Original research

Temperature variability and asthma hospitalisation in Brazil, 2000–2015: a nationwide case-crossover study

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ABSTRACT

Background Both cold and hot temperature have been associated with the onset of asthma, but it remains largely unknown about the risk of asthma hospitalisation associated with short-term temperature fluctuation or temperature variability (TV).

Objective To explore the association between short-term exposure to TV and asthma hospitalisation in Brazil.

Methods Data for asthma hospitalisation and weather conditions were collected from 1816 Brazilian cities between 2000 and 2015. TV was calculated as the SD of all daily minimum and maximum temperatures within 0–7 days prior to current day. A time-stratified case-crossover design was performed to quantify the association between TV and hospitalisation for asthma.

Results A total of 2 818 911 hospitalisations for asthma were identified during the study period. Each 1°C increase in 0–7 days' TV exposure was related to a 1.0% (95% CI 0.7% to 1.4%) increase in asthma hospitalisations. The elderly were more vulnerable to TV than other age groups, while region and season appeared to significantly modify the associations. There were 159 305 (95% CI 55 293 to 2 58 054) hospitalisations, US$48.41 million (95% CI US$16.92 to US$78.30 million) inpatient costs at 2015 price and 450.44 thousand inpatient days (95% CI 156.08 to 729.91 thousand days) associated with TV during the study period. The fraction of asthma hospitalisations attributable to TV increased from 5.32% in 2000 to 5.88% in 2015.

Conclusion TV was significantly associated with asthma hospitalisation and the corresponding substantial health costs in Brazil. Our findings suggest that preventive measures of asthma should take TV into account.

Key messages

What is the key question?

- Is short-term exposure to temperature variability associated with increased risk of hospitalisation for asthma and how much health and economic burden of asthma hospitalisations was attributable to temperature variability exposure in Brazil?

What is the bottom line?

- Temperature variability was significantly associated with hospitalisations for asthma, especially for the elderly, while region and season appeared to significantly modify the associations.

Why read on?

- This is the first national scale study with a considerably large sample size and time quantum to systematically assess the association between temperature variability and hospitalisation for asthma and to quantify the attributable costs associated with temperature variability exposure.

INTRODUCTION

Asthma is the second prevalent chronic disease of respiratory system,[1] affecting 272.68 million (242.30–304.70 million) people globally.[2] Brazil is a middle-income tropical country where the prevalence of asthma is among the highest worldwide.[3] The prevalence of asthma symptoms in Brazil was 20% and 23% in adolescents and adults aged 18–54, respectively.[3] In 2011, asthma ranked fourth among the leading causes of hospital admissions in Brazil.[4]

The causes of asthma exacerbations are complicated. The strongest risk factor is atopy involving a combination of genetic predisposition with environmental exposure such as allergens and pollutants.[1] Recently, ambient temperature has been identified as one of the important factors for morbidity/mortality, and its risk on asthma should also be highlighted.[5 6]

A growing body of research has provided evidence about temperature-related asthma exacerbation using indicators such as daily mean temperature or its transformation to reflect heat wave or cold spell, and shown both cold and hot temperatures could increase the risks of asthma onset.[7 8] However, these temperature indicators can only reflect the degree of temperature itself and cannot evaluate the impact of temperature fluctuations. Recent studies have found that temperature variability (TV), an indicator of short-term temperature fluctuations or stability, was positively associated with risks of all-cause, cardiovascular, respiratory mortality and morbidity, after adjusting for daily mean temperatures.[9 10] This suggests that a high TV may have adverse health impacts independent of temperatures. Up to now, limited evidence is available on the impacts of TV on asthma morbidity in the world. As temperature fluctuates greatly between day and night in most parts of Brazil, there is an urgent need to explore the association between TV and asthma morbidity in the country.

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Therefore, to fill the knowledge gap, we conducted a nationwide time-stratified case-crossover analysis to explore the association between short-term TV exposure and hospitalisations for asthma in 1816 cities in Brazil during 2000–2015.

METHODS

Study area

Brazil is the largest country in South America, with most of its territory lying in the tropics. It is composed of five regions, including the north, northeast, southeast, south and central west. The climate in Brazil varies considerably across diverse topography, with the hottest temperature in the northeast and the coolest temperature in the south region. The average temperature of Brazil is about 25°C.

Data collection

Hospitalisation data

Data on asthma hospitalisation were collected from 1816 cities representing 79% of the national population during 1 January 2000 and 31 December 2015 (online supplemental table S1). Individual-level hospitalisation records, including date of admission, length of stay and hospitalisation expenses were extracted from Brazilian Unified Health System database.[11] International Classification of Diseases, 10th revision was used to identify patients diagnosed with asthma. In this study, hospitalisations with principal cause coded as J45 asthma (including predominantly allergic asthma, non-allergic asthma, mixed asthma and asthma unspecified) and J46 status asthmaticus (acute severe asthma) were extracted. Demographic information including age, sex and residential city were collected. As it is not possible to identify individuals with multiple hospitalisations due to limited access to detailed data, all demographic information was recorded for each asthma-related hospitalisation. Emergency room visits without dispatching to hospital admission were not included in this study.

Meteorological data

Daily meteorological data including daily maximum temperature (T_{max}), minimum temperature (T_{min}) and daily mean relative humidity for each city were collected from interpolated grids (0.25° × 0.25°) estimated based on 735 nationwide weather stations in Brazil. Daily weather conditions of each city were represented by the observations of the grid cell located at the centroid of each city based on longitude and latitude.[9] Then, we linked the city-level meteorological data to hospitalisation records in the same city.

Exposure definition

In this study, TV was used to represent temperature stability/fluctuations. TV is a complex indicator established and validated in the previous study to estimate the combined risk related to intraday and interday temperature fluctuations and their lagged associations with asthma.[9] TV is calculated as the SD of T_{min} and T_{max} for the current day and lag days. For example, TV0–1 was calculated as SD of T_{min} and T_{max} for the current and preceding 1 day ($T_{max-lag0}$, $T_{max-lag1}$, $T_{min-lag0}$, $T_{min-lag1}$); TV0–2 was calculated as SD of T_{min} and T_{max} for the current and preceding 2 days ($T_{max-lag0}$, $T_{max-lag1}$, $T_{max-lag2}$, $T_{min-lag0}$, $T_{min-lag1}$, $T_{min-lag2}$), and so on for TV0–3 to TV0–7.

Study design

We modelled the TV–hospitalisation association using a time-stratified case-crossover design with a conditional logistic regression. The time-stratified case-crossover design is widely used to assess the association between short-term environmental exposure (eg, temperature and air pollution) and daily mortality/morbidity.[12] It compares the exposure level in the day when the health event occurs (case day) with the levels in control days which are selected in a relatively small window (eg, calendar month), to control for seasonality and long-term trend.[12] It can also adjust individual demographic characteristics which unlikely change within the small-time window, such as sex, weight and smoking. In this study, for each admission date of cases, control days matched by day of the week in the same calendar month, the same year and in the same city were assigned, to control for the impacts of day of the week, seasonality, long-term trend and spatial variation. Thus, each case has 3 or 4 control days (before and/or after the date of cases).

Statistical analysis

TV-asthma hospitalisation association

In the conditional logistic model, a linear function was applied to TV to assess the association between TV and asthma hospitalisation.[9] Different TV exposures (from TV0–1 to TV0–7) were put into model separately. Non-linear and delayed relationship between daily mean temperature/relative humidity and hospitalisation for asthma were controlled using a distributed lag non-linear model (DLNM), as several studies identified them as potential confounders.[9] A 3 df natural cubic spline allowing extrapolation in the tails of the boundary knots was applied for daily mean temperature, daily mean relative humidity and their lagged association with asthma up to 7 days.[13] A binary variable indicating whether the date was a public holiday was also included in the model to control for the influence of public holidays, such as travel and changes in hospital admissions. The association between TV and hospitalisation for asthma was presented as the relative risk (RR) with 95% CI associated with per 1°C increase in TV.

We further conducted stratified analyses. Analyses were repeated using the data stratified by age group (0–4, 5–19, 20–39, 40–59, 60–79 and ≥80 years), sex, region, season and type of asthma. Hot season and cold season were defined as the four adjacent hottest and coldest months for each city, respectively. The remaining months were coded as the moderate season.

Attributable health burden of hospitalisation for asthma

To identify the absolute impact of the TV, we used attributable fraction (AF) and attributable cases (AC) to quantify the attributable burden of hospitalisation for asthma due to TV. The equations are described as follows:

$$RR_{i,t} = \exp\left(\beta_{per\ 1\ increase} \times TV_{i,t}\right)$$

$$AC_{i,t} = Number\ of\ cases_i \times \left(RR_{i,t} - 1\right)/RR_{i,t}$$

$$\mathrm{AC} = \sum_i \sum_t AC_{i,t}$$

$$\mathrm{AF} = \frac{AC}{total\ cases}$$

where i stands for the city i, t denotes the day t, $\beta_{per\ 1\ increase}$ is the region-specific coefficient estimated from case-crossover analyses conducted in the region where the city is located.

In addition, we estimated the number of days in hospital for asthma due to TV by multiplying the AC by the case-average length of stay.

Attributable economic burden of hospitalisation for asthma

We calculated the total hospital admission cost due to TV in year y with the following equation[12]:

$$\text{Attributable cost}_{total} = \sum_{y} AC_y \times Cost_y \times CPI_y$$

where $Cost_y$ stands for the case-average hospital admission expenses in year y. CPI_y is the product of Customer Price Indexes (CPI) from year y+1 to year 2015. Annual CPI data in Brazil obtained from the World Bank were shown in online supplemental table S2).

Sensitivity analysis

Sensitivity analyses were performed to examine the robustness of our results. We changed the df (from 3 to 6) for daily mean temperature, relative humidity and their lag days. The statistical significance of differences between RRs estimated from sensitivity analyses and our primary models were assessed using fixed effect meta-regression model with no statistical adjustment. Fixed effect model was used because sensitivity analyses were based on the same samples. For example, the estimates for main model and sensitivity analysis were entered as the dependent variable (along with SE for weighting), and the binary predictor (main model and sensitivity analysis) was entered as the independent variable.

R software (V.3.6.2) was used to perform all analyses. R package 'dlnm' (V.2.4.2) and 'mvmeta' (V.1.0.3) was used to perform DLNM model and meta-regression. A two-sided $p<0.05$ was declared as statistically significant.

Patient and public involvement

This research was done without patient or public involvement. This study is exempted from ethics approval because anonymised data was used for analyses.

RESULTS

From 2000 to 2015, a total of 2 818 911 hospitalisations for asthma were identified. Among them, 87.4% were diagnosed with J45 asthma. Over 50% were children and teenagers under 19 years of age, with approximately 38% cases aged 0–4 years. A relatively large proportion of the included hospitalisations were recorded in the northeast (45.2% for J45% and 54.2% for J46) compared with other regions. The proportion of females was slightly higher than that of males (table 1).

Table 1 Summary of hospitalisations for asthma in 1816 Brazilian cities, 2000–2015

	Subtype	
Characteristic	**J45 asthma**	**J46 status asthmaticus**
Total, no (%)	2 463 963 (87.4)	354 948 (12.6)
Region, no (%)		
North	56 295 (2.3)	1763 (0.5)
Northeast	1 113 415 (45.2)	192 316 (54.2)
Central West	180 341 (7.3)	34 964 (9.9)
South	401 391 (16.3)	51 563 (14.5)
Southeast	712 521 (28.9)	74 342 (20.9)
Age, years*		
Mean (SD)	21.2 (25.4)	19.8 (24.5)
Median (P_{25}–P_{75})	6.9 (2.3–37.6)	6.7 (2.3–33.0)
No (%)		
0–4	932 488 (37.9)	134 626 (37.9)
5–19	652 765 (26.5)	105 852 (29.8)
20–39	281 120 (11.4)	36 478 (10.3)
40–59	272 036 (11.0)	36 241 (10.2)
60–79	250 486 (10.2)	32 096 (9.0)
≥80	75 065 (3.1)	9655 (2.7)
Sex, no (%)*		
Male	1 219 445 (49.5)	175 574 (49.5)
Female	1 244 517 (50.5)	179 371 (50.5)

*There are three missing values in age and four missing values in sex.

Table 2 shows the distributions of meteorological factors by region in 1816 cities. During the study period, the daily T_{max} and T_{min} showed a similar but marked variation between regions, with the highest values recorded in the north (32.3°C for T_{max} and 22.7°C for T_{min}) and the lowest values recorded in the south (25.8°C for T_{max} and 15.5°C for T_{min}). TV was highest in the lag 0–1 days and gradually decreased with longer windows. The central west had the highest TV for all exposure periods, with all values above 6°C. Relatively lower values of TV were found in the north and northeast.

Regional variation

Figure 1 shows the associations between TV and asthma hospitalisations at both national and regional levels. In general, there were significant associations between TV and hospitalisations for asthma at national level. The magnitude of the associations increased with longer exposure, with the strongest association recorded for the TV0–7 (RR 1.010, 95% CI 1.007 to 1.014). For different regions, significant and stronger associations were found in northeast and south region while the associations were not significant in north, central west and southeast region.

Demographic and seasonal variation

Figure 2 shows the age-specific associations between TV and asthma hospitalisations. Generally, the older, the more susceptible to TV, except those aged 60–79 years. The strength of associations increased with longer exposure, especially for children and young adults aged under 39 years. The RRs for asthma hospitalisations associated with per 1°C increase in TV0–7 were 1.007 (95% CI 1.002 to 1.012), 1.011 (95% CI 1.004 to 1.018), 1.015 (95% CI 1.005 to 1.024) for those aged 0–4 years, 5–19 years and 20–39 years, respectively. However, for the people aged above 80 years, the association stabilised at a higher level across all exposure periods.

Figure 3 shows the sex-stratified, subtype-stratified and season-stratified associations between TV and asthma hospitalisations. Female and male had similar associations. Hospitalisations for J46 status asthmaticus showed stronger association with TV than hospitalisations for J45 asthma. The association was strongest for moderate season with the highest risk of hospitalisation at TV0–7 exposure (RR 1.022, 95% CI 1.016 to 1.029).

Attributable burden

Table 3 shows the attributable burden of hospitalisations due to TV0–7. There were 5.65% (95% CI 1.96% to 9.15%) of asthma hospitalisations attributable to TV, corresponding to 159 305 (95% CI 55 293 to 258 054) hospital admissions, US$48.41 million (95% CI US$16.92 to US$78.30 million) inpatient costs at 2015 price and 450.44 thousand days

Table 2 Distributions of meteorological factors by region in 1816 Brazilian cities, 2000–2015

	Median (P_{25}, P_{75})				
Variables	North	Northeast	Central west	South	Southeast
T_{max}(°C)	32.3 (30.9, 33.5)	30.6 (28.6, 32.3)	30.5 (28.1, 32.6)	25.8 (21.6, 29.2)	27.9 (25.3, 30.3)
T_{min}(°C)	22.7 (21.5, 23.7)	21.4 (19.6, 22.8)	18.8 (16.4, 20.7)	15.5 (12.0, 18.2)	17.5 (14.7, 19.5)
TV0–1 (°C)	5.5 (4.7, 6.4)	5.3 (4.4, 6.5)	6.8 (5.8, 8.0)	6.2 (5.1, 7.3)	6.3 (5.2, 7.4)
TV0–2 (°C)	5.2 (4.5, 6.1)	5.1 (4.2, 6.2)	6.5 (5.6, 7.6)	6.0 (5.1, 7.0)	6.0 (5.1, 7.0)
TV0–3 (°C)	5.1 (4.4, 6.0)	5.0 (4.1, 6.0)	6.4 (5.5, 7.4)	6.0 (5.1, 6.8)	5.9 (5.1, 6.8)
TV0–4 (°C)	5.0 (4.4, 5.9)	4.9 (4.1, 5.9)	6.3 (5.4, 7.4)	5.9 (5.2, 6.8)	5.8 (5.1, 6.7)
TV0–5 (°C)	5.0 (4.4, 5.8)	4.9 (4.0, 5.9)	6.3 (5.4, 7.3)	5.9 (5.2, 6.7)	5.8 (5.1, 6.6)
TV0–6 (°C)	4.9 (4.4, 5.8)	4.9 (4.0, 5.8)	6.2 (5.4, 7.3)	5.9 (5.2, 6.7)	5.8 (5.1, 6.6)
TV0–7 (°C)	4.9 (4.3, 5.8)	4.8 (4.0, 5.8)	6.2 (5.4, 7.2)	5.9 (5.3, 6.7)	5.8 (5.1, 6.6)
Average relative humidity (%)	83.4 (78.4, 86.9)	75.1 (67.5, 81.5)	71.0 (60.2, 80.1)	77.0 (69.2, 84.1)	74.5 (67.5, 80.3)

T_{max}, maximum temperature; T_{min}, minimum temperature.

(95% CI 156.08 to 729.91 thousand days) in hospital. All groups had similar AF when stratified by sex, season and subtype. However, there existed considerable variation of AF between different regions, with the highest 8.16% of cases attributed to TV in the northeast region. When examining the economic burden due to TV, attributable costs were remarkably higher for children aged 0–4 years (US$18.75 million, 95% CI US$6.24 to US$30.61 million), northeast region (US$31.42 million, 95% CI US$19.79 to $42.65 million) and J45 asthma (US$42.72 million, 95% CI US$14.80 to US$69.22 million). Asthma-related length of hospitalisation stay attributed to TV varied by subgroups: children aged 0–4 years (177.07 thousand days, 95% CI 58.40 to 289.67 thousand days) generated the largest asthma-related length of hospitalisation stay attributed to TV, followed by children and adolescents aged 5–19 years (102.11 thousand days, 95% CI 37.47 to 163.49 thousand days).

During the study period, the annual hospital admissions showed a marked decrease, from 290.22 million in 2000 to 79.42 million in 2015. The asthma-related hospitalisation rates demonstrated a similar decline trend, with the highest 2.18‰ in 2000 and the lowest 0.50‰ in 2015 (figure 4A). However, the AF of asthma due to TV showed a tendency to increase from 5.32% in 2000 to 5.88% in 2015, which had parallels with the trend of TV0–7 exposure (figure 4B).

In the sensitivity analyses, changing the parameters in the model changed the results minimally (online supplemental tables S3–S7).

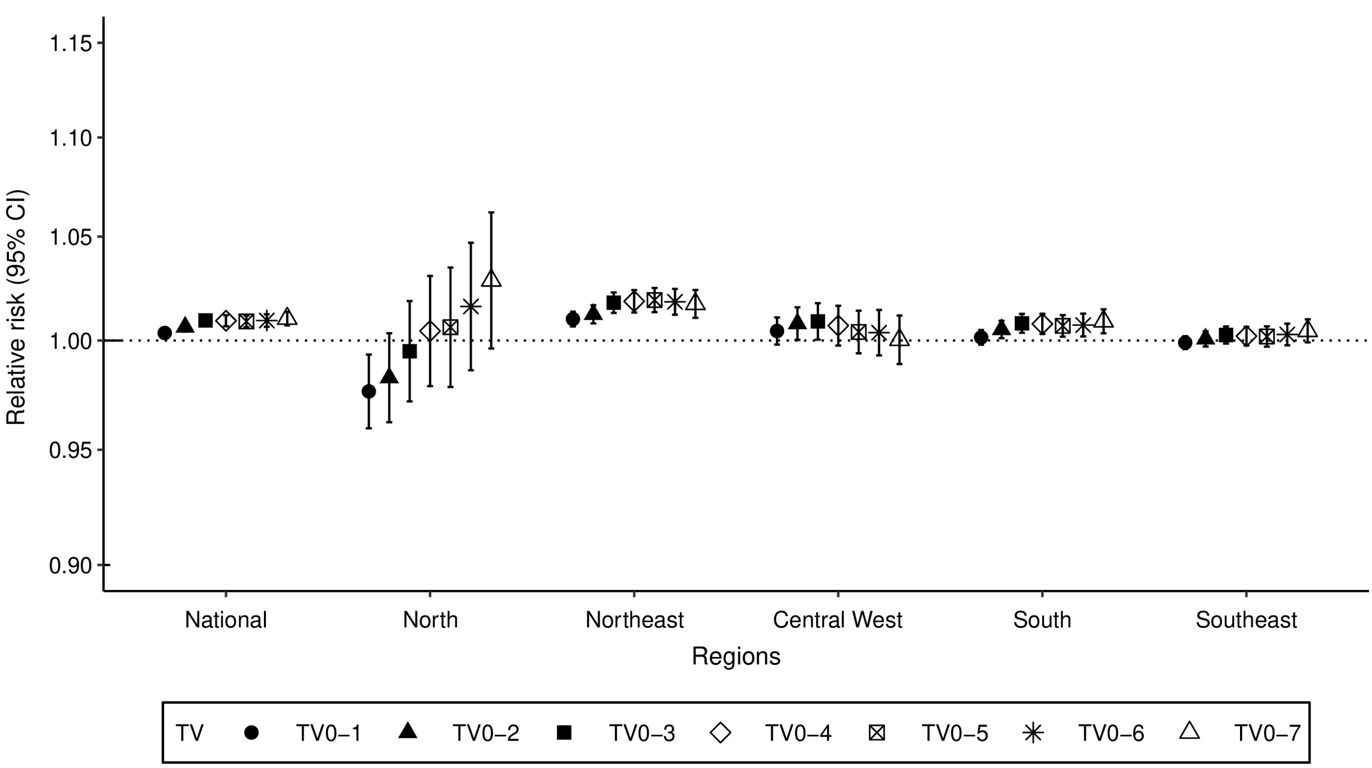

Figure 1 Relative risks (and 95% CIs) for asthma hospitalisations associated with every 1°C increase in TV from TV0–1 to TV0–7 at both national and regional levels. TV, temperature variability.

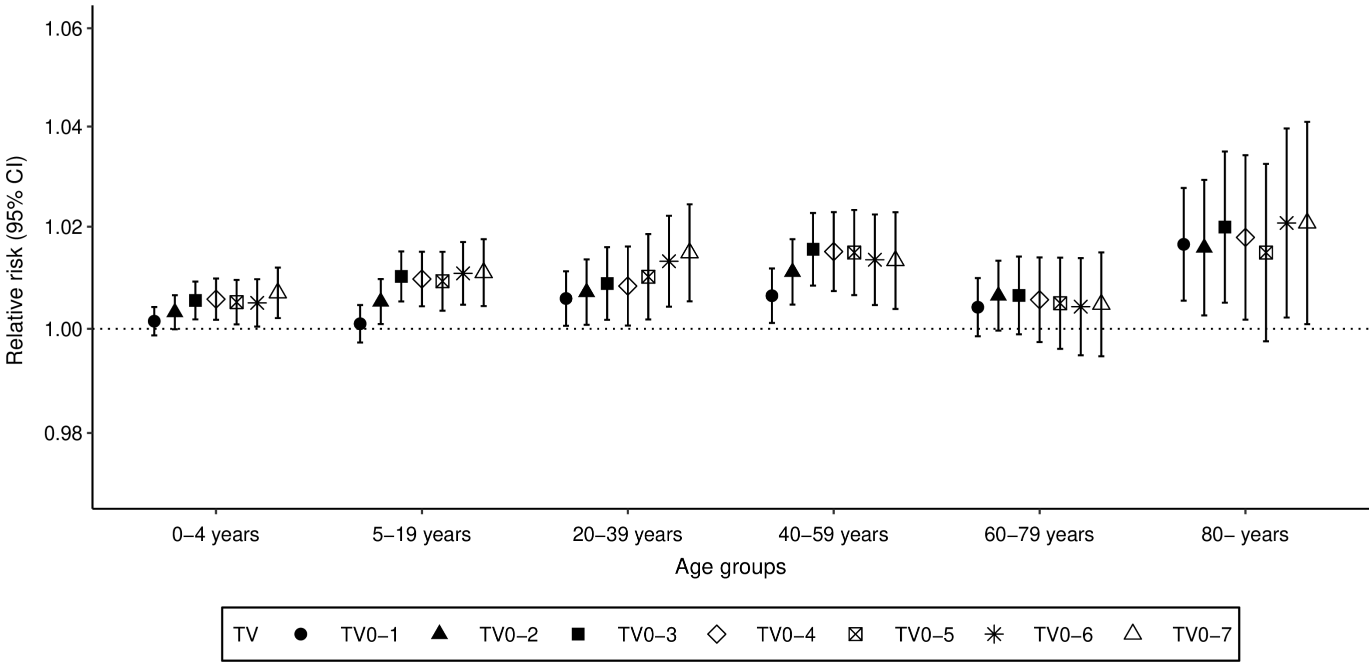

Figure 2 Relative risks (and 95% CIs) for asthma hospitalisations associated with every 1°C increase in TV from TV0–1 to TV0–7 in different age groups. TV, temperature variability.

DISCUSSION

To the best of our knowledge, this is the first and largest study to explore the association between TV and asthma hospitalisations on a national scale in Brazil, even in the world. We found that TV was significantly associated with hospitalisations for asthma. Assuming causality, TV was responsible for about 5.7% asthma hospitalisations in Brazil over 2000–2015, corresponding to considerable healthcare burden and costs.

There are several pathophysiological mechanisms behind the association between asthma onset and TV. First, sudden change in temperature may cause cooling of the upper respiratory tract and subsequent desquamation of mucosal epithelial cells, finally leading to the dysfunction of local respiratory defenses.[14 15] Second, bronchopulmonary vagal afferent nerves could be activated by temperature change. This process involves the provoking of autonomic nerve reflex, finally triggering a

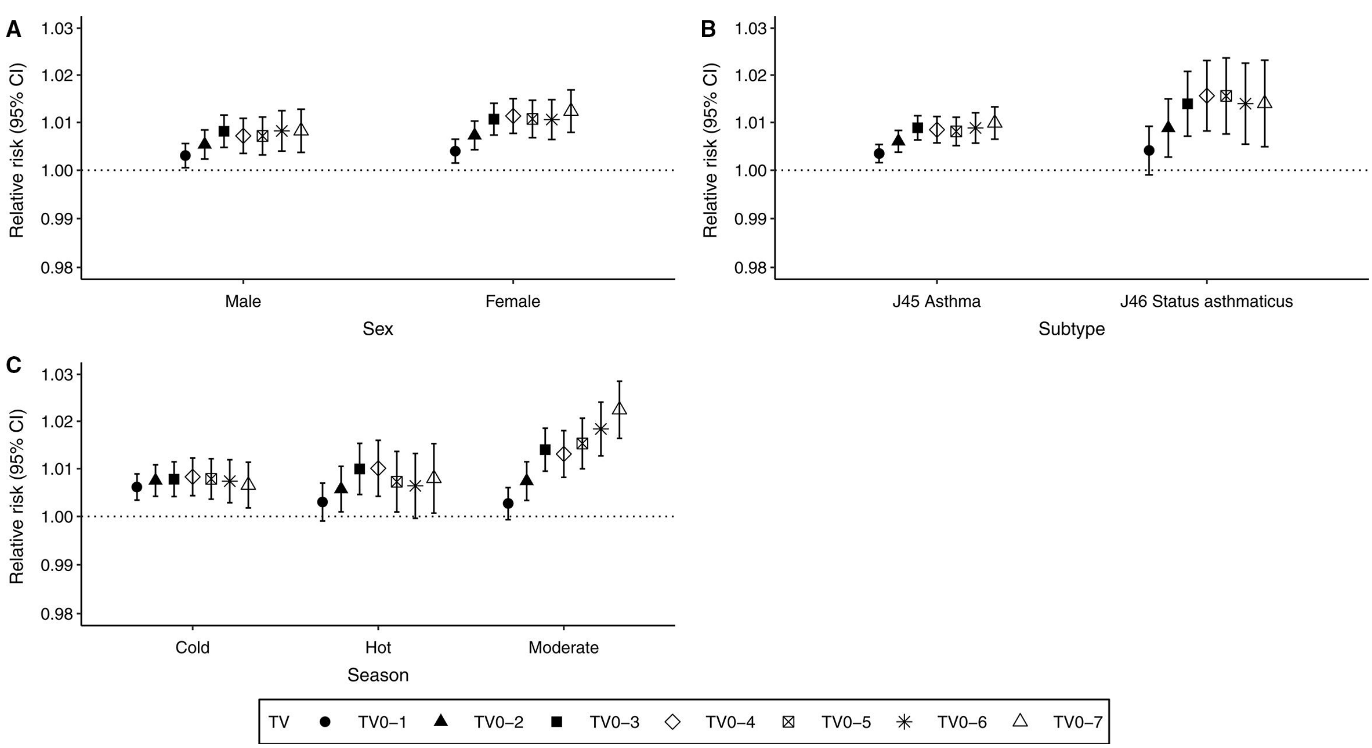

Figure 3 Relative risks (and 95% CIs) for asthma hospitalisations associated with every 1°C increase in TV from TV0–1 to TV0–7 in different subgroups. TV, temperature variability.

Table 3 The attributable fractions, attributable cases, attributable costs and attributable length of hospitalisation stay associated with TV0–7 exposure

Subgroup	Attributable fraction (95% CI, %)	Attributable cases (95% CI, no)	Attributable cost (95% CI, million US$)	Attributable length of hospitalisation stay (95% CI, thousand days)
Overall	5.65 (1.96 to 9.15)	159 305 (55293 to 258054)	48.41 (16.92 to 78.30)	450.44 (156.08 to 729.91)
Age, years				
0–4	5.40 (1.78 to 8.83)	61 825 (20420 to 101109)	18.75 (6.24 to 30.61)	177.07 (58.40 to 289.67)
5–19	5.78 (2.12 to 9.25)	39 812 (14635 to 63719)	11.83 (4.38 to 18.91)	102.11 (37.47 to 163.49)
20–39	5.84 (1.99 to 9.48)	18 471 (6311 to 30010)	5.47 (1.88 to 8.87)	49.38 (16.78 to 80.31)
40–59	5.69 (1.90 to 9.29)	17 546 (5858 to 28651)	5.37 (1.80 to 8.76)	52.77 (17.59 to 86.19)
60–79	5.94 (2.14 to 9.54)	16 643 (6011 to 26747)	5.37 (1.95 to 8.61)	53.25 (19.23 to 85.59)
≥80	6.30 (2.59 to 9.83)	5008 (2058 to 7817)	1.62 (0.66 to 2.53)	15.92 (6.54 to 24.85)
Sex				
Male	5.61 (1.91 to 9.12)	78 262 (26708 to 127177)	23.77 (8.18 to 38.56)	218.81 (74.56 to 355.68)
Female	5.69 (2.01 to 9.19)	81 042 (28585 to 130877)	24.64 (8.74 to 39.74)	231.67 (81.57 to 374.26)
Region				
North	13.60 (–1.97 to 26.68)	7897 (–1145 to 15490)	2.32 (–0.34 to 4.55)	20.01 (–2.90 to 39.26)
Northeast	8.16 (5.14 to 11.08)	106 607 (67149 to 144731)	31.42 (19.79 to 42.65)	292.68 (184.35 to 397.35)
Central West	0.21 (–7.28 to 7.16)	458 (–15673 to 15412)	0.14 (–4.65 to 4.57)	1.27 (–43.54 to 42.81)
South	5.25 (2.01 to 8.38)	23 779 (9086 to 37968)	7.38 (2.82 to 11.78)	74.01 (28.28 to 118.18)
Southeast	2.61 (–0.52 to 5.65)	20 564 (–4123 to 44452)	6.47 (–1.30 to 13.99)	58.46 (–11.72 to 126.36)
Subtype				
J45 Asthma	5.66 (1.95 to 9.19)	139 539 (47 938 to 226 423)	42.72 (14.80 to 69.22)	394.68 (135.48 to 640.55)
J46 Status asthmaticus	5.57 (2.07 to 8.91)	19 766 (7356 to 31631)	5.68 (2.13 to 9.07)	55.72 (20.56 to 89.33)
Season				
Cold	5.57 (1.79 to 9.15)	53 044 (17073 to 87079)	16.03 (5.21 to 26.26)	151.47 (48.66 to 248.74)
Hot	5.78 (2.12 to 9.25)	46 392 (17032 to 74229)	14.21 (5.26 to 22.70)	129.27 (47.39 to 206.91)
Moderate	5.58 (2.00 to 9.00)	48 886 (17502 to 78833)	14.86 (5.34 to 23.93)	138.42 (49.48 to 223.28)

TV, temperature variability.

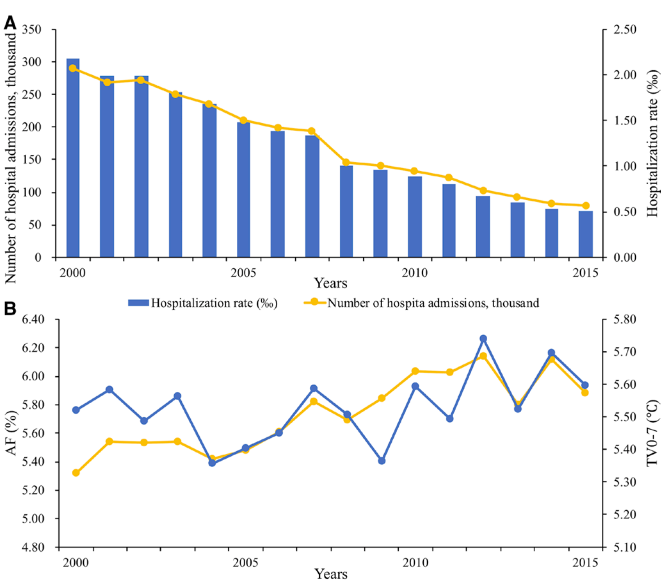

Figure 4 (A) The number of hospitalisations and hospitalisation rates of asthma in 1816 Brazilian cities from 2000 to 2015. (B) The trend of attributable fractions of asthma due to TV and the trend of TV0–7 in 1816 Brazilian cities from 2000 to 2015. AF, attributable fraction; TV, temperature variability.

reduction in peak expiratory flow.[16] Third, temperature change could be responsible for the release of inflammatory mediators by mast cells, affecting the balance of humoral or cellular immunity.[17 18] Fourth, temperature change might act as a mediator to accelerate the transmission of inhalable allergens by a dehydrating effect.[19]

In this study, we used a novel TV indicator which combines both intraday and interday variability of temperature. Although no study has assessed the association between this novel TV indicator and asthma hospitalisations, several studies have assessed the impacts of intra-day changes in temperature (eg, diurnal temperature range).[20–23] Three studies observed a significant relationship between diurnal temperature range and hospital visits for asthma.[20–22] However, a study among children aged 3–18 years reported a significant negative correlation between asthma-related emergency department and diurnal temperature change.[23] The potential reasons might be that the study excluded hospitalisation related to emergency department visits and did not consider the potential lagged associations with temperature change. Notably, using intraday changes in temperature as the sole exposure factor is not sufficient when depicting the impact of temperature change as it cannot capture interday variability of temperature.[9] In this study, TV was used to fully account for both intraday and interday changes in temperature and their lagged associations with hospitalisation for asthma. Our results demonstrated that per 1°C increase in TV0–7 corresponded to a 1.0% (RR 1.010, 95% CI 1.007 to 1.014) increase in the risk of asthma hospitalisation. Although the estimates were small in magnitude, the health and economic burden attributable to TV were considerable.

To our knowledge, few studies focused on the association between asthma and TV among adults. Our study showed that adults, especially the elderly, were also vulnerable to TV related asthma hospitalisations. Particularly, contrary to the younger generations who had increasing association between TV and asthma hospitalisation with longer exposure, the risk in the elderly changed slightly across different exposure periods. Due to the lack of self-management ability, children tend to dress inappropriately when facing a large fluctuation in temperature.[24] In addition, their underdeveloped immune systems may be incapable of offsetting the thermal stress and regulating inflammatory response caused by swings in temperature.[25] Another study summarised that the elderly were vulnerable to change in temperature which might be partly attributed to their weak thermoregulation ability.[26 27] Our results indicated that equal attention should be paid to children, younger adults and the elderly when preventing asthma induced by TV and further research is warranted to focus on the potential differentiated mechanisms.

The associations between TV and asthma hospitalisations were stronger in moderate season than in cold and hot seasons. This might be interpreted by the human behaviour, for example, outdoor activities. In moderate season, people are willing to spend more time to exercise in nature, which has been linked to an increase in allergen exposure and to the increased risk of asthma attack.[28 29] Another reason could be the relatively high level of ozone in springtime.[30 31] Ground-level ozone is a pulmonary irritant that affects the respiratory mucous membranes and respiratory function.[32] Besides, we also observed regional variation in TV vulnerability, which might be the result of different socioeconomic background. The northeast is comparatively underdeveloped, resulting in limited access to asthma control and rescue medications.[33] Conversely, south region is the richest area in Brazil, where people might have more access to asthma treatment.[33] However, there was a misuse of short-acting β-agonist (SABA) to provide quick relief of asthma symptoms in Brazil.[34] Excessive use of SABA was associated with increased risk of severe asthma exacerbations.[35]

In this study, we identified a reduction in asthma-related hospital admissions, which could be the benefit of increasing access to control and rescue medications resulting from economic development.[36] However, both TV and the AF of asthma due to TV had increase trends, implying that there might be an increase in the proportion of health burden for asthma attributed to TV. Our study indicated that rapid change in temperature in a single day and continuous temperature change in several days should be paid more attention in order to prevent the recurrence or exacerbation of asthma.

Strengths and limitations of this study

Our study had several strengths. First, this is a national scale study with a considerably large sample size and time quantum, which allowed us to provided sufficient power for statistical analyses. Second, the time-stratified case-crossover design used in our study allowed us to adjust many risk factors of asthma identified in previous studies (such as obesity and psychosocial problems).[37] Third, Brazil is home to an extraordinary variety of climatic regions with more significant temperature change between night and day than between seasons, which enabled us to give a more complete view of the association between TV and asthma.

The study also had some limitations. First, temperature exposure used in this study was measured at city level, which was less accurate compared with individual-level exposure and might induce underestimation of associations. Second, we could not identify individuals with multiple hospitalisations due to limited access to data. However, this cannot influence our findings, as hospitalisation for asthma is related to severe health status which is not scheduled. Repeated hospitalisation is not only affected by the first admission but also affected by other risk factors (eg, temperature). Our study has ability to examine the impacts of TV on all hospitalisations for asthma. Third, those with mild intermittent asthma might be not included in this study because it is possible for them to receive treatment in the emergency room visits without dispatching to hospital admission. Fourth, there might be misdiagnosis for children <5 years, as there is no gold standard for diagnostic criteria of asthma exacerbation in this age group. However, as doctors had to check any details related to the final diagnosis (eg, family history of asthma, child's history of asthma, comprehensive physical examinations and a series of laboratory tests), the chance for misdiagnosis is small. Therefore, the effect estimates for children <5 years should be slightly affected by the misdiagnosis. Finally, data on pollutants were not controlled in this study, despite its association with increased risk of respiratory diseases.[38 39] However, previous studies suggested that changes in temperature could influence the concentration of air pollutants and not the converse, which means air pollutants tend to act as a mediator and it might be inappropriate to control air pollutants in studies of temperature.[40]

CONCLUSIONS

In conclusion, our study showed that TV was significantly associated with asthma hospitalisations and the corresponding substantial health costs in Brazil. Our findings suggested that preventive measures of asthma should take TV into account. Further investigation is also needed to help clarify the underlying mechanism behind this relationship.

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Contributors YW performed the main analysis and wrote the original draft. RX, MdSZSC and PHS prepared the data and made substantial contributions to the design of the study. BW assisted the analysis and interpretation of data. SL and YG conceived the study, revised the manuscript and was responsible for funding of the study.

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Competing interests None declared.

Patient consent for publication Not required.

Ethics approval Ethical approval was not required for secondary analysis of aggregate anonymised data from the Brazilian Hospital Information System.

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Data availability statement No data are available.

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Supplementary material

Temperature variability and asthma hospitalization in Brazil, 2000-2015: A nationwide case-crossover study

Table S1. Baseline characteristics of 1,816 Brazilian cities, 2000-2015.

Characteristic	Number of cities	Population coverage (%)
Total	1,816	79.0
Region		
North	30	27.0
Northeast	662	78.0
Central west	128	80.7
South	374	83.2
Southeast	622	87.0

Table S2. Consumer price index in Brazil from 2000 to 2015.

Year	Consumer price index compared to previous year (%)	Index	Consumer price index of 2015 compared to current year (%)
2000	107.044	y_{16}	$y_1 \times y_2 \times y_3 \times y_4 \times y_5 \times y_6 \times y_7 \times y_8 \times y_9 \times y_{10} \times y_{11} \times y_{12} \times y_{13} \times y_{14} \times y_{15}$
2001	106.840	y_{15}	$y_1 \times y_2 \times y_3 \times y_4 \times y_5 \times y_6 \times y_7 \times y_8 \times y_9 \times y_{10} \times y_{11} \times y_{12} \times y_{13} \times y_{14}$
2002	108.450	y_{14}	$y_1 \times y_2 \times y_3 \times y_4 \times y_5 \times y_6 \times y_7 \times y_8 \times y_9 \times y_{10} \times y_{11} \times y_{12} \times y_{13}$
2003	114.715	y_{13}	$y_1 \times y_2 \times y_3 \times y_4 \times y_5 \times y_6 \times y_7 \times y_8 \times y_9 \times y_{10} \times y_{11} \times y_{12}$
2004	106.597	y_{12}	$y_1 \times y_2 \times y_3 \times y_4 \times y_5 \times y_6 \times y_7 \times y_8 \times y_9 \times y_{10} \times y_{11}$
2005	106.870	y_{11}	$y_1 \times y_2 \times y_3 \times y_4 \times y_5 \times y_6 \times y_7 \times y_8 \times y_9 \times y_{10}$
2006	104.184	y_{10}	$y_1 \times y_2 \times y_3 \times y_4 \times y_5 \times y_6 \times y_7 \times y_8 \times y_9$
2007	103.641	y_9	$y_1 \times y_2 \times y_3 \times y_4 \times y_5 \times y_6 \times y_7 \times y_8$
2008	105.679	y_8	$y_1 \times y_2 \times y_3 \times y_4 \times y_5 \times y_6 \times y_7$
2009	104.888	y_7	$y_1 \times y_2 \times y_3 \times y_4 \times y_5 \times y_6$
2010	105.039	y_6	$y_1 \times y_2 \times y_3 \times y_4 \times y_5$
2011	106.636	y_5	$y_1 \times y_2 \times y_3 \times y_4$
2012	105.403	y_4	$y_1 \times y_2 \times y_3$
2013	106.204	y_3	$y_1 \times y_2$
2014	106.329	y_2	y_1
2015	109.030	y_1	100

Table S3. Results of sensitivity analyses for TV using different lag period of mean temperature.

Exposure	Lag period	RR (95%CI)	*P* value	*P* for difference
TV0-1	Lag 0-4 days	1.006 (1.004, 1.007)	< 0.001	0.111
TV0-1	Lag 0-5 days	1.005 (1.003, 1.007)	< 0.001	0.317
TV0-1	Lag 0-6 days	1.004 (1.002, 1.006)	< 0.001	0.756
TV0-1	Lag 0-7 days *	1.004 (1.002, 1.005)	< 0.001	Ref.
TV0-1	Lag 0-8 days	1.003 (1.002, 1.005)	< 0.001	0.944
TV0-1	Lag 0-9 days	1.004 (1.002, 1.005)	< 0.001	0.966
TV0-1	Lag 0-10 days	1.004 (1.002, 1.005)	< 0.001	0.965
TV0-2	Lag 0-4 days	1.008 (1.006, 1.010)	< 0.001	0.318
TV0-2	Lag 0-5 days	1.008 (1.006, 1.010)	< 0.001	0.369
TV0-2	Lag 0-6 days	1.007 (1.005, 1.009)	< 0.001	0.673
TV0-2	Lag 0-7 days *	1.006 (1.004, 1.008)	< 0.001	Ref.
TV0-2	Lag 0-8 days	1.006 (1.004, 1.008)	< 0.001	0.847
TV0-2	Lag 0-9 days	1.006 (1.004, 1.008)	< 0.001	0.687
TV0-2	Lag 0-10 days	1.006 (1.004, 1.008)	< 0.001	0.649
TV0-3	Lag 0-4 days	1.010 (1.007, 1.012)	< 0.001	0.893
TV0-3	Lag 0-5 days	1.009 (1.007, 1.011)	< 0.001	0.752
TV0-3	Lag 0-6 days	1.009 (1.007, 1.012)	< 0.001	0.869
TV0-3	Lag 0-7 days *	1.009 (1.007, 1.012)	< 0.001	Ref.
TV0-3	Lag 0-8 days	1.009 (1.007, 1.012)	< 0.001	0.974
TV0-3	Lag 0-9 days	1.009 (1.007, 1.011)	< 0.001	0.761
TV0-3	Lag 0-10 days	1.008 (1.006, 1.011)	< 0.001	0.562
TV0-4	Lag 0-4 days	1.012 (1.009, 1.014)	< 0.001	0.219
TV0-4	Lag 0-5 days	1.009 (1.006, 1.012)	< 0.001	0.869
TV0-4	Lag 0-6 days	1.009 (1.006, 1.011)	< 0.001	0.694
TV0-4	Lag 0-7 days *	1.009 (1.007, 1.012)	< 0.001	Ref.
TV0-4	Lag 0-8 days	1.010 (1.007, 1.012)	< 0.001	0.902
TV0-4	Lag 0-9 days	1.009 (1.007, 1.012)	< 0.001	0.992
TV0-4	Lag 0-10 days	1.009 (1.006, 1.011)	< 0.001	0.807
TV0-5	Lag 0-4 days	1.013 (1.010, 1.016)	< 0.001	0.043
TV0-5	Lag 0-5 days	1.012 (1.009, 1.015)	< 0.001	0.146
TV0-5	Lag 0-6 days	1.010 (1.007, 1.012)	< 0.001	0.788
TV0-5	Lag 0-7 days *	1.009 (1.006, 1.012)	< 0.001	Ref.
TV0-5	Lag 0-8 days	1.009 (1.006, 1.012)	< 0.001	0.942
TV0-5	Lag 0-9 days	1.009 (1.006, 1.012)	< 0.001	0.945
TV0-5	Lag 0-10 days	1.009 (1.006, 1.012)	< 0.001	0.998
TV0-6	Lag 0-4 days	1.014 (1.011, 1.017)	< 0.001	0.038
TV0-6	Lag 0-5 days	1.013 (1.010, 1.016)	< 0.001	0.063
TV0-6	Lag 0-6 days	1.012 (1.009, 1.015)	< 0.001	0.231
TV0-6	Lag 0-7 days *	1.009 (1.006, 1.012)	< 0.001	Ref.
TV0-6	Lag 0-8 days	1.009 (1.006, 1.012)	< 0.001	0.798

TV0-6	Lag 0-9 days	1.009 (1.006, 1.012)	< 0.001	0.790
TV0-6	Lag 0-10 days	1.009 (1.006, 1.012)	< 0.001	0.809
TV0-7	Lag 0-4 days	1.014 (1.010, 1.017)	< 0.001	0.149
TV0-7	Lag 0-5 days	1.013 (1.010, 1.016)	< 0.001	0.273
TV0-7	Lag 0-6 days	1.012 (1.009, 1.015)	< 0.001	0.529
TV0-7	Lag 0-7 days *	1.010 (1.007, 1.014)	< 0.001	Ref.
TV0-7	Lag 0-8 days	1.009 (1.006, 1.012)	< 0.001	0.595
TV0-7	Lag 0-9 days	1.009 (1.005, 1.012)	< 0.001	0.426
TV0-7	Lag 0-10 days	1.008 (1.005, 1.012)	< 0.001	0.385

*: primary model. Definition of abbreviations: TV = temperature variability; RR = relative risk; CI = confidence interval; Ref. = reference.

Table S4. Results of sensitivity analyses for TV using different degrees of freedom for mean temperature.

Exposure	df for mean temperature	RR (95%CI)	*P* value	*P* for difference
TV0-1	3 *	1.004 (1.002, 1.005)	< 0.001	Ref.
TV0-1	4	1.003 (1.002, 1.005)	< 0.001	0.933
TV0-1	5	1.003 (1.002, 1.005)	< 0.001	0.941
TV0-1	6	1.003 (1.002, 1.005)	< 0.001	0.928
TV0-2	3 *	1.006 (1.004, 1.008)	< 0.001	Ref.
TV0-2	4	1.006 (1.004, 1.008)	< 0.001	0.946
TV0-2	5	1.006 (1.004, 1.008)	< 0.001	0.951
TV0-2	6	1.006 (1.004, 1.008)	< 0.001	0.941
TV0-3	3 *	1.009 (1.007, 1.012)	< 0.001	Ref.
TV0-3	4	1.009 (1.007, 1.012)	< 0.001	0.954
TV0-3	5	1.009 (1.007, 1.012)	< 0.001	0.953
TV0-3	6	1.009 (1.007, 1.012)	< 0.001	0.946
TV0-4	3 *	1.009 (1.007, 1.012)	< 0.001	Ref.
TV0-4	4	1.009 (1.007, 1.012)	< 0.001	0.945
TV0-4	5	1.009 (1.007, 1.012)	< 0.001	0.940
TV0-4	6	1.009 (1.007, 1.012)	< 0.001	0.934
TV0-5	3 *	1.009 (1.006, 1.012)	< 0.001	Ref.
TV0-5	4	1.009 (1.006, 1.012)	< 0.001	0.940
TV0-5	5	1.009 (1.006, 1.012)	< 0.001	0.934
TV0-5	6	1.009 (1.006, 1.012)	< 0.001	0.929
TV0-6	3 *	1.009 (1.006, 1.012)	< 0.001	Ref.
TV0-6	4	1.009 (1.006, 1.012)	< 0.001	0.947
TV0-6	5	1.009 (1.006, 1.012)	< 0.001	0.939
TV0-6	6	1.009 (1.006, 1.012)	< 0.001	0.935
TV0-7	3 *	1.010 (1.007, 1.014)	< 0.001	Ref.
TV0-7	4	1.010 (1.007, 1.013)	< 0.001	0.961
TV0-7	5	1.010 (1.007, 1.013)	< 0.001	0.952
TV0-7	6	1.010 (1.007, 1.013)	< 0.001	0.949

*: primary model. Definition of abbreviations: TV = temperature variability; df = degrees of freedom; RR = relative risk; CI = confidence interval; Ref. = reference.

Table S5. Results of sensitivity analyses for TV using different df for lag days of mean temperature.

Exposure	df for lag days	RR (95%CI)	*P* value	*P* for difference
TV0-1	3 *	1.004 (1.002, 1.005)	< 0.001	Ref.
TV0-1	4	1.004 (1.002, 1.006)	< 0.001	0.664
TV0-1	5	1.004 (1.003, 1.006)	< 0.001	0.549
TV0-1	6	1.004 (1.003, 1.006)	< 0.001	0.539
TV0-2	3 *	1.006 (1.004, 1.008)	< 0.001	Ref.
TV0-2	4	1.007 (1.005, 1.009)	< 0.001	0.799
TV0-2	5	1.007 (1.004, 1.009)	< 0.001	0.875
TV0-2	6	1.007 (1.005, 1.009)	< 0.001	0.824
TV0-3	3 *	1.009 (1.007, 1.012)	< 0.001	Ref.
TV0-3	4	1.009 (1.006, 1.011)	< 0.001	0.682
TV0-3	5	1.009 (1.006, 1.011)	< 0.001	0.664
TV0-3	6	1.009 (1.006, 1.011)	< 0.001	0.581
TV0-4	3 *	1.009 (1.007, 1.012)	< 0.001	Ref.
TV0-4	4	1.009 (1.006, 1.011)	< 0.001	0.680
TV0-4	5	1.009 (1.006, 1.011)	< 0.001	0.741
TV0-4	6	1.009 (1.006, 1.011)	< 0.001	0.797
TV0-5	3 *	1.009 (1.006, 1.012)	< 0.001	Ref.
TV0-5	4	1.009 (1.006, 1.012)	< 0.001	0.963
TV0-5	5	1.009 (1.006, 1.012)	< 0.001	0.979
TV0-5	6	1.009 (1.006, 1.012)	< 0.001	0.945
TV0-6	3 *	1.009 (1.006, 1.012)	< 0.001	Ref.
TV0-6	4	1.010 (1.007, 1.013)	< 0.001	0.859
TV0-6	5	1.010 (1.007, 1.013)	< 0.001	0.892
TV0-6	6	1.010 (1.007, 1.013)	< 0.001	0.924
TV0-7	3 *	1.010 (1.007, 1.014)	< 0.001	Ref.
TV0-7	4	1.010 (1.007, 1.014)	< 0.001	0.944
TV0-7	5	1.010 (1.007, 1.014)	< 0.001	0.965
TV0-7	6	1.010 (1.007, 1.014)	< 0.001	0.994

*: primary model. Definition of abbreviations: TV = temperature variability; df = degrees of freedom; RR = relative risk; CI = confidence interval; Ref. = reference.

Table S6. Results of sensitivity analyses for TV using different degrees of freedom for relative humidity.

Exposure	df for mean temperature	RR (95%CI)	*P* value	*P* for difference
TV0-1	3 *	1.004 (1.002, 1.005)	< 0.001	Ref.
TV0-1	4	1.003 (1.002, 1.005)	< 0.001	0.968
TV0-1	5	1.003 (1.002, 1.005)	< 0.001	0.942
TV0-1	6	1.003 (1.002, 1.005)	< 0.001	0.921
TV0-2	3 *	1.006 (1.004, 1.008)	< 0.001	Ref.
TV0-2	4	1.006 (1.004, 1.008)	< 0.001	0.986
TV0-2	5	1.006 (1.004, 1.008)	< 0.001	0.962
TV0-2	6	1.006 (1.004, 1.008)	< 0.001	0.941
TV0-3	3 *	1.009 (1.007, 1.012)	< 0.001	Ref.
TV0-3	4	1.009 (1.007, 1.012)	< 0.001	1.000
TV0-3	5	1.009 (1.007, 1.012)	< 0.001	0.993
TV0-3	6	1.009 (1.007, 1.012)	< 0.001	0.982
TV0-4	3 *	1.009 (1.007, 1.012)	< 0.001	Ref.
TV0-4	4	1.009 (1.007, 1.012)	< 0.001	0.982
TV0-4	5	1.009 (1.007, 1.012)	< 0.001	0.977
TV0-4	6	1.009 (1.007, 1.012)	< 0.001	0.981
TV0-5	3 *	1.009 (1.006, 1.012)	< 0.001	Ref.
TV0-5	4	1.009 (1.006, 1.012)	< 0.001	0.965
TV0-5	5	1.009 (1.006, 1.012)	< 0.001	0.959
TV0-5	6	1.009 (1.006, 1.012)	< 0.001	0.961
TV0-6	3 *	1.009 (1.006, 1.012)	< 0.001	Ref.
TV0-6	4	1.010 (1.007, 1.013)	< 0.001	0.961
TV0-6	5	1.010 (1.007, 1.013)	< 0.001	0.960
TV0-6	6	1.010 (1.007, 1.013)	< 0.001	0.962
TV0-7	3 *	1.010 (1.007, 1.014)	< 0.001	Ref.
TV0-7	4	1.010 (1.007, 1.014)	< 0.001	0.962
TV0-7	5	1.010 (1.007, 1.014)	< 0.001	0.963
TV0-7	6	1.010 (1.007, 1.014)	< 0.001	0.966

*: primary model. Definition of abbreviations: TV = temperature variability; df = degrees of freedom; RR = relative risk; CI = confidence interval; Ref. = reference.

Table S7. Results of sensitivity analyses for TV using different degrees of freedom for lag days of relative humidity.

Exposure	df for lag days	RR (95%CI)	*P* value	*P* for difference
TV0-1	3 *	1.004 (1.002, 1.005)	< 0.001	Ref.
TV0-1	4	1.005 (1.003, 1.007)	< 0.001	0.329
TV0-1	5	1.005 (1.003, 1.007)	< 0.001	0.280
TV0-1	6	1.005 (1.003, 1.007)	< 0.001	0.269
TV0-2	3 *	1.006 (1.004, 1.008)	< 0.001	Ref.
TV0-2	4	1.006 (1.004, 1.009)	< 0.001	0.955
TV0-2	5	1.006 (1.004, 1.008)	< 0.001	0.947
TV0-2	6	1.006 (1.004, 1.008)	< 0.001	0.941
TV0-3	3 *	1.009 (1.007, 1.012)	< 0.001	Ref.
TV0-3	4	1.009 (1.006, 1.011)	< 0.001	0.609
TV0-3	5	1.009 (1.006, 1.011)	< 0.001	0.695
TV0-3	6	1.009 (1.006, 1.011)	< 0.001	0.660
TV0-4	3 *	1.009 (1.007, 1.012)	< 0.001	Ref.
TV0-4	4	1.009 (1.006, 1.011)	< 0.001	0.813
TV0-4	5	1.009 (1.007, 1.012)	< 0.001	0.909
TV0-4	6	1.009 (1.007, 1.012)	< 0.001	0.955
TV0-5	3 *	1.009 (1.006, 1.012)	< 0.001	Ref.
TV0-5	4	1.009 (1.007, 1.012)	< 0.001	0.835
TV0-5	5	1.009 (1.007, 1.012)	< 0.001	0.855
TV0-5	6	1.009 (1.007, 1.012)	< 0.001	0.834
TV0-6	3 *	1.009 (1.006, 1.012)	< 0.001	Ref.
TV0-6	4	1.010 (1.007, 1.013)	< 0.001	0.783
TV0-6	5	1.010 (1.007, 1.013)	< 0.001	0.820
TV0-6	6	1.010 (1.007, 1.013)	< 0.001	0.860
TV0-7	3 *	1.010 (1.007, 1.014)	< 0.001	Ref.
TV0-7	4	1.010 (1.007, 1.014)	< 0.001	0.999
TV0-7	5	1.010 (1.007, 1.014)	< 0.001	1.000
TV0-7	6	1.010 (1.007, 1.014)	< 0.001	0.991

*: primary model. Definition of abbreviations: TV = temperature variability; df = degrees of freedom; RR = relative risk; CI = confidence interval; Ref. = reference.