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Seasonality in Symptom Severity Influenced by Temperature or Grass Pollen: Results of a Panel Study in Children with Eczema

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Although seasonal variations are well known in many patients with eczema, no systematic population-based panel study evaluating seasonality and quantifying the influence of factors like climate and pollen on symptom variations has been conducted so far. Thirty-nine children with eczema, who had been identified in 1996 in a cross-sectional study on 1673 6-y-olds in Augsburg (Germany), participated in the study. Between March and September 1999, they daily recorded itch, extent, and possibly triggering factors on quantitative scales. Daily temperature, humidity, radiation, and pollen concentration were measured. Mixed linear models, taking the time series structure and confounding into account, were used for analysis. Seasonal patterns were significantly different between children: twenty-one had symptoms mainly in winter. They were affected by changes in outdoor temperature: itch was reduced by 22% (95% confidence interval (CI): 16%–27%) and extent by 65% (CI: 54%–72%) per 15°C temperature increase. Eighteen children exhibited more symptoms in summer and especially during days with high grass-pollen exposure when itch was 16% higher (CI: 8%–24%) and extent 19% (CI: 2%–39%). This effect was stronger for children sensitized against pollen. Consideration of the individual type of eczema may help to arrange appropriate preventive and therapeutic measures.

Key words: eczema/panel/pollen/seasonality/temperature
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Eczema is a chronic inflammatory skin disease characterized by a relapsing course with typically distributed skin lesions, dry skin, and intense pruritus (Hanifin, 1982; Ruzicka *et al*, 1991). It is a disease caused by combined influences of genetic and environmental factors (Williams, 2000). A seasonal fluctuating course is a well-known clinical feature in many patients. Such a course of symptoms could be induced by all factors that influence symptom severity of eczema and that exhibit seasonality themselves: climatic conditions, allergen exposure, and patient's behavior pattern.

Climatic conditions, such as temperature, humidity, and radiation, have a strong seasonality and they all might affect eczema: low temperatures enhance skin irritability (Uter *et al*, 1998), low humidity increases skin roughness (Eberlein-König *et al*, 1996), and UV radiation is highly effective in reducing symptom severity of patients with eczema (Krutmann and Morita, 1999; Abeck *et al*, 2000).

Pollen exposure predominantly occurs in spring and summer. Whether outdoor exposure with pollen modifies symptom severity has not been shown before but it is known that eczematous lesions can be induced by epicutaneous application of air-borne allergens in a concentration-dependent fashion (Darsow *et al*, 1999; Ring *et al*, 2001).

Abbreviations: CI, confidence interval; RAST, radioallergosorbent test

Finally, patient's behavior pattern such as contact with animals, intake of different foods, and activities (for instance swimming in chlorinated water) might vary between seasons. These factors are known to influence symptoms in patients with eczema (Schäfer *et al*, 1996; Schäfer and Breuer, 2003; Seki *et al*, 2003) and may therefore introduce seasonality in symptom severity.

Our study was designed to test whether seasonality of symptoms can be observed in a population-based study of children with eczema and to quantify the long- and short-term effects of climatic conditions and pollen exposure.

We used the instrument of a panel study with daily observations of symptom severity. This instrument is well known to study factors influencing asthma severity (Hoek *et al*, 1998; Delfino *et al*, 2002). To our knowledge, this is the first application in Dermato-Epidemiology.

Thirty-nine children had been diagnosed with eczema in a cross-sectional study and observed symptoms over a period of 6 mo from end of winter during spring and summer to autumn. In addition to daily diary reports on itch and extent, activities, animal contacts, and ingested foods, daily regional meteorological and pollen pollution data as well as home environmental conditions were assessed.

Results

Panel participation Of the 56 children participating, 42 filled in the diary at least 113 d (60%) out of the maximum possible 188 d. Compared with the group of children with a lower degree of participation, these 42 children were characterized by a slightly higher prevalence of acute eczematous lesions in all dermatological investigations (57% *vs* 50%) and better parental school education (37% *vs* 23% with at least one of the parents holding a university degree).

Three of the 42 children participating at least 113 d had no symptoms of eczema during the study period; thus, the final group for analysis consisted of 39 children.

Seasonality of symptoms and panel description All children showed a seasonal pattern of symptoms: severity of itch and extent were different between spring and summer; however, this pattern was not homogeneous. Mixed linear regression as well as logistic regression analysis revealed a highly significant interaction "individual × season" (*F* test, $p < 0.001$) for itch as well as for extent, indicating at least two different patterns of seasonality between individuals. The differences of the mean summer and spring symptom scores (itch and extent) were used to define two groups. Twenty-one children had higher symptom scores at the beginning of the study period, the end of winter, than in summer. These children were said to have a "winter type" of eczema. Eighteen children had higher symptom scores in summer than in winter and spring; they had a "summer type" of eczema. All panel description and all analysis of possible influences were carried out for both these groups separately; we assumed that the influence of climatic conditions, pollen exposure, and behavior on symptom severity might differ between these groups.

Children of summer and winter type were not different in age and gender distribution (Table I). For 31 of the 39 children-specific IgE concentrations were known from the cross-sectional part of the *M*ulti-center *I*nternational Study on *R*isk Assessment of *I*ndoor and Outdoor Air Pollution on *A*llergy and Eczema *M*orbidity (MIRIAM) study. The prevalence of positive sensitization was similar in both groups. Sixty-five percent of the children exhibiting winter type of eczema were sensitized against any of the tested allergens and 71% of those exhibiting summer type of eczema. Sensitization against milk or egg occurred slightly more often in children of summer type than in those of winter type; however, this difference was not significant (small numbers). The pattern of sensitization in both groups was similar when

Table I. Characteristics of the panel of children with eczema

	Winter type		Summer type		Total	
	N	%	N	%	N	%
Girls	21	52	18	50	39	51
Sensitization (RAST)						
Any	17	65	14	71	31	68
Against birch pollen	17	47	14	36	31	42
Against grass pollen	17	35	14	50	31	42
Against house dust	17	29	14	36	31	32
Against milk	17	12	14	29	31	19
Against egg	17	6	14	21	31	13
N	21		18		39	
	Mean	Min–Max	Mean	Min–Max	Mean	Min–Max
Age (y)	9.2	8.7–9.7	9.2	8.8–9.5	9.2	8.7–9.7
Hours outdoors						
Total	4.0	2.2–7.1	3.5	1.6–5.7	3.8	1.6–7.1
March 11–May 15	2.6	1.2–4.6	2.4	1.1–4.1	2.5	1.1–4.6
May 16–September 14	4.9	2.7–9.1	4.2	1.7–7.7	4.6	1.7–9.1
Temperature indoors (°C)						
Total	21.3	17.8–22.6	21.2	19.6–23.0	21.2	17.8–23.0
March 11–May 15	20.2	17.2–21.7	20.1	17.8–22.8	20.1	17.2–22.8
May 16–September 14	22.1	18.7–23.4	21.9	20.5–23.1	22.0	18.7–23.4
Relative humidity indoors (%)						
Total	48.8	36.5–55.3	50.7	46.9–58.4	49.8	36.5–58.4
March 11–May 15	43.8	32.5–52.1	45.2	35.3–55.8	44.5	32.5–55.8
May 16–September 14	52.0	42.8–58.2	54.2	49.9–59.9	53.2	42.8–59.9

RAST, radioallergosorbent test.

using prick test results instead of radioallergosorbent test (RAST). Medication use was also slightly different between children of summer and winter type. No difference in the use of cortison (4% of days in both groups) but in the use of rich cream occurred. Children of summer type used such a cream in 35% of the days in spring and 39% of the days in summer and children of winter type used it in 27% of days in spring and 28% of days in summer. Participants spent an average of 3.8 h in outdoor activities, 4.6 h during the warmer season (from May 15 including the summer holidays) and 2.5 h during the colder season. Children with winter type of eczema on average spent 0.5 h per d longer outdoors than children of summer type of eczema. This difference was slightly larger in summer than in spring of the investigation period.

Table II describes mean symptom scores for all children and children of summer and winter type separately. During March 1999, all children participating in the panel study were investigated by one dermatologist (M. M.). The mean severity scoring of atopic dermatitis (SCORAD) of all children was 13.7, 14.4 for those of winter type, and 13.0 for those of summer type, indicating moderate and nearly equal mean severity for children of summer and winter type. Dryness of skin was evaluated among nine stigmata of an atopic constitution. All but one of the children were judged to have a dry skin but the degree differed: 12 of the 18 children of summer type and only six of the 21 children of winter type had a very dry skin. In the evening of the day when the dermatologist carried out his investigation, the children filled in their diaries additionally. Both these methods yielded similar values for severity of itch (1.6/1.5) and extent (1.3%/0.9%) of eczema. Differences in symptom scores between children of summer and winter type did not occur during spring, which is also reflected by the mean diary values during that season, but occur in summer when children of summer type had higher mean itch scores and a larger extent of affected skin, whereas children of winter type were nearly free of symptoms. Figure 1*b* shows a graphical representation of daily geometric mean values for winter-type children and Fig 2*b* for summer-type children. The seasonality is clearly visible.

Temperature, humidity, and global radiation During summer, the mean indoor temperature was only slightly higher than in spring; but the mean indoor relative humidity in summer was much higher than in spring (Table I). There were no (temperature) or only slight (humidity) differences in indoor climatic conditions between children of summer and winter type.

Outdoor temperature showed a strong seasonal variability with increasing trend between 1.5°C and 15°C during spring and a stable overall mean with fluctuations between 12°C and 27.5°C during summer (Table III and Fig 1*a*). The correlation between indoor and outdoor temperature was moderate and positive. The median correlation between daily indoor and outdoor temperature was 0.56 in spring time and 0.62 in summer. Correlation between indoor and outdoor humidity was low with a median of 0.20 in spring and 0.42 in summer. The correlations between indoor humidity and indoor temperature varied in the different house-

Table II. Mean symptom severity of children with eczema, Augsburg 1999

	Winter type, N = 21		Summer type, N = 18		Total, N = 39	
	Mean	Min–Max	Mean	Min–Max	Mean	Min–Max
Investigation by dermatologist at study begin						
SCORAD[a]	14.4	0–33.8	13.0	0–47.2	14.5	0–47.2
Itch[b,c]	1.6	1–3	1.5	1–3	1.6	1–3
Extent[d]	1.5	0–6	0.9	0–4	1.3	1–6
Diary values at day of investigation by dermatologist						
Itch[c]	1.5	1–4	1.5	1–3	1.5	1–4
Extent[d]	1.0	0–3	0.8	0–4	0.9	0–4
Mean diary values in the whole observation period (March 11–September 14)						
Itch[c]	1.2	1.0–2.8	1.5	1.0–2.9	1.4	1.0–2.9
Extent[d]	0.5	0.0–2.4	0.9	0.0–2.5	0.7	0.0–2.5
Mean diary values in spring (March 11–May 15)						
Itch[c]	1.3	1.0–2.3	1.4	1.0–2.5	1.4	1.0–2.8
Extent[d]	0.8	0.0–2.5	0.7	0.0–2.3	0.8	0.0–2.5
Mean diary values in summer (May 16–September 14)						
Itch[c]	1.1	1.0–1.4	1.6	1.0–3.2	1.4	1.0–3.2
Extent[d]	0.4	0.0–2.4	1.0	0.0–2.7	0.7	0.0–2.7

[a]SCORAD: severity scoring of atopic dermatitis values from 0 to 103 possible.
[b]Score: visual analogue scale transformed from values 0–10 to values 1–5.
[c]Score with values 1–5.
[d]% body surface.

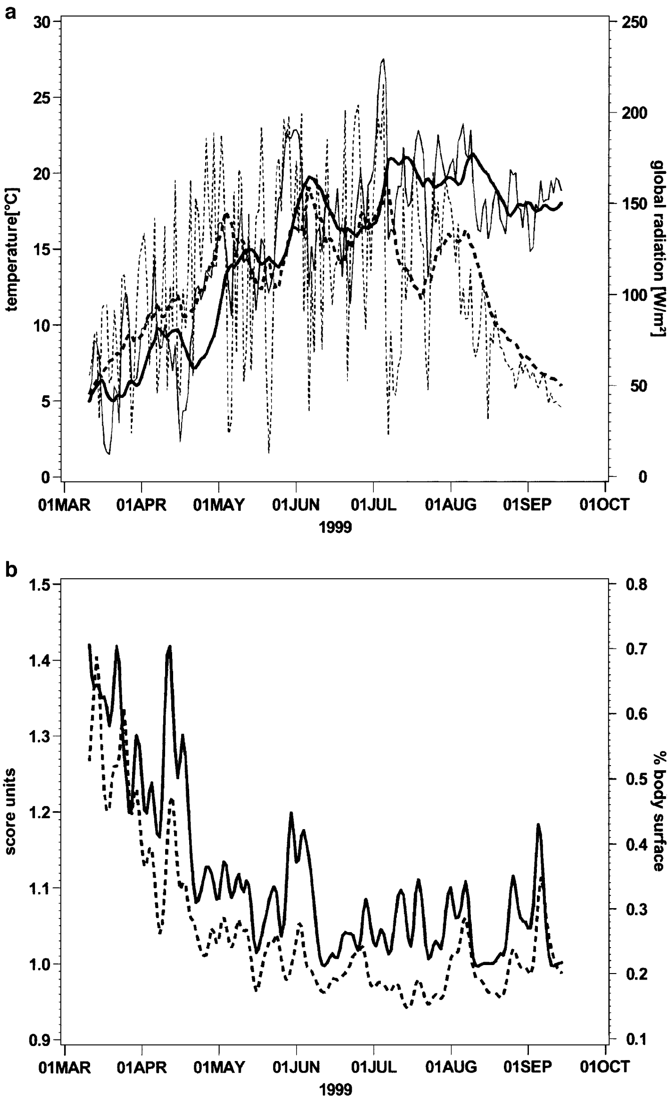

Figure 1
Outdoor temperature, radiation, and symptom severity of the 21 nine-y-old children with eczema of winter type. (*a*) Outdoor temperature (*solid lines*) and global radiation (*broken lines*); daily mean values (*thin lines*) and 14 d moving averages before that date (*bold lines*). (*b*) Mean symptom scores for itch (*solid lines*) and mean extent (percent body surface; *broken line*).

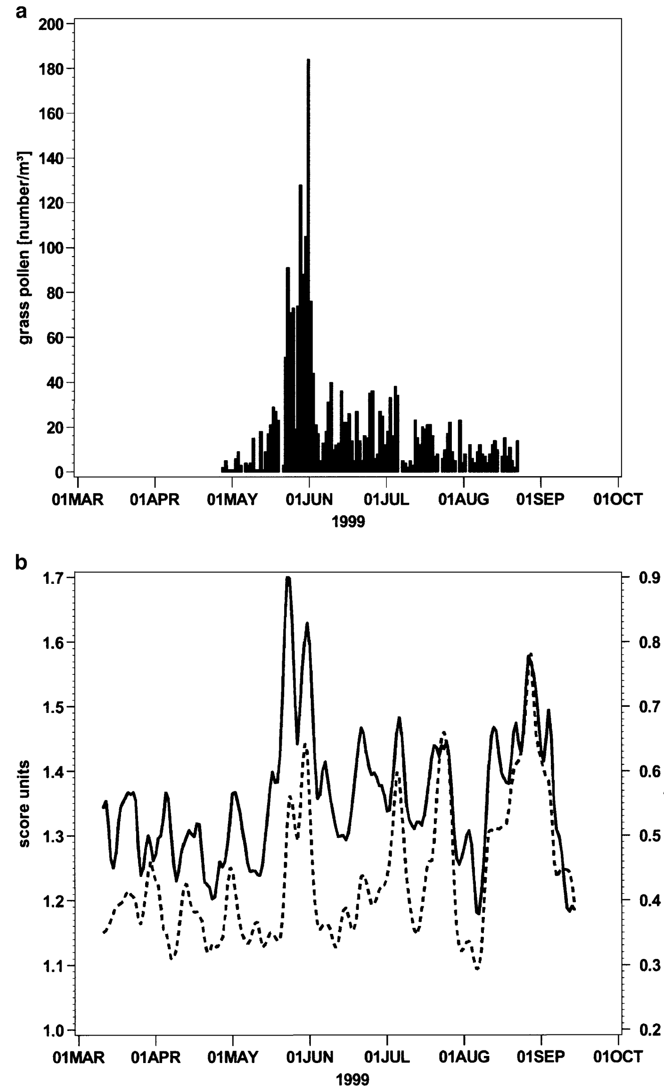

Figure 2
Grass pollen concentration in outdoor air and symptom severity of the 18 nine–y-old children with eczema of summer type. (*a*) Daily mean grass pollen concentration in outdoor air. (*b*) Mean symptom scores for itch (*solid lines*) and mean extent (percent body surface; *broken line*).

holds in spring between -0.42 and $+0.69$ and in summer between -0.26 and $+0.26$. Overall, they were not significantly different from zero.

Global radiation showed the expected seasonal pattern (Fig 1*a*). The seasonal pattern of temperature and global radiation was different as can be seen from the graphical representation of the moving averages (Fig 1*a*): the increase in spring was similar but the decrease of global radiation at the end of summer was not reflected by an equal decrease in temperature.

Outdoor pollen pollution The start and end of pollen seasons were defined according to the guidelines of the European Aeroallergen Network (http://www.univie.ac.at/ean). Hazel and alder blossom during the same time; therefore,

Table III. Characteristics of daily mean temperature, humidity and radiation in the study period March 11–September 14, 1999

	N	Mean	Min	Max	Percentiles	
					5th	95th
Outdoor temperature (°C)	188	15.2	1.5	27.5	5.3	22.7
Outdoor relative humidity (%)	188	71.0	47.9	94.0	53.8	91.0
Global radiation (W per m^2)	188	105	13	216	38	189

their effect was evaluated in combination. Hazel/alder pollen season ran from March 1 (prior to study start) to April 30 (Table IV) with high pollen counts between March 12 and 17. Birch-pollen season lasted from April 5 to 30. Days with pollen concentrations above 416 pollen per m^3 (25% of peak value) occurred between April 10–12 and April 22–24. Grass blossom season lasted 98 d from May 4 to August 9. The highest pollen count was found on June 1 (184 pollen per m^3) with pollen concentrations above 46 between May 23 and 26 as well as between May 28 and June 2. Daily grass-pollen counts during the investigation period are depicted in Fig 2*a*. Mugwort season lasted from July 22 to August 19 with a peak-pollen count on August 5 (10 pollen per m^3). Mugwort pollution is very low in Augsburg and days with higher pollen counts (>3 pollen per m^3) occurred scattered over the season.

Food ingestion, animal contacts, and swimming in chlorinated water Children reported consumption of eggs on 12% of the observation days, milk on 76%, nuts on 7%, fish on 7%, pork on 28%, fast food on 11%, lemons on 7%, tomatoes on 29%, and sweets on 81% of the days. Only the consumption of tomatoes showed a seasonal pattern. They were eaten in 22% of the days in spring and 33% of the days in summer. But no influence of tomato eating on symptoms of eczema was seen (linear and logistic regression) so food ingestion was not included in the final model.

Animal contacts were given in the following percentages of days: dog 20%, cat 20%, rabbit 14%, and guinea-pig 10%. No seasonal pattern in animal contacts was observed.

Children swam in chlorinated water in 6% of days in spring and 14% of days in summer. This seasonality was highly significant (F test, $p<0.001$). The effect of swimming, however, was not negative (linear and logistic regression). Therefore, neither animal contact nor swimming behavior was included in the final model.

Concentration of house dust mite allergens The median and the maximal concentration of Der p 1 and Der f 1 measured in dust from 14 children's mattresses give an estimate of seasonality of this exposure. The median (maximal) concentrations of Der p 1 at the end of winter, spring, summer, and beginning of autumn were: 0.61 (4.67), 0.39 (2.92), 0.30 (4.74), and 1.10 (10.45) μg per g. The corresponding values of Der f 1 concentrations were 3.31 (12.06), 2.61 (11.54), 4.03 (12.84), and 8.58 (28.86) μg per g. The autumn concentrations were significantly higher than the concentrations during the other seasons (paired t test with the logarithm of the concentration values, $p<0.05$).

Influence of temperature, humidity, global radiation, and pollen on symptom severity Table V gives the results for children of winter type. As can be seen, there were strong effects of temperature. Symptoms improved with higher outdoor temperatures. The mean itch was 22% lower and the mean extent was 65% lower per increase in outdoor temperature of 15°C. There was an additional local effect of cold temperature. Mean itch was 5% higher, when outdoor temperature was unusually low. Indoor temperature had the opposite effect. Itch and extent were higher if indoor temperature was higher. In contrast, pollen exposure, humidity, and global radiation had no additional significant effect on symptom severity. A local symptom peak occurred from April 10–12, when birch-pollen exposure was fairly high for the first time but no symptom peak was detected during the maximal birch-pollen exposure. The overall effect of birch-pollen exposure was not significant. The effects are visualized when comparing Fig 1*a* with *b*. The global trend of symptoms is similar to the global trend of temperature (14 d moving average) but not to the global trend of radiation, and also the local symptom peaks March 23 and April 17 occurred when temperature but not when global radiation was unusually low.

Table VI gives the result for children with summer type of eczema. Here grass-pollen exposure has a strong effect on symptom severity: the mean itch was 16% stronger and the mean extent was 19% larger when the grass-pollen count was above 46 pollen per m^3. This effect was highly significant. It is visualized when comparing Fig 2*a* with *b*: pollen exposure pattern and symptom pattern were similar during exposure with high concentration of pollen, although the reaction to the first (lower) pollen peak seems to be stronger than to the last (highest) pollen peak. The effect was more pronounced when restricting the analysis to the seven children with summer type of eczema and a grass-pollen sensitization (itch: 26%; extent: 22% higher). In the children with summer type of eczema and no grass-pollen sensitization, the effect was also positive but not significant.

Even after controlling for pollen pollution a significant negative effect of outdoor temperature remains. Symptoms were stronger when outdoor temperature was higher. No other effect was significant.

Seven of the children with winter type of eczema were sensitized against grass pollen too. They showed no effect of exposure with grass pollen (Fig 1*b* shows a small symptom peak during high grass-pollen exposure but this association is not statistically significant). The degree of sensitization of these seven children was similar to the degree of sensitization of the sensitized children of summer

Table IV. Characteristics of pollen load in the study period March 11–September 14, 1999

Type of pollen	Begin of season	Duration of season (d)	Day of peak exposure	Peak number of pollen per m^3
Hazel/Alder	March 1, 1999	31	March 16, 1999	215
Birch	April 5, 1999	25	April 22, 1999	1673
Grass	May 4, 1999	98	June 1, 1999	184
Mugwort	July 22, 1999	29	August 5, 1999	10

Table V. Winter type: influence of pollen, temperature, global radiation, and humidity on symptom severity of eczema

	Itch: change in score units, 3378 observations in 21 individuals			Extent: change in % surface, 3470 observations in 21 individuals		
	Relative change	95% confidence limits		Relative change	95% confidence limits	
Results of multiple linear regression analysis (autoregressive time series structure)						
Pollen						
Hazel/Alder >50 pollen per m^3	1.02	0.96	1.08	1.14	0.96	1.36
Birch >416 pollen per m^3	1.01	0.96	1.05	0.90	0.79	1.02
Grass >46 pollen per m^3	1.00	0.94	1.06	0.98	0.81	1.18
Mugwort >3 pollen per m^3	0.98	0.94	1.03	0.98	0.87	1.11
Mean daily temperature						
Outdoor 14 d moving average per 15°C increase	**0.78**	**0.73**	**0.84**	**0.35**	**0.28**	**0.44**
Outdoor above 22.7°C	0.97	0.93	1.01	1.01	0.90	1.13
Outdoor below 5.3°C	**1.05**	**1.00**	**1.10**	0.98	0.86	1.13
Indoor per 6°C increase	**1.13**	**1.06**	**1.20**	**1.30**	**1.08**	**1.57**
Mean daily relative humidity						
Indoor per 26% increase	0.97	0.92	1.03	1.10	0.92	1.31
Mean daily global radiation						
14 d moving average per 90 W per m^2 increase	1.00	0.95	1.06	0.95	0.78	1.16
Above 189 W per m^2	1.00	0.96	1.04	1.02	0.92	1.12
Below 38 W per m^2	0.99	0.96	1.03	0.99	0.91	1.10

Significant results ($p < 0.05$) are given in bold.

Table VI. Summer type: influence of pollen, temperature, global radiation, and humidity on symptom severity of eczema

	Itch: change in score units, 2843 observations in 18 individuals			Extent: change in % surface, 2869 observations in 18 individuals		
	Relative change	95% confidence limits		Relative change	95% confidence limits	
Results of multiple linear regression analysis (autoregressive time series structure)						
Pollen						
Hazel/Alder >50 pollen per m^3	0.93	0.88	1.01	0.88	0.77	1.00
Birch >416 pollen per m^3	1.00	0.95	1.05	0.99	0.89	1.09
Grass >46 pollen per m^3	**1.16**	**1.08**	**1.24**	**1.19**	**1.02**	**1.39**
Mugwort >3 pollen per m^3	0.99	0.94	1.04	1.01	0.92	1.11
Mean daily temperature						
Outdoor 14 d moving average per 15°C increase	**1.10**	**1.01**	**1.20**	**1.51**	**1.12**	**1.96**
Outdoor above 22.7°C	1.02	0.98	1.07	1.04	0.95	1.13
Outdoor below 5.3°C	0.99	0.94	1.04	0.96	0.86	1.07
Indoor per 6°C increase	1.00	0.94	1.07	1.04	0.91	1.20
Mean daily relative humidity						
Indoor per 26% increase	0.98	0.92	1.05	0.99	0.86	1.14
Mean daily global radiation						
14 d moving average per 90 W per m^2 increase	0.98	0.91	1.05	0.82	0.66	1.03
Above 189 W per m^2	1.00	0.96	1.04	1.04	0.97	1.13
Below 38 W per m^2	1.01	0.97	1.06	0.97	0.90	1.05

Significant results ($p < 0.05$) are given in bold.

type. In each group, six of the seven children had specific IgE concentrations above 0.7 KU per liter (RAST class 2).

The effects of grass-pollen exposure in children of summer type and of unusually low temperature in children of winter type disappear when evening records of symptoms were compared with measurements performed not on the same day but 1 d before (lag 1).

To test whether the pattern of effects is sensitive to different time series structures, we repeated the analysis with three different structures for the covariances besides the autoregressive one, Tables V and VI are based upon. The only change was that the association between indoor temperature and extent in summer-type children was formally significant under these structures chosen, but the pattern remained.

The direction and significance of results were also the same when using logistic regression and restricting the symptom scores to binary variables (symptoms above or below the individual geometric mean; data not shown).

Discussion

This first population-based panel study on eczema symptoms in children revealed results that were not detected with other methods. It provides evidence for different seasonal patterns in symptom severity of eczema; at least two patterns can be distinguished: a summer-type pattern with aggravation of symptoms in summer- and a winter-type pattern where symptoms mainly occurred at the beginning of the observation period, the end of winter. It was shown in a population-based study that outdoor grass-pollen exposure worsened symptoms in children with eczema, especially in those sensitized against grass pollen. Also shown was the local effect of low temperatures on itch.

Children of winter and summer type did not differ in age, gender, mean indoor humidity, and temperature, sensitization, or symptom severity during spring. Children of summer type used rich cream more often and a dermatological investigation at the beginning of the study period revealed a higher prevalence of very dry skin in children of summer type: this is the only hint that children's attributes might differ between both groups. The difference in the use of rich cream was higher in summer than in spring. Without medication, there probably would be a still larger difference between symptom scores in summer between both types of children.

The pattern of grass-pollen exposure was similar to that of symptoms during the pollen season. This hints at a causal relation because neither the day of peak exposure nor the exact pattern of exposure was known in advance. Grass-pollen exposure was the only pollen exposure associated with symptom severity. This does not necessarily mean that exposure with other types of pollen is harmless. Children from Augsburg spent, on average, only 2 h per d outdoors during spring when hazel/alder and birch were flowering and temperatures were still fairly cold. Peak grass-pollen exposure, however, occurred during days with beautiful weather where children spent 6 h outdoors on average. Therefore, the possible exposure time was much longer for grass pollen than for other types of pollen, which may explain the difference. Interestingly, the effect of grass-pollen exposure was very transient. It could only be observed on the evenings of the day when high exposure occurred (lag 0) but vanished the day after (lag 1).

The effect of the unusually low temperatures on the severity of itch in children of winter type was also transient. On the evening of the days where temperatures were unusually low, children complained about symptoms more strongly. This might be an effect of cold temperature indeed, but could also be caused by returning from cold outside temperatures into a warm indoor environment. Since the unusual low temperatures occurred in March when hazel/alder was flowering or in April when birch was flowering, it could be suspected that the effect of cold temperatures was triggered by pollen exposure. But there was no effect of pollen exposure after controlling for temperature but there was an effect of temperature after controlling for pollen exposure. Overall, the children of winter-type eczema seem to be more sensitive to deviations in temperature. This is also reflected in high indoor temperatures being associated with more symptoms in this group. Both local and global changes in outdoor temperature had a similar effect on symptom severity. This points to a causal influence of temperature. But the possibility that the global effect of temperature might be confounded by other factors that show seasonality and were not measured cannot be ruled out. But house dust mite exposure is no likely confounder. As the measurements performed in 14 households in Augsburg show, allergen concentrations from house dust mites were comparably low at the beginning of the study period, when symptom scores had their maximum values, and highest at the end when symptom severity was still very low.

Cold outdoor temperatures are usually associated with low indoor humidity. Our analysis indicates that outdoor temperature may be more important for symptom severity than indoor humidity. The latter had a significant effect when not controlling for temperature (results not shown), but after controlling for outdoor temperature, indoor humidity had no additional effect. This was different for the effect of outdoor temperature, which remains even after controlling for indoor humidity (Table V). But, as the seasonal patterns of outdoor temperature and indoor humidity are very similar, it may be rash to conclude that humidity is of no importance. The relative importance of both these factors could best be distinguished in an experimental setting.

An independent effect of radiation could not be identified either. The local and global pattern of outdoor temperature but not of radiation was similar to the local and global pattern of symptom severity. Radiation might have an effect in other climatic zones or other weather conditions than those observed in Augsburg in 1999. The highest hourly mean global radiation in the observation period was 755 W per m^2, measured on June 20. This corresponds to approximately 50 W per m^2 UVA radiation, which is relatively low when compared with the therapeutically used doses of 720 W per m^2 that are applied 15 times for 30 min each to the whole body (Krutmann, 2000).

The observed association between aggravation of eczema symptoms and low outdoor temperature in the subgroup of children with the winter type of eczema is in accordance to the findings of impairment of inflammatory and irritant dermatoses caused by dry air and low temperature (Sauer and Hall, 1996; Uter *et al*, 1998). Investigations of adults with eczema in a recreation clinic in the Swiss high-mountain area of Davos showed an inverse correlation of itch with air temperature (Vocks *et al*, 2001). The mechanisms by which low humidity and low temperature may contribute to skin irritancy, however, are still poorly understood. Previous investigations have shown an association between temperature and humidity and skin chapping (Gaul and Underwood, 1952), resistance to tearing (Wildnauer *et al*, 1971), and extensibility of stratum corneum (Middleton and Allen, 1974). It has been suggested that low temperature and/or low humidity lead to decreased epidermal hydration (Agner and Serup, 1989).

Exposure to grass pollen outdoors had a strong local effect on symptom severity of children with summer type of eczema and this effect was stronger in children with an additional sensitization against grass-pollen allergens. Although the role of allergy is still controversial, it is known that environmental substances such as aeroallergens can produce flares in some patients with eczema (Morren *et al*, 1994). In addition, several groups have demonstrated that in certain patients, eczematous lesions may be induced by epicutaneous application of aeroallergens. (Adinoff *et al*, 1988; Darsow *et al*, 1999). The cellular infiltrate of mainly lymphocytes and eosinophils in such a patch-test reaction to aeroallergens closely resembles eczematous lesions in patients with eczema (Bruijnzeel *et al*, 1993). In addition, high-affinity receptors for IgE are expressed on the surface of Langerhans cells, indicating the possibility for the involvement of allergen-specific IgE in the development of eczema (Bieber *et al*, 1992). Some reports indicate improvement of eczema after specific desensitization in patients who had a history of exacerbation following exposure to the suspected allergens (Ring, 1982).

Our findings imply that there are at least two different seasonal patterns in children with eczema: children exhibiting a strong temperature impact ("winter type") and those showing a clear-cut impact of grass pollen ("summer type"). It has to be taken into account, however, that these patterns were not expected before conducting the study and the *post hoc* analysis was based on a relatively small sample of children. The two groups were not sharply demarcated. The differences between summer and spring mean symptoms were only small for some children. If a larger dataset were available perhaps three groups could have been distinguished: a winter group, a summer group, and a group with no consistent seasonal pattern. Further research especially in other age groups is needed before such a pattern can be generalized to all eczema sufferers living in similar climatic conditions as Augsburg.

If stable seasonal patterns can be identified, then consideration of the individual type of eczema may help to arrange appropriate preventive and therapeutic measures. Creation of moderately and consistently warm and humid indoor conditions during the cold season may be of benefit for children with a winter type of eczema. The other subset of children with pollen allergen-specific history—ideally confirmed by atopy patch test (Darsow *et al*, 2000)—could benefit from avoidance strategies. In this distinct group of patients, specific desensitization might be successful.

Materials and Methods

Study area and population The panel study was carried out in Augsburg (Bavaria, Germany). The city of Augsburg has 250,000 inhabitants, is situated 500 m above sea level, and has a temperate climate. The mean winter temperature (1971–2001, December–February) is 0°C and the mean summer temperature (1971–2001, June–August) is 17°C.

Between March 11, 1999 and September 14, 1999 (188 d), a panel of 9-y-old children with eczema was followed with daily symptom diaries. The study was part of an international program on risk factors for allergic diseases and focused especially on risk factors for eczema (MIRIAM) (Krämer *et al*, 2004). The study was approved by the medical ethical committee of the Bayrische Landesärztekammer and the participants gave written informed consent. The study was conducted according to the Declaration of Helsinki principles. The MIRIAM study started in 1996 with a cross-sectional study on all school beginners ($n = 1673$). Eczema was diagnosed in 76 children by trained physicians from the Department of Dermatology and Allergy, Technical University, Munich. Conventional lancet skin prick tests and specific IgE measurements (enzyme immunoassay: CAP-FEIA, Pharmacia, Uppsala, Sweden) using a sample of common allergens (birch, grass, mugwort, Alternaria, house dust mite, cat, milk, egg) were carried out. Sensitization was defined as positive skin prick test (wheal diameter ≥ 2 mm) reaction or elevated serum concentration of specific IgE (≥ 0.35 kU per liter). In 1998, a nested case–control study was conducted with 377 participants, who were chosen from children with and without eczema from the 1996 cross-sectional study (Weidinger *et al*, 2004).

For the panel study, 63 children with eczema who had participated in the case–control study were selected. Seven of these children were excluded as they had moved from the area or did not give consent, resulting in 56 out of 63 children participating in the study. All children had been diagnosed with eczema in at least one of the repeated dermatological examinations and had reported continued existence of eczema symptoms within the last 6 mo prior to the study. At the beginning of the study, all children were examined by one dermatologist (M. M.). He evaluated stigmata of an atopic constitution (Przybilla *et al*, 1991), diagnosed eczema, and assessed severity (Stalder and Taieb, 1993). Part of the SCORAD is an assessment of itch on a visual analogue scale, with zero as the lowest and 10 as the highest value and of the extent of eczema in percent of body surface.

Symptom diary and indoor measurements of temperature, humidity, and house dust mite allergens All participating children received diaries in order to report every evening on symptoms of eczema, medication (rich cream, cortison), nutrition, whereabouts, and contacts with animals (dog, cat, rabbit, guinea-pig). Food items that were questioned included egg, milk, nuts, fish, pork, fast food, lemons, grapefruits, tomatoes, and sweets. The severity of eczema symptoms was specified as follows: itch on a scale from 1 (= absent) to 5 (= very intense) and extent of skin lesions by the number of the child's palm needed to cover the lesions (1 palm $\sim$1% of body surface). In addition, parents were asked for morning and evening measurements of indoor temperature and humidity of the living room and the child's bedroom. Thus, they were supplied with thermo- and hygrometers (Conrad Electronic, Nüremberg, Germany) that had been calibrated immediately prior to the start of the study. Children and parents were instructed during a personal visit at the beginning of the study and received written instructions on how to fill in the diary and measure temperature and humidity. Personal visits were repeated twice. After that, diaries were collected and new diaries were distributed every 14 d by mail. The diary data were keyed in manually twice and eventually corrected after comparison with ensure data quality.

To roughly estimate seasonality of exposure with house dust mite allergens, 14 families were chosen to participate in repeated dust collections on children's mattresses. Four measurements were carried out in the following periods: the first end of winter (March 8–19), the second in spring (May 5–15; 2 on June 8 because of holidays), the third in summer (June 30–July 13), and the last one at the beginning of autumn (September 13–September 22). Dust was collected under standardized conditions by trained persons using a 900 W vacuum cleaner with an integrated collection chamber. Vacuum cleaning was performed for 5 min over the whole surface of the mattresses. Dust was sampled into special filters (ALK, Hørsholm, Denmark), placed in a zip-lock bag, and stored at -20°C until analysis. Concentrations of Der p 1 and Der f 1 were determined (Dust screen, CMG, Fribourgh, Switzerland) and expressed as micrograms allergen per gram dust.

Season, outdoor temperature, humidity, and pollen counts The investigation period was divided into two seasons before starting the statistical analysis: the first one "spring" from March 11 until May 15, when indoor heating was necessary, and the second one ("summer") from May 16 until September 14.

The mean daily meteorological data including air temperature ($^{\circ}$C), relative humidity (%), and global radiation (W per m^2) were available from one of the three stations run in Augsburg by the Bavarian Institute for Environment Protection.

Daily atmospheric concentrations of birch, hazel, alder, grass, and mugwort pollen were determined by one person. Pollen were measured with a continuously operating volumetric pollen trap (Burkard Manufacturing, Rickmanswonth, UK) and expressed as average number of pollen grains per m^3 over periods of 24 h. The trap was installed on a 12 m high roof in the ancient city of Augsburg. There were no trees or meadows near the trap.

Data analysis Outcome measures were the daily-recorded values for the symptoms itch and extent of each child. To analyze the association between individual symptoms and possibly influencing factors mixed linear regression models with individuals as random factor were used. A first-order autoregressive structure for the dependency of symptoms between neighboring time points was assumed (SAS 8.2, 2001; PROC MIXED). The influence of choosing other covariance structures was investigated. The recorded values were $\log_{10}$ transformed before analysis. Zero values of extent (% body surface) were replaced by a value of 0.1 before transformation. The parameter estimates of the linear model b were transformed to 10^b. These transformed values can be interpreted as relative changes in outcome per unit of influencing factor. The units for quantitative influencing factors (temperature, humidity, global radiation) were chosen according to the inner 90% range of the ordered values. Most concern when applying linear models and *t* tests to ordinal or count data is about (a) equal variances, (b) additivity of the measure, and (c) symmetry of the distribution and outliers (see for instance discussion in internet newsgroup: sci.stat.consult). We applied the following: (a) we transformed ($\log_{10}$) the data to ensure homogeneity of variances; (b) we compared the measurements for itch performed on the same day on a quantitative scale (by the dermatologist) and on an ordinal scale (in the diaries): the association between these measures was linear after logarithmic transformation; and (c) the analysis was repeated with mixed logistic regression models after recoding the symptom variables to binary variables, with 0 representing a value below or equal to the individual's overall geometric mean value and 1 representing a value above the individual's geometric mean value (SAS 8.2, 2001; PROC GLIMMIX).

The following strategy was used to test for seasonality and the influence of climatic factors and pollen exposure:

(1) *Seasonality*: It was investigated whether the symptoms were higher or lower in the summer season than in spring. Additional to the main term for season an interaction term "individual × season" was included in the linear models to test whether seasonality was equal for all individuals.

(2) *Individual factors, pollen exposure, and climatic conditions*:

(2a) *Nutrition, whereabouts (swimming), and animal contacts* were included in the model only if they showed significant differences between spring and summer, because they can only induce seasonality in symptoms if they show seasonality themselves. They were also not included in the final model, if their influence on symptoms was not significant.

(2b) *Temperature*: a long-term influence (14 d temperature average before the day where symptoms were recorded) and a local influence of unusual high or unusual low temperatures were tested. Unusual high and low was defined in the context of the study as a mean daily temperature above the 95th percentile or below the fifth percentile in the observation period of 188 d.

(2c) *Global radiation*: mean daily radiation was highly correlated ($r = 0.98$) with mean daytime radiation or daily maximal radiation. Therefore, the first was used as an exposure measure only. A long-term influence (14 d radiation average before the day where symptoms were recorded) and a local influence of unusual high or unusual low radiation were tested. Unusual high and low was defined in the context of the study as a mean daily radiation above the 95th percentile or below the fifth percentile in the observation period of 188 d.

(2d) *Mean daily indoor temperature and humidity*: mean values of morning and evening measurements of indoor temperature and humidity of the living room and the child's bedroom were used.

(2e) *Outdoor pollen counts*: these counts were transformed to binary values before analysis. High values (more than 25% of the peak value) were distinguished from small values (less than 25% of the peak value).

Local temperature, pollen, and radiation effects were tested using different lags (lag 0: evening records of symptoms compared with measurement of the same day, lag 1: evening records of symptoms compared with measurements 1 d before).

The analysis is more of a hypothesis generating than hypothesis-testing type.

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