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Atopic Dermatitis – Research Article

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Environmental Exposure and Childhood Atopic Dermatitis in Shanghai: A Season-Stratified Time-Series Analysis

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Keywords
Atopic dermatitis · Children · Childhood · Environmental factors

Abstract
Background: Childhood atopic dermatitis (AD) is an inflammatory skin disease which sometimes predisposes to allergies. Environmental factors (low humidity, irritants, etc.) are prominent causative triggers of AD. ***Objectives:*** This study aims to explore the effects of both meteorological factors and air pollutants on childhood AD, and the modification effects by season in Shanghai, China. ***Methods:*** Quasi-Poisson generalized linear regression model, combined with a distributed lag nonlinear model was used to examine the nonlinear and lagged effects of environmental factors on childhood AD from 2009 to 2017 in Shanghai. We also performed a season-stratified analysis to determine the modification effects of environmental exposure by season on childhood AD. ***Results:*** There were 1,043,240 outpatient visits for childhood AD in total, at 3 major pediatric hospitals. Low temperature and relative humidity (RH), and high daily temperature difference (DTD) and air pollutants (i.e., NO_2) increased the relative risks (RRs) of outpatient visits for childhood AD in the whole year. In the cold season, an increased risk of outpatient visits for childhood AD was associated with low RH (RR 2.26, 95% CI 1.69–3.02) and high NO_2 (1.11, 95% CI 1.06–1.17). In the warm season, outpatient visits for childhood AD were associated with low temperature (3.49, 95% CI 3.22–3.77), low RH (1.89, 95% CI 1.74–2.06), high DTD (1.41, 95% CI 1.31–1.53), and high NO_2 (1.05, 95% CI 1.03–1.06). ***Conclusions:*** This study suggests that environmental exposure may be a key trigger for outpatient visits for childhood AD with apparent seasonal effects. Tailored preventive strategies to avoid environmental triggers of childhood AD should be developed.

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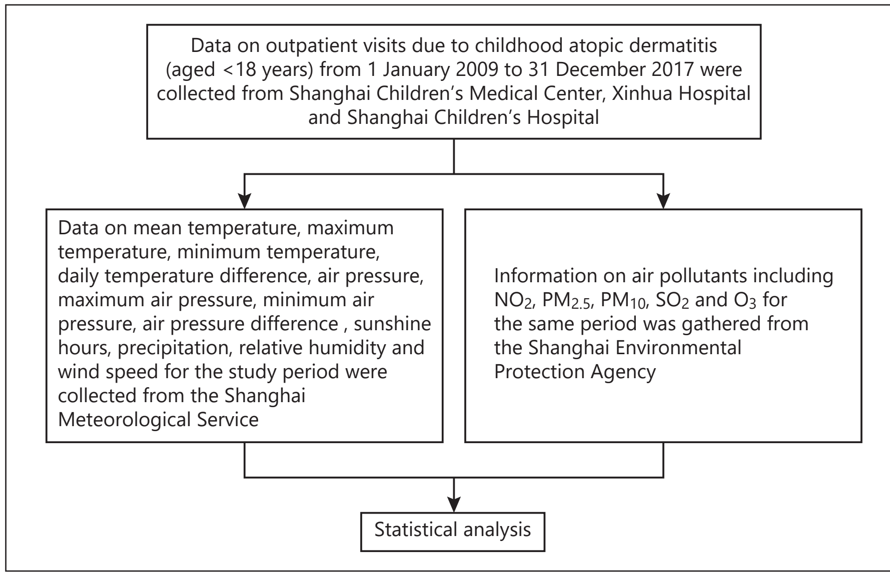

Fig. 1. Flowchart of materials and methods.

Introduction

Atopic dermatitis (AD) is a pruritic eczematous dermatitis, and its symptoms chronically fluctuate with remissions and relapses [1]. AD usually occurs in early childhood and can have a significant socioeconomic and emotional impact on the whole family [1, 2]. Recently, the prevalence of AD was estimated to be 15–30% in children worldwide [2–6]. A cross-sectional study in China included 48,219 children <18 years of age in 10 cities and found that the prevalence of AD varied from 4.8 to 15.8% [7]. Another population-based study on children aged 0–7 years in 12 Chinese cities reported that AD was the most common skin disease, with an average prevalence of 18.7% (range 9.0–24.7%) [8, 9].

Evidence suggests that the prevalence of AD has been increasing globally, particularly in Africa, eastern Asia, and some European countries (e.g., the UK) [5, 10]. Odhiambo et al. [11] analyzed data from the international study of asthma and allergy in childhood (ISAAC, a phase 3 study) and found that the prevalence rates of AD varied from 0.9% in India to 22.5% in Ecuador at the age of 6–7 years, and from 0.2% in China to 24.6% in Colombia at the age of 13–14 years. Comparison of prevalence estimates between phases 1 and 3 of the ISAAC study suggests an increasing prevalence of AD in children 6–7 years of age in both developing and developed nations, and an increasing prevalence in those aged 13–14 years in developing nations only [12]. A range of genetic, behavioral, atopic sensitization, and environmental risk factors influence the risk of childhood AD [1, 2, 13]. In particular, evolving environmental exposures may trigger and/or flare disease in predisposed individuals [4, 14].

Given that childhood AD is creating an enormous socioeconomic burden to families and communities [15–20], growing attention has been paid to the relationship between environmental factors and childhood AD [21–29]. Previous studies have mostly focused on the effects of air pollution on AD [21–23, 26], but a few examined seasonal effects [25]. Gaps in knowledge still exist regarding the impact of comprehensive environmental factors on childhood AD and the modification effects by season, especially in developing countries including China. We sought to explore the season-stratified effects of both meteorological factors and air pollutants on childhood AD in Shanghai and provide evidence for developing tailored strategies to prevent and control this common allergic disease.

Materials and Methods

For further details, see the online supplementary material (see www.karger.com/doi/10.1159/000514685 for all online suppl. material) [7–9, 24, 30–38] (Fig. 1).

Results

Distribution of Childhood AD and Environmental Factors over the Whole Year and in Different Seasons

The daily number of outpatient visits for childhood AD from 1 January 2009 to 31 December 2017 is shown in on-

Table 1. Summary statistics of daily outpatient visits for childhood AD, meteorological factors, and air pollutants from 2009 to 2017

	Mean	Minimum	25th percentile	50th percentile	75th percentile	Maximum
Daily outpatient visits	317	8	205	297	407	1,040
Boys, *n*	180	2	115	167	232	616
Girls, *n*	137	6	91	129	173	444
Meteorological factors						
T_{mean}, °C	17.2	–5.6	9.4	18.2	24.3	34.8
T_{max}, °C	21.3	–3.8	13.7	21.3	28.4	40.9
T_{min}, °C	13.9	–7.2	6.1	14.5	21.6	31.0
DTD, °C	7.5	0.8	4.7	7.1	9.9	19.5
Mean air pressure, hPa	1,016.1	992.6	1,008.5	1,016.1	1,023.0	1,039.4
Maximum air pressure, hPa	1,018.0	997.0	1,010.0	1,018.0	1,026.0	1,041.0
Minimum air pressure, hPa	1,013.8	984.9	1,006.4	1,013.7	1,020.4	1,037.2
Daily difference, hPa	4.6	1.3	3.0	3.9	5.4	20.2
Relative humidity, %	73.7	24.0	66.0	75.0	83.0	100.0
Precipitation, cm	3.8	0	0	0	1.7	164.0
Number of sunshine hours	4.9	0	0	5.5	8.5	12.2
Wind speed, m/s	1.5	0.1	1.0	1.5	1.9	6.1
Levels of air pollutants						
NO_2, μg/m^3	47.6	5.0	33.0	44.9	59.0	153.1
SO_2, μg/m^3	21.9	5.0	12.0	17.0	26.4	127.8
PM_{10}, μg/m^3	71.8	6.0	41.5	59.9	88.0	803.8
$PM_{2.5}$, μg/m^3	47.4	5.0	26.0	38.0	59.0	447.0
O_3, μg/m^3	69.6	8.2	46.0	69.0	87.0	277.9

T_{mean}, mean temperature; T_{max}, maximum temperature; T_{min}, minimum temperature; DTD, daily temperature difference.

line supplementary Figure 1. The number increased gradually over time. There were 1,043,240 outpatient visits for childhood AD in total, from 3 major pediatric hospitals, including 593,195 boys and 450,045 girls. Table 1 presents the summary statistics of daily outpatient visits for childhood AD, meteorological factors, and air pollutants during the same period. Online supplementary Table 1 shows the summary statistics of daily outpatient visits for childhood AD and environmental exposures in different seasons. The daily number of outpatient visits for childhood AD was higher in the cold season (mean 374; range 13–98) than in the warm season (mean 248; range 31–730; $p <$ 0.001). The daily number of boys was bigger than that of girls in both the warm (138 [19–414] and 110 [12–331], respectively) and cold (215 [6–566] and 159 [7–32], respectively) seasons. The results of the Spearman correlation analysis appear in online supplementary Tables 2–4.

Relationship between Childhood AD and Environmental Factors over the Whole Year and in Different Seasons

We analyzed the overall exposure-response relationships between outpatient visits for childhood AD and environmental factors over the whole year and in different seasons, using quasi-Poisson regression with a distributed lag non-linear model. As showed in Figure 2, low temperature and low RH increased the relative risk (RR) of daily outpatient visits for childhood AD both over the whole year and in the warm season. When DTD elevated, it increased the RR of daily outpatient visits for childhood AD over the whole year and in the warm season. High concentrations of NO_2 increased the RR of daily outpatient visits for childhood AD over the whole year and in different seasons.

Table 2 shows the lagged effects of meteorological factors and air pollutants on daily outpatient visits for childhood AD. Both over the whole year and different seasons, single-day and/or cumulative lagged effects of low (5th percentile of the value) or high (95th percentile of the value) levels of environmental factors on childhood AD were observed. For the single-day lagged effect, the RR was highest for low temperature (1.28, 95% CI 1.24–1.32) at lag 1, low RH (1.14, 95% CI 1.12–1.16) at lag 0, and high DTD (1.18, 95% CI 1.12–1.24) at lag 0 in the whole period. For air pollutants, NO_2, SO_2, PM_{10}, and $PM_{2.5}$ constituted the greatest risk for outpatient visits for childhood AD on the current day (lag 0) for both the whole year and differ-

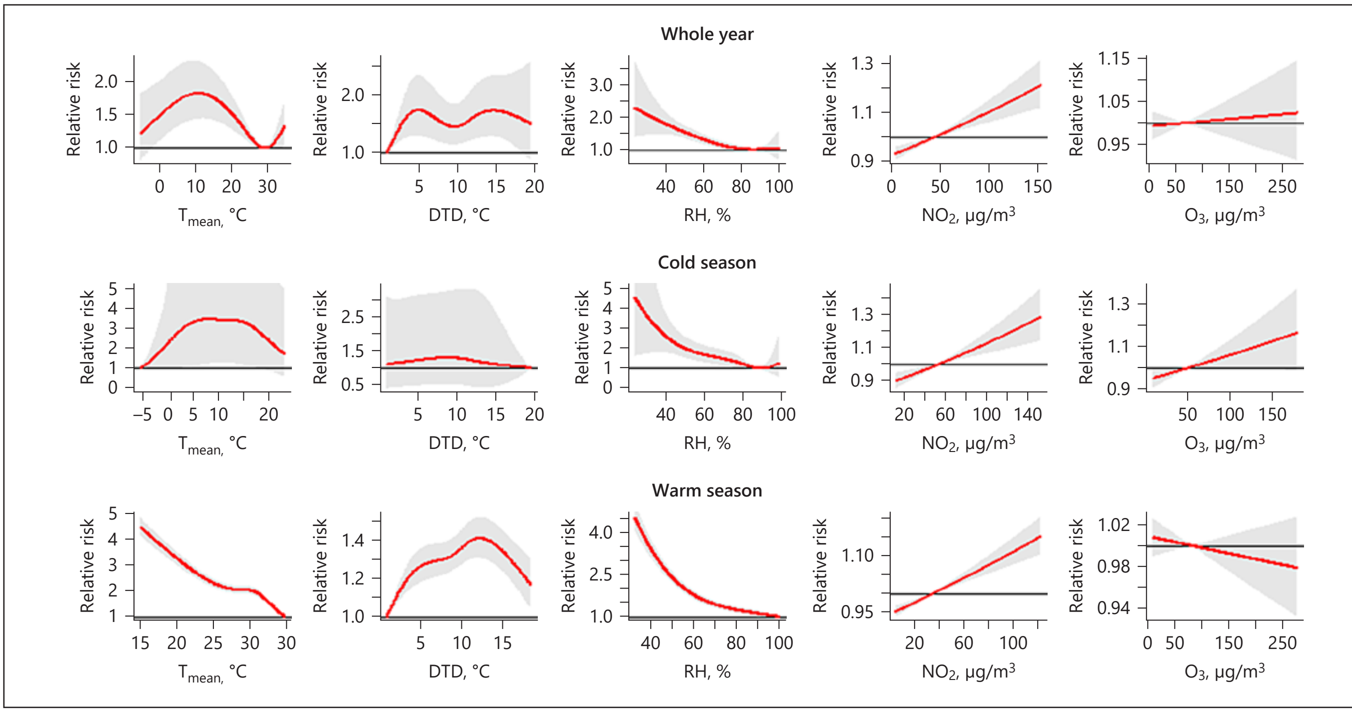

Fig. 2. The overall exposure-response relationships between outpatient visits for childhood AD and environmental factors over the whole year and in different seasons. Red line, relative risk; grey area, 95% CI of relative risk. The final model included the T_{mean}, DTD, RH, NO_2, O_3, and controlled the effect of public holidays, day of the week, seasonality, and long-term trends. T_{mean}, DTD, and RH indicate daily mean temperature, daily temperature difference, and relative humidity, respectively.

ent seasons. For the cumulative lagged effects, the RR increased for low temperature (1.65, 95% CI 1.26–2.17) and low RH (1.51, 95% CI 1.33–1.71), and high DTD (1.71, 95% CI 1.27–2.31) and high NO_2 (1.08, 95% CI 1.04–1.11) over the whole year. In the cold season, the RR was 2.69 (95% CI 1.02–7.08), 2.26 (95% CI 1.69–3.02), and 1.11 (95% CI 1.06–1.17) for low temperature, low RH, and high NO_2, respectively. In the warm season, the RR was 3.49 (95% CI 3.22–3.77), 1.89 (95% CI 1.74–2.06), 1.41 (95% CI 1.31–1.53), and 1.05 (95% CI 1.03–1.06) for low temperature, low RH, high DTD, and high NO_2, respectively.

Online supplementary Table 5 shows the results of sensitivity analyses using alternative df for calendar time and with different maximum lags. The trends are similar in Table 2.

Discussion

The key findings of this study were (a) mean temperature and RH were inversely associated with daily outpatient visits for childhood AD, but DTD and air pollutants (including NO_2, SO_2, PM_{10}, $PM_{2.5}$, and O_3) were positively associated with daily outpatient visits for childhood AD; (b) there were apparent seasonal effects of environmental exposure on outpatient visits for childhood AD: in the cold season, low RH and high NO_2 were significantly associated with an increased risk of outpatient visits for childhood AD whereas in the warm season, exposure to low temperature and RH, and high DTD and NO_2 increased the risk of outpatient visits for childhood AD; (c) there were lagged effects of environmental factors on outpatient visits for childhood AD over the whole year and in different seasons but NO_2, SO_2, PM_{10}, and $PM_{2.5}$ constituted the greatest risk of visits for childhood AD on the current day.

Our results are consistent with most previous studies. A study conducted in Chengdu, China, showed that environmental factors like RH and multiple air pollutants influenced the incidence and prevalence of AD and had lagged effects [36]. Another study including daily outpatient visits and environmental factors between 2007 and 2011 (1,826 days) in Shanghai observed that ambient air pollutants, high temperature, and low RH increased the

Table 2. The lagged effects of environmental factors on daily outpatient visits for childhood AD over the whole year and different seasons

	Whole year				Cold season				Warm season			
	lag, days	single-day effect	lag, days	cumulative effect	lag, days	single-day effect	lag, days	cumulative effect	lag, days	single-day effect	lag, days	cumulative effect
Meteorological factors[a]												
T_{mean}	1	**1.28 (1.24–1.32)**	0–21	**1.65 (1.26–2.17)**	0	**1.33 (1.16–1.52)**	0–21	**2.69 (1.02–7.08)**	1	**1.69 (1.56–1.83)**	0–3	**3.49 (3.22–3.77)**
DTD	0	**1.18 (1.12–1.24)**	0–21	**1.71 (1.27–2.31)**	0	**1.27 (1.11–1.46)**	0–21	1.12 (0.42–2.99)	0	**1.18 (1.14–1.23)**	0–3	**1.41 (1.31–1.53)**
RH	0	**1.14 (1.12–1.16)**	0–21	**1.51 (1.33–1.71)**	0	**1.15 (1.11–1.19)**	0–21	**2.26 (1.69–3.02)**	0	**1.37 (1.31–1.45)**	0–3	**1.89 (1.74–2.06)**
Single-pollutant models[b]												
NO_2	0	**1.05 (1.03–1.07)**	0–3	**1.08 (1.05–1.11)**	0	**1.07 (1.04–1.10)**	0–3	**1.09 (1.04–1.14)**	0	**1.03 (1.00–1.05)**	0–3	**1.05 (1.01–1.09)**
SO_2	0	**1.04 (1.01–1.06)**	0–3	**1.10 (1.06–1.15)**	0	**1.05 (1.01–1.10)**	0–3	**1.14 (1.07–1.22)**	0	**1.07 (1.03–1.10)**	0–3	**1.21 (1.14–1.28)**
PM_{10}	0	**1.02 (1.01–1.04)**	0–3	**1.03 (1.00–1.05)**	0	**1.03 (1.00–1.06)**	0–3	1.03 (0.99–1.08)	0	**1.03 (1.00–1.05)**	0–3	1.01 (0.98–1.04)
$PM_{2.5}$	0	**1.03 (1.01–1.04)**	0–3	1.01 (0.98–1.04)	0	**1.03 (1.00–1.05)**	0–3	1.02 (0.98–1.07)	0	**1.05 (1.02–1.08)**	0–3	**1.08 (1.04–1.12)**
O_3	0	1.00 (0.98–1.02)	0–3	0.98 (0.96–1.01)	0	1.00 (0.97–1.03)	0–3	0.99 (0.94–1.04)	0	1.01 (0.99–1.04)	0–3	1.00 (0.96–1.03)
Multi-pollutant models[c]												
$NO_2/(NO_2 + O_3)$	0	**1.06 (1.03–1.08)**	0–3	**1.08 (1.04–1.11)**	0	**1.10 (1.06–1.14)**	0–3	**1.11 (1.06–1.17)**	0	**1.03 (1.02–1.04)**	0–3	**1.05 (1.03–1.06)**
$SO_2/(SO_2 + O_3)$	0	**1.04 (1.01–1.06)**	0–3	**1.10 (1.06–1.15)**	0	**1.06 (1.01–1.10)**	0–3	**1.15 (1.08–1.24)**	0	**1.07 (1.03–1.11)**	0–3	**1.21 (1.14–1.28)**
$PM_{10}/(PM_{10} + O_3)$	0	**1.02 (1.01–1.04)**	0–3	**1.03 (1.00–1.05)**	0	**1.03 (1.00–1.06)**	0–3	1.03 (0.98–1.08)	0	**1.03 (1.00–1.05)**	0–3	1.01 (0.98–1.04)
$PM_{2.5}/(PM_{2.5} + O_3)$	0	**1.02 (1.01–1.04)**	0–3	1.01 (0.98–104)	0	1.03 (1.00–1.06)	0–3	1.02 (0.98–1.07)	0	**1.05 (1.02–1.08)**	0–3	**1.09 (1.05–1.14)**
$O_3/(NO_2 + O_3)$	0	1.02 (0.99–1.04)	0–3	1.02 (0.99–1.04)	0	**1.05 (1.02–1.09)**	0–3	1.05 (1.00–1.11)	0	1.01 (1.00–1.02)	0–3	0.99 (0.98–1.01)
$O_3/(SO_2 + O_3)$	0	1.00 (0.98–1.02)	0–3	0.99 (0.97–1.02)	0	1.01 (0.98–1.04)	0–3	1.03 (0.98–1.08)	0	1.00 (0.98–1.03)	0–3	0.99 (0.96–1.02)
$O_3/(PM_{10} + O_3)$	0	1.00 (0.98–1.02)	0–3	0.99 (0.96–1.01)	0	1.01 (0.98–1.04)	0–3	1.00 (0.95–1.05)	0	1.01 (0.98–1.03)	0–3	0.99 (0.96–1.03)
$O_3/(PM_{2.5} + O_3)$	0	1.00 (0.98–1.02)	0–3	0.99 (0.96–1.01)	0	1.01 (0.98–1.04)	0–3	1.00 (0.95–1.05)	0	0.99 (0.97–1.02)	0–3	0.97 (0.93–1.00)

Data are represented as relative risk (RR) and 95% CI. Bold type denotes statistical significance ($p < 0.05$). The results for meteorological factors were calculated with the 5th percentile of temperature and RH and the 95th percentile of DTD compared to the value which induced minimum relative risk of childhood AD. The results for air pollutants were calculated with the 95th percentile value compared to the median value; single-day effect reported the highest RR at a certain lag; cumulative effect reported the cumulative RR with the maximum lag. Cold season: January-March and November-December. Warm season: May-September. T_{mean}, mean temperature; DTD, daily temperature difference; RH, relative humidity; $NO_2/(NO_2 + O_3)$, the results of NO_2 in the model containing the 2 ($NO_2 + O_3$) air pollutants. [a] The final model, included the temperature, DTD, RH, NO_2, O_3, public holidays, day of the week, and ns (time, df/year). [b] The model only included 1 air pollutant, other independent variables were the same as above. [c] The model included 2 air pollutants like the final model, in which NO_2 might be changed with another air pollutant, respectively.

outpatient visits for AD [25]. A recent study in Beijing reported that effects of air pollutants on AD can be modified by meteorological factors, with enhanced effects on hot days [35]. The previous studies usually included the whole population or adults only, but our study focused on children. In addition, Kim et al. [39] found that increases in temperature and RH significantly reduced childhood AD symptoms. However, high DTD, ambient NO_2, PM_{10}, and O_3 increased the RR of childhood AD symptoms.

High temperature and RH may be biologically protective, possibly because they can improve skin barrier functions which restrain the cellular pathways related to AD [25]. However, Sargen et al. [27] reported that increased temperature and humidity are associated with poorly controlled childhood AD when they investigated the severity of eczema symptoms associated with environmental triggers. The reasons for the inconsistent findings might be attributed to the differences in regions (climate and pollution variation), populations (children vs. the whole population), study design (severity of AD symptoms vs. number of outpatient visits), and statistical methods.

AD is a multifocal disease with multiple etiologies. The mechanisms involved in AD are: genetic factors, inflammation, and skin hypersensitivity [1, 2]. Skin hypersensitivity may be partially caused by the extension of the cutaneous sensory nerve fibers to immediately below the horny cell layer of the skin surface due to dryness or inflammation [1, 40]. Exposure to low temperatures causes the secretion of the stress hormones norepinephrine and cortisol, lymphocytosis, decreased lymphoproliferative responses, altered cytokine levels, and also suppresses the immune system [41]. We found a significantly increased risk of outpatient visits for childhood AD associated with exposure to low temperatures.

Animal studies revealed that low RH induces epidermal DNA synthesis, causes mast cell degranulation, and leads to epidermal hyperplasia in response to barrier disruption. Human physiological studies found that low RH reduced the water content in the stratum corneum, decreased skin elasticity, and increased roughness [42]. Our study also found that low levels of RH or dryness could increase the RR of outpatient visits for childhood AD over the whole year and in different seasons.

DTD also plays a role in human health. Previous studies found adverse effects of DTD on mortality and morbidity in cardiovascular and respiratory diseases [38, 43, 44]. An increase in DTD of >10 °C was associated with increased emergency room admissions in asthmatic children [38]. However, the relationship between DTD and childhood AD is rarely reported. Kim et al. [39] also found that childhood AD symptoms increased by 284.9% (95% CI 67.6–784.2) per 5 °C increase in DTD when it was >14 °C. Our study found that high DTD increased the RR of outpatient visits for childhood AD over the whole year and in the warm season. These results suggest that children with AD should take more care on days with elevated DTD, i.e., pay more attention to the temperature and DTD as well as adjust clothing and outdoor activity accordingly.

To et al. [28] found that exposures to oxidant air pollutants (O_3 and NO_2) were associated with an increased risk of incident AD in children. Noh et al. [29] found that PM_{10}, NO_2, and SO_2 had a positive association, but that temperature and RH were inversely associated with childhood AD. Our findings are consistent with these studies. Air pollutants make it possible to disrupt skin barrier functions through oxidative stress and proinflammatory cytokines, leading to increased risks for childhood AD [1].

This study has several strengths, including its comprehensive data collection, a large sample of outpatient visits for childhood AD from 3 pediatric hospitals, multiyear aggregate estimations minimizing year-to-year random variations, and a distributed lagged nonlinear model to examine patterns of a range of environmental factors and uncover the lagged effects of environmental factors on childhood AD. We divided our data into the cold and warm seasons to determine season-stratified effects of environmental factors on outpatient visits for childhood AD in greater detail.

Our study also has some limitations. First, we could not obtain data on individual environmental exposures, so exposure to environmental factors like temperature, RH, and air pollutants was estimated from different monitoring stations. Like other time-series studies, this approach has the potential for measurement errors. However, this type of measurement error is likely nondifferential, which may bias effect estimates towards the null [45]. Second, we only used hospital-based clinical data, and no information was available on disease severity, disease localization, or disease activity assessments. Third, potential confounding factors such as life events [46], aeroallergens [47], and respiratory viral epidemics [48] were not controlled in this study as these data were unavailable.

Further research directions include (i) a cohort design needs to be adopted to test the causal/temporal relationship between environmental factors and childhood AD, and (ii) all potential confounding factors including life events, aeroallergens, and respiratory viral epidemics should be taken into account.

Conclusions

Our study provides evidence that low temperature and low RH and high DTD and high levels of air pollutants elevate the risk of outpatient visits for childhood AD and have apparent seasonal and lagged effects in Shanghai, China. If our findings are confirmed by further research, tailored preventive strategies to avoid environmental triggers of childhood AD should and can be developed. For instance, when relative humidity is at a low level, it may be necessary to appropriately increase the indoor humidity with humidifiers to improve children's health and reduce the burden of childhood AD.

Key Message

Environmental exposure may trigger outpatient visits for childhood AD with apparent seasonal effects.

Acknowledgments

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Statement of Ethics

Approval was granted by the Ethics Committee of Shanghai Children's Medical Center (No. 18411951600) prior to the data collection. Since the data on participants were deidentified and aggregated, no personal information was gathered throughout the study, and written consent was not needed.

Conflict of Interest Statement

The authors declare that they have no competing interests.

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Author Contributions

S.T. was responsible for the conception and design of the study. Y.H. carried out the statistical analysis and wrote the initial draft of the manuscript. All authors provided substantial contributions to the conception or design of the work, and the acquisition, analysis or interpretation of the data, revised the manuscript critically for important intellectual content, and approved the final version for submission.

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