

Prenatal factors associated with the development of eczema in the first year of life

Kurzius-Spencer M, Halonen M, Lohman IC, Martinez FD, Wright AL. Prenatal factors associated with the development of eczema in the first year of life.

Pediatr Allergy Immunol 2005; 16: 19–26. © 2005 Blackwell Munksgaard

Prenatal factors have been implicated in childhood eczema, but the relationship between maternal cytokine production during pregnancy and infant eczema is unknown. Non-selected women in their third trimester were enrolled in the Tucson Infant Immune Study. Data from three sources were used to define MD-eczema: parent-completed illness questionnaires at age 2, 3, 4, 6 and 9 months regarding physician-seen eczema, parent-completed questionnaires at 12 months regarding physician-diagnosed eczema, and medical record reviews. Blood samples were taken from mothers during their third trimester and from the umbilical cord at birth. Maternal peripheral blood mononuclear cells and cord blood mononuclear cells were stimulated with ConA/PMA, and supernatants were assayed for IFN- γ and IL-4, -5, -10, and -13. Of 364 children, 28% were seen by a physician for eczema by 1 yr of age. After adjustment for potential confounders using logistic regression, the odds for development of eczema in infancy were significantly higher when mothers had active eczema in pregnancy (OR, 2.46, CI 1.0–5.8, $p < 0.042$) and when mothers were in the highest tertile of serum IgE production (OR 2.28, CI 1.2–4.4, $p < 0.013$). Colds in the third trimester were associated with lower odds of eczema (OR 0.32, CI 0.16–0.63, $p < 0.001$). Our findings from this cohort study suggest that *in utero* factors, including maternal IgE, colds, and eczema, may influence the risk of infant eczema.

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Key words: infantile eczema; atopic dermatitis;
maternal–fetal exchange; IgE; IL-10; maternal asthma

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Accepted 14 October 2004

Eczema, a chronic or intermittent skin disease characterized by cutaneous reactivity and pruritus (1), is one of the earliest manifestations of allergic/atopic diseases in children (2–4). Unlike asthma and hay fever, eczema is commonly diagnosed during infancy (2, 5, 6), and is considered a significant risk factor for aeroallergen sensitization at 5 yr (2, 3) and for the subsequent development of asthma (3, 4). Thus, establishing early risk factors for eczema may help elucidate the mechanisms responsible for later allergy, atopy, and asthma.

Because the risk of allergic eczema in children is stronger with maternal, compared with paternal, history of allergy or asthma (5, 7), it has been speculated that *in utero* exposures may influence risk of eczema. Elevated IgE antibodies and

increased Th-2 cytokine expression associated with maternal allergic manifestations may directly influence early immune development (8, 9). Maternal IgE is absorbed by the fetus through swallowing and aspiration of amniotic fluid, and through the skin (10–12). Maternal exposure to allergens during pregnancy, similarly absorbed by the fetus, may trigger the establishment of allergic-type responses in the infant (13, 14). Febrile infections during pregnancy (15), maternal viral and respiratory infections (16), prenatal antibiotic use (16, 17), smoking during pregnancy (18), and low parity (15) have also been associated with an increased risk of childhood eczema, although the underlying mechanisms are unclear.

Whatever their origin, immunologic characteristics in early life also seem to precede and predict

later development of eczema. Allergic disease is associated with immature immune responses at birth, i.e., a general inhibition in cytokine production, at least in children with allergic parents (14, 19–21). More specifically, the development of allergic disease in infancy is associated with reduced secretion by neonates of interferon-gamma (IFN- γ) (22–26) and/or with increased production of IL-13 (27, 28). Finally, while there is conflicting evidence for a relationship between total cord blood IgE and infant eczema (29–33), at least some children with atopic dermatitis show IgE sensitization to food antigens in infancy (34). Hence, immune responses in early life, in particular the capacity to produce cytokines, may either indicate host susceptibility or may alter risk for allergic disease.

The objectives of this study were to assess the risk of prenatal maternal factors and immunologic profiles during pregnancy and at birth on the development of eczema in the first year of life.

Study population and methods

Data for this analysis come from the Tucson Infant Immune Study (IIS), a prospective birth cohort study on the development of the infant immune system and markers for asthma risk. Beginning in 1997, pregnant women in the third trimester of pregnancy were enrolled in the study through the offices of participating obstetricians. A total of 288 of 744 pregnant women refused enrollment in the study (39%). Although the women were non-selected with regard to history of allergies or asthma, 60% of enrollees

reported hay fever and 20% reported asthma, compared with 46% and 11%, respectively, of women who refused enrollment. Data were obtained at enrollment regarding pregnancy illness and smoking. Mothers and fathers both completed a questionnaire after the birth of the child to obtain a history of respiratory symptoms and illness and a more detailed smoking history.

Data regarding eczema came from three sources (Fig. 1). Illness questionnaires were administered by study nurses at 2 months (mean age, 2.1 ± 0.21 months), 3 months (3.1 ± 0.24), 4 months (4.2 ± 0.33), 6 months (6.3 ± 0.42), and 9 months (9.3 ± 0.57) of age, usually at well-visits to the pediatricians. On these questionnaires, parents were asked whether their child had been seen by a physician, usually the child's pediatrician, for eczema since their last questionnaire. The second source of data on eczema was from a questionnaire completed by parents when the child was 1 yr of age (mean age, 1.06 ± 0.11 yr). On this questionnaire, parents were asked whether they had been told by a physician that their child had eczema. The medical records from the pediatric offices, which were reviewed by study nurses after the child's first birthday, were the third source of information. Hence, MD-eczema in the first year of life, as defined in this study, includes a maternal report of a physician consultation and/or a physician diagnosis of eczema, and/or a notation in the child's medical records. All children included in this study were at least 1 yr of age by July 2003 when the analysis was begun. Of

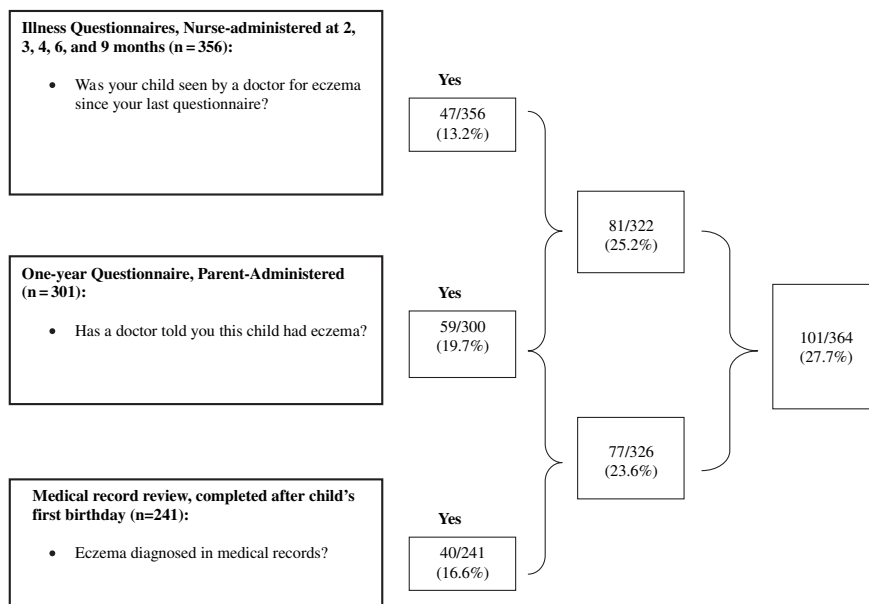


Fig. 1. Sources of data on eczema used and proportion of children with eczema by source.

379 children who met the age requirement, 364 (96.0%) had adequate follow-up data.

Blood samples were obtained from the mothers at enrollment, in about the eighth month of pregnancy (mean weeks gestation: 37.2). Umbilical cord blood was obtained at the time of the delivery. Total serum IgE was assayed in duplicate using the Pharmacia Diagnostics AUTOCAP system (Kalamazoo, MI, USA). Mitogen stimulations were performed on peripheral blood mononuclear cells (PBMCs) from the mothers and cord blood mononuclear cells (CBMCs) that were separated by standard density gradient centrifugation as described previously (35). Cells (2×10^6 /ml) were stimulated with 10 μ g/ml Concanavalin A and 10 ng/ml phorbol myristate acetate (Sigma Chemical Co., St Louis, MO, USA). The supernatant fluids from these cultures and from unstimulated control cells were harvested after 18–24 h and stored at -70°C . Cell culture supernatants were later assayed for IL-4, IL-5, IL-10 and IFN- γ using commercially available ELISA kits (R & D Systems, Minneapolis, MN, USA), and for IL-13 using a kit made by Diaclone Research (Cell Sciences, Inc., Canton, MA, USA).

Statistical methods

There were large numbers of undetectable and missing values for cytokine production and total serum IgE, particularly at birth. Hence these values were either dichotomized at the median or divided into undetectable/low vs. detectable/high. As maternal prenatal total IgE had few undetectable or missing values and was available for a larger number of subjects, it was divided into tertiles for analyses. The relationship between eczema in infancy and various maternal and perinatal risk factors was assessed using Pearson chi-square tests, and relative risk (RR) with 95% confidence intervals (CI) were calculated. Multiple logistic regression models were used to determine the independent effects of different factors associated with infant eczema in this population, and the results are expressed as adjusted odds ratios (adj OR) with 95% CIs. Host characteristics and prenatal factors that were statistically significant or near significant ($p < 0.10$) in bivariate analyses were included in the multivariate model. Different models were compared using the likelihood ratio test. Chi-square test for trend was used to test the association between pregnancy asthma and prenatal IgE. Kappa statistics were calculated to determine how well the different sources of data on eczema agreed.

Results

Table 1 shows the characteristics of the 376 children in the Tucson IIS who were at least 1 yr of age in July 2003. Males and females were equally represented, and non-Hispanic Caucasians made up almost 60% of the population. Over half of the children were first-born, and most of the mothers were in their mid-twenties to early-thirties at the time of enrollment. Over 77% of mothers had at least some college education. About 20% of mothers and 16% of fathers had a history of physician-diagnosed asthma.

Data on MD-eczema were available for 364 children (Fig. 1). The estimated prevalence of eczema in these children ranged from 13.2% using 2–9 month questionnaires ($n = 356$), 16.6% using medical records ($n = 241$), 19.7% using 1-yr questionnaires ($n = 300$), and 27.7% using all three sources of data ($n = 364$). There was substantial concordance between different sources of data on eczema. We observed approximately 85% concordance ($\text{Kappa} = 0.39$) between the two different sources of questionnaire data (2–9 months and 1 yr), 81% concordance ($\text{Kappa} = 0.40$) between the medical records and the 1-yr questionnaire, and 80% concordance ($\text{Kappa} = 0.22$) between the medical records and the 2–9 month questionnaire data. Although these values are significant (all $p < 0.001$), a $\text{Kappa} \leq 0.40$ denotes only marginal reproducibility (36). Combining all three sources of data from the questionnaires and medical records

Table 1. Characteristics of the study population ($n = 364$)

Characteristics	
Male	49.7 (181/364)
With MD-eczema	27.7 (101/364)
Ethnic background	
Anglo	58.4 (209/358)
Anglo/Hispanic	13.1 (47)
Hispanic	13.4 (48)
Other or missing	15.1 (54)
Birth order	
First born	52.2 (189/362)
Second born	29.3 (106)
Later born	18.5 (67)
Maternal age (years), mean ($\pm$ s.d.)	28.7 (± 6.2)
Paternal age (years), mean ($\pm$ s.d.)	30.9 (± 6.8)
Maternal education (years), mean ($\pm$ s.d.)	15.0 (± 2.8)
Paternal education (years), mean ($\pm$ s.d.)	14.8 (± 2.9)
Mothers who reported any problems with pregnancy	24.2 (88/363)
Mothers who smoked, any trimester	12.2 (44/362)
Fathers who smoked during pregnancy	17.3 (63)
Mothers with asthma (ever)*	20.3 (70/345)
Fathers with asthma (ever)*	15.5 (50/323)

Values are % (n).

*Self-reported, physician-diagnosed asthma.

identified a total of 101 children (27.7%) with physician-seen eczema at 1 yr of age.

Table 2 shows the relationship between the child's characteristics and eczema. Male children were significantly more likely to have MD-eczema than females (RR 1.42, CI 1.0–2.0). There were no significant associations, however, between MD-eczema and ethnicity, total IgE at birth, or cytokine production at birth. Children who were second- or later-born tended to have an increased risk of eczema (RR 1.4, CI 0.97–1.9), but the difference was not statistically significant ($p = 0.07$). Maternal age, education, smoking during pregnancy, child's birth weight, gestational age, and season of birth also showed no significant relation to MD-eczema in this population (data not shown). In addition, infant eczema was not significantly associated with maternal history of physician-diagnosed asthma (ever-asthma) (RR 1.33, CI 0.91–1.94), although paternal ever-asthma was associated with reduced eczema (RR 0.46, CI 0.23–0.94) (data not shown).

The prevalence and relative risk of MD-eczema associated with various prenatal factors or 'exposures' are shown in Table 3. The risk of

Table 3. Relative risk of MD-eczema associated with pregnancy conditions and/or exposures

	% (n)	RR (95% CI)	p*
Active asthma during pregnancy			
No	26.0 (86/331)	1.0	
Yes	46.7 (14/30)	1.80 (1.2–2.7)	0.015
Active eczema during pregnancy			
No	26.3 (88/334)	1.0	
Yes	44.8 (13/29)	1.70 (1.1–2.6)	0.033
Active hay fever during pregnancy			
No	25.0 (53/212)	1.0	
Yes	31.8 (48/151)	1.27 (0.91–1.8)	0.155
Any problems with pregnancy			
No	27.3 (75/275)	1.0	
Yes	29.5 (26/88)	1.1 (0.74–1.6)	0.679
Smoking during pregnancy			
No	28.6 (91/318)	1.0	
Yes	22.7 (10/44)	0.79 (0.45–1.4)	0.414
Cold in third trimester			
No	32.2 (87/270)	1.0	
Yes	14.9 (13/87)	0.46 (0.27–0.79)	0.002
Fever during any trimester			
No	29.48 (83/282)	1.0	
Yes	23.0 (17/74)	0.78 (0.50–1.2)	0.271
Antibiotic use during any trimester			
No	29.0 (84/290)	1.0	
Yes	22.9 (16/70)	0.79 (0.50–1.3)	0.306

*p-values based on Pearson chi-square.

Table 2. Relative risk of MD-eczema associated with infant characteristics

	MD-eczema, % (n)	RR (95% CI)	p*
Sex			
Female	23.0 (42/183)	1.0	
Male	32.6 (59/181)	1.4 (1.0–2.0)	0.040
Ethnicity			
Anglo	30.1 (63/209)	1.0	
Anglo/Hispanic	21.3 (10/47)	0.89 (0.79–2.5)†	0.224
Hispanic	25.0 (12/48)	0.93 (0.77–1.1)†	0.480
Other	27.8 (15/54)	0.97 (0.80–1.2)†	0.734
Birth order			
First born	23.8 (45/189)	1.0	
Second or later born	32.4 (56/173)	1.4 (0.97–1.9)	0.070
Cord total IgE			
Undetectable/low	26.9 (39/145)	1.0	
Detectable/high	27.5 (39/142)	1.01 (0.88–1.2)	0.914
Cord IL-4 production			
Low	26.5 (26/98)	1.0	
High	32.7 (33/101)	1.1 (0.91–1.3)	0.343
Cord IL-5 production			
Undetectable	32.4 (33/102)	1.0	
Detectable	26.0 (13/50)	0.91 (0.74–1.1)	0.423
Cord IL-10 production			
Low	29.5 (31/105)	1.0	
High	29.5 (28/95)	1.0 (0.84–1.2)	0.994
Cord IL-13 production			
Low	25.2 (26/103)	1.0	
High	32.7 (32/98)	1.1 (0.93–1.3)	0.246
Cord IFN- γ production			
Low	27.6 (29/105)	1.0	
High	31.9 (29/91)	1.1 (0.88–1.3)	0.516

*p-values based on Pearson chi-square.

†RR and p-values based in comparison with Anglos.

eczema was significantly elevated in children whose mothers had active asthma during pregnancy (RR 1.8, CI 1.2–2.7). This is in contrast to the lack of association between maternal 'ever-asthma' and eczema in infancy noted above. Risk of eczema was also significantly higher in children whose mothers had eczema during pregnancy (RR 1.70, CI 1.1–2.6). Type of delivery (vaginal vs. Caesarian), season of birth, problems with delivery, maternal fever during pregnancy, and maternal antibiotic use during pregnancy showed no relationship with infant eczema.

However, mothers who reported a cold in the third trimester of pregnancy (25% of mothers) had children who were significantly less likely to develop eczema than children whose mothers did not have colds (RR 0.50, CI 0.27–0.79). There was no significant relationship between a third trimester cold and maternal asthma, eczema, hay fever, total IgE, or cytokine production during pregnancy.

Fig. 2 shows the relative risk associated with aspects of the maternal immunologic profile during pregnancy. Children whose mothers were in the highest tertile of IgE were significantly more likely to develop eczema in infancy (RR 1.25, CI 1.05–1.49). High IL10 was associated with a reduction in eczema of borderline statistical significance (RR 0.59, CI 0.34–1.0).

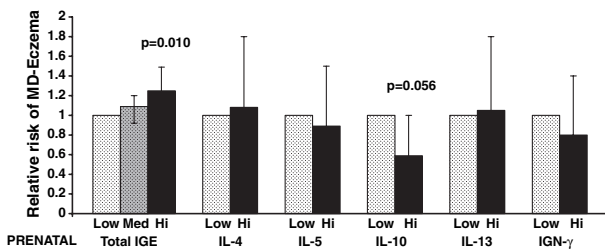


Fig. 2. Risk of MD-eczema by prenatal maternal IgE and cytokine production in the third trimester.

Maternal prenatal production of other cytokines showed no relationship with infant eczema.

Multivariate logistic regression was used to assess the independent effects of the various host and prenatal risk factors on the development of infant eczema (Table 4). All factors that approached significance in bivariate analyses (sex, birth order, eczema during pregnancy, asthma during pregnancy, paternal asthma, maternal 'cold' in the third trimester of pregnancy, maternal prenatal total IgE, and maternal prenatal IL-10 production) were included in the model. Maternal cold in the third trimester of pregnancy (adj OR 0.316, CI 0.16–0.63), high maternal prenatal IgE (adj OR 2.28, CI 1.2–4.4), maternal eczema during pregnancy (adj OR 2.46, CI 1.0–5.8), and paternal asthma (adj OR 0.385, CI 0.16–0.93) were significant predictors in the best-fitting model. Asthma during pregnancy was not a significant predictor of MD-eczema ($p = 0.126$) after adjustment for other factors, perhaps due to its highly significant association with maternal prenatal IgE levels (trend chi-square, $p = 0.000004$). Sex, birth order, and maternal prenatal IL-10 production were also not statistically significant predictors of MD-eczema in the best-fitting model.

To test whether different methods of defining eczema altered the risk profile substantially, we ran multivariate logistic regression analyses on each source of eczema data. Parent-reported physician-diagnosed eczema from the 12-month

questionnaire yielded similar results to those reported in Table 4. However, paternal asthma was not significant in the model ($p = 0.182$). When analyses were limited to parent-reported, physician-seen eczema in the 2–9-month questionnaires, only pregnancy colds and high prenatal IgE were significant predictors. In contrast, none of the potential risk factors considered showed a statistically significant relationship with eczema defined only from the medical records.

Discussion

This study shows an association between maternal allergic disease and immunologic characteristics during pregnancy with risk of developing eczema in the first year of life. Infants of mothers who had eczema or high total serum IgE levels during pregnancy had a significantly increased risk of eczema in their first year. Although these relations may be in part genetic, active asthma during pregnancy was associated with a significantly increased risk of MD-eczema in bivariate analyses, whereas a maternal history of asthma (prior to the pregnancy) was not. It may be that women with asthma symptoms during pregnancy have more severe asthma than those without, and this may be reflected in the highly significant association between pregnancy asthma and maternal prenatal IgE. In addition, a maternal cold in the last trimester was associated with reduced risk of eczema in infancy. These results suggest that differences in the *in utero* environment of mothers with eczema or asthma symptoms in pregnancy may be critical factors in the development of infant eczema.

We also found evidence of an apparent protective effect of paternal asthma. We cannot currently explain this finding, but it may enhance the argument against genetic risk for the development of eczema, thus emphasizing the potential role of *in utero* exposures.

Several researchers have postulated that the fetus is exposed to a significant amount of IgE through swallowing, aspiration, or absorption through the skin (10, 12, 37). Amniotic fluid, from as early as 16–18 wk gestation, contains intact IgE at levels that are highly positively correlated with maternal circulating levels (12). Hence, mothers with high IgE may expose the fetus to higher levels of IgE than mothers with lower IgE. The strong association between active asthma symptoms during pregnancy and high prenatal IgE levels suggests that exposure to high IgE prenatally may be one of the mechanisms by which eczema risk is increased in children of asthmatic mothers. How prenatal exposure to

Table 4. Multivariate logistic regression model of MD-eczema

	Adjusted odds ratio*	95% CI	p
Maternal cold during third trimester	0.316	0.16–0.63	0.001
Maternal prenatal IgE (IU/ml)			
Low (0.10–14.55)	1.0		
Medium (14.6–60.85)	1.18	0.62–2.2	0.615
High (60.9–865)	2.28	1.2–4.4	0.013
Paternal asthma	0.385	0.16–0.93	0.035
Maternal eczema during pregnancy	2.46	1.0–5.8	0.042

*Adjusted for sex, birth order, maternal asthma during pregnancy, and maternal prenatal IL-10 production.

increased IgE might influence later allergic susceptibility is unclear, but, in our study, prenatal maternal and cord total serum IgE concentrations were significantly correlated (Kendall's tau, $p = 0.0002$). We found, however, that the relationship between prenatal IgE and infant eczema was independent of both cord IgE and pregnancy eczema. Further, although others have reported an association between high cord IgE and subsequent eczema (31), no significant relation was found in the current study.

Our results also implicate a protective effect of certain other *in utero* exposures. A maternal cold, but only during the third trimester of pregnancy, was independently associated with decreased risk of eczema in the child ($p < 0.001$), even after controlling for host and prenatal factors that might cause confounding. This finding suggests that a third trimester cold might modify the *in utero* environment in such a way as to create a long-term impact on the child, although the mechanisms for such an effect remain to be determined. In contrast, other studies have reported that *in utero* exposure to maternal infections is associated with increased risk for allergic disease, including eczema, in early childhood. Specifically, conjunctivitis, *Candida*, bacterial infections, and febrile infections in the first trimester have been associated with a significantly increased risk of eczema, and maternal respiratory and viral infections were associated with an increased risk of asthma (15, 16). Differences in study design, assessment of maternal infection, and definitions of eczema may account for the conflicting results.

There has been speculation that the *in utero* immunologic environment may influence allergic susceptibility in infancy (8, 9, 13, 14). This study shows a relationship between prenatal cytokine production in maternal PBMCs and infant eczema. We found a decreased risk of eczema associated with high mitogen-stimulated IL-10 production. IL-10 is associated with the down-regulation of production of other cytokines (especially IFN- γ) and with the differentiation of Th2-type cells (8, 20). However, in the present study, maternal prenatal production of IL-10 was positively correlated with the production of all prenatal cytokines measured, and no association was noted between maternal prenatal IL-10 production and the cytokines measured in mitogen-stimulated CBMCs. IL-10 production, however, was not a significant predictor independent of other maternal factors in the best-fitting logistic model.

Estimates of the prevalence of eczema are influenced by how the condition is defined (7).

One UK study reported a prevalence of 14% by specific UK diagnostic criteria, 31% by maternal report of a physician's diagnosis of eczema, and 45% according to maternal opinion. Comparable estimates of prevalence of eczema in the IIS were 16.6% by medical records, 25.2% by maternal report of MD-diagnosed eczema, and 34.1% by maternal opinion, with or without physician confirmation. No effort was made to assess what criteria the pediatricians used in the determination of eczema, or to standardize their labeling practices.

However eczema is defined, there is the potential for bias because of problems with the ascertainment of cases and recall. Although there was 81% concordance in MD-diagnosed eczema between the medical records and 1-yr parent questionnaires, only 58% of cases identified through the medical records were also reported on the questionnaire, and only 46% of cases identified on the questionnaire were also noted in the medical records. The medical record reviews likely underestimated eczema, as some of the children may have been diagnosed by a physician outside of the medical practices used in this study. It is clear, as well, that physicians may be more likely to diagnose eczema if they know a family history of allergy or asthma exists. In addition, mothers who are themselves allergic may be more likely to assume their child's rash is eczema and may differ in their inclination to consult a physician about it. Hence, misclassification errors could have influenced our results. Nevertheless, the focus of the current analysis was on prenatal risk factors, and the risk factors identified for the most inclusive definition of eczema were also significant for cases identified through questionnaire data only.

There also appear to be temporal trends influencing the reported prevalence in different studies. For example, among children born between 1980 and 1984 in the Tucson Children's Respiratory Study, the overall prevalence of eczema in the first year of life, based on parent reports of MD-confirmed eczema on a 1-yr questionnaire, was only 8.2% (31). In the present study, composed of children born in Tucson between 1996 and 2002, response to a similar question at 1 yr yielded a substantially higher period prevalence of 19.7% for physician-diagnosed eczema. A recent study in the UK reported a sharp increase in atopic dermatitis between the 1970s and 1990s, with prevalence in the early 1990s exceeding 30% by age 3 (38).

In conclusion, our findings suggest that the risk of developing eczema in infancy may be altered by *in utero* exposures, including maternal

allergic conditions, maternal immunologic profiles, and infections during pregnancy.

Acknowledgments

We thank Stefano Guerra, Maria Cristina Minervini, and Catharine Holberg for useful discussions on the epidemiology and immunology of eczema. This research was funded by NIH A142268.

References

- LEUNG DY. Pathogenesis of atopic dermatitis. *J Allergy Clin Immunol* 1999; 104: S99–108.
- BERGMANN RL, EDENHARTER G, BERGMANN KE, et al. Atopic dermatitis in early infancy predicts allergic airway disease at 5 years. *Clin Exp Allergy* 1998; 28: 965–70.
- BECK LA, LEUNG DY. Allergen sensitization through the skin induces systemic allergic responses. *J Allergy Clin Immunol* 2000; 106(Suppl. 5): S258–63.
- ILLI S, von MUTIUS E, LAU S, et al. The pattern of atopic sensitization is associated with the development of asthma in childhood. *J Allergy Clin Immunol* 2001; 108: 709–14.
- RUIZ RG, KEMENY DM, PRICE JF. Higher risk of infantile atopic dermatitis from maternal atopy than from paternal atopy. *Clin Exp Allergy* 1992; 22: 762–6.
- BELTRANI VS. The clinical spectrum of atopic dermatitis (review). *J Allergy Clin Immunol* 1999; 104: S87–98.
- HARRIS JM, CULLINAN P, WILLIAMS HC, et al. Environmental associations with eczema in early life. *Br J Dermatol* 2001; 144: 795–802.
- WARNER JA, JONES CA, JONES AC, MILES EA, FRANCIS T, WARNER JO. Immune responses during pregnancy and the development of allergic disease. *Pediatr Allergy Immunol* 1997; 8(Suppl. 10): 5–10.
- WARNER JA, JONES CA, WILLIAMS TJ, WARNER JO. Maternal programming in asthma and allergy. *Clin Exp Allergy* 1998; 28(Suppl. 5): 35–8; discussion 50–1.
- JONES CA, WARNER JA, WARNER JO. Fetal swallowing of IgE. *Lancet* 1998; 351: 1859.
- WARNER JO, WARNER JA. Early life events in allergic sensitisation. *Br Med Bull* 2000; 56: 883–93.
- THORNTON CA, HOLLOWAY JA, POPPLEWELL EJ, SHUTE JK, BOUGHTON J, WARNER JO. Fetal exposure to intact immunoglobulin E occurs via the gastrointestinal tract. *Clin Exp Allergy* 2003; 33: 306–11.
- WARNER JA, JONES CA, JONES AC, WARNER JO. Prenatal origins of allergic disease. *J Allergy Clin Immunol* 2000; 105: S493–8.
- WILLIAMS TJ, JONES CA, MILES EA, WARNER JO, WARNER JA. Fetal and neonatal IL-13 production during pregnancy and at birth and subsequent development of atopic symptoms. *J Allergy Clin Immunol* 2000; 105: 951–9.
- XU B, JARVELIN MR, PEKKANEN J. Prenatal factors and occurrence of rhinitis and eczema among offspring. *Allergy* 1999; 54: 829–36.
- McKEEVER TM, LEWIS SA, SMITH C, HUBBARD R. The importance of prenatal exposures on the development of allergic disease: a birth cohort study using the West Midlands General Practice Database. *Am J Respir Crit Care Med* 2002; 166: 827–32.
- McKEEVER TM, LEWIS SA, SMITH C, et al. Early exposure to infections and antibiotics and the incidence of allergic disease: a birth cohort study with the West Midlands General Practice Research Database. *J Allergy Clin Immunol* 2002; 109: 43–50.
- SCHAFER T, DIRSCHEDL P, KUNZ B, RING J, UBERLA K. Maternal smoking during pregnancy and lactation increases the risk for atopic eczema in the offspring. *J Am Acad Dermatol* 1997; 36: 550–6.
- PRESCOTT SL, MACAUBAS C, SMALLACOMBE T, et al. Reciprocal age-related patterns of allergen-specific T-cell immunity in normal vs. atopic infants. *Clin Exp Allergy* 1998; 28(Suppl. 5): 39–44; discussion 50–1.
- WARNER JO, JONES CA, KILBURN SA, VANCE GH, WARNER JA. Pre-natal sensitization in humans. *Pediatr Allergy Immunol* 2000; 11(Suppl. 13): 6–8.
- JONES CA, HOLLOWAY JA, WARNER JO. Fetal immune responsiveness and routes of allergic sensitization. *Pediatr Allergy Immunol* 2002; 13(Suppl. 15): 19–22.
- HOLT PG, CLOUGH JB, HOLT BJ, et al. Genetic 'risk' for atopy is associated with delayed postnatal maturation of T-cell competence. *Clin Exp Allergy* 1992; 22: 1093–9.
- RINAS U, HORNE G, WAHN V. Interferon-gamma production by cord-blood mononuclear cells is reduced in newborns with a family history of atopic disease and is independent from cord blood IgE-levels. *Pediatr Allergy Immunol* 1993; 4: 60–4.
- TANG ML, KEMP AS, THORBURN J, HILL DJ. Reduced interferon-gamma secretion in neonates and subsequent atopy. *Lancet* 1994; 344: 983–5.
- WARNER JA, MILES EA, JONES AC, QUINT DJ, COLWELL BM, WARNER JO. Is deficiency of interferon gamma production by allergen triggered cord blood cells a predictor of atopic eczema? *Clin Exp Allergy* 1994; 24: 423–30.
- KONDO N, KOBAYASHI Y, SHINODA S, et al. Reduced interferon gamma production by antigen-stimulated cord blood mononuclear cells is a risk factor of allergic disorders – 6-year follow-up study. *Clin Exp Allergy* 1998; 28: 1340–4.
- KOPP MV, ZEHLE C, PICHLER J, et al. Allergen-specific T cell reactivity in cord blood: the influence of maternal cytokine production. *Clin Exp Allergy* 2001; 31: 1536–43.
- OHSHIMA Y, YASUTOMI M, OMATA N, et al. Dysregulation of IL-13 production by cord blood CD4+ T cells is associated with the subsequent development of atopic disease in infants. *Pediatr Res* 2002; 51: 195–200.
- MAGNUSSON CG. Cord serum IgE in relation to family history and as predictor of atopic disease in early infancy. *Allergy* 1988; 43: 241–51.
- RUIZ RG, RICHARDS D, KEMENY DM, PRICE JF. Neonatal IgE: a poor screen for atopic disease. *Clin Exp Allergy* 1991; 21: 467–72.
- HALONEN M, STERN D, TAUSSIG LM, WRIGHT A, RAY CG, MARTINEZ FD. The predictive relationship between serum IgE levels at birth and subsequent incidences of lower respiratory illnesses and eczema in infants. *Am Rev Respir Dis* 1992; 146: 866–70.
- BJERKE T, HEDEGAARD M, HENRIKSEN TB, NIELSEN BW, SCHIOTZ PO. Several genetic and environmental factors influence cord blood IgE concentration. *Pediatr Allergy Immunol* 1994; 5: 88–94.
- EDENHARTER G, BERGMANN RL, BERGMANN KE, et al. Cord blood-IgE as risk factor and predictor for atopic diseases. *Clin Exp Allergy* 1998; 28: 671–8.
- HEINE RG, HOSKING CS, HILL DJ. Risk factors for atopic dermatitis in infancy: are we closer to effective primary atopy prevention? *Clin Exp Allergy* 2003; 33: 1327–9.

35. KRISHNAN S, CRAVEN M, WELLIVER R, AHMAD N, HALONEN M. Differences in innate and adaptive immune responses to respiratory syncytial virus in adult and newborn mononuclear cells. *J Infect Dis* 2003; 188: 433–9.
36. LANDIS JR, KOCH GG. The measurement of observer agreement for categorical data. *Biometrics* 1977; 33: 159–74.
37. WARNER JA, WARNER JO. Early life events in allergic sensitisation. *Br Med Bull* 2000; 56: 883–93.
38. WADONDA-KABONDO N, STERNE JA, GOLDING J, KENNEDY CT, ARCHER CB, DUNNILL MG. A prospective study of the prevalence and incidence of atopic dermatitis in children aged 0–42 months. *Br J Dermatol* 2003; 149: 1023–8.