The relationship between ambient temperature and FPG, a series of cross-sectional studies in Guangdong Province, China

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1 **Abstract**

2 **Background:** There existed evidence that the incidence and glycemic control rate of
3 T2DM have seasonal variation, which can be attributed to the effect of temperature on
4 FPG. The present study aimed to examine the associations between short-term
5 ambient temperature exposure and FPG among different populations and calculate
6 temperature-FPG association adjusted prevalence and glycemic control rate of T2DM.

7 **Methods:** Four cross-sectional health surveys with 26,350 respondents were
8 conducted in Guangdong Province from 2007 to 2015. Multistage cluster sampling
9 was used to recruit study participants. Gaussian generalized additive model was
10 employed to evaluate the associations between daily mean ambient temperature and
11 FPG among different populations (total, non-T2DM, old-T2DM and new-T2DM
12 populations). Prevalence and glycemic control rate of T2DM were calculated based
13 on the exposure-response association between temperature and FPG.

14 **Results:** The exposure-response curve of temperature and FPG were downward
15 parabola in total, non-T2DM and old-T2DM populations, while the curve was
16 “U”-shaped but not significant in new T2DM population. When temperature increased
17 from 10th percentile to 50th percentile, the FPG significantly decreased 0.14 (95%CI:
18 -0.17, -0.11) mmol/L, 0.11 (95%CI: -0.12, -0.11) and 0.44 (95%CI: -0.80, -0.08) in
19 total, non-T2DM and old-T2DM populations, respectively. When temperature
20 increased from 50th to 90th percentile, the FPG significantly decreased 0.19 (95%CI:
21 -0.22, -0.16) mmol/L, 0.17 (95%CI: -0.17, -0.17) and 0.51 (95%CI: -0.79, -0.23) in
22 total, non-T2DM and old-T2DM populations, respectively. The alteration of rate
23 related to the temperature difference was observed from 5°C to 30°C, with gently
24 decreases from 10.03% to 9.39% in prevalence of T2DM and greatly increases from
25 32.1% to 58.6% in glycemic control rate of T2DM, respectively.

26 **Conclusion:** FPG, the prevalence and glycemic control rate of T2DM are affected by
27 ambient temperature, which suggests temperature and FPG association should be
28 considered and adjusted when estimating T2DM epidemiology and developing

29 clinical management of T2DM.

30 **Keywords** Ambient temperature, Fasting plasma glucose, T2DM, prevalence,
31 glycemic control rate.

Background

Type 2 diabetes mellitus (T2DM) is a metabolic disorder characterized by high blood glucose in the context of insulin resistance and relative insulin deficiency. T2DM has been a very serious public health problem worldwide and accounted for about 90% of diabetes cases. It was estimated that diabetes affected more than 425 million people worldwide in 2017, and 114.4 million diabetes cases were in China [1]. Diabetes is a major contributor to cardiovascular diseases and is the eleventh common cause of disability worldwide [1].

Many risk factors such as heredity, individual life style and insufficient activity are associated with T2DM [2-4]. Environmental factors such as seasonal variation and ambient temperature were related to fasting plasma glucose (FPG). There was much evidence on seasonal variation of FPG. For example, there was a mean 0.6 mmol/L difference in FPG between winter and spring in Southern California [5]. *Gikas et al.* found that mean FPG was higher during cold seasons than warm months in a diabetic clinic study, with the nadir in August (7.60 mmol/L) and the zenith in February (9.12 mmol/L) [6]. In terms of acute effect of ambient temperature, previous studies have observed a negative relationship between temperature and FPG [5, 7]. Nevertheless, *Li et al.* found that the association between temperature and FPG was U-shaped that FPG level was higher in cold or hot temperature [8].

There were also existed evidence that the incidence of T2DM and glycemic control rate had seasonal variation. A population-based study in *Csongrad*, Hungary revealed the seasonal variation in the incidence of T2DM that the peak occurred on March and the trough occurred on August [9]. Several studies also revealed seasonal variation of glycemic control rate for T2DM cases that lower control rate emerged in cold winter [6, 10]. These seasonal variations can be attributed to temperature variation to a certain extent.

Despite the confirmed effects of ambient temperature on FPG as well as the prevalence and glycemic control rate of T2DM, previous epidemiological surveys

60 conducted in different regions or seasons did not adjust temperature-FPG association
61 when computing T2DM prevalence and control rate [11]. However, different
62 nutritional prescription and hypoglycemic drug therapy made for diabetic cases by
63 considering temperature-FPG association can help achieve better diabetic clinic care
64 and management.

65 In order to fill the knowledge gap, in the current study, we examined the associations
66 of ambient temperature with FPG in different populations based on a series of
67 cross-sectional surveys, and further calculated temperature-FPG association adjusted
68 prevalence and control rate of T2DM. Our findings are informative for accurate
69 estimate prevalence of T2DM in large-scale surveys across different climate zones
70 and seasons, and clinic management of cases with T2DM in different seasons.

Methods

Study design and population

The Guangdong Chronic Disease and Risk Factors Surveys are a series of provincially representative investigation, which conducted by Guangdong Provincial Center for Disease Control and Prevention in 2007, 2010 and 2013. These surveys aimed to monitor the prevalence trend and risk factors of non-communicable diseases such as hypertension, T2DM, and obesity. The Guangdong Nutrition and Health Survey conducted in 2015 was designed to assess the nutrition and health status in Guangdong province. The data from the four surveys were combined to examine the association of ambient temperature with FPG. All participants agreed to participate and signed informed consents form prior to the surveys. The study was approved by the Ethics Committee of Guangdong Provincial Center for Disease Control and Prevention.

Similar sampling methods and protocols were adopted for the surveys of 2007, 2010 and 2013, which has been described previously elsewhere [12]. Briefly, in each of the surveys, 21 districts or counties in Guangdong province were randomly selected by stratified multistage cluster sampling with probability proportional to size. In the second stage, four neighborhoods or townships from each district or county were selected; In the third stage, three communities or villages from each neighborhood or township were selected; In the fourth stage, 50 to 100 households from each community or village were randomly selected; Finally, 1 resident aged ≥ 18 years from each sampled household was selected using the Kish grid method. If there is no resident aged ≥ 18 years in the selected household or if the selected resident did not agree to participate in the survey, the household was replaced with another randomly selected household nearby. Details of sampling methods and survey protocols for the nutrition and health survey conducted in 2015 have been described in the previous study [13].

FPG measurement and T2DM, prevalence and control rate definition

Participants were asked to fast at least 8 hours before blood collection. Fasting blood samples were collected by registered nurses. Fasting plasma glucose levels were measured on a Hitachi 7600 automatic biochemical analyzer (Hitachi, Ltd., Tokyo, Japan) using reagents obtained from Wako Pure Chemical Industries *Ltd.* at the National CDC of China. Old-T2DM population was defined as physician-diagnosed T2DM (confirmed with medical history). According to World Health Organization 2006 criteria, new-T2DM population was defined a new discovery of diabetes with an FPG level of 7.0 mmol/L or greater among undiagnosed diabetes; non-T2DM population was defined as participants with an FPG level less than 7.0 mmol/L [14]. T2DM prevalence was as the proportion of old-T2DM patients and undiagnosed diabetes with FPG level less than 7.0 mmol/L. Control was defined as the proportion of old-T2DM population with FPG less than 7.0 mmol/L [14].

Data collection

Questionnaire and anthropometric Measurements

Participants were interviewed and provided with onsite health examinations. All interviews and examinations were conducted following standard protocols by physicians who had received specific training for the survey and health examination. Questionnaires were used to collect a wide range of information including demographic characteristics, lifestyle, household location. Demographic characteristics included age, gender (male vs female), career (production staff vs technical staff vs nonworks/ houseworkers/retirees), education (less than junior high school vs high school/college). Physical activity time was defined as leisure time spend in high intensity sports or moderate intensity exercise, such as running, swimming, doing Tai Chi (in hour/day). Sedentary leisure time was defined as time spent in sitting-down activities outside work, such as watching TV, reading a newspaper and using a computer (in hour/day). Smoking status was measured by whether individual smoked in the past or present (yes vs no). Drinking status was defined as whether individual drank alcohol in the past 12 months (yes vs no). Height

and weight were measured following standard protocols. Body mass index (BMI) was calculated as weight divided by the square of standing height (in kg/m²).

Meteorological data

Daily meteorological data were obtained from the China National Weather Data Sharing System (<http://data.cma.cn/>). Monitoring locations included thirty-six areas and the number of survey areas was shown in Additional file 1: table S1. Daily meteorological variables from each survey's nearby weather station included daily mean, minimum, maximum temperature (°C), relative humidity (%) and sunlight (hour/day), which will be matched to other individual survey information based on the date of survey. Daily meteorological data was passed through quality control checks. The integrity of each meteorological data was closely to 99.9%.

Statistical analysis

We characterized distributions of all variables, continuous variables were expressed as the means±SD for normally distributed data and mean (IQR, 25%-75%) for skew distributed data. Categorical variables were expressed as numbers and percentages. T-test (for normally distributed continuous data), Kruskal–Wallis test (for skew distributed continuous data) or χ^2 test (for categorical variables) were used to compare the characteristics between non-T2DM, old T2DM and new T2DM participants. A generalized additive Gaussian model was used to investigate ambient temperature exposure on FPG among different populations after adjusting for covariates. Daily mean temperature was selected as exposure variable from daily minimum/mean/maximum temperature according to the minimum value of Akaike's Information criterion (*AIC*) in the model (Additional file 2: figure S1). And daily mean temperature, humidity, age and BMI were fitted using a penalized cubic spline function with a degree of freedom (*df*) of 3. Selection optimal *df* of daily mean temperature was based on graphic smoothness and minimum value of *AIC* (Additional file 3: figure S2). The regression model was established as following Y_{im} (1).

$$Y_{im} = \beta_{0m} + \beta_{1m} s(X_{temp}, k=3) + \beta_{2m} s(X_{humidity}, k=3) + \beta_{3m} s(X_{age}, k=3) + \beta_{4m} s(X_{BMI}, k=3) + \beta_{5m} X_{Li} + \dots + \beta_{nm} X_{ni} + \epsilon_{im} \quad (1)$$

Where m represents to groups (total/non-T2DM/new-T2DM/old-T2DM participants), Y_{im} represents to participant's FPG; β_{0m} is the overall intercept, $\beta_{1m} \dots \beta_{nm}$ corresponds to coefficients for variables. X_{temp} , $X_{humidity}$, X_{age} , X_{BMI} and $X_{Li} \dots X_{ni}$ denotes variables. $S()$ is a penalized cubic spline function and ϵ_{im} is the residual error.

After constructing the model, we obtained the exposure-response curve between daily mean temperature and the change of FPG compared to 50th percentiles of temperature. We used the change of FPG at different typical interval (10th, 50th, 90th percentiles of temperature) of the curve to demonstrate the effect of temperature. Based on exposure-response curve, we can obtain participant's change of FPG (ΔFPG_{ijm}) at survey day of temperature compared to 5°C, 10°C, 15°C, 20°C, 22.5°C, 25°C and 30°C. Temperature-adjusted FPG (FPG_{2ijm}) (2), prevalence ($Rate_{1j}$) (3) and glycemic control rate ($Rate_{2j}$) (4) of T2DM can be calculated as the follows:

$$FPG_{2ijm} = FPG_{lim} - \Delta FPG_{ijm} \quad (2)$$

$$Rate_{1j} = N_{1j}/N_3 \quad (3)$$

$$Rate_{2j} = N_{2j}/N_4 \quad (4)$$

Where m corresponds to groups (total/non-T2DM/new-T2DM/old-T2DM participants), j represents temperature reference points (5°C, 10°C, 15°C, 20°C, 22.5°C, 25°C and 30°C). ΔFPG_{ijm} corresponds to participant's change of FPG at survey day of temperature compared to temperature reference points. FPG_{lim} corresponds to each participant's FPG; N_{1j} represents the sum of the number of old & new T2DM patients and the number of non-T2DM population with FPG_{2ijm} level of 7 mmol/L or greater; N_3 is number of total population; N_{2j} represents the number of old-T2DM with a FPG_{2ijm} less than 7 mmol/L; N_4 is the number of old-T2DM patients.

For sensitivity analysis, we analysis the association between ambient temperature and

181 FPG across different lags (lag1 to lag6). We further added sunshine and precipitation
182 to the model to test the robustness of that association. We used R software (version
183 3.5.1, R foundation for Statistical Computing, Vienna, Austria). All statistical tests
184 were two-sided and P values of all statistical analyses less than 0.05 was considered
185 statistically significant. The GAM analysis was performed by using package “*mgcv*”.

Results

Characteristics of study participants

At baseline, total sample size was 26350, and 90.6% of subjects were non-T2DM; 5.8% of subjects were new-T2DM and 3.5% were old-T2DM. Overall, the mean (IQR) age of respondents was 50.1 (40.0-60.1) years old and 44.9% of them were males. Compared with non-T2DM participants, old-T2DM and new-T2DM participants were older and had higher levels in BMI, but lower education level. Moreover, there were more nonworkers/houseworkers/retirees, non-smokers and non-drinkers in old-T2DM and new-T2DM participants than non-T2DM participants (table 1). Density distribution of FPG among different populations and statistical description of FPG and daily mean temperature showed in additional file 4: figure S3 and additional file 5: table S2.

Monthly variation in FPG and ambient temperature

Fig 1 and additional file 6: Table S3 show monthly variation in FPG and ambient temperature. The climate is characterized by two main seasons: cold season (lasting from December to March) and warm season (April, May, October, November). Mean FPG levels were significantly higher during the cold season than warm season. The zenith of FPG was 6.57 mmol/L for total participants, 5.55 mmol/L for non-T2DM participants, 9.41 mmol/L for old T2DM participants, and 10.04 mmol/L for new T2DM participants in January or February or March, while the nadir of FPG was 5.29 mmol/L for total participants, 5.05 mmol/L for non-T2DM participants, 7.39mmol/L for old T2DM participants and 8.99 mmol/L for new T2DM participants in October or November.

Table 1. Characteristic of study participants among different populations.

Variable	Total population	Non-T2DM [†]	Old-T2DM [‡]	New-T2DM [§]	P value
Overall, n (%)	26350(100.0)	23877 (90.6)	916 (3.5)	1557 (5.9)	
Gender, n (%)					0.2
male	11834 (44.9)	10709 (44.9)	398 (43.4)	727 (46.7)	
female	14516 (55.1)	13168 (55.1)	518 (56.6)	830 (53.3)	
Education, n (%)					<0.001
≤Junior high school	12573 (47.7)	11212 (47.0)	506 (55.2)	855 (54.9)	
High school/college	13777 (52.3)	12665 (53.0)	410 (44.8)	702 (45.1)	
Career, n (%)					<0.001
production staff	9170 (34.8)	8428 (35.3)	242 (26.4)	500 (32.1)	
Technical staff	9504 (36.1)	8783 (36.8)	224 (24.5)	497 (31.9)	
Nonworkers/ houseworkers/retirees	7676 (29.1)	6666 (27.9)	450 (49.1)	560 (36.0)	
Smoking status, n (%)					<0.001
Yes (Former/Current)	10747 (40.8)	9835 (41.2)	357 (39.0)	555 (35.6)	
Never	15603 (59.2)	14042 (58.8)	559 (61.0)	1002 (64.4)	
Drinking status, n (%)					<0.001
Yes (past 12 months)	11380 (43.2)	10412 (43.6)	355 (38.8)	613 (39.4)	
Never (past 12 months)	14970 (56.8)	13465 (56.4)	561 (61.2)	944 (60.6)	
BMI (kg/m ²), n (%)					<0.001
<18.5	1945 (7.4)	1835 (7.7)	30 (3.3)	80 (5.1)	
18.5-23.9	15061 (57.2)	13945 (58.4)	396 (43.2)	720 (46.2)	
24.0-27.9	7280 (27.6)	6384 (26.7)	359 (39.2)	537 (34.5)	
≥28	2064 (7.8)	1713 (7.2)	131 (14.3)	220 (14.1)	
Age (year), median (IQR)	50.1 (40.0-60.1)	49.8 (39.0-59.9)	59.0 (52.0-67.0)	54.0 (44.8-63.0)	<0.001
Body mass index (kg/m ²), median (IQR)	22.7 (20.6-25.1)	22.6 (20.5-24.9)	24.3 (22.4-26.5)	23.9 (21.5-26.4)	<0.001
Physical activity time (hour/day)*, mean±SD	0.2±0.7	0.2±0.7	0.3±0.6	0.2±0.5	<0.001
Sedentary leisure time (hour/day), median (IQR)	4.0 (2.0-6.0)	4.0 (2.0-6.0)	4.5 (3.0-6.8)	4.0 (2.0-6.0)	<0.001
Daily mean humidity [#] , median (IQR)	75.0 (66.0-84.0)	75.0 (66.0-84.0)	78.0 (69.0-90.0)	75.0 (64.0-85.0)	<0.001

210 Data were expressed as median (IQR 25%-75%) for non-normal continuous variables and as
 211 number (percentage) for categorical variables. Statistics analysis: Kruskal-Wallis test for
 212 non-normal continuous variables and chi square test for categorical variables.

213 †: Non-T2DM, no medical history of type 2 diabetes mellitus with fasting plasma glucose less
 214 than 7.0 mmol/L.

215 ‡: Old T2DM, physician-diagnosed type 2 diabetes mellitus.

216 §: New T2DM, newly detected type 2 diabetes mellitus with fasting plasma glucose of 7.0 mmol/L
 217 or greater.

218 *: Physical activity time variable of median (IQR 25%-75%) was zero, so it was expressed as
 219 mean±SD.

220 #: Daily mean humidity was matched by the same date of health survey.

Figure1. Monthly variation in mean of FPG (mmol/L) and ambient temperature (°C) among total, non-T2DM, old T2DM and new T2DM populations.

Effects of ambient temperature on FPG

In total, non-T2DM, old-T2DM populations, the exposure-response curves were general downward parabola. As temperature increased FPG concentration significantly decreased and the rate of descent saw an increasing trend. However, the exposure-response curve was “U”-shaped but the effect of temperature was not statistically significant (Figure 2).

In the first day of temperature exposure (lag0), when temperature increased from 10th percentile to 50th percentile, the FPG significantly decreased 0.14 (95%CI: -0.17, -0.11) mmol/L, 0.11 (95%CI: -0.12, -0.11) and 0.44 (95%CI: -0.80, -0.08) in total, non-T2DM and old-T2DM populations, respectively, while we found no significant effect of temperature in new-T2DM participants (-0.19, 95%CI: -0.50, 0.12). In lag0, when temperature increased from 50th to 90th percentile, the FPG significantly decreased 0.19 (95%CI: -0.22, -0.16) mmol/L, 0.17 (95%CI: -0.17, -0.17) and 0.51 (95%CI: -0.79, -0.23) in total, non-T2DM and old-T2DM populations, respectively, while we found no significant effect of temperature in new-T2DM participants (0.10, 95%CI: -0.19, 0.39) (Table 2 and figure 3).

Temperature-adjusted FPG, prevalence and glycemic control rate of T2DM

Temperature adjusted FPG decreased when temperature increased for total, non-T2DM and old T2DM populations. For instance, the mean of temperature-adjusted FPG was 5.78 mmol/L at 5°C while 5.22 mmol/L at 30°C in total participants; 5.40 mmol/L at 5°C while 4.93 mmol/L at 30°C in non-T2DM participants, 9.04 mmol/L at 5°C while 7.49 mmol/L at 30°C in old T2DM participants. However, the association between temperature and temperature-adjusted FPG was a down and up trend in new T2DM population, such as the mean of temperature-adjusted FPG was 9.56 mmol/L at 5°C, 9.08 mmol/L at 20°C and 9.36 mmol/L at 30°C, respectively (figure4A).

Temperature-FPG association adjusted prevalence and glycemic control rate of T2DM

showed in figure4B. Based on temperature adjusted FPG, low ambient temperature resulted in gently increased of prevalence of T2DM and greatly decreased of glycemic control rate of T2DM. The alteration of rate related to the temperature difference was observed from 5°C to 30°C, with gently decreases from 10.03% to 9.39% in prevalence of T2DM and greatly increases from 32.1% to 58.6% in glycemic control rate of T2DM, respectively.

Sensitivity analyses

Similar exposure-response relationships between temperature and FPG were obtained using different lag times or additionally adjusted sunshine and precipitation, which suggested a robust relationship (Additional file 7: Figure S4 and Additional file 8: Figure S5). And there were no significant change effects at different typical interval of temperature on FPG compared to the result of the main model analysis, suggesting that our results were relatively robust (Table 2 and figure 3).

263

264 Figure 2. The exposure-response of daily mean temperature and FPG among total, non-T2DM, old T2DM and new T2DM populations.

265 Shade represent 95%CI Confidence band. Non-T2DM, no medical history of type 2 diabetes mellitus with fasting plasma glucose less than 7.0 mmol/L. Old T2DM,
 266 physician-diagnosed type 2 diabetes mellitus. New T2DM, newly detected type 2 diabetes mellitus with fasting plasma glucose of 7.0 mmol/L or greater. Gaussian
 267 generalized additive models were adjusted for age, sex, BMI, education, career, physical activity, sedentary leisure times, smoking status, drinking status and humidity
 268 variables.

Table 2 Change of FPG (mmol/L) at different typical interval of temperature.

	Interval 1 of temperature (P10(ref) vs P50 [#]) *				Interval 2 of temperature (P50 [#] (ref) vs P90) *			
	Total	Non-T2DM [†]	Old T2DM [‡]	New T2DM [§]	Total	Non-T2DM [†]	Old T2DM [‡]	New T2DM [§]
Temperature	11.3°C vs 19.4°C	11.4°C vs 19.4°C	10.9°C vs 19.8°C	11.0°C vs 18.5°C	19.4°C vs 25.1°C	19.4°C vs 25.1°C	19.8°C vs 25.3°C	18.5°C vs 24.6°C
Main model								
Lag 0	-0.14 (-0.17, -0.11)	-0.11 (-0.12, -0.11)	-0.44 (-0.80, -0.08)	-0.19 (-0.50, 0.12)	-0.19 (-0.22, -0.16)	-0.17 (-0.17, -0.17)	-0.51 (-0.79, -0.23)	0.10 (-0.19, 0.39)
Lag 1	-0.14 (-0.17, -0.12)	-0.11 (-0.11, -0.11)	-0.42 (-0.83, -0.01)	-0.21 (-0.52, 0.10)	-0.17 (-0.20, -0.15)	-0.16 (-0.16, -0.16)	-0.26 (-0.58, 0.06)	0.12 (-0.19, 0.42)
Lag 2	-0.16 (-0.19, -0.13)	-0.11 (-0.12, -0.11)	-0.52 (-0.93, -0.11)	-0.18 (-0.45, 0.09)	-0.19 (-0.21, -0.16)	-0.16 (-0.16, -0.16)	-0.34 (-0.67, -0.02)	0.00 (-0.26, 0.27)
Lag 3	-0.15 (-0.18, -0.12)	-0.12 (-0.13, -0.12)	-0.37 (-0.68, -0.06)	-0.11 (-0.38, 0.15)	-0.22 (-0.25, -0.19)	-0.17 (-0.17, -0.16)	-0.61 (-0.83, -0.40)	0.03 (-0.22, 0.28)
Lag 4	-0.11 (-0.14, -0.08)	-0.07 (-0.09, -0.05)	-0.48 (-0.83, -0.12)	-0.13 (-0.33, 0.07)	-0.24 (-0.27, -0.22)	-0.16 (-0.19, -0.14)	-0.61 (-0.84, -0.39)	-0.12 (-0.30, 0.07)
Lag 5	-0.11 (-0.14, -0.07)	-0.06 (-0.08, -0.03)	-0.32 (0.55, -0.09)	-0.16 (-0.38, 0.06)	-0.24 (-0.27, -0.22)	-0.18 (-0.21, -0.15)	-0.84 (-0.96, -0.71)	-0.13 (-0.31, 0.05)
Lag 6	-0.08 (-0.12, -0.05)	-0.04 (-0.08, -0.01)	-0.31 (-0.55, -0.07)	-0.01 (-0.24, 0.21)	-0.24 (-0.27, -0.22)	-0.20 (-0.23, -0.16)	-0.76 (-0.93, -0.59)	-0.01 (-0.19, 0.17)
Model 2	-0.13 (-0.16, -0.10)	-0.11 (-0.11, -0.10)	-0.40 (-0.76, -0.04)	-0.16 (-0.48, 0.15)	-0.16 (-0.19, -0.13)	-0.15 (-0.15, -0.15)	-0.45 (-0.73, -0.16)	0.12 (-0.18, 0.42)

270 †: Non-T2DM, no medical history of type 2 diabetes mellitus with fasting plasma glucose<7.0mmol/L.

271 ‡: Old T2DM, physician-diagnosed type 2 diabetes mellitus.

272 §: New T2DM, newly detected type 2 diabetes mellitus with fasting plasma glucose≥7.0mmol/L.

273 #: 50th percentiles (P50) of daily mean temperature: total and non-T2DM were at 19.4°C, old-T2DM was at 19.8°C and new-T2DM was at 18.5°C.

274 *: Interval 1 represents the change of FPG at 10th percentiles (P10) of daily mean temperature compared with P50. Interval 2 represents P50 of daily mean
 275 temperature compared with 90th percentiles (P90).

276 Main model was adjusted for age, sex, BMI, education, career, physical activity, sedentary leisure times, smoking status, drinking status and humidity variables.

277 Model2 were adjusted model 1 and additionally sunshine and precipitation variables.

Figure 3. The effect of temperature on FPG with different lag times. 50th percentiles (P50) of daily mean temperature: total and non-T2DM were at 19.4°C, old-T2DM was at 19.8°C and new-T2DM was at 18.5°C. Figure represents the change of FPG at P10 (ref) of daily mean temperature compared with P50 and P50 (ref) of daily mean temperature compared with P90. Error bar represents 95% CI.

284

285 Figure 4. (A) Temperature adjusted FPG concentrations. (B) Temperature-FPG association adjusted prevalence (%) and glycemic control rate (%) of T2DM. Adjusted

286 FPG, prevalence and glycemic control rate of T2DM at 5°C, 10°C, 15°C, 20°C, 22.5°C, 25°C, 30°C. Temperature adjusted FPG calculation was based on

287 exposure-respond curve of daily mean temperature and FPG. (*, annual mean temperature in Guangdong Province).

Discussion

In our study, we found that FPG levels were significantly higher in cold season than warm season among different populations, and the exposure-response curves between ambient temperature and FPG were downward parabola-shaped in total, non-T2DM and old-T2DM populations, while the curve was U-shaped in new T2DM population. The prevalence and glycemic control rate of T2DM varied across temperature. Temperature-FPG association adjusted T2DM prevalence decreased as temperature increased, while glycemic control rate of T2DM increased with the rising of temperature. This is the first large-scale study estimating temperature-FPG association adjusted prevalence and control rate of T2DM.

We found that FPG had apparent seasonal variation with high concentrations in cold season and low concentrations in warm season, which was consistent with previous studies [5, 6, 15]. For instance, a similar association was seen that the level of FPG was 0.6 mmol/L higher in winter (13°C) than in summer (23°C) in San Diego County, California [5]. A large study included 15 middle and high countries also found that higher FPG of adults was observed in winter than summer in both Northern Hemisphere and Southern Hemisphere [15].

Previous studies have reported that a negative association between ambient temperature and FPG [5, 7]. However, these researches just estimated their linear correlation coefficient rather than the actual curve linear relationship between ambient temperature and FPG, and they did not pay attention to the variation in sensitivity of temperature among various people, such as non-T2DM individuals and T2DM individuals. Our study therefore established their curve linear relationship and found that FPG concentration significantly decreased as temperature increased, while the rate of decent increased as temperature increased among total, non-T2DM and old T2DM populations. In addition, our results indicated that the influence of temperature on the FPG seems to be stronger in old T2DM populations than non-T2DM. The reason may be T2DM is associated with declining insulin sensitivity and beta-cell function, and the glucose regulation of T2DM was more poorly than non-T2DM [16]. For new T2DM population, we found that exposure-response curve of ambient temperature and FPG was U- shaped, but the effect of low and high temperature on FPG was not statistically significant. This result may be explained by that new T2DM

patients were under large fluctuation in FPG without taking hypoglycemic medicine, which may affect the stability of FPG. Future prospective studies were needed to investigate this among new T2DM patients with and without medication treatment. Secondly, as the present study was conducted in winter, spring and autumn when there are limited days with high temperature, which may not find the extreme hot ambient temperature effect on FPG. Future studies can further observe the association of temperature and FPG in hot season or high temperature.

Related mechanism on the effects of ambient temperature is that temperature variation of two major hormones known to affect glucose homeostasis including plasma insulin and glucagon [17, 18]. Sustained exposure to low ambient temperature increase energy expenditure and insulin resistance [19, 20]. Population study demonstrated that per 10°C increase of outdoor temperature was associated with 0.57 units increase of insulin sensitivity index [21]. Exposing extreme cold temperature could lead to increase in the thyrotropin and decrease in total thyroxine and free thyroxine (TF4), which related to decreased insulin sensitivity [22, 23].

Previous studies found that the incidence and glycemic control rate of T2DM varied with seasons, which may lead to underestimate of T2DM prevalence and overestimate of T2MD glycemic control rate when epidemiological surveys conducted in hot season [6, 9, 10]. To our knowledge, previous T2DM prevalence surveys rarely considered the effects of ambient temperature [11]. Our study estimated prevalence and glycemic control rate of T2DM after adjusting exposure response relationship of ambient temperature and FPG, and found that temperature-FPG association adjusted T2DM prevalence decline with the raise of temperature and glycemic control rate increase as temperature rose. These findings suggested the adjustment of temperature on FPG should be applied when estimating the prevalence and control rate of T2DM, as well as making nutritional prescriptions, exercise plans and treatment protocols for T2DM cases. For example, people with borderline high FPG in hot temperature would be diagnosed as T2DM in cold temperature, and the temperature and FPG association can help make the decision about starting early hypoglycemic treatment. The treatment for old T2DM patients may need to be adjusted in cold seasons.

Our study had several strengths. First, our study sample was relatively large. Secondly,

351 we analyzed the associations between FPG and temperature among different
352 populations. Thirdly, we calculated the temperature-FPG association adjusted T2DM
353 prevalence and control rate. However, several limitations should be warranted in this
354 study. First, ambient temperature was the daily mean temperature at nearest
355 meteorological station which is not the real measurement of individual temperature
356 exposure. Second, our study was cross-sectional, which restricted our ability to
357 explore and precisely understand the causal influence of temperature on individual's
358 FPG. Thirdly, some confounding factors were not included in our study, such as
359 dietary structure and heredity. Fourth, we just have data from October to May, which
360 limited our ability to evaluate the associations between temperature and FPG at hot
361 seasons.

362 **Conclusion**

363 In conclusion, FPG, prevalence and glycemic control rate of T2DM are affected by
364 ambient temperature, which suggests the ambient temperature-FPG association should
365 be considered and adjusted when estimating prevalence and glycemic control rate of
366 T2DM. For clinical implications of T2DM, the temperature and FPG association can
367 help improve the T2DM diagnosis and guide decisions regarding hypoglycemic
368 treatment to achieve normal FPG control.

Additional file

Additional file1: TABLE S1. Number (%) of participants in each survey area in Guangdong province during 2007 and 2016.

Additional file2: Figure S1. The non-linear relationships between daily mean, daily minimum, daily maximum temperature and FPG among different populations.

Additional file3: Figure S2. The non-linear relationships between daily mean and FPG among different population at k=3,4,5.

Additional file4: Figure S3. The density distribution of fasting plasma glucose among different population.

Additional file5: TABLE S2. Statistical description of fasting plasma glucose (FPG) and daily mean ambient temperature among different populations.

Additional file6: TABLE S3. Number (%), Mean and SE of fasting plasma glucose and daily mean temperature according to month.

Additional file7: Figure S4. The exposure-response relationships between lag1 to lag6 of ambient temperature and FPG among different populations.

Additional file8: Figure S5. The exposure-response relationships between ambient temperature and FPG among different populations additionally adjusted sunshine and precipitation.

Competing interests

The authors have declared that no conflict of competing financial interests.

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Authors contributions

JL carried out the statistical analyses, JL and GH drafted the manuscript and contributed equally to this research. YX, ZC, XX, GJ, WM participated in study design and data collection. SC, JH, TL, WZ, XL, JX, LG, WM reviewed and revised manuscript. All authors approved final version of the manuscript to be published.

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Ethics approval

The protocol was approved by the Ethics Committee of Guangdong Provincial Center for Disease Control and Prevention (Ethical review code: 2019009). All the participants agreed to participate and signed informed consents form prior to the surveys.

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Availability of data

Data are not publicly available and information on how to access the data can contact details: Email: mawj@gdiph.org.cn.

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