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 1, 2007, to December 31, 2017, were obtained from the two largest tertiary hospitals in Hefei, and the daily meteorological data at the same period were retrieved from China Meteorological Data Network. The generalized additive model (GAM) combined with distributed lag nonlinear model (DLNM) with Poisson link was 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 1658 SLE hospital admissions from 2007 to 2017, including 370 first admissions and 1192 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 2 weeks but disappeared in 3 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

Qian Wu and Zhiwei Xu contributed equally to this work.

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**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 a growing evidence suggesting that the disease may result from the 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 and sick leaves, and needs to increase the medication 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 on our knowledge, no studies have used advanced statistical models to assess the influence of ambient temperature on SLE. Therefore, we conducted this time series study in order to determine a more precise estimation on the relationship between the 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 and methods**

**Study area and study subjects**

This study was carried out in Hefei City, the economic and cultural center 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 January 1, 2007, to December 31, 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 re-admission). All SLE patients fulfilled the American College of Rheumatology (ACR) classification criteria (revised in 1997). The 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 January 1, 2007, to December 31, 2017, including ambient mean temperature (°C), maximum temperature (°C), minimum temperature (°C), relative humidity (%), rainfall (mm), and sun hour (0.1
Sensitivity analyses were done by using lags of 14 and 21 days and by changing the dfs for mean temperature from 3 to 5. 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 the 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.

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

Statistical analysis

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

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

$$\log(\mu_t) = \alpha + \beta \text{mean}_{t,l} + \text{Humidity} + \text{ns}(\text{Time}_t, 8)$$

$$+ \gamma \text{DOW}_t + \text{offset} \left(\log(\text{population})\right)$$

$Y_t$ refers to the daily number of SLE admissions on the observation day $t$, $\alpha$ represents the intercept, $\text{mean}_{t,l}$ means the cross-basis for ambient mean temperature, four degrees of freedom (dfs) were adopted for both ambient mean temperature and lag, $\beta$ denotes the matrix coefficient for $\text{mean}_{t,l}$ and $l$ means the number of lag days. $\text{ns}(\text{Time}_t, 8)$ was applied to adjust seasonality and long-term trend with eight dfs. $\text{DOW}$ indicates 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 (Figs. S1 and S2 (Supplementary material)). The Akaike information criterion (AIC) was applied to choose the best dfs for seasonality and long-term trend. A lag of 7 days (1 week) was applied for quantifying the influence of mean ambient temperature on SLE hospital admissions.

Results

There were totally 1658 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 1658 hospital admissions, there were 1523 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 the first admissions (range: 0–2). The median of mean temperature, maximum temperature, and minimum temperature from 2007 to 2017 were 18.1, 22.7, and 13.8 °C, respectively. As shown in Fig. 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.

The overall effects of exposure-response association between ambient temperature and SLE hospital admissions are revealed in Fig. 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, the 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 3 shows that the significant association of ambient mean temperature with SLE re-admissions remained for 2 weeks, but disappeared in 3 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 Fig. 5, the sensitivity analysis showed that the effects remained stable by changing the dfs ($df = 3$ and $df = 5$) for mean temperature.
relatively stable in those patients who are being followed up and receiving treatment. Furthermore, confounders such as other meteorological factors, seasonality, and the day of week effect 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 the 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

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   |
| Re-admissions      | 1192| 0       | 4       | 0         | 0   | 0   | 0    | 1    | 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 (0.1 h)  | -   | 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

Fig. 1 Daily distribution of SLE hospital admissions; mean, minimum, and maximum temperatures; and relative humidity in Hefei from 2007 to 2017
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 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
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 a 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 re-admission among chronic conditions, and early hospital re-admissions are 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 were 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 socioeconomic status, family background, educational levels, and 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 with especially treatment.

In spite of these limitations, our study also has several strengths. First, this is the first study that uses 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 re-admission 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 nonlinear 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 re-admission 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 re-admission of SLE in these areas.

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**Authors’ contributions** QW, ZX, DQY, 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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**Data availability** The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

**Compliance with ethical standards**

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

**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).

**Abbreviations** ACR, American College of Rheumatology; AIC, Akaike information criterion; CIs, confidence intervals; DLNM, distributed lag nonlinear model; DIs, degrees of freedom; DOW, day of week; GAM, generalized additive regression; LN, lupus nephritis; NO2, nitrogen...
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