



Contents lists available at ScienceDirect

Environmental Pollution

journal homepage: www.elsevier.com/locate/envpol

The cold effect of ambient temperature on ischemic and hemorrhagic stroke hospital admissions: A large database study in Beijing, China between years 2013 and 2014—Utilizing a distributed lag non-linear analysis[☆]



Yanxia Luo^{a, b, 1}, Haibin Li^{a, b, 1}, Fangfang Huang^{a, c, 1}, Nicholas Van Halm-Lutterodt^d, Qin Xu^{a, b}, Anxin Wang^{a, b}, Jin Guo^e, Lixin Tao^{a, b}, Xia Li^f, Mengyang Liu^{a, b}, Deqiang Zheng^{a, b}, Sipeng Chen^{a, b}, Feng Zhang^{a, b}, Xinghua Yang^{a, b}, Peng Tan^g, Wei Wang^h, Xueqin Xie^g, Xiuhua Guo^{a, b, *}

^a Department of Epidemiology and Health Statistics, School of Public Health, Capital Medical University, Beijing, China

^b Beijing Municipal Key Laboratory of Clinical Epidemiology, Capital Medical University, Beijing, China

^c Medical School, Henan University of Science and Technology, China

^d Department of Neurosurgery, Beijing Tiantan Hospital, Capital Medical University Beijing, China

^e Greenwood Medical Company, Australia

^f Department of Mathematics and Statistics, La Trobe University, Australia

^g Beijing Public Health Information Center, Beijing, China

^h Global Health and Genomics, School of Medical Sciences and Health, Edith Cowan University, Joondalup WA6027, Australia

ARTICLE INFO

Article history:

Received 31 March 2017

Received in revised form

2 August 2017

Accepted 7 September 2017

Available online 21 September 2017

Keywords:

Stroke

Hospital admissions

Ambient temperature

Attributable fraction

ABSTRACT

The effects of ambient temperature on stroke death in China have been well addressed. However, few studies are focused on the attributable burden for the incident of different types of stroke due to ambient temperature, especially in Beijing, China. We purpose to assess the influence of ambient temperature on hospital stroke admissions in Beijing, China. Data on daily temperature, air pollution, and relative humidity measurements and stroke admissions in Beijing were obtained between 2013 and 2014. Distributed lag non-linear model was employed to determine the association between daily ambient temperature and stroke admissions. Relative risk (RR) with 95% confidence interval (CI) and Attribution fraction (AF) with 95% CI were calculated based on stroke subtype, gender and age group. A total number of 147, 624 stroke admitted cases (including hemorrhagic and ischemic types of stroke) were documented. A non-linear acute effect of cold temperature on ischemic and hemorrhagic stroke hospital admissions was evaluated. Compared with the 25th percentile of temperature (1.2 °C), the cumulative RR of extreme cold temperature (first percentile of temperature, −9.6 °C) was 1.51 (95% CI: 1.08–2.10) over lag 0–14 days for ischemic type and 1.28 (95% CI: 1.03–1.59) for hemorrhagic stroke over lag 0–3 days. Overall, 1.57% (95% CI: 0.06%–2.88%) of ischemic stroke and 1.90% (95% CI: 0.40%–3.41%) of hemorrhagic stroke was attributed to the extreme cold temperature over lag 0–7 days and lag 0–3 days, respectively. The cold temperature's impact on stroke admissions was found to be more obvious in male gender and the youth compared to female gender and the elderly. Exposure to extreme cold temperature is associated with increasing both ischemic and hemorrhagic stroke admissions in Beijing, China.

© 2017 Elsevier Ltd. All rights reserved.

1. Introduction

Over the past two decades, stroke has gained public health concern on a global scale (Feigin et al., 2016). Stroke incidence varies by races and countries, especially in economically low income and developing countries (Carandang et al., 2006; Tsai et al.,

[☆] This paper has been recommended for acceptance by David Carpenter.

* Corresponding author. School of Public Health, Capital Medical University, No.10 Xitoutiao, You'anmen Wai, Fengtai District, Beijing 100069, China.

E-mail address: statguo@ccmu.edu.cn (X. Guo).

¹ Yanxia Luo, Haibin Li and Fangfang Huang contributed equally to this study.

2013; Wu et al., 2013; Zhang et al., 2012). According to the Global Burden of Disease Study in 2013, more than 90% of the stroke burden is attributable to the modifiable risk factors, including adopted lifestyle as well as low physical activity and metabolic status (Feigin et al., 2016). It is a remarkable fact that environmental conditions and meteorological factors, particularly ambient temperature and air pollution have significantly and affectedly shifted the global stroke burden, currently accounting for approximately 29.2% (Feigin et al., 2016).

Despite the consistent evidence of extreme weather conditions associated with an increased risk of cardiovascular diseases (Phung et al., 2016) and respiratory diseases (Lavigne et al., 2014), previously reported studies have demonstrated conflicting results on the correlation of ambient temperature and the incidence of stroke (Cevik et al., 2015; Jeong et al., 2013). Several published works suggest that a decline in ambient temperature is evidently linked with a higher susceptibility to ischemic stroke (Cevik et al., 2015; Hong et al., 2003; Mostofsky et al., 2014; Rakers et al., 2016). However, another research conducted in the United States about 6 years ago, reported no significant association between ambient temperature and any stroke subtype from 155 hospitals in 20 different States over a five-year study period (Cowperthwaite and Burnett, 2011). Furthermore, two recent meta-analyses have also concluded that a lower mean ambient temperature was significantly related to a higher risk of stroke incidence (Wang et al., 2016; Zorrilla-Vaca et al., 2016). Nevertheless, the meta-analyses by Wang et al. (2016) which included three studies from Taiwan (Chen et al., 1995; Fang et al., 2012; Lee et al., 2008) and one study from Hong Kong (Goggins et al., 2012). The other meta-analyses by Zorrilla-Vaca et al. (2016) only entailed one study from Taiwan (Chen et al., 1995) and one study from Shanghai, China (Meng et al., 2015). Therefore, suggesting that a reproducible large population-based and high quality evidence study from Beijing, China is certainly lacking.

The relationship between ambient temperature and stroke mortality has been reported in different areas of China (Chen et al., 2013b; Yang et al., 2012; Yang et al., 2016). However, the effect of ambient temperature on hospital stroke admissions is rarely addressed and inadequately accounted for. Recently, Guo et al. (2016) found that cold temperature is attributed to stroke hospital admission in Guangzhou, China. Comparably, ambient temperature in Beijing (North) is much lower than observed in Guangzhou (South), China (Chen et al., 2013b). Additionally, the effect of ambient temperature on stroke may differ by the stroke subtype (Ding et al., 2016). For instance, one study reported that a higher temperature was more detrimental to ischemic stroke than to hemorrhagic stroke (Lim et al., 2013), while another study reported a conflicting result (Guo et al., 2016). It is therefore critically important to investigate the relationship between ambient temperature and hospital admissions for different stroke subtypes.

The impacts of ambient temperature on hospital stroke admissions in Beijing, China, between 2013 and 2014 were investigated using distributed lag non-linear models (DLNMs) (Gasparrini et al., 2010; Gasparrini and Leone, 2014), and whether the associations differed by gender, age group and the stroke subtype were explored in this large population-based study.

2. Method

2.1. Study setting

Beijing, the capital of China, is an international metropolis with a population of over 20 million. It is in the Northern China Plain (39°26' to 41°03' north latitude, 115°25' to 117°30' east longitude) with an estimated area of about 16410 km². Beijing belongs to a

somewhat humid continental monsoon climate with an average temperature of 11.6 °C within the study period.

2.2. Data collection

Daily meteorological data from 1 January 2013 to 31 December 2014 were collected from the Chinese Meteorological Bureau, which included daily mean temperature (°C) and relative humidity (%). Daily mean levels of particulate matter with an aerodynamic diameter <2.5 μm (PM_{2.5}) for the same period were collected from the Centre of City Environmental Protection Monitoring Website Platform of Beijing.

Daily count of stroke admissions from 1 January 2013 to 31 December 2014 was extracted from the databases maintained by the Beijing Public Health Information Center. These databases encompassed 63 hospitals in Beijing which are highly recognized and approved by the Chinese government to diagnose and treat cardiovascular and cerebrovascular related diseases. Stroke was defined according to the International Classification of Diseases 10th Revision (ICD-10). The count of stroke admissions by stroke subtype (ischemic stroke, ICD10: I63 and hemorrhagic stroke, ICD10: I60–61) were also documented. A flowchart showing how these counts of stroke admissions were composed of was in the Supplementary materials (Fig. S1).

This study's protocol was approved by the School of Public Health, Capital Medical University Institutional Review Board (IRB00009511). Informed consent from patients was not necessary since only aggregated data was used in this study.

2.3. Statistical analysis

Descriptive statistics was used to describe for the participant's characteristics including gender, age group, and stroke subtype in this study. Time-series line figure was utilized to evaluate the long-term trends and seasonal patterns of stroke admissions, weather variables and air pollution. A distributed lag non-linear model (DLNM) was applied to investigate the delayed and non-linear effects of temperature on stroke admissions, after controlling the potential co-variables. A "cross-basis" function was used to evaluate the two-dimensional relationship between different number of lag days and temperature change by DLNM (Gasparrini et al., 2010). Specifically, according to the previous studies (Gasparrini and Leone, 2014), a natural cubic spline with three degrees of freedom (*df*) for the lag dimension and four *df* for the temperature change dimension were utilized in the "cross-basis" function. As from the prior knowledge, the impact of cold temperature on stroke mortality and emergency hospitalization could last for two or three weeks, however, the effect of hot temperature was shorter (Gasparrini et al., 2015b; Tian et al., 2016). Because the hot effects of temperature cannot be assessed by the short lags adequately due to the harvesting effects (Guo et al., 2011; Lavigne et al., 2014). The maximum lag period was chosen to 21 days to adequately capture the long-term delay effect of cold temperature effect and hot effect while also taking harvesting effect into account (Guo et al., 2014; Yang et al., 2015, 2016). A quasi-likelihood Poisson generalized additive model was used to model the natural logarithm of everyday stroke admission counts as functions of predictors, and is displayed as follows:

$$\begin{aligned} \text{Log}[E(Y_t)] = & \alpha + \beta_1 \times \text{Temp}_{t,l} + ns(t, df = 7 \times 2) \\ & + ns(RH_t, df = 3) + \beta_2 \times PM_{2.5(t)} + \beta_3 \times DOW_t \\ & + \beta_4 \times \text{Holiday}_t \end{aligned}$$

Here, $E(Y_t)$ is the expected daily counts of stroke hospital admission

at calendar day t ($t = 1, 2, \dots, 730$); α is the intercept and $\beta_1, \beta_2, \beta_3, \beta_4$ is the regression coefficient. $Temp_{t,l}$ is the “cross-basis” function in DLNM, where a natural cubic spline was used with 3 internal knots placed at an equal space in the temperature range for considering the nonlinear relationship of temperature (Gasparrini and Leone, 2014) and lag effect from lag 0 (current day) to lag l days, where the maximum of l was 21 days (Guo et al., 2014). $Ns(\cdot)$ is a natural cubic spline; we used 7 degrees of freedom (df) per year for time to control for the long term and seasonality (Bhaskaran et al., 2013); 3 df was used for relative humidity (RH) (Bhaskaran et al., 2013). $PM_{2.5}$ was controlled for air pollutant as a linear relationship in the model, as previous studies have labeled them as potential confounders (Huang et al., 2016; Yang et al., 2016). Day of the week (DOW) and Holiday were also included in the model as a categorical variable (Yang et al., 2016).

We plotted flexibly the exposure-lag-response relationships along temperature with stroke hospital admission over lags 0–14 days and a reference temperature of 13 °C (which was approximately the median value during the study period) was chosen. The impacts of extreme temperatures on stroke admissions in different day lag structures were explored. The relative risks (RR) [95% confidence interval (CI)] for stroke admissions at extreme cold (defined as the first percentiles of temperature distribution) and moderate cold (defined as the 10th percentiles) temperature, extreme hot (defined as the 99th percentiles) and moderate hot (defined as the 90th percentiles) temperature were reported, which were compared with the 25th and the 75th percentiles of temperature respectively. The selection of the cutoffs above for calculating the RR were based on those from the previously reported studies (Chen et al., 2013a), and the RR (95% CI) over different lag periods including 0–3, 0–7, 0–14, and 0–21 days were calculated.

To explore the burden of stroke admissions in regard to temperature, fractions of the hospital admissions attributed to hot and cold temperatures were evaluated below or above the reference temperature quartiles (75th and 25th percentiles of temperature distribution respectively). The definitions of extreme and moderate temperature conditions were the same as described before. These reference confinements were driven by the multi-geographic study conducted by Gasparrini and colleagues (Gasparrini et al., 2015a). In the current analysis, a backward method was chosen to calculate the over-all attributable fraction (AF) to the specific temperature exposure (Gasparrini et al., 2015a; Gasparrini and Leone, 2014). Equations of algebra were provided elsewhere, and monte carlo simulations were utilized to acquire the empirical confidence intervals (eCI) (Gasparrini and Leone, 2014).

Subgroup analyses were carried out to examine whether the relationships of temperature and stroke admissions differed by sex (man vs. women) and age group (>65 years old vs. ≤ 65 years old). The df of calendar time is crucial for the DLNM model. Sensitivity analyses were performed by changing the degrees of freedom, which range from 4 to 14 per year. The Akaike Information Criterion (AIC) was used to choose the df of smooth function of calendar time. Additionally, considering the impact of temperature differed by the type of hemorrhagic stroke, the relationship between temperature and subarachnoid hemorrhage (I60, SAH) as well as intracerebral hemorrhage (I61, ICH) were re-modelled.

All the statistical tests were two-tailed and a $P < 0.05$ was considered statistically significant. The “dlnm” package in R software (R Foundation for Statistical Computing, Vienna, Austria, and Version 3.2.3) was used to fit DLNM.

3. Results

In total, there were approximately 147,624 stroke admissions between the years 2013 and 2014 (Table S1, Fig. S1). The mean age

of study population was 68.2 ± 12.8 year. On an average, there were 205.1 stroke hospital admissions per day, of which 181.7 were IS and 23.4 were HS (Table 1). The daily mean temperature ranged from -12.9 °C to 30.1 °C with an average 11.6 °C. The means and (standard deviations, SD) of relative humidity and $PM_{2.5}$ were 56.0 (17.1) %, and 90.4 (65.8) $\mu\text{g}/\text{m}^3$, respectively. The time series of daily stroke admissions, weather factors and air pollution in Beijing was displayed in the Supplementary materials (Fig. S2). Seasonal patterns were observed for hemorrhagic stroke admissions, temperature, relative humidity and $PM_{2.5}$. There was a winter peak in hospital admissions for hemorrhagic stroke, rather than ischemic stroke.

An overall picture of the impacts of temperature on hospitalizations for ischemic and hemorrhagic stroke along 21-day lag was presented in Fig. 1, showing a 3-D plot of the RRs based on daily temperatures and lag days with the reference of 13 °C. A visual inspection of the figure clearly suggested the instance of immediate harmful effect and harvesting effect of high temperature on ischemic stroke, and subsequently harmful effect. However, for hemorrhagic stroke, an immediate protective effect of high temperature was observed. The maximum harmful effect of low temperature on ischemic stroke and hemorrhagic stroke were reached approximately at lag 7–8 and the concurrent day, respectively, and further declined over succeeding days.

The RRs of daily hospital admissions for ischemic and hemorrhagic stroke by temperature for specific lag structures (0, 7, 14, and 21 days) and by lag structures for specific temperatures (-9.6 , -4.2 , 25.7 , and 28.4 °C), corresponding approximately to the first, 10th, 90th and 99th percentiles of temperature distribution (termed as; moderate and extreme cold and hot) were shown in Fig. S3 and Fig. S4. There was a significant delayed harmful effect of extreme cold temperature on ischemic stroke at lag 7 day and immediate harmful on hemorrhagic stroke at lag 0 day ($P < 0.05$). The impacts of moderate cold, moderate hot and extreme hot temperatures on both ischemic and hemorrhagic stroke were not statistically significant ($P > 0.05$).

Table 2 provides the cumulative impacts of cold and hot temperatures on hospital admissions for ischemic stroke and hemorrhagic stroke at different amounts of lag, compared with the reference values respectively. For ischemic stroke, the effects of extreme cold temperature heightened along with the lag days increasing. At lags 0–14 days, the RR was 1.51 (95% CI: 1.08 to 2.10) for extreme cold temperatures compared to the 25th percentile of temperature (1.2 °C). For hemorrhagic stroke, the statistically significant adverse effects of cold temperatures were only found with extreme cold (RR: 1.28, 95% CI: 1.03 to 1.59) and moderate cold (RR: 1.08, 95% CI: 1.01 to 1.16) temperatures at lag 0–3 days compared to the 25th percentile of temperature (1.2 °C), which were more immediate. Table 2 also shows that hot temperatures were positively correlated with hospital admissions for ischemic stroke, whereas negatively correlated with hemorrhagic stroke. However, the effects were statistically insignificant ($P > 0.05$).

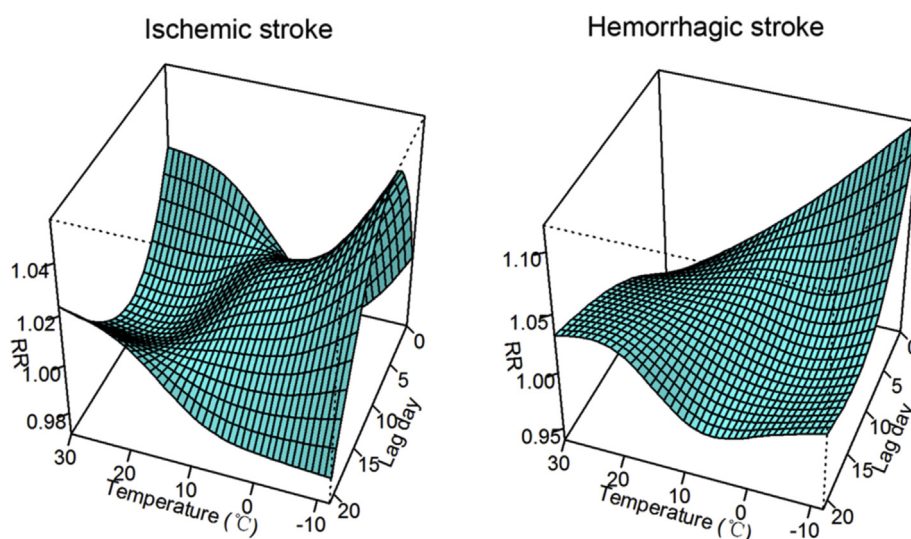
Table 3 reports the stroke admission fraction attributable to temperature with 95% CI by separating the components into contributions from moderate and extreme temperatures. For ischemic stroke, 1.57% (95% CI: 0.06%–2.88%) hospital admissions were attributable to extreme cold temperature at lag 0–7 days compared to the 25th percentile of temperature (1.2 °C). For hemorrhagic stroke, the contributions from extreme and moderate cold temperatures accounted for 1.90% (95% CI: 0.40%–3.41%) and 0.69% (95% CI: 0.03%–1.37%) at lag 0–3 days compared to the 25th percentile of temperature (1.2 °C), respectively.

Table 4 shows the RR of cold and hot temperatures for ischemic stroke admissions stratified by gender and age over lag 0–7 days and for hemorrhagic stroke over lag 0–3 days. For ischemic stroke,

Table 1Descriptive statistics of daily stroke admissions, temperature, relative humidity and PM_{2.5} during 2013–2014 in Beijing, China.

Variables	No. of Days	Mean	SD	Min	P1	P10	P25	P50	P75	P90	P99	Max
Stroke (count)	730	205.1	62.8	81.0	93.0	116.2	142.0	212.0	255.0	280.9	330.8	375.0
IS	730	181.7	57.8	59.0	79.3	101.0	122.0	188.0	227.0	252.0	294.0	344.0
HS	730	23.4	7.8	4.0	7.3	13.1	18.0	23.0	28.0	34.0	43.0	48.0
Men	730	125.7	40.1	42.0	54.0	70.0	87.0	128.5	157.0	174.0	206.0	225.0
Women	730	79.4	24.5	28.0	33.0	46.0	56.0	82.0	98.0	109.0	130.7	150.0
>65 years	730	119.2	37.9	41.0	49.6	66.0	80.0	126.0	149.0	164.9	195.4	215.0
≤65 years	730	85.8	26.7	27.0	37.0	50.0	62.8	85.0	106.0	121.0	144.0	179.0
T (°C)	730	11.6	11.4	-12.9	-9.7	-4.2	1.2	13.3	22.1	25.7	28.4	30.1
RH (%)	730	56.0	17.1	17.4	20.0	33.0	42.9	56.0	69.8	79.0	88.6	93.5
PM _{2.5} (μg/m ³)	689	90.4	65.8	6.7	8.8	24.0	44.3	76.1	116.6	171.9	326.7	482.8

IS, ischemic stroke; HS, hemorrhagic stroke; T, temperature; RH, relative humidity; PM_{2.5}, particulate matter that is 2.5 μm or less in diameter; SD, standard deviation; Min, minimum value; P1–P99, 1st–99th percentile; Max, maximum value.

**Fig. 1.** Three-dimensional plot of relative risk along temperatures and lag days, with reference at 13 °C.**Table 2**

Relative risks and their 95% confidence intervals of moderate and extreme cold and hot temperatures on stroke admissions over multiple lag days.

Variable	Lag	Extreme cold ^a	Moderate cold ^b	Moderate hot ^c	Extreme hot ^d
		(-9.6 °C)	(-4.2 °C)	(25.7 °C)	(28.4 °C)
IS	0–3	1.26 (1.04–1.52)	1.04 (0.97–1.11)	1.01 (0.94–1.10)	1.03 (0.91–1.16)
	0–7	1.33 (1.05–1.68)	1.07 (0.99–1.16)	1.01 (0.92–1.10)	1.01 (0.88–1.17)
	0–14	1.51 (1.08–2.10)	1.11 (1.00–1.24)	1.01 (0.91–1.13)	1.03 (0.86–1.23)
HS	0–21	1.57 (1.00–2.46)	1.13 (0.97–1.32)	1.02 (0.90–1.16)	1.04 (0.85–1.27)
	0–3	1.28 (1.03–1.59)	1.08 (1.01–1.16)	0.95 (0.85–1.03)	0.91 (0.78–1.07)
	0–7	1.24 (0.95–1.63)	1.07 (0.98–1.17)	0.89 (0.79–1.00)	0.83 (0.69–1.00)
	0–14	1.36 (0.92–2.01)	1.09 (0.96–1.24)	0.92 (0.80–1.06)	0.88 (0.70–1.11)
	0–21	1.56 (0.92–2.64)	1.14 (0.95–1.37)	0.94 (0.80–1.11)	0.91 (0.70–1.18)

IS, ischemic stroke; HS, hemorrhagic stroke.

^a The first percentile of temperature (-9.6 °C) relative to the 25th percentile of temperature (1.2 °C).

^b The 10th percentile of temperature (-4.2 °C) relative to the 25th percentile of temperature (1.2 °C).

^c The 90th percentile of temperature (25.7 °C) relative to the 75th percentile of temperature (22.1 °C).

^d The 99th percentile of temperature (28.4 °C) relative to the 75th percentile of temperature (22.1 °C).

the adverse effects of cold temperatures seemed to be higher among male gender and the younger population aged ≤65 years compared with female gender and population aged >65 years. For instance, compared to the 25th percentile of temperature (1.2 °C), the RR of extreme cold temperature on ischemic stroke were 1.43 (95% CI: 1.12 to 1.82) for male population and 1.19 (95% CI: 0.92 to 1.53) for female population. The RR of extreme cold temperature on ischemic stroke for above 65 years and 65 years and younger subjects were 1.28 (95% CI: 0.99 to 1.64) and 1.41 (95% CI: 1.10 to

1.80), respectively. The effects of cold temperatures on hemorrhagic stroke admissions and hot temperatures on both ischemic and hemorrhagic stroke admissions were also higher among male population and ≤65 years compared to female population and those aged over 65 years. However, the estimates were not statistically significant ($P > 0.05$).

Sensitivity analyses were performed to check the robustness of the results. Statistically significant effects of extreme cold temperature on the risk for SAH and ICH were observed (Table S2). Using

Table 3
Backward attributable fraction (%) of stroke admissions due to temperatures, reported as components from moderate and extreme cold and hot contributions with 95% empirical confidence intervals.

Variable	Lag	Extreme cold ^a	Moderate cold ^b	Moderate hot ^c	Extreme hot ^d
		(-9.6 °C)	(-4.2 °C)	(25.7 °C)	(28.4 °C)
IS	0–3	0.86 (-0.59–2.03)	0.16 (-0.44–0.69)	0.16 (-0.48 – -0.71)	0.34 (-0.98–1.68)
	0–7	1.57 (0.06–2.88)	0.44 (-0.24–1.03)	0.04 (-0.59–0.69)	0.11 (-1.70–1.67)
	0–14	2.15 (-0.08–4.10)	0.67 (-0.16–1.51)	0.08 (-0.74–0.91)	0.26 (-1.75–2.25)
	0–21	2.39 (-0.13–4.96)	0.86 (-0.46–2.10)	0.14 (-0.81–0.96)	0.39 (-1.93–2.62)
HS	0–3	1.90 (0.40–3.41)	0.69 (0.03–1.37)	-0.47 (-1.14–0.12)	-1.02 (-2.62–0.41)
	0–7	1.68 (-0.21–3.37)	0.62 (-0.18–1.38)	-0.79 (-1.54–0.02)	-1.88 (-3.90–0.10)
	0–14	1.93 (-0.80–4.47)	0.71 (-0.42–1.89)	-0.57 (-1.49–0.29)	-1.34 (-3.82–0.88)
	0–21	2.82 (-0.99–6.27)	1.06 (-0.59–2.55)	-0.36 (-1.50–0.65)	-0.94 (-3.47–1.46)

IS, ischemic stroke; HS, hemorrhagic stroke.

^a The first percentile of temperature (-9.6 °C) relative to the 25th percentile of temperature (1.2 °C).

^b The 10th percentile of temperature (-4.2 °C) relative to the 25th percentile of temperature (1.2 °C).

^c The 90th percentile of temperature (25.7 °C) relative to the 75th percentile of temperature (22.1 °C).

^d The 99th percentile of temperature (28.4 °C) relative to the 75th percentile of temperature (22.1 °C).

Table 4
Relative risks and their 95% confidence intervals of moderate and extreme cold and hot temperatures on stroke admissions by gender and age.

Variable		Extreme cold ^a	Moderate cold ^b	Moderate hot ^c	Extreme hot ^d
		(-9.6 °C)	(-4.2 °C)	(25.7 °C)	(28.4 °C)
IS*	Male	1.43 (1.12–1.82)	1.10 (1.01–1.19)	1.02 (0.93–1.12)	1.04 (0.89–1.21)
	Female	1.19 (0.92–1.53)	1.04 (0.96–1.13)	0.98 (0.89–1.08)	0.97 (0.83–1.13)
	>65 years	1.28 (0.99–1.64)	1.06 (0.98–1.15)	1.02 (0.92–1.12)	1.03 (0.88–1.20)
	≤65 years	1.41 (1.10–1.80)	1.10 (1.02–1.19)	0.99 (0.90–1.09)	0.99 (0.85–1.15)
HS#	Male	1.27 (0.97–1.66)	1.08 (0.99–1.17)	0.97 (0.86–1.09)	0.95 (0.79–1.15)
	Female	1.29 (0.95–1.75)	1.09 (0.98–1.21)	0.91 (0.77–1.03)	0.84 (0.67–1.06)
	>65 years	1.28 (0.94–1.74)	1.07 (0.97–1.19)	0.97 (0.84–1.11)	0.96 (0.77–1.20)
	≤65 years	1.29 (0.99–1.67)	1.09 (1.00–1.18)	0.93 (0.80–1.02)	0.86 (0.71–1.04)

IS, ischemic stroke; HS, hemorrhagic stroke; *, at lag0–7 days; #, at lag0–3 days.

^a The first percentile of temperature (-9.6 °C) relative to the 25th percentile of temperature (1.2 °C).

^b The 10th percentile of temperature (-4.2 °C) relative to the 25th percentile of temperature (1.2 °C).

^c The 90th percentile of temperature (25.7 °C) relative to the 75th percentile of temperature (22.1 °C).

^d The 99th percentile of temperature (28.4 °C) relative to the 75th percentile of temperature (22.1 °C).

the 25th percentile of temperature (1.2 °C) as reference, the overall cumulative RRs over lag 0–14 days of extreme cold temperature were 3.14 (1.25–7.85) and 2.05 (1.28–3.29) for the two subtypes of stroke, respectively. The value of Akaike Information Criterion (AIC) with different *df* of smooth function of calendar time for ischemic stroke (IS) and hemorrhagic stroke (HS) was showed in Fig. S5. The seven *df* per year was acceptable and adequate for controlling seasonal trends.

4. Discussion

We explored the associations of ambient temperature and stroke admissions in Beijing, China, during years 2013 and 2014, using the novel framework within DLNMs. Our study found that cold temperature had a mild impact on the increased risk of both ischemic and hemorrhagic stroke admissions to hospitals in Beijing, the capital of China.

Several large studies have shown that extremes of temperature were strongly connected with higher all-cause and stroke death rates across different counties and cities with different climatic conditions (Gasparrini et al., 2015b; Phung et al., 2016; Wang et al., 2016; Yang et al., 2016). Our study found that cold temperature, rather than hot temperature, had a significant and positive correlation with stroke admissions in Beijing, which is consistent with previously reported studies conducted in Guangzhou (Guo et al., 2016), Jinan (Wang et al., 2013), Hong Kong (Goggins et al., 2012), Mozambique (Gomes et al., 2015) and United States (Cowperthwaite and Burnett, 2011).

In China, previous studies mostly focused on the association of daily temperature with stroke mortality. Chen et al. (2013b) found that both hot and cold daily temperature increased stroke death rates in 8 large cities from 1996 to 2008. While Yang et al. (2016) found that the pooled AF was 14.5 (95% CI: 11.5%–17.0%) for cold temperature to stroke mortality from 16 large cities between 2007 and 2013. There were few studies that explored the impact(s) of cold temperature on stroke incidence in China than other these. In Jinan city, cold temperature was reported may increase approximately 43% (RR: 1.43, 95% CI: 1.10–1.85) the risk of ischemic stroke occurrence (Wang et al., 2013). Similarly, in Guangzhou, the AFs of ischemic stroke and hemorrhagic stroke admissions for cold temperature were 9.06% (95% CI: 1.84%–15.00%) and 15.09% (95% CI: 5.86%–21.96%) respectively (Guo et al., 2016). Our results show that the AFs of cold temperature for ischemic stroke and hemorrhagic stroke admissions in Beijing were lower than Guangzhou, which may imply that different region and climatic conditions have different impacts on stroke admissions.

The AFs of stroke admission burden to hot and cold temperature were different. According to a previously reported study which encompassed multiple cities from China, 13.9% (95% CI: 6.9%–20.4%) of stroke mortality burden was attributed to cold temperatures, but only 2.0% (95% CI: 1.2%–2.9%) was due to hot temperatures in Beijing (Yang et al., 2016). In this current analyses, we evaluated for significant outcomes between extreme cold temperature with ischemic and hemorrhagic stroke admissions, rather than hot temperature. There are several potential explanations. Lower ambient temperature may induce oxygen demand and

vasoconstriction and decrease blood flow to the brain (Croughwell et al., 1992), which will consequently result in a rise in both systemic vascular resistance and blood pressure (Charkoudian, 2010) potentially resulting in ischemic and/or hemorrhagic stroke. Exposure to cold ambient temperature results in an increased blood platelet count, blood viscosity, heart rate, and C-reactive protein due to stress reaction, consequently increasing the incidence of stroke admissions (Wolf et al., 2009). Additionally, there have been several studies reporting that extremes of ambient temperature may increase the risk of all-cause (Gasparrini et al., 2015a), cardiovascular (Yang et al., 2015) and stroke mortality (Chen et al., 2013b). However, hot effect on stroke admissions was not observed in the study. Notably, the highest mean of a 24-h daily temperature recorded 31.1 °C in Beijing which might not have reached the threshold of an ill-related temperature. Besides, the association may be influenced by the other climatic conditions, air pollution, population sizes, and housing types.

Contrary to the previous studies (Fang et al., 2012; Guo et al., 2016; Wolf et al., 2009; Yang et al., 2016), we found that younger patients were more susceptible to cold temperature for ischemic stroke admissions. One possible explanation is that younger people are more likely to go outdoors, which increases their exposure to cold temperature. The modified effect by gender was controversial. We found that the impact of cold temperature was greater for men. Similar results were observed in previously reported studies (Bell et al., 2008; Yang et al., 2012). The temperature-related susceptibility by gender may contribute to differences in work nature and physiological tolerance (Yang et al., 2016).

Our results show that the lag structures of cold temperature were different for ischemic and hemorrhagic stroke admissions. The impacts of cold temperatures were set to one week. For the ischemic stroke admission, the maximum of lag days was at the seventh day and 1.57% (95% CI: 0.06%–2.88%) risks attributed to extreme cold temperature over lag 0–7 days. For the hemorrhagic stroke admission, the maximum of lag days was at the same day and 1.90% (95% CI: 0.40%–3.41%) risks attributed to extreme cold temperature over lag 0–3 days. The determination of the optimal lag structures of cold temperature effect can help people make an early response to deal with cold temperature, such as wearing more warm-clothing and decreasing outdoor activities. However, the reasons for shorter lag days of the cold effect remain unknown. Previous studies have demonstrated that the overall cumulative cold effect may continue over lag 0–4 days (Goggins et al., 2012), lag 0–21 days (Yang et al., 2016), lag 0–28 days (Chen et al., 2013a). It is substantially important to know that the shorter lags may fail to capture the potential harvesting effects of hot temperature (Yang et al., 2012) and the longer lags may overrate the cold effect due to the multi-collinearity and seasonal residuals (Kinney et al., 2015).

Our study has several strengths. We assessed the temperature attributable risk to both ischemic and hemorrhagic stroke admissions in a large population using a novel frame-distributed lag linear and non-linear models for assessed parameters in the capital of China. To the best of our knowledge, this is the first and premier study conducted in Beijing, focusing on both ischemic and hemorrhagic stroke admissions. Additionally, we utilized a relatively large sample size: 147,624 stroke admitted subjects only from 2013 to 2014. We also controlled the potential confounding factors, particularly air pollution in Beijing, which have been implicated to have a greater impact on stroke admissions (Yang et al., 2016).

Several limitations should be addressed in this study as well. Firstly, similar to previous other time-series studies, in our study, the ambient temperature obtained by outdoor monitoring sites was also used to represent individual exposure, which induced exposure measurement errors and lead exposure misclassification bias and resulted in a bias towards to the null. Secondly, our findings

extended to other cities should be caution, especially with different populations, geographic characteristics, climate conditions and air pollutant. Because our results were derived from this single-city study-Beijing, which not was generalized to the whole China. Third, the classification of hemorrhagic and ischemic stroke was according to ICD-10th, which could be not completely correct and coding errors may occur, which may cause misclassification and information biases, especially patients had several subtypes of stroke. Fourth, we could not identify the re-admissions for patients with the same stroke from the available data.

5. Conclusions

Our study substantially suggests that cold ambient temperature is positively correlated with both ischemic and hemorrhagic stroke admissions in Beijing, China. It also has a potentially strong public health and clinical significance to advise and curb hospital stroke admissions during extreme temperature conditions which is evidently proven by this large population-based study.

Funding sources

The study was supported by the Program of Beijing Municipal Science & Technology Commission (D141100000114003), the Key Projects in the National Science & Technology Pillar Program in the Twelfth Five-year Plan Period of China (2011BAI08B01), and the Program of Natural Science Fund of China (81530087). YG was supported by the Career Development Fellowship of Australian National Health and Medical Research Council (#APP1107107).

Disclosures

None.

Acknowledgments

We sincerely thank those who participated in data collection and management.

Appendix A. Supplementary data

Supplementary data related to this article can be found at <http://dx.doi.org/10.1016/j.envpol.2017.09.021>.

References

- Bell, M.L., O'Neill, M.S., Ranjit, N., Borja-Aburto, V.H., Cifuentes, L.A., Gouveia, N.C., 2008. Vulnerability to heat-related mortality in Latin America: a case-crossover study in Sao Paulo, Brazil, Santiago, Chile and Mexico city, Mexico. *Int. J. Epidemiol.* 37, 796–804.
- Bhaskaran, K., Gasparrini, A., Hajat, S., Smeeth, L., Armstrong, B., 2013. Time series regression studies in environmental epidemiology. *Int. J. Epidemiol.* 42, 1187–1195.
- Carandang, R., Seshadri, S., Beiser, A., Kelly-Hayes, M., Kase, C.S., Kannel, W.B., Wolf, P.A., 2006. Trends in incidence, lifetime risk, severity, and 30-day mortality of stroke over the past 50 years. *JAMA* 296, 2939–2946.
- Cevik, Y., Doğan, N.O., Daş, M., Ahmedali, A., Kul, S., Bayram, H., 2015. The association between weather conditions and stroke admissions in Turkey. *Int. J. Biometeorol.* 59, 1–7.
- Charkoudian, N., 2010. Mechanisms and modifiers of reflex induced cutaneous vasodilation and vasoconstriction in humans. *J. Appl. Physiol.* 109, 1221–1228, 1985.
- Chen, R., Wang, C., Meng, X., Chen, H., Thach, T.Q., Wong, C.M., Kan, H., 2013a. Both low and high temperature may increase the risk of stroke mortality. *Neurology* 81, 1064–1070.
- Chen, R.J., Wang, C.C., Meng, X., Chen, H.L., Thach, T.Q., Wong, C.M., Kan, H.D., 2013b. Both low and high temperature may increase the risk of stroke mortality. *Neurology* 81, 1064–1070.
- Chen, Z.Y., Chang, S.F., Su, C.L., 1995. Weather and stroke in a subtropical area: Ilan, Taiwan. *Stroke* 26, 569–572.

- Cowperthwaite, M.C., Burnett, M.G., 2011. An analysis of admissions from 155 United States hospitals to determine the influence of weather on stroke incidence. *J. Clin. Neurosci.* 18, 618–623.
- Croughwell, N., Smith, L.R., Quill, T., Newman, M., Greeley, W., Kern, F., Lu, J., Reeves, J.G., 1992. The effect of temperature on cerebral metabolism and blood-flow in adults during cardiopulmonary bypass. *J. Thorac. Cardiovasc. Surg.* 103, 549–554.
- Ding, Z., Li, L.J., Xin, L.Y., Pi, F.H., Dong, W.Y., Wen, Y., Au, W.W., Zhang, Q.Y., 2016. High diurnal temperature range and mortality: effect modification by individual characteristics and mortality causes in a case-only analysis. *Sci. Total Environ.* 544, 627–634.
- Fang, C.W., Ma, M.C., Lin, H.J., Chen, C.H., 2012. Ambient temperature and spontaneous intracerebral haemorrhage: a cross-sectional analysis in Tainan, Taiwan. *BMJ Open* 2.
- Feigin, V.L., Roth, G.A., Naghavi, M., Parmar, P., Krishnamurthi, R., Chugh, S., Mensah, G.A., Norrving, B., Shiuie, I., Ng, M., Estep, K., Cercy, K., Murray, C.J., Forouzanfar, M.H., Global Burden of Diseases, I., Risk Factors, S., Stroke Experts Writing, G., 2016. Global burden of stroke and risk factors in 188 countries, during 1990–2013: a systematic analysis for the Global Burden of Disease Study 2013. *Lancet Neurol.* 15, 913–924.
- Gasparrini, A., Armstrong, B., Kenward, M.G., 2010. Distributed lag non-linear models. *Stat. Med.* 29, 2224–2234.
- Gasparrini, A., Guo, Y., Hashizume, M., Lavigne, E., Zanobetti, A., Schwartz, J., Tobias, A., Tong, S., Rocklöv, J., Forsberg, B., Leone, M., De Sario, M., Bell, M.L., Guo, Y.L., Wu, C.F., Kan, H., Yi, S.M., de Sousa Zanotti Stagliorio Coelho, M., Saldiva, P.H., Honda, Y., Kim, H., Armstrong, B., 2015a. Mortality risk attributable to high and low ambient temperature: a multicountry observational study. *Lancet* 386, 369–375.
- Gasparrini, A., Guo, Y.M., Hashizume, M., Lavigne, E., Zanobetti, A., Schwartz, J., Tobias, A., Tong, S.L., Rocklöv, J., Forsberg, B., Leone, M., De Sario, M., Bell, M.L., Guo, Y.L.L., Wu, C.F., Kan, H., Yi, S.M., Coelho, M.D.Z.S., Saldiva, P.H.N., Honda, Y., Kim, H., Armstrong, B., 2015b. Mortality risk attributable to high and low ambient temperature: a multicountry observational study. *Lancet* 386, 369–375.
- Gasparrini, A., Leone, M., 2014. Attributable risk from distributed lag models. *BMC Med. Res. Methodol.* 14, 55.
- Goggins, W.B., Woo, J., Ho, S., Chan, E.Y., Chau, P.H., 2012. Weather, season, and daily stroke admissions in Hong Kong. *Int. J. Biometeorol.* 56, 865–872.
- Gomes, J., Damasceno, A., Carrilho, C., Lobo, V., Lopes, H., Madede, T., Pravinrai, P., Silva-Matos, C., Diogo, D., Azevedo, A., Lunet, N., 2015. Triggering of stroke by ambient temperature variation: a case-crossover study in Maputo, Mozambique. *Clin. Neurol. Neurosurg.* 129, 72–77.
- Guo, P., Zheng, M., Feng, W., Wu, J., Deng, C., Luo, G., Wang, L., Pan, B., Liu, H., 2016. Effects of ambient temperature on stroke hospital admissions: results from a time-series analysis of 104,432 strokes in Guangzhou, China. *Sci. Total Environ.* 580, 307–315.
- Guo, Y., Barnett, A.G., Pan, X., Yu, W., Tong, S., 2011. The impact of temperature on mortality in Tianjin, China: a case-crossover design with a distributed lag nonlinear model. *Environ. Health Perspect.* 119, 1719–1725.
- Guo, Y., Gasparrini, A., Armstrong, B., Li, S., Tawatsupa, B., Tobias, A., Lavigne, E., de Sousa Zanotti Stagliorio Coelho, M., Leone, M., Pan, X., Tong, S., Tian, L., Kim, H., Hashizume, M., Honda, Y., Guo, Y.L., Wu, C.F., Punnasiri, K., Yi, S.M., Michelozzi, P., Saldiva, P.H., Williams, G., 2014. Global variation in the effects of ambient temperature on mortality: a systematic evaluation. *Epidemiology* 25, 781–789.
- Hong, Y.C., Rha, J.H., Lee, J.T., Ha, E.H., Kwon, H.J., Kim, H., 2003. Ischemic stroke associated with decrease in temperature. *Epidemiology* 14, 473–478.
- Huang, F., Luo, Y., Guo, Y., Tao, L., Xu, Q., Wang, C., Wang, A., Li, X., Guo, J., Yan, A., Guo, X., 2016. Particulate matter and hospital admissions for stroke in Beijing, China: modification effects by ambient temperature. *J. Am. Heart Assoc.* 5.
- Jeong, T.S., Park, C.W., Yoo, C.J., Kim, E.Y., Kim, Y.B., Kim, W.K., 2013. Association between the daily temperature range and occurrence of spontaneous intracerebral hemorrhage. *J. Cerebrovasc. Endovasc. Neurosurg.* 15, 152–157.
- Kinney, P.L., Schwartz, J., Pascal, M., Petkova, E., Tertre, A.L., Medina, S., Vautard, R., 2015. Winter season mortality: will climate warming bring benefits? *Environ. Res. Lett.* 10, 064016.
- Lavigne, E., Gasparrini, A., Wang, X., Chen, H., Yagouti, A., Fleury, M.D., Cakmak, S., 2014. Extreme ambient temperatures and cardiorespiratory emergency room visits: assessing risk by comorbid health conditions in a time series study. *Environ. Health* 13, 5.
- Lee, H.C., Hu, C.J., Chen, C.S., Lin, H.C., 2008. Seasonal variation in ischemic stroke incidence and association with climate: a six-year population-based study. *Chronobiol. Int.* 25, 938–949.
- Lim, Y.H., Kim, H., Hong, Y.C., 2013. Variation in mortality of ischemic and hemorrhagic strokes in relation to high temperature. *Int. J. Biometeorol.* 57, 145–153.
- Meng, G., Tan, Y., Fang, M., Yang, H., Liu, X., Zhao, Y., 2015. Meteorological factors related to emergency admission of elderly stroke patients in Shanghai: analysis with a multilayer perceptron neural network. *Med. Sci. Monit.* 21, 3600–3607.
- Mostofsky, E., Wilker, E.H., Schwartz, J., Zanobetti, A., Gold, D.R., Wellenius, G.A., Mittleman, M.A., 2014. Short-term changes in ambient temperature and risk of ischemic stroke. *Cerebrovasc. Dis. Extra* 4, 9–18.
- Phung, D., Thai, P.K., Guo, Y., Morawska, L., Rutherford, S., Chu, C., 2016. Ambient temperature and risk of cardiovascular hospitalization: an updated systematic review and meta-analysis. *Sci. Total Environ.* 550, 1084–1102.
- Rakers, F., Schiffner, R., Rupprecht, S., Brandstadt, A., Witte, O.W., Walther, M., Schlattmann, P., Schwab, M., 2016. Rapid weather changes are associated with increased ischemic stroke risk: a case-crossover study. *Eur. J. Epidemiol.* 31, 137–146.
- Tian, L., Qiu, H., Sun, S., Lin, H., 2016. Emergency cardiovascular hospitalization risk attributable to cold temperatures in Hong Kong. *Circ. Cardiovasc. Qual. Outcomes* 9, 135–142.
- Tsai, C.F., Thomas, B., Sudlow, C.L., 2013. Epidemiology of stroke and its subtypes in Chinese vs white populations: a systematic review. *Neurology* 81, 264–272.
- Wang, Q., Gao, C., Wang, H., Lang, L., Yue, T., Lin, H., 2013. Ischemic stroke hospital admission associated with ambient temperature in Jinan, China. *PLoS One* 8, e80381.
- Wang, X., Cao, Y., Hong, D., Zheng, D., Richtering, S., Sandset, E.C., Leong, T.H., Arima, H., Islam, S., Salam, A., Anderson, C., Robinson, T., Hackett, M.L., 2016. Ambient temperature and stroke occurrence: a systematic review and meta-analysis. *Int. J. Environ. Res. Public Health* 13.
- Wolf, K., Schneider, A., Bretnier, S., von Klot, S., Meisinger, C., Cyrys, J., Hymer, H., Wichmann, H.E., Peters, A., Augsburg, C.H.R.R., 2009. Air temperature and the occurrence of myocardial infarction in augsburg, Germany. *Circulation* 120, 735–U741.
- Wu, X., Zhu, B., Fu, L., Wang, H., Zhou, B., Zou, S., Shi, J., 2013. Prevalence, incidence, and mortality of stroke in the Chinese island populations: a systematic review. *PLoS One* 8, e78629.
- Yang, J., Ou, C.Q., Ding, Y., Zhou, Y.X., Chen, P.Y., 2012. Daily temperature and mortality: a study of distributed lag non-linear effect and effect modification in Guangzhou. *Environ. Health* 11, 63.
- Yang, J., Yin, P., Zhou, M., Ou, C.Q., Guo, Y., Gasparrini, A., Liu, Y., Yue, Y., Gu, S., Sang, S., Luan, G., Sun, Q., Liu, Q., 2015. Cardiovascular mortality risk attributable to ambient temperature in China. *Heart* 101, 1966–1972.
- Yang, J., Yin, P., Zhou, M., Ou, C.Q., Li, M., Li, J., Liu, X., Gao, J., Liu, Y., Qin, R., Xu, L., Huang, C., Liu, Q., 2016. The burden of stroke mortality attributable to cold and hot ambient temperatures: epidemiological evidence from China. *Environ. Int.* 92–93, 232–238.
- Zhang, Y., Chapman, A.M., Plested, M., Jackson, D., Purroy, F., 2012. The incidence, prevalence, and mortality of stroke in France, Germany, Italy, Spain, the UK, and the US: a literature review. *Stroke Res. Treat.* 2012, 436125.
- Zorrilla-Vaca, A., Healy, R.J., Silva-Medina, M.M., 2016. Revealing the association between cerebrovascular accidents and ambient temperature: a meta-analysis. *Int. J. Biometeorol.* 60, 1–12.