



Contents lists available at ScienceDirect

Environmental Research

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# Association of childhood asthma with intra-day and inter-day temperature variability in Shanghai, China

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## ARTICLE INFO

### Keywords:

Asthma

Children

Temperature variability

Relative risk

Tailored strategies

## ABSTRACT

**Objectives:** Short-term temperature variability (TV) is associated with the exacerbation of asthma, but little is known about the relative effects of intra- and inter-day TV. We aimed to assess the relative impacts of intra- and inter-day TV on childhood asthma and to explore the modification effects by season.

**Methods:** A quasi-Poisson generalized linear regression model combined with a distributed lag nonlinear model was adopted to evaluate the nonlinear and lagged effects of TV on childhood asthma in Shanghai from 2009 to 2017. Intra- and inter-day TV was measured with diurnal temperature range (DTR) and temperature changes between neighboring days (TCN), respectively.

**Results:** Increased DTR was associated with the elevated relative risk (RR) of daily outpatient visits for childhood asthma (DOVCA) in both the whole year ( $RR_{lag0-14}$  for the 99th percentile: 1.264, 95% confidence interval (CI): 1.052, 1.518) and cold season ( $RR_{lag0-12}$  for the 99th percentile: 1.411, 95% CI: 1.053, 1.889). Higher TCN in the warm season was associated with the increased RR of DOVCA ( $RR_{lag0-14}$  for the 99th percentile: 2.964, 95% CI: 1.636, 5.373). The number and fraction of DOVCA attributed to an interquartile range (IQR) increase of TCN were higher than those attributed to DTR in both the whole year period and warm season. However, the number and fraction of DOVCA attributed to an IQR increase of DTR were greater than those attributed to TCN in the cold season.

**Conclusions:** Our results provide novel evidence that both intra- and inter-day TV might be a trigger of childhood asthma. Higher DTR appeared to have greater impacts on childhood asthma in the cold season while an increase in TCN seemed to have bigger effects in the warm season.

## 1. Introduction

Asthma has been one of the most common chronic respiratory diseases globally, affecting over 300 million individuals, in which childhood asthma cannot be ignored (GAN, 2018; GBD, 2017; GBD, 2019). The prevalence of asthma has increased apparently during the past

decades corresponding to the economic development and urbanization in many regions of the world (Beasley et al., 2015; Gatford et al., 2017; Hu et al., 2021a; Radhakrishnan et al., 2014). About 9% of children and adults in Europe suffer from asthma (Selroos et al., 2015). In the United States, more than 19.2 million (7.6%) adults (>18 years) and 5.5 million (7.5%) children have asthma (NHIS, 2018; Table A-2; NHIS, 2018;

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<https://doi.org/10.1016/j.envres.2021.112350>

Received 31 July 2021; Received in revised form 28 September 2021; Accepted 3 November 2021

Available online 8 November 2021

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**Table C-1).** In China, prevalence of childhood asthma has been rapidly increasing, leading to a great burden on families, health care systems and the society. The national prevalence of asthma among children aged 0–14 years was 2.0% in 2000 (NCGCA, 2003), and rose to 3.0% in 2010 (NCGCA, 2013). The highest prevalence occurred in Shanghai, at 4.5% and 7.6%, respectively (NCGCA, 2003 and 2013). Recently, we observed that the overall prevalence of asthma in children aged 6–11 years was as high as 13.9% in Shanghai (Hu et al., 2021b).

Accumulating evidence has shown that both genetic and environmental factors can influence the occurrence and exacerbation of childhood asthma (Ahlwalia et al., 2020; Huang et al., 2021; Lavigne et al., 2021; Norbäck et al., 2021; Ntontsi et al., 2021; Shao et al., 2020; Turturice et al., 2021; Zhang et al., 2021). Genetic factors cannot convincingly explain the sharp increasing incidence and prevalence of asthma globally within such a short period of time (Ntontsi et al., 2021). Environmental factors, such as extreme weather events associated with climate change and air pollution, may play an important role (Lavigne et al., 2021; Rorie and Poole, 2021; Zhang et al., 2021). Some studies have shown that environmental factors including ambient temperature, humidity, temperature variability (TV), and air pollution are significantly associated with the risks of childhood asthma (Chen et al., 2016; Cong et al., 2017; He et al., 2021; Pan et al., 2020; Qiu et al., 2015; Ueda et al., 2010; Wasilevich et al., 2012; Wei et al., 2020; Xu et al., 2013). However, previous studies examining the association between short-term TV and childhood asthma only focused on one index, such as diurnal temperature range (DTR) (Qiu et al., 2015; Wasilevich et al., 2012; Wei et al., 2020; Xu et al., 2013) or temperature changes between neighboring days (TCN) (Lei et al., 2021; Li et al., 2016). DTR, also known as intra-day TV, calculated by the difference between daily maximum and minimum temperatures within a 24-h period, is an important meteorological factor reflecting the stability of climate conditions (Braganza et al., 2004). TCN, also known as inter-day TV, is generally defined as the mean temperature changes between neighboring days, which is directly driven by large-scale weather dynamics and regional atmospheric circulation (Cattiaux et al., 2015; Wu et al., 2017) and usually depends on topographical factors such as altitude, topography and basins (Babina and Semenov 2019; Guo et al., 2021). An increase of DTR or TCN was associated with the elevated risks of childhood asthma (Lei et al., 2021; Li et al., 2016; Qiu et al., 2015; Wei et al., 2020; Xu et al., 2013). It is unclear whether DTR or TCN is a superior indicator of short-term TV associated with childhood asthma.

Up to date, no study has considered the relative impacts of DTR and TCN on childhood asthma. Therefore, our study aimed to examine the relative role of DTR and TCN in the exacerbation of childhood asthma; assess the modification effects by season; and develop tailored strategies to protect children with asthma from the impacts of TV in Shanghai, China.

## 2. Materials and methods

### 2.1. Study participants

Shanghai, the national largest economic center with the biggest population, located in the east of China (N31°14', E121°29'), has a subtropical monsoon climate with four distinct seasons. Previous studies showed that Shanghai had the highest prevalence of asthma among children in China (NCGCA, 2003 & 2013). In this study, data on electronic health records including outpatient visits for asthmatic patients aged <18 years during January 1, 2009 to December 31, 2017 were obtained from Shanghai Children's Hospital, Shanghai Children's Medical Center and Xinhua Hospital, three large pediatric hospitals located at different parts of Shanghai (covering more than 70% of pediatric patients. Note: Xinhua Hospital has two sections – one for pediatric patients and another for adult patients). Principal diagnosis of childhood asthma was made by physicians according to the tenth version of the International Classification of Diseases (ICD-10, J45-J46).

This study was approved by the Ethics Committee of Shanghai Children's Medical Center (18411951600) before data collection.

### 2.2. Measurement of environmental exposure

As illustrated in our previous articles (Hu et al., 2020a, 2020b), data on meteorological factors including daily ambient mean temperature ( $T_{\text{mean}}$ ), maximum temperature ( $T_{\text{max}}$ ), minimum temperature ( $T_{\text{min}}$ ), air pressure (AP), maximum AP, minimum AP, relative humidity (RH), sunshine hours, precipitation and wind speed for the study period were gathered from the Shanghai Meteorological Service. Shanghai Meteorological Service is in the center of the city, providing meteorological data that are well verified and highly related to other stations' monitoring records. Information on air pollutants including  $\text{SO}_2$ ,  $\text{NO}_2$ ,  $\text{PM}_{2.5}$ ,  $\text{PM}_{10}$  and  $\text{O}_3$  was obtained from Shanghai Environmental Protection Agency. Daily averages of meteorological factors and air pollutants were computed by the 24-h records (Hu et al., 2020a, 2020b). DTR was calculated as the difference between daily maximum and minimum temperatures (i.e.,  $T_{\text{max}}$  minus  $T_{\text{min}}$ ) during a 24-h period. TCN was computed by the daily mean temperature minus the value of the previous day. Daily average values of air pollutants from 19 monitoring stations across regions of Shanghai were used (Hu et al., 2020a). In this study, we defined the values over 95th and 99th percentile as high and extreme high level, respectively. The lagged and seasonal effects of high or extreme high TV on daily outpatient visits for childhood asthma were identified.

### 2.3. Statistical analysis

In this study, we mainly conducted a three-step analysis. In the first step, descriptive analysis was conducted. We calculated the mean, standard deviation (SD), minimum value, 25th, 50th and 75th quartiles and maximum value of all variables. Spearman correlation analyses were performed to calculate the bivariate associations between all variables.

In the second step, a Quasi-Poisson generalized linear regression model, combined with distributed lag nonlinear model (DLNM) (Gasparrini et al., 2010), was adopted to assess the nonlinear and lagged effects of TV on childhood asthma in the whole year period and in the season-stratified analyses. We defined November to April of next year as the cold season and May to October as the warm season according to the distribution of monthly temperature. Due to the high correlation between variables, we only selected  $\text{O}_3$  and  $\text{NO}_2$  as air pollutants to control these confounders to avoid collinearity in the final model. Based on the values of Akaike information criterion (AIC), the model containing  $T_{\text{mean}}$ , RH, TV,  $\text{NO}_2$ , and  $\text{O}_3$  performed the best and with robust results after comparing all multivariable models. The results are presented as relative risks (RR) and 95% confidence interval (CI). The final multivariable DLNM is as follows:

$$\text{Log}[E(Y_t)] \sim \alpha + \text{cb}(\text{DTR/TCN}, \text{maxlag}, 3\text{df}) + \text{cb}(T_{\text{mean}}, \text{maxlag}, 3\text{df}) + \text{cb}(\text{RH}, \text{maxlag}, 3\text{df}) + \text{NO}_2 + \text{O}_3 + \text{ns}(\text{time}, \text{df/year}) + \text{as.factor}(\text{dow}) + \text{as.factor}(\text{public holiday})$$

$Y_t$  denotes the daily outpatient visits of asthma expected on day  $t$ ; maxlag for TV,  $T_{\text{mean}}$ , and RH was set at 14 for all models in both the whole year period and different seasons according to sensitivity analyses and previous studies (Chen et al., 2016; Lei et al., 2020; Xu et al., 2013);  $\alpha$  means the intercept; *dow* indicates day of the week; *public holiday* means Chinese statutory holidays; *ns (time, df/year)* refers to the natural cubic spline function (ns) for time (i.e. 1-3287 in total), with 9 *df/year* for both whole year period and different seasons where is based on the lowest AIC value, the minimum of the residuals and results of sensitivity analysis (Chen et al., 2016; Gasparrini et al., 2010; Xu et al., 2013); *cb* indicates the “cross-basis” function that defined the matrix about TV,  $T_{\text{mean}}$ , and RH (Gasparrini et al., 2010).

In the third step, we calculated the number and fraction of childhood asthma attributed to an interquartile range (IQR) increase of DTR or TCN compared with the minimum risk value as the reference, to assess the relative impacts of DTR and TCN on childhood asthma in both the whole year and different seasons.

Statistical analysis was performed with R software (version 3.6.3; R Core Team) where mainly using “dlnm”, “splines”, “tsmodel”, “mgcv”, and “attrdl.R” packages. Statistical significance level was set at  $p < 0.05$  (two-sided).

## 2.4. Sensitivity analysis

Sensitivity analyses were conducted to verify the robustness of the final results. We adopted 3–16 *df/year* for calendar time and 2–6 *df* for environmental factors in the model. The model that included DTR/TCN,  $T_{\text{mean}}$ , RH,  $\text{PM}_{2.5}$ , and  $\text{O}_3$  was also performed. We set the maximum lag up to 21 days in the model to compare the results (Fig. A2–A.4).

## 3. Results

### 3.1. Descriptive analysis of environmental exposure and daily outpatient visits for childhood asthma (DOVCA)

There were 1,289,896 DOVCA from 2009 to 2017, including 856,965 (66.4%) boys and 432,931 (33.6%) girls. Fig. A1 shows the time-series

decomposition of DOVCA. During nine years of the study period, there were an apparent upward trend and strong seasonality of DOVCA.

Table 1 depicts the distribution of DOVCA and environmental factors in the whole year period. The daily median (range) number of DOVCA was 348 (33–1306) in total, including 233 (26–829) boys and 114 (5–495) girls. The mean values of daily  $T_{\text{mean}}$ , RH, DTR, TCN,  $\text{SO}_2$ ,  $\text{NO}_2$ ,  $\text{O}_3$ ,  $\text{PM}_{2.5}$  and  $\text{PM}_{10}$  were 17.2 °C, 73.7%, 7.5 °C, 0.0 °C, 21.9  $\mu\text{g}/\text{m}^3$ , 47.6  $\mu\text{g}/\text{m}^3$ , 71.8  $\mu\text{g}/\text{m}^3$ , 69.6  $\mu\text{g}/\text{m}^3$  and 47.4  $\mu\text{g}/\text{m}^3$ , respectively. Table A.1 presents the season-stratified distribution of DOVCA and environmental factors. Daily median number (range) of DOVCA was 389 (43–1306) for the cold season and 304 (30–829) for the warm season.

Spearman correlation coefficients between independent and dependent variables in the whole year period (table A.2) and in different seasons (table A.3 and A.4) on the current day were calculated. DTR and TCN were generally positively correlated with  $T_{\text{mean}}$  and all air pollutants both in the whole year period and in different seasons. Air pollutants other than  $\text{O}_3$  (i.e.,  $\text{SO}_2$ ,  $\text{NO}_2$ ,  $\text{PM}_{2.5}$  and  $\text{PM}_{10}$ ) were moderately or highly correlated with each other (range of  $r_s$ : 0.56–0.84 for the whole year, 0.49–0.81 for the warm season, and 0.54–0.84 for the cold season, respectively, all  $p < 0.01$ ).

### 3.2. Associations of DOVCA with TV

There were significant exposure-response associations between TV and RR of childhood asthma at lags 0–7 and 0–14 days in the whole year

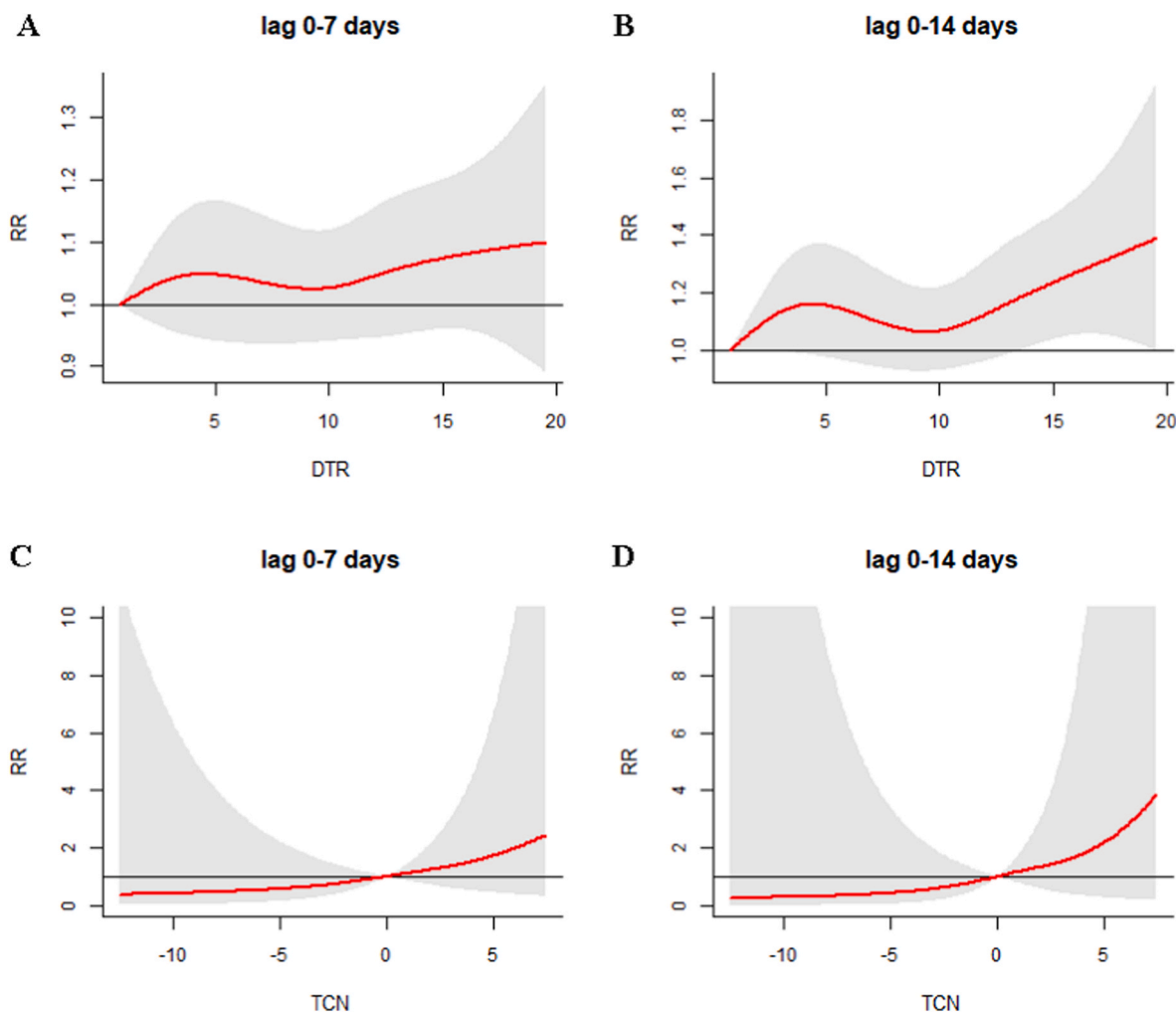


**Fig. 1.** The exposure-response curves for the cumulative effects of DTR (A, B) and TCN (C, D) on daily outpatient visits for childhood asthma in whole year period, stratified by lag periods. Gray areas indicate the 95% confidence interval. RR: relative risk. DTR: diurnal temperature range. TCN: temperature changes between neighboring days.

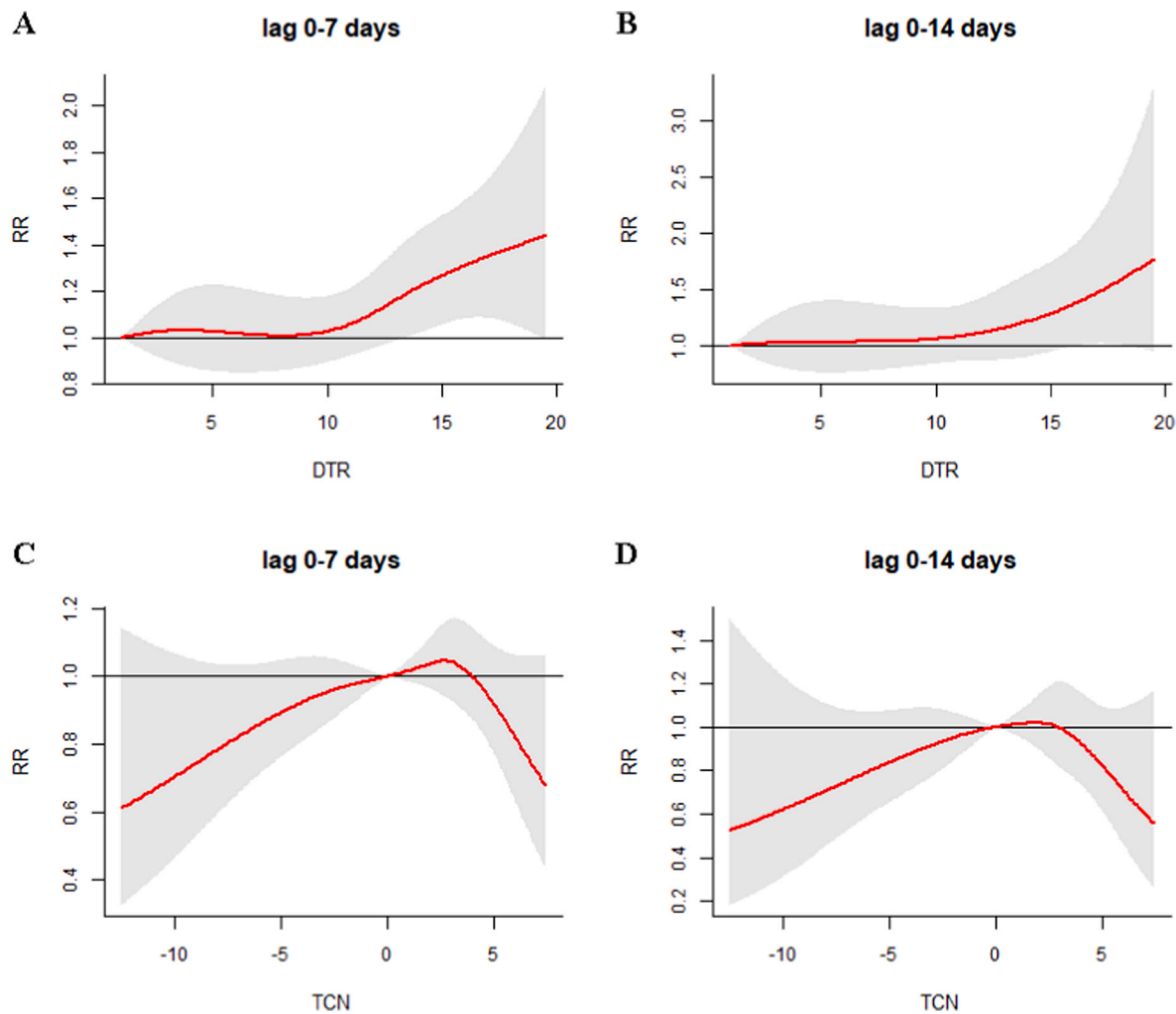


**Fig. 2.** The exposure-response curves for the cumulative effects of DTR (A, B) and TCN (C, D) on daily outpatient visits for childhood asthma in cold seasons, stratified by lag periods. Gray areas indicate the 95% confidence interval. RR: relative risk. DTR: diurnal temperature range. TCN: temperature changes between neighboring days.

**Table 1**

Summary statistics of daily outpatient visits for childhood asthma, weather conditions and air pollutants from 2009 to 2017.

| Variables                              | Mean | SD    | Minimum | P25  | P50  | P75  | Maximum |
|----------------------------------------|------|-------|---------|------|------|------|---------|
| Daily outpatient visits                | 392  | 239.4 | 33      | 212  | 348  | 524  | 1306    |
| Boys                                   | 261  | 155.8 | 26      | 143  | 233  | 347  | 829     |
| Girls                                  | 132  | 84.6  | 5       | 68   | 114  | 177  | 495     |
| Daily mean temperature (°C)            | 17.2 | 8.8   | -5.6    | 9.4  | 18.2 | 24.3 | 34.8    |
| Relative humidity (%)                  | 73.7 | 12.5  | 24.0    | 66.0 | 75.0 | 83.0 | 100.0   |
| Temperature variability                |      |       |         |      |      |      |         |
| DTR (°C)                               | 7.5  | 3.4   | 0.8     | 4.7  | 7.1  | 9.9  | 19.5    |
| TCN (°C)                               | 0.0  | 2.1   | -12.5   | -1.1 | 0.1  | 1.3  | 7.4     |
| Air pollutants                         |      |       |         |      |      |      |         |
| NO <sub>2</sub> (μg/m <sup>3</sup> )   | 47.6 | 20.6  | 5.0     | 33.0 | 44.9 | 59.0 | 153.1   |
| SO <sub>2</sub> (μg/m <sup>3</sup> )   | 21.9 | 15.4  | 5.0     | 12.0 | 17.0 | 26.4 | 127.8   |
| PM <sub>10</sub> (μg/m <sup>3</sup> )  | 71.8 | 48.4  | 6.0     | 41.5 | 59.9 | 88.0 | 803.8   |
| PM <sub>2.5</sub> (μg/m <sup>3</sup> ) | 47.4 | 32.8  | 5.0     | 26.0 | 38.0 | 59.0 | 447.0   |
| O <sub>3</sub> (μg/m <sup>3</sup> )    | 69.6 | 31.3  | 8.2     | 46.0 | 69.0 | 87.0 | 277.9   |

SD: standard deviation; P25, p50 and p75 indicates the 25th, 50th, and 75th percentile of the values, respectively; DTR: diurnal temperature range; TCN: temperature changes between neighboring days.

period (Fig. 1) and in different seasons (Figs. 2 and 3). High levels of DTR were associated with increased RRs of DOVCA in both the whole year (Fig. 1A–B) and cold season (Fig. 2A–B). A sharp increase of TCN was associated with elevated RRs of DOVCA in both the whole year (Fig. 1C–D) and warm season (Fig. 3C & D). All of the above results

suggested that the higher the TV, the bigger the RR for childhood asthma.

Table 2 depicts the highest RR of TV on DOVCA. Single-day and/or cumulative lagged effects of high levels of TV (the 95th and 99th percentile of DTR and TCN) on childhood asthma were observed in the

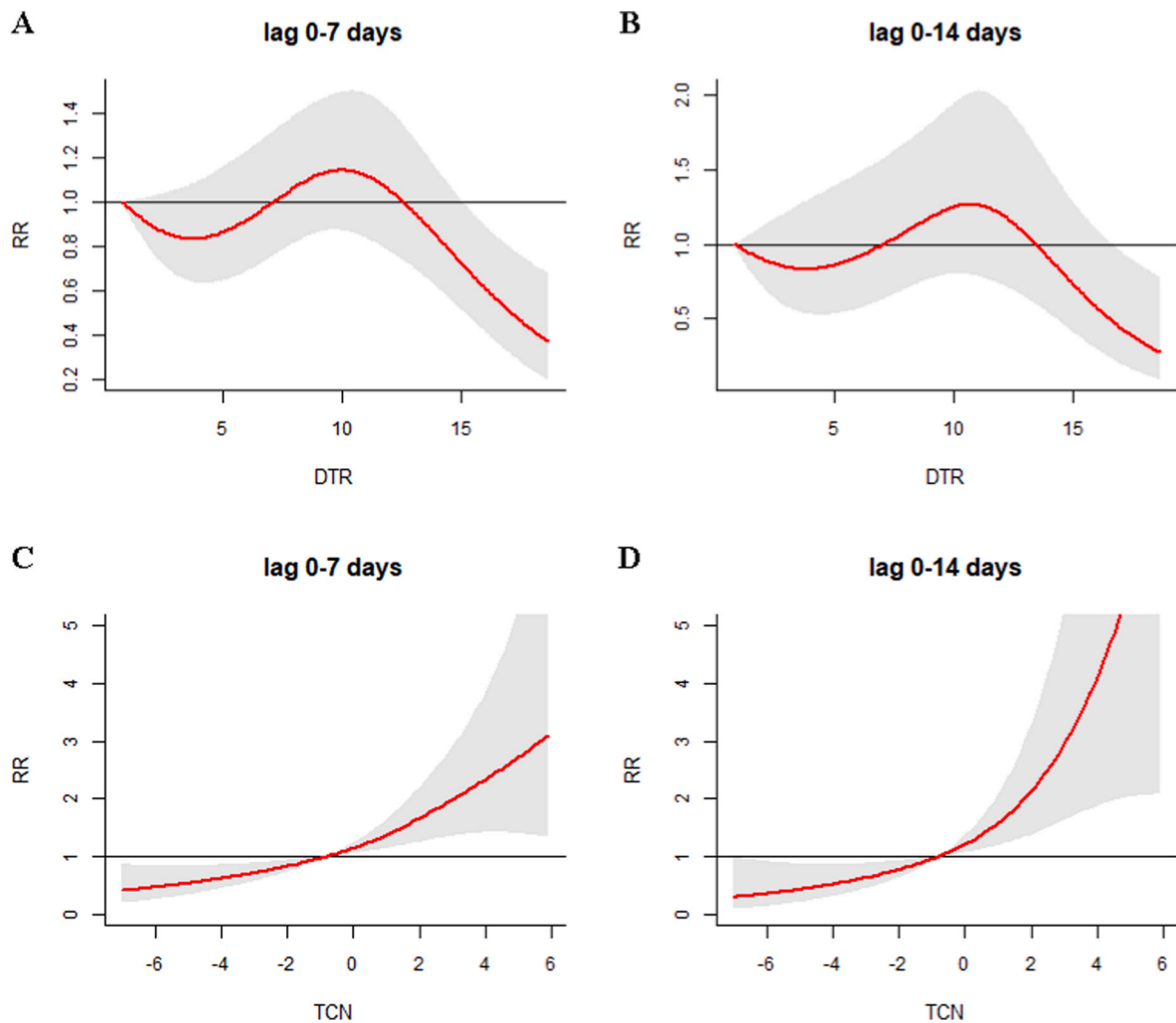


**Fig. 3.** The exposure-response curves for the cumulative effects of DTR (A, B) and TCN (C, D) on daily outpatient visits for childhood asthma in warm seasons, stratified by lag periods. Gray areas indicate the 95% confidence interval. RR: relative risk. DTR: diurnal temperature range. TCN: temperature changes between neighboring days.

**Table 2**

The lagged effects of temperature variability on daily outpatient visits for childhood asthma in the whole year and different seasons.

| Variables | Whole year |                             |           |                             | Cold season |                             |           |                             | Warm season |                             |           |                             |
|-----------|------------|-----------------------------|-----------|-----------------------------|-------------|-----------------------------|-----------|-----------------------------|-------------|-----------------------------|-----------|-----------------------------|
|           | Lag (day)  | Single-day effect           | Lag (day) | Cumulative effect           | Lag (day)   | Single-day effect           | Lag (day) | Cumulative effect           | Lag (day)   | Single-day effect           | Lag (day) | Cumulative effect           |
| DTR       |            |                             |           |                             |             |                             |           |                             |             |                             |           |                             |
| P95       | 12         | <b>1.017 (1.001, 1.034)</b> | 0–14      | <b>1.183 (1.000, 1.399)</b> | 1           | <b>1.034 (1.003, 1.066)</b> | 0–9       | <b>1.254 (1.010, 1.558)</b> | 14          | 1.034 (0.983, 1.087)        | 0–14      | 1.175 (0.718, 1.923)        |
| P99       | 10         | <b>1.024 (1.009, 1.039)</b> | 0–14      | <b>1.264 (1.052, 1.518)</b> | 1           | <b>1.042 (1.008, 1.077)</b> | 0–12      | <b>1.411 (1.053, 1.889)</b> | 14          | 1.027 (0.972, 1.085)        | 0–14      | 0.796 (0.463, 1.369)        |
| TCN       |            |                             |           |                             |             |                             |           |                             |             |                             |           |                             |
| P95       | 5          | 1.054 (0.924, 1.202)        | 0–12      | 1.568 (0.442, 5.563)        | 4           | 1.003 (0.985, 1.022)        | 0–7       | 1.011 (0.886, 1.153)        | 5           | <b>1.071 (1.031, 1.113)</b> | 0–14      | <b>2.002 (1.350, 2.970)</b> |
| P99       | 5          | 1.089 (0.888, 1.336)        | 0–13      | 2.140 (0.290, 15.777)       | 6           | 0.991 (0.963, 1.021)        | 0–14      | 0.776 (0.555, 1.084)        | 6           | <b>1.105 (1.044, 1.171)</b> | 0–14      | <b>2.964 (1.636, 5.373)</b> |

Cold season: January–April & November–December; warm season: May–October; DTR: diurnal temperature range; TCN: temperature changes between neighboring days; Data were represented with relative risk (RR) and 95% confidence interval; Bold value means statistically significant ( $p < 0.05$ ); The results of DTR were calculated with the 95th (p95) and 99th (p99) percentile of the values compared to the minimum value; the results of TCN were calculated with the 95th and 99th percentile value compared to 0, respectively; Both single-day and cumulative effect reported the highest RR at a certain lag; The final model included the DTR/TCN, daily mean temperature, relative humidity,  $\text{NO}_2$ ,  $\text{O}_3$ , public holidays, day of the week, and ns (time, df/year).

whole year period and in different seasons. Higher DTR was associated with increased RRs of DOVCA in both the whole year period (RR<sub>lag0-14</sub> for the 95th percentile: 1.183, 95% CI: 1.000, 1.399; RR<sub>lag0-14</sub> for the 99th percentile: 1.264, 95% CI: 1.052, 1.518) and the cold season (RR<sub>lag0-9</sub> for the 95th percentile: 1.254, 95% CI: 1.010, 1.558; RR<sub>lag0-12</sub> for the 99th percentile: 1.411, 95% CI: 1.053, 1.889) (Note: Different lags were used as the highest RRs were presented for different exposure indices). A sharp increase of TCN in the warm season was associated with an increased RR of DOVCA (RR<sub>lag0-14</sub> for the 95th percentile: 2.002, 95% CI: 1.350, 2.970; RR<sub>lag0-14</sub> for the 99th percentile: 2.964, 95% CI: 1.636, 5.373).

### 3.3. Relative impacts of DTR and TCN on DOVCA

Table 3 shows the number and fraction of DOVCA attributed to an IQR increment of DTR or TCN. An IQR increase of DTR and TCN was mostly positively associated with DOVCA. The number and fraction of DOVCA attributed to an IQR increase of TCN were higher than those attributed to DTR in both the whole year period and warm season. However, the number and fraction of DOVCA attributed to an IQR increase of DTR were greater than those attributed to TCN in the cold season.

## 4. Discussion

This is the first study to assess the relative impacts of intra- and inter-day TV on childhood asthma in Shanghai and explored whether the effect modified by season. The key findings include: i) high levels of TV increased the risks of DOVCA; ii) High DTR could increase the RR of DOVCA in both the whole year period and cold season. A sharp increase of TCN was associated with increased RRs of DOVCA in the warm season; iii) the number and fraction of DOVCA attributable to an IQR increase of TCN were higher than those attributed to DTR in both the whole year period and warm season, while the number and fraction of DOVCA attributable to an IQR increase of DTR were greater than those attributed to TCN in the cold season.

Asthma, one of the most common chronic respiratory diseases in children, is sensitive to climatic conditions. A number of previous studies reported that environmental factors (including meteorological factors and air pollutants) were associated with risks of asthma among children (Chen et al., 2016; Cong et al., 2017; He et al., 2021; Hu et al., 2020; Lavigne et al., 2021; Lei et al., 2021; Li et al., 2016; Pan et al., 2020; Rorie et al., 2021; Ueda et al., 2010; Wasilevich et al., 2012; Wei et al., 2020; Xu et al., 2013; Zhang et al., 2021). Ueda et al. (2010) in Fukuoka found that within-day temperature change was associated with childhood asthma exacerbation where the lag3 OR per 1 °C drop and rise was 1.033 (95% CI: 1.005, 1.063) and 1.027 (95% CI: 0.995, 1.060), respectively. Cong et al. (2017) reported that the odds ratio (OR) of childhood asthma for temperature drop was 1.09 (95% CI: 1.03, 1.15) through a systematic review and meta-analysis. Recently, He et al.

(2021) indicated that a dry environment with low temperature had the most significant impact on outpatient visits for respiratory diseases in Lanzhou and their finding was consistent with our previous research (Hu et al., 2020a).

Several studies assessed the association between TV and childhood asthma in which they only focused on one indicator such as DTR or TCN. We used both DTR and TCN as the short-term TV indices and explored the relative impacts of them on the exacerbation of childhood asthma in this study. The significant impact of high DTR on childhood asthma we observed in Shanghai is consistent with previous findings in Brisbane (Australia) (Xu et al., 2013), Hong Kong (China) (Qiu et al., 2015), Hefei (China) (Wei et al., 2020), and Korea (Lee et al., 2019). Xu et al. (2013) reported that per 5 °C increase of DTR was associated with an elevated RR of 0.31 (95% CI: 0.11, 0.58) for asthma emergency admissions in Australia. Qiu et al. (2015) found that higher DTR was a risk factor for childhood asthma where bigger effects were observed in the cold season and female children (younger than 15 years). Lee et al. (2019) showed that there was an increase of 5.6% (95% CI: 3.2%–8.1%) in the RR for asthma with an IQR increment of DTR (6.2 °C–9.9 °C) in Seoul. Recently, a study conducted in 21 cities, China, also found that high DTR was associated with the elevated risk of chronic respiratory diseases including asthma in both the cold and warm season (Wang et al., 2020). Our results provide additional supportive evidence that higher DTR was associated with increased RRs of DOVCA in both the whole year period and cold season.

There is relatively rare evidence on the association between TCN and childhood asthma. Liu et al. (2015) found that a large temperature (TCN) decrease was associated with an increased RR (1.03, 95% CI: 1.02, 1.05) of clinical visits for childhood respiratory tract infections in Guangzhou. However, Li et al. (2016) reported that per 1 °C increment of TCN was associated with a 4.2% (95% CI: 0.9%–7.6%) increase of hospital visits for asthma in children. Recently, Lei et al. (2021) found that an increase in TCN was associated with higher risks of DOVCA and TCN drop was associated with lower risks of DOVCA in warm seasons. Our results also suggest that a sharp increase of TCN was associated with the increased RR of DOVCA in both the whole year period and warm season.

Several biological mechanisms can partly explain the impacts of higher TV on childhood asthma. Immune systems are immature in early childhood (Gervassi and Horton., 2014; Munteanu et al., 2019), in which they could be more vulnerable to the pressure induced by the high TV. Toghias et al. (1985) found that a sudden TV increment was associated with inflammatory mediators released by mast cells. Graudenz et al. (2006) found that larger TV might lead to more inflammatory nasal responses. In addition, Li et al. (2014) reported that DTR was inversely associated with peak expiratory flow and might be a trigger of respiratory symptoms. In this study, we observed that higher DTR may have a greater impact on childhood asthma in the cold season while a sharp increase of TCN in the warm season may pose a bigger threat to childhood asthma. Interestingly, we also found that the number and fraction

**Table 3**

The number and fraction of outpatient visits for childhood asthma attributed to an IQR increase of DTR or TCN.

| Variables | Whole year |                    | Cold season |                   | Warm season |                   |
|-----------|------------|--------------------|-------------|-------------------|-------------|-------------------|
|           | AN         | AF (%)             | AN          | AF (%)            | AN          | AF (%)            |
| DTR       |            |                    |             |                   |             |                   |
| Ref = min | 63,300     | 4.9 (−0.1, 9.9)    | 10,318      | 1.4 (−13.5, 12.8) | −23845      | −4.2 (−15.5, 4.6) |
| Ref = p25 | −31181     | −2.4 (−4.1, −0.6)  | 3605        | 0.5 (−2.9, 4.0)   | 42,256      | 7.4 (3.7, 11.0)   |
| Ref = p75 | 15,264     | 1.2 (0.3, 2.1)     | 11,843      | 1.6 (−0.2, 3.4)   | 3577        | 0.6 (−1.2, 2.5)   |
| TCN       |            |                    |             |                   |             |                   |
| Ref = 0   | 83,582     | 6.5 (−11.7, 21.3)  | 3321        | 0.5 (−3.0, 3.6)   | 48,265      | 8.5 (3.6, 12.8)   |
| Ref = p25 | 140,296    | 10.9 (−15.3, 31.3) | 11,454      | 1.6 (−2.8, 5.4)   | 62,152      | 10.9 (4.3, 16.8)  |
| Ref = p75 | 28,634     | 2.2 (−6.3, 9.3)    | −4110       | −0.6 (−2.4, 1.1)  | 24,709      | 4.3 (1.8, 6.8)    |

Cold season: January–April & November–December; warm season: May–October; DTR: diurnal temperature range; TCN: temperature changes between neighboring days; AN: attributable number; AF: attributable fraction; IQR: interquartile range; min: minimum value; p25 and p75 indicate the 25th and 75th percentile of the values.

of DOVCA attributed to an IQR increase of TCN were higher than those attributed to DTR, especially in the warm season. The specific mechanism for these is unclear and needs further research.

This study has three major strengths. First, to the best of our knowledge, this is the first attempt to assess the relative impact of DTR and TCN on childhood asthma. Second, a 9-year study period with a big dataset was used to discern the association of childhood asthma with TV where short-term random variations could be reduced to a minimum. Finally, we also stratified our data into warm and cold seasons to assess the impacts of TV on childhood asthma and found that TV posed various impacts on childhood asthma in different seasons.

Some limitations should also be acknowledged. First of all, as an ecological time-series study, measurement bias is inevitable to some extent. However, Brenner and Loomis (1994) reported that this measurement error is probably non-differential, that may bias effect estimates towards the null. Second, some potential risk factors such as respiratory viral epidemics, aeroallergens and indoor pollutants (e.g. house dust mite, molds and NO<sub>2</sub>) that might affect the TV-asthma association were not included in this study since these data were not available. Finally, intra- and inter-day TV may jointly affect the exacerbation of childhood asthma but it is beyond the scope of this study to explore the interactive effects of DTR and TCN on asthma.

Future research may focus on the following directions:

1. It is desirable to conduct a cohort study using individual-level exposure data including all potential confounding factors such as respiratory viral epidemics, aeroallergens and indoor air pollutants;
2. The interactive effects of DTR and TCN on childhood asthma should be explored as these exposures may jointly impact the occurrence/exacerbation of asthma.

## 5. Conclusions

this study provides novel evidence that both intra- and inter-day tv was associated with the increased risk of outpatient visits for childhood asthma in shanghai, china, with apparent modification effects by season. higher dtr appeared to have greater impacts on childhood asthma in the cold season while a sharp increase of tcn seemed to exhibit bigger effects in the warm season. our results suggest that more attention is warranted to protect children with asthma from the impact of tv and tailored strategies are required to tackle this issue in different seasons.

## Credit author statement

**Shilu Tong:** Conceptualization, Methodology, Investigation, Writing – review & editing, Visualization, Supervision, Funding acquisition. **Yabin Hu:** Data curation, Formal analysis, Writing – original draft, & Editing. **Jian Cheng:** Methodology, Writing – review & editing, Visualization. **Yong Yin:** Conceptualization, Investigation, Resources, Writing – review & editing, Visualization, Supervision. **Shijian Liu:** Conceptualization, Writing – review & editing, Visualization, Supervision. **Jianguo Tan:** Conceptualization, Resources, Writing – review & editing, Visualization, Supervision. **Shenghui Li:** Conceptualization, Writing – review & editing, Visualization, Supervision. **Meiqin Wu:** Investigation, Resources, Writing – review & editing, Visualization, Supervision. **Chonghuai Yan:** Conceptualization, Investigation, Resources, Writing – review & editing, Visualization, Supervision. **Guangjun Yu:** Conceptualization, Investigation, Resources, Writing – review & editing, Visualization, Supervision. **Yi Hu:** Investigation, Resources, Writing – review & editing, Visualization, Supervision.

## Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

## Acknowledgments

We would like to thank Shanghai Children's Medical Center, Shanghai Children's hospital, Xinhua Hospital, Shanghai Meteorological Service and Shanghai Environmental Protection Agency for providing clinical data and environmental information.

## Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.envres.2021.112350>.

## Funding sources

Science and Technology Commission of Shanghai Municipality, Grant number: 18411951600.

## Data availability statement

Data are available on a reasonable request.

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# **Association of childhood asthma with intra-day and inter-day temperature variability in Shanghai, China**

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**Table A.1** Summary statistics of daily outpatient visits for childhood asthma and environmental factors

| variables                              | Whole year         | Warm season        | Cold season       | P value |
|----------------------------------------|--------------------|--------------------|-------------------|---------|
| Daily clinical visits                  | 348 (33, 1306)     | 304 (33, 1153)     | 389 (43, 1306)    | <0.001  |
| Boys                                   | 233 (26, 829)      | 202 (26, 789)      | 261 (30, 829)     | <0.001  |
| Girls                                  | 114 (5, 495)       | 103 (5, 389)       | 128 (13, 495)     | <0.001  |
| Daily mean temperature                 | 18.2 (-5.6, 34.8)  | 24.2 (12.4, 34.8)  | 9.3 (-5.6, 25.1)  | <0.001  |
| Relative humidity                      | 75.0 (24.0, 100.0) | 77.0 (33.0, 100.0) | 72.0 (24.0, 99.0) | <0.001  |
| DTR (°C)                               | 7.1 (0.8, 19.5)    | 7.0 (0.8, 18.6)    | 7.3 (1.0, 19.5)   | <0.001  |
| TCN (°C)                               | 0.1 (-12.5, 7.4)   | 0.1 (-7.1, 5.9)    | 0.3 (-12.5, 7.4)  | 0.069   |
| NO <sub>2</sub> (µg/m <sup>3</sup> )   | 44.9 (5.0, 153.1)  | 36.8(5.0,122.4)    | 54.0(13.0,153.1)  | <0.001  |
| SO <sub>2</sub> (µg/m <sup>3</sup> )   | 17.0 (5.0, 127.8)  | 13.0 (5.0, 70.3)   | 21.5 (7.0, 127.8) | <0.001  |
| PM <sub>10</sub> (µg/m <sup>3</sup> )  | 59.9 (6.0, 803.8)  | 50.0 (7.0, 803.8)  | 71.0 (6.0, 672.6) | <0.001  |
| PM <sub>2.5</sub> (µg/m <sup>3</sup> ) | 38.0 (5.0, 447.0)  | 33.1 (5.0, 214.0)  | 47.0 (8.0, 447.0) | <0.001  |
| O <sub>3</sub> (µg/m <sup>3</sup> )    | 69.0 (8.2, 277.9)  | 82.8(10.4,277.9)   | 54.6 (8.2, 184.0) | <0.001  |

Data are presented with median (range); Warm season: May-October; Cold season: January-April & November-December; DTR: diurnal temperature range; TCN: temperature changes between neighboring days; P value was calculated by Mann-Whitney U test corresponding to the difference between cold and warm seasons.

**Table A.2** Spearman correlation coefficients between environmental factors in the whole year on the current day

| variables         | T <sub>mean</sub> | RH           | DTR         | TCN         | NO <sub>2</sub> | PM <sub>10</sub> | PM <sub>2.5</sub> | SO <sub>2</sub> | O <sub>3</sub> |
|-------------------|-------------------|--------------|-------------|-------------|-----------------|------------------|-------------------|-----------------|----------------|
| RH                | <b>0.22</b>       | 1.00         |             |             |                 |                  |                   |                 |                |
| DTR               | <b>0.04</b>       | <b>-0.43</b> | 1.00        |             |                 |                  |                   |                 |                |
| TCN               | <b>0.10</b>       | -0.01        | <b>0.33</b> | 1.00        |                 |                  |                   |                 |                |
| NO <sub>2</sub>   | <b>-0.45</b>      | <b>-0.16</b> | <b>0.35</b> | <b>0.16</b> | 1.00            |                  |                   |                 |                |
| PM <sub>10</sub>  | <b>-0.25</b>      | <b>-0.40</b> | <b>0.47</b> | <b>0.09</b> | <b>0.69</b>     | 1.00             |                   |                 |                |
| PM <sub>2.5</sub> | <b>-0.23</b>      | <b>-0.16</b> | <b>0.34</b> | <b>0.11</b> | <b>0.66</b>     | <b>0.84</b>      | 1.00              |                 |                |
| SO <sub>2</sub>   | <b>-0.43</b>      | <b>-0.46</b> | <b>0.33</b> | <b>0.06</b> | <b>0.71</b>     | <b>0.72</b>      | <b>0.56</b>       | 1.00            |                |
| O <sub>3</sub>    | <b>0.42</b>       | <b>-0.15</b> | <b>0.20</b> | <b>0.05</b> | <b>-0.39</b>    | <b>-0.04</b>     | <b>-0.06</b>      | <b>-0.29</b>    | 1.00           |

T<sub>mean</sub>: daily mean temperature; RH: relative humidity; DTR: diurnal temperature range; TCN: temperature changes between neighboring days; Bold value means statistical significance (P < 0.05).

**Table A.3** Spearman correlation coefficients between environmental factors in the warm season on the current day

| variables         | T <sub>mean</sub> | RH           | DTR         | TCN         | NO <sub>2</sub> | PM <sub>10</sub> | PM <sub>2.5</sub> | SO <sub>2</sub> | O <sub>3</sub> |
|-------------------|-------------------|--------------|-------------|-------------|-----------------|------------------|-------------------|-----------------|----------------|
| RH                | -0.03             | 1.00         |             |             |                 |                  |                   |                 |                |
| DTR               | <b>0.16</b>       | <b>-0.56</b> | 1.00        |             |                 |                  |                   |                 |                |
| TCN               | <b>0.17</b>       | <b>-0.13</b> | <b>0.33</b> | 1.00        |                 |                  |                   |                 |                |
| NO <sub>2</sub>   | <b>-0.24</b>      | <b>-0.10</b> | <b>0.32</b> | <b>0.07</b> | 1.00            |                  |                   |                 |                |
| PM <sub>10</sub>  | -0.02             | <b>-0.40</b> | <b>0.53</b> | <b>0.16</b> | <b>0.65</b>     | 1.00             |                   |                 |                |
| PM <sub>2.5</sub> | -0.02             | <b>-0.13</b> | <b>0.39</b> | <b>0.15</b> | <b>0.62</b>     | <b>0.81</b>      | 1.00              |                 |                |
| SO <sub>2</sub>   | -0.03             | <b>-0.47</b> | <b>0.40</b> | <b>0.07</b> | <b>0.64</b>     | <b>0.67</b>      | <b>0.49</b>       | 1.00            |                |
| O <sub>3</sub>    | <b>-0.07</b>      | <b>-0.37</b> | <b>0.42</b> | <b>0.08</b> | 0.02            | <b>0.37</b>      | <b>0.36</b>       | <b>0.13</b>     | 1.00           |

T<sub>mean</sub>: daily mean temperature; RH: relative humidity; DTR: diurnal temperature range; TCN: temperature changes between neighboring days; Bold value means statistical significance (P < 0.05).

**Table A.4** Spearman correlation coefficients between environmental factors in the cold season on the current day

| variables         | T <sub>mean</sub> | RH           | DTR         | TCN         | NO <sub>2</sub> | PM <sub>10</sub> | PM <sub>2.5</sub> | SO <sub>2</sub> | O <sub>3</sub> |
|-------------------|-------------------|--------------|-------------|-------------|-----------------|------------------|-------------------|-----------------|----------------|
| RH                | <b>0.26</b>       | 1.00         |             |             |                 |                  |                   |                 |                |
| DTR               | <b>0.18</b>       | <b>-0.32</b> | 1.00        |             |                 |                  |                   |                 |                |
| TCN               | <b>0.26</b>       | <b>0.09</b>  | <b>0.33</b> | 1.00        |                 |                  |                   |                 |                |
| NO <sub>2</sub>   | 0.02              | <b>-0.06</b> | <b>0.41</b> | <b>0.24</b> | 1.00            |                  |                   |                 |                |
| PM <sub>10</sub>  | 0.00              | <b>-0.34</b> | <b>0.42</b> | 0.04        | <b>0.66</b>     | 1.00             |                   |                 |                |
| PM <sub>2.5</sub> | 0.01              | <b>-0.10</b> | <b>0.29</b> | <b>0.06</b> | <b>0.65</b>     | <b>0.84</b>      | 1.00              |                 |                |
| SO <sub>2</sub>   | <b>-0.32</b>      | <b>-0.40</b> | <b>0.27</b> | 0.03        | <b>0.62</b>     | <b>0.70</b>      | <b>0.54</b>       | 1.00            |                |
| O <sub>3</sub>    | <b>0.35</b>       | <b>-0.12</b> | <b>0.09</b> | <b>0.05</b> | <b>-0.53</b>    | <b>-0.23</b>     | <b>-0.25</b>      | <b>-0.45</b>    | 1.00           |

T<sub>mean</sub>: daily mean temperature; RH: relative humidity; DTR: diurnal temperature range; TCN: temperature changes between neighboring days; Bold value means statistical significance (P < 0.05).

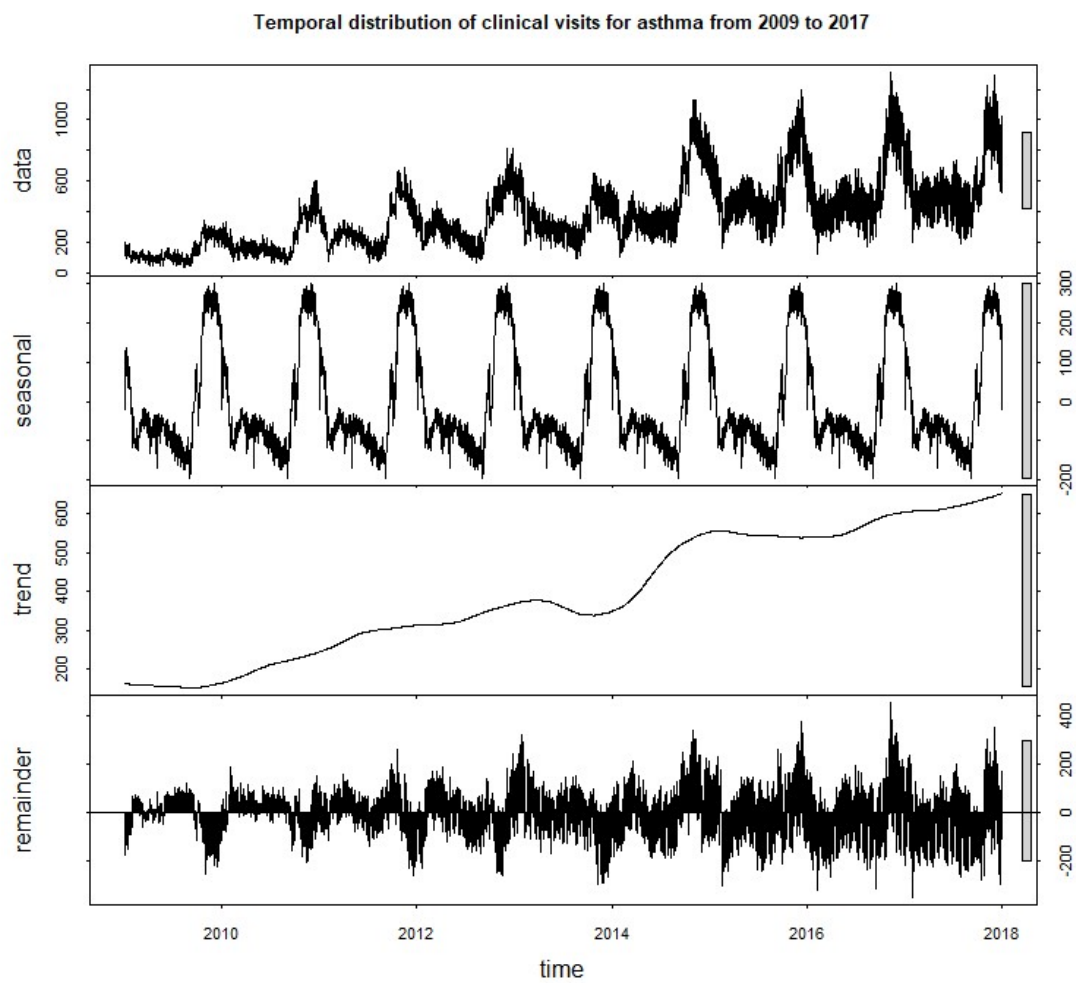


**Fig. A.1** Temporal distribution of daily outpatient visits for childhood asthma from 2009 to 2017.

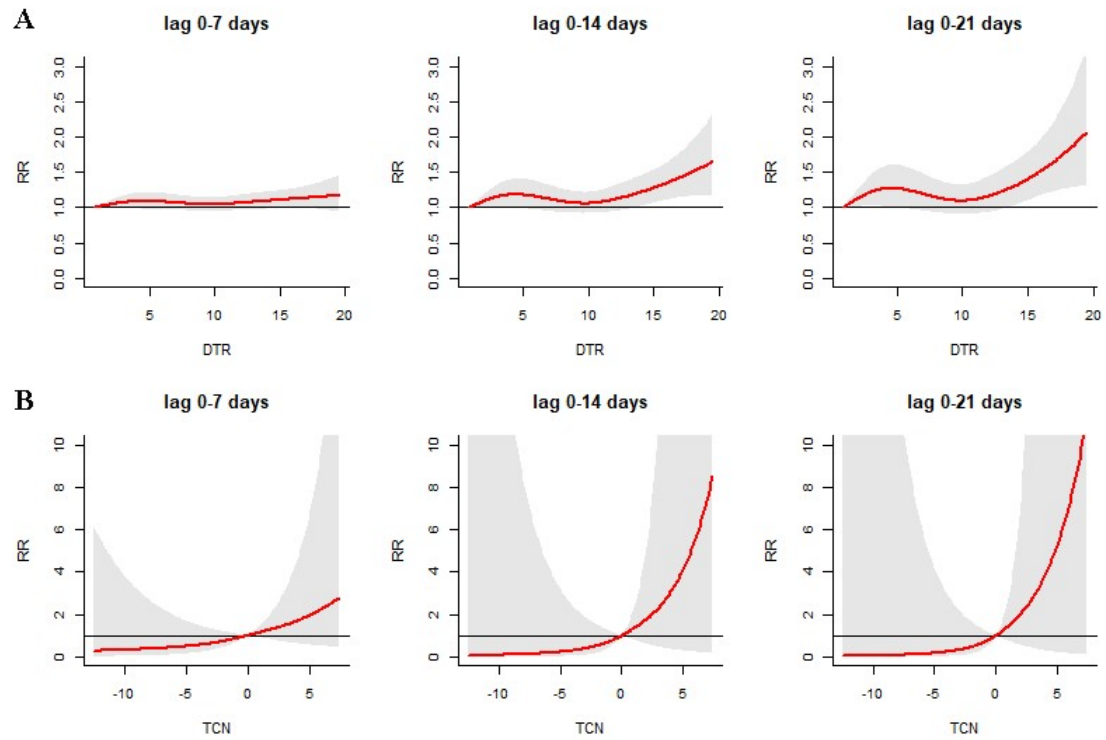


**Fig. A.2** The exposure-response curves for the cumulative effects of DTR (**A**) and TCN (**B**) on daily outpatient visits for childhood asthma in whole year with lag 21 days, stratified by lag periods. Gray areas indicate the 95% confidence interval. RR: relative risk. DTR: diurnal temperature range. TCN: temperature changes between neighboring days.

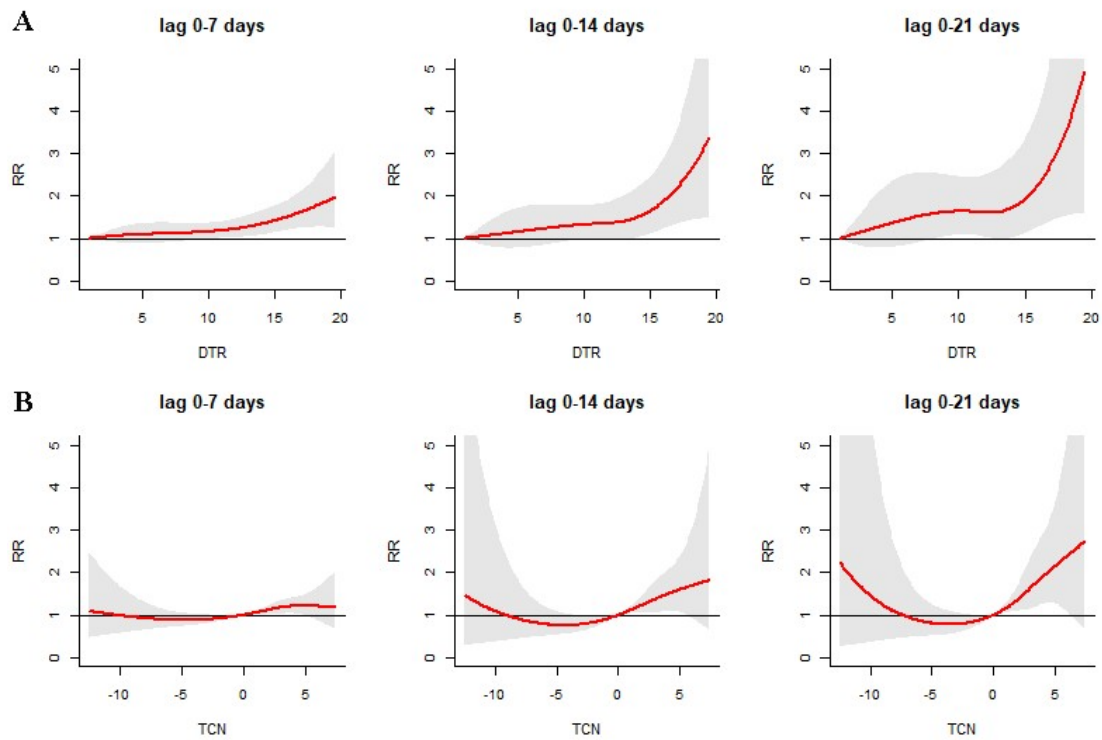


**Fig. A.3** The exposure-response curves for the cumulative effects of DTR (**A**) and TCN (**B**) on daily outpatient visits for childhood asthma in cold season with lag 21 days, stratified by lag periods. Gray areas indicate the 95% confidence interval. RR: relative risk. DTR: diurnal temperature range. TCN: temperature changes between neighboring days.

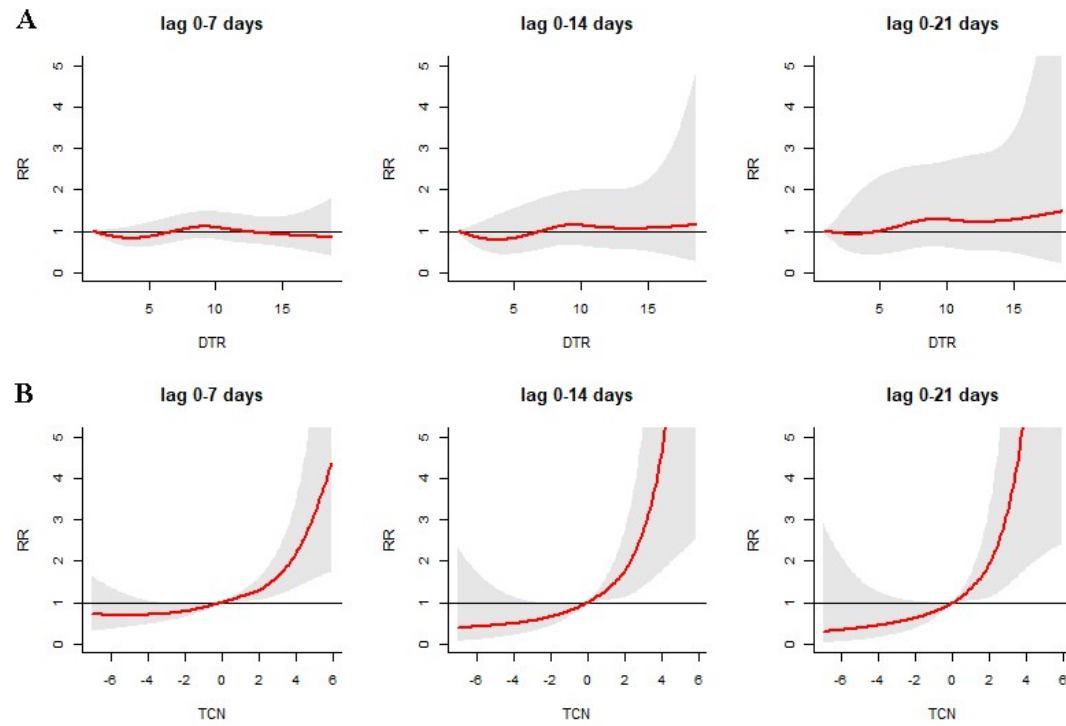


**Fig. A.4** The exposure-response curves for the cumulative effects of DTR (**A**) and TCN (**B**) on daily outpatient visits for childhood asthma in warm season with lag 21 days, stratified by lag periods. Gray areas indicate the 95% confidence interval. RR: relative risk. DTR: diurnal temperature range. TCN: temperature changes between neighboring days.