ORIGINAL ARTICLE

Stress-Related Maternal Factors During Pregnancy in Relation to Childhood Eczema: Results From the LISA Study

S Sausenthaler,[1] P Rzehak,[1,2] CM Chen,[1,3] P Arck,[4,5] A Bockelbrink,[6] T Schäfer,[7] B Schaaf,[8] M Borte,[9,10] O Herbarth,[11,12] U Krämer,[13] A von Berg,[14] HE Wichmann,[1,2] J Heinrich[1] for the LISA Study Group[a]

[1] Helmholtz Zentrum München, German Research Center for Environmental Health, Institute of Epidemiology, Neuherberg, Germany.
[2] Ludwig-Maximilians University Munich, Institute of Medical Data Management, Biometrics and Epidemiology, Chair of Epidemiology, Munich, Germany
[3] Ludwig-Maximilians-University of Munich, Dr. von Hauner Children's Hospital, Munich, Germany
[4] McMaster University, The Brain-Body Institute, Department of Medicine, Hamilton, Ontario, Canada
[5] Centre of Internal Medicine and Dermatology, Division of Psycho-Neuro-Immunology, Charité, University Medicine Berlin, Germany
[6] Institute for Social Medicine, Epidemiology, and Health Economics, Charité University Medical Center Berlin, Germany
[7] Department of Social Medicine, Medical University Lübeck, Germany
[8] Medical Practice for Pediatrics, Bahnhofstrasse 6, 53604 Bad Honnef, Germany
[9] University of Leipzig, Department of Pediatrics, Leipzig, Germany
[10] Municipal Hospital "St. Georg" Leipzig, Children's Hospital, Leipzig, Germany
[11] UFZ – Center for Environmental Research, Department of Human Exposure Research and Epidemiology, Leipzig, Germany
[12] University of Leipzig, Faculty of Medicine, Environmental Hygiene and Environmental Medicine, Leipzig, Germany
[13] IUF- Institut für Umweltmedizinische Forschung, University of Düsseldorf, Germany
[14] Marien-Hospital Wesel, Department of Pediatrics, Wesel, Germany
[a] The members of and institutions affiliated with the LISA study group are listed in the appendix.

Abstract

Background: Stress has been suggested to impact the onset and exacerbation of eczema and other atopic disorders. Whether early exposure to stress-related factors might exert long-term effects remains to be clarified.
Objective: The objective of this study was to investigate whether stress-related maternal factors during pregnancy are associated with childhood eczema during the first 6 years of life.
Methods: Data from 3004 children from a prospective German birth cohort study (LISA) were analyzed. Information from maternity certificates and questionnaire information on unwanted pregnancy were used to evaluate stress-related maternal factors during pregnancy. Prevalence data for physician-diagnosed eczema were available up to the age of 6 years.
Results: Maternal factors during pregnancy were positively associated with childhood eczema in terms of cumulative prevalence up to the age of 2 years (adjusted odds ratio, 1.48; 95% confidence interval, 0.95-2.30) after adjusting for potential confounders. Beyond the second year no increased risk was observed.
Conclusions: The results of this study suggest that stress-related maternal factors during pregnancy are associated with an increased risk of childhood eczema during the first 2 years of life. The impact of postnatal stress such as parental divorce or separation on this association

could not be clarified. Future studies should therefore further elucidate how prenatal and postnatal stress interact and whether prenatal stress might have a programming effect. If future studies confirm the findings of this study, reducing maternal stress during pregnancy might be a possible target in the primary prevention of eczema during childhood.

Key words: Stress-related maternal factors. Pregnancy. Eczema. LISA study. Birth cohort. Infants.

Resumen

Antecedentes: Se ha sugerido que el estrés afecta al inicio y exacerbación del eccema y otros trastornos atópicos. Está por clarificar si una exposición temprana a factores relacionados con el estrés podría ejercer efectos a largo plazo.
Objetivo: El objetivo de este studio fue investigar si los factores maternos relacionados con el estrés durante el embarazo están asociados al eccema infantil durante los 6 primeros años de vida.
Métodos: Se analizaron datos de 3004 niños de un estudio prospectivo de cohorte de recién nacidos alemanes (LISA). Se empleó información de certificados de maternidad y de cuestionarios de embarazos no deseados para evaluar los factores maternos relacionados con estrés durante el embarazo. Los datos de prevalencia para el eccema diagnosticado por un médico estaban disponibles hasta la edad de 6 años de edad.
Resultados: Los factores maternos durante el embarazo se asociaron positivamente con el eccema en la infancia en términos de prevalencia acumulada hasta la edad de 2 años (odds ratio ajustada, 1,48; intervalo de confianza al 95%, 0,95-2,30) después de ajustar por posibles factores de confusión. Por encima del segundo año no se observó un aumento del riesgo.
Conclusiones: El resultado de este estudio sugiere que los factores maternos relacionados con el estrés durante el embarazo están asociados con el aumento de riesgo de eccema infantil durante los dos primeros años de vida. No ha podido aclararse el impacto del estrés postnatal como el divorcio o separación parental en esta asociación. Por este motivo, estudios futuros deberían. dilucidar cómo interactúan el estrés prenatal y postnatal y si el estrés prenatal podría tener un efecto condicionante. Si los futuros estudios confirman los hallazgos de este estudio, reducir el estrés materno durante el embarazo podría ser una posible diana en la prevención primaria del eccema durante la infancia.

Palabras clave: Factores maternos relacionados con estrés. Embarazo. Eccema. Estudio LISA. Cohorte de recién nacidos. Lactantes.

Introduction

Eczema is a chronic inflammatory skin disease with a complex etiology [1] and high prevalence rates in developed countries [2]. It has been classified into an atopic, immunoglobulin (Ig) E–mediated form, affecting the majority of patients, and a nonatopic form [3]. Although eczema is now mainly considered to be the result of an interaction between genetically impaired skin barrier function and abnormal immune responses triggered by environmental factors [1], it was once believed to be psychogenic in origin and was commonly referred to as neurodermatitis in historical medical texts [4]. The term *neurodermatitis*, which implies a causal role of the autonomic nervous system in itch sensation, has been avoided, however, ever since a better understanding of the immunological processes behind eczema was achieved. Nonetheless, in the light of several recent studies, stress might be among the psychological factors that influence the development and exacerbation of eczema and other atopic disorders [5-9].

It has long been recognized that stress has the potential to modulate the immune system [10], probably through the activation of the hypothalamic-pituitary–adrenocortical axis and the sympathetic and adrenomedullary system. When activated, hormones and neuropeptides involved in the regulation of inflammatory and immune responses are released into the circulation [11]. While stress is generally regarded as immunosuppressive, the duration, intensity, and persistence of the stressor are important distinguishing features of the stress response [12]. Recent evidence further suggests that the stress hormones glucocorticoids and catecholamines have differential effects on cellular and humoral immunity by affecting the differentiation of type 1 and type 2 helper T (T_H1 and T_H2) cells [13]. Furthermore, in vitro studies have shown that glucocorticoids can influence cytokine responses in a way that favors T_H2-type reactions [14,15] by inhibiting the production of interleukin (IL) 12 and promoting the production of IL-4.

Stress might thus be among the factors that contribute to the development of a predominant T_H2 cytokine pattern, promoting IgE production and possibly initiating allergic inflammation. The underlying mechanisms, however, are probably much more complex and include a wide range of cytokines, neuropeptides, and other mediators [16].

Whether or not there is a time window of vulnerability early in life during which stress might, if at all, exert long-term effects on the development of the immune system remains to be clarified. Since it has been suggested that atopic diseases are programmed in utero [17,18], a prenatal programming effect of stress should be investigated.

The objective of this study was thus to determine whether stress-related maternal factors during pregnancy might be associated with childhood eczema during the first 6 years of life.

Participants and Methods

Participants

We analyzed data from the LISA (Influences of lifestyle related factors on the immune system and the development of allergies in childhood) study, a prospective birth cohort study

whose design and objectives have been described in detail elsewhere [19,20]. In brief, 3097 newborns were recruited between November 1997 and January 1999 in 4 German cities: Munich, Leipzig, Wesel, and Bad Honnef. Questionnaires on family history of atopy, parental education, smoking during pregnancy, maternal age at delivery, unwanted pregnancy, and other lifestyle factors were completed by the parents shortly after delivery. In addition, a face-to-face questionnaire-based interview on pregnancy characteristics, pregnancy complications, and birth outcomes was conducted by a physician with the mother at the corresponding maternity unit. Data on the child's health were collected by repeated parent-completed questionnaires at regular time intervals during the first 6 years (0.5, 1, 1.5, 2, 4, and 6 years). Retrospective information on psychosocial aspects of life and stressful life events during the first 6 years of life were also gathered by questionnaires sent to the parents in the 6-year follow-up period.

For the present analysis, participants with complete data on stress-related maternal factors during pregnancy were selected (n=3004). The local ethics committees approved the study protocol, and informed consent was obtained from all parents.

Stress-Related Maternal Factors During Pregnancy

Information on psychological stress, social stress, bleeding before and after 28 weeks' gestation, placental insufficiency, premature labor, anemia, positive indirect Coombs test, risk based on other serological findings, hypertension (>140/90) and proteinuria (≥1000 mg/L) was obtained from the *Mutterpass*, a maternity certificate routinely completed in obstetrical practices in Germany. This certificate contains a list of potential pregnancy complications, which can be marked as appropriate by the gynecologist or the midwife at preventive medical checkups. A copy of the maternity certificates was obtained during the interview at the maternity unit. While findings from serological tests for toxoplasma, rubeola, chlamydia and other infections are documented in the maternity certificate, they were not used for this study due to missing information for a large part of the study population. Based on the information obtained from the maternity certificate as well as information on unwanted pregnancies, stress-related factors during pregnancy were evaluated. The presence of stress-related maternal factors was defined as the presence of 2 or more of the 12 study factors, which represented the cutoff for the upper 5% of the study population.

Outcome Definition

The questionnaires sent to the parents included questions on physician diagnoses and symptoms of eczema and other medical conditions during the time periods evaluated. Eczema was recorded as present if parents reported a physician's diagnosis of neurodermatitis or allergic or atopic eczema in their child. As the requested time periods for physician diagnoses covered the first 6 years of life, we were able to analyze the cumulative prevalence of eczema for the ages 0-1, 0-2, 0-3, 0-4, 0-5, and 0-6 years.

Statistical Methods

Differences in the cumulative prevalence of eczema between children with and without stress-related maternal factors were analyzed using the χ^2 test. Crude associations between the presence of stress-related maternal factors during pregnancy and childhood eczema were calculated using odds ratios (ORs) with corresponding 95% confidence intervals (CIs). Multiple logistic regression analysis was performed to estimate ORs adjusted for study center (Munich/Leipzig/Wesel/Bad Honnef), maternal education (<10 grades/=10 grades/>10 grades), maternal age at delivery (≤31 years/>31 years), a family history of atopy (asthma, hay fever, and/or eczema) and divorce/separation during the first 2 years after childbirth.

All computations were performed using the statistical analysis package SAS for Windows, version 9.1 (SAS Institute, Cary, North Carolina, USA).

Results

Of the 3097 children recruited at birth, 2664 (86%) and 2203 (71%) children participated in the 2-year and the 6-year follow-up studies, respectively. Complete information on stress-related maternal factors during pregnancy derived from

Table 1. Basic Characteristics of the LISA Study Population

	No./Total	%
Study area		
Munich	1425/3004	47.4
Leipzig	942/3004	31.4
Wesel	339/3004	11.3
Bad Honnef	298/3004	9.9
Sex		
Male	1550/3004	51.6
Female	1454/3004	48.4
Maternal education		
< 10 grades	288/2966	9,7
=10 grades	1159/2966	39.1
>10 grades	1519/2966	51.2
Maternal age at delivery		
≤31 years	1618/3000	53.9
>31 years	1382/3000	46.1
Divorce/separation during the first 2 years of life		
Yes	60/1906	3.2
No	1846/1906	96.8
Parental history of atopic disease[a]		
None	1458/2998	48.6
1 parent	1157/2998	38.6
Both parents	383/2998	12.8
Exclusive breastfeeding for at least 4 months		
Yes	1552/2453	63.3
No	901/2453	36.7
Maternal smoking during pregnancy[b]		
Yes	335/2956	11.7
No	2521/2956	88.3

[a]Asthma, hay fever or eczema.
[b]During second and/or third trimester of pregnancy.

Table 2. Frequency of Stress Indicators During Pregnancy and Presence of Stress-Related Factors During Pregnancy in the LISA Study Population (n=3004)

	No.	%
Stress indicators during pregnancy		
Psychological stress[a]	44	1.5
Social stress[a]	24	0.8
Bleeding before 28 weeks' gestation[a]	169	5.6
Bleeding after 28 weeks' gestation[a]	37	1.2
Placental insufficiency[a]	10	0.3
Premature labor[a]	245	8.2
Anemia[a]	165	5.5
Positive Coombs test[a]	4	0.1
Risk based on other serological findings[a]	3	0.1
Hypertension (>140/90)[a]	54	1.8
Proteinuria (≥1000 mg/L)[a]	10	0.3
Unwanted pregnancy	273	9.1
Presence of stress-related factors during pregnancy[b]		
No	2846	94.7
Yes	158	5.3

[a]Information derived from maternity certificates.
[b]Defined as at least 2 of the 12 indicators shown above.

maternity certificates and the birth questionnaire was available for 3004 children (97%). The frequency of basic characteristics and possible confounding factors in our study population are shown in Table 1.

Table 2 shows the frequency of potential stress indicators during pregnancy. The most frequent indicators were unwanted pregnancy (9.1%), premature labor (8.2%), bleeding before 28 weeks' gestation (5.6%), and anemia (5.5%). In 5.3% of all mothers, at least 2 stress indicators were positive; the maximum number of positive stress indicators was 4.

The cumulative prevalence of eczema up to the age of 6 years according to the presence of stress-related maternal factors is shown in Table 3. In general, this prevalence was greater in children with maternal pregnancy stress than in those without but the differences were only significant (and marginally so) for the period 0 to 2 years (P<.10).

In crude logistic regression analysis, the presence of stress-related maternal factors was positively associated with childhood eczema, but the association was only of borderline significance for cumulative prevalence up to the age of 2 years (OR, 1.47; 95% CI, 0.95-2.26) (Table 4). The inclusion

Table 3. Cumulative Prevalence of Childhood Eczema According to Stress-Related Maternal Factors During Pregnancy in the LISA Study Population

		Presence of Stress-Related Maternal Factors				
Cumulative Eczema Prevalence	No/Total	No	%	Yes	%	*P* Value[a]
0-1 y	269/2647	253/2516	10.1	16/131	12.2	.426
0-2 y	429/2516	401/2393	16.8	28/123	22.8	.084
0-3 y	472/2290	448/2179	20.6	24/111	21.6	.787
0-4 y	495/2290	470/2179	21.6	25/111	22.5	.812
0-5 y	496/2081	469/1981	23.7	27/100	27.0	.446
0-6 y	517/2081	490/1981	24.7	27/100	27.0	.609

[a]Calculated using the χ^2 test.

Table 4. Logistic Regression Results Describing Associations Between the Presence of Stress-Related Maternal Factors During Pregnancy and Childhood Eczema During the First 6 Years of Life in the LISA Study Population

		Presence of Stress-Related Maternal Factors During Pregnancy				
Cumulative Eczema Prevalence	No	OR (95% CI)[a]	aOR (95% CI)[b]	aOR (95% CI)[c]	aOR (95% CI)[d]	aOR (95% CI)[e]
0-1 y	2647	1.25 (0.73-2.13)	1.25 (0.73-2.15)	1.25 (0.73-2.16)	1.25 (0.73-2.16)	1.24 (0.72-2.13)
0-2 y	2516	1.47 (0.95-2.26)	1.50 (0.97-2.32)	1.50 (0.97-2.32)	1.50 (0.97-2.33)	1.48 (0.95-2.30)
0-3 y	2290	1.07 (0.67-1.70)	1.07 (0.67-1.71)	1.07 (0.67-1.71)	1.08 (0.68-1.72)	1.06 (0.66-1.70)
0-4 y	2290	1.06 (0.67-1.67)	1.07 (0.68-1.70)	1.07 (0.68-1.69)	1.08 (0.68-1.71)	1.06 (0.67-1.68)
0-5 y	2081	1.19 (0.76-1.88)	1.22 (0.78-1.93)	1.22 (0.77-1.92)	1.23 (0.78-1.94)	1.21 (0.76-1.91)
0-6 y	2081	1.13 (0.72-1.77)	1.15 (0.73-1.81)	1.15 (0.73-1.81)	1.15 (0.73-1.82)	1.13 (0.71-1.79)

Abbreviations: aOR, adjusted odds ratio; CI, confidence interval.
[a]Crude OR.
[b]Adjusted for study center.
[c]Adjusted for study center and maternal education.
[d]Adjusted for study center, maternal education, and maternal age at delivery.
[e]Adjusted for study center, maternal education, maternal age at delivery, and family history of atopy.

of potential confounders (study center, maternal education, maternal age at delivery, and family history of atopy) did not alter the estimates substantially. After further adjustment for divorce/separation during the first 2 years after birth, previous positive associations attenuated to a null effect for all eczema definitions (0-2 years: adjusted OR, 1.04; 95% CI, 0.58-1.88).

Discussion

The results of this prospective birth cohort study suggest that the presence of stress-related maternal factors during pregnancy is associated with an increased risk of childhood eczema during the first 2 years of life. Beyond the second year, no increased risk was observed, suggesting that other factors may override the influence of prenatal stress.

There is evidence from earlier epidemiological [21-23] and animal studies [5] that psychological stress can exacerbate atopic eczema and may thus be an important predictor of symptom severity. Associations have also been prospectively described between parental stress and childhood wheezing [67], which can be an early sign of atopic or nonatopic asthma. In addition, it has been reported that children who experience stressful life events of potential psychosocial relevance have a higher risk for developing atopic diseases later in life [89]. On the basis of the LISA study, Bockelbrink et al [22] showed that parental divorce/separation was significantly associated with an increased incidence of eczema during the first 2 years of life, contrasting with severe disease in a family member, which had a protective effect at the age of 4 years, and unemployment, which had no effect.

A prenatal influence of maternal stress during pregnancy on immune functions in the offspring has been hypothesized recently [12]. Lin et al [24], for example, found that self-reported maternal nervousness during pregnancy was associated with elevated levels of cord blood IgE. An increase in umbilical cord IgE is, in turn, considered a risk factor for childhood atopy [25]. Furthermore, it has been demonstrated that pregnant women with psychosocial stress have increased serum levels of proinflammatory cytokines [26], and alterations in circulating maternal cytokines are suspected to be related to allergy later in life [27]. Although evidence in humans is scarce, these findings support the hypothesis that the prenatal period is a window of increased vulnerability in which stress might be particularly harmful to the immune system of the fetus.

Some limitations have to be considered when interpreting the findings of the present study. First, it is difficult to prove that the reported associations between the presence of stress-related maternal factors during pregnancy and childhood eczema do not reflect effects of postnatal stress. One potential postnatal stress factor—parental divorce or separation early in the child's life—was indeed seen to diminish the effects of prenatal stress on eczema in offspring when included in the final model. This, however, should be interpreted with caution. Divorce/separation during the first 2 years after birth could also be a consequence of prenatal stress and the attenuation might reflect the fact that the covariate treated as a confounder is actually an intermediate factor that is a critical link in the causal chain from prenatal stress to childhood eczema. If so, it would not be appropriate to adjust for divorce/separation. The attenuation observed might also be due to the fact that information on divorce/separation was only available for part of the study population. Stress-related maternal factors might also simply be a precursor of the postnatal event, which, as has been suggested, might actually be the key trigger of the development of childhood eczema [8]. In general, reverse causation is a matter of continuing debate [28] but it is practically impossible to overcome this problem by means of epidemiological studies alone.

Furthermore, we cannot ensure that the factors used as a proxy for maternal stress in this study are valid markers of psychological stress in mothers during pregnancy. We can only speculate that the selected factors, such as bleeding during early pregnancy and premature labor, cause such stress. This speculation is partly supported by observations from a Danish study showing that women in late pregnancy who were concerned about pregnancy complications such as vaginal bleeding had 27% higher evening cortisol levels than those who did not report such concerns [29]. However, due to the limited number of observations, stratification for physical against psychological stress was not possible.

Together with pregnancy complications, unwanted pregnancy was another major stress-related maternal factor in our study. Both unwanted pregnancies [30] and the death of a relative during the first trimester [31] have been associated with later schizophrenia in children and attributed to psychological stress of the mother during pregnancy. It is, however, also possible that mothers gradually accept the idea that they will give birth to a baby, even if the pregnancy was initially unwanted. Furthermore, certain pregnancy complications, in particular psychological and social problems, might be prone to underestimation, as they are probably only documented if mothers report them spontaneously.

Because the ability to cope with demanding events generally varies from one individual to another [6], it would be important to evaluate whether mothers perceive the same stressful situation with equal intensity and whether this causes similar stress responses.

In conclusion, the results of this study suggest that stress-related maternal factors during pregnancy are positively associated with the development of eczema in offspring during the first 2 years of life. The role of postnatal stress such as parental divorce or separation in this association could not be clarified. Future studies should therefore further elucidate how prenatal and postnatal stress interact and whether maternal stress during pregnancy might have a programming effect.

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Appendix

LISAplus Study Group:

Institute of Epidemiology, Helmholtz Zentrum Muenchen - German Research Center for Environmental Health, Neuherberg (Wichmann HE, Heinrich J, Bolte G, Belcredi P, Jacob B, Schoetzau A, Mosetter M, Schindler J, Höhnke A, Franke K, Laubereau B, Sausenthaler S, Thaqi A, Zirngibl A, Zutavern A.); Department of Pediatrics, University of Leipzig (Borte M, Schulz R, Sierig G, Mirow K, Gebauer C, Schulze B, Hainich J); Institute for Clinical Immunology and Transfusion Medicine (Sack U, Emmrich F); Department of Pediatrics, Marien-Hospital, Wesel (von Berg A, Schaaf B, Scholten C, Bollrath C, Groß I, Möllemann M); Department of Human Exposure-Research and Epidemiology, UFZ-Center for Environmental Research Leipzig-Halle (Herbarth O, Diez U, Rehwagen M, Schlink U, Franck U, Jorks A, Röder S); Department of Environmental Immunology, UFZ-center for Environmental Research Leipzig-Halle (Lehmann I, Herberth G, Daegelmann C); Ludwig Maximilians University Munich, Dr. von Hauner Children's Hospital, Department of Infectious Diseases and Immunology (Weiss M, Albert M); Friedrich-Schiller-University Jena, Institute for Clinical Immunology (Fahlbusch B), Institute for Social, Occupational and Environmental Medicine (Bischof W, Koch A)

IUF-Environmental Health Research Institute, Düsseldorf (Krämer U, Link E, Ranft U, Schins R); Clinic and Polyclinic for Child and Adolescent Medicine, University Hospital Rechts der Isar of the Technical University Munich (Bauer CP, Brockow I, Grübl A); Department of Dermatology and Allergy Biederstein, Technical University Munich (Ring J, Grosch J, Weidinger S)

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Stefanie Sausenthaler

Helmholtz Zentrum München
German Research Center for Environmental Health,
Institute of Epidemiology Ingolstaedter Landstr.
1, 85764 Neuherberg, Germany
E-mail: s.sausenthaler@helmholtz-muenchen.de