

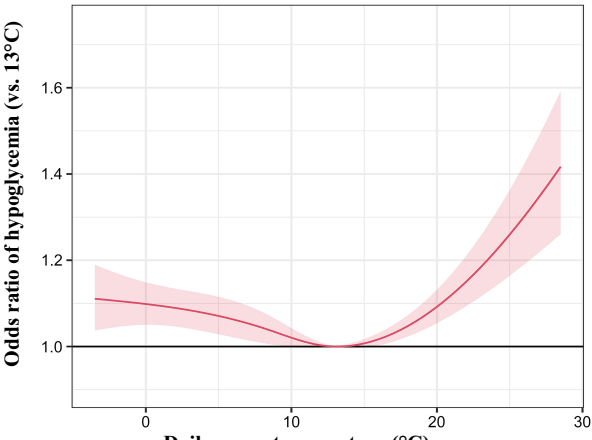



The Association Between Ambient Temperature and Hypoglycemia in People Living With Type 1 Diabetes: A Case Time Series Analysis Using Real-Time Continuous Glucose Monitoring

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Diabetes Care 2026;49(00):1–7 | <https://doi.org/10.2337/dc25-2383>

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Background	Findings	
<p>Global temperatures are rising. People with type 1 diabetes report more frequent hypoglycemia during hotter weather. Clinical guidelines are unclear if risk is higher for hyperglycemia or hypoglycemia.</p>	 <p>Increased risk of hypoglycemia at temperature extremes. Hotter temperatures showed the strongest effect. At 25°C, odds of hypoglycemia were ~30% higher than at 13°C (lowest risk temperature).</p> 	
<p>Methods</p> <p>We collected 33 million continuous glucose readings between 2017 and 2024 from 679 adults with type 1 diabetes in Sussex, U.K. The main exposure was daily mean outdoor temperature (°C) at the individual's residential postcode. The primary outcome was hypoglycemia (glucose <3.9 mmol/L (70 mg/dL) for ≥15 minutes).</p> 		<p>Insulin dosing guidance and automated insulin delivery systems may need to account for ambient temperature.</p>

ARTICLE HIGHLIGHTS

- Why did we undertake this study?**
 People with type 1 diabetes (T1DM) report seasonal changes in glucose patterns and insulin requirements. Clinical guidelines advise more frequent glucose monitoring during high temperatures but do not specify if the risk is higher for hyperglycemia or hypoglycemia.
- What is the specific question we wanted to answer?**
 What are the short-term effects of ambient temperature on the risk of hypoglycemia in people with T1DM?
- What did we find?**
 Elevated ambient temperatures increase the risk of hypoglycemia in people with T1DM.
- What are the implications of our findings?**
 Clinical teams should advise on the increased risk of hypoglycemia during hotter weather.



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OBJECTIVE

To investigate the short-term association between ambient temperature and risk of hypoglycemia in adults with type 1 diabetes mellitus (T1DM). We hypothesized that higher ambient temperature would increase the odds of hypoglycemia developing.

RESEARCH DESIGN AND METHODS

We applied a case time series design to assess the longitudinal association between ambient temperature and hypoglycemia measured using routine continuous glucose monitoring data from individuals with T1DM. A quasi-binomial fixed-effect regression with distributed lag nonlinear models was used to estimate potentially nonlinear and lagged risks of nonoptimal temperature on hypoglycemic episodes, defined as ≥ 15 min of glucose concentration < 3.9 mmol/L. The model was adjusted for long-term trends, seasonality, day of the week, and public holidays. A secondary outcome was change in daily mean glucose concentration.

RESULTS

We analyzed 32,966,282 glucose readings from 679 adults with T1DM attending two National Health Service clinics in Sussex, England, between 2017 and 2024. Higher ambient temperatures were associated with an increased risk of hypoglycemia. The risk increased nonlinearly for temperatures above 13°C , with the odds ratio reaching 1.26 (95% CI 1.13–1.26) at 25°C . The strongest effect was observed on the same day of the exposure, and it diminished over subsequent days. In the secondary analysis, higher temperatures were associated with lower mean glucose levels.

CONCLUSIONS

Elevated ambient temperature significantly increases the short-term risk of hypoglycemia in adults with T1DM. These findings are specific to the U.K. population and climate, which may limit generalizability. Our results support anticipatory insulin adjustments during hot weather and consideration of ambient temperature in hybrid closed-loop insulin algorithms.

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Received 26 September 2025 and accepted 1 February 2026

This article contains supplementary material online at <https://doi.org/10.2337/figshare.31423604>.

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See accompanying article, p. XXX.

Anticipatory insulin dose reduction may be required during hot weather and ambient temperature considered as a variable within hybrid closed-loop insulin delivery algorithms. Global land surface temperatures were 1.59°C higher between 2011 and 2020 than temperatures recorded between 1850 and 1900 (1), and projections indicate further increases (2). Higher temperatures are linked to adverse health outcomes (3,4) and, as record-breaking heat events become more frequent, it is essential that health care systems are prepared to manage and, where possible, prevent any additional burden.

Evidence consistently shows that higher temperatures are associated with increased risk of morbidity and mortality in different populations (4,5). However, there is less of a focus on the effects of heat on specific health conditions, each of which will have unique complications. Diabetes is a condition for which elevated temperatures can have serious adverse effects. There are well-established biological mechanisms linking heat exposure to increased risk of hypoglycemia, primarily through changes in insulin absorption and action (6). This is especially a concern for people living with type 1 diabetes mellitus (T1DM) who rely on exogenous insulin for self-management of glucose. Hypoglycemia is a serious clinical event associated with both increased mortality risk (7) and negatively affecting quality of life in people with T1DM (8). International diabetes guidelines advise people with diabetes to monitor glucose levels more frequently during periods of higher temperature, suggesting higher risks of both hyper- and hypoglycemia (9–11). However, although we observe frequent reports of hypoglycemia during hot weather, the extent and direction of this effect remain unclear. This uncertainty in clinical guidance reflects the lack of robust epidemiological evidence, which is related to difficulties in real-time monitoring in people with T1DM and modeling complex, individual-level, temporal relationships.

Epidemiological studies investigating the association between ambient temperature and glycemia in people with T1DM have reported both increased risk of hypoglycemia- and hyperglycemia-related emergencies (12,13). Study findings have limited clinical applicability to adults with T1DM, due to significant heterogeneity in study design, populations, and outcome measures. Studies

have assessed cohorts of individuals with T1DM and type 2 diabetes mellitus (13,14), and have included both adults and children (15,16). Outcome measures vary: some studies used hospital records (12–14) and others used markers of glycemia, such as HbA_{1c} (17) or continuous glucose monitor (CGM) data aggregated at population level (16,18), without individual-level location data to assign temperature exposure. A recent study from Spain (19) explored the relationship between ambient temperature and glycemia in people with T1DM. The study compared glycemia, measured using intermittently scanned CGM, over a 2-week period of extreme heat and the subsequent two cooler weeks. Results showed a higher proportion of time when glucose levels were between 3.9 and 10 mmol/L during the heat wave and shifted to hyperglycemia (glucose >10 mmol/L) in the following 2 weeks (19). The short time windows for comparison limited the ability to determine direction and strength of the association between glycemia and temperature, as well as any potential delayed effects.

In 2022, CGM became available to all individuals with T1DM through the National Health Service in the United Kingdom (20) and has revolutionized clinical care. CGM provides real-time interstitial-fluid glucose measurements every 5–15 min based on an electrochemical reaction (21). The large volume of glucose data provides the opportunity to address limitations of previous environmental studies. However, the complexity and volume of data pose analytical challenges. Advanced data science and statistical approaches are required to link individual-level environmental and CGM data and to perform analyses that account for complex associations with time-varying exposures while accounting for both inter- and intraindividual variability in glycemia.

The increasing frequency and intensity of heat waves, together with clinical reports of hypoglycemia during higher temperatures, biologically plausible mechanisms, and uncertainty in current clinical guidance, highlight the urgent need for robust evidence to inform people with T1DM. To address this gap, we conducted a study to investigate the short-term effects of ambient temperature on the risk of hypoglycemia, using CGM data from individuals with T1DM. We

applied a case time series (CTS) design, which uses advanced statistical methods to integrate multiple individual-level time-series data and enables a detailed assessment of exposure-response associations while controlling for time-invariant confounders.

RESEARCH DESIGN AND METHODS

Population

We downloaded all intermittently scanned and real-time CGM data available on LibreView, the platform where FreeStyle Libre CGM data are uploaded, from individuals registered at clinics with T1DM at Royal Sussex County Hospital and Princess Royal Hospital, both located in Sussex, England. Individuals receiving renal replacement therapy were excluded from the analysis. CGM data were downloaded from 23 February 2017 until 8 August 2024. Continuous CGM data were averaged over 15-min periods, creating a series of 96 measurements per day for each individual.

The study was discussed with the research Governance Office at University Hospitals Sussex, and it was confirmed to be classed as a health surveillance project and did not require health research authority, ethical, or National Health Service (NHS) approvals. All individual identifiable data were saved on NHS servers, and no identifiable data were shared outside of the direct clinical team. Data were de-identified before they were analyzed, with participants identified solely by study number. Linkage with environmental data requiring residential information was conducted separately, using pseudo-identifiers, by matching postcodes to lower super output areas (LSOAs). LSOAs are geographic areas used in England and Wales to report small-area statistics. They are designed to have a consistent population size, typically between 1,000 and 3,000 residents (22).

Study Design

We used a CTS design combined with distributed lag nonlinear models (DLNMs) to assess the potentially complex nonlinear and delayed relationships between temperature and hypoglycemia while controlling for underlying trends (23–25). The analysis integrates multiple individual-level daily time series data, allowing for a detailed assessment of longitudinal

patterns. A key strength of the CTS analysis is its self-matched design, which controls for time-invariant confounders while allowing for within-individual comparisons.

The main outcome was then specified as the daily proportion of hypoglycemia episodes, defined as 15-min CGM levels lower than 3.9 mmol/L. The daily average CGM was used as secondary outcome. The main exposure was daily mean temperature measured in degrees Celsius, retrieved by the ERA5-Land data set produced by the European Centre for Medium-Range Weather Forecasts (26). The original temperature data were provided over a 0.1×0.1 grid (~ 9 km), and daily series were assigned to the residential postcode coordinates of each participant, using bilinear interpolation of the gridded cells. The 1×1 km temperature data from the HadUK-Grid database from the Met Office (27) (available only until 2023 included) were used as an alternative exposure source.

We defined time variables as additional predictors to assess and control for temporal trends. In addition, we stratified the CGM series of each individual by calendar month. This structure allowed for within-person comparisons of CGM levels and hypoglycemia across the month. The model, therefore, controlled for factors that are constant or change slowly over the monthly time frame, such as socioeconomic status, baseline hypoglycemia risk, and BMI.

Statistical Analysis

We estimated hypoglycemia risks by fitting fixed-effect conditional models using participant-specific monthly risk sets (28). In the main analysis, we used fixed-effect quasi-binomial regression to model the odds of hypoglycemia episodes. In a secondary analysis, we modeled the daily average GCM levels as a continuous variable, using fixed-effect Gaussian regression. Given the self-matched nature of the study design, the estimation was based on the subset of informative risk sets, therefore excluding those with a single observation and (in the binary outcome) those with constant zero daily hypoglycemia episodes (28).

The association with the exposure of interest, ambient temperature, was modeled using DLNMs, allowing nonlinear and lagged effects (23). We applied a cross-basis parametrization over a lag

period of 0–7 days, using natural cubic splines for modeling both exposure and lag dimensions (29). Specifically, we placed internal knots at the 25th and 75th percentiles of the temperature distribution, and at lags 1 and 3. The lag period was supposed to cover the temporal window of effect, assumed to be short lagged.

Additional terms were added to the model to capture temporal trends across multiple timescales. First, we used natural cubic splines based on calendar date, with a single knot placed on 1 January 2023 for smooth adjustments of gradual long-term variation in baseline risks. To account for seasonality, a reported phenomenon affecting glycemia in individuals with T1DM (17), we used periodic B-splines based on day of the year with 3 df. To assess within-week differences in hypoglycemia risk, we included days of the week as a categorical variable, with Monday as the reference day. Finally, we included public holidays as an indicator variable within the model, based on previous work that reported altered glycemia over holiday dates (18).

Model Selection and Sensitivity Analysis

Modeling choices were guided by previous analyses of associations between temperature and health (25,30), as well as selection procedures. For the most critical choices regarding the exposure-response function in the DLNM, we compared models with one to three knots at the 25th, 50th, and/or 75th temperature percentiles. The best-fitting model was selected as that minimizing the quasi-version of the Akaike information

criterion (31), adapted here for quasi-binomial models.

Finally, in additional sensitivity analyses, we assessed differences in the estimated associations using different temperature data sources, temperature indices, and hypoglycemia outcome definitions. Specifically, we used the alternative 1×1 km Met Office data, minimum and maximum daily temperature, and the heat index combining temperature and humidity (32). We explored a lower glucose threshold of 3.0 mmol/L to explore level 2 hypoglycemia.

RESULTS

Descriptive Results

Table 1 presents the descriptive statistics for 679 individuals with T1DM. The mean age (SD) of individuals was 46.4 years (± 16.8), 53% were women, and the mean duration since diagnosis of T1DM was 23.7 years (SD ± 14.6). Most (82%) used multiple daily injections of insulin; 18% used continuous subcutaneous insulin infusion. The median number of days of CGM data from an individual was 602 days, with an interquartile range (IQR) of 366–770.

Table 2 describes the daily summary data for glucose and temperature data during the study period. The average number of follow-up days was 554 (range 14–1,891). In total, we analyzed 32,966,282 glucose readings aggregated in 376,152 person-days. The mean daily average glucose level was 10.1 mmol/L (SD ± 3.1). The median number of episodes of hypoglycemia recorded on each day was 0 (IQR 0–4), with a range of 0–80 episodes. The average daily temperature exposure over the study period was 12.0°C, with

Table 1—Summary statistics for 679 individuals with T1DM

Characteristic	Data value
Age (years)	
Range	20–91
Mean (SD)	46.4 (16.8)
Female sex, <i>n</i> (%)	358 (53)
Years since T1DM diagnosis	
Range	0–80
Median (IQR)	21 (12–33)
Management of T1DM	
Use multiple daily insulin injections, <i>n</i> (%)	559 (82)
Use continuous subcutaneous insulin infusion, <i>n</i> (%)	120 (18)
Days of CGM data, median (IQR)	602 (366–770)

Table 2—Summary of daily glucose and temperature data

Daily data	Recorded data value
Glucose	
Median episodes of hypoglycemia (IQR)	0 (0.4)
Range in episodes of hypoglycemia	0–80
Mean glucose (\pm SD), mmol/L	10.1 (3.1)
Temperature ($^{\circ}$C)	
Median (IQR)	12.1 (8.4–16.3)
Mean (\pm SD)	12 (5.2)
Range	–3.7 to 28.7

a minimum of -3.7° C and a maximum of 28.7° C.

Temperature and Hypoglycemia Risk

The analysis of temporal trends on the risk of hypoglycemia is reported as odds ratio (OR) of hypoglycemic episodes. The selected model included two knots

at 25th and 50th percentiles of the temperature distribution for the exposure-response function (Supplementary Table 1 and Supplementary Fig. 1). Results are illustrated graphically in Fig. 1. Within-year variations indicated strong seasonal patterns, with lower odds in late winter and early spring, followed by a peak

OR in the summer. When assessing weekly patterns, the lowest risk of hypoglycemia was on a Monday, and then the odds increased along the week and peaked toward the weekend, with an OR of 1.14 (95% CI 1.12–1.17) on Saturday compared with Monday. There was little evidence on differential risks of hypoglycemia during public holidays, with an OR of 0.98 (95% CI 0.94–1.01).

Estimates of the association between temperature and risk of hypoglycemia are displayed in Fig. 2. The graphs indicate an increase in risk for both heat and cold, with the minimum at about 13° C. The effect was particularly strong for heat, with a net OR cumulated across the lag 0–7 days of 1.26 (95% CI 1.16–1.36) at 25° C (vs. 13° C) and 1.10 (95% CI 1.05–1.15) for a cold temperature

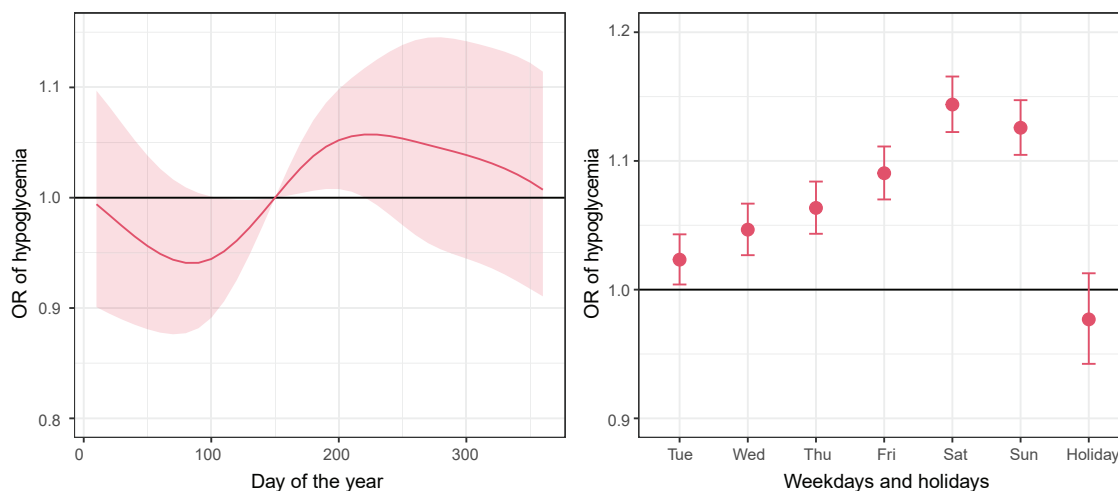


Figure 1—Temporal trends in the risk of hypoglycemia, as OR with 95% CIs. A: Seasonal variation reported as OR compared with the 150th day of the year (30 May) as the reference. B: Variation associated with day of the week (with Monday as the reference) and holidays (compared with nonholiday days).

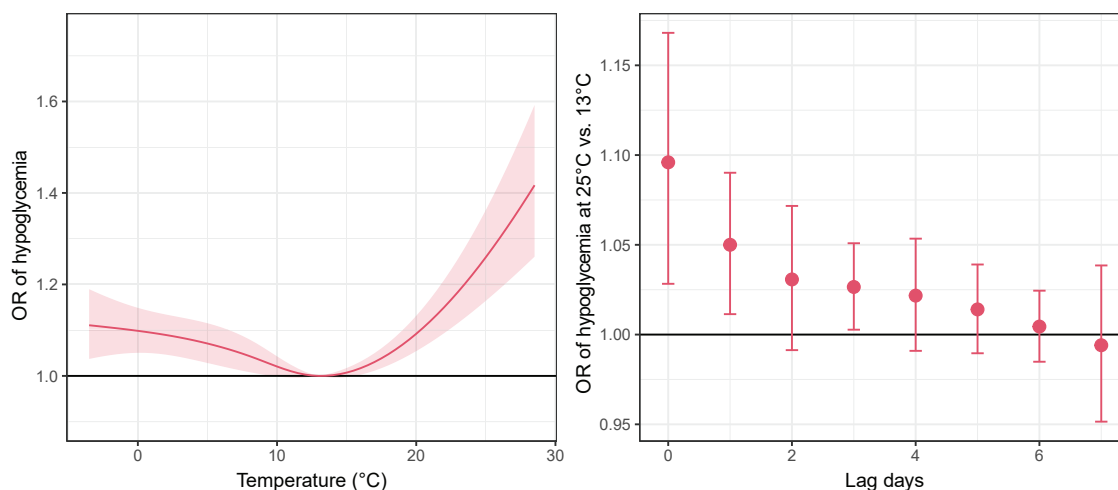


Figure 2—Association between ambient temperature and risk of hypoglycemia events, as OR with 95% CIs. A: Overall cumulative exposure-response relationship accounting for lagged effects over 0–7 days, with 13° C as the reference. B: Lag-response relationship, reporting lag-specific effects across 0–7 days.

of 0°C. The analysis of the lag structure indicates an immediate effect, with an OR of 1.10 (95% CI 1.03–1.17) for the same-day (lag 0) exposure at 25°C (vs. 13°C), with the odds then decreasing and returning to baseline after 7 days.

Additional and Sensitivity Analyses

The analysis using the continuous daily average of CGM glucose readings as outcome confirmed the same patterns, with a reduction of glucose level associated with temperatures colder and, in particular, hotter than 13°C, and similar lag structure (Supplementary Fig. 2). Sensitivity analyses indicated the results are robust to different temperature data sources and, to some extent, indices, with similar results, using the alternative 1 × 1 km Met Office data and the heat index, and stronger effects for daily maximum versus minimum temperature (Supplementary Figs. 3 and 4). Finally, the use of lower glucose threshold of 3.0 mmol/L for defining hypoglycemia episodes led to similar risk estimates. The magnitude of risk appeared greater at lower temperatures, but the estimates were less precise, with CIs overlapping (Supplementary Fig. 5).

CONCLUSIONS

To our knowledge, this is the first investigation of the association between temperature and hypoglycemia risk in people with T1DM, using individual-level longitudinal CGM measurements. The analysis takes advantage of the application of the novel CTS design and the DLNM modeling framework to assess complex temporal associations and reduce the risk of confounding for time-invariant and time-varying factors such as socioeconomic status, BMI, and baseline risk of hypoglycemia. The analysis provides strong evidence of an association, with high temperatures linked with increased short-term odds of hypoglycemia and smaller effects observed at low temperatures.

These findings are particularly relevant for people with T1DM who are already at higher risk of hypoglycemia, such as those with glycemia levels close to target, with a lower HbA_{1c} or with impaired hypoglycemia awareness. For individuals using multiple daily injections, proactive reduction in basal insulin may be required in anticipation of forecasted temperature

increases to minimize hypoglycemia. Currently, ambient temperature is not factored into the hybrid closed-loop insulin-delivery algorithms. Some closed-loop insulin pump devices have target glucose settings of 4.4 mmol/L (33), and high temperatures may pose a significant risk in these individuals.

The demographic characteristics of our cohort are consistent with those of other studies of people with T1DM (34–36). Data collection for this study ended in August 2024. The data showed 18% of people used insulin pumps. This compares with the latest available National Diabetes Audit data from 2022 (37) that reported 11.5% of people with T1DM in England used insulin pumps. The use of insulin pumps is increasing each year; the higher proportion of pump use in our cohort reflects current practice.

Our findings align with biological plausibility: higher temperatures result in increased cutaneous blood flow, which accelerates insulin absorption, enhances insulin action, and thereby increases the risk of hypoglycemia (38–40). They are also in keeping with clinical observations and previous research linking exposure to higher temperatures with risk of hypoglycemia (12–14), and potentially provide some insight into the results of the study conducted in Spain, in which CGM data were used (19). The increased proportion of CGM glucose concentrations between 3.9 and 10 mmol/L observed during the heatwave may reflect a lowering of glucose levels, with the subsequent return to glucose levels >10 mmol/L once temperatures fell. However, our findings do not explain previously reported increases in hyperglycemia-related emergencies, such as diabetic ketoacidosis (12), during periods of high temperature. These events may be explained by behavioral responses to heat, such as insulin omission due to concern of hypoglycemia or reduced oral intake in combination with the complex physiological effects of dehydration and thermoregulation.

Our study has significant strengths. We used a large data set of almost 33 million glucose readings linked to high-resolution temperature data from individual postcodes over a 7-year period. We applied state-of-the-art epidemiological designs and statistical methods to model the complex relationship between glycemia and temperature, delayed temperature effects,

long-term trends, and seasonality, isolating the temperature effects from individual baseline risk of hypoglycemia. Glucose measurements were collected using the same CGM manufacturer's system, Abbott FreeStyle Libre, which increased the internal validity of our findings.

There are important limitations when interpreting the findings. We used residential postcodes as a marker for location, and this may not reflect the temperature individuals were exposed to if, for example, they spent more time indoors, at work, or traveling. This exposure misclassification may affect the magnitude of the estimated association between ambient temperature and hypoglycemia risk. We do not have insulin dosing data, which limits the insight into behavioral response to temperature. Our findings are specific to the geographical climate and the ethnic makeup of the population in the southeast of England (temperature range for our study: –3.7°C to 28.7°C). This limits the generalizability to different climate patterns and ethnically diverse populations who may have different physiological responses to temperature.

To build on our findings, we recommend conducting larger studies with more glucose data to capture both level 1 (glucose <3.9 mmol/L) and level 2 (glucose <3.0 mmol/L) hypoglycemia episodes, collected using different available CGM devices. We recommend collecting insulin data with more accurate individual location and physical activity data to improve exposure assignment and investigate more complex causal mechanisms. Further work should explore the association between hypoglycemia and temperature in different climate settings and populations, to explore if the association varies by insulin delivery method (pump, multiple daily injections) and assess if there is a similar association in people with type 2 diabetes mellitus.

In summary, this study indicates that rising temperatures significantly increase the short-term risk of hypoglycemia in adults living with T1DM. Our findings provide robust, individual-level evidence to support clinically guided insulin adjustments during periods of elevated ambient temperature, particularly above 25°C. These results also suggest ambient temperature may be considered a variable within hybrid closed-loop insulin-delivery algorithms and included in structured education, especially during increasingly frequent severe-weather warnings. They also highlight the importance of

preparing clinical teams and health care systems to manage the increased risk of hypoglycemia during hotter weather.

Acknowledgments. Infrastructure support was provided by the National Institute for Health and Care Research Imperial Biomedical Research Centre.

Funding. The development of data linkage procedures, study design, and statistical methods applied in this study were supported by the Wellcome Trust (grant 320878/Z/24/Z) and the Medical Research Council-UK (grant MR/R013349/1).

Duality of Interest. N.S.O. has received research support from Dexcom, Medtronic, and Roche Diabetes; has participated in advisory groups for Dexcom, Medtronic, and Roche Diabetes; and has received fees for speaking from Astra Zeneca, Sanofi, Dexcom, Tandem, Medtronic, and Roche Diabetes. C.C.I. received research grant from Gilead Sciences for investigator-sponsored research on HIV paid to his institution. No other potential conflicts of interest relevant to this article were reported.

Author Contributions. H.E.D. and N.S.O. conceptualized the study. H.E.D. conducted the investigation and wrote the original draft of the manuscript. A.G. devised the methodology. H.E.D., A.C.L., and A.G. conducted the formal analysis. N.S.O., A.J.C., A.C.L., and C.C.I. reviewed and edited the manuscript. H.E.D. is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Handling Editors. The journal editors responsible for overseeing the review of the manuscript were John B. Buse and Sonia Y. Angell.

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