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Seasonal variation in hospital encounters with hypoglycaemia and hyperglycaemia

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Abstract

Aim To assess whether rates of hospital encounters with hypoglycaemia and hyperglycaemia display seasonal variation.

Methods Time series analyses of the monthly rates of hospital encounters (emergency room visits or inpatient admissions) with hypoglycaemia and hyperglycaemia from 2003 to 2012 using linked healthcare databases in Ontario, Canada.

Results Over the study period, there were 129 887 hypoglycaemia and 79 773 hyperglycaemia encounters. The characteristics of people at the time of their encounters were similar across the seasons in 2008 (median age 68 years for hypoglycaemia encounters and 53 years for hyperglycaemia encounters; 50% female; 90% with diabetes). We observed moderate seasonality in both types of encounters (R^2 autoregression coefficient 0.58 for hypoglycaemia; 0.59 for hyperglycaemia). The rate of hypoglycaemia encounters appeared to peak between April and June, when on average, there was an additional 49 encounters per month (0.36 encounters per 100 000 persons per month) compared with the other calendar months (5% increase). The rate of hyperglycaemia encounters appeared to peak in January, when on average, there was an additional 69 encounters per month (0.50 encounters per 100 000 persons per month) compared with the other calendar months (11% increase).

Conclusions In our region, there is seasonal variation in the rate of hospital encounters with hypoglycaemia and hyperglycaemia. Our findings may help to highlight periods of vulnerability for people, may inform future epidemiological studies and may aid in the appropriate planning of healthcare resources.

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Introduction

Whether due to changes in diet, bodyweight, physical activity or environmental factors, there is seasonal variation evident in glycaemia-related laboratory measures [1–3]. Fasting plasma glucose and plasma concentrations of glucagon, for example, are highest in the winter months [1,3]. HbA_{1c} values are higher from January to April compared with July to October, indicative of poorer glycaemic control in the winter [2].

Although an assessment of the seasonality of these laboratory measures is of interest, a detailed examination into how these patterns translate into the risk of clinically important glycaemic outcomes is of greater relevance to people, healthcare providers and policymakers. Previous studies on this theme have been limited to single centres in different countries [4–6], and specific subgroups (i.e. people with Type 1 diabetes only) [7]. This prompted us to carry out the current population-based study in Canada's most populous province, Ontario, to assess whether rates of hospital encounters with hypoglycaemia and hyperglycaemia display seasonal variation.

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People and methods

Study design and setting

Using linked healthcare databases, we performed time series analyses of the rates of hospital encounters with

What's new?

- In this large, population-based time series analysis, we found evidence of seasonal variation in hospital encounters with hypoglycaemia and hyperglycaemia.
- Hospital encounters with hypoglycaemia appear to peak between April and June, and hospital encounters with hyperglycaemia peak in January.
- Our findings may help to highlight periods of vulnerability for people, may inform future epidemiological studies and may aid in the appropriate planning of healthcare resources.

hypoglycaemia and hyperglycaemia in Ontario, Canada from 1 January 2003 to 31 December 2012. Our study time frame was divided into 1-month intervals.

There are currently > 13 million residents of Ontario who have universal coverage for hospitalizations, physician visits and diagnostic testing [8]. Information on their healthcare utilization is maintained in the records of several databases held at the Institute for Clinical Evaluative Sciences (ICES). Databases are linked using unique encoded identifiers.

Our study was approved by the research ethics board at Sunnybrook Health Sciences Centre (Toronto, Ontario) and was analysed at ICES under the guidance of a pre-specified protocol. Informed consent was not required as all data was maintained in anonymous form. Our reporting conforms with the guideline recommendations for observational studies (STROBE).

People

We considered all residents of Ontario, Canada for inclusion in our study. Prior to each 1-month interval we excluded: people with a missing or invalid identification number, age or sex, or those who had died prior the beginning of the study interval (for data cleaning purposes); and people who were not permanent residents of Ontario (to allow for adequate follow-up). If included individuals had more than one encounter for hypoglycaemia or hyperglycaemia during the monthly interval, we counted only their first encounter during the relevant interval.

Data sources

We used the records of several databases to ascertain study covariates and outcomes. The Registered Persons Database of Ontario was used to collect demographic information as it contains the vital statistics of all residents who have ever been issued a health card in our province. The Yearly Ontario Intercensal and Postcensal Population Estimates and Projection database was used to ascertain population denominators (Ontario Ministry of Health and Long-Term Care: IntelliHEALTH Ontario). We used the Ontario Drug Benefit (ODB) database to examine prescription medication use for people over the age of 65, because in Ontario, universal drug benefits are provided for these individuals and prescription records are accurately maintained within this database (error rate of < 1%) [9]. We assessed the diabetes status of people with the Ontario Diabetes Database [10]. We used the Canadian Institute for Health Information's Discharge Abstract Database and the National Ambulatory Care Reporting System Database to collect diagnostic and procedural information captured during hospital admissions and emergency department visits respectively. Additional covariate information was collected from the Ontario Health Insurance Plan (OHIP) Database, which contains physician billing and diagnostic information. We also obtained monthly median temperatures from Environment Canada meteorological data [11].

We used International Classification of Diseases 9th revision (ICD-9, pre-2002), International Classification of Diseases 10th revision (ICD-10, post-2002), the enhanced Canadian version of the 10th Revision of the International Statistical Classification of Diseases and Related Health Problems (ICD-10 CA, post-2002), Canadian Classification of Diagnostic, Therapeutic and Surgical Procedures (CPP, pre-2002), Canadian Classification of Health Interventions (CCI, post-2002), and OHIP fee and diagnostic codes to ascertain covariates and outcomes (coding definitions in Tables S1 and S2).

Outcomes

Our primary outcome was the seasonality in the rates of hospital encounters (emergency room visit or inpatient hospital admission) with hypoglycaemia and hyperglycaemia over the period of study. The administrative codes that we used to ascertain hypoglycaemia and hyperglycaemia encounters are entered into databases by trained personnel based upon diagnoses that are recorded in the medical record (i.e. coders do not interpret laboratory values). The ICD-10 coding algorithm we used for our assessment of hypoglycaemia has a positive predictive value of 94.0% in our region when compared with medical chart review [12]. To our knowledge, a validated ICD-10 coding algorithm for hyperglycaemia has not yet been established. Codes for both hypoglycaemia and hyperglycaemia likely have low sensitivity, especially when these outcomes are in their milder forms.

Statistical analysis

We used descriptive statistics to summarize the percentage of people with an encounter with hypoglycaemia and hyperglycaemia over the study period. Numerators were the total number of people with at least one encounter during each monthly interval. Denominators were the estimated population of Ontario (or population by age group) on 1 July of the

relevant year. To consider population changes over time, we calculated monthly encounter rates and their associated 95% confidence intervals (95% CI).

The population of Ontario was selected as our denominator because we were interested in examining the rates of these diabetes-related outcomes in the general population and with consideration of the changing prevalence of diabetes [13].

Based upon prior recommended methods [14], we then used time series analyses to assess for the presence of seasonality in the rates of these encounters, as well as the strength of the seasonal relationship. We first de-trended the data series to ensure stationarity using moving averages [14]. We then used spectral analyses to detect statistically significant seasonality, the Fisher Kappa test to determine if there was a major sinusoidal component evident within the white noise, and the Barlett Kolmogorov Smirnov test to examine for departures from the white noise hypothesis over all other frequencies [14]. To examine the strength of the seasonal relationships, we generated *R*-squared autoregression coefficients using the coefficient of determination of the autoregressive regression model fitted to the data. A coefficient of 0 to < 0.4 represents weak seasonality, 0.4 to < 0.7 moderate to strong seasonality, and 0.7 to 1 very strong to perfect seasonality [14,15].

In additional analyses, we evaluated seasonality by age category (i.e. 0–17, 18–45, 46–65 and 66+ years). We further ascertained the seasonal demographic characteristics, concomitant diagnoses and comorbidities of people who presented with each type of encounter in 2008 (the mid-point of our study). For this analysis, we used meteorological season definitions (winter was defined as 1 December to 28/29 February, spring as 1 March to 31 May, summer as 1 June to 31 August and autumn as 1 September to 30 November) [7]. If people had more than one encounter with hypoglycaemia or hyperglycaemia in 2008, we ascertained their characteristics at the time of their first encounter only.

Results

From January 2003 to December 2012, 88 685 people had a total of 129 887 encounters with hypoglycaemia in Ontario (20 916 people had more than one encounter). Over the same time interval, 56 576 people had a total of 79 773 encounters with hyperglycaemia (9,020 people had more than one encounter). There were 13 494 people who had an encounter with both hypoglycaemia and hyperglycaemia over the study period.

Hypoglycaemia encounters

Trends in hospital encounters with hypoglycaemia are illustrated in Fig. 1. Overall, the rate of hypoglycaemia encounters appeared to vary seasonally with a peak rate between April and June, when on average, there were an additional 49 encounters per month (0.36 encounters per 100 000 persons per month) compared with the other calendar months (5% increase) [8]. This seasonal relationship was statistically significant and was moderate in strength (R^2 autoregression coefficient 0.58) (Table 1).

Where examined by age category, we also noted similar peaks in the rates of hypoglycaemia encounters (Figs S1–S4). The strength of the seasonal relationship was strongest in the youngest and oldest age groups (i.e. people ≤ 17 years and > 65 years) (Table 1).

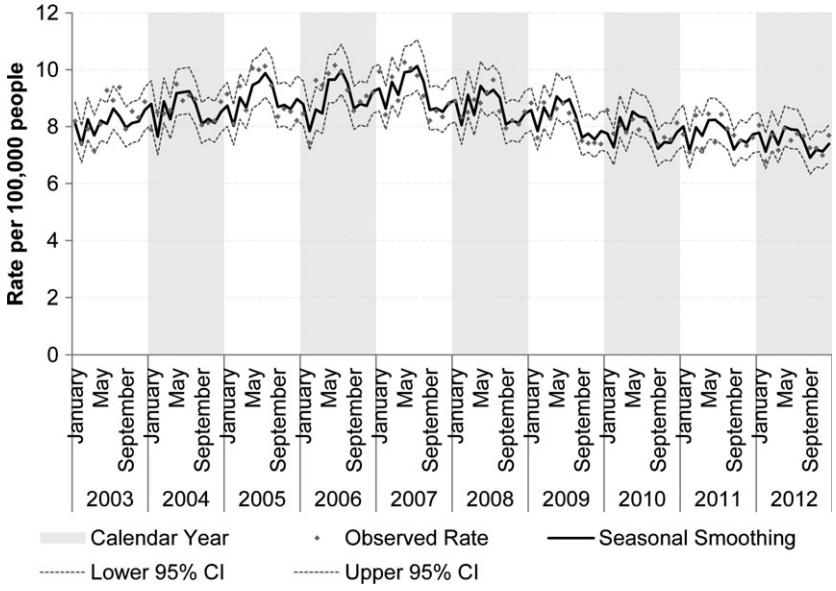

FIGURE 1 Monthly rate of encounters with hypoglycaemia per 100 000 people (2002–2013)

Table 1 Statistical summary of seasonality of encounters with hypoglycaemia

Age (years)	Fisher Kappa	*P*-value	Barlett Komogorov Smirnov	*P*-value	R^2 autoregression coefficient*
All	30.75	< 0.0001	0.56	< 0.0001	0.58
0–17	25.60	< 0.0001	0.45	< 0.0001	0.49
18–39	14.50	< 0.0001	0.38	< 0.0001	0.26
40–65	20.25	< 0.0001	0.52	< 0.0001	0.33
66+	30.75	< 0.001	0.63	< 0.0001	0.54

*An R^2 autoregression coefficient of 0 to < 0.4 is reflective of weak seasonality, 0.4 to < 0.7 is reflective of moderate to strong seasonality, and 0.7 to 1 is reflective of very strong to perfect seasonality.

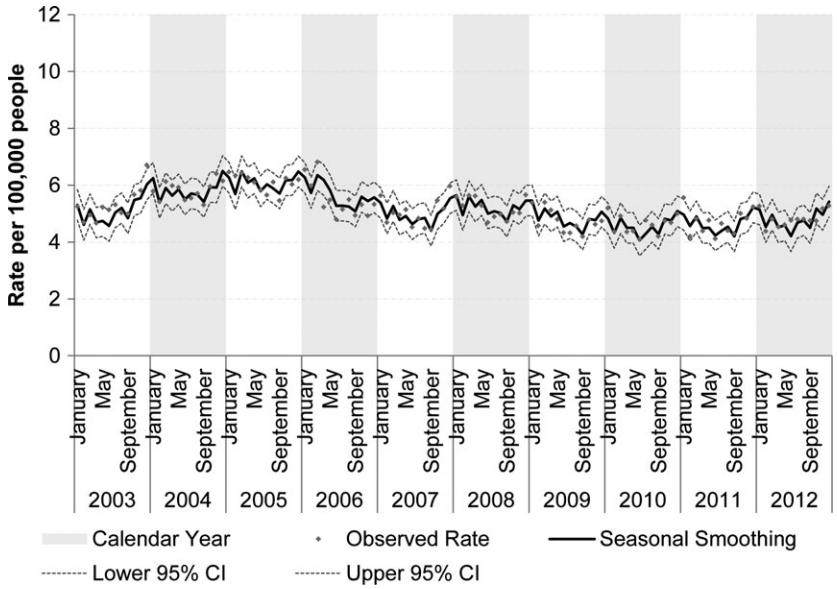

FIGURE 2 Monthly rate of encounters with hyperglycaemia per 100 000 people (2002–2013)

Hyperglycaemia encounters

Trends in encounters with hyperglycaemia are illustrated in Fig. 2. Seasonal variation was also apparent in the rates of these encounters. Encounters appeared to peak in January when on average, there were an additional 69 encounters per month (0.50 encounters per 100 000 persons per month) compared with the other calendar months (11% increase) [8]. The seasonality of these encounters was also statistically significant and moderate in strength (R^2 autoregression coefficient 0.59) (Table 2).

Where the rates of hyperglycaemia encounters were examined by age category, we also observed peaks in January (Figs S5–S8). With the exception of the youngest age group (0–17 years), where a weaker relationship was detected, seasonality was moderate across the categories of age (Table 2).

Additional analyses

The demographic characteristics, concomitant diagnoses and comorbidities of people with a hypoglycaemia and hyperglycaemia encounter at the mid-point of our study are illustrated in Tables S3 and S4. In general, the median age of people at the time of their encounter was similar across the seasons (median age 68 years for hypoglycaemia and 53 years for hyperglycaemia encounters), as was the proportion of women (~ 50% across the seasons). The majority of people with these healthcare encounters had a diagnosis of diabetes (~ 90%). We also found that the medical diagnoses that were coded at the time of their healthcare encounter remained relatively stable across the seasons, as did most of their baseline comorbidities (with the exception of previous episodes of hypo- or hyperglycaemia). These trends were also apparent across the categories of age (Tables S5 and S6).

Discussion

Main findings

In our region, hospital encounters with hypoglycaemia and hyperglycaemia vary seasonally. Hypoglycaemia encounters peak from April to June, and hyperglycaemia encounters peak in January.

Table 2 Statistical summary of seasonality of hospital encounters with hyperglycaemia

Age (years)	Fisher Kappa	*P*-value	Barlett Komogorov Smirnov	*P*-value	R^2 autoregression coefficient*
All	31.26	< 0.001	0.64	< 0.0001	0.59
0–17	11.74	< 0.001	0.20	0.02	0.25
18–39	9.99	< 0.001	0.25	0.001	0.41
40–65	31.93	< 0.001	0.64	< 0.0001	0.40
66+	37.83	< 0.001	0.73	< 0.0001	0.40

*An R^2 autoregression coefficient of 0 to < 0.4 is reflective of weak seasonality, 0.4 to < 0.7 is reflective of moderate to strong seasonality, and 0.7 to 1 is reflective of very strong to perfect seasonality.

The seasonality of these healthcare encounters is likely the result of a complex interplay between social, behavioural, environmental and physiological factors [7,16]. Social and behavioural influences including calorie consumption, physical activity and weight gain, have peaks and troughs throughout the year [2,17,18]. In the winter, calorie consumption increases, physical activity declines and weight gain ensues. The holiday season has also been linked with poorer glycaemic control [19]. These changes may have contributed to the peak in hyperglycaemia encounters that was observed in January [18]. In the spring and summer months, however, people may have adhered to a healthier diet, participated in more physical activity and may have lost weight, which in turn made them more susceptible to hypoglycaemia. Other contributing social factors may have included seasonal differences in the propensity to seek medical care, the postponement of care during the holiday season and monthly differences in referral patterns [14,16].

Temperature effects on glucose-monitoring devices, insulin absorption and anti-hyperglycaemic medication metabolism in people with diabetes (alongside with the failure of people or their providers to adjust diabetes therapies accordingly), may have also contributed to the seasonal patterns that we observed [20–25]. Glucometers and glucose test strips, for example, lose analytic stability when exposed to extremes in temperature [20,21,26]. Temperature extremes can also augment insulin absorption [22]. On hot days, dehydration and acute kidney injury can ensue [25], which may lead to the impaired metabolism of anti-hyperglycaemic medications and subsequent hypoglycaemia.

In addition, other physiological processes may have contributed to the seasonality that we observed. Cortisol, growth hormone and glucagon, which play a role in the pathogenesis of diabetic ketoacidosis, peak in the winter months and may have contributed to hyperglycaemia [27,28]. Seasonal trends in hospital encounters for congestive heart failure [29], myocardial infarction [30], stroke [30], infection [14] and sepsis [7] may have also contributed to associated dysglycaemia at those times. Higher rates of hyperglycaemia in January may have also reflected incident diabetes which has been observed to peak in the winter months [31].

In this study, we did note some differences in the strength of the seasonal relationships by age category. Younger and older people (≤ 17 and > 65 years) appeared to have stronger seasonality in their encounters for hypoglycaemia, and there was evidence of stronger seasonality in hyperglycaemia encounters in those aged > 18 years compared with younger individuals. Age-specific seasonality has been described previously in healthcare encounters, [16] and whether these findings are due to differences in their susceptibility to dysglycaemia, the prevalence of different subtypes of diabetes within each age category (i.e. Type 1 diabetes more common in younger people) [32], or due to differences in their healthcare-seeking behaviour, remains to be established.

Comparison with previous literature

The results of our study are similar to the findings of smaller, single-centre studies that have detected seasonality in encounters with hypoglycaemia and hyperglycaemia in people with Type 1 diabetes. In a single German hospital from 2007 to 2014, for example, people with Type 1 diabetes had significantly more severe hypoglycaemia encounters in the spring and summer compared with the autumn and winter (1080 hypoglycaemia encounters in total; 27.7% of encounters in the spring, 28.6% in the summer, 21.5% in the autumn and 22.2% in the winter) [6]. Similarly, in a hospital in Tokyo, Japan from 2006 to 2012, people with Type 1 diabetes had more encounters with hypoglycaemia in the summer than in the winter (578 hypoglycaemia encounters in total; 35.2% of encounters in the summer and 18.2% in the winter, $P = 0.01$) [5]. In both studies, seasonality was not apparent in people with Type 2 diabetes. In a Canadian study of people with Type 1 diabetes from 2004 to 2010 (21 568 ketoacidosis encounters and 5349 hypoglycaemia encounters), hospitalizations for hypoglycaemia were also noted to be highest in the summer, and hospitalizations with ketoacidosis were highest in the winter [7].

Our results differ from other reports. In a small study of severe hypoglycaemia in adults over the age of 60 who presented to a hospital in Morioka, Japan (67 hypoglycaemia encounters from 2004 to 2007) [4], hypoglycaemia encounters were less frequent in the warm season (April to September) than the cold season (October to March) (3.0 ± 2.2 encounters in the warm season vs. 6.7 ± 3.4 encounters in the cold season). This study, however, involved a much smaller number of people, and was carried out in a different climate from our own (mean daily temperature of 17.8 °C in the warm season and 6.7 °C in the cold season), which may have contributed to the observed differences.

Strengths and weaknesses

Our study has many strengths. Given the population of our province, we were able to examine the seasonality of 129 887 hypoglycaemia encounters and 79 773 hyperglycaemia encounters over a period of 9 years. We used the population of Ontario as our denominator to allow policymakers to monitor cause-specific hospitalizations at the population level, and inform healthcare planning [13]. We do not expect that the overall seasonal patterns that we observed would have been altered if we restricted our study to only people with diabetes. We also investigated seasonal trends by age group, and we detailed the characteristics of people at the time of their healthcare encounter to provide context for the observed patterns.

There are some weaknesses to our study. We used an ecological design and our results are thus applicable at the population level only. We could not then, for example, determine if events were related to the use of specific anti-hyperglycaemic medications. We also used administrative data to investigate our study covariates and outcomes, and these databases were not specifically created to answer our research question. In our assessment of the characteristics of people with these healthcare encounters, our databases did not allow us to assess for differences in social and behavioural factors (i.e. diet), or diabetes subtype (although we were able to examine seasonality by age category where the prevalence of diabetes subtypes do differ). We also assessed diabetes status using an administrative coding algorithm that has a sensitivity of 86% [10]. As such, some people with diabetes may not have been captured by this algorithm (including those who were newly diagnosed after their hyperglycaemia encounter). We also could not account for how the coding of hypoglycaemia and hyperglycaemia encounters may have changed over time. Further, we were only able to capture episodes of hypoglycaemia and hyperglycaemia that led to hospital presentation and thus we missed those events that were self-treated or treated by emergency medical service personnel. Hypoglycaemia and hyperglycaemia codes are also likely insensitive, and thus we probably underestimated the true number of events. Finally, our results are generalizable to Ontario, Canada, which is situated in the Northern Hemisphere. If replicated in other regions including the Southern Hemisphere (where the seasons differ), seasonal trends in these encounters may differ.

Conclusions

In our region, encounters with hypoglycaemia and hyperglycaemia vary seasonally. We anticipate that our study results may help to educate people about times when they might be more vulnerable to these outcomes so that efforts can be taken to prevent them. Physicians and healthcare administrators may also be able to better anticipate and prepare for seasonal fluctuations in these events (i.e. by stock-piling supplies including glucagon, insulin appropriately). Finally, our study may help to inform future research on the precipitants of these significant complications.

Funding sources

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Competing interests

Unrelated to this project, Amit Garg received an investigator-initiated grant from Astellas and Roche to support a Canadian Institute of Health Research study in living kidney donors and his institution received unrestricted research funding from Pfizer.

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Supporting Information

Additional Supporting Information may be found in the online version of this article:

Figure S1. Monthly rate of encounters with hypoglycaemia per 100 000 people (age 0–17).
Figure S2. Monthly rate of encounters with hypoglycaemia per 100 000 people (age 18–39).
Figure S3. Monthly rate of encounters with hypoglycaemia per 100 000 people (age 40–65).
Figure S4. Monthly rate of encounters with hypoglycaemia per 100 000 people (age 66 and over).
Figure S5. Monthly rate of encounters with hyperglycaemia per 100 000 people (age 0–17).
Figure S6. Monthly rate of encounters with hyperglycaemia per 100 000 people (age 18–39).
Figure S7. Monthly rate of encounters with hyperglycaemia per 100 000 people (age 40–65).
Figure S8. Monthly rate of encounters with hyperglycaemia per 100 000 people (age 66 and over).
Table S1. Coding definitions for demographic characteristics and comorbidities.

Table S2. Coding definitions for hypoglycaemia and hyperglycaemia encounters.
Table S3. Characteristics of people at the time of their hypoglycaemia encounter by season (2008).
Table S4. Characteristics of people at the time of their hyperglycaemia encounter by season (2008).
Table S5. Characteristics of people at the time of their hypoglycaemia encounter by age group and season (2008).
Table S6. Characteristics of people at the time of their hyperglycaemia encounter by age group and season (2008).