

Risk factors for atopic dermatitis in infants at high risk of allergy: the PIAMA study

M. Kerkhof*, L. P. Koopman†, R. T. van Strien‡, A. Wijga§, H. A. Smit§, R. C. Aalberse¶, H. J. Neijens†, B. Brunekreef‡, D. S. Postma||, J. Gerritsen|| and the PIAMA study group**

*Department of Epidemiology and Statistics, University of Groningen, Groningen, The Netherlands, †Department of Paediatrics, Sophia Children's Hospital, Rotterdam, The Netherlands, ‡IRAS, Utrecht University, The Netherlands, §National Institute of Public Health and the Environment, Bilthoven, The Netherlands, ¶Central Laboratory for Blood Transfusion, Amsterdam, The Netherlands, ||Departments of Paediatric and Respiratory Medicine, University Hospital Groningen, The Netherlands, and **The PIAMA study is a combined effort of the Utrecht University (Prof. B. Brunekreef), the Sophia Children's Hospital of the Rotterdam Medical School (Prof. H. J. Neijens and Prof. J. C. de Jongste), the Beatrix Children's Hospital of University Hospital Groningen (Dr J. Gerritsen, Prof. D. S. Postma), the Central Laboratory of the Red Cross Blood Transfusion Service (Prof. R. C. Aalberse) and the National Institute of Public Health and the Environment (Dr H. A. Smit).

Summary

Background It has been suggested that the period immediately after birth is a sensitive period for the development of atopic disease.

Objective We investigated whether birth characteristics and environmental factors are associated with the development of atopic dermatitis in the first year of life.

Methods Seventy-six children with and 228 without atopic dermatitis, all children of mothers with respiratory allergy or asthma (PIAMA birth cohort study) were included in the study. Atopic dermatitis was defined as a positive history of an itchy skin condition with at least two of the following characteristics: visible dermatitis, history of outer arms/leg involvement, or general dry skin. Multiple logistic regression analysis was performed to study the independent effects of various risk factors.

Results A birth weight ≥ 4000 g compared to 3000–4000 g was a significant risk factor for atopic dermatitis (odds ratio (OR) = 2.4; 95% CI: 1.1–5.1) as was day care attendance (OR = 2.9; 95% CI: 1.5–5.9). Exclusive breastfeeding in the first 3 months was negatively associated with atopic dermatitis (OR = 0.6; 95% CI: 0.3–1.2), especially with visible dermatitis (OR = 0.4; 95% CI: 0.2–1.0). Gender, gestational age, the presence of siblings or pets, and parental smoking were not significantly associated with atopic dermatitis.

Conclusion This study shows that a high birth weight and day care attendance increase the risk of atopic dermatitis in the first year of life, while exclusive breastfeeding is a protective factor when dermatitis is found on inspection.

Keywords atopic dermatitis, birth weight, breastfeeding, day care attendance, epidemiology, hygiene hypothesis, infants, risk factors

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Introduction

Atopic dermatitis is a common disease that starts primarily in infancy and childhood, with the peak age of onset before 3 months [1, 2]. It can be a distressing condition, both to the child and its parents, influencing the infant's well-being and social and educational development. Like other atopic diseases such as asthma and hayfever, the prevalence of atopic dermatitis has increased substantially over the past 30 years for reasons largely unknown [3]. There is growing evidence that the period just before and after birth is a susceptible time window for the development of atopic diseases. It has been suggested that infants who develop

atopic disease have an abnormally slow post-natal maturation of T cell function, in particular Th1-associated functions [4]. Therefore, it seems important to study as to which birth characteristics and environmental factors operating *in utero* and in early infancy play a role in the early development of atopic dermatitis.

So far, only a few studies have investigated this specifically. Factors increasing the risk to develop atopic dermatitis are a relatively high birth weight and birth after term [5], whereas a large number of siblings [6–8] and breastfeeding [9] appear to decrease the risk of atopic dermatitis. Other factors like day care attendance and exposure to pets have been associated with a decreased risk of atopy, yet atopic dermatitis has so far hardly been investigated [10, 11].

In 1996, a birth cohort study on *Prevention and Incidence of Asthma and Mite Allergy (PIAMA)* was initiated in which 1327 infants of mothers with asthma or respiratory allergy

Correspondence: M. Kerkhof, Department of Epidemiology and Statistics, University of Groningen, PO Box 196, 9700 AD Groningen, The Netherlands. E-mail: m.kerkhof@med.rug.nl

and 2819 infants of mothers without these disorders are being followed from birth until age 8. We investigated whether birth characteristics and environmental factors are associated with the development of atopic dermatitis in the first year of life using data from 708 children who underwent a physical examination when they reached 12 months of age.

Methods

Subjects

The PIAMA study is a prospective birth cohort study on *Prevention and Incidence of Asthma and Mite Allergy*. The participating children were born between May 1996 and December 1997 in three regions of the Netherlands. They were selected using a validated screening questionnaire with questions on asthma and respiratory allergies [12] administered to the mother at her first visit to the midwife. The midwives were requested to ask every new pregnant woman to fill in the screening questionnaire. A total of 10 232 pregnant women completed the questionnaire and 2949 (29%) of them reported asthma or respiratory allergy and were defined as 'allergic'. 2015 allergic women were invited to participate in the intervention part of the PIAMA study, a double-blind placebo-controlled study on the primary preventive effect of the use of mattress covers on the development of asthma or allergy. Seven hundred and sixty-three allergic and a random sample of 5084 non-allergic women were invited to take part in the natural history part of the PIAMA study. Only children from the intervention part underwent a physical examination on atopic dermatitis when they were 12 months of age. Therefore, the current analyses were confined to this part of the study. Informed consent for the intervention part was obtained from 855 allergic mothers during pregnancy. Seven hundred and eight of their children underwent a physical examination on atopic dermatitis when they were 12 months of age.

Definitions

The parents completed questionnaires, which were sent by mail when the child was 3 and 12 months of age. Data on gender, birth weight, gestational age, maternal age, and the presence of siblings were obtained from the 3-month questionnaire; data on exposure to cigarette smoke and pets were obtained from both the 3- and 12-month questionnaire. Day care attendance (≥ 4 h a week) was assessed from the 12-month questionnaire. From 70 cases of atopic dermatitis and 204 controls, information was obtained about the age (in weeks) at first introduction of formula feeding (parents were asked to record first introduction of specified food on a 'food card' distributed at 3 months and collected at one year of age). From six cases and 24 controls included in the analyses, this information was missing and could be deduced from the 3-month questions about the current type of feeding and the duration of breastfeeding, taking into account the age in days at which the 3-month questionnaire was completed. In six of the 190 subjects the information from the food card and the 3-month questionnaire was inconsistent. In these cases, the 3-month questions were applied.

Cases of atopic dermatitis were defined according to a modification of the UK Working Party's Diagnostic Criteria for Atopic Dermatitis [13] suggested by Dr Williams [14]. This modification is mandatory for infants, since two of the criteria, i.e. early onset and the presence of other atopic diseases, are less useful in young children. Therefore, early onset was omitted and a personal history of atopic disease was replaced by family history of atopic disease. The latter criterium was fulfilled by all cases, since all children were from mothers with atopic disease. The physical examination was extended to the cheeks and outer aspects of the limbs, areas that are frequently affected in infants with atopic dermatitis.

Cases of atopic dermatitis were defined as children who, at physical examination at 12 months of age, had a positive history of an itchy skin condition plus at least two of the following:

- a history of involvement of outer arms or legs,
- a history of a general dry skin,
- the presence of visible dermatitis on flexural sites, cheeks, or outer aspects of the limbs.

Controls were all children who did not show any of the criteria listed above and of whom the parents also denied the presence ever of 'an itchy rash, which was coming and going' and 'eczema ever' in the 12-month questionnaire. These questions used to define controls were translated from the ISAAC questionnaire [15].

Analysis

Logistic regression analysis was performed to estimate odds ratios (OR) and 95% confidence interval (CI) of the association between atopic dermatitis and risk factors, adjusted for other risk factors, region, and education level of the parents.

The following risk factors were studied: birth weight, gestational age, age of the parents, exclusive breastfeeding in the first 13 weeks, presence of (older) siblings, day care attendance, cigarette smoking of the parents, and the presence of cats and/or dogs in the home. Birth weight was divided into three categories (≤ 3000 , 3001–4000, and > 4000 g) with 3001–4000 grams as a reference category that approximately corresponds to the interval of one standard deviation around the mean (2995–4055). Gestational age was divided into four categories with 40 weeks ± 7 days as the reference category and premature (< 37 weeks), 37 or 38 weeks, and more than 41 weeks as the other categories. Age of the mother was divided into quartiles: ≤ 28 , 29–30, 31–33, and > 33 years at the time of childbirth with the first quartile as reference.

Results

At 12 months of age, 99 children fulfilled the criteria for atopic dermatitis, i.e. 14% of the 708 children who were physically examined. The 76 cases of whom a completed questionnaire was obtained at three and 12 months of age were included in the analyses. Fifty-five (72%) of these children had visible dermatitis, 36 (47%) on the cheeks or outer aspect of the limbs, 68 (90%) had a history of

involvement of the outer arms or legs and 65 (87%) a history of a dry skin.

Although mean birth weight was not significantly higher in cases than in controls ($P = 0.10$), relatively heavy newborns of more than 4000 g were over-represented among cases (28% vs. 14%, $P = 0.01$). Cases were more frequently attending day care in the first year of life than controls (37% vs. 22%, $P = 0.01$). Univariately, no other significant differences in the prevalence of risk factors were found between cases with atopic dermatitis and controls (Table 1).

Results from logistic regression analysis after adjustment for the other factors showed that the risk of atopic dermatitis was significantly higher for infants who had a birth weight of at least 4000 g compared to the reference group weighing 3000–4000 g (OR = 2.4; 95% CI: 1.1–5.1) (Table 1). The negative association between exclusive breastfeeding and atopic dermatitis was not significant in the multivariate analysis ($P = 0.15$) (Table 1). There was no obvious dose-response relationship between the duration of breastfeeding and the presence of atopic dermatitis at the age of 12 months (Fig. 1). Day care attendance was a significant risk factor of atopic dermatitis (OR = 2.9; 95% CI: 1.5–5.9). Only for children who attended day care for less than 15 h a week, the probability of atopic dermatitis increased significantly with the number of hours (Fig. 2).

There was a borderline significant negative association between the presence of a cat in the household and atopic

dermatitis (OR = 0.6; 95% CI: 0.3–1.1, $P = 0.08$), while the presence of a dog had no association with atopic dermatitis. Gender of the infant, gestational age, maternal age, and cigarette smoking of the parents were not associated with atopic dermatitis in the first year of life. Additional adjustment for the type of intervention did not change these associations.

Since day care attendance usually starts at 3 months of age in the Netherlands, we also performed the analysis separately for cases whose parents reported the presence of 'an itchy rash which was coming and going' in the 3-month questionnaire and for cases whose parents denied this. When only including 27 cases whose parents reported an itchy rash at 3 months, the OR was significant for both day care (OR = 5.6; 95% CI: 1.8–17.9) and the presence of siblings (OR = 4.7; 95% CI: 1.5–14.6) (Table 2). Results from an analysis with 49 cases whose parents denied an itchy rash at 3 months showed no significant associations for day care (OR = 2.1; 95% CI: 0.9–4.8) and for the presence of siblings (OR = 1.0; 95% CI: 0.5–2.0) (Table 2).

Since 28% of the children defined as having atopic dermatitis did not show visible dermatitis at the moment of physical examination, we repeated the analyses after excluding these 21 cases. We did not find relevant changes in the associations, except for breastfeeding, which was shown to be a significant protective factor (OR = 0.4; 95% CI: 0.2–1.0) in the restricted sample (Table 1). The negative association for

Table 1. Prevalence of risk factors among children with and without atopic dermatitis (AD) and odds ratio (OR) and 95% confidence interval of the association between risk factors and atopic dermatitis ($n = 304$)

Risk factors	% (n) among		Adjusted* OR (95% CI)	
	AD+ ($n = 76$)	AD- ($n = 228$)	$n = 304$	Only cases with visible dermatitis $n = 283$
Male gender	53 (40)	49 (111)	1.1 (0.6–2.0)	1.3 (0.7–2.6)
Birth weight				
< 3000 g	15 (11)	17 (38)	1.1 (0.4–2.7)	1.7 (0.6–4.5)
3000–3999 g	58 (44)	69 (158)	Reference	Reference
> 4000 g	28 (21)†	14 (32)†	2.4 (1.1–5.1)†	2.5 (1.0–6.0)†
Gestational age				
< 37 weeks	5 (4)	5 (11)	1.9 (0.5–7.9)	2.0 (0.4–10.4)
37, 38 weeks	15 (11)	16 (36)	1.6 (0.7–3.8)	1.7 (0.6–4.6)
39, 40 weeks	57 (43)	62 (141)	Reference	Reference
> 41 weeks	24 (18)	18 (40)	1.4 (0.7–3.0)	1.7 (0.7–4.1)
Age of mother in years				
≤ 28	32 (24)	36 (83)	Reference	Reference
29–30	24 (18)	17 (38)	1.3 (0.6–2.9)	2.1 (0.8–5.5)
31–33	32 (24)	24 (54)	1.0 (0.5–2.2)	1.6 (0.6–4.0)
> 33	13 (10)	23 (53)	0.4 (0.1–1.1)	0.6 (0.2–1.9)
Exclusive breastfeeding first				
13 weeks	26 (20)	36 (81)	0.6 (0.3–1.2)	0.4 (0.2–1.0)†
Presence of siblings	51 (39)	47 (108)	1.5 (0.8–2.9)	1.9 (0.9–3.8)
Day-care attendance	37 (28)†	22 (49)†	2.9 (1.5–5.9)†	2.7 (1.2–6.0)†
Cigarette-smoking mother	15 (11)	10 (22)	2.1 (0.8–5.6)	2.3 (0.8–6.6)
Cigarette-smoking father	17 (13)	18 (42)	0.7 (0.3–1.7)	0.7 (0.3–1.8)
Cat in the house	28 (21)	34 (77)	0.6 (0.3–1.1)	0.5 (0.2–1.1)
Dog in the house	13 (10)	14 (32)	1.0 (0.4–2.4)	1.1 (0.4–3.1)

*Adjusted for other variables, region, and education level of parents. † $P < 0.05$. CI = confidence interval.

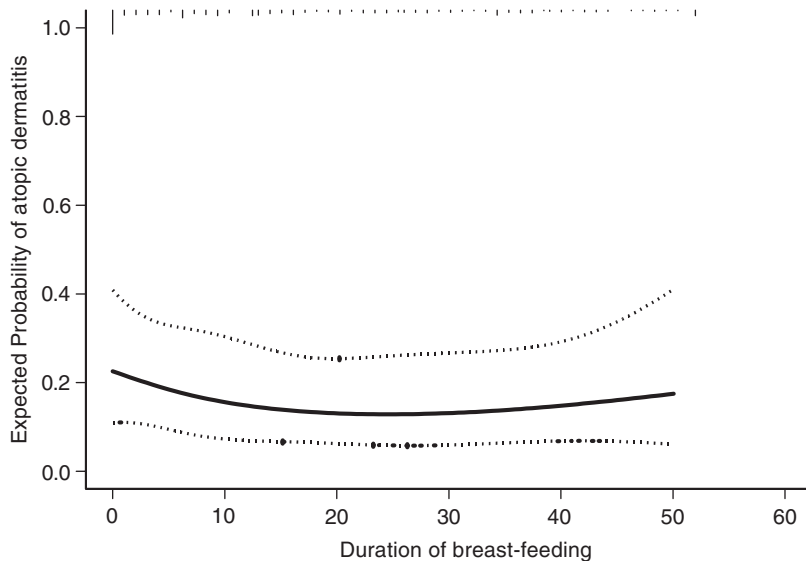


Fig. 1. Probability with 95% CI of atopic dermatitis by the duration of breastfeeding in weeks ($n = 274$) (plotted from the Restricted Cubic Spline function).

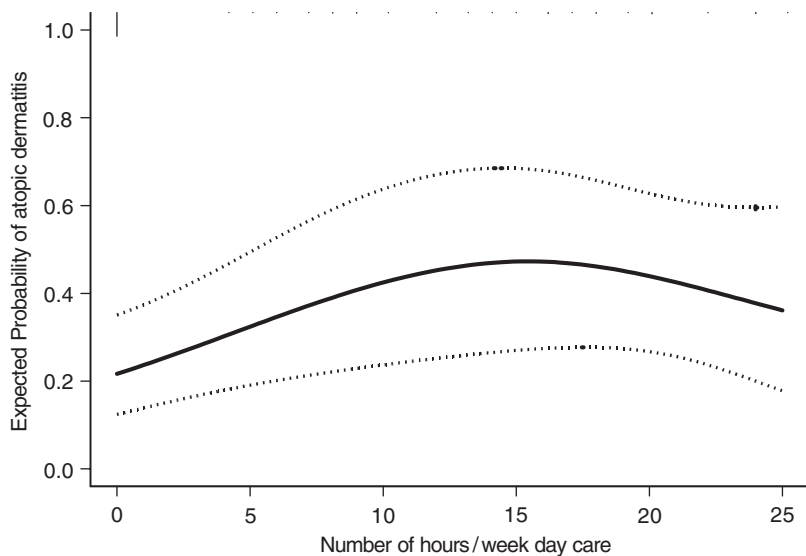


Fig. 2. Probability with 95% CI of atopic dermatitis by the number of hours a week of day care ($n = 304$) (plotted from the Restricted Cubic Spline function).

exclusive breastfeeding in the first 3 months was also found for 34 cases whose parents denied symptoms of an itchy rash at 3 months of age (OR = 0.4; 95% CI: 0.2–1.1).

Discussion

We show in a cohort of 708 children from mothers who had asthma or respiratory allergy that 14% of these children had atopic dermatitis at 12 months of age. Risk factors for atopic dermatitis in the first year of life were a high birth weight and day care attendance, while exclusive breastfeeding in the first 3 months of life was a protective factor.

There are some problems in identifying atopic dermatitis in the first year of life. Absence of any reliable laboratory investigation to confirm the diagnosis makes it difficult to differentiate it from other types of eczema like seborrheic

dermatitis, especially in infancy. The most important features that discriminate atopic dermatitis from seborrheic dermatitis are a history of scratching or rubbing, the typical location on flexural sites, cheeks and outer aspects of the limbs, and a positive family history of atopic disease [16]. All these three features were present in children with atopic dermatitis and absent in the controls of our study, except for a positive family history that by design was present in all subjects. Since 28% of children with atopic dermatitis had no visible dermatitis and some of these infants may have been misclassified, we examined whether exclusion of these cases affected the results. High birth weight and day care attendance remained significant risk factors for atopic dermatitis, whereas exclusive breastfeeding in the first 3 months reached significance as a protective factor.

The increased risk of atopic dermatitis for infants with a high birth weight is consistent with the findings of Olesen et

Table 2. Odds ratios (OR) and 95% confidence interval of the association between risk factors and atopic dermatitis for cases with and without symptoms at 3 months

Risk factors	OR* (95% CI)	
	Cases (<i>n</i> = 27) symptoms + 3 months	Cases (<i>n</i> = 49) symptoms – 3 months
Male gender	1.7 (0.6–4.5)	0.8 (0.4–1.6)
Birth weight		
< 3000 g	0.8 (0.1–5.4)	1.2 (0.4–3.2)
3000–3999 g	Reference	Reference
> 4000 g	3.5 (1.1–11.4)†	1.8 (0.7–4.7)
Gestational age		
< 37 weeks	7.7 (0.6–92.6)	1.0 (0.2–5.9)
37, 38 weeks	0.9 (0.1–5.9)	2.0 (0.8–5.2)
39, 40 weeks	Reference	Reference
> 41 weeks	1.5 (0.5–4.9)	1.7 (0.7–4.1)
Age of mother in years		
≤ 28	Reference	Reference
29–30	1.4 (0.3–5.6)	1.3 (0.5–3.4)
31–33	1.2 (0.3–4.2)	0.8 (0.3–2.1)
> 33	0.2 (0.0–1.4)	0.5 (0.2–1.6)
Exclusive breastfeeding		
first 13 weeks	0.5 (0.2–1.6)	0.7 (0.3–1.4)
Presence of siblings	4.7 (1.5–14.6)†	1.0 (0.5–2.0)
Day-care attendance	5.6 (1.8–17.9)†	2.1 (0.9–4.8)
Cigarette-smoking mother	1.7 (0.3–9.7)	2.5 (0.8–7.4)
Cigarette-smoking father	1.0 (0.2–4.1)	0.7 (0.2–1.7)
Cat in the house	0.9 (0.3–2.7)	0.4 (0.2–1.0)†
Dog in the house	1.0 (0.2–4.8)	1.0 (0.4–2.7)

*Adjusted for other variables, region, and education level of parents. †*P* < 0.05. CI = confidence interval.

al. [5]. We could, however, not confirm their observation that children with a gestational age of more than 41 weeks had a higher risk to develop atopic dermatitis [5]. This may be due to the relatively small number. Xu et al. [17] found atopy in young adults to be more common among those who were born more lean or more heavy than average. Other studies did not observe an association between birth weight and the development of atopic sensitization later in life [18, 19]. The mechanisms underlying associations between birth size and atopic disease are unknown. Factors that influence fetal growth, like maternal health and nutrition, may also influence the developing immune system. Alternatively, unknown factors associated with the western lifestyle that are responsible for the observed increase in atopic diseases in recent decades may also influence fetal growth.

The observed protective effect of exclusive breastfeeding in the first 3 months of life on the development of atopic dermatitis is consistent with the results of a recent meta-analysis of prospective studies [9]. The meta-analysis found exclusive breastfeeding during the first 3 months of life to be associated with lower incidence rates of atopic dermatitis during childhood in children with a family history of atopy (OR = 0.7). This effect was smaller in the general population and negligible in children without first-order atopic relatives. The protective effect of breastfeeding may be attributed to several mechanisms. Adverse reactions of the skin to cow's

milk proteins are an important cause of atopic dermatitis in infancy [20]. Formula-fed children are more exposed to cow's milk proteins and also to other external antigens, which may be an explanation for the higher prevalence of atopic dermatitis. Another explanation may be that human milk actively stimulates infant immunity [21]. Our finding that the protective effect of breastfeeding in the first 3 months was also present in children whose parents denied symptoms at 3 months of age, indicates that selective finishing of breastfeeding in cases does not explain the negative association.

As opposed to the generally accepted hypothesis that contact with other children protects against atopic disease (perhaps by facilitating the spread of infections), we found attendance at day care to increase the risk of atopic dermatitis. This effect of day care attendance was most pronounced in children in whom symptoms of atopic dermatitis were already present at 3 months of age, thus before day care attendance usually starts. Therefore, it is very unlikely that day care attendance plays a causal role in the development of atopic dermatitis, yet it may constitute a risk factor for the preservation of atopic dermatitis and thus for visible signs of atopic dermatitis at physical examination.

The higher risk of bacterial contamination associated with day care attendance might on the one hand be protective for allergic sensitization later in life, but on the other may precipitate colonization of the skin of patients with atopic dermatitis. *Staphylococcus aureus* is known to produce superantigenic exotoxins and their specific IgE antibodies are thought to be an important precipitating factor of atopic dermatitis [22]. Our findings underline the necessity to balance two risks when studying the hygiene hypothesis. First, there is a known serious risk of infectious disease caused by microbial exposure; second there may be protective effects of microbial exposure on the development of allergic disease.

The presence of (older) siblings was not significantly associated with atopic dermatitis, but there was a tendency in the same direction as for day care attendance. Our results suggest that the effect of the presence of siblings on the development of atopic dermatitis is confined to those cases starting before 3 months of age. We cannot exclude, however, that parents with older children report symptoms of atopic dermatitis earlier than parents of a first-born child and that selection bias may have played a role.

An additional explanation for the absence of a protective effect of day care and the presence of siblings may be that we studied atopic dermatitis in infancy as a phenotype of atopic disease, while previous studies reporting protective effects of day care attendance mainly concerned investigations on positive skin tests to inhalant allergens among school-children. The protective effect may be restricted to sensitization to inhalant allergens, which is rare in the first year of life [23]. This may also explain why the results from studies with asthma as the outcome variable are inconsistent, mostly reporting day care attendance to be a risk factor [10].

The presence of a cat in the household had a borderline significant negative association with early atopic dermatitis. This is consistent with the findings of Nafstad et al. [11]. However, this could partly be explained by a selective avoidance of cats by allergic families and a higher risk of atopic dermatitis for children from these families. In the

3-month questionnaire we asked whether allergy was the reason for not having a cat. After exclusion of subjects who confirmed this, the negative association between a cat in the home and atopic dermatitis disappeared.

A limitation of this study is that the results apply only to children from allergic mothers. We could not investigate whether the presence of a genetic constitution through the maternal line modifies the effects of environmental exposure on the development of atopic dermatitis.

In summary, we studied the influence of several birth characteristics and environmental factors on the risk of atopic dermatitis in the first year of life and found a high birth weight and attendance at day care to be risk factors for atopic dermatitis in the first year of life, while exclusive breastfeeding in the first 3 months of life was a protective factor. Our results confirm the beneficial effect of breastfeeding early in life and suggest a protective effect of hygiene on the prognosis of atopic dermatitis. At least for atopic dermatitis, the hygiene hypothesis appears not to be valid. This study has a long follow-up and further studies may reveal the importance of the found associations for the later development of asthma and atopy.

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