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ARTICLE

Impact of daily incremental change in environmental temperature on beta cell function and the risk of gestational diabetes in pregnant women

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Abstract

Aims/hypothesis The prevalence of gestational diabetes (GDM) is higher in summer months, possibly reflecting an association between ambient temperature and blood glucose levels. However, the specific exposure and mechanism by which temperature may affect glucose metabolism in pregnancy remains unclear. We systematically evaluated the relationships of environmental temperature and changes therein over varying durations of exposure time with beta cell function, insulin sensitivity and glucose tolerance in women undergoing antepartum screening for GDM.

Methods At a mean gestation of 29 weeks, 1464 women in Toronto (ON, Canada) underwent an OGTT, from which 318 were diagnosed with GDM. Blood glucose, beta cell function and insulin sensitivity were evaluated in relation to 18 temperature variables: mean temperature and change in temperature on the day of the OGTT and over the preceding 7, 14, 21, 28, 35, 42, 49 and 56 days, respectively.

Results Temperature changes in the preceding 14, 21, 28, 35, 42, 49 and 56 days (rather than mean temperatures) emerged as independent predictors of blood glucose. These relationships were evident in months where mean daily temperature was rising (February – July), but not in those where it was falling (August – January). Indeed, in February – July, the temperature changes in the preceding 21, 28 and 35 days emerged as predictors of both poorer beta cell function and higher blood glucose. Moreover, in February – July, the changes in temperature in the preceding 21 days (OR 1.16, 95% CI 1.01, 1.33) and 28 days (OR 1.20, 95% CI 1.03, 1.39) were independent predictors of GDM, while mean temperatures were not.

Conclusions/interpretation In pregnant women, rising environmental temperature in the 3–4 weeks prior to glucose tolerance testing may be associated with beta cell dysfunction and an increased risk of GDM.

Keywords Beta cell function · Gestational diabetes · Insulin sensitivity · Seasons · Temperature

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Research in context

What is already known about this subject?

- The prevalence of gestational diabetes (GDM) is higher in summer months, possibly reflecting an association between ambient temperature and blood glucose levels

What is the key question?

- What is the relevant temperature exposure that affects glucose metabolism in pregnancy and what is its pathophysiological basis?

What are the new findings?

- The change in temperature in the weeks prior to glucose tolerance testing, rather than the daily temperature per se, is the exposure that relates to blood glucose in pregnancy, and this association arises in the months in which temperatures are rising
- Rising environmental temperature in the 3–4 weeks prior to glucose tolerance testing is a significant independent predictor of GDM, after adjustment for clinical risk factors
- The change in temperature during this time window is also independently associated with beta cell dysfunction, thereby implicating a potential pathophysiological basis underlying the higher prevalence of GDM in summer months

How might this impact on clinical practice in the foreseeable future?

- Change in the environmental temperature in the preceding weeks thus emerges as a factor to consider for the optimisation of glucose tolerance testing in pregnancy and the identification of women with GDM

Abbreviations

AUC_{gluc}	AUC for glucose
AUC_{ins}	AUC for insulin
FDR	False-discovery rate
GCT	Glucose challenge test
GDM	Gestational diabetes mellitus
IGI	Insulinogenic index
ISSI-2	Insulin secretion-sensitivity index-2

Introduction

In the past 2 years, a series of studies collectively involving over half a million women has reported that the prevalence of gestational diabetes mellitus (GDM) is higher in summer months than in the winter in diverse geographic areas, including Australia, Canada, Sweden, Italy and Greece [1–6]. It has been suggested that this seasonal variation may be due to an association between ambient temperature and postprandial blood glucose [3, 4, 6, 7]. However, this putative association between temperature and blood glucose in pregnancy raises several questions. First, it is unclear if the specific biological exposure of interest is the actual environmental temperature per se or, instead, the change therein that occurs between seasons. Second, it is not known if a particular duration of exposure (e.g. days, weeks, months) is required for the relevant temperature stimulus to affect glucose metabolism. Third, the mechanistic basis by which environmental temperature may impact dysglycaemia in pregnancy and its pathophysiological determinants (beta cell dysfunction and insulin resistance) has not been evaluated. Thus, our objective in this study was to systematically evaluate the relationships of mean daily temperature and changes therein over varying durations of time with beta cell function, insulin sensitivity and gestational glucose tolerance in a cohort of women undergoing antepartum screening for GDM.

Methods

The study population consisted of 1464 women participating in a prospective observational cohort programme in Toronto (latitude 43°42′ N) which, according to the Köppen climate classification, has a moderate humid continental climate of large seasonal temperature differences, with warm to hot summers and cold winters [8]. In this study, pregnant women were recruited at the time of antepartum screening for GDM and underwent metabolic characterisation at that time [9]. The protocol for this cohort has been described in detail previously [9]. At our institution, all pregnant women are screened for GDM by 50 g glucose challenge test (GCT) in late second trimester, followed by referral for diagnostic OGTT if the GCT is abnormal (blood glucose ≥7.8 mmol/l at 1 h post-challenge). For this cohort study, women were recruited either before or after the GCT, and all participants then underwent a 3 h 100 g OGTT for determination of GDM status (regardless

of the GCT result). As previously described [9], the recruitment of women after an abnormal GCT served to enrich the study population for those with GDM. Metabolic characterisation performed during the OGTT enabled the assessment of insulin sensitivity/resistance and pancreatic beta cell function. The protocol was approved by the Mount Sinai Hospital Research Ethics Board and all women provided written informed consent for their participation.

Laboratory measurements and physiological indices

All OGTTs were performed in the morning after overnight fast. During the OGTT, venous blood samples were drawn for the measurement of glucose and specific insulin at fasting and at 30, 60, 120 and 180 min following the ingestion of the glucose load, as previously described [9]. GDM was diagnosed according to National Diabetes Data Group (NDDG) criteria [10].

AUCs for insulin (AUC_{ins}) and glucose (AUC_{gluc}) during the OGTT were calculated using the trapezoidal rule. Insulin sensitivity/resistance was assessed by: (1) Matsuda index, a validated measure of whole-body insulin sensitivity [11]; and (2) HOMA-IR [12]. Beta cell function was assessed by insulin secretion-sensitivity index-2 (ISSI-2) and by insulinogenic index (IGI)/HOMA-IR. ISSI-2 is a validated measure of beta cell function that is analogous to the disposition index obtained from the IVGTT, against which it has been directly validated; it correlates with the disposition index more strongly than other OGTT-derived measures of beta cell function [13, 14]. ISSI-2 is defined as the product of: (1) insulin secretion measured by the ratio of AUC_{ins} to AUC_{gluc}; and (2) insulin sensitivity measured by Matsuda index [9]. IGI/HOMA-IR is defined as the incremental change in insulin between 0 and 30 min divided by the incremental change in glucose over the same interval, divided by HOMA-IR [9].

Environmental temperature measurements

Temperature data in °C were obtained from the measurements of Environment Canada at the weather station at Pearson International Airport in Toronto [15]. These temperature data included the mean, maximum and minimum temperatures recorded on the day of each OGTT and for each of the preceding 56 days. With these data, we evaluated mean temperature and incremental changes in temperature on the day of the OGTT and over the preceding 8 weeks, with mean temperature and temperature change variables.

Mean temperature variables We determined the mean temperature on the day of the OGTT and the arithmetic mean temperature over the preceding 7, 14, 21, 28, 35, 42, 49 and 56 days, respectively (yielding nine mean temperature variables).

Temperature change variables We evaluated the change in temperature over the course of each day by calculating the temperature increment or difference between the minimum and maximum temperatures for the day. This increment was calculated for the day of the OGTT and for each of the preceding 56 days. We determined nine temperature change variables, consisting of the temperature increment on the day of the OGTT and the arithmetic mean of the temperature increment over the following numbers of days before the OGTT: the preceding 7, 14, 21, 28, 35, 42, 49 and 56 days, respectively.

Statistical analyses All analyses were conducted using SAS 9.4 (SAS Institute, Cary, NC, USA). Continuous variables were tested for normality of distribution both by visual inspection and by Shapiro–Wilk test, and natural log transformations of skewed variables were used in subsequent analyses, where necessary. Continuous variables with normal distributions are presented as mean ± SD, and those with skewed distributions are presented as median and interquartile range (25th–75th percentile). All tests were two-sided and performed at a significance level of $p = 0.05$. As the analyses were designed as exploratory to systematically evaluate the relationships of mean daily temperature and changes therein over varying durations of time with beta cell function, insulin sensitivity and blood glucose, we did not apply adjustment for multiple testing in the primary analyses. However, to address multiple testing, sensitivity analyses were performed with adjustment of the p value to address both: (1) the family-wise error rate to control the overall type 1 error (Bonferroni method); and (2) the false-discovery rate (FDR) to control the proportion of false-significant results among the significant associations (Benjamini and Hochberg method).

The characteristics of participants with GDM and those who did not have GDM were compared by Student's t test (continuous variables) or either χ^2 or Fisher exact test (categorical variables) (electronic supplementary material [ESM] Table 1). Mean monthly temperatures and prevalence of GDM by month are shown in Table 1.

Spearman correlation analysis was performed to first evaluate univariate associations between the 18 temperature variables and glucose measurements on the OGTT. Multiple linear regression analyses were then performed to evaluate adjusted associations of the 18 temperature variables with insulin sensitivity/resistance (Matsuda index, HOMA-IR), beta cell function (ISSI-2, IGI/HOMA-IR) and blood glucose (fasting glucose, AUC_{gluc}), after adjustment for age, ethnicity, family history of diabetes, pre-pregnancy BMI, gestational weight gain up to OGTT, and weeks' gestation at the time of the OGTT (ESM Table 2).

Daily temperature data for Toronto from 2004 to 2014 revealed that there are 6 months of the year in which mean daily temperature declines (August – January) and 6 months of the year in which mean daily temperature increases (February –

Table 1 Mean temperature, daily temperature increment, gestational weight gain up to OGTT, number of OGTTs and the proportion of OGTTs showing GDM, presented by month

Month	Mean temperature (°C)	Mean daily temperature increment (°C)	Number of OGTTs	GDM (%)	Gestational weight gain up to OGTT (kg)
January	−4.5 ± 6.0	6.9 ± 3.5	133	18.8	10.6 ± 4.6
February	−2.3 ± 4.3	6.5 ± 2.7	102	21.6	11.2 ± 6.7
March	1.9 ± 6.2	7.8 ± 3.2	140	22.9	9.3 ± 6.7
April	8.5 ± 3.6	7.8 ± 3.3	125	16	10.8 ± 5.4
May	15.6 ± 4.6	9.5 ± 3.5	128	27.3	11.1 ± 5.5
June	20.8 ± 3.4	9.3 ± 2.8	155	25.8	11.7 ± 6.2
July	23.2 ± 3.5	8.7 ± 2.6	140	20.7	10.3 ± 5.2
August	21.5 ± 2.9	8.7 ± 2.5	155	22.6	11.0 ± 9.2
September	17.7 ± 3.3	7.9 ± 2.6	110	19.1	8.9 ± 8.7
October	11.1 ± 3.7	7.1 ± 3.0	76	19.7	10.1 ± 6.4
November	5.2 ± 4.4	6.3 ± 2.7	115	20.9	10.7 ± 5.3
December	−0.9 ± 4.4	5.5 ± 2.2	85	23.5	10.2 ± 4.3

Continuous variables are shown as mean ± SD

July). In Fig. 1, we used the LOcal regrESSion (LOESS) method to fit the data, with GDM as the dependent variable and the temperature measure as the independent variable (in an unadjusted analysis), and generated spline plots of prevalence of GDM vs temperature increment in the preceding 7, 14, 21 and 28 days, respectively, in women whose OGTT was performed in months in which mean temperature was declining (August – January) and in those whose OGTT was performed in months in which mean temperature was rising (February – July). Each plot includes 95% CIs for the mean predicted prevalence of GDM. The multiple linear regression analyses from ESM Table 2 were then repeated in these two groups (August – January and February – July) to determine if the independent associations of the 18 temperature variables with insulin sensitivity/resistance (Matsuda index, HOMA-IR), beta cell function (ISSI-2, IGI/HOMA-IR) and blood glucose (fasting glucose, AUC_{gluc}) differed according to whether mean daily temperature was decreasing (August – January) or increasing (February – July) (Table 2).

Finally, multiple logistic regression analyses were performed to determine whether any of the 18 temperature variables were independent predictors of (dependent variable) GDM in either the months where temperature was decreasing or those in which it was increasing (Table 3). Covariates in each model were the temperature variable of interest, age, ethnicity, family history of diabetes, pre-pregnancy BMI, gestational weight gain up to the OGTT and weeks' gestation at the time of the OGTT.

Results

The study population comprised 1464 pregnant women with mean age 34 ± 4 years, who completed their OGTT at mean 29 ± 3 weeks' gestation. The OGTT revealed that there were 318 women with GDM and 1146 women who did not have GDM. ESM Table 1 shows the demographic, clinical and metabolic characteristics of the women with and without GDM. Consistent with the known clinical risk factors, women with GDM were older, had higher pre-pregnancy BMI and were more likely to be of non-white ethnicity and have a family history of diabetes than those without GDM (all $p \leq 0.001$). Moreover, as expected, the women with GDM had lower insulin sensitivity, poorer beta cell function and higher blood glucose levels on OGTT compared with women without GDM (all $p < 0.001$).

Table 1 shows the mean monthly temperatures and the proportion of women who had GDM among participants undergoing their OGTT in the indicated month. We first evaluated correlations of the nine mean temperature variables and nine temperature change variables with glucose measurements on the OGTT. This Spearman univariate correlation analysis revealed that, rather than the mean temperature variable, it was the temperature increments in the preceding 14, 21, 28, 35, 42, 49 and 56 days that were consistently associated with AUC_{gluc} and the glucose measurements at fasting, 120 min and 180 min (data not shown). This distinction was particularly evident when we next performed multiple linear regression analyses to evaluate independent associations of the 18 temperature variables with insulin sensitivity/resistance (Matsuda index, HOMA-IR), beta cell function (ISSI-2, IGI/HOMA-IR) and blood glucose (fasting glucose, AUC_{gluc}), after adjustment for potential covariates (age, ethnicity, family history of diabetes, pre-pregnancy BMI, gestational weight gain up to OGTT and weeks' gestation at the time of the OGTT). Specifically, as shown in ESM Table 2, the dominant findings on these analyses were positive independent

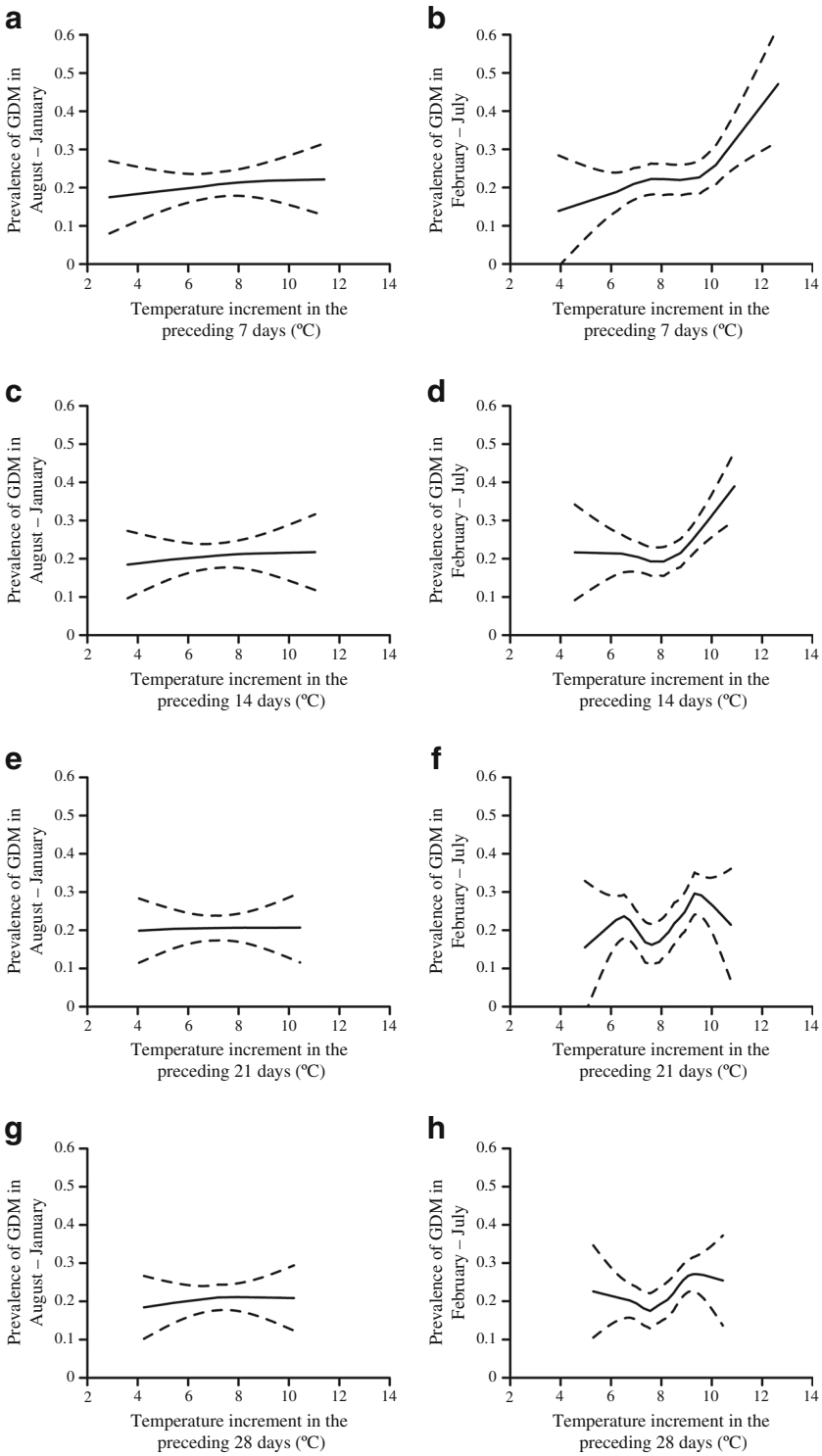

Fig. 1 Spline plots showing the prevalence of GDM in relation to the mean change in temperature in the 7 days (**a**, **b**), 14 days (**c**, **d**), 21 days (**e**, **f**) and 28 days (**g**, **h**) preceding OGTT performed in months in which the mean daily temperature was decreasing (August – January: **a**, **c**, **e**, **g**) or increasing (February – July: **b**, **d**, **f**, **h**). Each plot includes 95% CIs for the mean predicted prevalence of GDM

associations between the temperature changes (rather than mean temperatures) in the preceding 14, 21, 28, 35, 42, 49 and 56 days and blood glucose (fasting glucose, AUC_{gluc}). Moreover, the temperature changes in the preceding 28 and 35 days were inversely associated with both ISSI-2 and IGI/HOMA-IR, potentially implicating beta cell dysfunction as a pathophysiological basis.

As the temperature change variables were defined based on the difference between the minimum and maximum temperatures each day, any observed biological effect of these variables potentially could be due to either the rise or decline in temperature. To differentiate between these possibilities, we stratified participants into the following two groups: (1) those who completed their OGTT in a month in which mean daily

Table 2 Adjusted associations of temperature variables (per SD) with measures of insulin sensitivity/resistance, beta cell function and blood glucose in months where daily temperature was decreasing and months where daily temperature was increasing

Variable	Log Matsuda		Log HOMA-IR		ISSI-2		Log IGI/HOMA-IR		Fasting blood glucose		AUC_{gluc}	
	β	p	β	p	β	p	β	p	β	p	β	p
Mean temperature												
August – January												
Day of OGTT	−0.0009	0.96	−0.0138	0.54	4.3551	0.68	0.0023	0.93	0.0277	0.25	0.0591	0.68
Preceding 7 days	0.0128	0.52	−0.0265	0.24	8.8029	0.40	0.0227	0.39	0.0159	0.40	−0.0003	0.99
Preceding 14 days	0.0072	0.73	−0.0224	0.33	7.4071	0.49	0.0280	0.30	0.0153	0.43	0.0051	0.97
Preceding 21 days	0.0033	0.88	−0.0260	0.27	9.4367	0.39	0.0354	0.21	0.0125	0.53	0.0655	0.66
Preceding 28 days	0.0022	0.92	−0.0247	0.31	7.6671	0.49	0.0320	0.27	0.0126	0.54	0.0831	0.59
Preceding 35 days	0.0036	0.87	−0.0263	0.28	9.1707	0.41	0.0355	0.22	0.0101	0.62	0.0609	0.70
Preceding 42 days	0.0028	0.90	−0.0259	0.30	9.1826	0.42	0.0350	0.23	0.0101	0.63	0.0669	0.67
Preceding 49 days	0.0025	0.91	−0.0265	0.29	10.0393	0.39	0.0369	0.22	0.0101	0.63	0.0665	0.68
Preceding 56 days	0.0018	0.94	−0.0264	0.30	10.5755	0.37	0.0381	0.21	0.0100	0.64	0.0645	0.69
February – July												
Day of OGTT	−0.0313	0.10	0.0264	0.19	−11.75	0.22	−0.072	0.01	0.0341	0.09	0.2858	0.05
Preceding 7 days	−0.0336	0.08	0.0272	0.17	−11.54	0.23	−0.075	0.007	0.0341	0.09	0.3053	0.03
Preceding 14 days	−0.0299	0.11	0.0257	0.19	−11.64	0.22	−0.074	0.007	0.0338	0.08	0.2782	0.05
Preceding 21 days	−0.0306	0.10	0.0267	0.17	−12.82	0.17	−0.080	0.003	0.0365	0.06	0.3060	0.03
Preceding 28 days	−0.0308	0.09	0.0267	0.18	−12.94	0.16	−0.081	0.003	0.0389	0.04	0.3204	0.02
Preceding 35 days	−0.0209	0.26	0.0263	0.37	−12.44	0.19	−0.078	0.005	0.0362	0.06	0.2984	0.03
Preceding 42 days	−0.0137	0.46	0.0176	0.54	−11.60	0.22	−0.078	0.005	0.0344	0.08	0.2754	0.05
Preceding 49 days	−0.0142	0.46	0.0123	0.49	−11.89	0.22	−0.081	0.004	0.0370	0.06	0.2763	0.05
Preceding 56 days	−0.0098	0.61	0.0092	0.65	−9.720	0.32	−0.075	0.009	0.0337	0.10	0.2590	0.08
Temperature change												
August – January												
Day of OGTT	0.0379	0.07	−0.0419	0.08	3.7523	0.73	0.0415	0.14	0.0063	0.75	−0.0987	0.51
Preceding 7 days	0.0451	0.03	−0.0574	0.02	4.3637	0.69	0.0077	0.78	−0.0138	0.49	−0.0626	0.68
Preceding 14 days	0.0343	0.10	−0.0486	0.04	−3.5619	0.74	0.0069	0.80	−0.0047	0.81	0.0425	0.78
Preceding 21 days	0.0132	0.54	−0.0257	0.28	−4.0738	0.71	0.0175	0.54	0.0064	0.75	0.0279	0.86
Preceding 28 days	0.0041	0.85	−0.0180	0.44	−4.1109	0.70	0.0135	0.62	0.0102	0.60	0.0539	0.72
Preceding 35 days	0.0023	0.91	−0.0156	0.50	−1.2950	0.90	0.0238	0.38	0.0147	0.44	0.0167	0.91
Preceding 42 days	0.0000	0.99	−0.0170	0.46	−0.2811	0.98	0.0223	0.42	0.0159	0.40	0.0482	0.75
Preceding 49 days	0.0044	0.83	−0.0252	0.28	3.4810	0.74	0.0274	0.31	0.0102	0.59	0.0543	0.71
Preceding 56 days	0.0083	0.69	−0.0331	0.15	7.1294	0.50	0.0308	0.26	0.0081	0.67	0.0680	0.64
February – July												
Day of OGTT	−0.0201	0.27	0.0076	0.69	2.954	0.78	0.026	0.33	0.0225	0.24	0.0877	0.52
Preceding 7 days	−0.047	0.02	0.0388	0.06	−24.8	0.01	−0.066	0.02	0.0490	0.02	0.3880	0.01
Preceding 14 days	−0.049	0.02	0.0378	0.08	−19.23	0.06	−0.069	0.02	0.0539	0.01	0.4026	0.01
Preceding 21 days	−0.0399	0.05	0.0389	0.07	−25.2	0.01	−0.083	0.006	0.0619	0.004	0.3886	0.01
Preceding 28 days	−0.050	0.02	0.0530	0.02	−29.5	0.01	−0.11	0.0002	0.0704	0.001	0.4675	0.002
Preceding 35 days	−0.0342	0.09	0.0396	0.07	−23.0	0.03	−0.103	0.001	0.0605	0.005	0.3697	0.02
Preceding 42 days	−0.0333	0.10	0.0356	0.09	−17.61	0.08	−0.093	0.002	0.0541	0.01	0.3295	0.03
Preceding 49 days	−0.0245	0.21	0.0280	0.18	−17.03	0.09	−0.086	0.003	0.0492	0.02	0.2955	0.05
Preceding 56 days	−0.0188	0.33	0.0216	0.30	−14.94	0.13	−0.083	0.004	0.0407	0.05	0.2727	0.06

Daily temperatures were decreasing from August to January and increasing from February to July

Associations were adjusted for age, ethnicity, family history of diabetes, pre-pregnancy BMI, gestational weight gain up to the OGTT, and weeks' gestation at the time of the OGTT

All tests were two-sided and performed at a significance level of $p = 0.05$

Table 3 Adjusted ORs for each of the temperature variables as a predictor of GDM in the months when temperature was decreasing and increasing

Variable	August – January		February – July	
	OR	95% CI	OR	95% CI
Mean temperature				
Day of OGTT	1.00	0.98, 1.02	1.01	0.99, 1.03
Preceding 7 days	0.99	0.97, 1.01	1.01	0.99, 1.03
Preceding 14 days	0.99	0.97, 1.01	1.01	0.99, 1.03
Preceding 21 days	0.99	0.97, 1.01	1.01	0.99, 1.03
Preceding 28 days	0.99	0.97, 1.01	1.01	0.99, 1.03
Preceding 35 days	0.99	0.97, 1.01	1.01	0.99, 1.03
Preceding 42 days	0.99	0.97, 1.01	1.01	0.99, 1.03
Preceding 49 days	0.99	0.97, 1.01	1.01	0.99, 1.03
Preceding 56 days	0.99	0.96, 1.01	1.01	0.99, 1.03
Temperature change				
Day of OGTT	1.00	0.94, 1.07	1.03	0.98, 1.09
Preceding 7 days	0.96	0.85, 1.08	1.16	1.04, 1.29**
Preceding 14 days	0.96	0.84, 1.11	1.20	1.05, 1.37**
Preceding 21 days	0.94	0.80, 1.09	1.16	1.01, 1.33*
Preceding 28 days	0.94	0.81, 1.10	1.20	1.03, 1.39*
Preceding 35 days	0.92	0.79, 1.08	1.15	0.99, 1.34
Preceding 42 days	0.93	0.79, 1.09	1.14	0.98, 1.34
Preceding 49 days	0.95	0.80, 1.11	1.14	0.97, 1.33
Preceding 56 days	0.95	0.80, 1.12	1.11	0.95, 1.30

Daily temperatures were decreasing from August to January and increasing from February to July

ORs are expressed per °C

Each OR is adjusted for age, ethnicity, family history of diabetes, pre-pregnancy BMI, gestational weight gain up to the OGTT and weeks' gestation at OGTT

All tests were two-sided and performed at a significance level of $p = 0.05$

*$p < 0.05$ and **$p < 0.01$

temperature was declining (August – January; $n = 674$); and (2) those who completed their OGTT in a month where mean daily temperature was rising (February – July; $n = 790$). As shown in Fig. 1, spline plots of the prevalence of GDM vs the temperature increment in the preceding 7, 14, 21 and 28 days showed marked differences between these two groups. Specifically, there was no apparent association between change in temperature and prevalence of GDM in August – January (Fig. 1a, c, e, g). In contrast, in February – July, the likelihood of GDM on OGTT was increased in the setting of a temperature increment of ~10–12°C in the preceding 7 and 14 days, and an increment of ~8–9°C in the preceding 21 and 28 days. Indeed, stratification of the study population into four groups based on timing of the OGTT (February – July or August – January) and whether there was a temperature increase >8°C in the preceding 21 days revealed that such an increment before an OGTT in February – July was associated with poorer beta cell function and higher blood glucose levels (ESM Table 3). It thus emerges that the temperature change in the preceding weeks was associated with the risk of GDM in months where the weather was getting warmer (February – July), but not in those months where mean temperature was falling (August – January).

To further evaluate this apparent distinction between these 6 month periods of the year, we repeated the earlier multiple linear regression analyses separately in: (1) women whose OGTT was performed in months where the temperature was declining (August – January); and (2) those whose OGTT was performed in months where the temperature was rising (February – July). As shown in Table 2, this analysis revealed that there were almost no significant associations between any of the 18 temperature variables and insulin sensitivity/resistance, beta cell function and blood glucose in August – January. In contrast, in February – July, changes in temperature in the preceding 7, 14, 21, 28, 35 and 42 days were positive independent predictors of both fasting glucose and AUC_{gluc}. The strongest associations were with the changes in temperature in the preceding 21, 28 and 35 days, which also emerged as significant negative predictors of beta cell function (ISSI-2, IGI/HOMA-IR).

On sensitivity analyses with Bonferroni correction to control family-wise type 1 errors, the change in temperature in the preceding 28 days in particular was a significant predictor of higher blood glucose levels (fasting glucose, $p = 0.018$; AUC_{gluc}, $p = 0.036$) and poorer beta cell function (IGI/HOMA-IR, $p = 0.0036$) (ESM Table 4). Similarly, on sensitivity analyses with FDR correction, these findings were again unchanged (fasting glucose, $p = 0.018$; AUC_{gluc}, $p = 0.036$; IGI/HOMA-IR, $p = 0.0036$) (ESM Table 4). Furthermore, to address the possibility that maternal psychological stress in the months prior to school holidays in the summer could be contributing to the findings, we performed additional sensitivity analyses that were restricted to those women who were nulliparous at the time of the current pregnancy ($n = 793$). Again, the main findings were largely unchanged, with the change in temperature in the preceding 28 days for OGTTs performed in February – July emerging as a significant independent predictor of higher blood glucose levels (fasting glucose, $p = 0.007$; AUC_{gluc}, $p = 0.014$) and beta cell dysfunction (IGI/HOMA-IR, $p = 0.037$; ISSI-2, $p = 0.022$) (data not shown). These analyses thus consistently indicate that, in months where the mean daily temperature was rising, the temperature change in the month before the OGTT independently predicted poorer beta cell function and higher glucose levels.

Finally, we performed logistic regression analyses to determine whether any of the 18 temperature variables were independent predictors of GDM in either the months when the temperature was rising or the months when it was declining. As shown in Table 3, in February – July, the temperature changes in the preceding 7 days (OR 1.16 per °C, 95% CI

1.04, 1.29), 14 days (OR 1.20 per °C, 1.05, 1.37), 21 days (OR 1.16 per °C, 1.01, 1.33) and 28 days (OR 1.20 per °C, 1.03, 1.39) were all independent predictors of GDM. In contrast, none of the other temperature variables was a significant predictor of GDM.

Discussion

In this study, we report three main findings. First, we show that it is the change in temperature in the preceding weeks, rather than the daily temperature per se, that relates to blood glucose in pregnant women and this association emerges in the months where temperatures are rising (February – July in Toronto). Second, during these months, the temperature increment in the 3–4 weeks prior to glucose tolerance testing is a significant independent predictor of GDM, after adjustment for clinical risk factors. Third, the change in temperature during this window is also independently associated with beta cell dysfunction, thereby implicating a potential underlying mechanism by which this environmental factor may affect glucose metabolism.

In 1994, a study of pregnant women in Porto Alegre, Brazil, revealed that those who underwent their antepartum OGTT on warmer days (based on the temperature at 09:00 hours) had higher 1 h and 2 h post-challenge glucose levels than those who were tested on colder days, resulting in differences in the prevalence of glucose intolerance [7]. Subsequent reports from Australia and Sweden found that the mean monthly temperature was associated with 2 h glucose on the antepartum OGTT [4, 16]. In addition, a Canadian study using administrative data from over 500,000 pregnancies recently linked mean 30 day outdoor temperature with the risk of GDM [3]. Collectively, studies to date have consistently shown an association between temperature and post-challenge glucose concentrations (rather than fasting glucose) in large cohorts of pregnant women across a variety of geographic locations and climates [3, 4, 6, 7, 16]. It has been suggested that these findings may be due to higher core body temperature causing re-distribution of blood flow between arterial and venous systems, resulting in higher glucose levels in venous blood secondary to arterialisation [17–19]. Furthermore, it has been hypothesised that this effect may be amplified in pregnancy because of maternal physiological adaptations to the gravid state, such as a more hyperdynamic circulation and changes in fat distribution [1].

The use of different temperature variables in these preceding studies (e.g. 09:00 hours measurement on the day of the OGTT, mean monthly temperature, 30 day average) supports the existence of an association between temperature and glucose tolerance in pregnancy, but has not provided insight into either the precise biological exposure of interest or how it may adversely affect the physiology of glucose homeostasis. We undertook the current systematic evaluation of mean temperature and the changes therein over varying durations of time in relation to glucose tolerance and its determinants. With this approach, we also observed associations of post-challenge glucose (particularly at 30 min) with mean temperature measurements (data not shown). In contrast, however, far more striking and ubiquitous were the associations of blood glucose with mean temperature increments over the 2–8 weeks preceding the OGTT, suggesting that a more important biological exposure may be change in environmental temperature within this window.

Recognising that the temperature increment (defined here as the difference between the minimum and maximum measurements over the course of the day) could be reflecting the biological effect of either the rise or decline in temperature, we repeated the analyses within the 6 month intervals in which mean daily temperatures were increasing (February – July) and decreasing (August – January), respectively. These analyses showed marked differences between these two intervals (Fig. 1, Tables 2 and 3), revealing that the associations between changes in temperature and glucose homeostasis in pregnancy were really driven by events occurring when the weather was getting warmer (February – July). Although slightly more women had OGTTs in February – July (n = 790) than in August – January (n = 674), lack of statistical power in the latter group was probably not the basis for the observed differences, given the complete absence of any signal of association between temperature variables and glucose homeostasis in August – January (Fig. 1, Tables 2 and 3). For example, the differences between the GDM ORs for temperature increments over the preceding 7–56 days in February – July and those of all other temperature variables in Table 3 were striking (i.e. ~1.15–1.20 vs ~0.95–1.01). It thus appears that the change in temperature as the weather is getting warmer may be the biological exposure of interest.

The current analysis also provides insight into the duration of exposure that may potentially be relevant to glucose homeostasis. Specifically, as shown in Table 2 (February – July), temperature increments in the preceding 7, 14, 21, 28, 35 and 42 days were all significant independent predictors of fasting glucose and AUC_{gluc}. More precisely, however, the increments in the preceding 21, 28 and 35 days were inversely associated with both measures of beta cell function (Table 2), and increments in the preceding 21 and 28 days were significant independent predictors of GDM (Table 3). Taken together, these data suggest that rising mean daily temperature in the 3–4 weeks prior to the OGTT may have an adverse effect on maternal beta cell function and thereby raise the risk for GDM.

The current study has focused on outdoor environmental temperature rather than indoor temperature. Of note, a previous study from Boston (which has a similar climate to Toronto) reported that indoor and outdoor temperatures are strongly correlated when the latter exceeds 13°C, whereas

below this threshold, the indoor measure generally remains at 18°C [20]. In this context, two reassuring points should be noted. First, the acute effect of ambient indoor temperature on glucose tolerance that was previously reported in a study of seven male participants [18] was observed in the current analysis (e.g. mean temperature on the day of the OGTT was independently associated with fasting glucose [ESM Table 2]). Second, any effect of temperature misclassification when the weather outside was colder than 13°C would have biased our findings towards the null. In this regard, the robust associations that were consistently observed between changes in outdoor temperature in the preceding 3–4 weeks and glucose homeostasis on OGTTs performed in February to July are both reassuring and supportive of the relevance of the environmental exposure.

A limitation of this study is that lifestyle factors (such as diet and physical activity) that might change with the weather were not evaluated. Notably, seasonal dietary changes have been demonstrated on meta-analysis of the literature [21]. Conversely, because of the cold winters in Toronto, warmer weather is usually associated with increased physical activity, which would generally have a beneficial effect on glucose tolerance (in contrast to the worsening thereof observed with rising temperatures in this study). Moreover, it should be noted that weight gain in pregnancy prior to the OGTT did not differ across the months of the year and all of the analyses were adjusted for this factor. While the single-centre design of this study is a limitation, it is also reassuring that our findings in Toronto of associations between environmental temperature variables and post-challenge blood glucose and glucose homeostasis in pregnancy mirror those observed in other countries with different climates, such as Australia, Brazil, Sweden, Italy and Greece [1, 2, 4–7]. Future studies should now determine if the relationships of incremental changes in temperature with beta cell dysfunction and GDM observed herein extend to these and other climates.

From a clinical perspective, the findings from this study raise the possibility that women diagnosed with GDM in months in which the weather is getting warmer might differ from those who develop GDM at other times of the year (i.e. without the extra influence of rising temperature), and hence may have differential risks for health outcomes. Although the association between environmental temperature and glucose homeostasis in pregnancy appears to be generally modest in its magnitude, the clinical question of whether it may impact maternal and fetal outcomes should be addressed in future studies. In linking changes in environmental temperature with effects on beta cell function, this study also has implications for fundamental research. Specifically, the physiological mechanisms by which changes in environmental temperature may impact beta cell compensation in pregnancy warrant evaluation and may provide novel insight that is relevant to both beta cell biology and adaptation to the gravid state. Indeed, there exists precedence for environmental temperature affecting metabolic function (particularly insulin sensitivity) through the activation of brown adipose tissue in response to cold exposure [22, 23]. Moreover, Spiegelman and colleagues have reported that fat cells can directly sense temperature to activate thermogenesis in response to cold stimuli [24]. In the context of the growing literature linking environmental temperature and metabolism, the current findings suggest that future research to elucidate the physiological effects of changes in temperature on beta cell biology in pregnancy is warranted.

In summary, rising environmental temperature in the 3–4 weeks prior to glucose tolerance testing in pregnancy is independently associated with maternal beta cell dysfunction and blood glucose levels. Notably, the mean temperature increment during this interval is an independent predictor of the risk of GDM. These data provide insight into both the environmental exposure and the pathophysiological basis underlying the higher prevalence of GDM in summer months that has been observed across populations, geographic locations and climates.

Data availability Data may be obtained from the corresponding author on request.

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Contribution statement RR, AJH, PWC, MS and BZ designed and implemented the study. CKK, CY and RR contributed to the analysis plan and interpretation of the data. CY performed the statistical analyses. RR and CKK wrote the manuscript. All authors critically revised the manuscript for important intellectual content. All authors approved the final manuscript. RR is the guarantor of this work.

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