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Published in:
Diabetes Care

DOI:
10.2337/dc21-0689

Publication date:
2021

Document Version
Peer reviewed version

Rising Rates And Widening Socio-economic Disparities In Diabetic Ketoacidosis In Type 1 Diabetes In Scotland: A Nationwide Retrospective Cohort Observational Study

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Running Title: DKA IN TYPE 1 DIABETES IN SCOTLAND

Abstract

Objective - Whether advances in the management of type 1 diabetes are reducing rates of diabetic ketoacidosis (DKA) is unclear. We investigated time trends in DKA rates in a national cohort of individuals with type 1 diabetes followed for 14 years, overall and by socioeconomic characteristics.

Research Design and Methods - All individuals in Scotland who were alive with type 1 diabetes and at least one year old between 2004-01-01 and 2018-12-31 were identified using the national register (N=37939). DKA deaths and hospital admissions were obtained through linkage to Scottish national death and morbidity records. Bayesian regression was used to test for DKA time trends and association with risk markers, including socioeconomic deprivation.

Results - 30427 DKA admissions, and 472 DKA deaths were observed over 393223 person-years at risk. DKA event rates increased over the study period (IRR per year=1.058 [1.054-1.061]). Males had lower rates than females (IRR Male:Female=0.814 [0.776-0.855]). DKA incidence rose in all age groups other than 10-19 year-olds, in whom rates were the highest but fell over the study. There was a large socioeconomic differential (IRR least:most deprived quintile=0.446 [0.406-0.490]) which increased during follow-up. Insulin pump use or completion of structured education were associated with lower DKA rates, antidepressant and methadone prescription were associated with higher DKA rates.

Conclusion - DKA incidence has risen since 2004, except in 10-19 year olds. Of particular concern are the strong and widening socioeconomic disparities in DKA outcomes. Efforts to prevent DKA, especially in vulnerable groups, require strengthening.

Introduction

Diabetic ketoacidosis (DKA) is a significant contributor to mortality in type 1 diabetes, and we recently showed that this acute complication is second only to cardiovascular disease as the most frequent cause of death below 50 years of age in these individuals (1). DKA events are often precipitated by infection, acute comorbidites, insulin omission, or substance use disorders (2–4), and occur as a consequence of insulin deficiency in the context of these precipitating factors. Further established risk factors associated with higher rates of DKA include insulin pump failure, higher HbA1c, disordered eating, lower socioeconomic status and depression (5–10).

DKA is a preventable cause of death, and reducing DKA mortality would lower the excess mortality associated with type 1 diabetes (1,11). Recent studies have suggested that DKA admission rates and the proportion of people with DKA at diagnosis of type 1 diabetes are increasing (12,13). In addition to this, we recently reported that DKA mortality rates have not significantly improved in Scotland in recent years for people below 50 years of age (11). Improving early diagnosis of type 1 diabetes, identification of DKA, and the reduction of the impact of deprivation on diabetes care and outcomes are key priorities in the Scottish Government's Diabetes Improvement Plan (14).

Accurate quantification of DKA event rates and identification of associated risk factors are required to inform future DKA prevention strategies and health care delivery models. Few studies have quantified DKA event rates over time in large population representative cohorts (3,5), and even fewer have attempted to estimate the association of socioeconomic status with these rates. Consequently, identifying the characteristics of individuals at elevated risk of DKA admission or mortality remains a priority. This current study aimed to quantify trends in DKA events in a comprehensive nationwide cohort of individuals with type 1 diabetes over a 14 year period using electronic healthcare records, and to identify the association of socieoeconomic status with DKA event rates and their associated time trends.

Research Design and Methods

Dataset And Cohort Definition

Scottish Care Information - Diabetes (SCI-Diabetes) is the national disease management system of individuals diagnosed with any form of diabetes in Scotland , achieving over 99% coverage. This register can be linked to death data provided by the Information Services Division of NHS Scotland and National Records of Scotland (NRS). We identified a cohort of all people with a clinical diagnosis of type 1 diabetes who were alive at any point between 2004-01-01 and 2018-12-31. Clinician assigned diabetes type was accepted unless there was contradictory prescription historys data. Cohort members contributed data from 2004-01-01 or the date of their diagnosis with type 1 diabetes, whichever was later, up to date of death during the study period, leaving the jurisdiction, or the end of the study period. Periods of observability were defined using routine observation and prescription data. The number of hospital admissions for DKA for each individual were collected from

Scottish Morbidity Record (SMR-01) data and DKA mortality data was taken from the Medical Certificate of Cause of Death (MCCD) for each individual who died during the study period, as provided by NRS. The presence of an ICD-10 code for DKA (i.e. E10.1, E11.1, E12.1, E13.1, E14.1) anywhere on an admissions record or MCCD was considered to be a hospital admission or a death with DKA, respectively. We combined DKA hospital admissions and DKA deaths into a composite count of DKA events experienced for each individual; this count included both DKA at diagnosis events and any subsequent events.

Statistical Methods

Directly standardised rates of DKA were calculated using the 2011 population structure of people with type 1 diabetes in Scotland as the standard. Bayesian generalised linear regression (GLM) analyses were performed to estimate the association of a number of covariates with event rates. Each individual's longitudinal electronic healthcare record data was time sliced to produce a survival table with each time-slice being a single calendar year in length. To summarise the results from Bayesian analysis we report median posterior estimates, 95% credibility intervals (95% CrI), and a measure which is equivalent to a p-value assessed at the posterior median.

To investigate the association of covariates with recurrent DKA we performed a Bayesian poisson regression analysis in which the outcome was a binary measure of whether or not an individual experienced more than one DKA event in a given time slice. To investigate DKA case-fatality we used a Bayesian logistic regression model in which each DKA event was an observation and the outcome was the fatality status of the DKA event. If an individual died during a hospital admission with an ICD-10 code for DKA mentioned at any point on their MCCD, we determined this to be an instance of case-fatality. Similarly, any out-of-hospital death for which DKA was identified on the MCCD was also considered to be an incidence of case-fatality.

We explored several factors previously reported as being associated with increased risk of DKA (6,9,15,16). To test the basic association of social deprivation with each DKA outcome we performed a set of minimally adjusted analyses in which the adjustment covariates were age, sex, level of social deprivation, and diabetes duration. Area-based social deprivation was measured using the Scottish Index of Multiple Deprivation (SIMD), with each individual assigned to a quintile of SIMD at baseline. SIMD is constructed from several domains of area based deprivation; including income, education, housing, and crime (17). Consequently, SIMD provides a high level overview of social deprivation but cannot be used to assess associations between individual aspects of deprivation and health outcomes. Further adjustment was performed to account for potential risk factors that had been observed to vary with SIMD quintile (ESM Figure 1) (18). Subsequent fully adjusted models included annualised median HbA1c in categories previously used in (18), SIMD quintile, use of continuous subcutaneous insulin infusion (CSII), completion of any level 3 (i.e. delivered in a group setting) structured education course, the prescription of methadone (ATC = N07BC02), the prescription of an antidepressant (ATC = N06A, N06CA). All covariates were time updated except for quintile of social deprivation, which was only available at baseline. The risk factors for DKA events caused by delayed diagnosis of diabetes may differ from those for DKA events following diagnosis. Consequently, we performed DKA event rate regression analyses excluding DKA at diagnosis as sensitivity analysis. We also performed DKA case-fatality regression sensitivity analyses restricted to only the deaths in which DKA was assigned as the underlying cause on the associated MCCD.

Age-band stratified subgroup analyses were also performed to identify age specific associations between covariates and DKA outcomes, with broad age-bands of <30, 30-59, and >59 used for this purpose.

We also calculated the annual percentage of individuals presenting with DKA at diagnosis of type 1 diabetes over the study period and used a univariate Bayesian linear model to investigate the effect of calendar time on the annual percentage change in this outcome. Further details of the statistical methods outlined here are presented in the ESM methods.

Results

Cohort Characteristics And Event Counts

We identified 37939 individuals with type 1 diabetes alive in Scotland at any point between 2004-01-01 and 2018-12-31. These individuals contributed a total of 393223 person-years to the study. 96.84 % of all possible person time was observable. Over the study period, there were 30427 hospital admissions for DKA (which occurred in 10397 individuals), of which 1490 were at the time of diagnosis with type 1 diabetes. There were 472 deaths in which DKA was present anywhere on a MCCD and 413 where DKA was the underlying cause of death. These event counts correspond to a crude mortality rate of 120 and a crude DKA event rate of 7858, per 100,000 person-years. 72.6 % of the cohort never had a hospital admission with DKA during the study period, 15.1 % had one admission, and 12.3 % had multiple admissions. Of all deaths for which DKA was a cause, 83.47 % occurred outside of a hospital admission. A detailed characterisation of the cohort at the time of entry is presented in ESM Table 1, grouped by number of DKA events experienced over the study period.

Figure 1. Directly Standardised DKA Event Rate

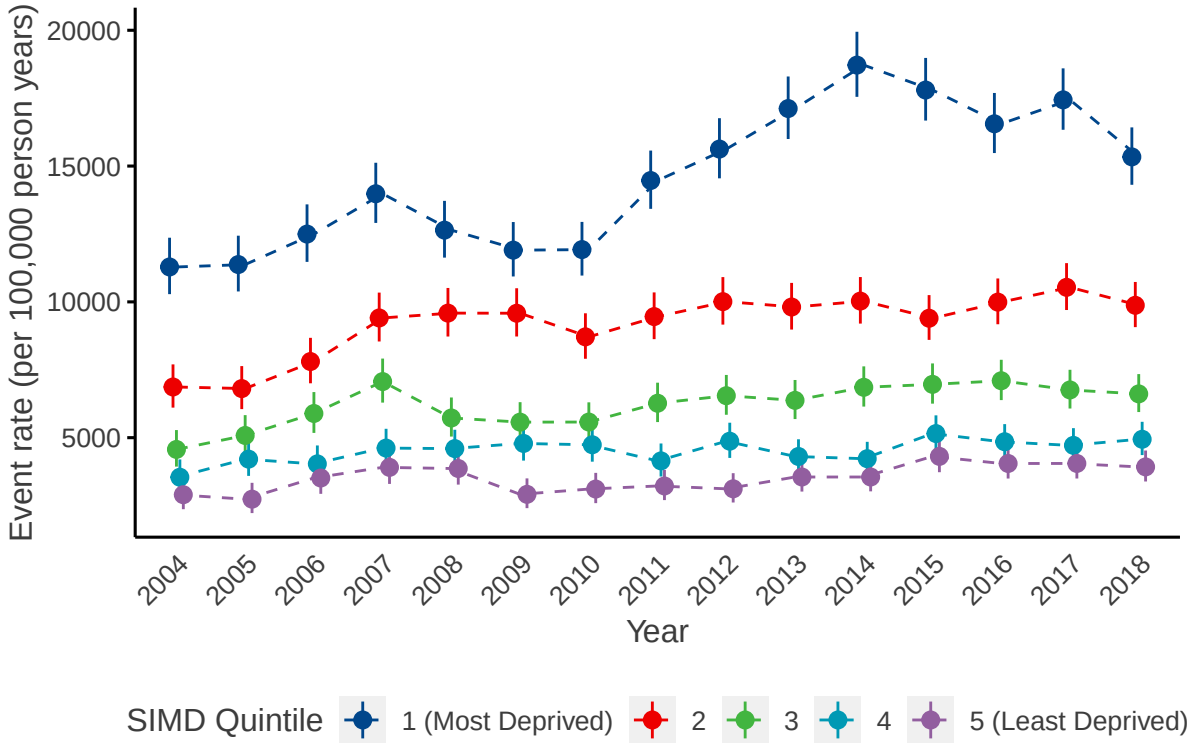


Figure 2. Directly Standardised DKA Event Rate By Age Band

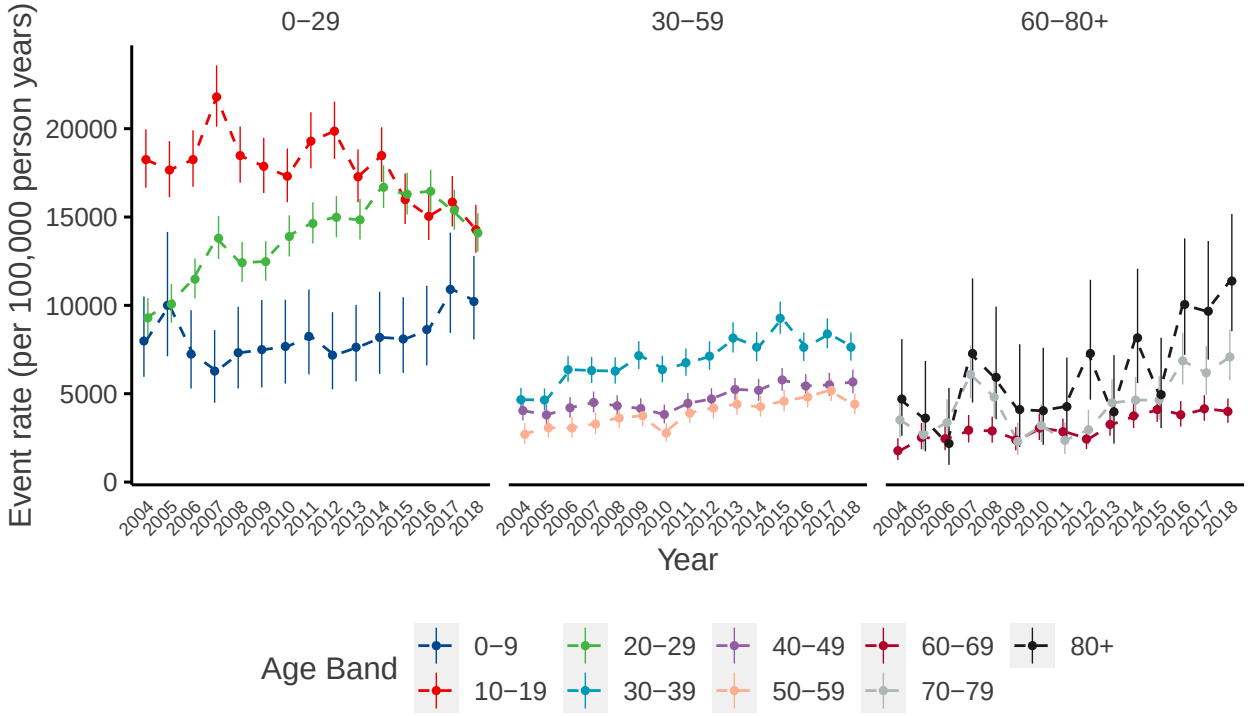
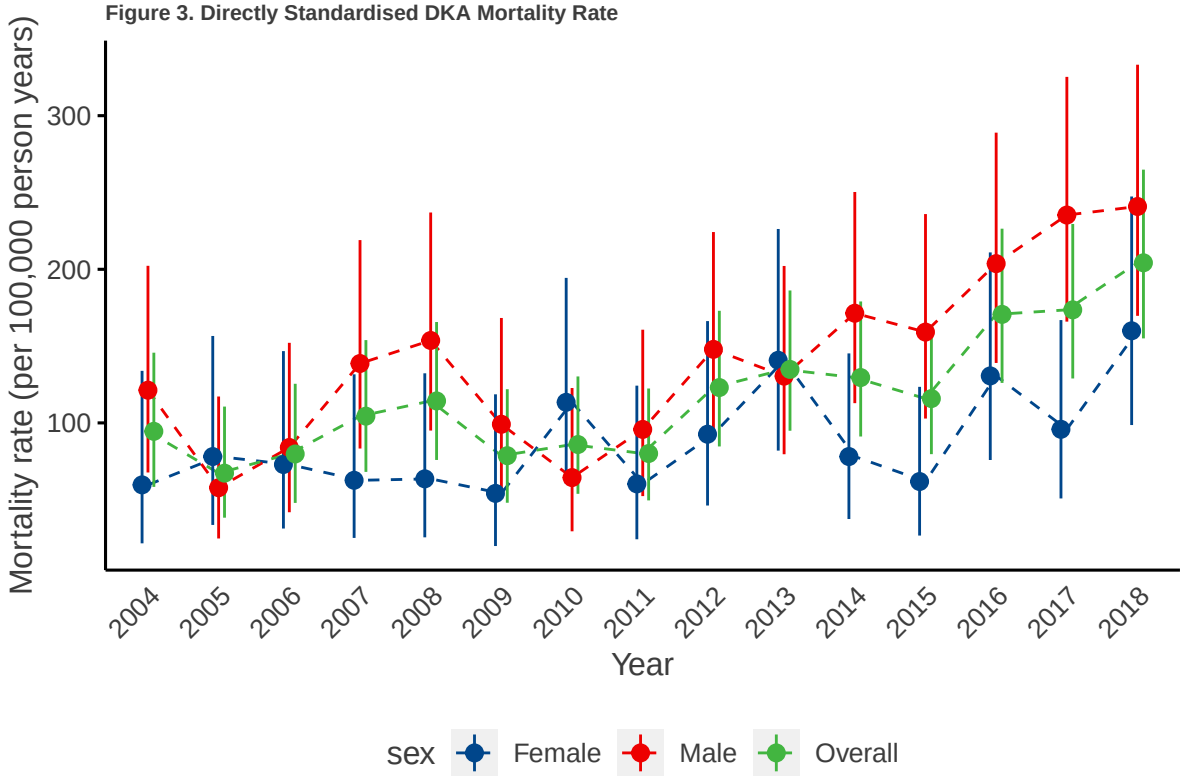


Figure 3. Directly Standardised DKA Mortality Rate



Trends In DKA Outcomes Over The Study Period

There was a gradual increase in the standardised rate of DKA events across the study period, starting at 6182 events per 100,000 person years in 2004 and finishing at 8261 per 100,000 person years in 2018 (ESM Figure 2). This pattern was seen in both sexes, and across SIMD quintiles (Figure 1), with the event rate in the most deprived quintile increasing the most over the study period.

A non-linear relationship between standardised event rate and age was observed (Figure 2). Across all age bands, the general trend over the study period has been toward increasing standardised DKA event rates. The exception to this pattern was the reduction in event rate in the final years of the study period for 10-19 year olds. The association of calendar time with DKA event rates varied across broad age-bands (ESM Table 2), with DKA event rates increasing the least in individuals under 30 years of age (IRR = 1.044 [1.039-1.050]), and increasing most rapidly in individuals aged 60 and above (IRR = 1.096 [1.081- 1.110]).

Rates of recurrent DKA increased over the study period (ESM Table 3). The rate of DKA at diagnosis was 13.35 % and this increased over the study period from 8.93% in 2004 to 17.68% in 2018, $\beta = 0.57$ [0.39-0.74] (ESM Figure 3).

Directly standardised DKA mortality rates were 95 deaths per 100,000 person years in the first year of the study period and 204 deaths per 100,000 person years in the final year. The annual directly standardised mortality rate is presented in Figure 3, and the age-band specific directly standardised mortality rate is presented in ESM Figure 4. The case-fatality rate over the entire study period was 1.53%, OR for year = 1.03 [1-1.05]. In age-band stratified analyses, evidence of an annual increase in case-fatality was identified for individuals aged 30 and above only.

Risk Factors For DKA Outcomess

Age had a non-linear effect on DKA event rates (Table 1) and DKA recurrence rates (ESM Table 3), with rates elevated in children, teenagers and younger adults and individuals aged 70+, as seen in the IRR for each age band. Conversely, the effect of age on case fatality was linear (ESM Table 4).

Table 1: DKA Event IRR Estimates Obtained With Multivariable Poisson Regression

Covariate	IRR	Q2.5	Q97.5	Approx. p-value
Year	1.058	1.054	1.061	<0.001
Age 1-10	Ref.	-	-	-
Age 11-19	1.023	0.938	1.121	0.579
Age 20-29	0.649	0.591	0.713	<0.001
Age 30-39	0.399	0.361	0.441	<0.001
Age 40-49	0.329	0.296	0.366	<0.001
Age 50-59	0.312	0.278	0.350	<0.001
Age 60-69	0.320	0.282	0.365	<0.001
Age 70-79	0.476	0.412	0.550	<0.001
Age 80+	0.780	0.653	0.933	0.007
Median HbA1c <7.5 %, <58 (mmol/mol)	Ref.	-	-	-
Median HbA1c 7.5-9.0 %, 58-75 (mmol/mol)	1.560	1.459	1.664	<0.001
Median HbA1c 9.1-10.0 %, 76-86 (mmol/mol)	2.801	2.621	2.995	<0.001
Median HbA1c >10.0 %, >86 (mmol/mol)	4.848	4.509	5.187	<0.001
Diabetes duration	0.984	0.982	0.986	<0.001
Male	0.814	0.776	0.855	<0.001
Female	Ref.	-	-	-
SIMD Quintile 1 (most deprived)	Ref.	-	-	-
SIMD Quintile 2	0.747	0.694	0.805	<0.001
SIMD Quintile 3	0.591	0.552	0.632	<0.001
SIMD Quintile 4	0.506	0.471	0.543	<0.001
SIMD Quintile 5 (least deprived)	0.446	0.406	0.490	<0.001
Current CSII therapy	0.792	0.731	0.858	<0.001
Current methadone prescription	1.468	1.234	1.747	<0.001
Current antidepressant prescription	1.474	1.428	1.522	<0.001
Completed a structured education course	0.841	0.787	0.898	<0.001

Male sex was associated with elevated DKA case fatality, but a lower DKA event rate and recurrence rate IRR = 0.814 [0.776-0.855]. Age band stratified analyses showed that the association of male sex with elevated DKA case-fatality was not present in the 60+ age-band (ESM Table 5).

Minimally adjusted analyses showed a clear association between level of social deprivation and DKA event and recurence rate, although the association of increasing levels of social deprivation with case-fatality was less consistent (ESM Table 6). The association of social deprivation with each DKA outcome in minimally adjusted analyses was maintained after adjustment for further covariates. Higher HbA1c was associated with elevated rates of DKA events and DKA recurence, but no association between the highest HbA1c category and increased DKA case fatality was observed. Age-band stratified analyses did not support an association between HbA1c category and case fatality (ESM Table 5). Prescription for an antidepressant and prescription for methadone were both associated with elevated rates of each analysed DKA outcome. Age-band stratified analyses supported the association of elevated DKA case fatality with antidepressant prescription in all age-bands apart from the 0-29 age-band.

The use of CSII therapy or completion of a structured education course were both associated with reduced rates of DKA events and reduced DKA recurence, but an association between these covariates and DKA case-fatality could was not supported in these analyses. Age-band stratified analyses did not support the association of CSII with reduced DKA event rates in the 30-59 age band. Similarly, age-band stratified analyses did not support the association of CSII with reduced rates of recurrent DKA after the age of 29 (ESM Table 7), they also did not support the association of completion of structured education with reduced rates of DKA below the age of 30.

Sensitivity analyses showed that, apart from lowering the event rate in the youngest age band, excluding DKA at diagnosis events from DKA event rate regression analysis did not meaningfully alter the association between each covariate and DKA event rates (ESM Table 8). Excluding deaths for which DKA appeared on the MCCD, but not as the underlying cause of death, resulted in no association between HbA1c category and case-fatality being established (ESM Table 9).

Conclusions

Key Findings

Through the analysis of a national cohort of individuals with type 1 diabetes, we have identified patterns in rates of DKA, and estimated the association of several risk factors with DKA outcomes. We identified a gradual increase in DKA event rates, mortality rates, and DKA recurrence rates over the study period. Increases in DKA event rates over time were identified across all age bands excluding individuals aged 10-19, with rates for individuals aged 10-19 now similar to those of 20-29 year olds. The largest relative increase in event rates was identified in individuals aged 60 or over. Age-band stratified regression analyses showed that the greatest elevation in event rates over the study period were for individuals aged 60 years or older. These results suggest that global increases in DKA admission rates could be partially driven by increases in DKA rates in older individuals. The association of age with DKA case-fatality appears to be similar across all age bands, suggesting that this association is linear and that DKA events are more likely to be fatal for older individuals. The observation that older individuals are experiencing increasing rates of DKA, coupled with DKA events being more likely to result in death for this age group is concerning.

Elevated HbA1c was associated with increased DKA event rates, and prescription for methadone and antidepressants were both associated with considerably elevated DKA event and case-fatality rates. For some covariates we found differences in the estimated effect on DKA event rates and case-fatality rates, suggesting that the factors which elevate the risk of the occurrence of a DKA event may be different to the factors that elevate the risk of an event being fatal. Completion of a structured education course and the use of CSII were associated with reduced DKA event rates, but there was little evidence that completion of a structured education course or CSII are associated with reduced case-fatality. We found that females experienced DKA events at a higher rate than males, but a given DKA event was more likely to be fatal for males. A potential contributing factor in elevated DKA rates for females in Scotland is elevated HbA1c, which has been observed in this subgroup in a previous study (18).

Associations between social deprivation and mortality or morbidity in type 1 diabetes have previously been identified in Scotland (18–20). The association of social deprivation with DKA outcomes is supported by the results presented here. Adjustment for several covariates suggests that this association occurs independently of HbA1c, which is higher on average in more socially deprived areas (18), and CSII or completion of structured education, which are less prevalent in more deprived areas (ESM Figure 1). This suggests that factors other than those included in these models contribute to the elevated DKA rates observed in more socially deprived areas.

Comparison To Previous Literature

Increases in DKA admission rates have been identified in England, Wales, Australia and New Zealand, Denmark, and the United States (21–25), although reductions in DKA admission rates have been observed in Italy and Taiwan (26,27). A lower threshold for hospital admission, prevalence of basal-bolus insulin regimes, and alterations to DKA diagnositic criteria have all been proposed as potential contributors to increasing DKA rates (23,25). The reduction in DKA event rates for 10-19 year olds in the final years of our study period represents a deviation from the general trend of increasing DKA rates. While the cause of this reduction has not been established by these analyses, across a similar time period these younger individuals

experienced the greatest improvement in HbA1c and the widest initiation of CSII amongst all individuals with type 1 diabetes in Scotland (18).

We found that the rate at which individuals presented with DKA at the time of diagnosis increased over the study period, but the absolute rate did appear to be comparatively low. A recent study found that the prevalence of DKA at diagnosis in children with type 1 diabetes ranged from 18.4% to 53.2% across a number of different nations (13), whereas the annual prevalence reported here, amongst both children and adults , never exceeded 17.68 %.

There are few published studies focusing on DKA mortality rates in large cohorts (3), making it difficult to compare the mortality trends identified here to other populations. Another study using the Scottish diabetes register found that DKA mortality rates in individuals under the age of 50 had not significantly reduced in the period 2004 to 2017 (11). The results presented here demonstrate that this trend is also observed when this population is extended to include individuals aged 50 and over.

One previous study found that CSII therapy was not associated with a significant decrease in DKA admission rates (6). Conversely, the results presented here and by Jeyam et al. (28) suggest that CSII therapy is associated with reduced DKA event rates. Other studies have demonstrated that structured education courses are associated with lower rates of DKA admission (15,16), and our results provide further observational evidence to support this association across all age groups. Similarly, previously observed associations between recurrent DKA and antidepressant use, social deprivation, or higher HbA1c (9) are supported by our results.

Strengths And Limitations

A strength of these analyses was the use of a national level cohort with almost complete coverage of all individuals with type 1 diabetes. The follow-up of these individuals was extensive, with only a small percentage of possible person-time being unobserved. One potential weakness in the construction of outcomes in these analyses was the lack of confirmation of DKA through biochemical tests. However, an evaluation of DKA discharge coding for a Scottish cohort (2002-2009) found that the sensitivity of SMR data is adequate for epidemiological study (29). It is possible that changes in DKA diagnosing and discharge coding practices over the study period have contributed to increasing rates of DKA, although a simultaneous increase in DKA mortality rate suggests that any such change is unlikely to be driving the observed DKA event rate increases. Generalisation of the results presented here to other countries is likely to be limited by the fact that Scotland has universal healthcare that is free at the point of use with free access to prescribed medications, including insulin. There is also potential allocation bias associated with CSII referral and initiation in Scotland (30), meaning that a causal relationship between CSII and DKA outcomes cannot be established in these analyses. While we included prescription for antidepressants and methadone as covariates in these analyses, their accuracy as markers for depression and opioid dependence is limited by certain antidepressants being indicated for the treatment of neuropathy and methadone being indicated for the treatment of severe pain. A further potential weakness of using methadone prescription as a marker for opioid dependence is that this approach will not capture individuals with opioid dependence who did not receive a methadone prescription. Despite this potential wekaness, we still observed a consitent association between methadone prescription and elevated DKA event rates and mortality.

Policy Implications And Future Work

The significant contribution of DKA to excess mortality means that prevention of this acute complication should remain a priority, particularly as DKA rates are rising. The association of social deprivation with DKA outcomes suggests that more work is required to reduce rates of DKA in people living in more deprived areas. Mair et al. (18) identified higher HbA1c in people living in more socially deprived areas in Scotland, and here we demonstrate the consistent association of high HbA1c with DKA event and recurrence rates. Similarly, while CSII therapy and structured education completion are associated with lower DKA event and recurrence rates, they have lower cumulative incidence amongst people living in more deprived areas (ESM Figure 1). Consequently, improved glycaemic control, more widespread usage of CSII, and completion of structured

education may improve DKA outcomes for people living in the most deprived areas. The association of social deprivation with DKA event rate is still significant after adjustment for several confounders, this suggests that socioeconomic factors not included in these models play a key role in DKA event rates for people living in more socially deprived areas. Future work must identify these factors and establish effective interventions to reduce health inequalities. Furthermore, as the prevalence of CSII increases, future work must assess rates of DKA as a consequence of CSII failure, particularly following initiation of treatment (31).

Drug-related deaths in the general population in Scotland have risen over the previous 25 years (32). Whilst the association of methadone prescription with elevated DKA rates has been established here, methadone is only implicated in approximately 44% of all drug-related deaths in Scotland, with 94% of all drug-related deaths involving multiple substances. Consequently more work is required to investigate the broader effect of drug misuse on DKA admission and mortality in Scotland, particularly as DKA mortality rates have increased in the same age groups in which drug-related deaths in the general population have increased the most.

More studies utilising electronic healthcare records are required to accurately quantify the incidence of DKA in other countries and to identify the underlying causes of the association of each risk factor with DKA outcomes (5,33). Of particular concern are the causes of the association of social deprivation with DKA and whether the higher rate of DKA in young females is influenced by the prevalence of disordered eating in this group (10,34).

Acknowledgements

Information Governance: Analysed data was provided de-identified, with approval from the Public Benefit and Privacy Panel (PBPP refs. 1617-0147), originally set up under PAC 33/11, with approval from the Scotland A Research Ethics Committee (ref. 11/AL/0225). NHS data governance rules do not permit us to secondarily share the analysed data directly. However, *Bone fide* researchers can apply to the Scottish Public Benefits Protection Committee for access to these data.

Contributions: HMC, PMK, and JOR created the concept and design of the analysis. RM, SW, JP, JAM, BK, JC, SP, GL, RSL, NS, and FG contributed to data acquisition. HMC, PMK, JOR, AJ, TMC, JM, and AH created the first draft of the manuscript, all authors contributed to the writing and revising of the final manuscript. SM and LAB constructed the analysed dataset, JOR performed all analyses. JOR and HMC are the guarantors of this work.

Declaration Of Interests: TMC reports receiving the Diabetes UK 'Sir George Alberti' Clinical Research Training Fellowship: 18/0005786. JP reports personal fees from Merck KGaA, Novo Nordisk, Boehringer-Ingelheim, and Biocon, and non-financial support from AstraZeneca. RM reports personal fees from Novo Nordisk and Sanofi Aventis. HMC reports grants and personal fees from Eli Lilly and Novo Nordisk, grants from AstraZeneca LP, Regeneron, Pfizer Inc, and other from Novartis and Sanofi Aventis, and Roche Pharamceuticals. All other co-authors declare no competing interests.

Acknowledgements: We thank the SDRN Epidemiology Group: J. Chalmers (Diabetes Centre, Victoria Hospital, UK),C. Fischbacher (Information Services Division, NHS National Services Scotland, Edinburgh, UK), B. Kennon (Queen Elizabeth University Hospital, Glasgow, UK), G. Leese (Ninewells, Hospital, Dundee, UK) R. Lindsay (British Heart Foundation Glasgow Cardiovascular Research Centre, University of Glasgow, UK), J. McKnight (Western General Hospital, NHS, UK), J. Petrie, N. Sattar (Institute of Cardiovascular & Medical Sciences, University of Glasgow, UK) R. McCrimmon (Divison of Molecular and Clinical Medicine, University of Dundee, Dundee, UK), S.Philip (Grampian Diabetes research unit, Diabetes Centre, Aberdeen Royal Infirmary, Aberdeen, UK), D.Mcallister (Institute of Health & Wellbeing, University of Glasgow, Glasgow, UK), E. Pearson (population Health and Genomics, School of Medicine, University of Dundee, Dundee, UK) and S.Wild (Usher Institute, University of Edinburgh, Edinburgh, UK)

Funding: This study was supported by funding from the Diabetes UK (17/0005627)

Figure Captions

- Figure 1 - Directly standardised diabetic ketoacidosis (DKA) event rate over the study period, separated into quintiles of social deprivation. Vertical lines represent 95% confidence intervals for the standardised rate. There is a clear social deprivation effect that is maintained across the study period.
- Figure 2 - Directly standardised diabetic ketoacidosis (DKA) event rate over the study period, separated in to 10 year age bands. Vertical lines represent 95% confidence intervals for the standardised rate. The general trend in DKA event rates over the study period appears to vary by age band, with 10-19 year olds experiencing a reduction in DKA rate across the study period and other bands experiencing varying degrees of an increase in DKA event rate.
- Figure 3 - Directly standardised diabetic ketoacidosis (DKA) mortality rate over the study period, separated by sex and also calculated for both males and females jointly. Vertical lines represent 95% confidence intervals for the standardised rate. Over the course of the study period there has been a general trend toward an increase in DKA mortality rates.

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