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RESEARCH ARTICLE

Association between ambient temperature and childhood respiratory hospital visits in Beijing, China: a time-series study (2013–2017)

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Abstract

Little is known on the potential impact of temperature on respiratory morbidity, especially for children whose respiratory system can be more vulnerable to climate changes. In this time-series study, Poisson generalized additive models combined with distributed lag nonlinear models were used to assess the associations between ambient temperature and childhood respiratory morbidity. The impacts of extreme cold and hot temperatures were calculated as cumulative relative risks (cum.RRs) at the 1st and 99th temperature percentiles relative to the minimum morbidity temperature percentile. Attributable fractions of respiratory morbidity due to cold or heat were calculated for temperatures below or above the minimum morbidity temperature. Effect modifications by air pollution, age, and sex were assessed in stratified analyses. A total of 877,793 respiratory hospital visits of children under 14 years old between 2013 and 2017 were collected from Beijing Children's Hospital. Overall, we observed J-shaped associations with greater respiratory morbidity risks for exposure to lower temperatures, and higher fraction of all-cause respiratory hospital visits was caused by cold (33.1%) than by heat (0.9%). Relative to the minimum morbidity temperature (25 °C, except for rhinitis, which is 31 °C), the cum.RRs for extreme cold temperature (-6 °C) were 2.64 (95%CI: 1.51–4.61) for all-cause respiratory hospital visits, 2.73 (95%CI: 1.44–5.18) for upper respiratory infection, 2.76 (95%CI: 1.56–4.89) for bronchitis, 2.12 (95%CI: 1.30–3.47) for pneumonia, 2.06 (95%CI: 1.27–3.34) for rhinitis, and 4.02 (95%CI: 2.14–7.55) for asthma, whereas the associations between extreme hot temperature (29 °C) and respiratory hospital visits were not significant. The impacts of extreme cold temperature on asthma hospital visits were greater at higher levels of ozone (O_3) exposure (> 50th percentile). Our findings suggest significantly increased childhood respiratory morbidity risks at extreme cold temperature, and the impact of extreme cold temperature on asthma hospital visits can be enhanced under higher level exposure to O_3.

Keywords Ambient temperature · Respiratory disease · Air pollution · Outpatient visits · Emergency room visits · Children

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Introduction

Climate change has become a global public health challenge with increasing concern on the adverse health effects, including respiratory diseases (Patz et al. 2014). Several studies have also used the attributable fraction (AF), defined as the fraction of cases that would not have occurred in the absence of a specific risk factor in the exposed population, to assess the disease burden (Li et al. 2020; Wang et al. 2020). In China, the AF due to non-optimum temperature was 10.57% for respiratory mortality in recent years (Chen et al. 2018b). The optimum temperatures that correspond to minimum morbidity refer to the minimum morbidity temperature and the temperatures higher or lower than "optimum temperature" can be an airway stimulus to the airway to induce bronchoconstriction (Chen et al. 2018b; Deng et al. 2020).

For respiratory diseases, both extreme cold and hot temperatures can likely activate transient receptor potential proteins (TRPs) in upper and lower respiratory tract and cause airway inflammation and hyper-responsiveness (Deng et al. 2020). Population studies have reported J- or U-shaped relationships between daily mean temperature and respiratory mortality, with increasing mortality risks from minimum mortality temperature to lowest and highest temperatures (Ma et al. 2014; Xu et al. 2012). Studies also reported that the impacts of extreme cold temperature were stronger than those of extreme hot temperature, because general population tend to be more adapted to warm weather than cold weather even under the context of global warming (Lam et al. 2016; Li et al. 2020). Compared with adults and the elderly, children and adolescents appeared to be more susceptible to temperature changes (Ma et al. 2019; Chai et al. 2020), who might be more vulnerable respiratory and immune systems under development (Strosnider et al. 2019). However, epidemiological study on respiratory morbidity among children has been limited and warrants more research.

Little is known about whether air pollution can modify the respiratory effects of ambient temperature to some extents. Several studies have assessed the impact of environmental risk factors on respiratory morbidity, such as ambient temperature and air pollutants (Karakatsani et al. 2017; Lam et al. 2016; Li et al. 2015; Sun et al. 2018). Few studies of mortality have found that ozone (O_3) significantly modified the impacts of temperature on total and cardiovascular mortality, but the modification effect on respiratory health has been barely investigated (Breitner et al. 2014; Chen et al. 2018a).

In this study, we aimed to examine the associations between ambient temperature and respiratory hospital visits for all-cause, URI, bronchitis, pneumonia, rhinitis, and asthma in children under 14 years old in Beijing, China, as well as to quantify the burdens of corresponding respiratory disease burden attributable to both cold and heat. We also explored the potential effect modifications by air pollution and other risk factors, such as age and sex, on ambient temperature and children respiratory morbidity.

Methods

Participants

We collected daily data on hospital utilization, including outpatient visits and emergency room visits (ERVs), for respiratory diseases between October 2013 and November 2017 from Beijing Children`s Hospital. Outpatient data was unscheduled and first-come first-served in China; thus, the analytical database by including both outpatient visits and ERVs was likely to provide reliable morbidity information for a geographically defined population in our study (Tian et al. 2017; Xu et al. 1995). The database also included information on the date of hospital visits, identification number, sex, age, residential address, and discharge diagnoses with corresponding International Classification of Diseases codes (the 10th Revision, ICD-10). Participants with residential addresses outside metropolitan Beijing area were excluded. The outcomes included hospital visits on all-cause respiratory diseases (J00–J99), upper respiratory infection (URI) (J00–J06), bronchitis (J21), pneumonia (J12–J18, J69), rhinitis (J31), and asthma (J45–46). Participants were classified into three age groups, including those younger than 2 years old (infants), between 2 and 5 years old (preschool children), and between 6 and 14 years old (school-age children) (Lee et al. 2019). This study was approved by the Institutional Review Board of Beijing Children's Hospital, Capital Medical University (IEC-C-028-A10-V.05). The influenza weekly of reports from October 2013 to November 2017 were obtained from the Chinese National Influenza Center (http://www.chinaivdc.cn/); we assigned 1 to influenza epidemics when reports wrote that influenza activities were at intra-seasonal levels in northern China, or 0 otherwise.

Environmental data

Daily 24-h ambient temperature and relative humidity (RH) from October 2013 to November 2017 were obtained from the Chinese Meteorological Bureau (http://data.cma.cn/). Concurrently, hourly particulate matter with aerodynamic diameter less than 2.5 μm ($PM_{2.5}$), nitrogen dioxide (NO_2), sulfur dioxide (SO_2), and O_3 measurements were obtained from the Beijing Environmental Protection Bureau (http://beijingair.sinaapp.com/). We computed 24-h averages for $PM_{2.5}$, NO_2, and SO_2 and calculated the 8-h daily maximum from 8-h running averages for ozone (O_3-8h max) (Wu et al. 2018).

Statistical analysis

Ambient temperature and air pollution data were processed following procedures described earlier (Wu et al. 2019). We then applied Poisson generalized additive models (GAMs) and distributed lag nonlinear models (DLNMs) to provide flexibility for modelling the potentially nonlinear and lagged association between ambient temperature and childhood respiratory hospital visits, with adjustment for influenza epidemic, RH, time trend, public holidays, and day of the week (DOW) (Wu et al. 2018).

First, we built basic models without including ambient temperature and air pollutant variables. A smooth function for time trend with 7 degrees of freedom (DF) per year was chosen to control for seasonality and long-term trends according to previous studies (Lam et al. 2016). We included a smooth function for RH on the same day of hospital visits (lag day 0) with the 6 DF determined by minimizing Akaike's information criterion (AIC) (Rich et al. 2012). Public holidays and DOW were classified as categorical variables. After defining the basic models, we introduced the cross basis function of daily temperature built by the DLNM, which included a cubic B-spline to model the nonlinear temperature effects and a natural cubic spline with 4 DF to examine the lagged effects (Breitner et al. 2014; Lam et al. 2016). A maximum lag of 14 days was used to model the effects of temperature, because the effects of high temperature were usually within 1–3 days and the effects of low temperatures could last about 2–3 weeks (Chen et al. 2018b). The minimum morbidity temperature, which was defined as the temperature that had minimum impact on morbidity risk, was derived from the lowest point of overall cumulative exposure-response curve between temperature and respiratory morbidity (Li et al. 2020; Tobías et al. 2017; Zhao et al. 2019). We then used minimum morbidity temperature as the reference value to calculate the relative risks (RRs) and calculated the impacts of extreme cold and hot temperatures as cumulative morbidity risks at the 1st and 99th percentile relative to the minimum morbidity temperature percentile. The minimum morbidity temperature was also used as the reference for calculating the AFs during the present day and 7 lagged days. For all-cause and cause-specific respiratory hospital visits, we calculated 95% empirical CIs (95% eCIs) of AFs associated with cold or heat by summing the subsets of days with temperatures below or above than the minimum morbidity temperature (Chen et al. 2018b; Gasparrini and Leone 2014; Wang et al. 2020).

We further introduced air pollutant variables ($PM_{2.5}$, NO_2, SO_2, and O_3) separately into the models and used single- and multiple-day lags to estimate the associations between air pollution and respiratory hospital visits in both single- and two-pollutant models. The multiple-day exposure lags were calculated as the average levels of current day and several prior days (e.g., lag days 0–3) (Wu et al. 2018). To examine potential effect modifications by air pollution, we divided the levels of air pollutants into two categories: high (> median value) and low (≤ median value). We further introduced the interaction terms between temperature and categorized air pollutants into the main models (Chen et al. 2018a). The statistical significance of difference in effect estimates across strata of air pollutants was tested by *Z*-test (Xu et al. 2019). Subgroup analyses by age and sex were also performed to identify the most susceptible subpopulation.

Finally, sensitivity analyses were conducted to examine the robustness of associations for extreme temperatures on all-cause and cause-specific respiratory hospital visits reported in main models by (1) applying alternative DF (6–10 per year) for time trend in the models (Ma et al. 2019) and (2) adjusting for the impacts of $PM_{2.5}$, NO_2, SO_2, and O_3. All models were implemented using R version 3.5.3, and a two-sided $P < 0.05$ was considered statistically significant. The effect estimates were presented as RRs and 95% confidence interval (95%CIs).

Results

Data characterization

A total of 877,793 respiratory hospital visits over 1521 days of study period were included in this analysis, including 678,934 outpatient visits and 198,859 ERVs (Table 1). The major

Table 1 Summary statistics of daily all-cause and cause-specific childhood respiratory hospital visits in Beijing, China, 2013–2017

Characteristic	Total, no. (%)	Daily counts, mean
All-cause	877,793 (100)	577
Cause-specific		
URI	383,459 (43.7)	252
Bronchitis	189,180 (21.6)	124
Pneumonia	173,036 (19.7)	114
Rhinitis	60,670 (6.9)	40
Asthma	22,169 (2.5)	15
Hospital utilization		
Outpatient visits	678,934 (77.3)	446
ERVs	198,859 (22.7)	131
Age, year		
<2 years old	229,149 (26.1)	151
2–5 years old	466,328 (53.1)	306
6–14 years old	182,316 (20.8)	120
Sex		
Male	511,009 (58.2)	336
Female	366,784 (41.8)	241

URI upper respiratory infection, *ERVs* emergency room visits

causes were URI, bronchitis, pneumonia, rhinitis, and asthma, accounted for 383,459 (43.7%), 189,180 (21.6%), 173,036 (19.7%), 60,670 (6.9%), and 22,169 (2.5%) of total hospital visits, respectively. A mean daily number of respiratory hospital visits were 577, 151, 306, and 120 for all age combined, infants, preschool children, and school-age children, 336 for male and 241 for female children, respectively. The average temperature and RH during study period were 12.6 °C and 54.0%, ranging from -15.5 to 31.2 °C and from 9.6 to 95.3%, respectively (Table 2). The mean temperatures were -1.5 °C, 15.0 °C, 25.4 °C, and 11.6 °C for winter, spring, summer, and fall, respectively. Average daily concentrations were 75.5 μg/m^3 for $PM_{2.5}$, 45.7 μg/m^3 for NO_2, 11.2 μg/m^3 for SO_2, and 101.4 μg/m^3 for O_3, and the interquartile range (IQR) of $PM_{2.5}$, NO_2, SO_2, and O_3 were 69.3, 25.2, 10.6, and 88.6 μg/m^3, respectively. Figure S1 presents the variations in annual averages of daily levels for temperature and RH, and daily concentrations for $PM_{2.5}$, NO_2, SO_2 and O_3 with decreasing trend of $PM_{2.5}$, NO_2, and SO_2 levels over time. Table S1 shows the Spearman correlation coefficients for the environmental variables, with positive correlations observed between temperature and O_3 concentrations (r = 0.82, P < 0.05) and inversely weak correlations between temperature and $PM_{2.5}$ (r = -0.10, P < 0.05). NO_2 and SO_2 were negatively correlated with temperature (r = -0.34 and -0.54, respectively).

Ambient temperature and respiratory morbidity

Figure S2 showed that the RRs of extreme cold temperature (25 °C) were the strongest on the present day, attenuated drastically to lag day 7, and followed by a significant morbidity displacement (i.e., RRs below 1) on the subsequent days for all-cause respiratory hospital visits. Figure 1 illustrated the cumulative exposure-response curves for the associations between temperature and all-cause and cause-specific respiratory hospital visits (including URI, bronchitis, pneumonia, rhinitis, and asthma) prior to 0–7 days. For all-cause, URI, bronchitis, pneumonia, and asthma hospital visits, the curves were consistently inversely J-shaped, and the cum.RRs increased sharply when the mean temperature decreased from 25 °C to about 6 °C, and then plateaued for a temperature lower than 6 °C. The cum.RRs for temperature higher than 25 °C suggested that the associations were not significant in this temperature range, possibly because of the small number of days with mean temperature higher than 25 °C during the study period (Fig. S3). For rhinitis hospital visits, the cum.RRs increased sharply when the mean temperature decreased from 31 °C to about 10 °C, and then plateaued for a temperature lower than 10 °C.

Table 3 summarized cumulative associations between temperature and daily respiratory hospital visits prior to 0–7 days. The minimum morbidity temperatures were all 25 °C (except for rhinitis, which was 31 °C), corresponding to the 80th centile of temperature distribution. For all-cause respiratory hospital visits, the cum.RR for extreme cold temperature was 2.64 (95%CI: 1.51–4.61) and for extreme hot temperature was 1.13 (95%CI: 0.92–1.38). The results were similar for outpatient visits and ERVs. We only calculated the cum.RR for extreme cold temperature on rhinitis hospital visits, because the minimum morbidity temperature (31 °C) was larger than the 99th percentile of temperature (29 °C). Exposure to extreme cold temperature was also associated with increased risk of URI (2.73; 95%CI: 1.44–5.18), bronchitis (2.76; 95%CI: 1.56–4.89), pneumonia (2.12; 95%CI: 1.30–3.47), rhinitis (2.06; 95%CI: 1.27–3.34), and asthma (4.02; 95%CI: 2.14–7.55). However, the cum.RRs for extreme hot temperature were not significant. For all-cause respiratory hospital visits, the cum.RRs for extreme cold temperature varied in magnitude by age and sex groups. The cum.RRs of extreme cold temperature were highest in infants (4.52; 95%CI: 2.54–

Table 2 Summary statistics of meteorological and air pollution levels in Beijing, China, 2013–2017

Exposure variables	Min	25th percentile	Median	Mean (SD)	75th percentile	Max	IQR
Temperature, °C	-15.5	2.1	13.9	12.6 (10.9)	22.9	31.2	20.8
Winter[a]	-15.5	-3.4	-1.6	-1.5 (64.7)	0.4	7.7	
Spring[a]	-0.9	10.4	15.5	15.0 (21.6)	20.2	30.0	
Summer[a]	16.5	23.8	25.6	25.4 (11.7)	27.2	31.2	
Fall[a]	-7.6	5.8	11.5	11.6 (63.1)	17.6	25.3	
RH, %	9.6	38.2	54.1	54.0 (19.5)	70.1	95.3	31.9
$PM_{2.5}$, μg/m^3	5.6	29.8	58.6	75.7 (64.7)	99.1	446.3	69.3
NO_2, μg/m^3	8.4	30.6	40.3	45.7 (21.6)	55.8	145.4	25.2
SO_2, μg/m^3	2.0	3.5	6.8	11.2 (11.7)	14.1	82.4	10.6
O_3, μg/m^3	4.3	54.1	88.9	101.4 (63.1)	142.7	308.7	88.6

[a] Winter: 12 and 1–2; Spring: 3–5; Summer: 6–8; Fall: 9–11

RH relative humidity, *$PM_{2.5}$* particulate matter with aerodynamic diameter less than 2.5 μm, *NO_2* nitrogen dioxide, *SO_2* sulfur dioxide, *O_3* ozone, *SD* standard deviation, *IQR* interquartile range

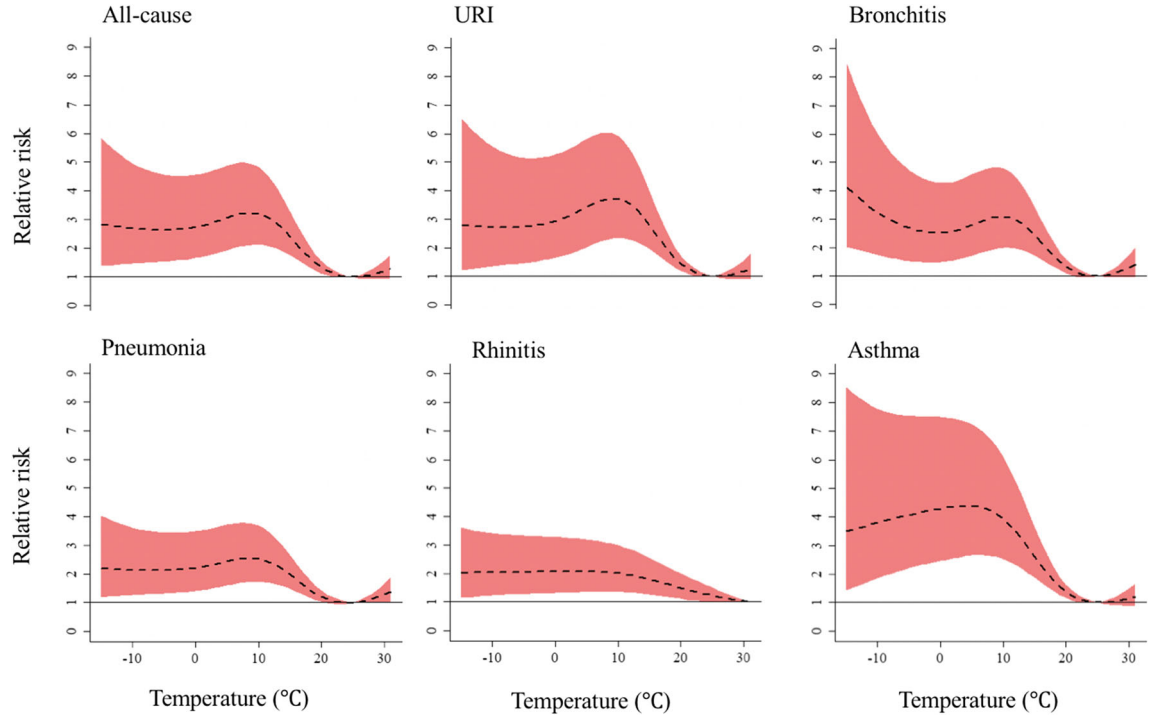

Fig. 1 Cumulative exposure-response curves for associations between temperature and all-cause and major cause-specific childhood respiratory hospital visits prior 0–7 days in Beijing, 2013-2017. Cumulative exposure-response relationships between temperature and all-cause and major cause-specific childhood respiratory hospital visits, including URI, bronchitis, pneumonia, rhinitis, and asthma. The effect estimate is shown by the dotted line, and the red areas represent the 95% confidence intervals. *URI* upper respiratory infection

8.03) and in male children (3.15; 95%CI: 1.75–5.64), but the differences in effect estimates examined by using *Z*-test were not significant ($P > 0.05$). Table S3 shows the cum.RRs for respiratory morbidity in association with daily mean temperature exposure at different percentiles during lag days 0–7.

Table 3 also illustrated the AFs of all-cause and cause-specific respiratory visits associated with different components of non-optimum temperatures. The overall AFs of non-optimum temperatures were 33.1% for all-cause respiratory hospital visits, 26.2% for URI, 36.5% for bronchitis, 23.1% for pneumonia, 44.0% for rhinitis, and 39.7% for asthma. Cold was responsible for most of the burden, due to the right shifted minimum morbidity temperature in the temperature distribution leading to more cold days and higher effects at lower temperatures. In addition, the cold-related burdens in subgroups of infants and male children were also higher than in other groups.

Air pollution and respiratory morbidity

We observed statistically significant positive associations between O_3 and respiratory hospital visits (Table 4). The RRs per IQR increase in O_3 (lag day 1) for all-cause, URI, bronchitis, pneumonia, and asthma hospital visits in single-pollutant models were 1.10 (95%CI: 1.06–1.15), 1.13 (95%CI: 1.08–1.19), 1.10 (95%CI: 1.05–1.15), 1.09 (95%CI: 1.05–1.13), and 1.05 (95%CI: 1.00–1.11), respectively, and the RRs remained positive and significant after adjusting for $PM_{2.5}$, NO_2, and SO_2 in two-pollutant models. The association between O_3 and rhinitis hospital visits in single-pollutant model was not significant, but became significant after adjusting for NO_2. However, no significant and consistent associations were observed for $PM_{2.5}$, NO_2, and SO_2 (Table S3).

Modification effects and sensitivity analyses

Table 5 reported the cum.RRs of all-cause and cause-specific respiratory hospital visits in associations with extreme cold temperature stratified by O_3 levels. For rhinitis hospital visits, the cum.RRs for extreme cold temperature were 0.99 (95%CI: 0.68–1.44) at low O_3 level and 1.92 (95%CI: 1.32–2.78) at high O_3 level, with significant difference between low and high O_3 levels. For asthma hospital visits, the cum.RRs for extreme cold temperature were 2.50 (95%CI: 1.38–4.53) at low O_3 level and 15.89 (95%CI: 8.77–28.80) at high O_3 level, with significant difference between low and high O_3 levels. However, for all-cause, URI, bronchitis, and pneumonia hospital visits, the cum.RRs for extreme cold temperature were generally stronger at high O_3 level than at low O_3 level without significant difference between low and high O_3 levels.

In the sensitivity analyses, for all-cause respiratory hospital visits, the models with alternative DF (6–10 per year) for time trend were comparable to the base model (Fig. S4). For all-

Table 3 Cumulative relative risks of all-cause and cause-specific childhood respiratory hospital visits in associations with extreme temperatures stratified by cause, hospital utilization, age, and sex in Beijing, China, 2013–2017

Hospital visits	Minimum morbidity temperature (°C)	Relative risk (95%CI)[a]		Attributable fraction (95% eCI)[d]		
		At extreme cold temperature[b]	At extreme hot temperature[c]	Overall	Cold	Heat
All-cause	25	2.64 (1.51, 4.61)*	1.13 (0.92, 1.38)	33.1 (-8.3, 52.2)	32.2 (-8.0, 52.8)	0.9 (-0.5, 2.1)
Cause-specific						
URI	25	2.73 (1.44, 5.18)*	1.12 (0.90, 1.40)	26.2 (-23.6, 47.3)	25.1 (-26.5, 48.6)	1.2 (-0.7, 2.9)
Bronchitis	25	2.76 (1.56, 4.89)*	1.20 (0.96, 1.51)	36.5 (-2.8, 58.3)	35.6 (-7.0, 58.0)	0.9 (-0.3, 2.1)
Pneumonia	25	2.12 (1.30, 3.47)*	1.20 (0.98, 1.46)	23.1 (-22.8, 49.6)	22.0 (-23.7, 49.4)	1.2 (0.2, 2.0)*
Rhinitis	31	2.06 (1.27, 3.34)*		44.0 (28.6, 54.4)*	44.0 (28.6, 54.4)*	
Asthma	25	4.02 (2.14, 7.55)*	1.09 (0.89, 1.34)	39.7 (13.3, 53.6)*	39.6 (13.3, 55.4)	0.1 (-1.8, 2.0)
Hospital utilization						
Outpatient visits	25	2.77 (1.58, 4.85)*	1.11 (0.90, 1.37)	33.4 (-4.4, 53.6)	32.6 (-10.5, 53.0)	0.8 (-0.6, 2.1)
ERVs	25	2.13 (1.20, 3.80)*	1.17 (0.96, 1.43)	30.8 (-12.0, 51.6)	29.5 (-12.0, 51.0)	1.4 (-0.1, 2.8)
Age, year						
< 2 years old	25	4.52 (2.54, 8.03)*	1.09 (0.89, 1.34)	40.0 (6.5, 56.7)	38.9 (8.1, 55.5)*	1.2 (-0.4, 2.6)
2–5 years old	25	2.23 (1.28, 3.91)*	1.15 (0.94, 1.42)	29.4 (-12.4, 52.5)	28.7 (-15.8, 50.2)	0.7 (-0.7, 2.0)
6–14 years old	25	2.15 (1.18, 3.92)*	1.09 (0.88, 1.36)	33.6 (-9.2, 53.1)	32.7 (-8.2, 53.4)	0.9 (-0.9, 2.4)
Sex						
Male	25	3.15 (1.75, 5.64)*	1.16 (0.94, 1.44)	35.2 (-1.2, 54.6)	34.2 (-7.2, 54.8)	1.0 (-0.5, 2.3)
Female	25	1.84 (1.08, 3.14)*	1.07 (0.89, 1.29)	22.3 (-17.8, 45.7)	21.5 (-20.4, 46.2)	0.8 (-0.5, 2.0)

*$P < 0.05$.

[a] Data presented as means and 95% confidence intervals; [b] extreme cold temperature = 1st percentile of temperature distribution (-6 °C); [c] extreme hot temperature = 99th percentile of temperature distribution (29 °C); [d] data presented as the means and 95% empirical confidence intervals

URI upper respiratory infection, *ERVs* emergency room visits

cause and cause-specific respiratory hospital visits, the cum.RRs for extreme cold temperature were slightly attenuated but did not change substantially after adjusting for $PM_{2.5}$, but moderately increased after adjusting for NO_2, SO_2, or O_3 (Table S4).

Discussion

This study took advantage of a comparatively large sample of database to assess environmental factor associated respiratory morbidity in children under 14 years old in Beijing, China, and found inversely J-shaped associations between temperature exposure and all-cause and cause-specific respiratory hospital visits. The fraction of all-cause respiratory hospital visits caused by cold was 33.1%, and by heat was 0.9%. The cum.RRs for extreme cold temperature were 2.73 (95%CI: 1.44–5.18), 2.76 (95%CI: 1.56–4.89), 2.12 (95%CI: 1.30–3.47), 2.06 (95%CI: 1.27–3.34), and 4.02 (95%CI: 2.14–7.55) for URI, bronchitis, pneumonia, rhinitis, and asthma. We also observed significant positive association between O_3 exposure and all-cause and cause-specific respiratory hospital visits. The cum.RRs for extreme cold temperature on all-cause and cause-specific respiratory hospital visits were generally stronger at high O_3 level than at low O_3 level. Our results supported continuing efforts to mitigate air pollution exposure under the context of climate change.

In the context of global climate change, extreme weather events become more frequent and intense, and prior studies have found that both extreme cold and hot temperatures were associated with increased respiratory morbidity (Chai et al. 2020; Gasparrini et al. 2015; Lam et al. 2016; Ma et al. 2019; Qiu et al. 2016; Scovronick et al. 2018; Zhang et al. 2020a). In the present analysis, we found inversely J-shaped associations between ambient temperature and respiratory morbidity, and most of the respiratory disease burden was attributable to the coldness (35.7%). A multicity time-series study conducted in Jiangsu Province, China, reported that cold was responsible for 18.10% of respiratory mortality, larger than the fraction attributable to heat (4.93%) (Ma et al. 2020). Human experiments in

Table 4 Cumulative relative risks of all-cause and cause-specific childhood respiratory hospital visits in associations with O_3 levels stratified by cause, hospital utilization, age, and sex in both single-pollutant and two-pollutant models (lag day 1)

Hospital visits	Single-pollutant models	Adjusting for $PM_{2.5}$	Adjusting for NO_2	Adjusting for SO_2
All-cause	1.10 (1.06, 1.15)*	1.11 (1.06, 1.16)*	1.04 (1.02, 1.06)*	1.02 (1.01, 1.02)*
Cause-specific				
URI	1.13 (1.08, 1.19)*	1.13 (1.07, 1.19)*	1.05 (1.03, 1.07)*	1.02 (1.01, 1.03)*
Bronchitis	1.10 (1.05, 1.15)*	1.11 (1.05, 1.16)*	1.04 (1.02, 1.06)*	1.02 (1.01, 1.02)*
Pneumonia	1.09 (1.05, 1.13)*	1.09 (1.05, 1.14)*	1.03 (1.02, 1.05)*	1.01 (1.01, 1.02)*
Rhinitis	1.01 (0.98, 1.04)	1.01 (0.98, 1.05)	1.01 (1.00, 1.02)*	1.00 (0.99, 1.01)
Asthma	1.05 (1.00, 1.11)*	1.06 (1.01, 1.12)*	1.02 (1.01, 1.04)*	1.01 (1.00, 1.02)*
Hospital utilization				
Outpatient visits	1.10 (1.06, 1.15)*	1.11 (1.05, 1.16)*	1.04 (1.02, 1.06)*	1.02 (1.01, 1.02)*
ERVs	1.11 (1.06, 1.16)*	1.10 (1.05, 1.15)*	1.04 (1.02, 1.05)*	1.01 (1.01, 1.02)*
Age, year				
<2 years old	1.11 (1.06, 1.16)*	1.10 (1.05, 1.16)*	1.04 (1.02, 1.05)*	1.02 (1.01, 1.02)*
2–5 years old	1.12 (1.07, 1.17)*	1.12 (1.06, 1.17)*	1.04 (1.02, 1.06)*	1.02 (1.01, 1.02)*
6–14 years old	1.07 (1.02, 1.13)*	1.08 (1.03, 1.14)*	1.03 (1.01, 1.05)*	1.01 (1.00, 1.02)*
Sex				
Male	1.12 (1.06, 1.17)*	1.11 (1.06, 1.17)*	1.04 (1.02, 1.06)*	1.02 (1.01, 1.02)*
Female	1.09 (1.05, 1.13)*	1.10 (1.05, 1.14)*	1.03 (1.02, 1.05)*	1.01 (1.01, 1.02)*

*$P < 0.05$

O_3 ozone, *URI* upper respiratory infection, *ERVs* emergency room visits, *$PM_{2.5}$* particulate matter with aerodynamic diameter less than 2.5 μm, *NO_2* nitrogen dioxide, *SO_2* sulfur dioxide

environmental chambers found that when exercising in conditions of coldness, the subjects with asthma had significant decreases in forced expiratory volume in 1 s (FEV_1) (20–21%) and increases in specific airway resistance (SRaw) (72–96%) (Eschenbacher et al. 1992). Xing et al. found that inhalation of cold air may cause autonomic respiratory responses such as airway constriction and mucosal secretion through the autonomic nerve reflex (Xing et al. 2008).

The minimum morbidity temperatures for the associations between temperature and childhood respiratory hospital visits for all-cause, URI, bronchitis, pneumonia, and asthma were all

Table 5 Cumulative relative risks of all-cause and cause-specific childhood respiratory hospital visits in associations with extreme cold temperature by O_3 levels strata

Hospital visits	O_3 level[a]	At extreme cold temperature	*P* value for difference
All-cause[b]	≤ Median level	2.20 (1.32, 3.68)*	
	> Median level	3.13 (1.69, 5.78)*	> 0.05
URI[b]	≤ Median level	2.67 (1.47, 4.87)*	
	> Median level	4.35 (2.08, 9.12)*	> 0.05
Bronchitis[b]	≤ Median level	2.46 (1.44, 4.20)*	
	> Median level	3.96 (2.11, 7.46)*	> 0.05
Pneumonia[b]	≤ Median level	1.70 (1.08, 2.65)*	
	> Median level	2.60 (1.54, 4.39)	> 0.05
Rhinitis[c]	≤ Median level	0.99 (0.68, 1.44)	
	> Median level	1.92 (1.32, 2.78)*	< 0.05
Asthma[b]	≤ Median level	2.50 (1.38, 4.53)*	
	> Median level	15.89 (8.77, 28.80)*	< 0.05

*$P < 0.05$

[a] The median value (88.9 μg/m^3) for O_3 was used as cut-offs for air pollution levels. [b] The minimum morbidity temperature and extreme low temperature (1st percentile) were 25 °C and -6 °C. [c] The minimum morbidity temperature and extreme low temperature (1st percentile) were 31 °C and -6 °C

URI upper respiratory infection, *$PM_{2.5}$* particulate matter with aerodynamic diameter less than 2.5 μm, *O_3* ozone

25 °C. Song et al. reported that the minimum morbidity temperature was 21.5 °C for respiratory ERVs and the cum.RR for extreme cold temperature (12 °C vs 25 °C) was 1.81 (95%CI: 1.26–2.76) (Song et al. 2018). Lam et al. reported that the minimum morbidity temperature was 25 °C for asthma hospitalizations during the cold season and the cum.RR for extreme cold temperature was 1.33 (95%CI: 1.13–1.58) (Lam et al. 2016). The minimum morbidity temperature and cold relative RRs for rhinitis were higher than those for other respiratory diseases, which can be partly explained by the fact that the nose serves as the portal of entry to the respiratory tract and is more vulnerable to ambient temperature (Shusterman 2016). The cum.RRs for all-cause and cause-specific respiratory hospital visits plateaued and even slightly decreased for a temperature lower than 10 °C, which might be explained by a longer duration of central heating in Beijing in winter and increased adaptive capability against cold exposure (Chen et al. 2018b; Ma et al. 2019). In addition, we observed stronger associations between extreme cold temperature and all-cause respiratory morbidity in infants (< 2 years old) and in male children, although the differences examined by using *Z*-test were not significant. Compared with older children (2–14 years old), infants have a more undeveloped respiratory system which make them suffer more from extreme cold temperature (Xu et al. 2012). Sex differences might be dependent on breathing patterns and immunologic responses, and Muenchhoff et al. observed stronger Th1 immune responses in females and higher susceptibility in males for many pathogens (Muenchhoff and Goulder 2014).

Among pollutants, we observed the significant positive associations between O_3 and all-cause, URI, bronchitis, pneumonia, and asthma respiratory hospital visits, and the associations remained significantly positive after adjusting for $PM_{2.5}$, NO_2, and SO_2. Previous studies have also reported that exposure to O_3 was positively associated with URI, pneumonia, and asthma morbidity (Lam et al. 2016; Strosnider et al. 2019). O_3 is a reactive gaseous pollutants and powerful oxidant and can react with proteins or lipids in the lung surface. The secondary oxidation products can induce respiratory tract inflammation and epithelial cell injury, which results in a range of respiratory symptoms (Zu et al. 2018). Karakatsani et al. conducted a panel study among school-age children and showed that an increase of 10 $\mu g/m^3$ in weekly O_3 concentration was associated with a 11.10% (95%CI: 4.23–18.43%) increase in the fractional concentration of nitric oxide in exhaled air (F_{eNO}), a marker of airway inflammation (Karakatsani et al. 2017). However, we found that the association between O_3 and rhinitis respiratory hospital visits was not consistent, which has been barely investigated and needs further investigation. In addition, we did not find evidence of significant positive associations between $PM_{2.5}$ and respiratory morbidity as reported in other studies (Lam et al. 2016; Peel et al. 2005; Strosnider et al. 2019; Szyszkowicz et al. 2018; Zhang et al. 2020b), which was likely due to the extensive use of personal-level protection device outdoors during high pollution episodes (Langrish et al. 2009; Shi et al. 2017).

Only a few studies have investigated the effect modification by O_3 on ambient temperature-mortality relationships (Breitner et al.2014; Burkart et al. 2013; Chen et al.2018a). Chen et al. reported that the impacts of both extreme cold and hot temperatures on total and cardiovascular mortality were stronger at high O_3 level (Chen et al.2018a). Breitner et al. reported that the impact of extreme hot temperatures on non-accidental and cardiovascular mortality were stronger at high O_3 level (Breitner et al.2014). However, the effect modification by O_3 on ambient temperature and respiratory health has been barely investigated. In this analysis, we observed significantly impacts at extreme cold temperature on childhood respiratory hospital visits for rhinitis and asthma on days with higher O_3 level. Cheng et al. also reported significant interaction between O_3 and extreme low temperature for respiratory mortality in Shanghai, China (Cheng and Kan 2012). The underlying mechanisms for the observed temperature effect modification by O_3 level were still unclear, but exposure to O_3 can increase the stimulus to the hyperreactive airway and aggravate airway inflammation in people with asthma, which may lead to a higher susceptibility to temperature changes (Chen et al. 2018a; Lam et al. 2016). However, we should note several study limitations. Firstly, the use of ambient monitoring measurements might not well represent population environmental exposure levels. We did not consider the amount of time spent indoors and outdoors, as well as the use of air conditioning and heating, which tend to bias the effect estimates towards null. Secondly, though we observed increased RRs of respiratory morbidity at higher temperature, the number of days with daily mean temperature higher than 25 °C was small during the study period, which limited our ability to examine the potential impact of extreme hot temperature on respiratory hospital visits. Further studies are needed to investigate the effect modification of ambient temperature and O_3 on respiratory health in hotter areas.

Conclusion

Our study found nonlinear associations between ambient temperature and respiratory morbidity among children, as well as the corresponding disease burden that is mainly attributable to cold in Beijing, China. The impacts of extreme cold temperature on asthma morbidity can be significantly modified by O_3. Our findings support reducing air pollution concentrations to further reduce the health burdens attributable to ambient temperature under the context of climate change.

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Data availability The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate This study did not contain confidential patient data. The Institutional Review Board of Beijing Children's Hospital, Capital Medical University approved this study (IEC-C-028-A10-V.05). The patient's consent to participate is not applicable in this study.

Consent for publication Not applicable.

Competing interests The authors declare no competing interests.

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