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Effects of diurnal temperature range on first-ever strokes in different seasons: a time-series study in Shenzhen, China

Lin Lei,[1] Junzhe Bao ,[2,3] Yanfang Guo,[4] Qiong Wang,[3,5] Ji Peng,[1] Cunrui Huang[2,3,5,6]

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LL and JB contributed equally.

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For numbered affiliations see end of article.

Correspondence to
Professor Cunrui Huang; huangcr@mail.sysu.edu.cn and Mr Ji Peng; pengji126@126.com

ABSTRACT

Objective Diurnal temperature range (DTR) is an important meteorological indicator of global climate change; high values of DTR may induce stroke morbidity, while the related high-risk periods and sensitive populations are not clear. This study aims to evaluate the effects of DTR on first-ever strokes in different seasons and in relation to sensitive populations.

Methods We collected data on 142 569 first-ever strokes during 2005–2016 in Shenzhen. We fitted a time-series Poisson model in our study, estimating the associations between DTR and first-ever strokes, with a distributed lag non-linear model. Then, we calculated strokes attributable to high DTR in different genders, age groups, education levels and stroke subtypes.

Results High DTR had a significant association with first-ever strokes, and the risk of stroke increased with the rise of DTR in the summer and winter. In total, 3.65% (95% empirical CI (eCI) 1.81% to 5.53%) of first-ever strokes were attributable to high DTR (5.5°C and higher) in the summer, while 2.42% (95% eCI 0.05% to 4.42%) were attributable to high DTR (8°C and higher) in the winter. In the summer, attributable fraction (AF) was significant in both genders, middle-aged and old patients, patients with different levels of education, as well as patients with cerebral infarction (CBI); in the winter, AF was significant in middle-aged patients, patients with primary and lower education level, as well as patients with CBI.

Conclusions High DTR may trigger first-ever strokes in the summer and winter, and CBI is more sensitive than intracerebral haemorrhage to DTR. Most people are sensitive to high DTR in the summer, while middle-aged and low-education populations are sensitive in the winter. It is recommended that the DTR values be reported and emphasised in weather forecast services, together with the forecasts of heat and cold.

Strengths and limitations of this study

- ► This study explored the association between diurnal temperature range and first-ever strokes in different seasons, as well as the related sensitive populations.
- ► This study included more than 142 000 first-ever strokes ensuring robust statistical power.
- ► Meteorological data extracted from a single monitoring site rather than from individual exposure measures may lead to measurement errors.
- ► This single-city study limited the generalisation of the findings.

INTRODUCTION

According to the WHO, 12.6 million deaths (23% of all deaths worldwide) were attributable to modifiable environmental factors, and a large proportion of these deaths was influenced by climate change.[1] The 2015 Lancet Commission concluded that 'tackling climate change could be the greatest global health opportunity of the 21st century'.[2] Numerous studies confirmed that extreme temperatures, both heat and cold, could threaten people's health, especially the elderly, children, and patients with cardiovascular and respiratory system diseases, with U-shaped, V-shaped or J-shaped exposure-response curves.[3–5] In addition to heat and cold, temperature variation could also harm human health by influencing blood pressure, blood viscosity, and humoral or cellular immunity.[6 7]

The diurnal temperature range (DTR) reflects the temperature variation within a day and is defined as the difference between daily maximum and minimum temperatures. It indicates whether the weather is stable or not, and it is an important meteorological indicator of global climate change.[8 9] Increasingly more studies have focused on the health effects of DTR and found that DTR had an independent effect on population health, apart from the effect of temperature extremes.[7 9 10] Previous studies have reported that the average value of DTR has decreased during recent decades, caused by climate change factors such as greenhouse gases, urbanisation and aerosol use.[11 12] However, Lee *et al*[13] found that the influence of DTR on mortality rates in the future might increase after consideration of the fact that there will be an increase in the number of extremely or moderately hot days, based on their findings which suggested that the DTR-related mortality may be modified by daily mean temperature and be most elevated during extremely hot temperatures. So far, most of these studies focused on mortality. The effects of DTR on morbidity require further investigation, as do the health effects of DTR in different seasons and subgroups.

Stroke is the second leading cause of death globally, and the first leading cause of death in China, according to the 2017 disease burden report from *The Lancet*.[14] It is also the second leading disease affecting disability-adjusted life years (DALYs) throughout the world and is the chief disease affecting DALYs in China.[15] The stroke burden in China has increased over the past 30 years.[16] Ischaemic stroke, intracerebral haemorrhagic stroke and subarachnoid haemorrhagic stroke are the three primary subtypes of stroke.

High DTR may increase oxygen uptake, blood pressure and blood viscosity,[17–19] then trigger stroke events. A study in China found that stroke mortality was most sensitive to DTR compared with other cause-specific mortality.[9] Compared with stroke mortality, stroke morbidity can reflect the early stage of the disease, especially for first-ever strokes. About 77% of strokes are first events each year in the USA;[20] the average age of people in America and England who have a stroke for the first time has fallen over the past decade.[21 22] Therefore, primary prevention of first-ever strokes is of immense public health importance. At present, the effects of DTR on first-ever strokes in different seasons and the relevant sensitivity populations are not clear.

In this study, we studied the influence of DTR on first-ever strokes and the relevant sensitive populations in different seasons based on 12-year first-ever stroke data from 2005 to 2016. We conducted our analysis based on the framework of attributable risk assessment within distributed lag non-linear models (dlnms).

MATERIALS AND METHODS

Study area

Shenzhen is one of the most developed cities in China. It's a coastal city located in southern China, with a subtropical oceanic monsoon climate. The annual average temperature was 23.2°C during 2005–2016, while the yearly average DTR was 6.0°C, with the highest average DTR in the winter. A map showing the spatial distribution of Shenzhen in China, and the hospitals included in this study can be found in online supplemental figure S1.

Data collection

Stroke data were collected from the Shenzhen Centre for Chronic Disease Control, derived from 69 hospitals in 10 administrative districts, and the time range is from 1 January 2005 to 31 December 2016. Every stroke case in this study had been diagnosed by a doctor in the hospital; first-ever strokes were in those who did not have a history of previous strokes on medical charts and the registration system.[23 24] For detailed descriptions of these data, please refer to our previously published papers.[25 26] The stroke data were anonymised before access. Due to confidentiality requirements, the data involved in this study are currently not publicly available.

All the first-ever strokes were coded according to the WHO's International Classification of Diseases, the 10th version (ICD-10), ranging from I60 to I64. In this study, all the first-ever strokes were classified into five types based on the ICD-10 code: (1) Subarachnoid haemorrhage, coded as I60; (2) Intracerebral haemorrhage (ICH), coded as I61; (3) Other non-traumatic intracranial haemorrhage, coded as I62; (4) Cerebral infarction (CBI), coded as I63; (5) Stroke, not specified as haemorrhage or infarction, coded as I64. We primarily focused on CBI and ICH in this study, representing ischaemic and haemorrhagic stroke, respectively, and accounting for 94.66% of all the strokes.

Daily meteorological data were obtained from the National Meteorological Data Sharing Platform (http://data.cma.cn/), including daily mean, maximum and minimum temperatures, mean relative humidity, atmospheric pressure and wind speed. Air pollution data during 2014–2016 were obtained from the National Urban Air Quality Real-time Publishing Platform (http://106.37.208.233:20035/).[27]

Statistical analysis

We applied dlnm combined with quasi-Poisson regression to examine non-linear and lagged effects of DTR on first-ever strokes in different seasons, after controlling for the potential covariates, such as temperature, relative humidity and long-term trend. The model is expressed as follows:

$$\begin{aligned} Log\left[E\left(Yt\right)\right] &= \alpha + \beta DTRt, l + NS\left(RHt, 3\right) + NS\left(Pret, 3\right) \\ &+ NS\left(Wint, 3\right) + NS\left(Tempt, 3\right) + \mathrm{NS}\left(\mathrm{Time}, 3 * 12\right) \\ &+ \lambda DOWt + \gamma Holidayt \end{aligned}$$

Where Y_t represents the observed daily number of first-ever strokes at day t, while $E\left(Y_t\right)$ represents the expected number of strokes at day t; $DTR_{t,l}$ is a cross-basis matrix assessing non-linear and lag effects of DTR on first-ever strokes over the current day (lag 0) to l days' lag; *NS* denotes a natural cubic spline, *RH* and *Pre* represent daily mean relative humidity and atmospheric pressure, and 3 degrees of freedom (df) were used for them; *Temp* denotes temperature, and we adopted a moving average of lag 0–14 days for daily mean temperature.[28] *Time* denotes long-term trends, and we adopted 3 df per year for each season in this study;[29 30] day of the week (*DOW*) and public holiday (*Holiday*) were included in the model as indicator variables. The choice of df for each variable was based on the Akaike information criterion for the quasi-Poisson models.[31]

We created a seasonal time series data set, with spring starting on 1 March, summer starting on 1 June, 1 September for fall and 1 December for winter.[6 32] We added an argument called 'group' in the cross-basis matrix in the analysis of each season, which broke the series at the end of each group and replaced the first rows up to the maximum lag of the cross-basis matrix in the following series with NA (vignette ('dlnmTS') in the package dlnm).

We estimated the risk of first-ever strokes attributable to high DTR based on an approach proposed by Gasparrini *et al*, by calculating the daily attributable strokes caused by DTR that were higher than the minimum-morbidity DTR, which was derived from the overall DTR-morbidity curve in each season, and the corresponding empirical CIs (eCIs) were calculated through Monte Carlo simulations.[3]

We performed subgroup analysis to identify the subpopulations sensitive to DTR and calculated the attributable strokes and fractions of attributable strokes caused by high DTR in each subgroup. We adopted the Cochran's Q test to test differences between subpopulations.[33] In this study, we mainly focused on various genders, age groups, education levels and stroke subtypes.

We carried out sensitivity analysis by changing df values for time trend and relative humidity, different temperature sets, and the lag days of DTR in the model, as well as adjusting the influence of air pollution using the available subset period (during 2014–2016). All statistical analyses were completed using R software (V.3.4.0), with the 'dlnm' package (V.2.3.2) to create dlnm. A two-tailed value of $p<0.05$ was considered statistically significant.

Patient and public involvement

This study is an ecological research and does not reveal any personal information. Therefore, patients or the public were not involved in the design, or conduct, or reporting, or dissemination of our research.

RESULTS

There was a total of 142569 first-ever strokes during 2005–2016 in Shenzhen, most of them occurring in men (60.8%), at a mean age of 60.4 (SD 32.6) years; most of them had education less than high school and most of them had CBI (73.2%) (table 1).

The hottest months in Shenzhen were from June to August (summer), while the coldest months were December, January and February (winter). DTR was the highest in December and January, and the lowest in June. The daily mean of first-ever strokes was 32.4 (SD 15.9) (figure 1, table 2).

Figure 2 shows the overall cumulative exposure-response association of DTR with first-ever strokes over a lag of 0–5 days. The risk increased with the rise of DTR after it was higher than 5.5°C in the summer and with the rise of DTR after it was higher than 8°C in the winter. The exposure-response relationships between DTR and first-ever strokes were not significant in the spring and autumn.

Figure 3 shows the distribution of relative risk (RR, 95% CI) for the 99th centile of DTR (compared with minimum-morbidity DTR) in different lag structures in the summer and winter. We can see that the effects of DTR mainly occurred within five lag days in the summer and winter.

Table 3 shows the estimated AF and the attributable number of first-ever strokes caused by high DTR in different subgroups. AFs were 3.65% (95% eCI 1.81% to 5.53%) and 2.42% (95% eCI 0.05% to 4.42%) for total first-ever strokes in the summer and winter, respectively. In

Table 1 Distribution of demographic characteristics and disease entities of patients who had a first-ever stroke

Variables	N	Percent (%)
Gender		
Male	86709	60.8
Female	55860	39.2
Age (years old)		
<40	11624	8.2
40–64	71493	50.1
≥65	59452	41.7
Education		
Primary and below	45805	32.1
Junior high school	56388	39.6
Senior high school and above	40376	28.3
Disease category		
CBI	104339	73.2
ICH	30656	21.5
SAH	5952	4.2
ONIH	1253	0.9
SNSHI	331	0.2

CBI, cerebral infarction; ICH, intracerebral haemorrhage; ONIH, other non-traumatic intracranial haemorrhage; SAH, subarachnoid haemorrhage; SNSHI, stroke, not specified as haemorrhage or infarction.

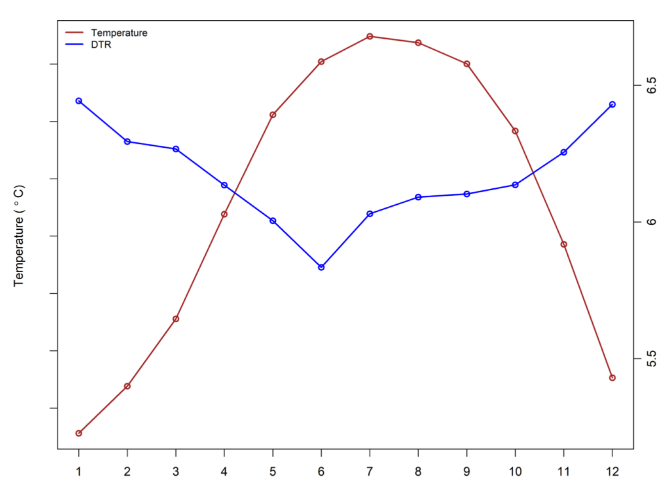

Figure 1 The distribution of monthly mean temperature and diurnal temperature range during 2005–2016. DTR, diurnal temperature range.

Table 2 Distribution of daily meteorological factors and daily counts of first-ever strokes during 2005–2016

Variable	Mean	SD	Min	25th centile	50th centile	75th centile	Max
DTR (°C)	6.0	1.9	1.2	4.6	6.0	7.3	14.0
Temperature (°C)	23.2	55.5	3.5	19.1	24.7	27.9	33.0
Humidity (%)	72.8	13.0	17.0	67.0	75.0	82.0	100.0
Air pressure (hPa)	1005.7	65.8	985.7	1000.8	1005.6	1010.5	1029.1
First strokes (n)	32.5	16.0	4.0	20.0	30.0	42.0	130.0

DTR, diurnal temperature range.

the summer, AF was significant in both genders, middle-aged and old patients, patients with different levels of education, as well as patients with CBI; in the winter, it was significant in middle-aged patients, patients with primary and lower education levels, as well as patients with CBI. AF in the summer was statistically higher than in the winter; in the summer, the differences in AF between different subgroups were not significant.

Sensitivity analyses showed that AFs for total first-ever strokes were generally similar using various dfs for time (2–6 df/year for the summer) and relative humidity (2–5 df), using various lag times in the model, as well as before and after adjusting for various air pollutants (see the online supplemental tables S1–S3), suggesting the robustness of our analysis.

DISCUSSION

Based on this data set, we have published two papers. We evaluated the effects of heat on first-ever strokes, the possible sensitive populations and the modification effect of atmospheric pressure on the heat-stroke relationship. We found that high temperatures in hot months may trigger first-ever strokes, and low atmospheric pressure may exacerbate the effect. Patients with CBI, middle-aged and old patients, as well as immigrant patients were the possible sensitive populations;[25] we also investigated the association between ambient air pollution and stroke morbidity in different subgroups and seasons and found that short-term exposure to fine particulate matter ($PM_{2.5}$), nitrogen dioxide (NO_2) and ozone (O_3) may induce stroke morbidity. Both men and women,

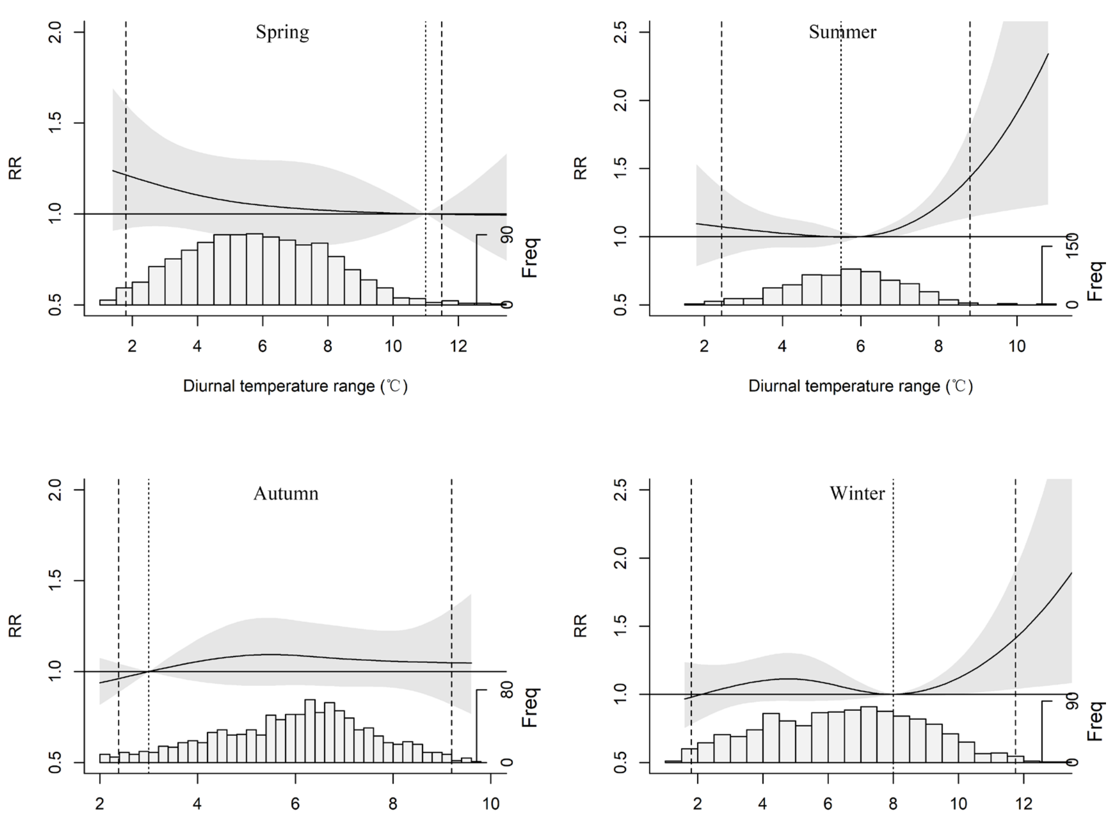

Figure 2 Overall cumulative exposure-response associations between DTR and first-ever strokes in four seasons. DTR, diurnal temperature range; RR, relative risk.

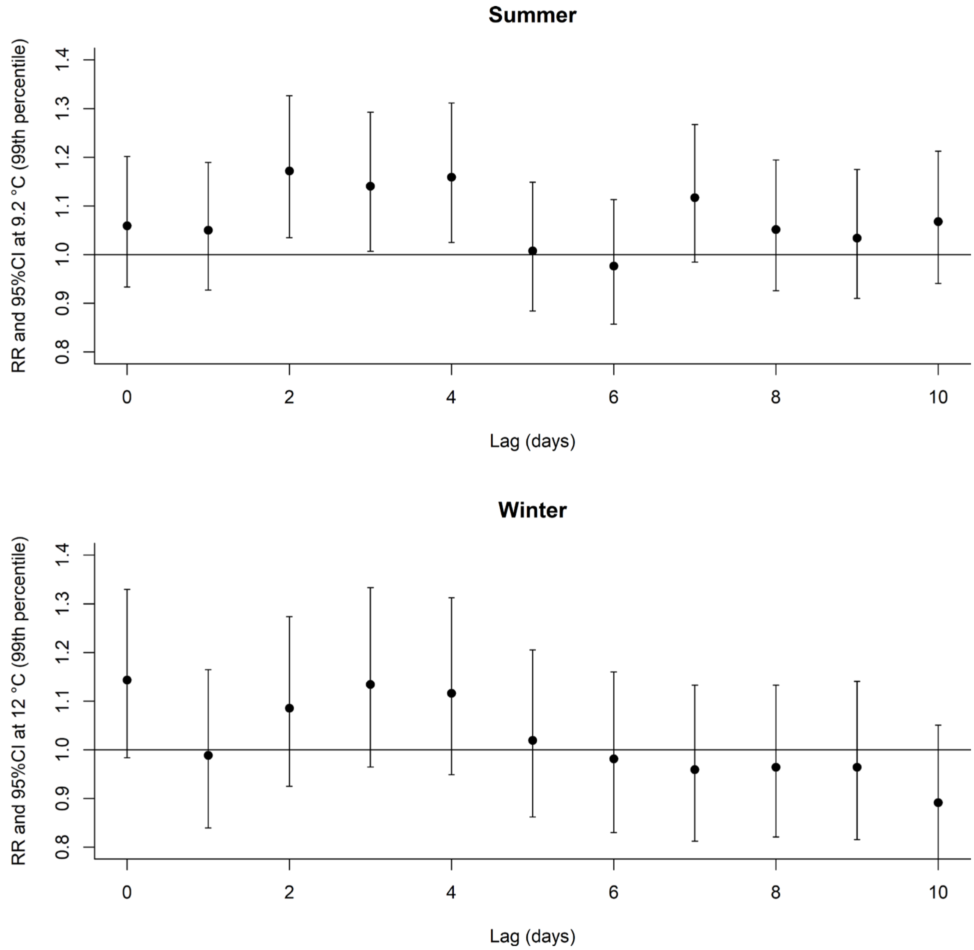

Figure 3 The distribution of RR (95% CI) for the 99th centile of DTR in the summer and winter using different lag structures. The RR was calculated between the 99th centile of DTR and minimum-morbidity DTR. DTR, diurnal temperature range; RR, relative risk.

middle-aged and older populations, and both CBI and ICH were sensitive to air pollution. As for seasonal analyses, statistically significant associations were found only in the winter.[26]

There are many ecological studies on the effects of extreme temperatures, such as heat and cold, and air pollution on population mortality and morbidity. On the other hand, the impact of temperature variability in different seasons, such as DTR, on the onset of first-ever strokes is still unclear. Therefore, we carried out this research further. We found a significant non-linear association between DTR and first-ever strokes in the summer and winter. High DTR accounted for 3.65% (95% eCI 1.81% to 5.53%) and 2.42% (95% eCI 0.05% to 4.42%) of first-ever strokes in the summer and winter, respectively, with its effects mainly lasting within 5 days of lag. Male and female patients, patients with different levels of education, middle-aged and old patients, as well as patients with CBI were sensitive to high DTR in the summer; middle-aged patients, patients with primary and lower education levels, as well as patients with CBI were sensitive to high DTR in the winter. Our findings can provide useful references for government managers and sensitive populations.

Our findings on the relationship between DTR and increased stroke risk were in agreement with some previous studies, although most of these studies focused on stroke mortality.[6 7 10 34 35] Zhou *et al* found that a 1°C increment of DTR could result in 0.42% (95% CI, 0.14% to 0.70%), 0.45% (0.26%–0.65%) and 0.76% (0.24%–1.29%) increases in total non-accidental mortality, cardiovascular mortality and respiratory mortality in cool seasons, respectively.[35] Yang *et al* found that a 1°C increment of DTR corresponded to 0.66% (95% CI 0.28% to 1.05%), 0.12% (95% CI −0.2 to 0.51%) and 0.67% (95% CI 0.26% to 1.07%) increases in stroke mortality during the total, hot and cold days, respectively; the adverse health effects of DTR on stroke mortality were more serious in southern China than in northern China.[34] We found a non-linear exposure-response relationship between DTR and first-ever strokes in this study. We also calculated the attributable stroke risk due to high DTR, which could serve as a useful reference for the identification and planning of public health interventions.[3 36]

Several possible mechanisms may underlie DTR-related effects on first-ever strokes. High DTR may trigger atherothrombotic events and may cause vasoconstriction or spasm, as well as changes in platelet viscosity, blood

Table 3 The distribution of DTR-related attributable fraction (AF) (%, 95% eCI) and attributable number (AN) (95% eCI) in various subgroups of first-ever stroke in the summer and winter

	Summer		Winter	
Variables	**AF (%, 95% eCI)**	**AN (95% eCI)**	**AF (%, 95% eCI)**	**AN (95% eCI)**
Total stroke	3.65* (1.81 to 5.53)	1276 (622 to 1880)	2.42 (0.05 to 4.42)	823 (–80 to 1529)
Gender				
Male	3.90 (1.81 to 5.71)	832 (420 to 1227)	1.85 (–0.89 to 4.18)	384 (–121 to 866)
Female	3.23 (0.73 to 5.45)	438 (103 to 750)	2.63 (–0.41 to 5.34)	353 (–44 to 688)
Age (years)				
<40	1.79 (–2.40 to 5.46)	52 (–74 to 159)	1.85 (–3.40 to 6.34)	48 (–76 to 162)
40–64	3.59 (1.66 to 5.45)	636 (260 to 972)	2.74 (0.31 to 4.75)	460 (49 to 854)
≥65	4.06 (1.56 to 6.52)	581 (228 to 899)	1.56 (–1.64 to 4.33)	230 (–224 to 636)
Education				
Primary and below	4.13 (1.32 to 6.66)	473 (173 to 755)	4.07 (1.22 to 6.70)	451 (114 to 757)
Junior high school	4.26 (1.78 to 6.55)	578 (239 to 900)	2.17 (–1.10 to 4.77)	299 (–119 to 675)
Senior high school and above	2.42 (0.13 to 4.52)	240 (9 to 446)	0.11 (–2.63 to 2.75)	10 (–262 to 256)
Disease category				
CBI	4.27 (2.26 to 6.10)	1127 (570 to 1616)	2.63 (0.08 to 5.08)	630 (–28 to 1232)
ICH	1.47 (-1.50 to 3.99)	99 (-90 to 283)	1.15 (–2.05 to 3.96)	96 (-164 to 328)

*p<0.01, the differences of AF between subpopulations were tested by the Cochran's Q test.
CBI, cerebral infarction; DTR, diurnal temperature range; eCI, empirical CI; ICH, intracerebral haemorrhage.

pressure, blood cholesterol levels and plasma fibrinogen concentrations;[13 18] these factors may lead to intracerebral thrombosis, local blood circulation disorders, cerebral ischaemia and hypoxia, and cerebral vascular rupture, eventually leading to CBI or cerebral haemorrhage. In addition, high DTR can also increase the levels of catecholamines and fibrinolytic parameters in the blood, thereby stimulating the sympathetic nervous system and causing strokes.[37]

The reason for the lag effect of DTR on stroke morbidity is not clear, especially from a physiopathological perspective. The possible reason could be: when there is a significant change in ambient temperature, it induces formation of or changes in some of the high-risk factors of stroke mentioned above, such as the formation of thrombus and changes in blood viscosity. These processes require a certain amount of time. It may also take a certain amount of time for the onset of stroke induced by these high-risk factors, eventually leading to a specific lag time from the occurrence of temperature variability to the onset of stroke.

We found that the adverse health effects of high DTR mainly occurred in the summer and winter months. A study in England and Wales found that high DTR exhibited a greater influence in hot seasons,[7] and a study in Korea found that adverse effects were mainly in the autumn and summer.[6] On the other hand, based on a data set of eight Chinese cities, Zhou *et al* found that the adverse health effects of DTR were greater in the cool season.[35] A possible explanation was that the temperatures in the summer and winter were very hot or cold, and relatively large temperature changes easily exceed the human body's temperature regulation ability, eventually triggering strokes. In this study, we found that AF in the summer was higher than in the winter. Similarly, Lee *et al*[13] found that the DTR during extreme hot days was more likely to induce adverse health effects, than other temperature strata. Therefore, in the context of global warming, the risk of DTR on stroke may increase.

We found that high DTR was harmful to most subgroups in the summer while it was harmful to middle-aged and low-education populations in the winter. A study in Shanghai and Guangzhou found that the harmful effects of DTR were greater in the elderly.[9 38] In comparison, a study in Korea observed greater adverse effects for the elderly only in three cities and greater effects for relatively younger people in three other cities.[6] The ability to regulate body temperature is lower in the elderly, and their sweating thresholds are generally elevated;[39 40] therefore, they are more sensitive to changes in temperature. In addition, compared with the retired elderly population, the middle-aged population needs to go to work; they are more likely to be exposed to adverse outdoor meteorological conditions, and their self-protection awareness may not be as strong as the elderly. Therefore, they may be more susceptible to high DTR in the winter. Some relevant studies also found that people with low educational attainment were more susceptible to temperature changes.[6 9 34] Low education attainment has been regarded as an indicator of low socioeconomic status, and people with low education may also be less self-protective.

In our study, CBI appeared to be sensitive to DTR, while the effect of DTR on ICH was not significant. Some studies revealed that ischaemic stroke was more sensitive to heat,[30 41] while haemorrhagic stroke was more sensitive to cold.[42 43] Studies about the adverse effects of DTR on stroke subtypes are rare. Ding *et al* also found that the adverse effects of DTR were mainly related to ischaemic stroke compared with ICH,[44] but the underlying mechanism remained unclear. A possible explanation for this phenomenon is that high DTR may trigger atherothrombotic events and cause blockage of blood vessels in the brain,[18] eventually leads to CBI.

In this study, we found that the adverse effects of DTR mainly occurred around 2–4 days after the occurrence of high DTR in the summer, which meant that if timely intervention measures are taken when high DTR occurs, it is possible to reduce stroke morbidity; it is recommended that the values of DTR could be reported and emphasised in weather forecast services, together with the forecasts of heat and cold.

There are several limitations to this study. First, meteorological data adopted in this study were extracted from one monitoring site rather than from individual exposure measures. The former was not accurate and may have led to measurement errors. Second, some socioeconomic factors, such as the use of air conditioners and the income of patients, may modify the relationship between DTR and first-ever strokes, but we did not include these factors because of the difficulties in data acquisition. The possible confounding effect of influenza epidemics was also not considered due to the difficulty of data acquisition. Finally, this study is an ecological research, so our findings cannot prove causality.

CONCLUSIONS

High DTR was an independent risk factor for first-ever strokes in addition to temperature extremes, especially in the summer and winter. Most people are sensitive to high DTR in the summer, while middle-aged and low-education populations are sensitive in the winter; CBI is more sensitive to DTR compared with ICH. The government should take action to address the health threats of DTR against the backdrop of global warming, and sensitive people should be taken care of first.

Author affiliations
[1]Department of Non-Communicable Disease Control and Prevention, Shenzhen Center for Chronic Disease Control, Shenzhen, Guangdong, China
[2]College of Public Health, Zhengzhou University, Zhengzhou, Henan, China
[3]School of Public Health, Sun Yat-Sen University, Guangzhou, Guangdong, China
[4]Department of Non-Communicable Disease Control and Prevention, Bao'an District Hospital for Chronic Diseases Prevention and Cure, Shenzhen, Guangdong, China
[5]Shanghai Typhoon Institute, China Meteorological Administration, Shanghai, China
[6]Shanghai Key Laboratory of Meteorology and Health, Shanghai Meteorological Service, Shanghai, China

Contributors The study was conceived and designed by JB and CH; LL and JB conducted statistical analysis and drafted the manuscript; JP, LL and YG contributed to data collection and processing; JB and QW helped in study management and the interpretation of the results; JP and CH reviewed the manuscript for important intellectual content; all authors read and approved the final version.

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Competing interests None declared.

Patient consent for publication Not required.

Ethics approval The institutional review board at the School of Public Health, Sun Yat-sen University, approved the study protocol (number 2019-029) with a waiver of informed consent. Data were analysed at the aggregate level. All patients were anonymous, and no patient's privacy was revealed.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement No data are available. Due to confidentiality requirements, the data involved in this study are currently not publicly available.

ORCID iD
Junzhe Bao http://orcid.org/0000-0002-8165-1838

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