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Heat exposure and pediatric immune thrombocytopenia in Japan from 2011 to 2022: a nationwide space-time-stratified case-crossover study

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draft of the manuscript. All authors critically reviewed and revised the first draft. All authors approved the final draft of the manuscript. Additionally, all authors had full access to all the data in the study and bear final responsibility for the decision to submit for publication. The corresponding author attests that all listed authors meet the authorship criteria and that no one meeting the criteria has been omitted.

Pediatric immune thrombocytopenia (ITP) is a hematological disorder in children, with an estimated annual incidence of 2–7 cases per 100,000 (1). ITP is caused by an autoimmune reaction targeting circulating platelets in the peripheral blood and megakaryocytes in the bone marrow, resulting in thrombocytopenia and an increased risk of bleeding (1). Research suggests that environmental factors, such as viral infections, may play a role in triggering pediatric ITP (2-4). However, the environmental triggers for pediatric ITP onset remain largely unexplored.

Previous studies have reported mixed findings regarding seasonal changes in the number of pediatric ITP hospitalizations. A large study involving approximately 2,000 patients from the Intercontinental Childhood ITP Registry found a seasonal variation in the onset of pediatric ITP (5), with a higher incidence observed in spring and early summer and lower rates in autumn. In contrast, a study from Japan reported no significant seasonal variation (3). However, these studies were based on monthly patient data, and research examining the influence of daily temperature fluctuations on pediatric ITP hospital admissions remains lacking. To address this gap, this study aims to investigate the association between daily ambient temperature and pediatric ITP hospitalizations in Japan.

Drawing on methods used in our previous studies (6, 7), we obtained data from the Diagnosis Procedure Combination (DPC) database, Japan's nationwide administrative claims database. Patients under 15 years of age who were hospitalized for pediatric ITP from 2011 to 2022 were identified based on the corresponding ICD-10 codes (D693). We focused our analysis on hospitalizations during the five hottest months (May to September), as heat was the primary exposure of interest (7). Hospitalizations due to recent, recurrent cases of pediatric ITP were excluded. This study was approved by the Medical Research Ethics Committee at Institute of Science Tokyo. Since the data were anonymized, obtaining informed consent was not required.

We obtained temperature data for each prefecture from May to September for the years 2011–2022 from the Japan Meteorological Agency. Daily mean temperature was calculated by averaging hourly measurements from 1:00 a.m. to midnight. We applied a space-time-stratified case-crossover design to examine the association between daily mean temperature and pediatric ITP hospitalization within each prefecture (8). We matched case days with control days that occurred in the same month, same year, and day of the week within the same prefecture. We compared the temperature on the case day with the temperatures on the control days within the same stratum to estimate the relative risk (RR), adjusting for the effects of day of the week, seasonality, and long-term trend through stratification of time by month and day of the week (8). We used a conditional quasi-Poisson regression model to estimate the RR of pediatric ITP hospitalization associated with daily mean temperature. Furthermore, we used distributed lag nonlinear models to explore the nonlinear association between daily mean temperature and the risk of pediatric ITP, taking lagged effects into account (6).

For the association between exposure and response, we applied a natural cubic spline for temperature, placing three knots at the 25th, 50th, 75th percentiles of the exposure range across the 47 prefectures. For the association between lag and response, we used a natural cubic spline with two knots spaced equally on a logarithmic scale for lag days. We used a lag period of 0-4 days to examine the lagged effect of each exposure on pediatric ITP hospitalization, with the temperature associated with the lowest risk used as the reference. In order to examine potential geographical differences, we performed a meta-regression using region indicators as fixed-effect meta-predictors (9). A multivariate Wald test was applied to assess the significance of the meta-predictors.

We also performed sensitivity analyses by adjusting the position of the three knots for temperature to the 10th, 50th, and 90th percentiles of the exposure range, changing the

number of knots for temperature from three to two, and modifying the lag days from four to three, five, and six. In an additional sensitivity analysis, regionally aggregated data were used to examine the association between heat exposure and pediatric ITP hospitalizations. For this analysis, the classification of regions was determined based on climatic similarities, following the categorization by the Japan Meteorological Agency. As the data is available only at the prefectural level, Okinawa and Amami were combined with the western region, resulting in a three-region classification: Northern region, Eastern region, and Western region. The daily mean temperature for each prefecture within a region was averaged to calculate the regional mean temperature. A space-time-stratified case-crossover design was applied to assess the association between daily mean temperature and pediatric ITP hospitalizations within each region, by matching case days to control days that corresponded to the same month, year, and day of the week within the same region (8). All analyses were performed using R version 4.4.1 (R Development Core Team, Vienna, Austria, 2014).

Table 1 presents summary statistics for hospitalizations due to pediatric ITP in each prefecture. A total of 3,908 hospitalizations occurred during the study period, with male patients accounting for 53.7% of cases and a mean age of 4.4 years (SD = 3.9). The median temperature across all prefectures during this period was 24.0□.

Figure 1a illustrates the association between daily mean temperature and hospitalizations for pediatric ITP, based on the cumulative RR for the 0-4 day lag period. Higher mean temperatures were associated with an increased risk of hospitalization. Specifically, exposure to extreme high daily mean temperatures (99th percentile high temperature) was associated with a 67% higher risk of hospitalization (RR 1.67, 95% CI:1.33, 2.09). Figure 1b depicts the lag-response curve, showing a delayed effect of elevated temperatures on hospitalizations, with a notable increase in risk occurring around 2–3 days after exposure. We also conducted a meta-regression using region indicators as fixed-effect

meta-predictors to examine potential geographical differences. The analysis revealed no geographical differences in the association between daily mean temperature and pediatric ITP hospitalizations.

Table 2 presents the results of the sensitivity analyses. Similar results were observed in the sensitivity analysis. Supplementary Table 1 presents the summary statistics for daily mean temperature and pediatric ITP hospitalizations by region. Supplementary Figure 1a illustrates the association between daily mean temperatures and hospitalizations for pediatric ITP using regionally aggregated data. Supplementary Figure 1b shows the lag-response curve. Our findings remained consistent when regionally aggregated data were used.

Earlier research has shown inconsistent results concerning seasonal fluctuations in pediatric ITP hospitalizations (3, 5). It is important to note that these studies were based on monthly patient data. A key strength of our study is the use of daily ambient temperature data and daily pediatric ITP hospitalization data from Japan's administrative claims database, which includes approximately 4,000 pediatric ITP patients. Additionally, distributed lag nonlinear models allow us to capture the nonlinear relationship between daily mean temperature and the risk of pediatric ITP, while also accounting for lagged effects.

There are several potential mechanisms that could explain the association between high temperature and pediatric ITP. First, it is well known that more than half of pediatric ITP cases are preceded by viral infections (2, 4). Viral infections can contribute to ITP through molecular mimicry between viral antigens and host platelet proteins, as well as through nonspecific stimulation of the immune system (10-12). When children are exposed to high ambient temperatures during a viral infection that increases the risk of ITP, this exposure could potentially lead to excessive inflammation and nonspecific immune system activation, triggering an autoimmune response and ultimately resulting in the development of pediatric ITP. Secondly, pollen may be another potential mechanism (13). Higher

temperatures are associated with increased levels of airborne pollen (14). A previous study in children reported a link between allergic diseases and ITP (15), suggesting that the association between high temperatures and the risk of ITP hospitalization in our study could be partially explained by elevated pollen levels associated with higher temperatures. However, the association between pollen levels and ITP hospitalizations has only been briefly mentioned in previous research (13), and no empirical studies have yet confirmed this link, underscoring the need for further investigation.

Our study has several limitations (7). First, we relied on daily meteorological data from fixed observatories as a proxy for individual exposure, which may subject to non-differential misclassification bias in exposure. Second, there is a potential for non-differential misclassification of the outcome. Third, because not all hospitals in Japan utilize the DPC system, our findings may be subject to sampling bias.

In conclusion, this study found that exposure to extreme high daily mean temperatures was associated with an increased risk of hospitalization for pediatric ITP. To our knowledge, this is the first study to show the association between higher mean temperatures and an increased risk of pediatric ITP. Our study suggests that healthcare providers should prepare for a possible increase in pediatric ITP cases on days with higher temperatures, which are anticipated to occur more frequently and with greater intensity due to ongoing climate change (7).

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Table 1. Descriptive statistics on hospitalizations for pediatric immune thrombocytopenia by prefecture from May through September, 2011–2022.

Prefecture	Hospitalizations	
	Cases (n)	Male (%)
Hokkaido	159	56.0
Aomori	40	55.0
Iwate	41	56.1
Miyagi	52	59.6
Akita	23	47.8
Yamagata	54	48.1
Fukushima	64	54.7
Ibaraki	78	66.7
Tochigi	75	49.3
Gunma	26	65.4
Saitama	176	44.9
Chiba	187	53.5
Tokyo	326	50.3
Kanagawa	260	56.2
Niigata	41	46.3
Toyama	23	65.2
Ishikawa	46	73.9
Fukui	35	65.7
Yamanashi	15	40.0
Nagano	80	45.0
Gifu	58	50.0
Shizuoka	122	49.2
Aichi	251	54.2
Mie	55	41.8
Shiga	34	41.2
Kyoto	78	59.0
Osaka	266	50.4
Hyogo	134	56.0
Nara	24	66.7
Wakayama	17	64.7
Tottori	25	52.0
Shimane	17	58.8

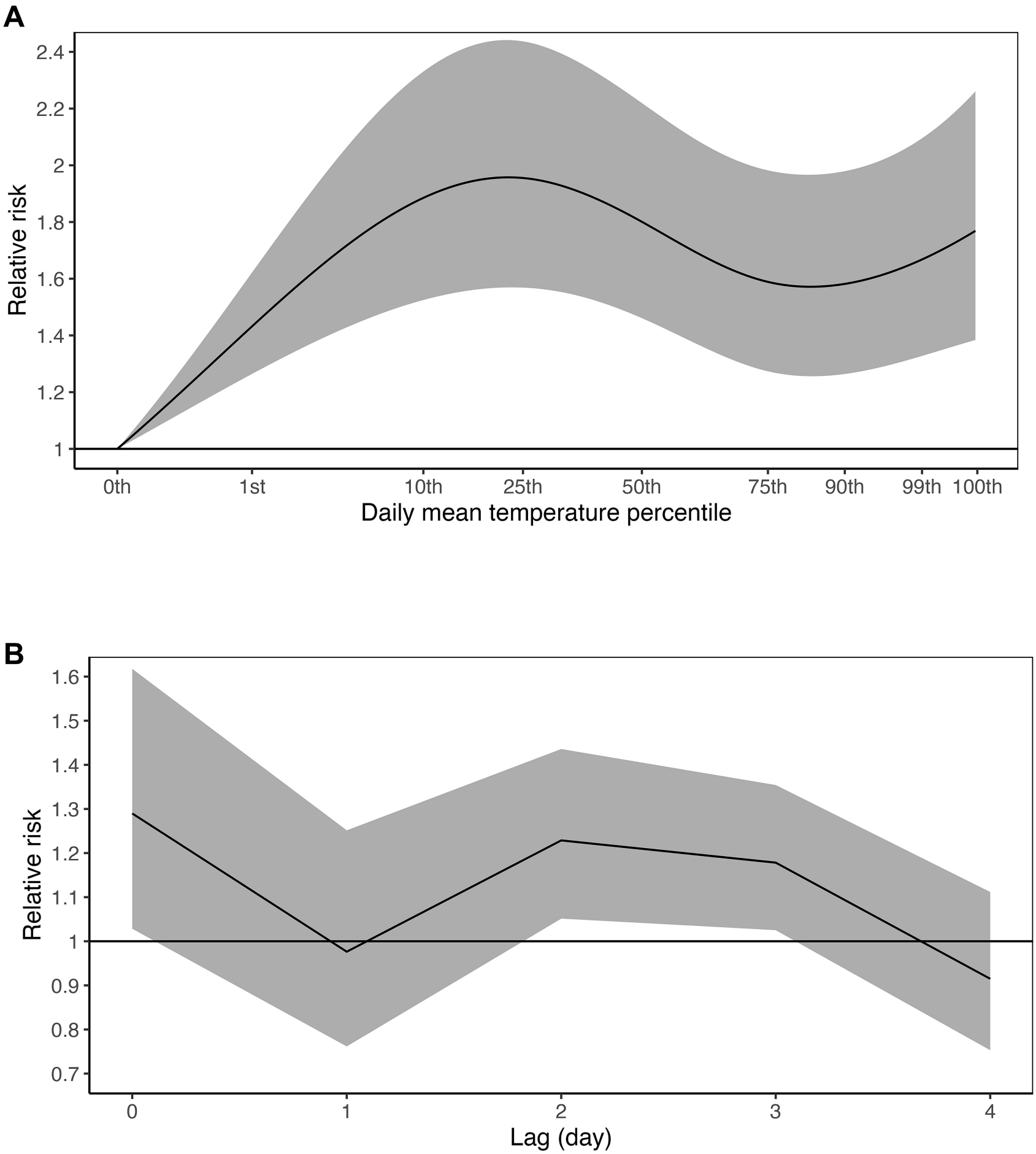
Okayama	70	55.7
Hiroshima	117	46.2
Yamaguchi	66	50.0
Tokushima	15	40.0
Kagawa	56	55.4
Ehime	35	45.7
Kochi	34	35.3
Fukuoka	248	54.4
Saga	45	64.4
Nagasaki	51	60.8
Kumamoto	74	60.8
Oita	47	74.5
Miyazaki	27	63.0
Kagoshima	68	55.9
Okinawa	73	60.3
Total	3,908	53.7

Table 2. Sensitivity analysis of pooled association between daily mean temperature and hospitalization for pediatric immune thrombocytopenia

Model	RR (95% CI)
Lag 3 days	1.61 (1.30, 2.00) [a]
Lag 5 days	1.46 (1.16, 1.85) [a]
Lag 6 days	1.34 (1.05, 1.72) [a]
2 Knots (33th, 67th)	1.67 (1.34, 2.08) [a]
3 Knots (10th, 50th, 90th)	1.67 (1.32, 2.11) [a]
Three regions	2.02 (1.12, 3.63) [a]

[a] $p<0.05$.

Figure 1. Association between daily mean temperatures and hospitalizations for pediatric immune thrombocytopenia using prefectural data. (a) Relative risks of hospitalization for pediatric immune thrombocytopenia associated with daily mean temperature over a lag of 0-4 days. (b) Relative risks of hospitalization for pediatric immune thrombocytopenia associated with extreme high daily mean temperatures (99th percentile) along a lag of 0-4 days.


A
Relative risk
2.4
2.2
2
1.8
1.6
1.4
1.2
1
0th
1st
10th
25th
50th
75th
90th
99th
100th
Daily mean temperature percentile
B
Relative risk
1.6
1.5
1.4
1.3
1.2
1.1
1
0.9
0.8
0.7
0
1
2
3
4
Lag (day)

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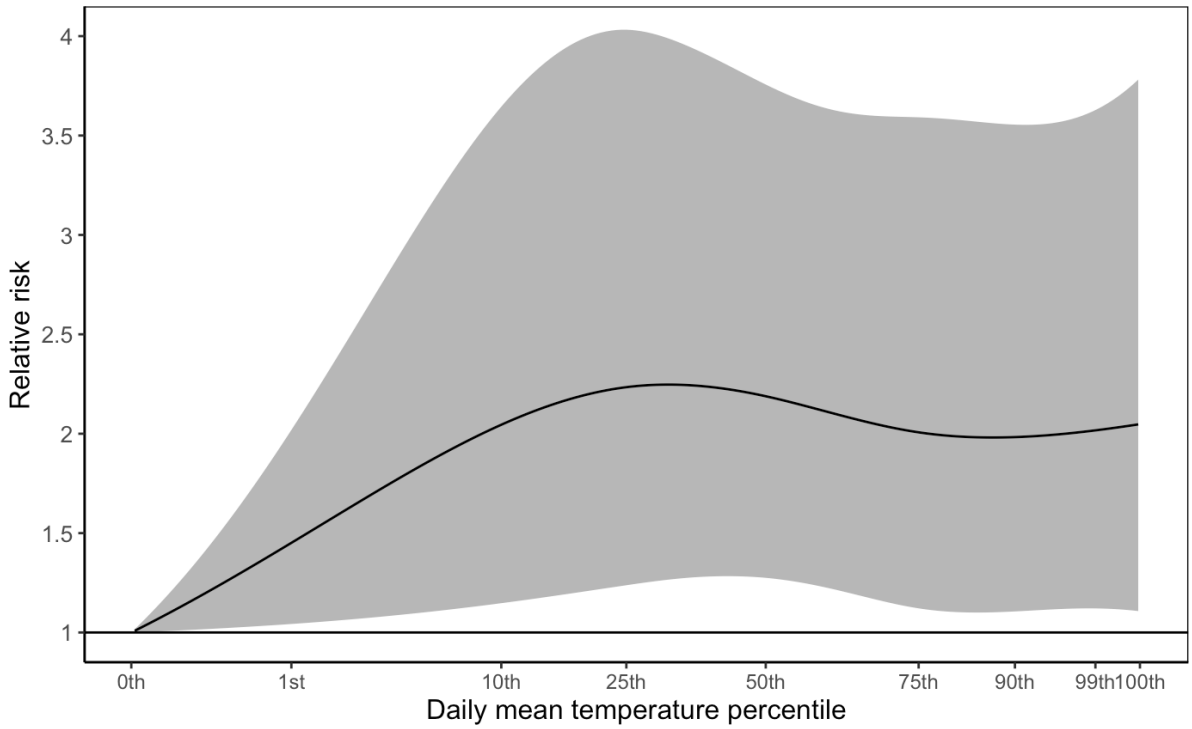
Supplementary Table 1. Descriptive statistics on daily mean temperature and hospitalizations for pediatric immune thrombocytopenia by region from May through September, 2011–2022.

Region	Hospitalizations		Daily mean temperature (℃)								
	Cases (n)	Male (%)	Min	1st	10th	25th	50th	75th	90th	99th	100th
Northern	433	54.7	7.5	10.7	15.3	18.2	21.1	24.0	26.4	28.4	29.3
Eastern	1,854	52.6	11.6	14.5	18.7	21.0	23.6	26.9	28.8	30.3	31.4
Western	1,621	54.5	13.1	16.4	20.1	22.3	25.0	27.9	29.3	30.6	31.2
Total	3,908	53.7	10.7	13.9	18.0	20.5	23.2	26.3	28.2	29.8	30.6

Supplementary Figure 1 Association between daily mean temperatures and hospitalizations for pediatric immune thrombocytopenia using regionally aggregated data

(a) Relative risks of hospitalization for pediatric immune thrombocytopenia associated with daily mean temperature over a lag of 0–4 days



(b) Relative risks of hospitalization for pediatric immune thrombocytopenia associated with extreme high daily mean temperatures (99th percentile) along a lag of 0–4 days