Global associations between UV exposure and current eczema prevalence in children from ISAAC Phase Three

Elaine Fuertes[1,2,3], Carsten Flohr[4], Jonathan I Silverberg[5,6], Marie Standl[7], David P Strachan[8], and the ISAAC Phase Three Study Group[9]

1. ISGlobal, Centre for Research in Environmental Epidemiology (CREAL), Barcelona, Spain
2. Universitat Pompeu Fabra (UPF), Barcelona, Spain
3. CIBER Epidemiologia y Salud Publica (CIBERESP), Barcelona, Spain
4. Unit for Population-Based Dermatology Research, St John's Institute of Dermatology, King's College London and Guy's & St Thomas' NHS Foundation Trust, London, United Kingdom.
5. Departments of Dermatology, Preventive Medicine and Medical Social Sciences, Northwestern University Feinberg School of Medicine, Chicago, United States
6. Northwestern Medicine Multidisciplinary Eczema centre, Chicago, United States
7. Institute of Epidemiology I, Helmholtz Zentrum München - German Research Centre for Environmental Health, Neuherberg, Germany
8. Population Health Research Institute, St George's, University of London, London, United Kingdom
9. The ISAAC Phase Three Study Group is listed in the Supplementary Material

Corresponding author:

Elaine Fuertes
elaine.fuertes@isglobal.org
Doctor Aiguader, 88 · E-08003 Barcelona
Phone: +34 93 214 7300 Fax: +34 93 214 73 02

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ABSTRACT

We sought to examine the relationship globally between UV dose exposure and current eczema prevalences.

ISAAC Phase Three provided data on eczema prevalence for 13-14 year-olds in 214 centres in 87 countries and for 6-7 year-olds in 132 centres in 57 countries. Linear and non-linear 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 13-14 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) UV dose exposure. Linear and non-linear associations were also observed for other metrics of UV. Results were similar in trend, but non-significant, for the fewer centres with 6-7 year-olds (e.g. 1.24 [0.96, 1.59] per kJ/m^2 for country-level monthly mean UV). 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 UV, for the 13-14 and 6-7 year-olds, respectively).

These ecological results support a role for UV exposure in explaining some of the variation in global childhood eczema prevalence.

INTRODUCTION

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

Although the evidence of the effectiveness of short-term ultraviolet radiation treatment on eczema (in adults) is increasing (Garritsen et al. 2014), little is known about the effects of long-term exposure. Climatic and ultraviolet radiation (UV) 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 UV exposure, may influence eczema prevalence and symptoms, although the direction and consistency of the effects vary across studies. Indeed, 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, no study has yet included data from developing countries, where eczema prevalences are increasing (Williams et al. 2008) and where UV 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 regimes (Langan and Irvine et al 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 behaviour and sun exposure, which would also be correlated with temperature and latitude (Weiland et al. 2004). The current study extends this work by using the substantially larger ISAAC Phase Three data set (Odhiambo et al. 2009) to examine associations between metrics of UV dose exposures and the prevalence of current eczema among children and adolescents in a global context.

RESULTS

For the 214 centres with 13-14 year-olds, the median centre-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 centre-level prevalence for the 132 centres with 6-7 year-olds was 6.99 (range: 0.95-22.5). Centre-level prevalences between the age groups were highly correlated for the 129 centres that had information for both age groups (Spearman correlation = 0.76). Centre-specific sample sizes, eczema prevalences and monthly mean UV dose exposures are reported in Tables S1 and S2 for the 13-14 year-olds and 6-7 year-olds, respectively.

Spearman correlations between the modeled variables and centre-level eczema prevalences for the centres with 13-14 year-olds are provided in Table 2. Among the many correlations, centre-level eczema prevalence was positively correlated with country-level gross national income (GNI) and centre-level relative humidity, and negatively correlated with the centre-level standard deviation and range of monthly UV levels. The different measures of UV exposures were inter-correlated. These correlations were very similar for the centres with 6-7 year-olds (Table S3).

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 Figure S1 for the 13-14 and 6-7 year-olds, respectively. For the centres with 13-14 year-olds, country-level monthly mean, maximum and minimum UV 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 UV, as this

represents a better model fit to the data, the quadratic terms were all statistically significant, suggesting the existence of non-linear relationships. When replicated in the centres with 6-7 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 Table S4 (this type of presentation is inappropriate for models containing linear and quadratic terms).

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

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

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

The removal of centres with the lowest and highest centre-level eczema prevalences or centre-

level UV 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 UV exposure metrics (4 countries in total out of 87) also yielded fairly consistent results, although the between-country associations for monthly mean and minimum UV were attenuated and no longer significant. When 10% of the sample was removed based on country-level UV 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 centres 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 UV exposure and current eczema prevalence were observed among centres with 13-14 year-oldsOur results suggest a positive linear association between country-level eczema prevalence with country-level mean and minimum monthly UV dose levels (which were highly correlated, $r_s = 0.98$) and non-linear relationships between the country-level maximum, standard deviation and range of monthly UV dose levels (the latter two of which were highly correlated, $r_s = 0.99$). When replicated in the centres with 6-7 year-olds, these associations were similar in trend but were not statistically significant, most likely because of the fewer number of centres 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 of America 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 UV 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 of America demonstrated the complexity that likely exists between 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 non-linear associations (on a global scale) with different metrics of UV dose exposure. The possibility that extremes of UV exposure in either direction might increase the risk of eczema is not implausible and could help reconciliate 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 due to the smaller number of countries in the other climate groups.

Possible Mechanisms

Several biological mechanisms by which UV exposure may affect eczema symptoms have been proposed, including UV-epidermal interactions (Schwarz and Schwarz 2011), UV-induced DNA methylation and gene-environment interactions. Indirect or interactive effects with other climatic factor, such as humidity and temperature, are also probable (Langan and Irvine 2013). It is unknown how these interactions may have resulted in the non-linear relationships observed for certain metrics of UV dose exposure. Sensitivity analyses in which up to 10% of the sample were removed did not largely change the non-linear associations, suggesting that these relationships are not driven by a small subset of outlying centres. 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 as 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 UV exposure (Cascella et al. 2015). Further, areas of the skin more exposed to climatic and 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). Interestingly, 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 two years of age. One could thus speculate that any effect of UV 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 only be conducted in centres with 6-7 year-olds.

Strengths and Limitations of Study

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 as only countries with more than one centre 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 centres followed the same protocol. The fact that similar patterns with UV exposures were observed for eczema symptoms classified as severe supports the existence of a harmonized approach as 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 UV exposure levels. We could not examine season-specific associations as 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 UV dose exposures and current eczema prevalence However, there remain areas of the world which are poorly covered in this analysis, such as countries with colder climates. It should also be noted that the participating centres were not randomly selected. 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 UV exposure data was selected to overlap with the beginning of the health data collection period for ISAAC Phase Three. Any temporal changes in UV exposures that occurred between the time of birth of the participants and the time the health data were collected are expected to be minimal compared to the differences in UV exposures between countries and centres. 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 UV, such as time spent outdoors and wearing sun-protective clothing. Nonetheless, the collection of data from both 13-14 year-olds and 6-7 year-olds allowed nearly all analyses to be replicated in an independent population. We focused on associations that were statistically significant in the larger group of centres (the 13-14 year olds) and that replicated at least in trend in the fewer centres with 6-7 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 UV dose exposure and current eczema prevalence were observed, with some indication that non-linear 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 centres in 87 countries for the 13-14 year-olds and 132 centres in 57 countries for the 6-7 year-olds for which the required health and environmental data were available (flow chart in Figure S2). Ethical approval from local ethics committees or boards were obtained for all collaborating centres. Parental completion of the questionnaire for the 6-7 year-olds implied consent. For the older age group, passive consent for the teenager to complete their own questionnaire at school was mostly used.

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 centre prevalences of this outcome were calculated (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, centre-level prevalences of eczema with first onset before versus at/after age two years, as well as severe eczema (kept the participant awake one or more nights per week) were calculated. The exact wording of the questions are provided in the Supplementary Material.

Methods Relating to Environmental Assessments

Monthly data on UV radiation dose in the erythema range (280-400nm, 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^{o} x 0.5^{o} (European Space Agency). UV dose data were used, instead of UV index data, as the former is a measure of the total amount of UV radiation 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 arc minutes) were obtained from the Socioeconomic Data and Applications centre (Socioeconomic Data and Applications Center 2004). Data on GNI per capita in 2001 were obtained from the World Bank (Atlas Method 2003; (World Bank 2012)). For the seven countries for which this information was missing, GNI data were imputed using information from the Central Intelligence Agency World Fact Book (2003) (Central Intelligence Agency 2007).

Data on monthly mean daily temperature and precipitation averaged for 1991 - 2000 for 0.5^{o} x 0.5^{o} grids were obtained from the Intergovernmental Panel on Climate Change Data Distribution centre (Mitchell 2004; Mitchell and Jones 2005). These data were used to classify centres into five climate types according to the Köppen climate classification system ((Kottek et al. 2006)). Monthly mean relative humidity data, averaged for 1961-1990 and available at a 10' resolution, was also obtained (New et al. 2002).

The assignment of environmental variables to the centres has been described (Anderson et al.

2012; Fuertes et al. 2014). Coordinates for the study population were assigned to a 0.1^o x 0.1^o square and compared with the eight surrounding 0.1^o x 0.1^o squares. The square with the highest population density was considered the centre grid and used for mapping. UV dose and climate data were mapped to this single coordinate. For population density, the mean values of the centre grid and eight surrounding grids (each sized 0.07^o x 0.07^o) were used. For UV dose, climate and population density variables, which were available at the centre-level, country-level means were calculated (Begg and Parides 2003), which may not reflect the true mean of a country.

Analytic Strategy

Correlations between centre-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 UV dose exposures and current eczema prevalence (lme4 package (Bates et al. 2014) in the statistical program R, version 3.3.0 (R Core Team 2012), assuming a symmetric variance-covariance matrix). 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 UV exposure variable were calculated and are presented. High-order relationships were subsequently tested by including quadratic terms (e.g. UV^2). Evidence of non-linearity was observed for the maximum, standard deviation and

range of monthly UV dose exposures for the between-country associations in the 13-14 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 centre- 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 centre-level exposure for the within-country associations. For the models containing only linear UV terms, the beta estimates can be interpreted as prevalence ratios after natural exponentiation, per increase in UV 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 UV terms can be compared to those containing linear and quadratic UV terms.

Sensitivity analyses

To assess the impact of outliers, separate analyses were conducted in which 1) the five centres

with the lowest and highest centre-level eczema prevalence (~5% of sample) were removed, 2) the five centres with the lowest and highest centre-level UV exposure metric were removed (~5% sample), and 3) the two countries with the lowest and highest country-level UV exposure metric were removed (~5% of the 87 country-level UV exposures). These analyses were replicated with ~10% of the sample removed instead.

CONFLICTS OF INTEREST

The authors state no conflict of interest

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Table 1: Distribution of current centre-level eczema symptom prevalence and centre-level UV dose exposure variables overall, and by climate type, for centres with 13-14 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)**	
	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
UV 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
UV 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
UV 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
UV 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
UV 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

Table 2: Spearman correlations between modeled centre-level variables for the centres 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**	-0.06	0.04	0.33***	0.10	0.06	0.12	-0.17*	-0.17*
GNI per capita per 1000	2001	3.3 (10.6)		1	-0.14*	-0.39***	0.36***	-0.48***	-0.44***	-0.48***	0.14*	0.13
Population density per 1000	2000	0.9 (2.4)			1	0.27***	-0.02	0.24**	0.15*	0.27***	-0.23***	-0.22**
Monthly mean temperature (°C)	1991-2000	18.0 (12.7)				1	-0.02	0.78***	0.55***	0.84***	-0.46***	-0.45***
Monthly mean relative humidity (%)	1961-1990	73.9 (12.7)						-0.08	-0.23***	-0.03	-0.42***	-0.43***
UV monthly mean	2001	3.3 (2.3)						1	0.84***	0.98***	-0.46***	-0.44***
UV monthly maximum	2001	5.2 (1.4)							1	0.79***	-0.01	0.01
UV monthly minimum	2001	1.1 (2.6)								1	-0.52***	-0.51***
UV monthly standard deviation	2001	1.3 (0.6)									1	0.99***
UV monthly range	2001	3.3 (1.5)										1

*<0.05; **<0.01; ***<0.001

Table 3: Between- and within-country associations for current eczema symptom prevalence and UV exposures for the centres with 13-14 year olds and 6-7 year olds. Beta estimates (not back-transformed from the natural logarithmic scale) and their corresponding 95% confidence intervals are presented[1]

UV exposure	13-14 yr olds		6-7 yr olds	
	Linear term	**Quadratic term**	**Linear term**	**Quadratic term**
	Between-country associations (comparing country-level information)			
	N = 214 centres in 87 countries		N = 132 centres in 57 countries	
Mean	**0.27 [0.05, 0.49]**	-	0.21 [-0.04, 0.47]	-
Max[2]	0.22 [0.00, 0.45]	-	0.22 [-0.02, 0.46]	-
	0.31 [0.08, 0.53]	**0.20 [0.05, 0.34]**	0.23 [-0.02, 0.48]	0.11 [-0.04, 0.27]
Min[2]	**0.22 [0.06, 0.39]**	-	0.14 [-0.07, 0.34]	-
SD[2]	-0.34 [-0.78, 0.09]	-	-0.02 [-0.63, 0.59]	-
	-0.23 [-0.66, 0.20]	**1.15 [0.28, 2.02]**	0.00 [-0.62, 0.62]	0.21 [-0.75, 1.18]
Range[2]	-0.13 [-0.30, 0.05]	-	0.02 [-0.21, 0.26]	-
	-0.10 [-0.27, 0.06]	**0.19 [0.06, 0.33]**	0.02 [-0.22, 0.25]	0.07 [-0.09, 0.22]
	Within-country associations (comparing centres within countries)			
	N = 161 centres in 34 countries		N = 96 centres in 21 countries	
Mean	0.04 [-0.12, 0.20]	-	-0.08 [-0.34, 0.17]	-
Max	-0.13 [-0.31, 0.05]	-	-0.08 [-0.35, 0.19]	-
Min	0.13 [-0.01, 0.28]	-	-0.07 [-0.27, 0.12]	-
SD	**-0.74 [-1.16, -0.32]**	-	0.19 [-0.32, 0.70]	-
Range	**-0.31 [-0.47, -0.14]**	-	0.03 [-0.17, 0.24]	-

[1]Adjusted for centre mean exposure of interest (for between-country associations) or country mean exposure of interest (for within-country associations), as well as the centre and country mean population density, mean monthly temperature and mean monthly relative humidity, as well as 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] Results from two models are presented: one including only a linear term for the UV exposure and one including a linear and quadratic term for the UV exposure. The significant positive quadratic terms observed for the maximum, standard deviation and range of monthly UV measurements among the 13-14 year-olds suggest the existence of a non-linear (convex) association with eczema prevalence.

Bold: p-value < 0.05

Table 4: Between- and within-country associations for current eczema symptom prevalence and UV exposures for the centres with 6-7 year olds, stratified by whether eczema onset was before or after age two years. Beta estimates (not back-transformed from the natural logarithmic scale) and their corresponding 95% confidence intervals are presented[1]

UV exposure	Eczema onset before age two years		Eczema onset at/after age two years	
	Linear term	**Quadratic term**	**Linear term**	**Quadratic term**
	Between-country associations (comparing country-level information)			
Mean	0.05 [-0.31, 0.41]	-	**0.31 [0.05, 0.57]**	-
Max[2]	0.12 [-0.22, 0.47]	-	**0.28 [0.02, 0.53]**	-
	0.11 [-0.24, 0.46]	0.03 [-0.20, 0.25]	**0.28 [0.02, 0.54]**	0.12 [-0.04, 0.28]
Min	-0.01 [-0.30, 0.28]	-	0.20 [-0.03, 0.42]	-
SD[2]	0.26 [-0.59, 1.10]	-	-0.04 [-0.69, 0.62]	-
	0.23 [-0.61, 1.08]	-0.87 [-2.18, 0.43]	-0.03 [-0.69, 0.62]	0.62 [-0.37, 1.61]
Range[2]	0.13 [-0.20, 0.46]	-	0.00 [-0.25, 0.26]	-
	0.14 [-0.18, 0.47]	-0.11 [-0.32, 0.10]	-0.02 [-0.27, 0.23]	0.12 [-0.03, 0.28]
	Within-country associations (comparing centres within countries)			
Mean	0.08 [-0.27, 0.43]	-	-0.24 [-0.58, 0.11]	-
Max	0.14 [-0.24, 0.51]	-	-0.20 [-0.57, 0.17]	-
Min	0.04 [-0.24, 0.32]	-	-0.21 [-0.49, 0.06]	-
SD	0.12 [-0.60, 0.85]	-	0.43 [-0.29, 1.15]	-
Range	0.04 [-0.26, 0.34]	-	0.11 [-0.19, 0.41]	-

[1]Adjusted for centre mean exposure of interest (for between-country associations) or country mean exposure of interest (for within-country associations), as well as the centre and country mean population density, mean monthly temperature and mean monthly relative humidity, as well as 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] Results from two models are presented: one including only a linear term for the UV exposure and one including a linear and quadratic term for the UV exposure.

Bold: p-value < 0.05

Table 5: Between-country associations (comparing country-level information) for current eczema symptom prevalence and UV exposures for the centres with 13-14 year-olds, stratified by climate type. Beta estimates (not back-transformed from the natural logarithmic scale) and their corresponding 95% confidence intervals are presented[1]

UV exposure	Arid (N=24 centres in 18 countries)		Equatorial (N=61 centres in 31 countries)		Warm temperate with dry winter (N=20 centres in 13 countries)		Warm temperate fully humid (N=97 centres in 139 countries)	
	Linear term	**Quadratic term**	**Linear term**	**Quadratic term**	**Linear term**	**Quadratic term**	**Linear term**	**Quadratic term**
Mean	0.12 [-0.54, 0.79]	-	-0.11 [-0.88, 0.67]	-	-0.54 [-2.92, 1.85]	-	**0.45 [0.21, 0.69]**	-
Max[2]	**0.67 [0.04, 1.30]**	-	0.05 [-1.05, 1.15]	-	-0.72 [-1.87, 0.43]	-	**0.51 [0.22, 0.79]**	-
	0.77 [-0.39, 1.94]	0.03 [-1.43, 1.49]	-2.86 [-6.68, 0.96]	2.23 [-0.57, 5.03]	-1.94 [-4.93, 1.05]	-0.60 [-2.02, 0.83]	**0.52 [0.26, 0.79]**	**0.22 [0.05, 0.38]**
Min	-0.07 [-0.57, 0.42]	-	0.04 [-0.36, 0.44]	-	-0.17 [-6.15, 5.80]	-	**0.29 [0.10, 0.47]**	-
SD[2]	0.63 [-0.71 1.96]	-	-0.04 [-1.03, 0.94]	-	-3.29 [-8.11, 1.54]	-	-0.37 [-0.99, 0.26]	-
	0.21 [-1.53 1.95]	1.48 [-2.12, 5.08]	0.83 [-1.03, 2.68]	1.47 [-1.19, 4.14]	-0.40 [-8.73, 7.92]	-7.36 [-23.92, 9.21]	-0.37 [-0.93, 0.19]	**2.40 [0.99, 3.82]**
Range[2]	0.30 [-0.20, 0.79]	-	-0.01 [-0.43, 0.40]	-	-1.02 [-2.32, 0.28]	-	-0.13 [-0.37, 0.12]	-
	0.12 [-0.55, 0.78]	0.27 [-0.34, 0.87]	0.22 [-0.52, 0.97]	0.16 [-0.25, 0.56]	-0.48 [-2.82, 1.86]	-0.83 [-3.07, 1.42]	-0.19 [-0.41, 0.02]	**0.40 [0.18, 0.62]**

[1]Adjusted for centre mean exposure of interest, centre and country mean population density, mean monthly temperature and mean monthly relative humidity, as well as country gross national per capita income. Results for snow/polar climates not presented due to an insufficient sample size (12 centres in 8 countries). Estimates from the models containing only linear terms can be interpreted as prevalence ratios after natural exponentiation.

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

Bold: p-value < 0.05

FIGURE LEGENDS

Figure 1: Effect plots for the between-country associations (comparing country-level information) for current eczema symptom prevalence and UV exposures for the centres with 13-14 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.