Warm, Humid, and High Sun Exposure Climates are Associated with Poorly Controlled Eczema: PEER (Pediatric Eczema Elective Registry) Cohort, 2004–2012

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Abstract

Anecdotal reports of children experiencing eczema flares during winter and summer months along with global variation in eczema prevalence has fueled speculation that climate may modulate disease activity. The aim of this study was to determine if long-term weather patterns affect the severity and persistence of eczema symptoms in children. We performed a prospective cohort study of U.S. children (N=5,595) enrolled in PEER (Pediatric Eczema Elective Registry) between 2004 and 2012 to evaluate the effect of climate (daily temperature, daily sun exposure, daily humidity) on the severity of eczema symptoms. Odds ratios were calculated for the patient evaluated outcome of disease control. Multivariate logistic regression modeling adjusting for gender, race, income, and topical medication use demonstrated that higher temperature (OR=0.90, 95% CI: 0.87–0.93, p<0.001) and increased sun exposure (OR=0.93, 95% CI: 0.89–0.98, p=0.009) were associated with poorly controlled eczema. Higher humidity (OR=0.90, 95% CI: 0.812–0.997, p=0.44) was also associated with poorly controlled disease, but the statistical significance of this association was lost in our multivariate analysis (p=0.44).

Introduction

Eczema, otherwise known as atopic dermatitis, is a chronic, recurring inflammatory condition that is associated with severe itching and dryness of the skin. The pathogenesis of disease is multifactorial resulting from a combination of genetic and environmental factors that predispose individuals to a defective skin barrier and that trigger an abnormal immune response when environmental antigens penetrate the skin.(Fennessy et al., 2000; Fergusson et al., 1982; Schultz Larsen, 1993) One of the genetic factors thought to play a key role in the development of eczema is the protein filaggrin (FLG), which aligns keratin intermediate filaments in the skin in order to prevent transepidermal water loss, which is a characteristic
clinical feature of eczema. Individuals with FLG null mutations are at an increased risk for developing disease.

There currently exists widespread variation in eczema prevalence worldwide. (1998; Asher et al., 2006; Leung and Bieber, 2003; Shaw et al., 2011; Williams, 2011) Several studies have interpreted global variation in eczema prevalence as a possible indication that climatic factors may have some influence on disease susceptibility. (Osborne et al., 2012; Silverberg et al., 2013; Suarez-Varela et al., 2008) Osborne and colleagues demonstrated that the prevalence of disease amongst Australian children decreases in areas with increased sun exposure and warmer temperatures that are closer to the equator. (Osborne et al., 2012) Silverberg and colleagues found similar findings in the United States showing that the prevalence of eczema is decreased in parts of the country where there is higher sun exposure, humidity and temperature. (Silverberg et al., 2013) The effect of climate on the severity and persistence of eczema symptoms is also a clinically important question that has not been previously examined in any large prospective study. Many patients anecdotally report eczema flares during certain seasons of the year, particularly during winter and summer months, and flares in response to weather effects such as sweating. (Kramer et al., 2005; Langan, 2009; Langan et al., 2009) In this study, we analyze the effect of long-term weather patterns (temperature, humidity, and UVA/UVB sun exposure) on disease severity or persistence in a prospective, national cohort of U.S. children with eczema.

Results

Patient Demographics

The PEER cohort enrolled 5,595 children between November 2004 and April 2012, and enrollees were followed for an average of 2.9 person-years. Study participants were enrolled from every region of the continental United States with a slight predominance of females within the study cohort (53.3% female vs. 46.7% male). The majority of patients had either good (47.5%) or limited (37.6%) disease control at enrollment, and children were drawn from a wide spectrum of socioeconomic backgrounds. A more detailed description of the PEER cohort can be found in Table 1. Correlation between the climate variables was generally weak (Pearson coefficients<0.1), except for temperature and sun exposure, which were moderately correlated (Pearson coefficient=0.5871, p<0.001).

Temperature

Logistic regression analysis revealed that higher temperatures were associated with poorly controlled eczema. For every 5°F increase in temperature, the odds (OR=0.85, 95% CI: 0.82–0.89, p<0.001) of patients describing their disease as poorly controlled increased by 15% (Table 2). This association between temperature (OR=0.90, 95% CI: 0.87–0.93, p<0.001) and disease control was also statistically significant after adjusting for potential confounders including race, ethnicity, gender, annual household income, and the use of topical medications (topical steroids, topical tacrolimus, topical pimecrolimus) (Table 2).
Sun Exposure

Increased daily sun exposure was also associated with poorly controlled disease. The odds (OR=0.89, 95% CI: 0.84–0.94, p<0.001) of poorly controlled eczema grew by 11% for each 5% increase in sun exposure for our study cohort (Table 2). The statistical significance of this association (OR=0.93, 95% CI: 0.89–0.98, p=0.009) was also maintained after adjusting for potential confounders in our multivariate analysis (Table 2). Additionally, higher cumulative UVA (Adjusted OR=0.91, 95% CI: 0.87–0.95, p<0.001) and UVB (Adjusted OR=0.88, 95% CI: 0.84–0.92, p<0.001) exposure was associated with poorly controlled disease (Table 2).

Humidity

Higher humidity was associated with poorly controlled eczema. There was a 10% rise in the odds (OR=0.90, 95% CI: 0.81–1.00, p=0.04) of poorly controlled disease for every 10% increase in humidity (Table 2). The statistical significance of this association (OR=0.93, 95% CI: 0.84–1.02, p=0.14) was lost in our multivariate analysis (Table 2).

Subgroup Analysis

The odds of poorly controlled disease were increased for each of the subgroups in regions of the country with higher temperatures, increased sun exposure, and increased humidity. The statistical significance (p<0.05) of these associations was generally maintained after adjusting for potential confounders such as patient use of topical medications and income (Supplementary Table 1).

Filaggrin Genotyping Subgroup

A total of 416 children (50.7% of genotyped sub-cohort, N=820), who described themselves as white on their initial enrollment form, submitted saliva samples for genotyping of the four most common null alleles amongst Caucasians of European ancestry. The genotyped subgroup of children within the PEER cohort was geographically and socioeconomically diverse and saliva samples were collected from every region of the country. Additional demographic information for this subgroup, including allelic frequencies, is available in Supplementary Table 2. For the subgroup of white children who submitted saliva samples and were found to have FLG null alleles, their distribution in the United States was not correlated with any of the climate variables (Pearson coefficients <0.10, p<0.001).

Discussion

We performed a large-scale prospective, longitudinal cohort study evaluating the effect of long-term weather patterns on the severity of eczema symptoms in children. Our analysis revealed that geographic areas with increased temperature, sun exposure (total, UVA, and UVB), and humidity were associated with poorly controlled disease.

Several cross-sectional studies have attempted to elucidate the relationship between climate and eczema symptoms. In a large Australian study, researchers found that the prevalence of eczema decreases in areas with increased sun exposure and warmer temperatures that are closer to the equator. (Osborne et al., 2012) Additionally, Silverberg and colleagues recently
reported that the prevalence of eczema is decreased in parts of the United States where there is increased humidity, UV index, and temperature. Prevalence studies are excellent for evaluating the burden of disease within an area, but they are unable to provide information regarding risk for a defined outcome following a particular exposure.

Disease incidence or flares following an exposure are best evaluated through a prospective analysis. Previous studies examining the effect of weather on eczema symptoms have been underpowered and of too short duration to effectively answer this question. Langan and colleagues recruited a cohort of 25 Irish children to record their eczema symptoms for a period of 28 days. At the end of the study, the authors found that increased humidity and heat were associated with a higher incidence of disease flares. (Langan et al., 2006)

However, Kramer and colleagues found mixed results when studying the effects of climate on eczema symptoms in a cohort of 39 German children.

The authors observed this cohort for several months (March through September 1999) and each of the children recorded daily itch scores and the extent of skin involvement. Twenty-one of the children in the study had worse symptoms during winter months, and the itch and extent scores for this cohort were reduced with higher temperatures. In contrast, of the 18 children with worse symptoms during summer months, higher temperatures were associated with more severe disease. (Kramer et al., 2005) The results of the study by Kramer and colleagues suggest two different phenotypes of eczema. Their finding that a subgroup of children with eczema developed worsening symptoms during summer months is consistent with the results in our study. It is unclear why some children developed flares of their disease more frequently during colder winter months. However, the purpose of these small-scale prospective studies was to determine the short-term effects of weather on eczema symptoms, while our study is focused on the effect that long-term weather patterns have on disease activity.

The explanation for increased temperatures, humidity, and sun exposure resulting in poorly controlled eczema is not entirely clear. It is possible that warm and humid weather leads to increased sweating, which has an irritant effect on the skin. (Langan et al., 2006; Langan et al., 2009) The irritation mediated by the acidic pH of sweat, may promote Th2 and Th17-mediated inflammation, which downregulates filaggrin expression. (Kubo et al., 2012; Patterson et al., 2000) Warm and humid weather also promotes the evaporation of water on the skin surface, which may further exacerbate skin dryness, which is a characteristic clinical feature of eczema. It is also possible that temperature, humidity, and sun exposure may affect the functioning of the skin barrier through yet unknown mechanisms.

Limitations

The prevalence and type of FLG mutations varies considerably by population and country. (Barker et al., 2007; Brown et al., 2012; Chen et al., 2011; Henderson et al., 2008; Irvine et al., 2011; Palmer et al., 2006; Rodriguez et al., 2009; Sandilands et al., 2006; Sandilands et al., 2007; van den Oord and Sheikh, 2009) FLG mutations are associated with more severe and persistence eczema symptoms. In our analysis, a potential confounder would be the distribution of children with FLG null alleles in parts of the United States with warm, humid, and high sun exposure climates. We performed a secondary analysis evaluating for
any correlation between our climate variables and the location of children with FLG mutations. The power of the subgroup analysis was limited by a low overall submission rate (15% for the entire cohort, N=820) of saliva samples amongst the cohort participants. Additionally, our genetic screening test was only equipped to detect mutations of the filaggrin locus that are most commonly seen amongst whites of European ancestry. Therefore, we limited our subgroup analysis to children who described themselves as Caucasian (N=416, 50.7%) on their initial enrollment form. The subgroup of white children who submitted saliva samples comprised 7.4% of the total PEER cohort, and for this small geographically diverse subgroup, our climate-outcome associations were independent of filaggrin genotype. However, the limited number of saliva samples prevents us from determining whether geographic clustering of children with filaggrin mutations is functioning as a confounder in our overall analysis.

The objective of this study was to identify associations between long-term weather patterns and eczema severity. Statistically significant odds ratios in our analysis do not prove causality. A temporal analysis with local weather data at or around the time each child completed their 6-month survey would provide insights into the short-term effects that weather has on eczema symptoms, but would not necessarily provide information on the long-term impact that climate has on disease activity, which is the focus of our particular study. Both questions are equally important and should be evaluated in follow-up studies. It is also important to point out, that weather may be serving as a proxy for other environmental factors that can exacerbate eczema symptoms. Previous studies have shown that sweating, diet, water hardness, and pollen exposure are each associated with eczema flares. (Kramer et al., 2005; Langan et al., 2009; McNally et al., 1998; Reekers et al., 1999) Each of these external factors is influenced by climate. Warmer temperatures also result in earlier and greater overall seasonal production of tree (spring), grass (summer), and ragweed (fall) pollen, which can trigger eczema flares. (Ziska and Beggs, 2012)

Future studies may also want to evaluate climate data for the specific time interval of the cohort study. However, weather patterns in the United States have been relatively stable over the past century and climate data for the period of 2004–2012 is unlikely to change the findings in our analysis.

Lastly, all patients in the PEER cohort used pimecrolimus prior to the start of the study, and this medication is FDA-approved for mild to moderate eczema. Therefore, the effect of long-term weather patterns on eczema severity may not be generalizable to children with severe eczema. However, 37.6% and 10.6% of the children reported limited disease control or uncontrolled disease, respectively, at enrollment suggesting that many children within the PEER cohort suffered from moderate-to-severe eczema. Therefore, our results may also be applicable to children with severe disease.

Conclusions

We present data from a geographically diverse longitudinal prospective analysis examining the effect of long-term weather patterns on symptom severity in children with eczema. The results of this study demonstrate that warm, humid, and high sun exposure climates are associated with poorly controlled disease.
Materials and Methods

Study Cohort

The study population included children less than 18 years of age enrolled in the PEER (Pediatric Eczema Elective Registry) cohort, which is an ongoing prospective longitudinal post-marketing safety analysis that was initiated in 2004 to evaluate whether topical pimecrolimus is associated with systemic or cutaneous malignancies. All children were required to have parental consent and a physician (dermatologist, pediatrician, allergist, primary care physician) diagnosis of eczema prior to enrollment. Per the FDA-approved protocol, each study participant was also required to have a treatment history of either 6 continuous weeks of topical 1% pimecrolimus or 6 total weeks of intermittent drug exposure within the 6 months preceding enrollment. However, once enrolled in the study, the treating physician was not expected to continue treatment with pimecrolimus if other medications were determined to be more appropriate for the child’s clinical symptoms. Children were excluded from the PEER cohort if they had a history of lymphoproliferative disease, systemic malignancy, cutaneous malignancy, or had used systemic immunosuppressive medications such as cyclosporine, tacrolimus, or methotrexate in the past. Each child in conjunction with their parent or legal guardian completed an initial enrollment form describing their baseline eczema symptoms. Individuals subsequently completed a follow-up survey every 6 months evaluating their disease severity and describing their use of topical medications. Informed written consent was obtained from each of the study participants and our research protocol was approved by the IRB at the Hospital of the University of Pennsylvania in accordance with the Declaration of Helsinki Ethical Principles for Medical Research.

Outcome of Interest

Our outcome of interest was disease control. Patients were asked to qualitatively evaluate the severity of their eczema symptoms every 6 months. PEER children were given four options to describe their disease: complete disease control, good disease control, limited disease control, or uncontrolled disease. We dichotomized this outcome into a “well-controlled disease” category, which included patients who responded with one of the first two options, and a “poorly controlled disease” category for individuals who responded with one of the latter two choices. In evaluating their disease, children and their parents were asked to consider the extent of skin involvement and the severity of symptoms such as itching. The patient self-described outcome of disease control is a well-validated measure of eczema severity that correlates with Eczema Area and Severity Index (EASI) scores. (Barbier et al., 2004; Eichenfield et al., 2002; Hanifin et al., 2001; Housman et al., 2002; Kapoor et al., 2009; Kapoor et al., 2008; Kapp et al., 2002; Schmitt et al., 2007; van Velsen et al., 2010; Wahn et al., 2002)

Covariates

The initial enrollment questionnaire contained 39 questions with greater than 62 variables including information on gender, U.S. census categories for race/ethnicity (White, Black or African American, Asian, American Indian or Alaskan Native, Hawaiian or other Pacific Islander, Hispanic or Latino), annual household income, and baseline eczema symptoms.
Study participants also completed a follow-up questionnaire every 6 months with 24 questions evaluating disease control and the use of topical medications in the previous 6 months (topical pimecrolimus, topical tacrolimus, and topical corticosteroids). Survey questions addressing disease severity were modeled after the UK Working Party’s Diagnostic Criteria for Atopic Dermatitis and the ISAAC (International Study of Asthma and Allergies in Childhood) questionnaire, which is freely available online [http://isaac.auckland.ac.nz/].

**Climate Data**

Data for temperature, sun exposure, and humidity was downloaded from the National Climatic Data Center (NCDC), which is funded by the U.S. National Oceanic and Atmospheric Administration (NOAA): [http://hurricane.ncdc.noaa.gov/cgi-bin/climaps/climaps.pl?directive=quick_results&subrnum=&pop=YES]. Temperature and humidity values were measured directly, while sun exposure was reported as the percentage of daylight hours in which sunshine was observed for a particular day. Daily values for each variable were recorded at 5,808 weather stations from across the United States between 1961–1990 to calculate 30-year mean daily values, which were used in our statistical analysis. This was the most comprehensive climate data that was available at the time of our study and weather patterns in the United States have been relatively stable over the past century with less than a 1–2°F change in most parts of the country [http://www.epa.gov/climatechange/pdfs/print_temperature-2012.pdf]. UVA and UVB data was downloaded from the University Corporation for Atmospheric Research (UCAR) website. (Lee-Taylor J, 2007) Daily UVA and UVB measurements (kJ/m²/day) were recorded from three TOMS (Total Ozone Mapping Spectrometer) weather satellites between 1978–2000. These daily measurements were subsequently used to calculate mean annual cumulative UVA and UVB exposures at a given location, which were used in our analysis. All measurements were corrected for cloud cover and ozone, which filter UV radiation. The climate data was subsequently matched to each patient via their geographic location (as determined by latitude and longitude) using a kriging data interpolation algorithm in the mapping program ArcGis 10·1 (ESRI Corporation: Redlands, CA).

**Statistical Analysis**

The objective of this study was to identify associations between long-term weather patterns and eczema severity. Patients were enrolled in the PEER registry from all across the United States beginning in November 2004. For this study, we included patients who were being enrolled in PEER up to April 2012. We performed univariate and multivariate GLLAMM (Generalized Linear Latent and Mixed Models) logistic regression modeling for each climate variable in the statistical program STATA 12·1 (StataCorp LP: College Station, TX) to evaluate for changes in disease control for each patient over time. Our odds ratios reflect the odds of well-controlled disease with increasing temperature, sun exposure (total, UVA, and UVB), and humidity. Patients were grouped for each climate variable into ranges of approximately equal intervals (eg. 5°F for temperature, 5% for sun exposure, and 10% for humidity) in order to calculate the change in odds for every interval change in a particular climate variable. Patients were also grouped into approximate tertiles for comparison, which is an accepted methodology for evaluating dichotomized outcomes when there is an
exposure with continuous variation. (Arkema et al., 2013) The tertiles are composed of unequal numbers of children because the geographic distribution of children along the spectrum of temperature, sun exposure, and humidity climates in the United States was non-uniform (Table 1). The cut-off points for each tertile were created to ensure that each group was sufficiently powered to detect associations between weather exposure and disease severity. In our multivariate analysis, we adjusted for race, ethnicity, gender, annual household income, and topical medication use (topical tacrolimus, topical pimecrolimus, topical corticosteroids).

**Subgroup Analyses**

We performed univariate and multivariate logistic regression analyses for the following self-designated subgroups: White, Non-White, Males, and Females. All patients in the PEER cohort were also asked to submit saliva samples for FLG genotyping. (Margolis et al., 2011) DNA self-collection kits (DNA Genotek, Kanata, Ontario, Canada) were used to collect all specimens. The filaggrin locus was genotyped for the four most common null alleles amongst whites of European ancestry (R501X, 2282del14, R2447X, S3247X) using custom-made TaqMan allelic discrimination assays (Applied Biosystems, Foster City, Calif) according to previously published protocols. (Sandilands et al., 2007; Smith et al., 2006) Additional details of our genetic analysis have been previously published elsewhere. (Margolis et al., 2012; Margolis et al., 2011) Pearson coefficients were calculated for each of the climate variables to determine if they were correlated with the distribution of white children with FLG mutations, which is a potential confounder in our primary analysis. (Margolis et al., 2012)

As was previously stated, the filaggrin locus was genotyped for the four most common null alleles amongst whites of European ancestry (R501X, 2282del14, R2447X, S3247X). Therefore, non-white children who submitted saliva samples (N=404) may harbor a filaggrin mutation that was not tested for in our screen. In contrast, a negative mutation screen in white children likely represents a true negative as the majority of these children are of European descent. As a result of the unknown sensitivity of genetic testing for non-white children, only the genetic results of Caucasian children were included in our subgroup analysis.

**Supplementary Material**

Refer to Web version on PubMed Central for supplementary material.

**Acknowledgments**

Role of the Funding Source

This research project was funded by NIH grant AR056755 and Valeant Pharmaceuticals through a sponsored research agreement with the University of Pennsylvania. The funding sources had no role in the study design, data collection, data analysis, data interpretation, or writing of the manuscript. Michael Sargen and David Margolis had full access to the data in the study and had final responsibility for the decision to submit for publication.
Abbreviations

FLG Filaggrin
OR Odds Ratio

References

Worldwide variation in prevalence of symptoms of asthma, allergic rhinoconjunctivitis, and atopic eczema: ISAAC. The International Study of Asthma and Allergies in Childhood (ISAAC) Steering Committee. Lancet. 1998; 351:1225–32. [PubMed: 9643741]

Arkema EV, Hart JE, Bertrand KA, Laden F, Grodstein F, Rosner BA, et al. Exposure to ultraviolet-B and risk of developing rheumatoid arthritis among women in the Nurses’ Health Study. Ann Rheum Dis. 2013; 72:506–11. [PubMed: 23380431]

Asher MI, Montefort S, Bjorksten B, Lai CK, Strachan DP, Weiland SK, et al. Worldwide time trends in the prevalence of symptoms of asthma, allergic rhinoconjunctivitis, and eczema in childhood: ISAAC Phases One and Three repeat multicountry cross-sectional surveys. Lancet. 2006; 368:733–43. [PubMed: 16935684]

Barbier N, Paul C, Luger T, Allen R, De Prost Y, Papp K, et al. Validation of the Eczema Area and Severity Index for atopic dermatitis in a cohort of 1550 patients from the pimecrolimus cream 1% randomized controlled clinical trials programme. Br J Dermatol. 2004; 150:96–102. [PubMed: 14746622]

Barker JN, Palmer CN, Zhao Y, Hull PR, Lee SP, et al. Null mutations in the filaggrin gene (FLG) determine major susceptibility to early-onset atopic dermatitis that persists into adulthood. J Invest Dermatol. 2007; 127:564–7. [PubMed: 16990802]

Brown SJ, Kroboth K, Sandilands A, Campbell LE, Pohler E, Kezic S, et al. Intragenic copy number variation within filaggrin contributes to the risk of atopic dermatitis with a dose-dependent effect. J Invest Dermatol. 2012; 132:98–104. [PubMed: 22071473]

Chen H, Common JE, Haines RL, Balakrishnan A, Brown SJ, Goh CS, et al. Wide spectrum of filaggrin-null mutations in atopic dermatitis highlights differences between Singaporean Chinese and European populations. Br J Dermatol. 2011; 165:106–14. [PubMed: 21428977]

Eichenfield LF, Lucky AW, Boguniewicz M, Langley RG, Cherill R, Marshall K, et al. Safety and efficacy of pimecrolimus (ASM 981) cream 1% in the treatment of mild and moderate atopic dermatitis in children and adolescents. J Am Acad Dermatol. 2002; 46:495–504. [PubMed: 11907497]

Fennessy M, Coupland S, Popay J, Naysmith K. The epidemiology and experience of atopic eczema during childhood: a discussion paper on the implications of current knowledge for health care, public health policy and research. J Epidemiol Community Health. 2000; 54:581–9. [PubMed: 10890869]

Fergusson DM, Horwood LJ, Shannon FT. Risk factors in childhood eczema. J Epidemiol Community Health. 1982; 36:118–22. [PubMed: 6896887]

Grice K, Sattar H, Baker H. The effect of ambient humidity on transepidermal water loss. J Invest Dermatol. 1972; 58:343–6. [PubMed: 5030655]

Grice K, Sattar H, Baker H, Sharratt M. The relationship of transepidermal water loss to skin temperature in psoriasis and eczema. J Invest Dermatol. 1975; 64:313–5. [PubMed: 1141706]

Hanifin JM, Thurston M, Omoto M, Cherill R, Toft S, Graeber M. The eczema area and severity index (EASI): assessment of reliability in atopic dermatitis. EASI Evaluator Group. Exp Dermatol. 2001; 10:11–8. [PubMed: 11168575]

Henderson J, Northstone K, Lee SP, Liao H, Zhao Y, Pembrey M, et al. The burden of disease associated with filaggrin mutations: a population-based, longitudinal birth cohort study. J Allergy Clin Immunol. 2008; 121:872–7. e9. [PubMed: 18325573]

Housman TS, Patel MJ, Camacho F, Feldman SR, Fleischer AB Jr, Balkrishnan R. Use of the Self-Administered Eczema Area and Severity Index by parent caregivers: results of a validation study. Br J Dermatol. 2002; 147:1192–8. [PubMed: 12452870]
Irvine AD, McLean WH, Leung DY. Filaggrin mutations associated with skin and allergic diseases. N Engl J Med. 2011; 365:1315–27. [PubMed: 21991953]

Kapoor R, Hoffstad O, Bilker W, Margolis DJ. The frequency and intensity of topical pimecrolimus treatment in children with physician-confirmed mild to moderate atopic dermatitis. Pediatr Dermatol. 2009; 26:682–7. [PubMed: 20199441]

Kapoor R, Menon C, Hoffstad O, Bilker W, Leclerc P, Margolis DJ. The prevalence of atopic triad in children with physician-confirmed atopic dermatitis. J Am Acad Dermatol. 2008; 58:68–73. [PubMed: 17692428]

Kapp A, Papp K, Bingham A, Folster-Holst R, Ortonne JP, Potter PC, et al. Long-term management of atopic dermatitis in infants with topical pimecrolimus, a nonsteroid anti-inflammatory drug. J Allergy Clin Immunol. 2002; 110:277–84. [PubMed: 12170269]

Kramer U, Weidinger S, Darsow U, Mohrenschlager M, Ring J, Behrendt H. Seasonality in symptom severity influenced by temperature or grass pollen: results of a panel study in children with eczema. J Invest Dermatol. 2005; 124:514–23. [PubMed: 15737191]

Kubo A, Nagao K, Amagai M. Epidermal barrier dysfunction and cutaneous sensitization in atopic diseases. J Clin Invest. 2012; 122:440–7. [PubMed: 22293182]

Kramer U, Weidinger S, Darsow U, Mohrenschlager M, Ring J, Behrendt H. Seasonality in symptom severity influenced by temperature or grass pollen: results of a panel study in children with eczema. J Invest Dermatol. 2005; 124:514–23. [PubMed: 15737191]

Lee-Taylor JMS. Climatology of UV-A, UV-B, and Erythemal Radiation at the Earth’s Surface, 1979–2000. Report no NCAR/TN-474+STR. 2007

Leung DY, Bieber T. Atopic dermatitis. Lancet. 2003; 361:151–60. [PubMed: 12531593]

Margolis DJ, Apter AJ, Gupta J, Hoffstad O, Papadopoulos M, Campbell LE, et al. The persistence of atopic dermatitis and filaggrin (FLG) mutations in a US longitudinal cohort. J Allergy Clin Immunol. 2012; 130:912–7. [PubMed: 22951058]

Margolis DJ, Papadopoulos M, Apter AJ, McLean WH, Mitra N, Rebbeck TR. Obtaining DNA in the mail from a national sample of children with a chronic nonfatal illness. J Invest Dermatol. 2011; 131:1765–7. [PubMed: 21509047]

McNally NJ, Williams HC, Phillips DR, Smallman-Raynor M, Lewis S, Venn A, et al. Atopic eczema and domestic water hardness. Lancet. 1998; 352:527–31. [PubMed: 9716057]

Osborne NJ, Ukoumunne OC, Wake M, Allen KJ. Prevalence of eczema and food allergy is associated with latitude in Australia. J Allergy Clin Immunol. 2012; 129:865–7. [PubMed: 22305679]

Palmer CN, Irvine AD, Terron-Kwiatkowski A, Zhao Y, Liao H, Lee SP, et al. Common loss-of-function variants of the epidermal barrier protein filaggrin are a major predisposing factor for atopic dermatitis. Nat Genet. 2006; 38:441–6. [PubMed: 16550169]

Patterson MJ, Galloway SD, Nimmo MA. Variations in regional sweat composition in normal human males. Exp Physiol. 2000; 85:869–75. [PubMed: 11187982]

Reekers R, Busche M, Wittmann M, Kapp A, Werfel T. Birch pollen-related foods trigger atopic dermatitis in patients with specific cutaneous T-cell responses to birch pollen antigens. J Allergy Clin Immunol. 1999; 104:466–72. [PubMed: 10452773]

Rodriguez E, Baurecht H, Herberich E, Wagenpfeil S, Brown SJ, Cordell HJ, et al. Meta-analysis of filaggrin polymorphisms in eczema and asthma: robust risk factors in atopic disease. J Allergy Clin Immunol. 2009; 123:1361–70. e7. [PubMed: 19501237]

Sandilands A, O’Regan GM, Liao H, Zhao Y, Terron-Kwiatkowski A, Watson RM, et al. Prevalent and rare mutations in the gene encoding filaggrin cause ichthyosis vulgaris and predispose individuals to atopic dermatitis. J Invest Dermatol. 2006; 126:1770–5. [PubMed: 16810297]

Sandilands A, Terron-Kwiatkowski A, Hull PR, O’Regan GM, Clayton TH, Watson RM, et al. Comprehensive analysis of the gene encoding filaggrin uncovers prevalent and rare mutations in ichthyosis vulgaris and atopic eczema. Nat Genet. 2007; 39:650–4. [PubMed: 17417636]

Schmitt J, Langan S, Williams HC. What are the best outcome measurements for atopic eczema? A systematic review. J Allergy Clin Immunol. 2007; 120:1389–98. [PubMed: 17910890]
Schultz Larsen F. Atopic dermatitis: a genetic-epidemiologic study in a population-based twin sample. J Am Acad Dermatol. 1993; 28:719–23. [PubMed: 8496415]

Shaw TE, Currie GP, Koudelka CW, Simpson EL. Eczema prevalence in the United States: data from the 2003 National Survey of Children’s Health. J Invest Dermatol. 2011; 131:67–73. [PubMed: 20739951]

Silverberg JI, Hanifin J, Simpson EL. Climatic factors are associated with childhood eczema prevalence in US. J Invest Dermatol. 2013

Smith FJ, Irvine AD, Terron-Kwiatkowski A, Sandilands A, Campbell LE, Zhao Y, et al. Loss-of-function mutations in the gene encoding filaggrin cause ichthyosis vulgaris. Nat Genet. 2006; 38:337–42. [PubMed: 16444271]

Suarez-Varela MM, Garcia-Marcos Alvarez L, Kogan MD, Gonzalez AL, Gimeno AM, Aguinaga Ontoso I, et al. Climate and prevalence of atopic eczema in 6–7-year-old school children in Spain. ISAAC phase III. Int J Biometeorol. 2008; 52:833–40. [PubMed: 18779981]

Thyssen JP, Elias PM. Xerosis is latitude dependent and affects the propensity to develop atopic disease. J Allergy Clin Immunol. 2012; 130:820–1. [PubMed: 22841767]

van den Oord RA, Sheikh A. Filaggrin gene defects and risk of developing allergic sensitisation and allergic disorders: systematic review and meta-analysis. BMJ. 2009; 339:b2433. [PubMed: 19589816]

van Velsen SG, Knol MJ, Haeck IM, Bruijnzeel-Koomen CA, Pasmans SG. The Self-administered Eczema Area and Severity Index in children with moderate to severe atopic dermatitis: better estimation of AD body surface area than severity. Pediatr Dermatol. 2010; 27:470–5. [PubMed: 20796235]

Wahn U, Bos JD, Goodfield M, Caputo R, Papp K, Manjra A, et al. Efficacy and safety of pimecrolimus cream in the long-term management of atopic dermatitis in children. Pediatrics. 2002; 110:e2. [PubMed: 12093983]

Williams HC. Eczema across the world: the missing piece of the jigsaw revealed. J Invest Dermatol. 2011; 131:12–4. [PubMed: 21157423]

Ziska LH, Beggs PJ. Anthropogenic climate change and allergen exposure: The role of plant biology. J Allergy Clin Immunol. 2012; 129:27–32. [PubMed: 22104602]
## Table 1
Demographic Characteristics of Children in PEER (Pediatric Eczema Elective Registry) Cohort at Enrollment

| Demographic Variable                      | Number | Percent of Total Cohort |
|-------------------------------------------|--------|-------------------------|
| Size of Cohort                            | 5,595  | 100.0                   |
| Mean Age at Enrollment, Years (SD)        | 7.3 (4.1) |                      |
| Median Age at Enrollment, Years           | 6.3    |                         |
| Mean Age of First Rash, Years (SD)        | 2.2 (3.0) |                      |
| Total Person-Years of Follow-Up           | 16,360 |                         |
| Sex                                       |        |                         |
| Male                                      | 2,612  | 46.7                    |
| Female                                    | 2,982  | 53.3                    |
| Race/Ethnicity                            |        |                         |
| Hispanic or Latino                        | 555    | 9.9                     |
| Black                                     | 2,946  | 52.7                    |
| White                                     | 2,245  | 40.1                    |
| Native                                    | 76     | 1.4                     |
| Asian                                     | 242    | 4.3                     |
| Pacific                                   | 26     | 0.5                     |
| Disease Control at Enrollment             |        |                         |
| Complete Disease Control                  | 230    | 4.1                     |
| Good Disease Control                      | 2,656  | 47.5                    |
| Limited Disease Control                   | 2,103  | 37.6                    |
| Uncontrolled Disease                      | 594    | 10.6                    |
| Not Reported                              | 12     | 0.2                     |
| Average Household Income/Year             |        |                         |
| $0–$24,999                                | 2,253  | 40.3                    |
| $25,000–$49,999                           | 909    | 16.2                    |
| $50,000–$74,999                           | 492    | 8.8                     |
| $75,000–$99,999                           | 296    | 5.3                     |
| $100,000 or more                          | 360    | 6.4                     |
| Prefer Not to Answer                      | 1,285  | 23.0                    |
| Geographic Distribution                    |        |                         |
| New England                               | 76     | 1.4                     |
| Middle Atlantic                           | 401    | 7.2                     |
| East North Central                        | 1,040  | 18.6                    |
| West North Central                        | 286    | 5.1                     |
| South Atlantic                            | 1,525  | 27.3                    |
| East South Central                        | 1,251  | 22.4                    |
| West South Central                        | 710    | 12.7                    |
| Demographic Variable | Number | Percent of Total Cohort |
|----------------------|--------|-------------------------|
| Mountain             | 115    | 2.1                     |
| Pacific              | 187    | 3.3                     |
| Unknown              | 4      | 0.1                     |

1 Percentages do not total 100% because study participants could check more than one box for race/ethnicity

2 Study participants (or the parent of the child) were asked to describe the severity of disease at the time of study enrollment. Surveyed individuals were asked to consider the extent of skin involvement and the severity of itching in the previous six months when evaluating their disease severity.

3 United States Census Regions
### Table 2

Univariate and Multivariate Logistic Regression Analysis for Outcome of Disease Control

|                      | Unadjusted Odds Ratios | Adjusted\(^I\) Odds Ratios |
|----------------------|------------------------|-----------------------------|
|                      | OR  95% CI P-value      | OR  95% CI P-value          |
| Daily Temperature\(^2,3\) |                        |                             |
| Low                  | Ref Ref Ref             | Ref Ref Ref Ref             |
| Medium vs. Low       | 0.65 0.57–0.74 <0.001  | 0.82 0.72–0.94 0.003        |
| High vs. Low         | 0.57 0.49–0.67 <0.001  | 0.67 0.57–0.79 <0.001      |
| Trend (for every 5°F increase in temperature) | 0.85 0.82–0.89 <0.001 | 0.9 0.87–0.93 <0.001       |
| Percentage Daily Sun Exposure\(^2,3\) |                     |                             |
| Low                  | Ref Ref Ref             | Ref Ref Ref Ref             |
| Medium vs. Low       | 0.85 0.74–0.98 0.03    | 1.02 0.88–1.19 0.79        |
| High vs. Low         | 0.57 0.49–0.66 <0.001  | 0.7 0.61–0.81 <0.001       |
| Trend (for every 5% increase in daily sun exposure) | 0.89 0.84–0.94 <0.001 | 0.93 0.89–0.98 0.009       |
| Cumulative Annual UVA Exposure\(^1,4\) |                   |                             |
| Low                  | Ref Ref Ref             | Ref Ref Ref Ref             |
| Medium vs. Low       | 0.95 0.83–1.08 0.42    | 1.09 0.95–1.26 0.21        |
| High vs. Low         | 0.65 0.56–0.76 <0.001  | 0.77 0.66–0.90 0.001       |
| Trend (for every 40,000 kJ/m2/day increase in cumulative annual UVA exposure) | 0.86 0.82–0.90 <0.001 | 0.91 0.87–0.95 <0.001     |
| Cumulative Annual UVB Exposure \(^3,4\) |                     |                             |
| Low                  | Ref Ref Ref             | Ref Ref Ref Ref             |
| Medium vs. Low       | 1.09 0.96–1.25 0.19    | 1.21 1.05–1.39 0.007       |
| High vs. Low         | 0.55 0.47–0.64 <0.001  | 0.69 0.60–0.80 <0.001      |
| Trend (for every 1,000 kJ/m2/day increase in cumulative annual UVB exposure) | 0.85 0.82–0.89 <0.001 | 0.88 0.84–0.92 <0.001     |
| Daily Humidity\(^2,3\) |                       |                             |
| Low                  | Ref Ref Ref             | Ref Ref Ref Ref             |
| Medium vs. Low       | 0.87 0.72–1.06 0.17    | 0.96 0.78–1.18 0.72        |
| High vs. Low         | 0.6 0.41–0.88 0.009    | 0.67 0.46–0.97 0.034       |
| Trend (for every 10% increase in daily humidity) | 0.9 0.81–0.997 0.04 | 0.93 0.84–1.02 0.14         |

\(^I\) Odds ratios adjusted for medication use (topical steroids, topical tacrolimus, topical pimecrolimus), gender, race (white vs. non-white), and income.
Daily values for temperature, percentage sun exposure, and humidity were recorded at 5,808 weather stations from across the United States between 1961–1990 to calculate 30-year mean daily values, which were used in our statistical analysis.

Daily Temperature Tertiles: Low (<55 F, N=2,111), Medium (55.1–65 F, N=2,549), High (>65 F, N=911)

Percentage Daily Sun Exposure Tertiles: Low (<55%, N=1,471), Medium (56–60%, N=1,949), High (>60%, N=2,127)

Daily Humidity Tertiles: Low (<65%, N=400), Medium (66–75%, N=5,032), High (>75%, N=139)

Cumulative Annual UVA Exposure Tertiles: Low (<309,940 kJ/m²/day, N=1,428), Medium (309,941–368,660 kJ/m²/day, N=2,717), High (>368,660 kJ/m²/day, N=1,450)

Cumulative Annual UVB Exposure Tertiles: Low (<6,492 kJ/m²/day, N=1,455), Medium (6,493–8,820 kJ/m²/day, N=2,472), High (>8,820 kJ/m²/day, N=1,668)

Daily UVA and UVB measurements (kJ/m²/day) were recorded from three TOMS (Total Ozone Mapping Spectrometer) weather satellites from 1978–2000. These daily measurements were subsequently used to calculate mean cumulative annual UVA and UVB exposures for a given location. All measurements have been corrected for cloud cover and ozone, which filter UV radiation.