

Association between attendance of day care centres and increased prevalence of eczema in the German birth cohort study LISApplus

C. Cramer¹, E. Link¹, C.-P. Bauer^{2,3}, U. Hoffmann², A. von Berg⁴, I. Lehmann⁵, O. Herbarth⁶, M. Borte^{7,8}, B. Schaaf⁹, S. Sausenthaler¹⁰, H.-E. Wichmann^{10,11}, J. Heinrich¹⁰ & U. Krämer¹ for the LISApplus study group

¹IUF-Institut für Umweltmedizinische Forschung, Düsseldorf; ²Department of Pediatrics, Technical University of Munich; ³LVA Oberbayern, Munich; ⁴Children's Department, Research Institute, Marien-Hospital, Wesel; ⁵Department of Environmental Immunology, Helmholtz Centre for Environmental Research – UFZ; ⁶Faculty of Medicine, Environmental Medicine and Environmental Hygiene, University of Leipzig; ⁷Department of Pediatrics, University of Leipzig; ⁸Municipal Hospital St. Georg, Leipzig; ⁹Pediatric Practice Bad Honnef; ¹⁰Helmholtz Centre Munich, German Research Centre for Environmental Health, Institute of Epidemiology; ¹¹Chair of Epidemiology, Institute of Medical Data Management, Biometrics and Epidemiology, Ludwig-Maximilians-University, Munich, Germany

To cite this article: Cramer C, Link E, Bauer C-P, Hoffmann U, von Berg A, Lehmann I, Herbarth O, Borte M, Schaaf B, Sausenthaler S, Wichmann H-E, Heinrich J, Krämer U, for the LISApplus study group. Association between attendance of day care centres and increased prevalence of eczema in the German birth cohort study LISApplus. *Allergy* 2010; DOI: 10.1111/j.1398-9995.2010.02446.x.

Keywords

children; day care attendance; East/West comparison; eczema; regional patterns.

Correspondence

Claudia Cramer, IUF-Institut für Umweltmedizinische Forschung, Düsseldorf, Germany.

Tel.: +49 211 3389 284

Fax: +49 211 3389 283

E-mail: claudia.cramer@uni-duesseldorf.de

Accepted for publication 16 June 2010

DOI:10.1111/j.1398-9995.2010.02446.x

Edited by: Antonella Muraro

Abstract

Background: Day care centre attendance is much more common in East than in West Germany. Although there is evidence that early day care might be protective against atopic diseases, several studies have shown a higher prevalence of childhood eczema in East Germany compared to West Germany.

Objectives: To compare prevalence and cumulative incidence of eczema in a birth cohort study in East and West Germany and to identify risk factors that are associated with eczema, which might explain regional differences.

Methods: We used data from the ongoing population-based birth cohort study Influence of Life-style factors on the development of the Immune System and Allergies in East and West Germany Plus the influence of traffic emissions and genetics. In 1997, 3097 children from study areas in East and West Germany were recruited. Cumulative incidence and 1-year prevalences of eczema up to the age of 6 years were determined from yearly questionnaires. Cox regression and generalized estimating equations/logistic regression were used to quantify regional differences and to identify risk factors that might explain them.

Results: Prevalence and incidence of eczema were higher in children living in East Germany than those living in West Germany. We identified 11 risk factors that showed significant regional differences. From these factors, only 'day care attendance during the first 2 years of life' was significantly associated with eczema (odds ratio 1.56, 95% confidence interval CI 1.31–1.86). The regional differences in eczema could be explained by differences in early day care utilization.

Conclusion: Day care centre attendance is associated with an increased prevalence and incidence of eczema. Regional differences in eczema prevalence could be explained by regional differences in utilization of early day care.

Abbreviations

CI, 95% confidence interval; GEE, generalized estimating equations; HR, hazard ratio; LISApplus, influence of Life-style factors on the development of the Immune System and Allergies in East and West Germany Plus the influence of traffic emissions and genetics study; OR, odds ratio.

Background

Eczema is the most common inflammatory skin disorder in the paediatric population and significantly impacts the quality of life. In young children with eczema, sleep disruption, psychological abnormalities and social isolation have been described as disease-related consequences (1).

There is evidence to support the idea that environmental and lifestyle factors are important for determining eczema expression (2). Various risk factors for childhood eczema have been discussed in the literature including sex, socioeconomic status, pet exposure, tobacco smoke, air pollution, nutrition-related aspects, day care attendance and stress (3–6). There is a great body of evidence that day care attendance is associated with an increased prevalence of respiratory infections early in life (7–12). According to the hygiene hypothesis (13), it is postulated that infections during early childhood might protect children from the development of atopic diseases later in life. Krämer et al. (14) showed that children from small families who entered day nursery early in life had less atopic sensitizations, asthma and hay fever than children who first attend day care at an older age. The study of Krämer et al. (14) was carried out in different towns in East Germany, where early day care centre attendance is much more common than in West Germany (10). However, after the reunification of Germany, several epidemiological studies consistently demonstrated that the prevalence of eczema was higher in children from East Germany (15–17). In contrast, hay fever and allergic sensitizations were significantly less prevalent in this region (18). However, to date, the causes for the different regional patterns of eczema prevalence are largely unknown.

Therefore, the aim of our study was to investigate the prevalence and cumulative incidence of eczema in East and West Germany and to identify risk factors that might explain regional differences. We analysed the data from the Influence of Life-style factors on the development of the Immune System and Allergies in East and West Germany Plus the influence of traffic emissions and genetics (LISApplus) birth cohort study conducted in Germany and included children up to 6 years of age. To our knowledge, this is the first longitudinal study that focuses on the identification of explanatory risk factors for regional differences in eczema prevalence between East and West Germany.

Subjects and methods

Study population

The study includes data from the ongoing German birth cohort study LISApplus. The design of the study has been described elsewhere in detail (19). Briefly, 3097 healthy, full-term neonates from parents with German nationality were recruited between 1997 and 1999. The cohort was followed until the age of 6. Study areas in West Germany were Munich, Wesel and Bad Honnef. Leipzig was chosen as the study area in East Germany (Fig. 1). The study was approved by the respective local ethics committees.

Phenotypes

Data on childhood eczema were obtained using self-administered, parental questionnaires that were sent to the LISApplus cohort participants at 6, 12, 18, 24, 48 and 72 months after birth. The dichotomous outcome variables considered were



Figure 1 Study regions in the LISApplus cohort.

parental report of eczema symptoms and of doctor-diagnosed eczema. Children were classified as having eczema symptoms if parents gave affirmative answer on having an intermittent, itchy skin rash that affected places other than the nappy area and lasted at least 2 weeks or appeared repeatedly in the last 12 months. With regard to doctor-diagnosed eczema, parents were asked whether a physician had diagnosed the child with atopic eczema since the last follow-up. At 6 years of age, the members of the cohort were invited to participate in a medical examination by trained paediatricians, who determined visible flexural dermatitis according to the ISAAC II protocol (20).

Study region

The variable 'East/West' was defined as dichotomous variable. Children from the study region Leipzig were defined as children from 'East' (East/West = 1) and children from Munich, Bad Honnef and Wesel as children from 'West' (East/West = 0).

Potential risk factors

Based on our previous knowledge, we investigated the following 16 covariates: parental allergy, sex, day care centre attendance during the first 2 years of life, elder siblings, parental years of

schooling >10 years, high professional qualification of parents, maternal smoking during pregnancy, contact with dog or cat in the first year of life, maternal age at childbirth >30 years, relocation during the last 6 years, passive smoking in household, single father or single mother, fully breast-fed for at least 4 months, pregnancy unwanted, income over at-risk poverty threshold (682 €) and indoor renovation activities during the last 12 months before birth.

Statistical analysis

Descriptive statistics for qualitative values are given by absolute and relative frequencies. Significant differences between study regions were determined using chi-squared-test. The association between the outcome variable eczema and the variable East/West and potential explanatory risk factors was analysed by Cox regression and logistic regression using generalized estimating equations (GEE) for longitudinal analyses. Proportionality of effects over time was tested.

From all covariates, we selected those variables as potential explanatory variables that demonstrated East/West differences as well as an association with eczema. The explainable proportion of a risk factor was determined by comparing the odds ratio (OR) and the hazard ratio (HR) for the variable East/West in two different models: model 1 adjusted only for sex and parental allergy, and model 2 additionally controlled for the risk factor under investigation. Finally, risk factors that changed the OR and the HR for the variable East/West of at least 10% towards one were identified as explanatory risk factors. Odds ratio and HR are presented with 95% confidence intervals (CI). All analyses were completed using SAS version 9.1 (SAS Institute Inc., Cary, NC, USA).

Results

Characterization of the study population

At birth, 3097 children were recruited into the LISApplus cohort (Fig. 2). The proportion of loss to follow-up in the first year was 12%. Thereafter, follow-up rates were over 90%. Response rates to 6-year questionnaires were over 90%.

Characteristics of the LISApplus cohort are presented in Table 1. Children from East Germany were more likely to have eczema at the age of 4 and 6 years. They also had a higher cumulative incidence of eczema symptoms up to 6 years of age. Furthermore, several putative risk factors for eczema demonstrated significant regional differences.

Prevalence and cumulative incidence of eczema in East and West Germany

One-year prevalences and cumulative incidences were higher in children living in East Germany than in those living in West Germany (Fig. 3). Between 2 and 4 years of age, differences in prevalence and cumulative incidence were most pronounced. However, we found no significant interaction between the variable 'East/West' and age of the children.

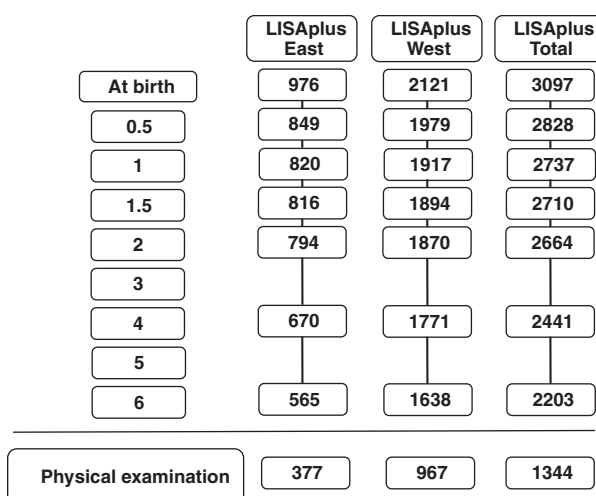


Figure 2 Participation in the LISApplus cohort.

Putative explanatory risk factors for regional differences in eczema prevalence and cumulative incidence

Eleven of 16 covariates evaluated displayed significant regional differences (Table 1). These factors might explain the regional patterns of eczema if they also had an association with eczema. Therefore, we investigated the association between eczema and the eleven covariates using Cox regression with doctor-diagnosed eczema up to the age of 6 as outcome variable. As parental allergy and sex are well-known risk factors for eczema, they were principally considered as potential confounders. Results of Cox regression showed that only day care attendance during the first 2 years of life and smoking in household were significantly associated with eczema. Although the HR for smoking in household was significantly lower than 1, smoking was not considered as explanatory variable, because this finding is not plausible and might be owing to reverse causation. With regard to day care centre attendance, the HR was 1.56 (1.31–1.86). However, as exposure to the risk factor has to occur prior to the development of eczema, we confined the analysis to children who developed eczema after attending day care and found also a strong association (HR: 1.71, 1.31–2.23).

Day care attendance in East and West Germany and association with eczema

Attendance in day care centres in the first 2 years of life was more common in East than in West Germany (55.1% in East Germany vs 5.7% in West Germany, Table 1). The association between eczema and day care centre attendance was independent of study region. Children attending day care centres were at higher risk for eczema in East Germany as well as in West Germany (Fig. 4). The HR for day care centre attendance using eczema from the second life year up to the sixth life year as outcome variable was 1.65 (1.05–2.60) in East Germany and 1.93 (1.19–3.15) in West Germany.

Table 1 Description of the study population

	East		West	
	N	%	N	%
One-year prevalence in the age of 4				
Doctor-diagnosed eczema	634	13.3***	1728	8.4
Eczema symptoms	667	15.7*	1760	12.4
Cumulative incidence up to the age of 6				
Doctor-diagnosed eczema	842	27.0	1964	23.6
Eczema symptoms	836	33.9*	1947	30.2
One-year prevalence in the age of 6				
Doctor-diagnosed eczema	560	11.1*	1611	7.8
Eczema symptoms	558	13.3	1613	10.7
Visible flexural eczema: point prevalence at the age of 6	377	5.6	967	4.0
Sex, male	864	49.7	1995	52.2
Parental allergy	864	42.3***	1989	56.7
Maternal age >30 years at birth of child	864	11.2***	1995	42.1
Elder siblings	861	34.8***	1991	47.5
Passive smoking in household	864	37.9***	1995	29.6
Maternal smoking during pregnancy	854	18.2	1982	15.3
Relocation during the last 6 years	864	48.5***	1995	40.7
Contact with cat or dog in the first year of life	864	23.5	1995	20.3
Single father/single mother	802	28.9***	1894	9.3
Indoor renovation activities in the last 12 month before birth	849	79.5	1978	71.8
Pregnancy unwanted	857	10.7**	1956	7.1
Fully breastfeeding for at least 4 months	864	52.2	1995	57.1
Day care attendance during the first 2 life years	862	55.1***	1987	5.7
Parental professional qualification high	835	63.7***	1972	77.3
Parental school education >10 years	820	59.2***	1978	74.9
Income over at-risk poverty threshold (682 €)	718	73.1***	1693	91.8

Chi-square test: * $P < 0.05$, ** $P < 0.01$, *** $P < 0.001$.

Adjusting for further covariates (e.g. parental school education) did not change the parameter estimates for day care centre attendance.

We additionally calculated the effect of day care attendance in the group of children without elder siblings: the effect in this subgroup was in the same order of magnitude as for the whole group.

Identification of 'day care attendance' as an explanatory risk factor

The association between the variable 'East/West' and eczema was investigated using Cox regression and GEE (Table 2). In each case, the HR or OR for the variable 'East/West' was calculated in two different regression models (model 1 before adjusting for day care attendance and model 2 after adjusting for day care attendance). To insure that only cases that developed eczema after exposure (day care centre attendance in the first 2 years of life) were considered, we additionally calculated the HR from the second life year up to the sixth life year.

Before adjusting for day care attendance (model 1), the ORs and HRs for the variable 'East/West' were significantly greater than one. After additionally adjusting for day care attendance (model 2), parameter estimates diminish towards

one. In model 2, the variable 'East/West' is no longer a risk factor for eczema.

With regard to GEE, we additionally calculated the ORs for day care (using eczema from the second life year up to the sixth life year as outcome) separately for children who already had eczema before attending day care and for those children who had not. The OR was highly significant in the group of children who had no eczema before attending day care (1.91, 1.32–2.74). In contrast, we found no significant effect in the group of children who had eczema before attending day care (OR 1.06, 0.63–1.79).

We observed that the effect of day care attendance was strongest on eczema at 2 and 4 years of age: the OR for day care attendance using model 2 by logistic regression was 1.51 (1.11–2.03) for eczema symptoms at 2 years of age. By 6 years of age, the effect of day care attendance on symptoms was no longer significant (OR: 1.09, 0.74–1.59). The same was true using the point prevalence of flexural eczema at 6 years of age as an outcome variable (OR: 1.09, 0.51–2.29).

Discussion

Our results demonstrate that different regional patterns of eczema in Germany still exist more than 10 years after the

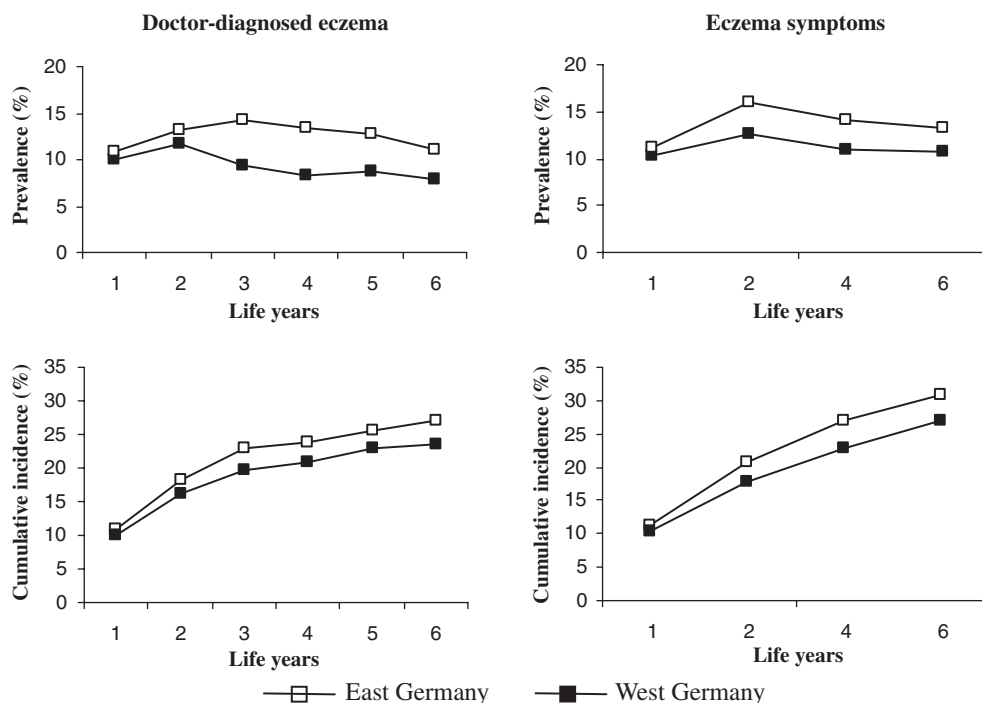


Figure 3 Prevalence and cumulative incidence of eczema in East and West Germany.

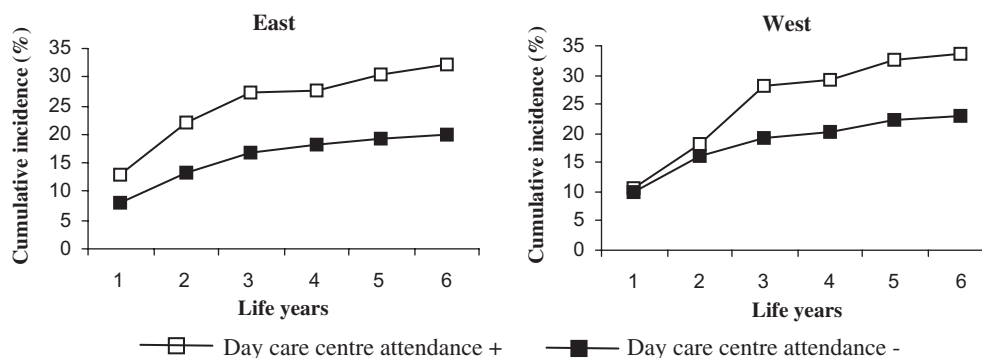


Figure 4 Cumulative incidence of eczema and day care attendance.

German reunification. The nationally representative German Health Interview and Examination Survey for Children and Adolescents (KiGGS) from 2003 to 2006 (21) demonstrated a higher prevalence of eczema in East Germany too, but the difference between East and West Germany was not significant.

From a broad range of potential risk factors, we identified day care centre attendance in the first 2 years of life as the only explanatory risk factor for the observed regional differences in eczema prevalence and incidence. Several epidemiological studies in different countries have focused on the relationship between day care and atopic diseases (7, 14, 22–27). In our previous study (14), we demonstrated that in

children aged 5–14 years from small families who entered day nursery at age 6–11 months, the prevalence of atopic sensitizations, asthma and hay fever was lower than in children who entered day nursery at an older age. However, there was no effect of age at entry to day nursery on eczema development (Krämer U, personal communication).

Most studies do not militate in favour of a significant association between day care attendance (2, 23, 25, 26) and eczema. A few studies have reported a protective effect (22, 24) or, as in our case, a promotional (7) effect of day care attendance on eczema. These controversial results might partly be because of different study designs, different age groups and different type or intensity of day care attendance.

Table 2 East/West differences in eczema before and after adjusting for day care centre attendance†

Cox regression	N	Model 1‡	Model 2§
		HR (95% CI)	HR (95% CI)
Doctor-diagnosed eczema	2288	1.29* (1.00–1.67)	0.94 (0.67–1.31)
2nd–6th year			
Eczema symptoms	2227	1.26* (1.01–1.58)	1.15 (0.88–1.51)
2nd–6th year			
GEE analyses	N	Model 1‡	Model 2§
		OR (95% CI)	OR (95% CI)
Doctor-diagnosed eczema	2843	1.48*** (1.19–1.85)	1.10 (0.85–1.44)
2nd–6th year			
Eczema symptoms	2843	1.38** (1.13–1.69)	1.22 (0.96–1.55)
2nd–6th year			

CI, 95% confidence interval; GEE, generalized estimating equations; HR, hazard ratio; OR, odds ratio.

†Within the first 2 years of life.

‡Adjusted for gender and parental allergy, significance indicated by * $P < 0.05$, ** $P < 0.01$, *** $P < 0.001$.

§Adjusted for gender, parental allergy and day care centre attendance.

Most of these studies investigated eczema prevalence among school-aged children, whereas children in our study were younger. Although we found no significant deviation from proportionality over time, our data displayed a slight trend that the effect of early day care centre attendance on eczema weakened as the children grew older. This might explain why most of the aforementioned studies did not find an effect of day care centre attendance on eczema. Our results are in line with findings from a large cross-sectional study in Sweden (7) in which children between 1 and 6 years of age had an increased risk for eczema if they attended a public day care centre. As in our study, the effect was strongest in the younger age groups.

Contradictory to our findings, results from a birth cohort study in Denmark (24) and one from the United States (22) indicated that day care attendance had a protective effect against eczema. The study from Celedón et al. (22) only included children with parental history of atopy and Benn et al. (24) evaluated children who attended day care before 6 months of age and who were up to 18 months old. Therefore, these studies are not directly comparable to our study. Furthermore, it has to be taken into consideration that type and intensity of day care attendance differ between countries. There is a great body of evidence that day care attendance is associated with an increased prevalence of respiratory infections early in life (10–12). According to the hygiene hypothesis (13), it is postulated that infections during early childhood might protect children from the development of atopic diseases later in life. Therefore, our results are surprising. Quite recently, results from a Dutch birth cohort study demonstrated that children who attend day care early in life had an increase in airway symptoms until 4 years of age but were

not protected from asthma symptoms, hyperresponsiveness or allergic sensitization at the age of 8 (27).

With regard to eczema, in addition to immunological factors, defects in skin barrier function seem to play an important role (28). Attendance of day care might coincide with a higher exposure to allergens and micro-organisms. In the case of children with an impaired epithelial barrier, these substances easily penetrate into the subepidermal layer. This might result in a higher predisposition for secondary eczema manifestation (29). However, other factors such as stress should also be taken into consideration. Several studies report an association between stress and day care centres (30, 31), and there is a growing body of evidence that psycho-neuroimmunological factors and emotional stress are important for the development of eczema (8, 9). Recent studies have suggested that stress impairs the barrier function of the skin and favours a shift in immunity towards a T-helper type 2 cell (Th2) response, which might result in higher predisposition for the development of eczema (8, 9, 32).

The strengths of our study are the prospective study design and the good follow-up rates. One limitation is the fact that our results might not be fully representative for Eastern and Western Germany as they are mainly based on a comparison between the city of Leipzig in Eastern Germany and Munich in Western Germany. On the other hand, the best-known epidemiological study, which showed regional differences of allergic diseases in East and West Germany shortly after reunification, was also performed in these two study regions (18). The 1-year prevalence of eczema was assessed using questionnaire-based data. Although there is scepticism regarding the validity of questionnaire-based data, it has been shown that questionnaire-derived symptom prevalences can be sufficiently precise for comparison between populations (33). The association between day care attendance and eczema was found for doctor-diagnosed eczema as well as for eczema symptoms as outcome variable. However, it cannot be excluded that the observed effect might be because of reporting bias associated with day care centre attendance. Using the point prevalence of visible flexural eczema observed by a physician at 6 years of age as an additional outcome measure, we did not observe an effect of day care attendance of eczema prevalence. However, this result does not conflict with our findings as there was a slight trend showing that the effect of day care attendance on eczema plateaued when children were in school age. The LISAPlus study was conducted with focus on the immune system and allergies. Therefore, we have no in-depth information with regard to type and intensity of day care centre attendance. However, to identify the underlying factors that are causal for the higher prevalence of eczema in children who attend day care centres, such information would be necessary.

We recommend future studies on the relationship between day care attendance and eczema, with a focus on different conditions (e.g. time spent in day care and type of day care) under which day care attendance influences immune reactivity and stress level in children.

Conclusions

Using data from the German birth cohort LISAplus, we demonstrated that more than 10 years after the German reunification, the prevalence and incidence of eczema in children up to the age of 6 years were still higher in East Germany compared to West Germany. Day care centre attendance in the first 2 years of life was much more common in East Germany than in West Germany. Day care centre attendance is associated with an increased prevalence and incidence of eczema in East Germany as well as in West Germany. However, the effect of day care centre attendance appears to level out as children get older. In our study, the regional differences in eczema prevalence and incidence could be explained by regional differences in utilization of early day care. Further longitudinal studies are needed to replicate our findings and to identify the causal factors for the higher risk of eczema in children who attend day care centres within the first 2 years of life.

References

- Schmitt J, Apfelbacher C, Chen C-M, Romanos M, Sausenthaler S, Koletzko S et al. Infant-onset eczema in relation to mental health problems at age 10 years: results from a prospective birth cohort study (GINIplus). *J Allergy Clin Immunol* 2010;**125**:404–410.
- Bisgaard H, Halkjaer LB, Hinge R, Giwercman C, Palmer C, Silveira L et al. Risk analysis of early childhood eczema. *J Allergy Clin Immunol* 2009;**123**:1355–1360.
- Biagini Myers JM, Wang N, Lemasters GK, Bernstein DI, Epstein TG, Lindsey MA et al. Genetic and Environmental Risk Factors for Childhood Eczema Development and Allergic Sensitization in the CCAAPS Cohort. *J Invest Dermatol* 2010;**130**:430–437.
- Williams HC, Strachan DP, Hay RJ. Childhood eczema: disease of the advantaged? *BMJ* 1994;**308**:1132–1135.
- Kramer U, Sugiri D, Ranft U, Krutmann J, von Berg A, Berdel D et al. Eczema, respiratory allergies, and traffic-related air pollution in birth cohorts from small-town areas. *J Dermatol Sci* 2009;**56**:99–105.
- Von Berg A, Filipiak-Pittroff B, Kramer U, Link E, Bollrath C, Brockow I et al. Preventive effect of hydrolyzed infant formulas persists until age 6 years: long-term results from the German Infant Nutritional Intervention Study (GINI). *J Allergy Clin Immunol* 2008;**121**:1442–1447.
- Hagerhed-Engman L, Bornehag CG, Sundell J, Aberg N. Day-care attendance and increased risk for respiratory and allergic symptoms in preschool age. *Allergy* 2006;**61**:447–453.
- Buske-Kirschbaum A, Geiben A, Hellhammer D. Psychobiological aspects of atopic dermatitis: an overview. *Psychother Psychosom* 2001;**70**:6–16.
- Arndt J, Smith N, Tausk F. Stress and atopic dermatitis. *Curr Allergy Asthma Rep* 2008;**8**:312–317.
- Zutavern A, Rzehak P, Brockow I, Schaaf B, Bollrath C, Von BA et al. Day care in relation to respiratory-tract and gastrointestinal infections in a German birth cohort study. *Acta Paediatr* 2007;**96**:1494–1499.
- Koopman LP, Smit HA, Heijnen ML, Wijga A, van Strien RT, Kerkhof M et al. Respiratory infections in infants: interaction of parental allergy, child care, and siblings – The PIAMA study. *Pediatrics* 2001;**108**:943–948.
- Celedon JC, Litonjua AA, Weiss ST, Gold DR. Day care attendance in the first year of life and illnesses of the upper and lower respiratory tract in children with a familial history of atopy. *Pediatrics* 1999;**104**:495–500.
- Strachan DP. Hay fever, hygiene, and household size. *BMJ* 1989;**299**:1259–1260.
- Kramer U, Heinrich J, Wjst M, Wichmann HE. Age of entry to day nursery and allergy in later childhood. *Lancet* 1999;**353**:450–454.
- Weiland SK, von ME, Hirsch T, Duhme H, Fritzsche C, Werner B et al. Prevalence of respiratory and atopic disorders among children in the East and West of Germany five years after unification. *Eur Respir J* 1999;**14**:862–870.
- Schafer T, Dockery D, Kramer U, Behrendt H, Ring J. Experiences with the severity scoring of atopic dermatitis in a population of German pre-school children. *Br J Dermatol* 1997;**137**:558–562.
- Krämer U, Oppermann H, Ranft U, Schäfer T, Ring J, Behrendt H. Differences in allergy trends between East and West Germany and possible explanations. *Clin Exp Allergy* 2010;**40**:289–298.
- von Mutius E, Martinez FD, Fritzsche C, Nicolai T, Roell G, Thiemann HH. Prevalence of asthma and atopy in two areas of West and East Germany. *Am J Respir Crit Care Med* 1994;**149**:358–364.
- Zirngibl A, Franke K, Gehring U, von Berg A, Berdel D, Bauer CP et al. Exposure to pets and atopic dermatitis during the first two years of life. A cohort study. *Pediatr Allergy Immunol* 2002;**13**:394–401.
- Asher MI, Montefort S, Björkstén B, Lai CK, Strachan DP, Weiland SK et al. Worldwide time trends in the prevalence of symptoms of asthma, allergic rhinoconjunctivitis, and eczema in childhood: ISAAC Phases One and Three repeat multicountry cross-sectional surveys. *Lancet* 2006;**368**:733–743.
- Schlaud M, Atzpodien K, Thierfelder W. [Allergic diseases. Results from the German Health Interview and Examination Survey for Children and Adolescents (KiGGS)]. *Bundesgesundheitsblatt Gesundheitsforschung Gesundheitsschutz* 2007;**50**:701–710.
- Celedon JC, Litonjua AA, Ryan L, Weiss ST, Gold DR. Day care attendance, respiratory tract illnesses, wheezing, asthma, and total serum IgE level in early childhood. *Arch Pediatr Adolesc Med* 2002;**156**:241–245.
- Pekkanen J, Remes S, Kajosaari M, Husman T, Soininen L. Infections in early childhood and risk of atopic disease. *Acta Paediatr* 1999;**88**:710–714.
- Benn CS, Melbye M, Wohlfahrt J, Björkstén B, Aaby P. Cohort study of sibling effect, infectious diseases, and risk of atopic dermatitis during first 18 months of life. *BMJ* 2004;**328**:1223.
- de Meer G, Janssen NA, Brunekreef B. Early childhood environment related to

Acknowledgments

We thank all the families who participated in the LISAplus study. Furthermore, we thank all members of the LISAplus study group (see Appendix S1) for their excellent work.

Supporting Information

Additional Supporting Information may be found in the online version of this article:

Appendix S1. Members of the LISAplus study group.

Please note: Wiley-Blackwell are not responsible for the content or functionality of any supporting materials supplied by the authors. Any queries (other than missing material) should be directed to the corresponding author for the article.

- microbial exposure and the occurrence of atopic disease at school age. *Allergy* 2005; **60**:619–625.
26. Nicolaou NC, Simpson A, Lowe LA, Murray CS, Woodcock A, Custovic A. Day-care attendance, position in sibship, and early childhood wheezing: a population-based birth cohort study. *J Allergy Clin Immunol* 2008; **122**:500–506.
 27. Caudri D, Wijga A, Scholtens S, Kerkhof M, Gerritsen J, Ruskamp JM et al. Early daycare is associated with an increase in airway symptoms in early childhood but is no protection against asthma or atopy at 8 years. *Am J Respir Crit Care Med* 2009; **180**:491–498.
 28. Elias PM, Steinhoff M. “Outside-to-inside” (and now back to “outside”) pathogenic mechanisms in atopic dermatitis. *J Invest Dermatol* 2008; **128**:1067–1070.
 29. Cramer C, Link E, Horster M, Koletzko S, Bauer CP, Berdel D et al. Elder siblings enhance the effect of filaggrin mutations on childhood eczema: results from the 2 birth cohort studies LISApplus and GINIplus. *J Allergy Clin Immunol* 2010; **125**(6): 1254–1260.
 30. Geoffroy MC, Cote SM, Parent S, Seguin JR. Daycare attendance, stress, and mental health. *Can J Psychiatry* 2006; **51**:607–615.
 31. Vermeer HJ, van Ijzendoorn MH. Children’s elevated cortisol levels at daycare: a review and meta-analysis. *Early Child Res Q* 2006; **21**:390–401.
 32. Herberth G, Weber A, Roder S, Elvers HD, Kramer U, Schins RP et al. Relation between stressful life events, neuropeptides and cytokines: results from the LISA birth cohort study. *Pediatr Allergy Immunol* 2008; **19**:722–729.
 33. Flohr C, Weinmayr G, Weiland SK, Addo-Yobo E, Annesi-Maesano I, Bjorksten B et al. How well do questionnaires perform compared with physical examination in detecting flexural eczema? Findings from the International Study of Asthma and Allergies in Childhood (ISAAC) Phase Two. *Br J Dermatol* 2009; **161**:846–853.