Global Associations between UVR Exposure and Current Eczema Prevalence in Children from ISAAC Phase Three

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We sought to examine the relationship globally between UVR dose exposure and current eczema prevalences. ISAAC Phase Three provided data on eczema prevalence for 13- to 14-year-olds in 214 centers in 87 countries and for 6- to 7-year-olds in 132 centers in 57 countries. Linear and nonlinear associations between (natural log transformed) eczema prevalence and the mean, maximum, minimum, standard deviation, and range of monthly UV dose exposures were assessed using linear mixed-effects regression models. For the 13- to 14-year-olds, the country-level eczema prevalence was positively and linearly associated with country-level monthly mean (prevalence ratio = 1.31 [95% confidence interval = 1.05–1.63] per kJ/m^2) and minimum (1.25 [1.06–1.47] per kJ/m^2) UVR dose exposure. Linear and nonlinear associations were also observed for other metrics of UV. Results were similar in trend, but nonsignificant, for the fewer centers with 6- to 7-year-olds (e.g., 1.24 [0.96–1.59] per kJ/m^2 for country-level monthly mean UVR). No consistent within-country associations were observed (e.g., 1.05 [0.89–1.23] and 0.92 [0.71–1.18] per kJ/m^2 for center-level monthly mean UVR for the 13- to 14- and 6- to 7-year-olds, respectively). These ecological results support a role for UVR exposure in explaining some of the variation in global childhood eczema prevalence.

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INTRODUCTION

Childhood atopic dermatitis, also known as eczema, is a highly prevalent condition strongly associated with genetic risk factors, such as mutations in the filaggrin gene (Irvine et al., 2011; Weidinger and Novak, 2015). However, differences in global prevalence (Williams et al., 2008), associations with family size, and results from migrant studies (Williams, 1995) all suggest that environmental factors are also likely to play a role.

Although the evidence of the effectiveness of short-term UVR treatment on eczema (in adults) is increasing (Garritsen et al., 2014), little is known about the effects of long-term exposure. Climatic and UVR long-term exposures have been associated with eczema prevalence and severity of symptoms in studies in North America and Europe (Kathuria and Silverberg, 2016; Krämer et al., 2005; Sargen et al., 2014; Silverberg et al., 2013; Suárez-Varela et al., 2008; Vocks et al., 2001). Overall, these studies suggest that climatic factors, such as temperature and humidity, as well as UVR exposure, may influence eczema prevalence and symptoms, although the direction and consistency of the effects vary across studies. Langan and Irvine (2013) recently reviewed the existing conflicting evidence and called for additional large studies to clarify the associations and elucidate potential mechanisms. In particular, to our knowledge, no study has yet included data from developing countries, where eczema prevalences are increasing (Williams et al., 2008) and where UVR exposures can be high. A better understanding of the existing relationships between the environment and eczema development and prevalence could lead to opportunities for early intervention and (possibly) climate-specific treatment regimens (Langan and Irvine, 2013).

A previous study using data from the International Study of Asthma and Allergies in Childhood (ISAAC) Phase One reported that childhood and adolescent eczema prevalence were positively correlated with latitude and negatively correlated with annual outdoor temperature in Western Europe. One explanation provided was a potential indirect effect due to changes in behavior and sun exposure, which would also be correlated with temperature and latitude (Weiland et al., 2004). This study extends this work by using the substantially larger ISAAC Phase Three data set

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Abbreviations: GNI, gross national income; ISAAC, International Study of Asthma and Allergies in Childhood

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Table 1. Distribution of current center-level eczema symptom prevalence and center-level UVR dose exposure variables overall, and by climate type, for centers with 13- to 14-year-olds (N = 214)

	Overall (N = 214)		Snow/polar (n = 12)		Arid (n = 24)		Equatorial (n = 61)		Warm temperate with dry winter (n = 20)		Warm temperate, fully humid (n = 97)	
Characteristic	**Median**	**IQR**	**Median**	**IQR**	**Median**	**IQR**	**Median**	**IQR**	**Median**	**IQR**	**Median**	**IQR**
Eczema symptoms	5.7	5.5	3.8	4.9	4.6	4.7	6.9	6.5	4.9	4.6	7.0	6.3
UVR monthly mean	3.3	2.3	2.0	0.8	3.1	1.2	4.5	0.3	1.7	0.6	2.6	1.7
UVR monthly maximum	5.2	1.4	4.0	1.1	5.4	1.0	5.5	0.3	3.5	0.8	4.9	1.7
UVR monthly minimum	1.1	2.6	0.4	0.4	0.9	1.0	3.4	0.7	0.2	0.2	0.7	1.3
UVR monthly SD	1.3	0.6	1.3	0.3	1.5	0.4	0.7	0.3	1.3	0.2	1.4	0.4
UVR monthly range	3.3	1.5	3.6	0.8	4.2	1.0	2.2	0.8	3.3	0.5	3.7	1.2

Abbreviations: IQR, interquartile range; SD, standard deviation.

(Odhiambo et al., 2009) to examine associations between metrics of UVR dose exposures and the prevalence of current eczema among children and adolescents in a global context.

RESULTS

For the 214 centers with 13- to 14-year-olds, the median center-level eczema prevalence was 5.73 (range = 0.17–24.6) and varied by climate type (analysis of variance, $P = 0.06$) (Table 1). The median center-level prevalence for the 132 centers with 6- to 7-year-olds was 6.99 (range = 0.95–22.5). Center-level prevalences between the age groups were highly correlated for the 129 centers that had information for both age groups (Spearman correlation = 0.76). Center-specific sample sizes, eczema prevalences, and monthly mean UVR dose exposures are reported in Supplementary Tables S1 and S2 online for the 13- to 14-year-olds and 6- to 7-year-olds, respectively.

Among the many correlations observed between the modeled variables (presented in Table 2 for the centers with 13- to 14-year-olds), center-level eczema prevalence was positively correlated with country-level gross national income (GNI) and center-level relative humidity and was negatively correlated with the center-level standard deviation and range of monthly UVR levels. The different measures of UVR exposures were intercorrelated. These correlations were very similar for the centers with 6- to 7-year-olds (see Supplementary Table S3 online).

Between-country associations (comparing country-level information) are reported in Table 3 (both age groups), and the shape of these associations are depicted in Figure 1 and in Supplementary Figure S1 online for the 13- to 14- and 6- to 7-year-olds, respectively. For the centers with 13- to 14-year-olds, country-level monthly mean, maximum, and minimum UVR levels were positively associated with country-level current eczema prevalence (prevalence ratio = 1.31 [95% confidence interval = 1.05–1.63], 1.25 [1.00–1.57], and 1.25 [1.06–1.47], respectively). When quadratic terms (exposure^2) were introduced into the models for maximum, standard deviation, and range of monthly UVR, because this represents a better model fit to the data, the quadratic terms were all statistically significant, suggesting the existence of nonlinear relationships. When replicated in the centers with 6- to 7-year-olds, the effect estimates were similar in trend but were attenuated, and none were statistically significant. The results from the models containing linear terms only are presented as prevalence ratios in Supplementary Table S4 online. (This type of presentation is inappropriate for models containing linear and quadratic terms).

Two significant negative linear within-country associations (comparing centers within countries) were observed for centers with 13- to 14-year-olds, but these were not replicated in the centers with 6- to 7-year-olds (Table 3).

Stratification by whether or not eczema first occurred before or at/after the age of 2 years suggested that the between-country associations (comparing country-level information) could be driven by the later phenotype (Table 4). This analysis could be conducted only among centers with 6- to 7-year-olds, because this information was not collected from the 13- to 14-year-olds.

Although statistical significance was occasionally lost, the effect estimates were highly consistent when the outcome was restricted to eczema symptoms that kept the participant awake one or more nights per week (severe eczema, see Supplementary Table S5 online), despite a substantial reduction in center-level prevalences (median prevalence = 7.0% for current eczema and 0.8% when restricted to severe symptoms).

The removal of centers with the lowest and highest center-level eczema prevalences or center-level UVR exposures (up to 10% of the sample removed) did not alter the between-country associations (comparing country-level information). Removal of the two countries with the lowest and highest country-level UVR exposure metrics (four countries in total out of 87) also yielded fairly consistent results, although the between-country associations for monthly mean and minimum UVR were attenuated and no longer significant. When 10% of the sample was removed based on country-level UVR exposure extremes, the between-country effect estimates were similar in trend, but nearly all were no longer significant.

Stratification by climate type suggested that the between-country associations (comparing country-level information) were most apparent among areas with climates classified as warm temperate and fully humid, although there may be an insufficient number of centers in the other climate groups to detect associations (Table 5).

DISCUSSION

Main findings

In this worldwide ecological analysis, several between-country associations between metrics of UVR exposure and

Table 2. Spearman correlations between modeled center-level variables for the centers with 13- to 14-year-olds (n = 214)

Variable	Period	Median (IQR)	Eczema Symptoms	GNI per Capita	Population Density	Temperature	Relative Humidity	Mean	Max	Min	SD	Range
Eczema symptoms	2000–2003	5.7 (5.5)	1	0.18[2]	−0.06	0.04	0.33[3]	0.10	0.06	0.12	−0.17[1]	−0.17[1]
GNI per capita per 1,000	2001	3.3 (10.6)		1	−0.14[1]	−0.39[3]	0.36[3]	−0.48[3]	−0.44[3]	−0.48[3]	0.14[1]	0.13
Population density per 1,000	2000	0.9 (2.4)			1	0.27[3]	−0.02	0.24[2]	0.15[1]	0.27[3]	−0.23[3]	−0.22[2]
Monthly mean temperature, °C	1991–2000	18.0 (12.7)				1	−0.02	0.78[3]	0.55[3]	0.84*[3]	−0.46[3]	−0.45[3]
Monthly mean relative humidity, %	1961–1990	73.9 (12.7)						−0.08	−0.23[3]	−0.03	−0.42[3]	−0.43[3]
UVR monthly mean	2001	3.3 (2.3)						1	0.84[3]	0.98[3]	−0.46[3]	−0.44[3]
UVR monthly maximum	2001	5.2 (1.4)							1	0.79[3]	−0.01	0.01
UVR monthly minimum	2001	1.1 (2.6)								1	−0.52[3]	−0.51[3]
UVR monthly standard deviation	2001	1.3 (0.6)									1	0.99[3]
UVR monthly range	2001	3.3 (1.5)										1

Abbreviations: GNI, gross national income; IQR, interquartile range; Max, maximum; Min, minimum; SD, standard deviation.
[1]$P < 0.05$.
[2]$P < 0.01$.
[3]$P < 0.001$.

current eczema prevalence were observed among centers with 13- to 14-year-olds. Our results suggest a positive linear association between country-level eczema prevalence with country-level mean and minimum monthly UVR dose levels (which were highly correlated: $r_s = 0.98$) and nonlinear relationships between the country-level maximum, standard deviation, and range of monthly UVR dose levels (the latter two of which were highly correlated: $r_s = 0.99$). When replicated in the centers with 6- to 7-year-olds, these associations were similar in trend but were not statistically significant, most likely because of the fewer number of centers in this age group.

Comparison with other studies

Previous studies on this topic point to a complex relationship. The most recent efforts include a longitudinal study in Germany in which some participants reported that their eczema symptoms were worse in the summer, yet others reported worse symptoms in the winter (Krämer et al., 2005). This effect was thought to be at least partly driven by environmental allergen exposure and sensitization. Two recent studies in the United States published a year apart came to rather different conclusions. A large-scale ecological study reported reduced eczema prevalence in areas with (among other things) high relative humidity, high UVR index, and high mean temperature (Silverberg et al., 2013), whereas a prospective cohort study reported that warm, humid, and high sun exposure climates were associated with poorly controlled eczema (Sargen et al., 2014). Furthermore, a recent large population-based ecological study in the United States showed the complexity that likely exists among coexisting climatic factors and pollutants. For example, this study reported that areas classified as hot, sunny, and with high levels of ozone and particulate matter with an aerodynamic diameter of 10 μm or less had lower eczema prevalence (Kathuria and Silverberg, 2016). The results of the current analysis add to this complexity by suggesting the existence of both linear and nonlinear associations (on a global scale) with different metrics of UVR dose exposure. The possibility that extremes of UVR exposure in either direction might increase the risk of eczema is not implausible and could help reconcile the current seemingly conflicting data from different regions and study designs. Our finding that associations were strongest in countries classified as warm temperate and fully humid is also interesting but should be interpreted cautiously because of the smaller number of countries in the other climate groups.

Possible mechanisms

Several biological mechanisms by which UVR exposure may affect eczema symptoms have been proposed, including UVR-epidermal interactions (Schwarz and Schwarz, 2011), UVR-induced DNA methylation, and gene-environment interactions. Indirect or interactive effects with other climatic factors, such as humidity and temperature, are also probable (Langan and Irvine, 2013). It is unknown how these interactions may have resulted in the nonlinear relationships observed for certain metrics of UVR dose exposure. Sensitivity analyses in which up to 10% of the sample were removed did not largely change the nonlinear associations, suggesting that these relationships are not driven by a small subset of outlying centers. Although all models were adjusted for a variety of important factors, these adjustments are unlikely to address all potential relevant factors and interactions.

We were unable to investigate whether differences in the distribution of important genetic risk factors may be confounding our associations, because it was not feasible to collect genetic data. It is known that the prevalence and profiles of mutations in the *FLG* gene vary geographically, and it has been suggested that certain mutations may correlate with UVR exposure (Cascella et al., 2015). Furthermore, areas of the skin more exposed to climatic and

Table 3. Between- and within-country associations for current eczema symptom prevalence and UVR exposures for the centers with 13- to 14-year-olds and 6- to 7-year-olds[1,2]

	13- to 14-Year-Olds		6- to 7-Year-Olds	
UVR Exposure	**Linear Term**	**Quadratic Term**	**Linear Term**	**Quadratic Term**
Between-Country Associations (Comparing Country-Level Information)				
	n = 214 Centers in 87 Countries		**n = 132 Centers in 57 Countries**	
Mean	**0.27 (0.05–0.49)**	—	0.21 (−0.04 to 0.47)	—
Max[3]	0.22 (0.00–0.45)	—	0.22 (−0.02 to 0.46)	—
	0.31 (0.08–0.53)	**0.20 (0.05–0.34)**	0.23 (−0.02 to 0.48)	0.11 (−0.04 to 0.27)
Min	**0.22 (0.06–0.39)**	—	0.14 (−0.07 to 0.34)	—
SD[3]	−0.34 (−0.78 to 0.09)	—	−0.02 (−0.63 to 0.59)	—
	−0.23 (−0.66–0.20)	**1.15 (0.28–2.02)**	0.00 (−0.62 to 0.62)	0.21 (−0.75 to 1.18)
Range[3]	−0.13 (−0.30 to 0.05)	—	0.02 (−0.21 to 0.26)	—
	−0.10 (−0.27 to 0.06)	**0.19 (0.06–0.33)**	0.02 (−0.22 to 0.25)	0.07 (−0.09 to 0.22)
Within-Country Associations (Comparing Centers within Countries)				
	n = 161 Centers in 34 Countries		**n = 96 Centers in 21 Countries**	
Mean	0.04 (−0.12 to 0.20)	—	−0.08 (−0.34 to 0.17)	—
Max	−0.13 (−0.31 to 0.05)	—	−0.08 (−0.35 to 0.19)	—
Min	0.13 (−0.01 to 0.28)	—	−0.07 (−0.27 to 0.12)	—
SD	**−0.74 (−1.16 to −0.32)**	—	0.19 (−0.32 to 0.70)	—
Range	**−0.31 (−0.47 to −0.14)**	—	0.03 (−0.17 to 0.24)	—

Abbreviations: Max, maximum; Min, minimum; SD, standard deviation.

[1]Beta estimates (not back-transformed from the natural logarithmic scale) and their corresponding 95% confidence intervals are presented. Adjusted for center mean exposure of interest (for between-country associations) or country mean exposure of interest (for within-country associations), as well as the center and country mean population density, mean monthly temperature and mean monthly relative humidity, and country gross national per capita income and climate type. Estimates from the models containing only linear terms can be interpreted as prevalence ratios after natural exponentiation.

[2]Boldface indicates $P < 0.05$.

[3]Results from two models are presented: one including only a linear term for UVR exposure and one including a linear and a quadratic term for UVR exposure. The significant positive quadratic terms observed for the maximum, standard deviation, and range of monthly UVR measurements among the 13- to 14-year-olds suggest the existence of a nonlinear (convex) association with eczema prevalence.

physical stressors have been shown to be affected more often in *FLG* mutation carriers, suggesting that filaggrin-deficient individuals may have a reduced ability to adapt to environmental exposures (Carson et al., 2012). Genetic risk factors appear to have the strongest influence on early-life eczema (by the first year [Bønnelykke et al., 2010]), whereas the associations in our study were most consistent for eczema with first onset at/after 2 years of age. One could thus speculate that any effect of UVR exposure would be more apparent (or easier to detect) after the influence of genetic risk factors has taken place. The results of our age-stratified analyses should, however, be interpreted with caution given that this analysis could be conducted only in centers with 6- to 7-year-olds.

Strengths and limitations

The between-country associations are based on the entire data set and thereby take advantage of the large number and exposure contrasts of the participating countries. However, these associations are more likely than the within-country associations to be influenced by unmeasured factors that differ by country and issues related to the translation of questionnaires (Ellwood et al., 2009). We thus cannot confirm that the between-country associations are not driven by residual confounding. We found no consistent within-country associations, possibly because of a smaller exposure range and sample size, because only countries with more than one center could contribute.

Our definition of eczema was identical to the standardized and validated definition used to assess worldwide differences and changes in eczema prevalences in the successive phases of ISAAC (Williams et al., 2008) and has been shown to provide adequate prevalence estimates at the population level (Flohr et al., 2009). It nevertheless remains possible that there may be variation in the way the questionnaires were completed or administered, although all study centers followed the same protocol. The fact that similar patterns with UVR exposures were observed for eczema symptoms classified as severe supports the existence of a harmonized approach, because severe symptoms are less likely to be deferentially reported than mild symptoms. Previous studies have reported that eczema flares during particular times of the year and in response to weather effects (Krämer et al., 2005; Langan et al., 2009), which could be associated with UVR exposure levels. We could not examine season-specific associations, because the questionnaire asked for eczema prevalence over a 12-month period. This gap should be addressed in future work.

The size and coverage of ISAAC, which includes regions rarely or never studied in this context, makes this study unique in its ability to investigate global associations between ecologic metrics of UVR dose exposures and current eczema prevalence However, there remain areas of the world that are poorly covered in this analysis, such as countries with colder climates. It should also be noted that the participating centers were not randomly selected.

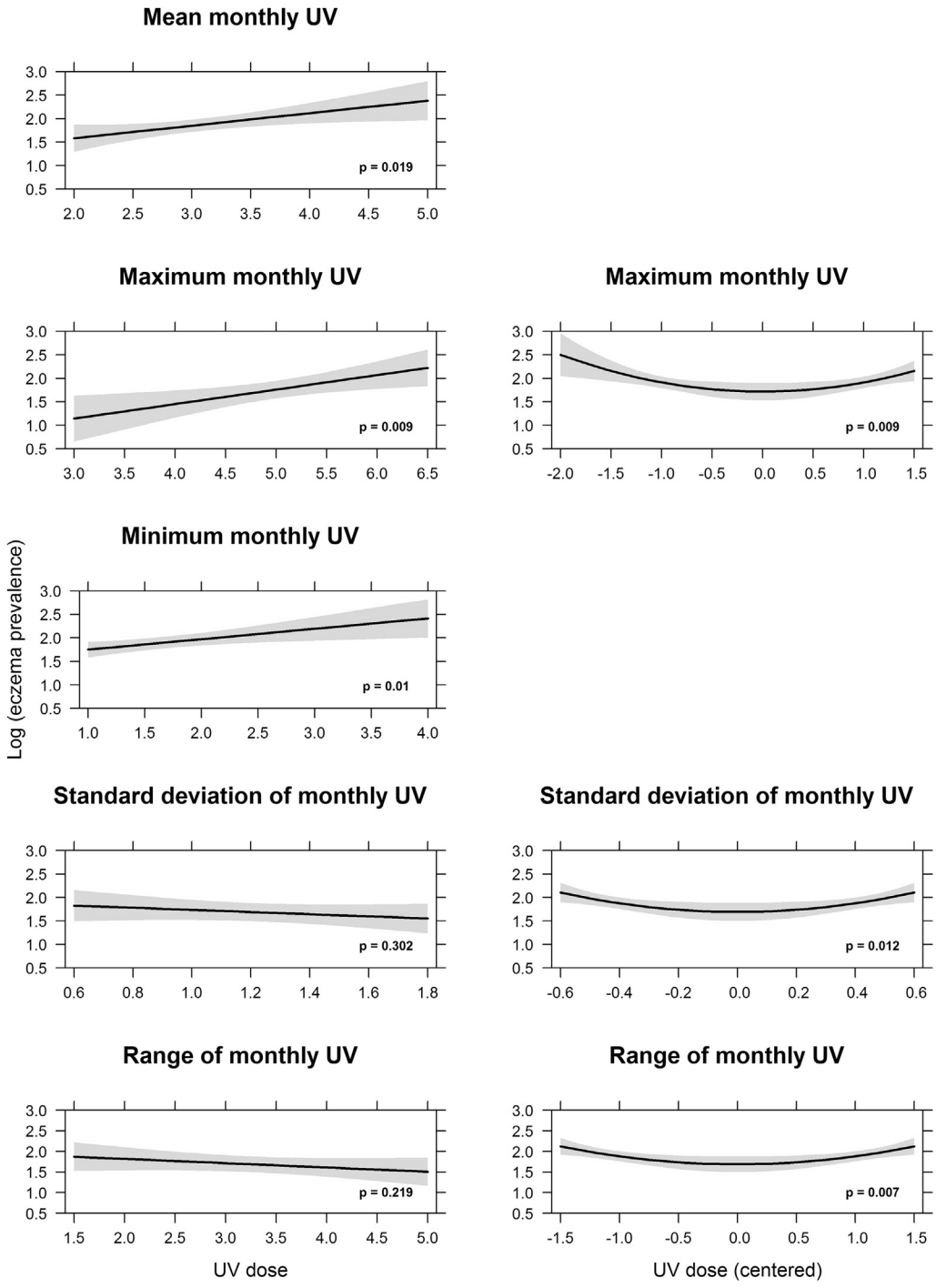

Figure 1. Effect plots for the between-country associations (comparing country-level information) for current eczema symptom prevalence and UVR exposures for the centers with 13- to 14-year-olds. The linear effects are presented in the left column, and the quadratic effects are presented in the right column. The corresponding 95% confidence intervals are shown in grey.

Thus, it is unknown whether the results may be generalizable worldwide. Given these limitations, we recommend focusing on the trends of the associations presented (Figure 1), which may indicate new directions for research, and not on the exact values of the effect estimates reported.

The UVR exposure data were selected to overlap with the beginning of the health data collection period for ISAAC Phase Three. Any temporal changes in UVR exposures that occurred between the time of birth of the participants and the time when health data were collected are expected to be minimal compared with the differences in UVR exposures among countries and centers. For the rest of the adjustment covariates, we attempted to use data from the same period, although not all data sets overlap. Common to all ecological studies, we had no information on potentially relevant individual-level factors, such as race or skin type, and were thus unable to explore effect modification by behavioral factors that could influence an individual's exposure to UVR, such as time spent outdoors and wearing sun-protective clothing. Nonetheless, the collection of data from both 13- to 14-year-olds and 6- to 7-year-olds allowed

Table 4. Between- and within-country associations for current eczema symptom prevalence and UVR exposures for the centers with 6- to 7-year-olds, stratified by whether eczema onset was before or after age 2 years[1,2]

	Eczema Onset before Age 2 Years		Eczema Onset at/after Age 2 Years	
UVR Exposure	**Linear Term**	**Quadratic Term**	**Linear Term**	**Quadratic Term**
Between-Country Associations (Comparing Country-Level Information)				
Mean	0.05 (−0.31 to 0.41)	—	**0.31 (0.05−0.57)**	—
Max[3]	0.12 (−0.22 to 0.47)	—	**0.28 (0.02−0.53)**	—
	0.11 (−0.24 to 0.46)	0.03 (−0.20 to 0.25)	**0.28 (0.02−0.54)**	0.12 (−0.04 to 0.28)
Min	−0.01 (−0.30 to 0.28)	—	0.20 (−0.03 to 0.42)	—
SD[3]	0.26 (−0.59 to 1.10)	—	−0.04 (−0.69 to 0.62)	—
	0.23 (−0.61 to 1.08)	−0.87 (−2.18 to 0.43)	−0.03 (−0.69 to 0.62)	0.62 (−0.37 to 1.61)
Range[3]	0.13 (−0.20 to 0.46)	—	0.00 (−0.25 to 0.26)	—
	0.14 (−0.18 to 0.47)	−0.11 (−0.32 to 0.10)	−0.02 (−0.27 to 0.23)	0.12 (−0.03 to 0.28)
Within-Country Associations (Comparing Centers within Countries)				
Mean	0.08 (−0.27 to 0.43)	—	−0.24 (−0.58 to 0.11)	—
Max	0.14 (−0.24 to 0.51)	—	−0.20 (−0.57 to 0.17)	—
Min	0.04 (−0.24 to 0.32)	—	−0.21 (−0.49 to 0.06)	—
SD	0.12 (−0.60 to 0.85)	—	0.43 (−0.29 to 1.15)	—
Range	0.04 (−0.26 to 0.34)	—	0.11 (−0.19 to 0.41)	—

Abbreviations: Max, maximum; Min, minimum; SD, standard deviation.

[1]Beta estimates (not back-transformed from the natural logarithmic scale) and their corresponding 95% confidence intervals are presented. Adjusted for center mean exposure of interest (for between-country associations) or country mean exposure of interest (for within-country associations), as well as the center and country mean population density, mean monthly temperature and mean monthly relative humidity, and country gross national per capita income and climate type. Estimates from the models containing only linear terms can be interpreted as prevalence ratios after natural exponentiation.

[2]Boldface indicates $P < 0.05$.

[3]Results from two models are presented: one including only a linear term for UVR exposure and one including a linear and a quadratic term for UVR exposure.

nearly all analyses to be replicated in an independent population. We focused on associations that were statistically significant in the larger group of centers (the 13- to 14-year-olds) and that replicated at least in trend in the fewer centers with 6- to 7-year-olds. This was the case for all the between-country associations but no within-country associations.

In conclusion, we provide further support for a role of environmental factors on eczema. Several between-country associations between metrics of UVR dose exposure and current eczema prevalence were observed, with some indication that nonlinear associations may exist on a global scale. Given the ecological design of this study and the possibility of residual confounding, these results should be interpreted with caution until replicated using individual exposure data in a prospective study design.

METHODS

Study population

The rationale and methods for ISAAC Phase Three have been published (Ellwood et al., 2005). The current analysis includes information on 214 centers in 87 countries for the 13- to 14-year-olds and 132 centers in 57 countries for the 6- to 7-year-olds for which the required health and environmental data were available (see flow chart in Supplementary Figure S2 online). Ethical approval from local ethics committees or boards was obtained for all collaborating centers. Parental completion of the questionnaire for the 6- to 7-year-olds implied consent. For the older age group, passive consent for the teenagers to complete their own questionnaires at school was mostly used. In each age group, the person completing the questionnaire was informed about the nature and purpose of the study before commencing the questionnaire.

Health outcomes

Using standardized self-completed (for adolescents 13−14 years old) or parent-completed (for children 6−7 years old) ISAAC questionnaires, individuals were asked to indicate if they (or their child) had an itchy rash at any time in the last 12 months and whether this itchy rash had affected any of the following places: the folds of the elbows, behind the knees, in front of the ankles, under the buttocks, or around the neck, ears, or eyes. A positive answer to both questions was used to define current eczema, and center prevalences of this outcome were calculated as the mean prevalence of each center (Odhiambo et al., 2009). Subsequent questions asked about the age of first onset of the itchy rash symptoms and how often these symptoms kept the participant awake at night. Using this information, center-level prevalences of eczema with first onset before versus at/after age 2 years, as well as severe eczema (kept the participant awake one or more nights per week), were calculated. The exact wording of all questions on eczema is provided in the Supplementary Materials online.

Methods relating to environmental assessments

Monthly data on UVR dose in the erythema range (280−400 nm, believed to be important for the effects on human skin [McKinlay and Diffey, 1987]) were obtained from the Tropospheric Emission Monitoring Internet Service for the year 2001, at a resolution of 0.5° × 0.5° (European Space Agency, n.d.). UVR dose data were used, instead of UV index data, because the former is a measure of the total amount of UVR absorbed by the human skin during the day (kJ/m^2) after considering cloud cover.

Population density data for 2000 (at a spatial resolution of 2.5 arcminutes) were obtained from the Socioeconomic Data and Applications Center (2004). Data on GNI per capita in 2001 were

Table 5. Between-country associations (comparing country-level information) for current eczema symptom prevalence and UVR exposures for the centers with 13- to 14-year-olds, stratified by climate type[1,2]

	Arid (n = 24 Centers in 18 Countries)		Equatorial (n = 61 Centers in 31 Countries)		Warm Temperate with Dry Winter (n = 20 Centers in 13 Countries)		Warm Temperate Fully Humid (n = 97 Centers in 139 Countries)	
UVR Exposure	Linear Term	Quadratic Term	Linear Term	Quadratic Term	Linear Term	Quadratic Term	Linear Term	Quadratic Term
Mean	0.12 (−0.54 to 0.79)	—	−0.11 (−0.88 to 0.67)	—	−0.54 (−2.92 to 1.85)	—	**0.45 (0.21–0.69)**	—
Max[3]	**0.67 (0.04–1.30)**	—	0.05 (−1.05 to 1.15)	—	−0.72 (−1.87 to 0.43)	—	**0.51 (0.22–0.79)**	—
	0.77 (−0.39 to 1.94)	0.03 (−1.43 to 1.49)	−2.86 (−6.68 to 0.96)	2.23 (−0.57 to 5.03)	−1.94 (−4.93 to 1.05)	−0.60 (−2.02 to 0.83)	**0.52 (0.26–0.79)**	**0.22 (0.05–0.38)**
Min	−0.07 (−0.57 to 0.42)	—	0.04 (−0.36 to 0.44)	—	−0.17 (−6.15 to 5.80)	—	**0.29 (0.10–0.47)**	—
SD[3]	0.63 (−0.71 to 1.96)	—	−0.04 (−1.03 to 0.94)	—	−3.29 (−8.11 to 1.54)	—	−0.37 (−0.99 to 0.26	—
	0.21 (−1.53 to 1.95)	1.48 (−2.12 to 5.08)	0.83 (−1.03 to 2.68)	1.47 (−1.19 to 4.14)	−0.40 (−8.73 to 7.92)	−7.36 (−23.92 to 9.21)	−0.37 (−0.93 to 0.19)	**2.40 (0.99–3.82)**
Range[3]	0.30 (−0.20 to 0.79)	—	−0.01 (−0.43 to 0.40)	—	−1.02 (−2.32 to 0.28)	—	−0.13 (−0.37 to 0.12)	—
	0.12 (−0.55 to 0.78)	0.27 (−0.34 to 0.87)	0.22 (−0.52 to 0.97)	0.16 (−0.25 to 0.56)	−0.48 (−2.82 to 1.86)	−0.83 (−3.07 to 1.42)	−0.19 (−0.41 to 0.02)	**0.40 (0.18–0.62)**

Abbreviations: Max, maximum; Min, minimum; SD, standard deviation.

[1]Beta estimates (not back-transformed from the natural logarithmic scale) and their corresponding 95% confidence intervals are presented. Adjusted for center mean exposure of interest, center and country mean population density, mean monthly temperature, mean monthly relative humidity, and country gross national per capita income. Results for snow/polar climates not presented because of an insufficient sample size (12 centers in eight countries). Estimates from the models containing only linear terms can be interpreted as prevalence ratios after natural exponentiation.

[2]Boldface indicates $P < 0.05$.

[3]Results from two models are presented: one including only a linear term for UVR exposure and one including a linear and a quadratic term for UVR exposure. The significant positive quadratic terms observed for the maximum, standard deviation, and range of monthly UVR measurements suggest the existence of a nonlinear (convex) association with eczema prevalence.

obtained from the World Bank (2012; Atlas Method, 2003). For the seven countries for which this information was missing, GNI data were imputed using information from the Central Intelligence Agency World Fact Book for 2003 (Central Intelligence Agency, 2007).

Data on monthly mean daily temperature and precipitation averaged for 1991 through 2000 for 0.5° × 0.5° grids were obtained from the Intergovernmental Panel on Climate Change Data Distribution Center (Intergovernmental Panel on Climate Change, 2013; Mitchell and Jones, 2005). These data were used to classify centers into five climate types according to the Köppen climate classification system (Kottek et al., 2006). Monthly mean relative humidity data, averaged for 1961 through 1990 and available at a 10′ resolution, was also obtained (New et al., 2002).

The assignment of environmental variables to the centers has been described (Anderson et al., 2012; Fuertes et al., 2014). For each center, coordinates for the study population were assigned to a 0.1° × 0.1° square and compared with the eight surrounding 0.1° × 0.1° squares. The square with the highest population density was considered the center grid and used for mapping. UVR dose and climate data were mapped to this single coordinate. For population density, the mean values of the center grid and eight surrounding grids (each sized 0.07° × 0.07°) were used. For UVR dose, climate and population density variables, which were available at the center level, country-level means were calculated (Begg and Parides, 2003), which may not reflect the true mean of a country.

Analytic strategy

Correlations between center-level variables were assessed using Spearman correlation coefficients. Eczema prevalences were (natural) log-transformed before modeling. Linear regression mixed models were used to assess associations between the mean, maximum, minimum, standard deviation, and range of monthly UVR dose exposures and current eczema prevalence (lme4 package [Bates et al., 2016] in the statistical program R, version 3.3.0 [R Core Team, 2016], unstructured covariance structure). Effect plots (from the effects package [Fox et al., 2016]) were created to graphically display the terms of the regression models. Given this study's ecological design, the unit of analysis was *country* for the between-country associations in which country-level information was compared and *center* for the within-country associations in which center-level information within countries was compared.

Initially, models containing only a linear term for each UVR exposure variable were calculated and are presented. High-order relationships were subsequently tested by including quadratic terms (e.g., UV^2). Evidence of nonlinearity was observed for the maximum, standard deviation, and range of monthly UVR dose exposures for the between-country associations in the 13- to 14-year-old age group. Thus, for these exposures only, models containing linear and quadratic terms (which better fit the data) are also presented.

Models were adjusted for potential confounding factors including GNI per capita, population density, climate type and monthly mean temperature, and relative humidity. All models included country as a random intercept and fixed effects for both the center- and country-level representation of each variable, except for GNI per capita, which was available only at the country level.

The regression coefficients (betas) and their corresponding 95% confidence intervals, calculated as 1.96*(standard error) assuming a normal distribution, are presented for the linear and quadratic terms per 1-unit increase in country-level exposure for the between-country associations and per 1-unit increase in center-level exposure for the within-country associations. For models containing only linear UVR terms, the beta estimates can be interpreted as prevalence ratios after natural exponentiation, per increase in UVR exposure. For the models containing linear and quadratic terms, it is not possible to summarize the results using a single number that reflects additive or relative changes (Barrera-Gómez and Basagaña, 2015). Thus, in all tables, the beta estimates are not back-transformed from the (natural) logarithmic scale so that the models containing only linear UVR terms can be compared with those containing linear and quadratic UVR terms.

Sensitivity analyses

To assess the impact of outliers, separate analyses were conducted in which (i) the five centers with the lowest and highest center-level eczema prevalence (~5% of sample) were removed, (ii) the five centers with the lowest and highest center-level UVR exposure metric were removed (~5% sample), and (iii) the two countries with the lowest and highest country-level UVR exposure metric were removed (~5% of the 87 country-level UVR exposures). These analyses were replicated with approximately 10% removed instead.

CONFLICT OF INTEREST

The authors state no conflict of interest.

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SUPPLEMENTARY MATERIAL

Supplementary material is linked to the online version of the paper at www.jidonline.org, and at http://dx.doi.org/10.1016/j.jid.2017.02.966.

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