

Atopic dermatitis, extrinsic atopic dermatitis and the hygiene hypothesis: results from a cross-sectional study

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Summary

Background Atopic Dermatitis (AD), hayfever and asthma are commonly summarized as atopic diseases. The spatial distribution of AD differs from that of asthma and hayfever, suggesting that AD might follow a different risk pattern than these diseases. AD can be differentiated into an allergic extrinsic form (EAD) and a non-allergic intrinsic form (IAD). Only EAD might follow the distribution and risk pattern that have been ascribed to asthma and hayfever.

Objective To investigate the distribution and risk factor profile of AD and EAD focusing on environmental factors relating to the hygiene hypothesis.

Methods Population-based cross-sectional study on 12 601 children aged 5–7 and 9–11 years from Dresden (Eastern Germany) and Munich (Western Germany). Information was obtained by International Study of Asthma and Allergic Childhood questionnaires, dermatological examinations and skin prick testing. AD-diagnosis ever, current AD-symptoms and visible eczema were investigated with their respective extrinsic forms.

Results Maternal and paternal history of AD were equally strong determinants of the child's AD status. Factors related to the hygiene hypothesis like day-care attendance and number of older siblings were not associated with a decreased risk of AD. The proportion of EAD within AD was higher in Eastern than in Western Germany. The determinants of the diseases appeared to be similar for both EAD and IAD.

Conclusions There was no evidence of the hygiene hypothesis holding true for AD or EAD. AD might be a separate entity than respiratory atopic diseases. Little is known about the risk factors of AD and factors different from those of respiratory allergic diseases should be considered in future research.

Keywords atopic dermatitis, eczema, extrinsic, hygiene hypothesis, intrinsic, sensitization

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Introduction

Atopic dermatitis (AD), hayfever and asthma are commonly summarized as atopic diseases. Because of the variation in the geographic distribution of atopic diseases [1] and their rising prevalence in the last decades [2, 3], environmental factors are thought to play a crucial role in the aetiology of these diseases. Observations of inverse associations between sibling order, day care attendance and farming lifestyle and inhalant atopic diseases and sensitization [4–6] support the hygiene hypothesis, which is currently a widely used concept in atopic diseases research. However, most studies investigating the hygiene hypothesis have focused on asthma and hay fever.

Recent publications failed to find a protective effect of early childhood infections on AD [7–9], and the literature on other hygiene-related factors such as siblings, day care attendance, vaccinations and antibiotics is inconclusive [9, 10]. Moreover, the spatial distribution of AD differs from that of asthma and hayfever, suggesting that AD might follow a different risk pattern than these diseases [1, 11]. Little is known about the determinants of AD. While the importance of genetic factors is unquestioned, results from studies on environmental determinants of AD remain inconclusive. Sex, socio-economic status, family size, infant feeding and environmental pollutants have been found to be determinants of the disease in some studies but not in others [3, 10, 12–14]. It has been suggested that AD can be differentiated into an allergic extrinsic form (EAD) and a non-allergic intrinsic form (IAD) [15, 16]. Only EAD might follow the distribution and risk pattern that have been ascribed to asthma and hayfever.

We analysed data from the German part of International Study of Asthma and Allergic Childhood (ISAAC), a large

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cross-sectional population-based study on the prevalence, geographical distribution and risk factors of atopic diseases.

The aim of the current analysis was to examine the distribution and risk factor profile of AD, with a special focus on environmental factors relating to the hygiene hypothesis.

Materials and methods

Study design

This study is part of Phase II ISAAC, a population-based, cross-sectional study that has been described before elsewhere [17, 18]. Between August 1995 and December 1996, self-completion ISAAC questionnaires were given to parents of randomly selected school beginners (aged 5–7) and 4th graders (aged 9–11) in Dresden (former East Germany) and Munich (former West Germany). All of the selected 4th graders and a random sample of the selected school beginners were invited for physical examination and skin-prick testing. Ethical approval for the study was obtained from the ethics committee of the University of Münster (co-ordinating centre).

Results from 12601 questionnaires, 7882 physical examinations and 7042 skin-prick tests (SPTs) were obtained. The response rates were similar overall for Munich and Dresden, ranging from 79% to 88% for questionnaires, from 61% to 77% for skin examinations and from 58% to 62% for skin prick testing. Only minor differences in participation were observed [17, 18]. Children aged 9–11 were less likely to participate in skin-prick testing in Dresden when the child had hayfever or asthma and more likely to participate in Munich when the parents had atopic diseases [18].

Questionnaires

Questionnaires included questions about child characteristics, lifestyle, environmental and hygiene factors and the ISAAC core questions on symptoms of asthma, hay fever and atopic dermatitis [1, 19, 20]. *AD diagnosis ever* was defined as a lifetime doctor diagnosis of AD. *Current AD symptoms* was considered positive when parents reported the presence of an itchy rash in the last 12 months that had affected the skin creases. Hayfever was defined as lifetime doctor diagnosis. Asthma was defined as lifetime doctor diagnosis or a lifetime doctor diagnosis of asthmatic, spastic or obstructive bronchitis more than once. Parental history of atopic diseases was considered positive if at least one parent reported a history of the respective disease. High parental education was defined if at least one parent completed high school. The number of courses of fever within the first year of life, the number of antibiotic courses within the first 3 years of life and the onset temperature for antipyretic treatment were recorded. Day-care attendance was only assessed in Dresden. Date of birth and date of examination were categorized into four seasons.

Skin-prick tests

Due to the study design only sensitization to inhalant allergens was included. *Sensitization* was defined as a mean weal diameter of at least 3 mm greater than the negative

control in at least one of the six tested common aeroallergens (*Dermatophagoides pteronyssinus*, *D. farinae*, tree pollen, mixed grass pollen, *Alternaria tenuis*, cat dander; ALK, Horsholm, Denmark). The definitions of extrinsic atopic dermatitis (EAD) and intrinsic atopic dermatitis (IAD) follow the widely used definitions by Wuethrich et al. [15, 16]. *EAD* was defined as sensitization-positive AD without concomitant asthma or hayfever. *IAD* was defined as sensitization-negative AD without concomitant asthma or hayfever.

Physical examination

Children were examined by specially trained field workers (no physicians) for visible flexural dermatitis on skin sites around the eyes, around the sides and front of the neck, in front of the elbows, inner sides of the wrists, behind the knees and in front of ankles according to the ISAAC protocol [20]. *Visible eczema* was considered positive if signs of visible flexural dermatitis were recorded at any of these sites on the date of examination.

Statistical analysis

The analysis was restricted to German children ($n = 11\,094$). Associations between each of the exposure factors and AD outcomes were assessed using logistic regression analysis. The complete list of exposures under examination is given in Tables 1a and 1b.

Factors associated with a $P < 0.1$ in bivariate analysis were tested in the multivariate models. Multivariate models were built for each outcome. Factors were included one at a time dependent on their significance level. They were retained in the model if they showed a statistically significant association in relation to AD or if they caused an appreciable change in the main exposure estimates. The final models included all risk factors and confounding variables found to be relevant in any of the three models. For EAD and IAD, models were built separately and in the same way as the AD models. Factors that were not significant in bivariate analyses were tested again in the final models as they could become important in the multivariate analyses. However, none of the factors became significant and the final models remained unchanged. The statistical significance of the associations was assessed by likelihood ratio tests. Results are reported as adjusted odds ratios with 95% confidence intervals. Children with EAD and IAD were compared with the common baseline group of SPT-negative children without AD.

Tests for interaction were performed for city as an a priori defined effect modifier in relation to different environmental, lifestyle and hygiene factors identified as potential risk factors by multivariate analysis. All statistical analyses were performed with STATA 8.0 (Stata Corp., College Station, TX, USA).

Results

Data of 11 094 children, 57% children from Dresden (Eastern Germany) and 43% children from Munich (Western Germany), were analysed. Forty-nine percent of children were 1st graders with a median age of 6 years (90% range 5–6) and 51% were 4th graders with a median age of 10 years (90%

Table 1a. Child characteristics and parental history of atopic diseases in relation to different atopic dermatitis (AD) outcomes. Prevalences (%)

	<i>n</i>	AD diagnosis ever (<i>n</i> = 10630 % (95%CI))	Current AD symptoms (<i>n</i> = 10864) % (95%CI)	Visible eczema (<i>n</i> = 6970) % (95%CI)
Total	11094	16.9	10.2	6.7
<i>Atopic diseases of child</i>				
<i>Asthma</i>				
No	9920	15.6*	9.4*	6.1*
Yes	893	31.8	19.6	12.7
<i>Hay fever</i>				
No	10070	15.5*	9.3*	6.3*
Yes	760	35.1	21.6	11.4
<i>Child characteristics</i>				
<i>Sex</i>				
Boy	5679	16.0*	8.3*	5.7*
Girl	5412	17.9	12.3	7.7
<i>Grade</i>				
1 st Grade	5465	16.8	8.9*	8.5*
4 th Grade	5629	17.0	11.5	5.6
<i>Birth weight</i>				
<2500 grams	1142	14.7*	10.8	5.3
>2500 grams	9748	17.3	10.2	6.8
<i>Parental history of atopic diseases</i>				
<i>Maternal AD</i>				
No	9180	13.7*	8.9*	5.9*
Yes	1158	41.2	19.8	12.4
<i>Paternal AD</i>				
No	9108	15.0*	8.9*	6.0*
Yes	596	42.6	25.5	14.8
<i>Maternal hay fever</i>				
No	8404	15.3*	9.5*	6.7
Yes	2083	23.6	13.5	7.0
<i>Paternal hay fever</i>				
No	8138	15.7*	9.3*	5.9*
Yes	1767	23.4	13.9	9.9
<i>Maternal asthma</i>				
No	10052	16.3*	10.1	6.6
Yes	533	24.7	12.2	8.3
<i>Paternal asthma</i>				
No	9665	16.6*	9.9*	6.4*
Yes	450	24.5	15.3	10.3

n = number of observations.

**P* < 0.05 (*P*-values of χ^2 -test). Factors tested, not shown and not statistically significant: pre-term birth, maternal age and paternal age.

range 9–10). The study population contained more boys (51.2%) than girls (48.8%). Approximately 15% of the participants had a positive parental history of AD.

Atopic dermatitis

In the study population, AD diagnosis ever had a prevalence of 16.9%, 10.2% current AD symptoms and 6.7% visible eczema. All prevalences were higher in the East than in the West (Tables 1a and 1b).

Tables 1a and 1b show the prevalence of AD in relation to child characteristics, parental history of atopic diseases and factors related to the hygiene hypothesis. Factors significant in multivariate analysis are listed in Table 2. Hayfever and

Table 1b. Environmental factors relating to the hygiene hypothesis in relation to three different atopic dermatitis (AD) outcomes. Prevalences %

	<i>n</i>	AD diagnosis ever (<i>n</i> = 10630 95%CI)	Current AD symptoms (<i>n</i> = 10864) 95%CI)	Visible eczema (<i>n</i> = 6970) 95%CI)
<i>City</i>				
Dresden	6317	17.1	11.8*	7.6*
Munich	4777	16.8	8.2	5.2
<i>Parental education</i>				
Low	5446	14.4*	9.2*	6.3
High	5222	20.2	11.6	7.1
<i>Day care attendance†</i>				
No	1306	15.0*	9.7*	6.0*
Yes	4833	17.8	12.4	8.1
<i>Number of older siblings</i>				
None	5362	16.1	9.6*	6.5
One	3983	18.9	11.1	7.0
> One	1478	14.9	10.7	6.6
<i>Own sleeping room 1st year</i>				
No	7020	17.9*	11.3*	7.1*
Yes	3322	15.9	8.8	5.7
<i>Measles vaccination</i>				
No	580	20.2*	10.9	7.5
Yes	9016	16.8	10.1	6.6
<i>Antibiotics up to year 3</i>				
None	2363	13.3*	7.9*	5.7
1–2 times	3694	15.5	9.1	7.1
3–5 times	2763	19.4	11.9	6.9
> 5 times	1453	21.8	14.4	6.3
<i>Fever first year</i>				
None	2116	15.4*	9.7*	6.6
1–2 times	5329	16.4	9.9	6.7
> 2 times	2896	19.5	11.6	6.0
<i>Onset of antipyretic medication</i>				
38.5°	3983	15.7*	11.0	7.2
39°	4083	16.6	9.8	6.1
39.5°	2160	19.7	10.5	6.2
<i>Breastfeeding</i>				
None	1578	13.8	7.4	6.0
< 6 months	5533	16.0	10.2	6.8
> 6 months	3636	20.2	11.8	6.8
<i>Dampness in 1st year</i>				
No	8271	16.7	9.8	6.2
Yes	1914	20.3	13.3	8.6
<i>Draughty rooms in 1st year</i>				
No	6155	16.1	9.5	6.8
Yes	4096	19.2	11.9	6.5

**P* < 0.05 (*P*-values of χ^2 -test and test for trend).

†Only data from Dresden. Factors tested, not shown but statistically significant: smoking in pregnancy. Factors tested, not shown and not statistically significant: season of birth, season of physical examination and gas heating.

asthma were significantly positively associated with AD. However, as these conditions were not considered causal for AD (AD generally precedes asthma and hayfever), they were not included in multivariate analysis. AD was more prevalent in girls than in boys. The age effect differed according to the AD definition chosen. Maternal or paternal history of AD influenced the odds of the child of developing AD in a similar

Table 2. Multivariate analysis. Associations between exposure factors and atopic dermatitis (AD) outcomes

	AD diagnosis ever (n = 8132)	Current AD symptoms (n = 8271)	Visible eczema (n = 5401)
<i>Child characteristics</i>			
Girl	1.2 (1.09–1.39)	1.7 (1.46–1.94)	1.5 (1.22–1.91)
4th Grade	0.97 (0.86–1.09)	1.3 (1.12–1.49)	0.68 (0.54–0.85)
<i>Parental characteristics</i>			
Parental AD	4.2 (3.66–4.79)	2.6 (2.18–3.01)	2.3 (1.79–2.93)
Parental hay fever	1.5 (1.29–1.65)	1.5 (1.30–1.75)	1.4 (1.07–1.70)
<i>Environmental, lifestyle and hygiene factors</i>			
Munich (baseline: Dresden)	1.02 (0.88–1.18)	0.70 (0.59–0.84)	0.65 (0.49–0.86)
High parental education	1.3 (1.16–1.49)	1.2 (1.00–1.35)	1.2 (0.92–1.45)
Day care attendance*	1.2 (0.97–1.47)	1.4 (1.12–1.81)	1.6 (1.08–2.33)
Antibiotics up to year 3 (baseline: none)			
1–2 times	1.2 (0.98–1.40)	1.02 (0.82–1.27)	1.1 (0.82–1.58)
3–5 times	1.5 (1.28–1.86)	1.4 (1.10–1.72)	1.1 (0.80–1.60)
> 5 times	1.7 (1.40–2.15)	1.6 (1.24–2.03)	1.0 (0.68–1.49)
Onset of antipyretic medication (baseline: 38.5°)			
39.0°	1.08 (0.93–1.24)	0.96 (0.81–1.14)	0.96 (0.75–1.24)
39.5°	1.3 (1.10–1.58)	1.1 (0.89–1.37)	1.04 (0.74–1.46)
Breastfeeding (Baseline: none)			
< 6 months	1.06 (0.88–1.29)	1.3 (0.98–1.58)	1.1 (0.80–1.62)
> 6 months	1.3 (1.02–1.54)	1.5 (1.14–1.89)	1.08 (0.74–1.59)
Dampness in 1st year	1.2 (1.01–1.37)	1.2 (1.04–1.48)	1.5 (1.14–1.96)
Draughty rooms in 1st year	1.2 (1.02–1.32)	1.07 (0.92–1.24)	0.75 (0.59–0.96)

aOR, adjusted Odds ratio: Models adjusted for all variables shown in the table except day-care attendance.

*only data from Dresden: models adjusted for all variables shown.

way. The crude prevalences are shown in Table 1a. The adjusted odds ratios were slightly higher for paternal than for maternal history of atopic diseases (data not shown). For multivariate analyses both factors were combined to parental AD.

Environmental factors relating to the hygiene hypothesis such as having at least two older siblings, the number of fever episodes, measles vaccination and a child's own sleeping room within the 1st year of life did not show significant protective effects on AD in multivariate analyses. The respective adjusted odds ratios with 95% confidence intervals for current AD symptoms were 1.1 (0.94–1.4), 0.92 (0.73–1.2), 0.79 (0.56–1.1) and 0.92 (0.78–1.1). The odds ratios for AD diagnosis ever and visible eczema did not differ substantially and were not statistically significant either (data not shown).

Day-care attendance among East German children, and high parental education increased the adjusted odds ratios of all AD outcomes. Frequent antibiotic use showed a statistically significant dose–response relationship with AD diagnosis ever and current AD symptoms, but no such relation was seen for visible eczema. Late-onset antipyretic treatment was associated with an increased odds ratio of AD diagnosis ever. Data on pet keeping within the 1st year of life were collected and did not show a protective effect on any AD outcome. However, because of a high proportion of missing values, these results were not included in the tables. There was no evidence for significant interaction of city in relation to hygiene factors. Additional adjustment for asthma, hayfever and wheezing made little or no difference.

Among the other factors tested, breastfeeding, dampness within the 1st year of life and draughty rooms were statistically significantly positively associated with AD in multivariate analyses (Table 2). In turn, birth weight, parental asthma, smoking during pregnancy, maternal and paternal age, season of birth, season of examination, pre-term birth and gas heating did not reach statistical significance in multivariate analyses.

Extrinsic atopic dermatitis and Intrinsic atopic dermatitis

SPT were carried out in 6174 children. Of these, 20.1% were sensitized to at least one of the inhalant allergens tested. Sensitization was present in 33% of children with AD diagnosis ever, 35% of children with current AD symptoms and 36% of the children with visible eczema. When, according to the EAD definition children with asthma or hayfever were excluded, sensitization was present in 23%, 25% and 27% of children with the respective AD definition. The proportion of EAD was consistently higher in the East than in the West (Fig. 1).

EAD seemed to be more severe than IAD. In children with EAD, symptoms started significantly more often before 2 years of age than in children with IAD (AD diagnosis ever: 46% vs. 26%), caused more sleep disturbances within the previous year (current AD symptoms: 34% vs. 28%) and more skin eruptions were diagnosed at physical examination (visible eczema: 48% vs. 39%). However, only the first result reached statistical significance ($P < 0.001$). Symptoms also

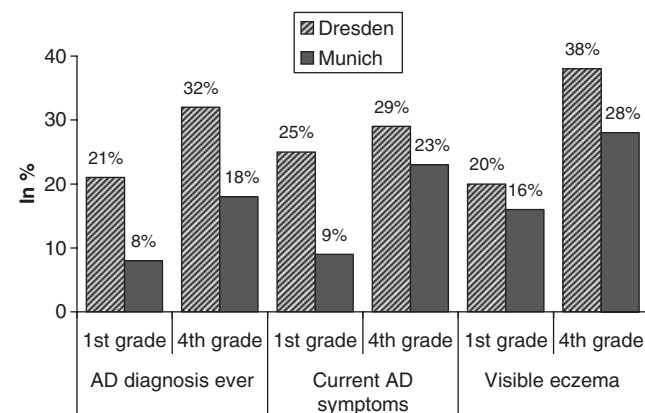


Fig. 1. Percentage of children with EAD of all children with AD (without concomitant asthma or hayfever) by city and grade (1st grade: children aged 5–7; 4th grade: children aged 9–11).

Table 3. Multivariate analysis. Associations between exposure factors and extrinsic and intrinsic atopic dermatitis (AD) outcomes

	AD diagnosis ever		Current AD symptoms		Visible eczema	
	Extrinsic <i>n/N</i> † = 169/2808 aOR (95%CI)	Intrinsic <i>n/N</i> † = 578/3127 aOR (95%CI)	Extrinsic <i>n/N</i> † = 127/2985 aOR (95%CI)	Intrinsic <i>n/N</i> † = 376/3177 aOR (95%CI)	Extrinsic <i>n/N</i> † = 80/3118 aOR (95%CI)	Intrinsic <i>n/N</i> † = 218/3208 aOR (95%CI)
<i>Child characteristics</i>						
Girl	1.06 (0.74–1.52)	1.5 (1.25–1.91)	1.4 (0.93–2.13)	1.9 (1.47–2.47)	1.6 (0.92–2.71)	1.7 (1.22–2.44)
4 th Grade	1.5 (1.02–2.31)	0.91 (0.73–1.13)	1.6 (0.98–2.45)	1.5 (1.12–1.95)	0.96 (0.55–1.66)	0.48 (0.34–0.67)
Birth weight >2500 g	1.4 (0.68–2.84)	1.2 (0.82–1.76)	0.98 (0.49–1.96)	1.1 (0.72–1.75)	1.2 (0.46–3.11)	3.1 (1.23–7.60)
<i>Parental characteristics</i>						
Parental AD	4.7 (3.26–6.90)	4.0 (3.16–5.02)	3.3 (2.12–5.02)	2.5 (1.88–3.28)	4.1 (2.39–7.05)	1.9 (1.28–2.81)
Parental hayfever	1.5 (1.03–2.19)	1.4 (1.08–1.68)	1.9 (1.28–2.95)	1.4 (1.08–1.83)	2.0 (1.19–3.46)	1.3 (0.90–1.84)
Paternal age at birth (change per year)	1.03 (1.00–1.06)	1.01 (0.99–1.02)	1.05 (1.01–1.08)	1.01 (0.98–1.03)	1.03 (0.98–1.07)	0.99 (0.97–1.02)
<i>Environmental, lifestyle and hygiene factors</i>						
Munich (baseline: Dresden)	0.54 (0.35–0.84)	1.3 (0.98–1.59)	0.34 (0.20–0.58)	0.65 (0.48–0.88)	0.29 (0.15–0.59)	0.65 (0.44–0.98)
High parental education	1.4 (0.98–2.12)	1.4 (1.12–1.75)	1.4 (0.93–2.20)	1.1 (0.84–1.42)	1.1 (0.66–1.94)	1.1 (0.77–1.56)
Day care attendance*	1.9 (0.98–3.53)	1.05 (0.73–1.52)	1.5 (0.80–2.97)	1.4 (0.92–2.14)	2.4 (0.92–6.51)	1.4 (0.80–2.39)
Measles vaccination	0.53 (0.24–1.16)	0.90 (0.57–1.43)	0.65 (0.25–1.71)	0.47 (0.29–0.78)	0.29 (0.11–0.80)	0.58 (0.29–1.17)
Antibiotics up to Year 3 (baseline: none)						
1–2 times	2.1 (1.11–3.84)	1.06 (0.78–1.43)	1.02 (0.57–1.84)	1.2 (0.83–1.74)	0.97 (0.46–2.02)	1.1 (0.70–1.78)
3–5 times	2.4 (1.23–4.48)	1.5 (1.13–2.11)	0.94 (0.50–1.77)	1.6 (1.07–2.31)	0.69 (0.31–1.55)	0.92 (0.55–1.53)
> 5 times	2.2 (1.08–4.58)	1.6 (1.06–2.25)	1.09 (0.54–2.19)	1.6 (1.03–2.49)	0.70 (0.28–1.77)	0.94 (0.51–1.73)
Breastfeeding (baseline: none)						
< 6 months	1.08 (0.59–1.98)	0.99 (0.70–1.40)	1.2 (0.63–2.44)	1.4 (0.91–2.26)	1.05 (0.48–2.31)	0.93 (0.52–1.66)
> 6 months	1.06 (0.55–2.02)	1.3 (0.90–1.86)	0.82 (0.39–1.73)	1.8 (1.10–2.83)	0.30 (0.11–0.82)	1.2 (0.63–2.09)
Dampness in 1st year	1.1 (0.73–1.80)	1.3 (1.00–1.68)	1.6 (0.99–2.55)	1.1 (0.83–1.54)	0.86 (0.42–1.74)	1.8 (1.20–2.58)

aOR, adjusted odds ratio: models adjusted for all variables shown in the table except day care attendance.

*only data from Dresden: models adjusted for all variables shown.

†*n/N* = number of cases by total number of observations in the model. Numbers do not completely add up because of missing values.

started significantly earlier in relation to visible eczema and current AD symptoms, possibly reflecting persistence or severity of EAD.

Results from multivariate analyses are presented in Table 3. Parental history of AD and hayfever were significant risk factors for extrinsic and intrinsic AD over all applied outcome definitions. Factors related to the hygiene hypothesis were not associated with decreased odds of EAD or IAD. Living in Munich and measles vaccination were more likely to decrease, and high parental education and day-care attendance more likely to increase the odds of having an AD irrespective of sensitization status. However, not all of these associations were statistically significant.

Discussion

Maternal and paternal history of AD were equally strong determinants of the child's AD status in our population. Factors related to the hygiene hypothesis like day care attendance and number of older siblings were not associated with a decreased risk of AD. The proportion of EAD within AD was higher in Eastern than in Western Germany. The determinants of the diseases appeared to be similar for both EAD and IAD. EAD was associated with a significantly earlier onset of eczema and slightly more severe symptoms.

Major difficulties in the interpretation and comparison of epidemiological studies on AD arise from the use of different

disease definitions. Definitions relate alternatively to life time prevalence, last-year prevalence and point prevalence of AD. We have used these three definitions in parallel. In this way, it was possible to compare the internal and external consistency of the results and to assess their different implications. Only effects that were consistently seen in more than one disease definition were considered meaningful, thereby avoiding false interpretation of significant results because of multiple testing. There were substantial differences between the definitions in relation to some of the exposure variables. The odds ratio for parental history of AD in relation to AD diagnosis ever for instance was considerably higher than the odds ratio relating to current AD symptoms and visible eczema. This could indicate a stronger association of genetic factors with early, non-persistent AD or reflect recall bias, as parents with a personal history of AD would be more likely to recognize and to recall AD in their child. For current AD symptoms and visible dermatitis, it was difficult to differentiate between causal factors and factors merely triggering AD.

We consider the three outcome definitions, the large number of subjects and the high quality of data because of the validation of ISAAC study instruments as major strengths of this study. Limitations resulted mainly from the cross-sectional design, as the time sequence of events cannot be established with certainty and reporting of early life exposures might have been affected by recall bias. The selected definitions of EAD and IAD excluding children with asthma and hayfever might have resulted in the exclusion of a subgroup since infants with early AD and concomitant wheezing have been shown to have a higher risk of asthma at school age [21]. The slightly higher participation in skin prick testing of 9–11-year-old children from Munich with a positive parental history of atopic diseases [18] could have resulted in higher proportions of EAD in children of this age group from Munich.

Atopic dermatitis

Being a girl and having a parental history of AD or hayfever were positively associated with AD in the child, parental AD being a stronger predictor for the child's AD status than parental hayfever. The importance of genetic factors in the pathogenesis of AD is unquestioned. Based on observations of a stronger maternal influence of atopy in relation to AD of the child [13, 22], the maternal influence is generally considered more important. The early onset of AD suggests that environmental factors acting *in utero* or early infancy may play an important role in the expression of the disease. This might suggest a transmission of maternal factors to the child *in utero*. However, in this large study we found maternal and paternal history of AD to be equally strong predictors for child's AD status over all applied definitions. Our findings give therefore no indication of an interaction between environmental and maternal factors taking place during pregnancy.

Our finding of increased prevalence of AD with increased parental education confirms earlier reports that have linked affluence with an increased prevalence of AD [13, 23, 24]. The higher prevalence of atopic diseases in individuals and regions of higher socio-economic standing and in children with fewer

siblings has led to the proposition of the hygiene hypothesis [4]. However, many studies that have observed protective effects of hygiene-related factors on respiratory allergies have not observed the effects of these factors on AD [5, 25, 26] and the literature on hygiene-related factors is inconclusive. Many studies on indirect measures of hygiene and infection like family size and day-care attendance found inverse associations with AD [9, 27, 28]. However, in relation to farming lifestyle, inverse associations were mainly seen for respiratory allergies [25, 26]. Most studies investigating the direct effect of infections on subsequent development of AD failed to find a protective effect [7–9]. In our study, living in Dresden and day care attendance were positively associated with AD and no significant protective effects on AD was found for other factors relating to the hygiene hypothesis such as number of older siblings, pet ownership, frequency of fever episodes and child's own bedroom within the 1st year of life. A positive association between, early life antibiotic treatment and AD could be demonstrated in one study [29] but not in others [7, 30]. Our findings of positive associations between the frequency of antibiotic and antipyretic treatments and AD can be interpreted in a cross-sectional study in two ways: as true harmful effects of these medications or as markers for multiple infections (reverse causality). The associations were most pronounced for lifetime diagnosis, possibly indicating a selection bias as frequent visits to the doctor would increase both the probability of a prescription of medication and the probability of a doctor diagnosing AD [7]. Overall, our findings do not support a protective effect of environmental factors related to the hygiene hypothesis for AD.

Extrinsic atopic dermatitis/intrinsic atopic dermatitis

The overall proportions of EAD ranged from 8% to 38% depending on the AD definition, city and age group and were consistently higher in Eastern Germany than in Western Germany (Fig. 1). These results are conflicting with the results of previous studies that have reported percentages of EAD within AD between 55% and 85% depending on the case definition and the study site [16, 31]. We found the differences in proportions of EAD to be highly dependent on the definition of AD (e.g. strictness of case definition and whether children with asthma and hayfever were excluded from the definition of EAD and IAD), the definition of sensitization status and factors such as age of participants and study site. The population-based study design has most likely contributed to the low proportion of EAD in our survey. Most studies assessing the relationship between IAD and EAD have been hospital based. Children selected in hospitals are likely to suffer more severe symptoms of AD than children participating in a population-based study. Sensitization *per se* and the degree of sensitization have both been shown to be positively associated with the severity of AD [32, 33]. The proportions of EAD in this study were also considerably smaller than that from another German population-based study. In that study EAD contributed for 75% of AD cases [32]. However, the overall prevalence of AD in that study was only 2.5% and children with asthma and hayfever were not excluded from the EAD definition. Probably a stricter case definition of AD may have added to the high proportion of EAD.

When attempting to identify predictors of EAD and IAD in separate models, no different risk factor profile for the two forms of AD was identified in multivariate analysis.

The discussion about whether to differentiate AD into EAD and IAD is ongoing. Based on observations of differences in immunologic and clinical characteristics between the two forms, a different pathogenesis of IAD and EAD has been proposed. The two forms have been interpreted as two different types of disease with a similar clinical phenotype [15, 16, 34, 35]. It is claimed that through a more precise subtype definition of AD, genetic, immunopathological and therapeutical studies would be improved upon and prevention through allergen avoidance would be facilitated for EAD [16, 36]. However, the role of sensitization in the aetiology of AD and the impact of such a differentiation for patients, practitioners and researchers have also been questioned [37]. A change from IAD into EAD over the years has been demonstrated. A dynamic relationship between IAD and EAD, IAD presenting only a transitory state, has therefore been proposed [34, 38]. In our data, there was no evidence for a different risk factor profile between EAD and IAD. In accordance with earlier studies, children with EAD had a significantly earlier onset of eczema and seemed to have more severe symptoms than children with IAD. These observations might support the notion that sensitization might be an indicator of severity and/or persistence of AD rather than a different sub-type of disease. However, it cannot be completely excluded that severity and early onset of AD themselves might be characteristics of a different phenotype.

Overall, the distribution and risk factors for AD were distinct from risk factors that have been described for asthma and hayfever. Particularly, there was no evidence of the hygiene hypothesis holding true for AD. We therefore conclude that AD might be a separate entity than respiratory atopic diseases. Little is known about the risk factors for AD and factors different from those for respiratory allergic diseases should be considered in future research.

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