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Title: Association between small particle air pollution, climate and childhood eczema prevalence and severity: a US population-based study

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Abbreviations used: CI=confidence interval, OR=odds ratio, PM = particulate matter; AD = atopic dermatitis

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Abstract

Background: We sought to determine the relationship between childhood eczema, climate and environmental pollutants.

Methods: We analyzed data from the 2007-2008 National Survey of Children's Health including a representative sample of 91,642 children age 0–17 years and the 2006–2007 Environmental Protection Agency measurements of carbon monoxide (CO), nitrate (NO₃), nitrogen dioxide (NO₂), organic carbon (OC), sulfate (SO₃), sulfur dioxide (SO₂), particulate matter ≤ 2.5 micrometer (PM-2.5) and <10 micrometer (PM-10) and tropospheric ozone levels, and the National Climate Data Center measurements of relative humidity (%), issued UV index, outdoor air temperature and precipitation levels.

Results: In multivariate survey logistic regression models controlling for age, sex, race/ethnicity, household income, US birthplace and history of moving to a new location, eczema was associated with higher mean annual NO₂ (P=0.008), SO₂ (P=0.006), SO₃ (P=0.0002), arsenic (P=0.0007), nickel (P=0.0002), lead (P=0.03), vanadium (P<0.0001) and zinc (P=0.003), but lower NO₃ (P=0.002), OC (P=0.03), PM-2.5 (P=0.006), cadmium (P<0.0001), copper (P=0.004) and potassium (P<0.0001). In contrast, moderate-severe eczema was associated with higher NO₃ (P=0.03), OC (P=0.008) and PM-2.5 (P=0.01), copper (P=0.04), lead (P=0.008) and zinc (P=0.01), but lower CO (P=0.03). Principal component analysis was used and identified 4 combinations of pollutants and climate factors occurring in the US, of which 1 was associated higher prevalence and 2 were associated with lower prevalences of eczema (P<0.05).

Conclusions: Pollutants in conjunction with climate factors may differentially impact eczema prevalence and severity, some with apparent harmful effects.

Key Words: eczema prevalence; eczema severity; atopic dermatitis; small particle air pollution; air pollutants; nitrate; nitrogen dioxide; sulfate; sulfur dioxide; ozone; particulate matter under 2.5 micrometer; particulate matter under 10 micrometer; climate; relative humidity; ultraviolet index; air temperature; pediatric; children

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Introduction

Atopic dermatitis (AD or eczema) is one of the most prevalent skin conditions seen in infants and children, with the prevalence in the United States reported to be 10.7% with significant statewide variation ranging from 8.7-18.1%(1). The clinical course of AD often varies seasonally, with many patients experiencing disease flares in the wintertime or summertime. Previous studies suggested that seasonal climate factors may play a role in AD(2, 3). However, there may be other factors at play other than climate factors *per se*. In particular, seasonal changes of climate are accompanied by variation of levels of tropospheric ozone and air pollutants(4).

Few studies examined the role of pollutants in eczema and found conflicting results(5-7). However, no studies have examined the role of outdoor pollutants on the prevalence of eczema in the US. We hypothesized that areas with higher levels of pollutants have higher prevalences of eczema, as well as potentially worsening of disease severity via irritant or allergenic effects. Further, many pollutants have seasonal trends that vary along with climate. We hypothesized that some pollutants may impact the prevalence of eczema independent of climate factors, while others may act in concert with climate factors. In the present study, we sought to determine the relationship between pollutants and climate with eczema prevalence and severity in the US.

Methods

National Survey of Children's Health (NSCH)

We used data from the 2007 NSCH survey of 91,642 households, which was designed to estimate the prevalence of various child health issues including physical, emotional, and behavioral factors. The NSCH was sponsored by the Maternal and Child Health Bureau and the U.S. Department of Health and Human Services. The National Center for Health Statistics conducted using the State and Local Area Integrated Telephone Survey program with a goal of >1,800 subjects per state. The telephone numbers were chosen at random, followed by identification of the households with one or more children under the age of 18. Subsequently, one child was randomly selected for interview. Surveys were conducted in English, Spanish, Korean, Mandarin, Cantonese and Vietnamese. The survey results were weighted to represent the population of non-institutionalized children nationally and in each state. Using the data from U.S. Bureau of the Census, weights were adjusted for age, sex, race, ethnicity, household size, and educational attainment of the most educated household member to provide a dataset that was more representative of each state's population of non-institutionalized children less than 18 years of age. The National Center for Health Statistics of Center for Diseases Control and Prevention oversaw sampling and telephone interviews. Verbal informed consent was obtained before interview. The study was approved by the Northwestern University institutional review board.

History of eczema

Prevalence of eczema, the primary outcome of the study, was determined using the NSCH question, "During the past 12 months, have you been told by a doctor or other health professional that (child) had eczema or any kind of skin allergy?" This is referred to as eczema throughout the manuscript. Severity of eczema was determined using the NSCH

question, “Would you describe (child’s) eczema or skin allergy as mild, moderate, or severe?”

Pollutants

Data on all pollutants was downloaded from the Environmental Protection Agency. A summary of the monitoring systems in place to measure the major pollutants is described in the Supplemental Methods. Climate data were obtained as previously described (3).

Data processing and statistical methods

All data processing and statistical analyses were performed in SAS version 9.4. The climate variables mentioned above were limited to 2006–2007 and were chosen for each subject of the NSCH by the current state of residence. In scenarios where there were climate observations for multiple cities within a state, the mean value of all the cities was used. Mean levels of pollutants, both annually and during cold and warm months, were used for statistical modeling. Cold (November-April) and warm (May-October) weather months were determined by visual inspection of the distribution of pollutants throughout the year.

Analyses of survey responses were performed using SURVEY procedures. Univariate and multivariate associations were tested by logistic regression. The dependent binary variables were eczema (yes vs. no) or eczema severity (moderate-severe vs. mild) and the independent variables included the abovementioned pollutants tested individually in regression models. Crude and adjusted odds ratio (OR) and 95% confidence intervals (CI) were estimated. The OR represent the odds of having eczema vs. not having eczema for each unit increase of a pollutant. Complete data analysis was performed, i.e. subjects with missing data were excluded. All population estimates were determined using the predefined sampling weights for the NSCH.

Most of the pollutants were highly correlated with each other and with certain climate factors. Therefore, principal component analysis (PCA) with varimax rotation was used to estimate the combined effects of these pollutant and climate variables(8). PCA was used to determine the best combination and weighting of variables in order to best explain how they are correlated. Factors were retained if eigenvalue >1, proportion of variance accounted for >10% and loading value >0.4. Retained factors represent the dominant combinations of these pollutants and climate variables occurring in the US. Logistic regression was then performed using factor scores from the retained factors to determine the odds of eczema or moderate-severe eczema under these common climate conditions.

A two-sided P-value <0.05 was taken to indicate statistical significance for all estimates. However, the large number of dependent statistical tests raises the Type I error rate. Therefore, P-values near 0.05 should be interpreted with caution.

Results

Population characteristics

Data were collected in 91,642 children and adolescents across all 50 states. The prevalence of eczema was 12.98% (95% CI: 12.43–13.54), with significant statewide variation (Figure 1A). Eczema was associated with younger age, African-American race and birthplace in the US (Supplemental Table 1). Since eczema prevalence is related to both intrinsic and extrinsic factors, we used generalized linear models (GLM) to generate least-squares mean estimates for history of eczema in each state that controlled for age, race/ethnicity, gender, household income and US birthplace. We then mapped these least-squares mean estimates to identify relative hotspots related to additional factors (Figure 1B). There are two apparent regions of highest prevalence located in the Northeastern and

Northwestern US. Among children with eczema in the past year, 33.1% (95% CI: 31.0–35.2%) reportedly had moderate–severe disease.

Environmental pollutants

Several airborne pollutants were examined, including tropospheric ozone, carbon monoxide (CO), nitrate (NO₃), nitrogen dioxide (NO₂), sulfate (SO₃), sulfur dioxide (SO₂), organic carbon (OC), particulate matter under 2.5 micrometer (PM-2.5) and <10 micrometer (PM-10). The daily distributions of these variables are presented in Figure 2. Most of the variables had seasonal peaks, either in the cold (NO₃, SO₂, NO₂, CO) or warm weather months (SO₃, OC, PM-2.5). Therefore, we considered mean levels for each variable annually, as well as the cold and warm weather months. Statewide distribution of these pollutants in the cold and warm weather months are presented in Figure 1C-T. Upon visual inspection, higher levels of SO₃, NO₃, SO₂, NO₂ and PM-2.5 occurred in the Northeastern US during the cold and/or warm weather months.

Association between environmental pollutants and eczema prevalence

In survey weighted logistic regression models, residing in states with higher mean annual NO₂ (OR [95% CI]: 1.003 [1.001–1.004], *P*=0.002), SO₂ (1.009 [1.003–1.015], *P*=0.006) and SO₃ (1.008 [1.004–1.012], *P*=0.0002) was associated with higher prevalence of eczema (Table 1). In particular, NO₂, SO₂ and SO₃ levels in the cold and warm months were associated with higher odds of eczema (Supplemental Table 2).

In contrast, higher mean annual NO₃ (0.981 [0.969–0.993]), OC (0.993 [0.987–0.999]), PM-2.5 (0.993 [0.989–0.998]) and PM-10 (0.847 [0.739–0.971]) were associated with lower prevalence of eczema. In particular, higher levels of tropospheric ozone in the

warm months, CO and PM-2.5 in the cold months and NO₃, OC and PM-10 in the cold and warm months were associated with lower odds of eczema (Supplemental Table 2).

In particular, residence in states with higher levels of arsenic (1.228 [1.090–1.383]), lead (1.017 [1.002–1.032]), nickel (1.084 [1.039–1.131]), vanadium (1.096 [1.048–1.146]) and zinc (1.006 [1.002–1.010]) was associated with higher odds of eczema (Table 1). Whereas, cadmium (0.680 [0.567–0.815]), copper (0.949 [0.916–0.983]) and potassium (0.993 [0.990–0.997]) were associated with lower odds of eczema.

Association between environmental pollutants and eczema severity

Higher mean annual NO₃ (1.249 [1.028–1.517]), OC (1.323 [1.077–1.625]) and PM-2.5 (1.070 [1.013–1.130]) was associated with higher odds of moderate-severe eczema (Table 2); NO₃ and OC were significant in both the cold and warm months, whereas PM-2.5 was significant only in the cold months (Supplemental Table 3). In contrast, higher mean annual CO was associated with lower prevalence of moderate-severe eczema (0.557 [0.327–0.949]; Table 2), particularly in the warm months (Supplemental Table 3).

In particular, higher levels of copper (1.085 [1.005–1.170]), lead (1.041 [1.011–1.072]) and zinc (1.009 [1.002–1.017]) were associated with higher rates of moderate-severe eczema (Table 2).

Principal component analysis

PCA was used to determine the most common combinations of pollutants (factors) occurring in the US. We included mean annual humidity, temperature, issued UV index and precipitation in the models, since most of the abovementioned pollutants have seasonal variation together with different climate variables. Four factors were identified by principal components analysis: factor 1) hot, humid and rainy with OC, SO₂ and PM-2.5; factor 2) hot

and sunny with high PM-10 and tropospheric ozone; factor 3) high NO₃ and PM-2.5; and factor 4) high CO (Table 3). Factor 1 was associated with higher odds of eczema, whereas factors 2 and 3 were associated with lower odds of eczema. In contrast, factor 4 was associated with lower odds of moderate-severe vs. mild eczema.

Discussion

The present study found that multiple pollutants influence the prevalence of pediatric eczema in the United States. Individually, NO₂, SO₂ and SO₃ were associated with higher odds of eczema, whereas NO₃, OC, PM-2.5 and PM-10 were inversely associated with eczema prevalence. In particular, higher levels of arsenic, lead, nickel, vanadium and zinc in PM-2.5 were associated with increased eczema prevalence, whereas cadmium, copper and potassium were inversely associated with eczema. The inverse associations of some pollutants with eczema prevalence may be due to the co-occurrence of higher levels in areas with protective climate factors. Though, we cannot rule out the unlikely possibility that one or more of these pollutants directly or indirectly has some beneficial effects on skin with respect to eczema.

It is interesting that NO₃, OC, PM-2.5 and copper were associated with more moderate-severe AD, despite being associated with lower eczema prevalence overall; this was true even when accounting for differences of levels in the cold and warm weather months. It is possible that these pollutants worsen the severity of active eczema in a subset of patients, but are not major drivers of mild disease or overall disease prevalence at the population-level.

Since many pollutants are correlated with each other and with different climate variables, we also analyzed the effects of the most dominant combinations of pollutants and climate variables in the US. In combination, significantly higher eczema prevalence was

found in areas with hot, humid and rainy climate and high OC, SO₂, SO₃ and PM-2.5.

Whereas, lower eczema prevalence was found in areas with hot and sunny climate along with high PM-10 and areas with high NO₂, NO₃ and PM-2.5. In contrast, CO was inversely associated with eczema severity. Of note, the PCA models showed different results for some pollutants than individual analyses. These are not contradictory, since PCA identifies the dominant patterns of co-occurrence of the variables. Together, the results suggest that some pollutants may contribute toward higher rates of eczema in the population, while others may accompany or be overshadowed by concomitant climate factors. The higher prevalence of eczema observed under certain pollutant conditions may be attributed to the environmental triggering of subclinical disease in predisposed children. Moreover, some pollutants likely also aggravate eczema resulting in persistent and/or more severe disease. Together, it appears that some pollutants may have independent effects on eczema, whereas others may act in conjunction with co-occurring climate factors.

CO was not associated with higher eczema prevalence and inversely associated with moderate-severe eczema. Previous international studies found conflicting results about the effects of pollutants on eczema(5-7). A study of 317,926 Taiwanese schoolchildren found associations between flexural eczema and traffic-related air pollution, including nitrogen oxides and CO(5). A study of 4,907 French children ages 9-11 years found associations between lifetime and 1-year history of eczema and concentrations of PM₁₀, nitrogen oxides and CO(6). In contrast, a study of 1,880 Turkish children found no association between level of pollutants and symptoms of current itchy rash(7). The different results observed in the abovementioned studies are likely due to differences of distributions of pollutants in different regions, indoor vs. outdoor pollutant levels and socio-demographics of study participants.

Previous studies linked the abovementioned pollutants to a variety of health conditions. NO_x levels have also been implicated in a number of other disorders, including impaired lung host defense(9), airway inflammation(10) and hyperresponsiveness(11), increased ED visits/hospital admissions(12). Ambient SO₂ exposure has been linked to increased ED utilization and hospitalizations for respiratory illnesses(13-16). Exposure to PM_{2.5} has been associated with adverse cardiovascular effects(17-19), respiratory effects(20-22), and all-cause mortality(23, 24). Similarly, exposure to PM-10 may be linked to adverse cardiovascular effects(17, 18, 25, 26), respiratory effects(22), and all-cause mortality(27). The present study suggests that NO₂, SO₂ and SO₃ may also have a harmful role in eczema.

Many of the pollutants fluctuate seasonally along with climate variables such as temperature and humidity. It is therefore impossible to determine the “pure” population-based effects of pollutants on eczema without also including climate effects. Thus, it is possible that some of the observed effects of pollutants may actually be related to coexistent climate factors. On the other hand, previous studies have argued for the protective and/or harmful effects of certain climate factors on eczema(3, 28). It may be that the effects of climate factors are due in part to coexistent pollutants.

The results of this study have a number of potential implications. First, these pollutants are highly regulated by the EPA and other state and federal government regulatory agencies. It may be that even stricter regulation of these pollutants may lead to decreased eczema prevalence in the US. Moreover, differential effects of certain pollutants on eczema prevalence and severity suggest that there may be specific signaling pathways or mechanisms at play. Finally, there may be specific subsets of patients who are affected by environmental pollutants. Future studies are needed to elucidate these points.

Strengths and limitations

This study has several strengths, including prospective data collection, population-based, having a very large and diverse sample of children with and without eczema, and the use of principal components analysis to examine patterns of climate variables not otherwise identified in univariate analyses. This study has potential limitations. Eczema was defined using self-report by parental questionnaire. However, we recently performed a multi-center validation the NSCH question used in NSCH and found excellent specificity and positive predictive value(29). We were only able to examine the dominant patterns of climate and pollution in the US with PCA. Thus, we were unable to determine if there are less common patterns that may have different effects on eczema prevalence and severity. NSCH only recorded the state of residence, but not city or county. Therefore, climate variables used in the study were limited to statewide values, which precludes calculation of distance between the residence and monitoring stations or the differential effects of exposure outside the residence, e.g. the workplace. This may result in decreased accuracy of estimates of effect size as well as ‘ecological fallacy’(30). Future, longitudinal clinical cohort studies are needed to confirm the observed associations.

Conclusions

In conclusion, this study provides evidence that multiple pollutants influence the prevalence and severity of eczema. In particular, combined hot and sunny climate with high PM10 and ozone appear to have protective effects specific to eczema, whereas high CO is associated with less severe eczema.

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Table 1: Association between eczema prevalence and mean annual levels of air pollutants.

Pollutant (unit) [n=50 states]	No AD		AD	
	Mean (95% CI)	Mean (95% CI)	OR (95% CI)	P-value
Ozone (ppb)	29.684 (29.629–29.379)	29.457 (29.313–29.602)	0.727 (0.396–1.334)	0.30
Carbon monoxide (CO) (ppm)	0.495 (0.493–0.496)	0.494 (0.491–0.497)	0.992 (0.949–1.038)	0.73
Nitrate (NO ₃) (mcg/m ³)	1.221 (1.203–1.240)	1.161 (1.121–1.200)	0.981 (0.969–0.993)	0.002
Nitrogen dioxide (NO ₂) (ppm)	12.604 (12.540–12.668)	12.851 (12.674–13.027)	1.003 (1.001–1.004)	0.008
Organic carbon (OC) (mcg/m ³)	1.505 (1.495–1.515)	1.476 (1.454–1.499)	0.993 (0.987–0.999)	0.03
Particulate matter 10 (PM-10) (mcg/m ³)	25.713 (25.587–25.840)	24.996 (24.663–25.329)	0.847 (0.739–0.971)	0.02
Sulfur dioxide (SO ₂) (ppm)	2.851 (2.823–2.880)	2.953 (2.886–3.020)	1.009 (1.003–1.015)	0.006
Sulfate (SO ₃) (mcg/m ³)	2.632 (2.609–2.655)	2.738 (2.686–2.790)	1.008 (1.004–1.012)	0.0002
Particulate matter 2.5, local conditions (mcg/m ³)	6.307 (6.274–6.339)	6.187 (6.115–6.258)	0.993 (0.989–0.998)	0.006
PM-2.5 species (ng/m³)				
Arsenic	0.641 (0.636–0.646)	0.664 (0.651–0.677)	1.228 (1.090–1.383)	0.0007
Cadmium	1.029 (1.025–1.034)	1.006 (0.996–1.016)	0.680 (0.567–0.815)	<0.0001
Copper	3.662 (3.616–3.707)	3.501 (3.404–3.598)	0.949 (0.916–0.983)	0.004
Lead	2.959 (2.936–2.982)	3.029 (2.968–3.089)	1.017 (1.002–1.032)	0.03
Nickel	1.182 (1.165–1.199)	1.281 (1.228–1.337)	1.084 (1.039–1.131)	0.0002

Potassium	65.163 (64.835–65.491)	63.455 (62.679–64.231)	0.993 (0.990–0.997)	<0.0001
Vanadium	1.192 (1.903–1.922)	1.971 (1.943–1.999)	1.096 (1.048–1.146)	<0.0001
Zinc	11.387 (11.276–11.497)	11.843 (11.551–12.135)	1.006 (1.002–1.010)	0.003

Daily statewide mean values of ozone and small particle pollutants for 2006–2007 were downloaded from the Environmental Protection Agency (EPA). Mean (95% CI) annual levels were estimated.

* Logistic regression models were constructed with eczema (yes/no) modeled as the dependent variable and pollutants as the continuous independent variables.

Table 2: Association between eczema severity and mean annual levels of air pollutants.

Pollutant (unit) [number of states]	Mild AD	Moderate-severe AD		P-value
	Mean (95% CI)	Mean (95% CI)	OR (95% CI)	
Ozone (ppb)	29.562 (29.393–29.731)	29.375 (29.128–29.621)	0.988 (0.969–1.007)	0.22
Carbon monoxide (CO) (ppm)	0.497 (0.493–0.501)	0.489 (0.484–0.494)	0.557 (0.327–0.949)	0.03
Nitrate (NO ₃) (mcg/m ³)	1.124 (1.081–1.167)	1.218 (1.146–1.289)	1.249 (1.028–1.517)	0.03
Nitrogen dioxide (NO ₂) (ppm)	12.732 (12.563–12.937)	12.867 (12.571–13.162)	1.007 (0.989–1.025)	0.46
Organic carbon (OC) (mcg/m ³)	1.452 (1.427–1.476)	1.515 (1.475–1.555)	1.323 (1.077–1.625)	0.008
Particulate matter 10 (PM-10) (mcg/m ³)	25.175 (24.793–25.557)	24.940 (24.373–25.507)	0.996 (0.986–1.007)	0.50
Sulfur dioxide (SO ₂) (ppm)	2.953 (2.878–3.028)	2.930 (2.811–3.050)	0.988 (0.918–1.064)	0.75
Sulfate (SO ₃) (mcg/m ³)	2.730 (2.672–2.787)	2.726 (2.631–2.820)	0.997 (0.922–1.079)	0.95
Particulate matter 2.5, local conditions (mcg/m ³)	6.130 (6.052–6.208)	6.317 (6.183–6.451)	1.070 (1.013–1.130)	0.01
PM-2.5 species (ng/m³)				
Arsenic	0.659 (0.645–0.673)	0.672 (0.648–0.696)	1.118 (0.881–1.419)	0.36
Cadmium	1.006 (0.995–1.018)	1.012 (0.993–1.030)	1.092 (0.754–1.581)	0.64
Copper	3.415 (3.311–3.520)	3.632 (3.453–3.811)	1.085 (1.005–1.170)	0.04
Lead	2.970 (2.901–3.039)	3.148 (3.029–3.266)	1.041 (1.011–1.072)	0.008
Nickel	1.226 (1.167–1.284)	1.316 (1.222–1.409)	1.067 (0.987–1.154)	0.10
Potassium	63.226 (62.377–64.074)	64.203 (62.809–65.596)	1.004 (0.997–1.011)	0.24
Vanadium	1.938 (1.907–1.969)	1.994 (1.946–2.042)	1.084 (0.999–1.177)	0.05
Zinc	11.576 (11.247–11.905)	12.350 (11.794–12.905)	1.009 (1.002–1.017)	0.01

Daily statewide mean values of ozone and small particle pollutants for 2006–2007 were downloaded from the Environmental Protection Agency (EPA). Mean (95% CI) annual levels were estimated.

* Logistic regression models were constructed with eczema severity (moderate-severe vs. mild) modeled as the dependent variable and pollutants as the continuous independent variables.

Table 3. Principal component analysis of the association between eczema prevalence, small particle air pollutants and climate variables.

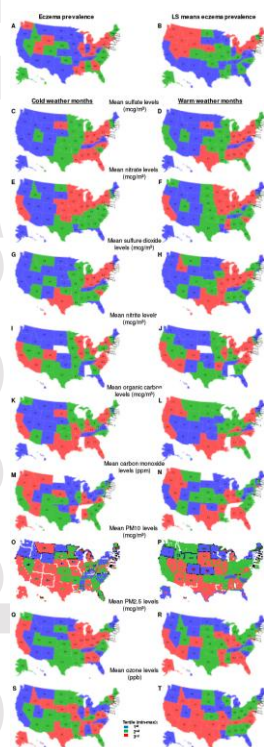
Variable	Factor 1		Factor 2		Factor 3		Factor 4	
	Loading values	Std. Coef	Loading values	Std. Coef	Loading values	Std. Coef	Loading values	Std. Coef
Carbon monoxide (CO)	-1	-0.04	4	-0.02	7	0.04	94*	0.80*
Nitrate (NO3)	30	-0.03	-13	-0.06	75*	0.37*	-29	-0.25
Sulfur dioxide (NO2)	2	-0.16	-2	-0.06	83*	0.47*	23	0.20
Organic carbon (OC)	80*	0.27*	21	0.13	14	-0.08	-6	-0.09
Sulfate (SO4)	60*	0.16*	-11	-0.02	27	0.05	4	0.02
Sulfur dioxide (SO2)	80*	0.25*	7	0.07	26	-0.01	-15	-0.15
Particulate matter 10 (PM10)	-29	-0.12	72*	0.25*	35	0.21	-15	-0.14
Particulate matter 2.5 (PM2.5)	51*	0.06*	19	0.07	70*	0.29*	8	0.05
Ozone	-17	0.02	43*	0.17*	-29	-0.16	-4	-0.04
Relative humidity	75*	0.24*	-40	-0.11	1	-0.11	0	-0.01
Issued UV index	-10	0.05	92*	0.37*	-14	-0.11	4	0.00
Temperature	41*	0.17*	81*	0.33*	9	-0.07	25	0.17
Precipitation	77*	0.25*	-36	-0.10	0	-0.12	21	0.16
Eigenvalues	3.44		2.62		2.14		1.18	
(Percent variance)	(31.7%)		(20.3%)		(11.1%)		(10.0%)	
Factor description	Hot, humid and rainy with high OC, SO ₂ , SO ₃ and PM-2.5		Hot and sunny with high PM-10 and ozone		High NO ₂ , NO ₃ and PM-2.5		High CO	
Eczema								
OR (95% CI)	1.046 (1.001–1.093)		0.872 (0.827–0.919)		0.947 (0.897–0.999)		1.036 (0.997–1.077)	
P-value	0.047		<0.0001		0.049		0.07	
Moderate-severe eczema								
OR (95% CI)	1.072 (0.986–1.164)		0.991 (0.886–1.109)		1.110 (0.986–1.250)		0.893 (0.821–0.972)	
P-value	0.10		0.87		0.08		0.009	

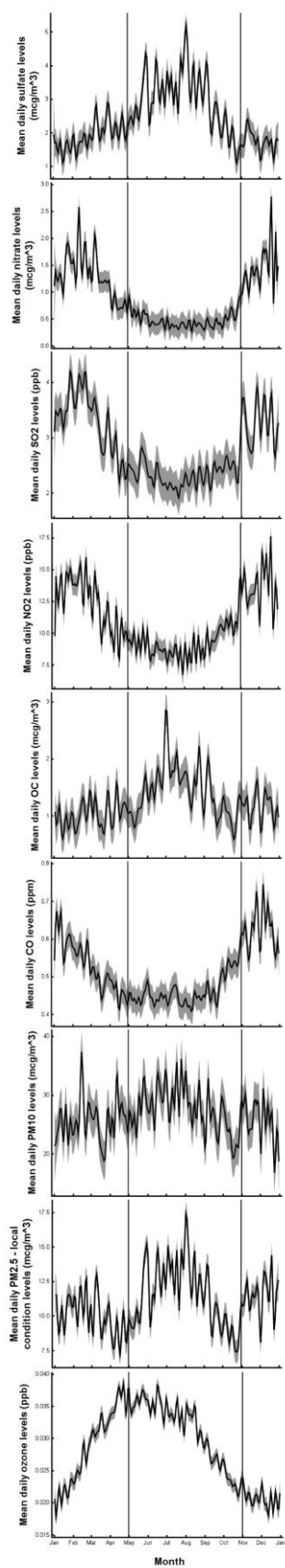
Principal component analysis with varimax rotation was used to estimate the combined effects of carbon monoxide, nitrate, sulfur dioxide, organic carbon, sulfate, sulfur dioxide, particulate matter 10, particulate matter local conditions 2.5, ozone, relative humidity, issued UV index, temperature and precipitation. Factors were retained if eigenvalue >1, proportion of variance accounted for ≥ 10% and loading value > 0.4. Logistic regression was then performed using separate factor scores for each of the retained factors. Odds ratios (OR) and 95% confidence intervals (95% CI) were calculated.

Figure Legends.

Figure 1. The distribution of childhood eczema and associated pollutants in the United States. (A) Eczema prevalence (%), (B) least-squares means of eczema prevalence, mean sulfate levels in the (C) cold and (D) warm weather months, mean nitrate levels in the (E) cold and (F) warm weather months, mean sulfur dioxide levels in the (G) cold and (H) warm weather months, mean nitrite levels in the (I) cold and (J) warm weather, mean organic carbon in the (K) cold and (L) warm weather, mean carbon monoxide in the (M) cold and (N) warm weather, mean PM10 in the (O) cold and (P) warm weather, mean PM2.5 in the (Q) cold and (R) warm weather, mean ozone in the (S) cold and (T) warm weather where available. Data were divided into tertiles and color-coded: tertile-1 = blue, tertile-2 = green, tertile-3 = red.

Figure 2. Seasonal variation of tropospheric ozone and air pollutants. Smoothed mean daily values for each pollutant (2006 and 2007) are presented with 95% CI.





Supplemental Table 1. Subject characteristics*.			
Variable	No eczema	Eczema	P-value[#]
Age (yr)–no. (%)			<0.0001
0-5	23187 (85.4)	4344 (14.6)	
6-11	24301 (87.5)	3471 (12.5)	
12-17	32725 (90.3)	3515 (9.7)	
Race/ethnicity–no. (%)			< 0.0001
African-American	7165 (81.4)	1699 (18.6)	
Hispanic	10176 (90.5)	1332 (9.5)	
White	54394 (88.5)	6927 (11.5)	
Other/mixed	7123 (87.1)	1185 (12.9)	
Sex–no. (%)			0.25
Male	35930 (87.3)	5385 (12.7)	
Female	33165 (86.7)	5016 (13.3)	
Household income (Poverty level)–no. (%)			0.65
0–99%	9569 (88.2)	1385 (11.8)	
100–199%	13651 (88.1)	1921 (11.9)	
200–399%	26933 (87.4)	3828 (12.6)	
≥400%	30060 (87.7)	4196 (12.3)	
US birthplace			<0.0001
Yes	66655 (86.7)	10133 (13.3)	
No	1813 (93.9)	174 (6.1)	
History of child moving to new address			0.35
No	25526 (87.3)	3928 (12.7)	
Yes	42724 (86.8)	6356 (13.2)	

Rao-Scott chi square test.

* Missing data were encountered in 79 subjects (0.001%) for the eczema outcome, 0 (0.0%) for age, 4,517 for race/ethnicity (5.7%), 79 for sex (0.001%), 0 (0.0%) for household income, 23 (0.03%) for US birthplace and 255 (0.06%) for history of child moving to a new address.

Supplemental Table 2: Association between eczema prevalence and level of air pollutants during cold and warm weather months.

Pollutant (unit) [number of states]	No AD		AD	P-value
	Mean (95% CI)	Mean (95% CI)	Adjusted OR (95% CI)	
Cold weather				
Ozone (ppb)	26.896 (26.813–26.980)	26.736 (26.526–26.946)	0.994 (0.986–1.002)	0.17
Carbon monoxide (CO)	0.539	0.535	0.760	0.03

(ppm)	(0.538–0.541)	(0.531–0.538)	(0.589–0.980)	
Nitrate (NO ₃) (mcg/m ³)	1.746 (1.723–1.769)	1.674 (1.625–1.724)	0.926 (0.873–0.983)	0.01
Nitrogen dioxide (NO ₂) (ppm)	14.380 (14.306–14.552)	14.641 (14.437–14.844)	1.010 (1.002–1.019)	0.02
Organic carbon (OC) (mcg/m ³)	1.384 (1.373–1.394)	1.355 (1.330–1.379)	0.908 (0.831–0.991)	0.03
Particulate matter 10 (PM-10) (mcg/m ³)	24.859 (24.688–25.030)	23.794 (23.369–24.218)	0.988 (0.982–0.993)	<0.0001
Sulfur dioxide (SO ₂) (ppm)	3.261 (3.226–3.297)	3.403 (3.321–3.485)	1.047 (1.018–1.077)	0.002
Sulfate (SO ₃) (mcg/m ³)	1.988 (1.970–2.005)	2.077 (2.037–2.117)	1.131 (1.064–1.203)	<0.0001
Particulate matter 2.5, local conditions (mcg/m ³)	11.419 (11.375–11.462)	11.281 (11.185–11.377)	0.964 (0.937–0.991)	0.01

Warm weather

Ozone (ppb)	32.472 (32.413–32.530)	32.179 (32.033–32.325)	0.983 (0.974–0.992)	0.0002
Carbon monoxide (CO) (ppm)	0.450 (0.449–0.452)	0.453 (0.449–0.457)	1.277 (0.910–1.792)	0.16
Nitrate (NO ₃) (mcg/m ³)	0.692 (0.678–0.707)	0.643 (0.612–0.673)	0.786 (0.661–0.935)	0.006
Nitrogen dioxide (NO ₂) (ppm)	10.827 (10.772–10.882)	11.060 (10.906–11.215)	1.017 (1.005–1.029)	0.005
Organic carbon (OC) (mcg/m ³)	1.625 (1.616–1.635)	1.598 (1.576–1.620)	0.888 (0.800–0.987)	0.03
Particulate matter 10 (PM-10) (mcg/m ³)	26.568 (26.460–26.676)	26.199 (23.369–24.218)	0.992 (0.986–0.999)	0.02
Sulfur dioxide (SO ₂) (ppm)	2.442 (2.418–2.465)	2.503 (2.448–2.557)	1.041 (1.002–1.081)	0.04
Sulfate (SO ₃) (mcg/m ³)	3.273 (3.245–3.302)	3.395 (3.329–3.462)	1.051 (1.020–1.083)	0.001
Particulate matter 2.5,	12.452	12.502	0.998	0.75

local conditions (mcg/m³) (12.406–12.497) (12.384–12.621) (0.985–1.011)

Daily statewide mean values of ozone and small particle pollutants for 2006–2007 were downloaded from the Environmental Protection Agency (EPA). Mean (95% CI) levels were estimated for the cold (November, December, January, February, March and April) and warm (May, June, July, August, September, October) weather months.

* Logistic regression models were constructed with eczema (yes/no) modeled as the dependent variable and pollutants as the continuous independent variables.

Supplemental Table 3: Association between eczema severity and level of air pollutants during cold and warm weather months.

Pollutant (unit) [number of states]	Mild AD	Moderate-severe AD		
	Mean (95% CI)	Mean (95% CI)	OR (95% CI)	P-value
Cold weather				
Ozone (ppb)	26.933 (26.693–27.172)	26.527 (26.162–26.893)	0.985 (0.970–1.001)	0.07
Carbon monoxide (CO) (ppm)	0.537 (0.533–0.542)	0.531 (0.525–0.537)	0.677 (0.425–1.078)	0.10
Nitrate (NO ₃) (mcg/m ³)	1.629 (1.575–1.684)	1.747 (1.658–1.836)	1.146 (1.016–1.293)	0.03
Nitrogen dioxide (NO ₂) (ppm)	14.528 (14.289–14.767)	14.621 (14.284–14.957)	1.003 (0.988–1.019)	0.66
Organic carbon (OC) (mcg/m ³)	1.328 (1.301–1.356)	1.390 (1.346–1.434)	1.233 (1.035–1.470)	0.02
Particulate matter 10 (PM-10) (mcg/m ³)	23.924 (23.449–24.398)	23.844 (23.099–24.590)	0.999 (0.989–1.009)	0.86
Sulfur dioxide (SO ₂) (ppm)	3.395 (3.305–3.486)	3.375 (3.230–3.521)	0.993 (0.935–1.055)	0.82
Sulfate (SO ₃) (mcg/m ³)	2.075 (2.031–2.118)	2.062 (1.989–2.134)	0.982 (0.874–1.104)	0.76
Particulate matter 2.5, local conditions (mcg/m ³)	11.201 (11.095–11.306)	11.424 (11.253–11.595)	1.070 (1.007–1.138)	0.03
Warm weather				
Ozone (ppb)	32.191 (32.020–32.362)	32.222 (31.977–32.466)	1.002 (0.983–1.021)	0.84
Carbon monoxide (CO) (ppm)	0.456 (0.452–0.461)	0.448 (0.442–0.454)	0.490 (0.245–0.977)	0.04
Nitrate (NO ₃) (mcg/m ³)	0.614 (0.582–0.647)	0.685 (0.629–0.741)	1.512 (1.051–2.174)	0.03
Nitrogen dioxide (NO ₂) (ppm)	10.936 (10.758–11.114)	11.113 (10.851–11.375)	1.012 (0.991–1.034)	0.27
Organic carbon (OC)	1.575	1.641	1.343	0.005

(mcg/m ³)	(1.550–1.599)	(1.602–1.679)	(1.096–1.646)	
Particulate matter 10 (PM-10) (mcg/m ³)	26.426 (26.088–26.764)	26.035 (25.552–26.518)	0.992 (0.980–1.004)	0.20
Sulfur dioxide (SO ₂) (ppm)	2.511 (2.449–2.572)	2.485 (2.388–2.582)	0.982 (0.906–1.065)	0.66
Sulfate (SO ₃) (mcg/m ³)	3.381 (3.307–3.455)	3.387 (3.268–3.507)	1.003 (0.946–1.062)	0.93
Particulate matter 2.5, local conditions (mcg/m ³)	12.452 (12.306–12.598)	12.603 (12.401–12.806)	1.010 (0.985 – 1.036)	0.44

Daily statewide mean values of ozone and small particle pollutants for 2006–2007 were downloaded from the Environmental Protection Agency (EPA). Mean (95% CI) levels were estimated for the cold (November, December, January, February, March and April) and warm (May, June, July, August, September, October) weather months.

* Logistic regression models were constructed with eczema severity (moderate-severe vs. mild) modeled as the dependent variable and pollutants as the continuous independent variables.

Supplemental Methods

Pollutant data collection methods

Carbon monoxide

Carbon monoxide (CO) in outdoor (ambient) air comes mostly from the incomplete combustion of carbon-based fuels and other photochemical reactions that occur in the atmosphere, primarily from on-road motor vehicles (4). Carbon monoxide in indoor (nonambient) air typically comes from movement of outdoor air indoors and from indoor sources such as tobacco smoke and gas stoves. Individual exposure to CO predominantly occurs from riding in motor vehicles. Carbon monoxide displays a seasonal trend in that levels in ambient air are highest during the cold months and lowest during the warm months, possibly because cars spend more time on the road during the colder months. Long-term CO exposure is associated with ischemic heart disease (31-33).

Data on carbon monoxide is collected over 1 hour and 8 hours in units of parts per million. As of 2011, the CO monitoring network consisted of 63 urban and 20 rural monitoring sites. Sites are designed to monitor one of three types of areas: microscale (within 100 meters of the monitor), middle scale (between 100-500 meters of the monitor), and neighborhood scale (between 500 meters and 4 kilometers of the monitor).

Nitrogen oxides (NO_x)

Nitrogen oxides (NO_x) refer to all forms of oxidized nitrogen compounds, including NO, NO₂, NO₃ and all other oxidized nitrogen-containing compounds formed from NO, NO₂ and NO₃. NO_x emitted into ambient air are converted to nitrogen dioxide (NO₂) in the atmosphere (4). NO_x are emitted primarily from both on-road and off-road sources (60%) and electrical utilities

and industry tools (40%). A small portion of NO levels also comes from non-human sources such as wildfires, lightning, and microbial activity in soil. Ambient levels of NO_x are highest in the Los Angeles area, Midwest and Northeast. NO_x vary seasonally in different regions. Human exposure to NO_x typically occurs predominantly while being in near-traffic outdoor environments, in vehicles, and residential indoor environments (34-39).

Data on nitrogen dioxide is collected over 1 hour in units of parts per billion. Data on nitrates is collected over 24 hours in units of micrograms/cubic meter. The NO_x monitoring network was established in 1971. In October of 2008, there were 409 monitors in the United States inputting data to the EPA's Air Quality System. There are six different types of NO_x monitoring sites: one to determine the highest concentration expected to occur, one to measure the typical concentrations in densely populated areas, one to determine the location of significant sources, one to determine general background levels, one to determine pollution from regional transportation, and one to measure impact of pollution on visibility, vegetation, and other welfare-based impacts.

Tropospheric ozone (O₃)

Ozone occurs in two layers of the atmosphere: stratosphere and troposphere. In the stratosphere, ozone occurs naturally and provides protection against UV radiation. In the troposphere, ozone is formed from the combination of volatile organic compounds (VOCs) and nitrogen oxides (NO_x) in presence of sunlight, as well as CO and methane (4). Ozone does not always vary directly from increased emissions of its precursors, as fresh NO_x emissions can combine with radicals such as hydroxyl (OH) and hydroperoxy (HO₂) to form nitric acid (HNO₃), thus decreasing ozone formation. VOCs in ambient air primarily come from vegetation, as well as solvent use, highway vehicles, agriculture, forestry and fires. Ozone emissions are

highest in the summer due to a dependence on temperature and sunlight. Ozone exposure has been shown to be associated with adverse respiratory (40-42), adverse effects on the central nervous system (43-45), cardiovascular effects (46, 47), reproductive and developmental effects such as increased risk of intrauterine growth retardation and sudden infant death syndrome (48, 49), and all-cause mortality (27).

Data on ozone is collected over 8 hours in units of parts per billion. There are currently 1468 sites monitoring ambient ozone levels in the United States, with data being sent to the EPA's Air Quality System. In order to assess whether ambient ozone levels meet the national standard, the EPA calculates a statistic known as a 'design value'. For ozone, the design value is calculated as the 3-year average of the annual fourth highest daily maximum 8-hour ozone concentration in parts per billion. Between 2006 and 2008, there were 518 ozone monitors in the United States with design values that exceeded the national standard.

Sulfur oxides (SO_x)

SO_x include both gaseous (SO₂, SO₃) and particulate (sulfate) species (4). Gaseous levels of SO₂ are much higher than SO₃ levels. SO₂ primarily comes from fossil fuel combustion, extraction of metal from ore, as well as volcanoes (e.g. Pacific Northwest, Alaska, and Hawaii), wildfires, and burning vegetation. SO₂ levels are much higher in eastern regions than in western regions, largely due to the coal-powered electric utility plants clustered in the Ohio River Valley and Southeast regions. A few minutes of SO₂ exposure has been linked to decreases in lung function in asthmatics (50-52).

Data on sulfur dioxide is collected over 1 hour, 3 hours, and 24 hours in units of parts per billion. Data on sulfate is collected over 1 hour and 24 hours in units of micrograms/cubic meter. In 2008, there were approximately 488 sites in the United States sending data to the EPA's Air

Quality System. There are six different types of SO_x monitoring sites identical to the six described above for NO_x.

Particulate matter

Particulate matter is a broad term for substances that exist as discrete particles (liquids or solids) in ambient air (4). Particulate matter is measured at two sizes: particulate matter under 2.5 micrometers (PM_{2.5}), classified as fine particles, and particulate matter between 2.5 and 10 micrometers (PM₁₀), classified as inhalable coarse particles. PM_{2.5} is produced from the combustion of fossil fuel and includes OC, elemental carbon, sulfates, and nitrates (53-55). PM₁₀ is composed of particles emitted from abrasion and crushing processes, plant and insect fragments, pollens, and soil disturbances. PM_{2.5} levels vary considerably across the US with highest levels areas in California, Alabama and Pennsylvania. PM₁₀ levels are highest in southern California, southern Arizona, and central New Mexico.

Data on PM-2.5 and PM-10 is collected over 1 hour and 24 hours in units of micrograms/cubic meter. In 2007, there were 2194 PM-2.5 monitors and 4693 PM-10 monitors reporting data to the EPA's Air Quality System. The areas covered by these monitors vary due to the different sizes of particles being measured. In any given metropolitan area, there are between 0 and 3 PM-2.5 monitors and between 0 and 8 PM-10 monitors. Mean statewide values were ultimately used. Thus, even if a particular metropolitan area had 0 monitors, there were always multiple monitors per state.

Species of particulate matter

Species of particulate matter were assessed by Speciation Air Sampling System (SASSTM) and the second generation of the SASSTM called SuperSASSTM. Data are averaged at 5 minute intervals. Arsenic, cadmium, copper, lead, nickel, potassium, vanadium and zinc were measured in units of micrograms/cubic meter. Monitoring for PM species was established in

1999 with ~300 x-ray fluorescence monitors in the United States. There are six different types of PM species monitoring devices used: Andersen RAAS Teflon, R&P MDL 2300 PM_{2.5} SEQ SPEC TEF, URG MASS400 Teflon WINS, IMPROVE Module A with Cyclone Inlet-Teflon Filter, 2.2 cm², IMPROVE Module A with Cyclone Inlet-Teflon Filter, 2.2 cm², Met One SASS Teflon, BGI PQ200/200A and R & P Model 2025 PM_{2.5} Sequential w/WINS.