Males	All	308/150465.64 (2.05)	319/153865.93 (2.07)	349/156743.86 (2.23)	347/159236.87 (2.18)	275/160695.97 (1.71)	302/161536.62 (1.87)	243/134723.48 (1.80)
	20–59	26/37772.21 (0.69)	23/41366.08 (0.56)	38/44891.66 (0.85)	51/48388.59 (1.05)	32/51691.69 (0.62)	51/55014.92 (0.93)	35/47986.99 (0.73)
	60–74	125/67976.52 (1.84)	120/69931.90 (1.72)	136/71521.16 (1.90)	144/72786.75 (1.98)	116/73601.24 (1.58)	146/73943.61 (1.97)	126/61776.85 (2.04)
	≥75	157/44716.91 (3.51)	176/42567.95 (4.13)	175/40331.04 (4.34)	152/38061.54 (3.99)	127/35403.04 (3.59)	105/32578.09 (3.22)	82/24959.64 (3.29)

Data for year 2022 available until 31 October. Age corresponds to the age at the midpoint of the observability period of people. People under the age of 20 are excluded for type 2 diabetes.

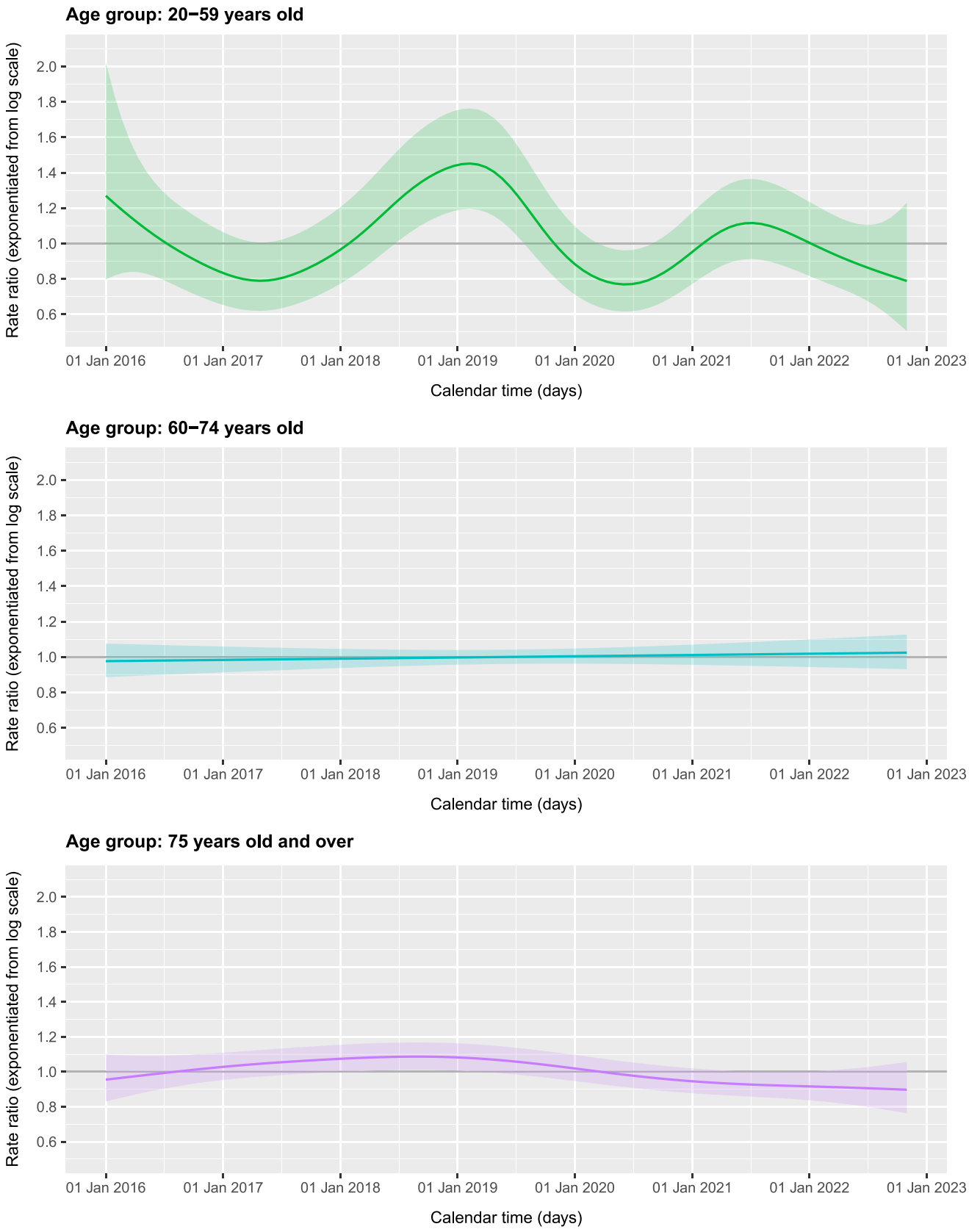

Fig. 3. Smoothed curves showing the relation between daily counts of severe hospitalised hypoglycaemia events and calendar time in people with type 2 diabetes in Scotland, stratified by age. Curves were fitted using a generalised additive model, adjusting for age, sex, seasonality, weekday/weekend, and Scottish Index of Multiple Deprivation (SIMD). Shaded ribbons represent the 95 % confidence interval around the fitted curves. A rate ratio of 1.0 corresponds to the 7-year average within each age stratum.

Over the study period, there were 58 deaths in people with T2D with a selected ICD-10 code on the death certificate as previously detailed, with peaks in 2016 and 2019, due to higher numbers of deaths in people aged 60–74 years especially. The number of deaths during the COVID-19 years 2020 and 2021 was half the number of 2019.

3.2.2. Sociodemographic variation in SHH

Higher crude SHH rates were seen in the older versus younger age band in T2D and this was consistent across the study period. Females exhibited higher rates than males and this sex difference was seen across all years. The adjusted GAM yielded a significant 15 % higher female rate overall (RR 1.15, 95 % CI 1.08–1.22).

Fig. 4 shows that SHH rates were overall highest in SIMD1; in the adjusted GAM across all years, SIMD1 was associated with SHH rates 2.33 times higher (95 % CI 2.08–2.62) than SIMD5. This socioeconomic differential appears to have narrowed over time. The crude rate ratio for SIMD1 versus SIMD5 was 2.24 [1.65–3.03] in 2016 and 1.56 [1.12–2.18] in 2022.

4. Discussion

4.1. Principal findings

The key finding from this study is that there has been a substantial fall in SHH in younger people with T1D since prior to the COVID-19 pandemic. Compared to the study period average, SHH rates in younger people with T1D fell by approximately 30 % during the pandemic. Rates in this group have risen since their lowest point during that period but remain well below rates seen in 2016–2018. Rates have also slowly decreased somewhat in middle aged persons with T1D, while there has been little change in the older group since 2016. In people with T2D, there is no evidence that rates of SHH have significantly improved since 2016 when looking at stratified data by age band. Although rates fell in people aged 20–59 and, to some extent, in those aged 75 and higher, overall there was no consistent downward trend.

The other key findings are that there are very large socioeconomic differentials in SHH in both T1D and T2D with rates overall being more than double in the most versus least deprived quintiles of the population. This differential appears to have narrowed across the study period, however it remains substantial. We also note that females with T2D overall experience a modestly higher rate of SHH than males. The fall in SHH in people with T1D is encouraging, but hospitalised hypoglycaemia remains a substantial problem for people with T1D and T2D.

4.2. Comparison with previous studies

Several studies have reported on time trends in rates of severe hypoglycaemia in different countries though the only long term (>2 years) time trend analyses we could find predated 2019. In Denmark, SHH decreased by 66 % for people with T1D and by 61 % for people with T2D between 2003 (approximately 10 and 0.8 episodes per 100-person years in people with T1D and T2D, respectively) and 2018 (approximately 3.5 and 0.4 episodes per 100-person years in people with T1D and T2D, respectively) [5]. In South Korea, the incidence of severe hypoglycaemia events in people with T2D who visited the emergency department increased from 2002 to 2012 and then gradually decreased between 2012 and 2019. In 2019, the incidence rate was 4.43 per 1,000 person-years of similar magnitude to what we observed [11]. An Australian analysis reported stable rates of SHH in T1D and declining rates in T2D in the decade up to 2019 [7]. In Germany, there was a rise in severe hypoglycaemia events between 2006 and 2011 followed by a decrease in 2016 [8].

The explicit focus of this work was to examine the population level rates of SHH to determine the level of ongoing need for further reduction in SHH and how this is distributed in various sociodemographic groups rather than a causal analysis of determinants of SHH. Although we cannot precisely discern the causes of the large fall in SHH in younger persons with T1D, it seems likely that this is in part due to the programme of nationwide access to flash monitors that started in 2018 with further impact of specific aspects of the COVID-19 pandemic in 2020 and

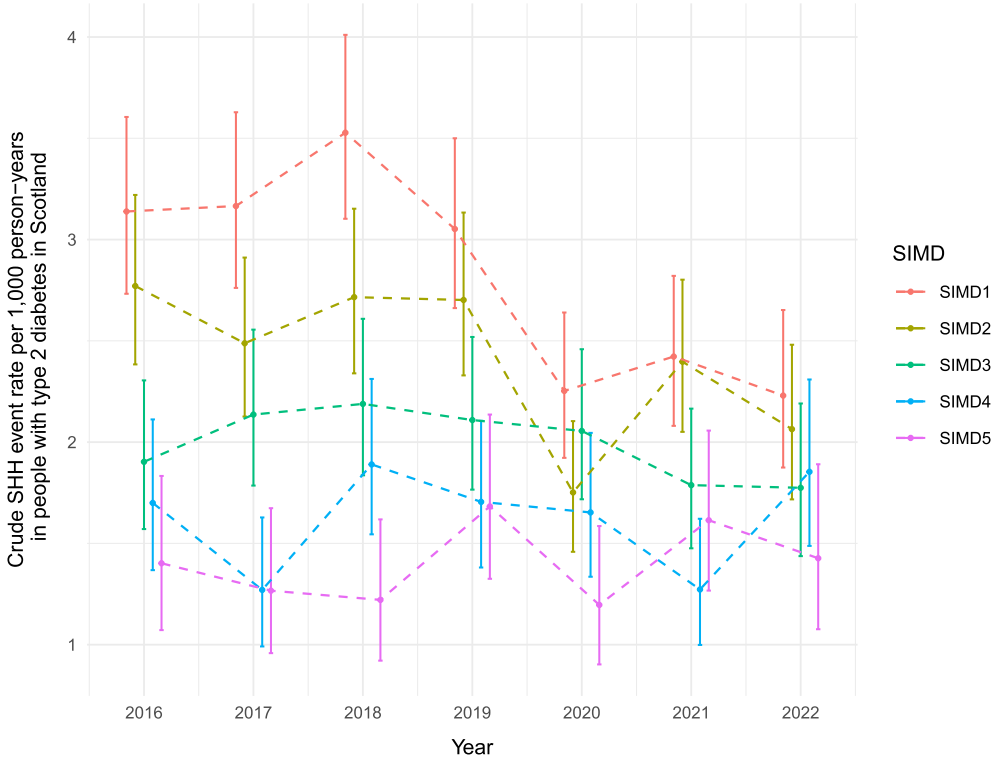

Fig. 4. Crude severe hospitalised hypoglycaemia (SHH) event rates per year (95 % CI) in people with type 2 diabetes in Scotland between 2016 and 2022, stratified by Scottish Index of Multiple Deprivation (SIMD) quintile.

2021 or other factors. Consistent with this, we have previously shown that, at an individual level, intermittently-scanned CGM (iCGM) reduced SHH rates by 75 % in those with a history of SHH [14]. Other real world observational studies have also reported reductions in hypoglycaemia with flash monitors [22–27]. Data also suggest that the fall in rates among younger persons started before the pandemic onset, with notably a steep drop during 2019, which is consistent with the flash monitor rollout making a contribution to this decrease. The observed reductions in SHH rates align with the increasing prevalence of use of glucose monitoring devices from the end of 2017 (0.2 %) to 2019 (39.4 %) and further to 2022 (68.8 %) that we revealed using dispensing data of people with T1D in Scotland. While this does not prove causality, it is consistent with the idea that the use of these devices has contributed at least partly to the changes in SHH rates noted over the study period. There has been an uptick in rates for 2022 and further years of data will be needed to see if this now stabilises to a lower level than the pre-pandemic years. It will also be of interest to investigate the potential impact of the nationwide availability of the Freestyle Libre 2 in the UK from November 2020 on SHH rates. This device has glucose level alert functions and its use has been associated with improved low glucose metrics [28].

It is likely that there was an impact of the pandemic on reducing rates of SHH. However, if so, it would appear this had a greater impact on younger people with T1D and people aged 20–59 with T2D. Possible factors that may have contributed to the fall during the pandemic include greater parental supervision, ability to intervene early in a hypoglycaemic episode during lockdown, and altered eating or exercise or other altered behavioural patterns such as reduced alcohol intake. The data attest to the potential to improve SHH in young people greatly by better support systems. A study by Fernández et al. (2020) on the impact of COVID-19 lockdown on glycaemic control in Basque Country (Northern Spain) in people with T1D reported that mean glucose levels decreased and HbA1c declined during the lockdown period. They concluded that an improvement in glycaemic control after eight weeks of lockdown and that additional time for self-management could potentially contribute to the amelioration of glycaemic control [29]. Similarly, a systematic review by Eberle & Stichling (2021) found that glycaemic values significantly improved during COVID-19 lockdown in people with T1D, probably in association with positive changes in self-care and digital management of their diabetes. Regarding individuals with T2D, the authors reported a short-term deterioration in glycaemic parameters with an increase of HbA1c levels during lockdown. They note, however, that lockdown measures and restrictions were very heterogeneous depending on the country [30].

We noted important fluctuations in SHH rates across the study period in people with T2D, especially in those aged 20–59 and those aged 75 and higher, without being able to attest that rates have been significantly reduced since 2016. This period has seen rapidly increasing therapeutic alternatives to insulin and sulphonylurea therapy in T2D that are expected to reduce SHH [1]. However, there has also been an increase in polypharmacy over this period that may have limited this progress [31,32]. Further work will ascertain individual level data and individual level predictors of SHH in this age group and the extent to which new treatments have been adopted, particularly in those with greater propensity to hypoglycaemia.

We noted stark socioeconomic (SES) differences in SHH in both types of diabetes. This is consistent with other smaller studies [33,34] from other countries. This finding is of particular concern because we have also reported previously that individuals in lower socioeconomic groups have poorer glycaemic control [35], as well as higher rates of diabetic ketoacidosis [36]. Taken together, this suggests greater glycaemic variability, which has been linked to an increased risk of complications in diabetes [37]. It seems likely that a complex mix of factors will determine this SES disparity, including different levels of support, health care and structured education access and uptake, comorbidities, and concurrent medications. A simplistic interpretation that differences in purchasing power of health care and devices underlies this disparity is not appropriate, as health care is free at the point of access in Scotland. We have previously showed socioeconomic differences in early uptake of flash glucose monitoring devices and other insulin technologies, even when these are provided without cost in the health care system [14]. The data attest to the importance of a more nuanced understanding of the socioeconomic barriers to health care and support in future policies to reduce SHH beyond simply device provision. On a positive note, it is reassuring to observe a narrowing of the socioeconomic differential in our cohort for both diabetes types across the study period. It is also worth mentioning that SHTG (Scottish Health Technologies Group) guidance from 2022 included the importance of Equity of Access and highlighted the need for clinical care teams to ensure equal access to technologies.

We noted that females had a 15 % higher rate of SHH in T2D, with a non-significant 5 % higher rate in females with T1D. The literature on sex differences in hypoglycaemia is sparse and conflicting with some small studies finding more SHH in boys than girls [38] with T1D or no difference [39], but other studies finding a female excess [40–42]. Our study is much larger than any in the literature with attendant great power to detect differences. Some studies have shown that C-peptide persistence is associated with a reduced risk of hypoglycaemia and is more common in males than females in T1D [43,44]. In addition, the menstrual cycle appears to interact with insulin sensitivity in some women, which could have an impact on the risk of hypoglycaemia [45]. Further research is needed to explore the gender differences in modifiable predictors of hypoglycaemia to inform care models on how to reduce this imbalance.

4.3. *Strengths and limitations*

Major strengths of our study are the comprehensive capture of all hospitalised hypoglycaemia in more than 99 % of the population with diabetes, the contemporaneous nature of the data and the ability to describe important sociodemographic variation. A limitation of the study is that, as with many hypoglycaemia studies internationally, it focusses on hospital admissions for hypoglycaemic events. We do not have access to blood glucose data, home or ambulance managed events within the linked dataset though we hope to include this information available from SCI-Diabetes in future years. Only the most severe hypoglycaemia events require hospitalisation [46]; for example Villani et al. (2019) indicated that only approximately 50 % of individuals with severe hypoglycaemia required transport to the hospital, and that, of that group, 41.3 % were admitted to the hospital [47]. A questionnaire-based study of Canadian adults with T1D or T2D taking secretagogues alone or with insulin found higher than expected real-world incidence rates of severe and non-severe hypoglycaemia events [48]. However, SHH remains a useful barometer used by many countries of the overall burden of hypoglycaemia and the need for further initiatives to reduce it. Given the observational nature of our study, interpretations of the revealed trends should remain cautious and alternative explanations should be considered. The focus of this paper was on the overall burden of SHH at population level; further work will model and explore the determinants or factors associated with SHH using individual level data, including diabetes duration, HbA1c levels, use of glucose monitoring devices, insulin and other diabetes medication prescriptions.

5. Conclusions and perspectives

In this observational study, we have seen a substantial fall in hospitalised hypoglycaemia in type 1 diabetes since the period prior to 2020 in younger people and a year-on-year decrease in middle aged people. The glucose monitoring devices have likely contributed to the reduction of SHH rates in these groups while the effects of the COVID-19 pandemic on SHH need to be better understood. However, it is of critical importance that we continue to make advances to reduce rates further and that

we address the lack of significant improvement in older persons with T1D. There is clearly scope for closed loop systems to reduce rates further, particularly in those most vulnerable, though additional evidence is required. Development of insulins with less hypoglycaemic potential is also important, as is improved education and better support systems for people with diabetes. In T2D, although we observed a substantial fall in rates between 2019 and 2020 in people aged 20–59 and, to a lesser extent, in those aged 75 and higher, rates have risen again and there is no evidence of an overall progress since 2016. Given the changing demographics in many societies with a growing percentage of the population aged over 65 years, the risk of severe hypoglycaemia in the elderly needs to be addressed. Our data emphasise that there is an ongoing need to optimise drug therapy in this age group, and to enact policies that specifically target the reduction of SHH. Such policies might consider the role of polypharmacy in hypoplycaemia in the elderly and whether or not there is a case for increasing CGM use in older persons both with T1D and T2D in particular settings such as in nursing homes. It also emphasizes the need for maintaining a focus on patient education and ensuring equitable uptake of devices that have been shown to reduce SHH. Reducing the burden of SHH has broader public health implications, including the potential to improve the overall quality of life for individuals with diabetes and yield economic benefits by decreasing healthcare utilisation and associated costs. Further work will explore the individual determinants of SHH, including concurrent medications, devices, and multimorbidity in those with T1D and T2D, to better inform preventive policies.

Ethics approval

The Scottish Diabetes Research Network Epidemiology Group has an overarching approval from West of Scotland Research Ethics Committee (ref. 21/WS/0047) for research using the national diabetes research platform that we used in this study across a broad range of areas, including this. We report annually to the Research Ethics Committee on the conducted studies. Approval for use of the diabetes data was also provided by the Public Benefit and Privacy Panel for Health and Social Care (HSC-PBPP - ref 1617-0147).

Funding

This work was supported by funding from the Innovative Medicines Initiative 2 Joint Undertaking (Agreement no. 777460; Project ref. H2020-GTI-IMI2-2016-10) and from Diabetes UK (17/0005627). We acknowledge the financial support of NHS Research Scotland (NRS), through Diabetes Network. The NHS Research Scotland Diabetes Network (formerly Scottish Diabetes Research Network) receives funding from the Chief Scientist Office of the Scottish Government. H.M.C. is supported by an endowed chair from the AXA Research Fund. S.H. was supported by EU IMI HypoRESOLVE programme.

CRediT authorship contribution statement

William Berthon: Writing – review & editing, Writing – original draft, Visualization, Methodology, Investigation, Formal analysis. **Stuart J. McGurnaghan:** Data curation, Methodology, Software, Supervision, Writing – review & editing. **Luke A.K. Blackbourn:** Data curation, Methodology, Software, Writing – review & editing. **Joseph Mellor:** Writing – review & editing. **Fraser W. Gibb:** Writing – review & editing. **Simon Heller:** Writing – review & editing. **Brian Kennon:** Writing – review & editing. **Rory J. McCrimmon:** Writing – review & editing. **Sam Philip:** Writing – review & editing. **Naveed Sattar:** Writing – review & editing. **Paul M. McKeigue:** Writing – review & editing, Supervision, Methodology, Conceptualization. **Helen M. Colhoun:** Investigation, Funding acquisition, Conceptualization, Methodology, Project administration, Supervision, Validation, Writing – original draft, Writing – review & editing.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: P. M.M. declares stock ownership in the following: Bayer and Roche Pharmaceuticals. H.M.C. declares grants from Juvenile Diabetes Research Foundation International, Diabetes UK, IQVIA, Chief Scientist Office, Medical Research Council (UK Research and Innovation), and European Union Commission, honoraria from Novo Nordisk, advisory board fees paid through her institution from Novo Nordisk and Bayer, and stock ownership in Bayer and Roche Pharmaceuticals. S.H. declares consulting fees paid through his institution from Vertex Pharma, Zucara Pharmaceuticals, and Zealand Pharma, honoraria from Medtronic and Novo Nordisk, and has served as Chair of DSMB for Eli Lilly development programme and as a Member of Novo Nordisk Independent Advisory Board. R.J.M. declares honoraria from Sanofi and Novo Nordisk for lectures and presentations, travel support from Sanofi, and is a non-executive member of NHS Tayside Health Board. F.W.G. declares advisory board fees from Abbott Diabetes and Insulet, speaker fees from Abbott Diabetes, Insulet, Novo Nordisk, and Lilly, and travel support from Abbott Diabetes and Novo Nordisk. S.P. declares grants from Novo Nordisk, Lilly, and Amgen, travel support from Novo Nordisk, and has participated on an Advisory board for Roche Pharmaceuticals. N.S. has consulted for and/or received speaker honoraria from Abbott Laboratories, Abbvie, Amgen, AstraZeneca, Boehringer Ingelheim, Eli Lilly, Hanmi Pharmaceuticals, Janssen, Menarini-Ricerche, Novartis, Novo Nordisk, Pfizer, Roche Diagnostics, and Sanofi; and received grant support paid to his University from AstraZeneca, Boehringer Ingelheim, Novartis, and Roche Diagnostics outside the submitted work. No other potential conflicts of interest relevant to this article were reported.

Data availability

The SDRN-EPI team welcomes external collaborative research proposals that use the research data platform. SDRN-EPI are not data custodians and are not permitted to directly provision data externally. However, the component datasets can be obtained by data governance trained bone fide researchers through the Public Benefit and Privacy Panel for Health and Social Care. See https://www.informationgovernance.scot.nhs.uk/pbpphsc/ for how to apply.

Acknowledgements

We are thankful for the contributions of people with diabetes, National Health Service staff, and organisations (the Scottish Care Information-Diabetes Development Team and Steering Group, the Scottish Diabetes Group, the Scottish Diabetes Survey Group, and the diabetes managed clinical networks) involved in providing data and setting up, maintaining, and overseeing collation of data for people with diabetes in Scotland. Data linkage was performed by colleagues at Public Health Scotland.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.diabres.2024.111642.

References

[1] Dunkley AJ, Fitzpatrick C, Gray LJ, Waheed G, Heller SR, Frier BM, et al. Incidence and severity of hypoglycaemia in type 2 diabetes by treatment regimen: a UK multisite 12-month prospective observational study. Diabetes Obes Metab 2019;21:1585–95. https://doi.org/10.1111/DOM.13690.

[2] Uduku C, Pendolino V, Godsland I, Oliver N, Reddy M, Fothergill RT. Cross-sectional analysis of emergency hypoglycaemia and outcome predictors among people with diabetes in an urban population. Diabetic Medicine 2021;38. doi: 10.1111/dme.14654.

[3] Yun JS, Park YM, Han K, Cha SA, Ahn YB, Ko SH. Severe hypoglycemia and the risk of cardiovascular disease and mortality in type 2 diabetes: a nationwide population-based cohort study. Cardiovasc Diabetol 2019;18:1–12. https://doi.org/10.1186/s12933-019-0909-y.
[4] Gerhardsson P, Schwandt A, Witsch M, Kordonouri O, Svensson J, Forsander G, et al. The SWEET project 10-year benchmarking in 19 countries worldwide is associated with improved HbA1c and increased use of diabetes technology in youth with type 1 diabetes. Diabetes Technol Ther 2021;23:491–9. https://doi.org/10.1089/dia.2020.0618.
[5] Jensen MH, Hejlesen O, Vestergaard P. Epidemiology of hypoglycaemic episodes leading to hospitalisations in Denmark in 1998–2018. Diabetologia 2021;64:2193–203. https://doi.org/10.1007/s00125-021-05507-2.
[6] Lee SE, Kim KA, Son KJ, Song SO, Park KH, Park SH, et al. Trends and risk factors in severe hypoglycemia among individuals with type 2 diabetes in Korea. Diabetes Res Clin Pract 2021;178:108946. https://doi.org/10.1016/J.DIABRES.2021.108946.
[7] Morton JI, Lazzarini PA, Shaw JE, Magliano DJ. Trends in the incidence of hospitalization for major diabetes-related complications in people with type 1 and type 2 diabetes in Australia, 2010–2019. Diabetes Care 2022;45:789–97. https://doi.org/10.2337/DC21-2268.
[8] Müller N, Lehmann T, Klöss A, Günster C, Kloos C, Müller UA. Changes in incidence of severe hypoglycaemia in people with type 2 diabetes from 2006 to 2016: analysis based on health insurance data in Germany considering the antihyperglycaemic medication. Diabet Med 2020;37:1326–32. https://doi.org/10.1111/dme.14294.
[9] Orozco-Beltrán D, Guillen-Mollá A, Cebrián-Cuenca AM, Navarro-Pérez J, Gil-Guillén VF, Quesada JA, et al. Hospital admissions trends for severe hypoglycemia in diabetes patients in Spain, 2005 to 2015. Diabetes Res Clin Pract 2021;171:108565. https://doi.org/10.1016/J.DIABRES.2020.108565.
[10] Pilla SJ, Kraschnewski JL, Lehman EB, Kong L, Francis E, Poger JM, et al. Hospital utilization for hypoglycemia among patients with type 2 diabetes using pooled data from six health systems. BMJ Open Diabetes Res Care 2021;9:e002153. https://doi.org/10.1136/BMJDRC-2021-002153.
[11] Yun JS, Han K, Ko SH. Trends of severe hypoglycemia in patients with type 2 diabetes in Korea: a longitudinal nationwide cohort study. J Diab Invest 2022;13:1438–43. https://doi.org/10.1111/JDI.13786.
[12] Zaccardi F, Davies MJ, Dhalwani NN, Webb DR, Housley G, Shaw D, et al. Trends in hospital admissions for hypoglycaemia in England: a retrospective, observational study. Lancet Diabetes Endocrinol 2016;4:677–85. https://doi.org/10.1016/S2213-8587(16)30091-2.
[13] Nefs G. The psychological implications of automated insulin delivery systems in type 1 diabetes care. Front Clin Diab Healthcare 2022;3:846162. https://doi.org/10.3389/FCDHC.2022.846162.
[14] Jeyam A, Gibb FW, McKnight JA, O'Reilly JE, Caparrotta TM, Höhn A, et al. Flash monitor initiation is associated with improvements in HbA1c levels and DKA rates among people with type 1 diabetes in Scotland: a retrospective nationwide observational study. Diabetologia 2022;65:159. https://doi.org/10.1007/S00125-021-05578-1.
[15] Carr MJ, Wright AK, Leelarathna L, Thabit H, Milne N, Kanumilli N, et al. Impact of COVID-19 on diagnoses, monitoring, and mortality in people with type 2 diabetes in the UK. Lancet Diabetes Endocrinol 2021;9:413–5. https://doi.org/10.1016/S2213-8587(21)00116-9.
[16] Utli H, Doğru BV. The effect of the COVID-19 pandemic on self-management in patients with type 2 diabetics. Prim Care Diabetes 2021;15:799–805. https://doi.org/10.1016/J.PCD.2021.07.009.
[17] Dover AR, Ritchie SA, McKnight JA, Strachan MWJ, Zammitt NN, Wake DJ, et al. Assessment of the effect of the COVID-19 lockdown on glycaemic control in people with type 1 diabetes using flash glucose monitoring. Diabet Med 2021;38:e14374. https://doi.org/10.1111/DME.14374.
[18] McGurnaghan SJ, Blackbourn LAK, Caparrotta TM, Mellor J, Barnett A, Collier A, et al. Cohort profile: the Scottish diabetes Research network national diabetes cohort – a population-based cohort of people with diabetes in Scotland. BMJ Open 2022;12:e063046. https://doi.org/10.1136/BMJOPEN-2022-063046.
[19] SIMD (Scottish Index of Multiple Deprivation) 2020. https://simd.scot/#/simd2020/bttftft/9/-4.0000/55.9000. Accessed 10 june 2023.
[20] McKeigue PM, McGurnaghan S, Blackbourn L, Bath LE, McAllister DA, Caparrotta TM, et al. Relation of incident type 1 diabetes to recent COVID-19 infection: cohort study using e-health record linkage in Scotland. Diabetes Care 2023;46:921–8. https://doi.org/10.2337/dc22-0385.
[21] Wood SN. Fast stable restricted maximum likelihood and marginal likelihood estimation of semiparametric generalized linear models. J R Stat Soc (B) 2011;73:3–36. https://doi.org/10.1111/j.1467-9868.2010.00749.x.
[22] Deshmukh H, Wilmot EG, Gregory R, Barnes D, Narendran P, Saunders S, et al. Effect of flash glucose monitoring on glycemic control, hypoglycemia, diabetes-related distress, and resource utilization in the Association of British Clinical Diabetologists (ABCD) nationwide audit. Diabetes Care 2020;43:2153–60. https://doi.org/10.2337/dc20-0738.
[23] Karges B, Tittel SR, Bey A, Freiberg C, Klinkert C, Kordonouri O, et al. Continuous glucose monitoring versus blood glucose monitoring for risk of severe hypoglycaemia and diabetic ketoacidosis in children, adolescents, and young adults with type 1 diabetes: a population-based study. Lancet Diabetes Endocrinol 2023;11:314–23. https://doi.org/10.1016/S2213-8587(23)00061-X.
[24] Nathanson D, Svensson AM, Miftaraj M, Franzén S, Bolinder J, Eeg-Olofsson K. Effect of flash glucose monitoring in adults with type 1 diabetes: a nationwide, longitudinal observational study of 14,372 flash users compared with 7691 glucose sensor naive controls. Diabetologia 2021;64:1595–603. https://doi.org/10.1007/S00125-021-05437-Z.
[25] Roussel R, Riveline J-P, Vicaut E, de Pouvourville G, Detournay B, Emery C, et al. Important drop in rate of acute diabetes complications in people with type 1 or type 2 diabetes after initiation of flash glucose monitoring in France: the relief study. Diabetes Care 2021. https://doi.org/10.2337/dc20-1690.
[26] Sundberg F, Nåtman J, Franzen S, Åkesson K, Särnblad S. A decade of improved glycemic control in young children with type 1 diabetes: a population-based cohort study. Pediatr Diabetes 2021;22:742–8. https://doi.org/10.1111/PEDI.13211.
[27] Tsur A, Cahn A, Israel M, Feldhamer I, Hammerman A, Pollack R. Impact of flash glucose monitoring on glucose control and hospitalization in type 1 diabetes: a nationwide cohort study. Diabetes Metab Res Rev 2021;37:e3355. https://doi.org/10.1002/DMRR.3355.
[28] Stimson RH, Dover AR, Strachan MWJ, Wright RJ, Forbes S, Gibb FW. Changes in continuous glucose monitoring metrics and predictors of improvement 12 months after conversion from Freestyle Libre to Freestyle Libre 2. Diabet Med 2023. https://doi.org/10.1111/dme.15130.
[29] Fernández E, Cortazar A, Bellido V. Impact of COVID-19 lockdown on glycemic control in patients with type 1 diabetes. Diabetes Res Clin Pract 2020;166:108348. https://doi.org/10.1016/J.DIABRES.2020.108348.
[30] Eberle C, Stichling S. Impact of COVID-19 lockdown on glycemic control in patients with type 1 and type 2 diabetes mellitus: a systematic review. Diabetol Metab Syndr 2021;13:1–8. https://doi.org/10.1186/S13098-021-00705-9.
[31] Wang X, Liu K, Shirai K, Tang C, Hu Y, Wang Y, et al. Prevalence and trends of polypharmacy in U.S. Adults, 1999-2018. Global Health Research and Policy 2023;8:25. doi:10.1186/S41256-023-00311-4.
[32] Tarrant C, Lewis R, Armstrong N. Polypharmacy and continuity of care: medicines optimisation in the era of multidisciplinary teams. BMJ Qual Saf 2023;32:121–4. https://doi.org/10.1136/bmjqs-2022-015082.
[33] Majidi S, Ebekozien O, Noor N, Lyons SK, McDonough R, Gandhi K, et al. Inequities in health outcomes in children and adults with type 1 diabetes: data from the T1D exchange quality improvement collaborative. Clin Diab 2021;39:278–83. https://doi.org/10.2337/CD21-0028.
[34] Talbo MK, Katz A, Dostie M, Legault L, Brazeau AS. Associations between socioeconomic status and patient experience with type 1 diabetes management and complications: cross-sectional analysis of a cohort from Québec, Canada. Can J Diab 2022;46:569–77. https://doi.org/10.1016/J.JCJD.2022.02.008.
[35] Mair C, Wulaningsih W, Jeyam A, McGurnaghan S, Blackbourn L, Kennon B, et al. Glycaemic control trends in people with type 1 diabetes in Scotland 2004–2016. Diabetologia 2019;62:1375–84. https://doi.org/10.1007/S00125-019-4900-7.
[36] O'Reilly JE, Jeyam A, Caparrotta TM, Mellor J, Hohn A, McKeigue PM, et al. Rising rates and widening socioeconomic disparities in diabetic ketoacidosis in type 1 diabetes in Scotland: a nationwide retrospective cohort observational study. Diabetes Care 2021;44:2010–7. https://doi.org/10.2337/DC21-0689.
[37] Ceriello A, Monnier L, Owens D. Glycaemic variability in diabetes: clinical and therapeutic implications. Lancet Diabetes Endocrinol 2019;7:221–30. https://doi.org/10.1016/S2213-8587(18)30136-0.
[38] de Vries SAG, Verheugt CL, Mul D, Nieuwdorp M, Sas TCJ. Do sex differences in paediatric type 1 diabetes care exist? A systematic review. Diabetologia 2023;66:618–30. https://doi.org/10.1007/S00125-022-05866-4.
[39] Lin YK, Richardson CR, Dobrin I, Dejonckheere MJ, Mizokami-Stout K, Fetters MD, et al. Beliefs around hypoglycemia and their impacts on hypoglycemia outcomes in individuals with type 1 diabetes and high risks for hypoglycemia despite using advanced diabetes technologies. Diabetes Care 2022;45:520–8. https://doi.org/10.2337/DC21-1285.
[40] Talbo MK, Lebbar M, Wu Z, Vanasse A, Lalanne-Mistrih ML, Brazeau AS, et al. Gender differences in reported frequency and consequences of hypoglycemia among adults living with type 1 diabetes: results from the better registry. Diabetes Res Clin Pract 2023;202. https://doi.org/10.1016/J.DIABRES.2023.110822.
[41] Cariou B, Fontaine P, Eschwege E, Lièvre M, Gouet D, Huet D, et al. Frequency and predictors of confirmed hypoglycaemia in type 1 and insulin-treated type 2 diabetes mellitus patients in a real-life setting: results from the dialog study. Diabetes Metab 2015;41:116–25. https://doi.org/10.1016/J.DIABET.2014.10.007.
[42] Kautzky-Willer A, Kosi L, Lin J, Mihaljevic R. Gender-based differences in glycaemic control and hypoglycaemia prevalence in patients with type 2 diabetes: results from patient-level pooled data of six randomized controlled trials. Diabetes Obes Metab 2015;17:533–40. https://doi.org/10.1111/DOM.12449.
[43] Dover AR, Strachan MWJ, McKnight JA, Stimson RH, Mackenzie SD, Lyall MJ, et al. Socioeconomic deprivation, technology use, C-peptide, smoking and other predictors of glycaemic control in adults with type 1 diabetes. Diabet Med 2021;38:e14445. https://doi.org/10.1111/DME.14445.
[44] McKeigue PM, Spiliopoulou A, McGurnaghan S, Colombo M, Blackbourn L, McDonald TJ, et al. Persistent C-peptide secretion in type 1 diabetes and its relationship to the genetic architecture of diabetes. BMC Med 2019;17:1–11. https://doi.org/10.1186/S12916-019-1392-8.
[45] Gamarra E, Trimboli P. Menstrual cycle, glucose control and insulin sensitivity in type 1 diabetes: A systematic review. Journal of Personalized Medicine 2023, Vol 13, Page 374 2023;13:374. doi:10.3390/JPM13020374.
[46] Bengtsen MB, Knudsen JS, Bengtsen MB, Møller N, Thomsen RW. Hospitalization for hypoglycaemia in people with diabetes in Denmark, 1997–2017: time trends in incidence and HbA1c and glucose-lowering drug use before and after

hypoglycaemia. Endocrinol, Diab Metab 2021;4:e00227. https://doi.org/10.1002/edm2.227.

[47] Villani M, Earnest A, Smith K, Giannopoulos D, Soldatos G, de Courten B, et al. Outcomes of people with severe hypoglycaemia requiring prehospital emergency medical services management: a prospective study. Diabetologia 2019;62:1868–79. https://doi.org/10.1007/S00125-019-4933-Y.

[48] Ratzki-Leewing A, Harris SB, Mequanint S, Reichert SM, Brown JB, Black JE, et al. Real-world crude incidence of hypoglycemia in adults with diabetes: Results of the InHypo-DM Study, Canada. BMJ Open Diabetes Research & Care 2018;6. doi: 10.1136/BMJDRC-2017-000503.