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Low ambient temperature increases hospital re-admissions for systemic lupus erythematosus in humid subtropical region: a time series study

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Abstract

Currently, the correlation between ambient temperature and systemic lupus erythematosus (SLE) hospital admissions remains not determined. The aim of this study was to explore the correlation between ambient temperature and SLE hospital admissions in Hefei city, China. An ecological study design was adopted. Daily data on SLE hospital admissions in Hefei city, from January 1st 2007 to 31st December 2017 were obtained from two largest tertiary hospitals in Hefei, and the daily meteorological data at the same period were retrieved from China Meteorological Data Network. Generalized additive model (GAM) combined with distributed lag non-linear model (DLNM) with Poisson link were applied to evaluate the influence of ambient temperature on SLE hospital admissions after controlling for potential confounding factors, including seasonality, relative humidity, day of week and long-term trend. There were 1,658 SLE hospital admissions from 2007 to 2017, including 370 first admissions and 1,192 re-admissions (there were 96 admissions with admission status not stated). No correlation was observed between ambient temperature and SLE first admissions, but a correlation was found between low ambient temperature and SLE re-admissions (RR: 2.53, 95% CI: 1.11, 5.77) (3.5 °C *vs* 21 °C). The effect of ambient temperature on SLE re-admissions remained for two weeks, however, disappeared in three weeks. Exposure to low ambient temperature may increase hospital re-admissions for SLE, and thus it is important for SLE patients to maintain a warm living environment and avoid exposure to lower ambient temperature.

Keywords: Ambient temperature; Hospital re-admissions; Systemic lupus erythematosus

Introduction

Systemic lupus erythematosus (SLE) is a chronic inflammatory autoimmune rheumatic disorder in which immune regulation is aberrant and is featured by inflammation and damages to multiple organs or systems. As one of the most severe complications of SLE, lupus nephritis (LN) significantly influenced the disease outcome (Borchers et al. 2012). While SLE can occur in both males and females, it is found far more often in females (Li et al. 2012; Zou et al. 2014). In recent years, SLE is among the leading death causes in young females, which became an important public health issue (Yen and Singh 2018).

To date, the etiologies and pathogenesis of SLE are still unknown, but there is growing evidence suggests that the disease may resulted from interactions between genetic and environmental factors (Rahman and Isenberg 2008). Environmental factors, such as ultraviolet radiation (UVR), and melatonin, have been implicated in the occurrence of SLE and other autoimmune diseases. UVR, which is higher in the middle of the day and during summer, can induce cellular apoptosis, inflammation and tissue damage, thereby leading to SLE occurrence or flare (Mok and Lau 2003). Melatonin, which is lowest during spring, possesses immunomodulatory function and could ameliorate the severity of several autoimmune diseases including SLE (Watad et al. 2017). Interestingly, all of the abovementioned environmental factors have seasonal variations that could contribute to disease onset and development. In fact, many autoimmune rheumatic diseases are affected by weather conditions, and seasonal variation has been shown in a number of rheumatic diseases (Sabio et al. 2015; Schlesinger and Schlesinger 2005). It has been revealed that patients with SLE has a trend of exacerbation in winter, such as increased risk of fatigue, weakness, joint pains, and Raynaud's phenomenon, as well as elevated hospitalizations, sick leaves, and needs to increase the medications dose (Krause et al. 1997). Compared with summer and autumn, the prevalence of LN with class V was higher during spring and winter (Schlesinger et al. 2005). A study conducted in Hong Kong revealed that the incidence of noncutaneous flare in patients with SLE has significant seasonal variation, with peak incidence occurring in December and January (Szeto et al. 2008). All these findings support the involvement of seasonal variation in the occurrence and disease activity of SLE.

Despite the overwhelming evidence on the seasonality of SLE, the association between meteorological factors (e.g., ambient temperature) and SLE has rarely been examined. A previous study has explored the seasonal pattern of active SLE and the impacts of meteorological factors containing ambient temperature and relative humidity on active SLE (Hua-Li et al. 2011). Their results showed that in winter, when UVR was weaker than in other seasons, the proportion of patients with active SLE in the total hospitalized patients was significantly higher than those of other seasons. The number of SLE patients in the active phase was negatively associated with mean ambient temperature, but not with mean humidity, which indicates that low ambient temperature may be a risk factor for SLE (Hua-Li et al. 2011). Our previous study also showed that in autumn, the relative rate of patients with active SLE was lower than that in spring and winter, but no correlation was observed between ambient temperature and the number of active SLE patients (Yang et al. 2012).

Most prior studies suggested a correlation between ambient temperature and SLE risk, but no our knowledge, no studies have used advanced statistical models to assess the influence of ambient temperature on SLE. Therefore, we conducted this times series study in order to determine a more precise estimation on the relationship between ambient temperature and SLE hospital admissions and to explore the lagged effect of ambient temperature on SLE hospital admissions under different admission conditions (first admission and re-admission).

Materials & Methods

Study area and study subjects

This study was carried out in Hefei city, the economic and cultural center of of Anhui Province, located in the eastern part of China (31°52 N, 117°17 E). The city features a humid subtropical climate with four distinct seasons. The annual average temperature of Hefei is 16.18 °C (61.1 °F). There is no central heating in winter in most areas of Hefei city. Data on daily hospital admissions (including both first admissions and re-admissions) for SLE in Hefei from 1 January 2007 to 31 December 2017 were obtained from the Department of Rheumatology at the First Affiliated Hospital to Anhui Medical University and Anhui Provincial Hospital, the two largest tertiary hospitals in Anhui Province. The case information included age, gender, date of birth, date of hospital admission, and admission status (i.e., first admission or readmission). All SLE patients fulfilled the American College of Rheumatology (ACR) classification criteria (revised in 1997). Data on the yearly population in Hefei during the same study period were obtained from Hefei Bureau of Statistics. The study complies with the Declaration of Helsinki, and was approved by the Ethics Committee of Anhui Medical University prior to the data collection.

Meteorological and pollutant data

The daily meteorological data from 1st January 2007 to 31st December 2017 including ambient mean temperature (°C), maximum temperature (°C), minimum temperature (°C), relative humidity (%), rainfall (mm) and sun hour (0.1h) were collected from China Meteorological Data Sharing Service System (http://data.cma.cn/). Daily air pollution data including particulate matter <10 μm in aerodynamic diameter (PM_{10} and $PM_{2.5}$), nitrogen dioxide (NO_2) and ozone (O_3), from 1st January 2014 to 31st December 2017 were retrieved from ten air quality monitoring stations, which were widely distributed in Hefei. Data on PM_{10}, $PM_{2.5}$ and NO_2 were daily (24h) average concentrations (μg/m^3), while data on O_3 was 8h maximum concentrations (μg/m^3).

Statistical analysis

A generalized additive regression model (GAM) that follows the Poisson distribution was applied in combination with distributed lag non-linear model (DLNM). The final model is as follows:

$$Y_t \sim \text{Poisson}(\mu_t)$$

$$Log(\mu_t) = \alpha + \beta Tmean_{t,l} + Humidity + ns(Time_t,8) + \eta DOW_t + \text{offset}(\log(\text{population}))$$

Y_t refers to the daily number of SLE admissions on the observation day t, α represents the intercept, $Tmean_{t,l}$ means the cross-basis for ambient mean temperature, four degrees of freedom (*df*s) were adopted for both ambient mean temperature and lag, β denotes the matrix coefficient for $Tmean_{t,l}$ and l means the number of lag days. $ns(Time_t,8)$ was applied to adjust seasonality and long-term trend with eight *df*s. *DOW* is short for day of week. Population was controlled for in the model as the study period covered 11 years. Sun hour and air pollutants were not controlled for in the model as our preliminary analyses found that there was no association of rainfall, sun hour or air pollutants with hospital admissions for SLE in Hefei (Figure S1 and S2 (supplementary material)). Akaike information criterion (AIC) was applied to choose the best *df* for seasonality and long-term trend. A lag of seven days (one week) was applied for quantifying the influence of mean ambient temperature on SLE hospital admissions.

Sensitivity analysis

Sensitivity analyses were done by using lags of 14 days and 21 days and by changing the *df*s for mean temperature from three to five. The statistical analyses were conducted by R (V.3.5.1) applying the "DLNM" package. The effects were described as the relative risk (RR) of daily hospital admissions for SLE and its 95% confidence intervals (CIs) with increase of ambient mean temperature. The results of statistical tests were considered to be significant when *p* value of both two tailed less than 0.05 .

Results

There were totally 1,658 hospital admissions for SLE during the study period (of which 96 admission status were not recorded in detail), including 370 first admissions and 1192 re-admissions. Among the 1,658 hospital admissions, there were 1,523 females and 135 males, with an average age of 41.8 years. The summary statistics of daily hospital admissions for SLE, meteorological variables and air pollutants are depicted in **Table 1**. The daily number of SLE hospital admissions ranged from 0 to 6, with more re-admissions (range: 0-4) than first admissions (range: 0-2). The median of mean temperature, maximum temperature and minimum temperature from 2007 to 2017 were 18.1 °C, 22.7 °C, and 13.8 °C, respectively. As shown in **Figure 1,** the daily distribution of SLE hospital admissions, mean temperature, minimum temperature, maximum temperature and relative humidity from 2007 to 2017 in Hefei revealed a clear seasonal pattern.

Table 1 Summary statistics for meteorological variables, air pollutants and daily hospital admissions for SLE in Hefei, China, from 2007 to 2017

Variables	Sum	Minimum	Maximum	Percentile						
				5	10	25	50	75	90	95
Total	1658	0	6	0	0	0	0	1	1	2
First admissions	370	0	2	0	0	0	0	0	0	1
Readmissions	1192	0	4	0	0	0	0	0	1	1
Mean temperature (°C)	-	-5.9	35.6	1.5	3.5	8.4	18.1	24.8	28.5	30.3
Maximum temperature (°C)	-	-2.3	41.1	5.3	7.7	13.5	22.7	29.4	33.3	35.1
Minimum temperature (°C)	-	-11.2	30.6	-2.4	-0.4	4.6	13.8	21.4	25.3	26.8
Relative humidity (%)	-	21	100	49	55	65	76	85	92	95
Sun hours (0.1h)	-	0	125	0	0	0	52	85	103	111
Rainfall (mm)	-	0	1466	0	0	0	0	9	94	188.2
PM_{10} (mg/m^3)	-	3	408	27	35.5	56	84	114	149.5	175.5
$PM_{2.5}$ (mg/m^3)	-	5	353	20	24	37	55	79	110	135
O_3 (mg/m^3)	-	8	185	18	21	31	43	65	88	102.3
NO_2 (mg/m^3)	-	8	132	16	19	25	33	45.3	62	73.3

SLE: systemic lupus erythematosus

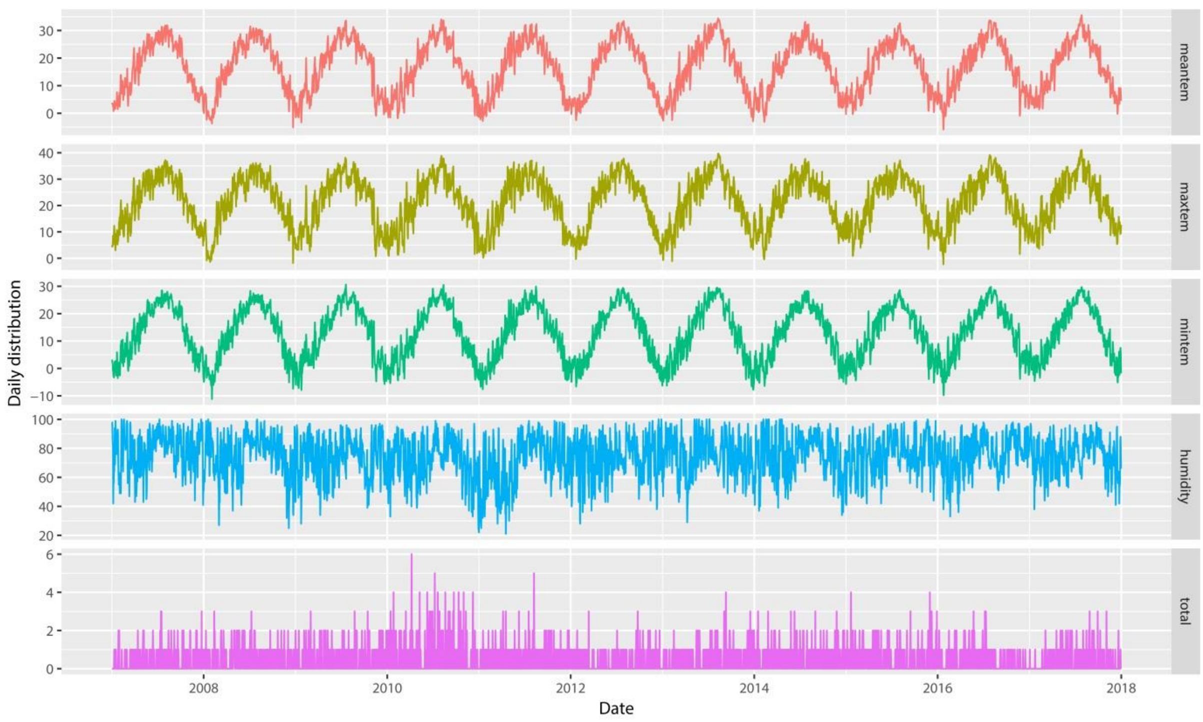

Figure 1 Daily distribution of SLE hospital admissions, mean, minimum, maximum temperatures and relative humidity in Hefei from 2007 to 2017

SLE: systemic lupus erythematosus

The overall effects of exposure-response association between ambient temperature and SLE hospital admissions are revealed in **Figure 2.** With the minimum admission risk ambient temperature as a reference value, the effects of ambient mean temperature on re-admissions were presented as a parabolic curve below 21 °C. Moreover, the relative risk reached the maximum at 3.5 °C (RR: 2.53, 95% CI: 1.11, 5.77). However, ambient temperature below -0.2 °C had no significant effect on re-admissions of patients with SLE. In addition, no significant association of ambient temperature with all hospital admissions and first hospital admissions for SLE was observed.

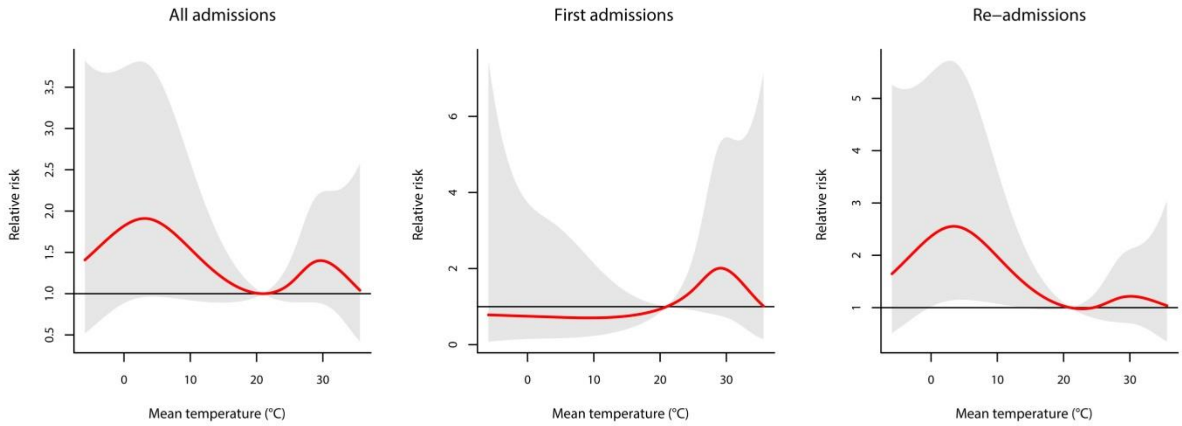

Figure 2 Overall effects of exposure-response associations between mean temperature and SLE hospital admissions

SLE: systemic lupus erythematosus

Figure 3 shows that the significant association of ambient mean temperature with SLE re-admissions remained for two weeks, but disappeared in three weeks. **Figure 4** illustrates the lag-response curves specific to different low temperatures of 1.5 °C (q5) and 3.5 °C (q10), with reference at 21°C. As shown in **Figure 5**, sensitivity analysis showed that the effects remained stable by changing the *df*s (*df*=3 and *df*=5) for mean temperature.

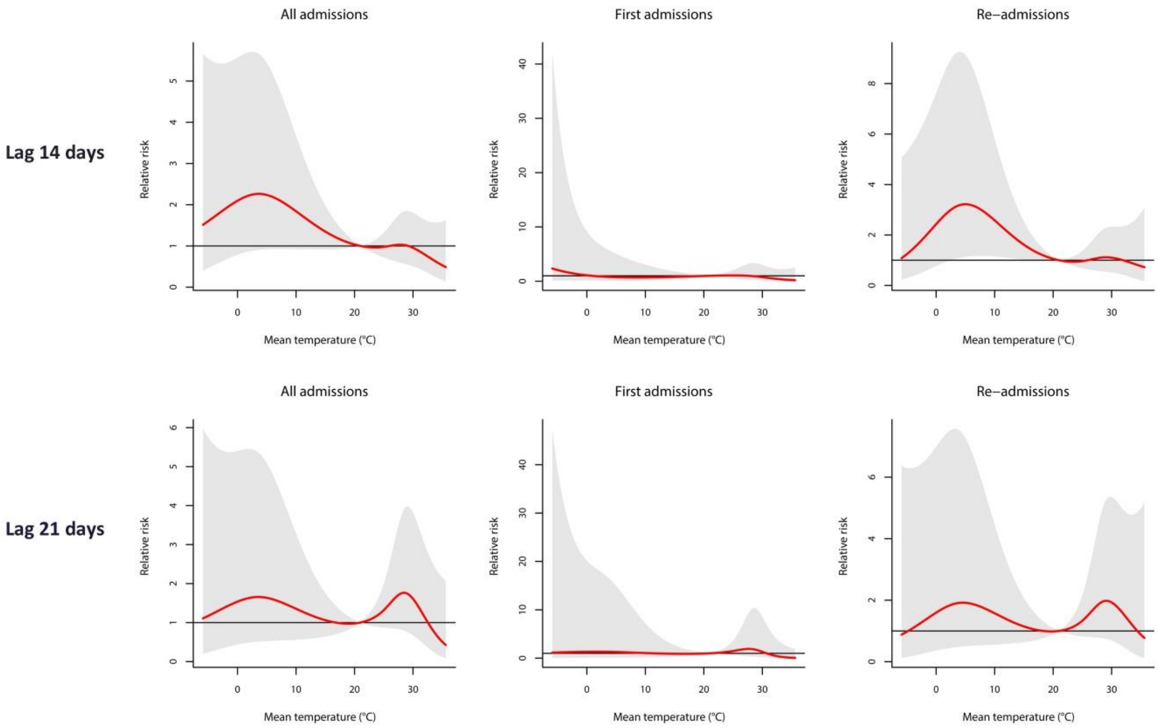

Figure 3 Overall effects of exposure-response associations between mean temperature and SLE hospital admissions with different lags (14 days and 21 days)

SLE: systemic lupus erythematosus

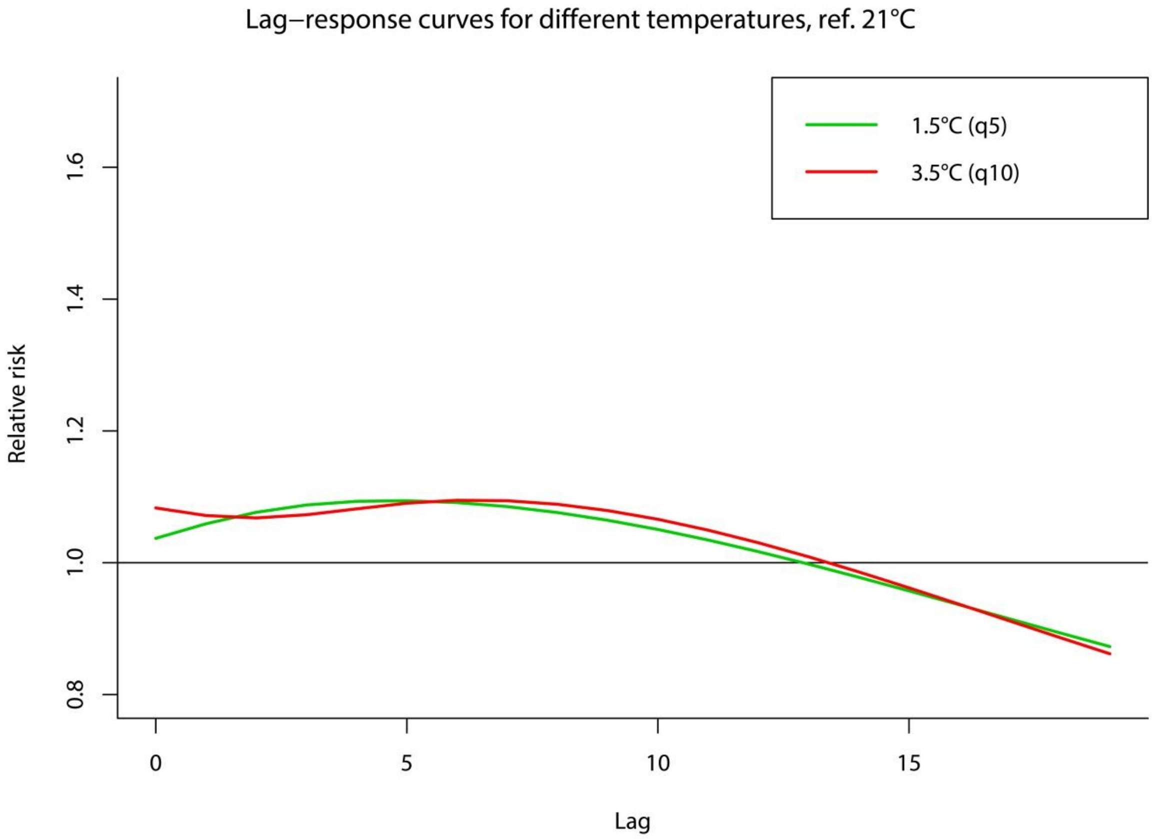

Figure 4 Lag-response curves for different low temperatures of 3.5 °C and 1.5 °C (with reference at 21°C)

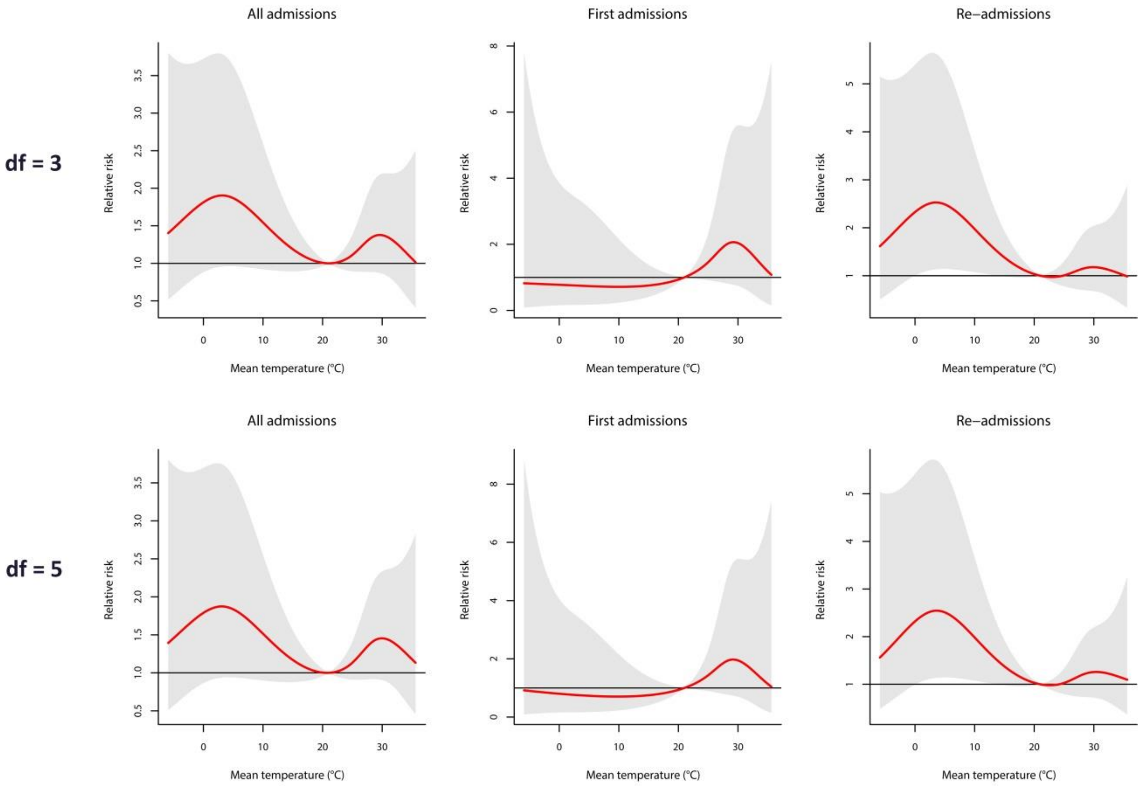

Figure 5 The overall effects of mean temperature on SLE hospital admission when varying the *df*s

SLE: systemic lupus erythematosus

df: degree of freedom

Discussion

While genetic factors play a key role in the development of SLE, environmental risk factors are also implicated in SLE pathogenesis. Nevertheless, there have been inconsistent findings about the seasonal distribution of SLE (Haga et al. 1999; Hasan et al. 2004; Steup-Beekman et al. 2006; Szeto et al. 2008). Similarly, contradictory results regarding the association of ambient temperature with hospital admission of SLE have been reported (Hua-Li et al. 2011; Szeto et al. 2008; Yang et al. 2012). These inconsistent results may be explained by three reasons: (1) patients from different geographical areas; (2) the relatively small sample sizes, and (3) SLE is relatively stable in those patients who are being followed-up and receiving treatment. Furthermore, confounders such as other meteorological factors, seasonality, the day of week effect, *etc*. were not controlled for in the prior studies (Hua-Li et al. 2011; Yang et al. 2012). Therefore, in the current study, we further explored the relationship between ambient temperature and SLE risk using GAM combined with DLNM. Our result revealed a negative association of ambient temperature with SLE re-admissions, suggesting that moderately low ambient temperature was associated with higher number of SLE admissions. However, when temperature was extremely low, the number of SLE re-admissions dropped, because at an extremely low temperature people tend to go out less and pay more attention to keeping warm. No significant association of ambient temperature with SLE first admissions was observed. A previous study in China showed that the number of active SLE patients was negatively correlated with mean ambient temperature (Hua-Li et al. 2011). Therefore, a lower temperature may be a important factors to induce SLE flare.

The association of low ambient temperature with higher risk of SLE is biologically plausible, although the exact mechanisms are still unknown. In general, lower ambient temperature may exert additional stress on the human body, which is usually harmful for those suffering from a variety of disease conditions. Therefore, generalized stress can enhance the severity of autoimmune conditions, simply by adding to the heightened physiological demands of the body during such period. This physical stress can leave a patient with autoimmune diseases more prone to flares, which might be better controlled in a temperate weather. More specifically, under lower ambient temperatures, the smaller blood vessels tend to spasm, leading to a restriction of blood flow to the associated areas, namely Raynaud's phenomenon, which is often secondary to an established autoimmune disease like SLE (Richter et al. 2010). The spasms in smaller blood vessels can cause extreme pain, swelling, numbness and discoloration, which occur mostly in the fingers and toes. As the tissues in the fingers and toes are starved of oxygen, they become damaged and begin to hurt badly (Shinjo and Bonfa 2011). Furthermore, an early study suggested that the accumulation of UVR might cause exacerbations in SLE patients after prolonged exposure to sunlight in summer (Krause et al. 1997). Regarding the immunological mechanism of low temperature in the development of SLE, it has been revealed that the percentage of $CD4^{+}CD25^{+}Foxp3^{+}$ Treg cells was significantly reduced upon cold stress, and that greater temperature decreases led to more significant reduction in the percentage of $CD4^{+}CD25^{+}Foxp3^{+}$ Treg cells (Hu et al. 2016), which play a crucial role in the maintenance of peripheral immunological self-tolerance and exert protective role in lupus pathogenesis (Bonelli et al. 2010; Ohl and Tenbrock 2015). These immunological mechanism findings further support that low ambient temperature facilitates the development and occurrence of SLE. Nevertheless, the exact mechanism of a higher reoccurrence of SLE in cold weather remains to be further elucidated. Notably, SLE has relatively higher rates of hospital readmission among chronic conditions, and early hospital re-admissions is a common and costly event (Nangit et al. 2018; Thorburn and Ward 2003). Thus our findings highlight the importance of improving the quality of care during initial hospitalizations as well as during ambulatory care transition.

However, several limitations of the present study should be addressed. First of all, the outdoor fixed-site monitoring data were used to represent the individual exposure levels, which may cause exposure measurement errors, since people usually spend most of their time indoors (Ge et al. 2018; Niu et al. 2016). Nevertheless, the exposure errors was likely to be random and non-differential in the general population, underestimating the influence of ambient temperature on hospital admissions (Lee et al. 2016). Second, the admission data of SLE were obtained from only one single city, which may weaken its generalization for other geographic regions with different climate conditions. Third, the study design is naturally ecological and the individual differences such as socio-economic status, family background, educational levels, medication cannot be adjusted. Fourth, we had no detailed information on disease activity and complications of SLE, which are critical for precisely evaluating the effect of ambient temperature on SLE admission. Finally, there is no adjustment on several important factors that can interfere especially treatment.

In spite of these limitations, our study also has several strengths. First, this is the first study to use time series method to systemically quantify the effect of ambient temperature on SLE hospital admissions in a subtropical monsoon climate region and it provides evidence that low ambient temperature can increase the risk of hospital re-admissions for SLE. Second, grouping the patients into first admission and readmission may be helpful in identifying subpopulations with higher risk of hospital admissions for SLE. In addition, advanced statistical methods were applied to evaluate the relationship between ambient temperature and SLE, which include both non-linear and lagged effects of ambient temperature in the same model (Gasparrini et al. 2017; Wang et al. 2018).

Conclusions

Our results suggest that low ambient temperature can increase the hospital readmission of SLE patients in subtropical countries, thus maintaining a warm living environment and avoiding exposure to extremes of ambient temperature may help to avoid an unnecessary and costly hospital readmission of SLE in these areas.

Availability of data and materials: The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Conflict of Interest: The authors confirm that there are no conflicts of interest.

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List of abbreviations

ACR: American College of Rheumatology

AIC: Akaike information criterion

CIs: Confidence intervals

DLNM: Distributed lag non-linear model

Dfs: Degrees of freedom

DOW: Day of week

GAM: Generalized additive regression

LN: Lupus nephritis

NO_2: Nitrogen dioxide

O_3: Ozone

RR: Relative risk

SLE: Systemic lupus erythematosus

UVR: Ultraviolet radiation

Declarations

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Ethics approval and consent to participate: This study was approved by the Ethical Committee of Anhui Medical University (Hefei, Anhui, China).

Consent for publication: Not applicable (This study do not contain any individual person's data in any form).

Competing interests: The authors declare that they have no competing interests.

Authors' contributions: QW, ZX, DQY, WH and HFP conceptualized the study, participated in the study design, and revised the manuscript. QW and ZX wrote the manuscript. YMM, CNZ and YLD collected the data, and participated in the study design. QW, ZX, PW and YFZ conducted the statistical analysis. All authors read and approved the final manuscript.

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