

Association of atopic and non-atopic asthma with emotional symptoms in school children

Gabriele Kohlboeck¹, Sibylle Koletzko², Carl-Peter Bauer³, Andrea von Berg⁴, Dietrich Berdel⁴, Ursula Krämer⁵, Beate Schaaf⁴, Irina Lehmann⁶, Olf Herbarth⁷, Joachim Heinrich¹, for the GINI-plus Study groups* & LISA-plus Study groups†

¹Helmholtz Zentrum Muenchen, German Research Center for Environmental Health, Institute of Epidemiology I, Neuherberg, Germany; ²Dr von Hauner Children's Hospital, Ludwig-Maximilians-University of Munich, Munich, Germany; ³Department of Pediatrics, Technical University of Munich, Munich, Germany; ⁴Department of Pediatrics, Marien-Hospital Wesel, Wesel, Germany; ⁵Institut fuer Umweltmedizinische Forschung, University of Duesseldorf, Duesseldorf, Germany; ⁶UFZ-Center for Environmental Research, Leipzig, Germany; ⁷Faculty of Medicine Environmental Medicine & Hygiene, University Leipzig, Leipzig, Germany

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Correspondence

Gabriele Kohlboeck, Helmholtz Zentrum München, Institut für Epidemiologie, Ingolstädter Landstr. 1, D-85764 Neuherberg, Germany.
Tel.: +49 (0)89 3187 4578
Fax: +49 (0)89 3187 3380
E-mail: gabriele.kohlboeck@helmholtz-muenchen.de

*The GINI-plus Study Group (see Appendix S1).

†The LISA-plus Study Group (see Appendix S1).

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Abstract

Objective: To date, there is conflicting evidence whether the association between asthma and depression depends on the atopic or non-atopic asthma phenotype. This study investigates associations between emotional symptoms and atopic and non-atopic asthma in school-aged children.

Methods: Cross-sectional data on asthma and allergic diseases at the 10-year follow-up of two birth cohorts were collected by parent-reported physician diagnoses. Specific IgE levels including most common inhalant allergens (SX1) and food allergens (FX5) were measured by RAST-CAP FEIA. Atopic asthma was defined as asthma ever and positive specific IgE test, non-atopic asthma as asthma ever and no IgE sensitization. Emotional symptoms were assessed by parent-reported strength and difficulty questionnaire. Logistic regression modeling were applied to determine likelihood of emotional symptoms in children with atopic and non-atopic asthma controlling for socio-demographic factors, body mass index, atopic eczema, allergic rhinitis, and pubertal development.

Results: Non-atopic asthma was associated with about 3-fold higher likelihood of emotional symptoms compared to children with no asthma (OR_{adj} = 2.90, CI_{95%} = 1.46–5.73). Atopic asthma was not associated with emotional symptoms (OR_{adj} = 1.35, CI_{95%} = 0.81–2.26).

Conclusions: Atopic and non-atopic asthma in children might have different etiologies, whereas for non-atopic asthma, emotional symptoms are relevant, this is not the case in atopic asthma. The relationship between the non-atopic asthma phenotype and emotional symptoms might be dependent on gender.

Abbreviations

ADHD, attention-deficit/hyperactivity disorder; Adj, adjusted; BMI, body mass index; CI_{95%}, confidence interval 95%; FX5, food-specific IgE antibodies; GINI-plus, German Infant Study on the influence of Nutrition Intervention PLUS environmental and genetic influences on allergy development; IgE, immunoglobulin E; LISA-plus, influences of lifestyle-related factors on the immune system and the development of allergies in childhood study; OR, odds ratio; p, p-value; RAST, radioallergosorbent test; SDQ, strength and difficulty questionnaire; SX1, inhalant-specific IgE antibodies; Unadj, unadjusted.

To date, there has been considerable research on the relationship between asthma, anxiety, and depression (1). Several attempts were made to explain the mechanism underlying the association between asthma and depression. Environmental concepts suggest a role for familial communication and interaction style, such as parental criticism (2). Results from twin studies suggest a shared genetic risk for atopic and depressive symptoms (3). The interaction concept between behavioral, neural, endocrine, and immune processes suggests a role for chronic stress inducing deregulation of the hypothalamus–pituitary–adrenal axis (HPA), and altered regulation of inflammatory responses in the development of asthma (4).

A further explanation that has been put forward is that atopy or IgE-mediated immune mediators (5, 6), such as cytokines, could be responsible for the mechanisms behind both allergic and depressive symptoms (3). To date, a few studies investigated whether IgE levels or atopic or non-atopic phenotypes of asthma could explain the asthma/depression relationship. The Finnish birth cohort study showed that women with positive skin prick tests were slightly more likely to report that they had been diagnosed with depression by a doctor (6.9 vs. 4.3% women with negative skin prick tests) (6). Another population-based study on adults also reported an association between asthma and depression in the atopic asthma phenotype (5). However, a small study investigating the likelihood of depression in youth with atopic and non-atopic asthma, does not support the hypothesis that atopic status explains the relationship between asthma and depression (7). They reported that youth with non-atopic asthma were twice more likely to have depressive symptoms compared with those who had no asthma. Thus, there are currently inconsistent results whether atopy increases the risk for individuals with asthma to experience depression. So far, no population-based study had explored the association between depression and emotional symptoms with atopic vs. non-atopic asthma in children yet.

The aim of this study was to investigate whether atopic asthma based on sensitization indexed by specific IgE would be associated with higher likelihood for emotional problems than children with non-atopic asthma or children not diagnosed with asthma.

Material and methods

Study population

Data from two ongoing German birth cohort studies were combined for the present analysis. The German Infant Study on the influence of Nutrition Intervention PLUS environmental and genetic influences on allergy development (GINI-plus) is a prospective birth cohort study that was initiated to investigate the influence of nutritional intervention during infancy as well as air pollution and genetics on allergy development. Details on study design, recruitment, and exclusion criteria have been described elsewhere (8). In brief, between September 1995 and June 1998, a total of 5991 healthy full-term newborns were recruited in obstetric clinics in two regions of Germany (urban Munich and rural Wesel). 3317 children (55.4%) of the original study population participated in the 10-year follow-up. Loss to follow-up was associated with a lower level of parental education, a negative history of parental atopy, the absence of atopic diseases of the child during the first 2 years of life and residency in Wesel.

The 'Influence of lifestyle factors on the development of the immune system and allergies in East and West Germany Plus the influence of traffic emissions and genetics' (LISA-plus) study is a population-based birth cohort. Details on study design are described elsewhere (9). 1761 children (56.9%) of the original study population participated in the 10-year follow-up. Higher loss to follow-up was found in children with a lower level of parental education and residency in Wesel or Leipzig,

whereas the absence of elder siblings, a negative history of parental atopy, and the absence of atopic diseases of the child during the first 2 years of life showed higher compliance.

Of the 2892 subjects from GINI-plus ($n = 1802$) and LISA-plus ($n = 1090$) with IgE test data at age 10 years, complete data were available for 2814 participants [1440 male (51%), 1374 female (49%)] of the 10-year follow-up. These data constituted the analysis sample, which is presented in this article. For both studies, approval by the local Ethics Committees (Bavarian General Medical Council, University of Leipzig, Medical Council of North-Rhine-Westphalia) and written consent from participant's families were obtained.

Measurement of emotional symptoms

Parents filled out the German version of the strengths and difficulties questionnaire (SDQ), a valid and reliable behavioral screening questionnaire (10, 11). The SDQ comprises 25 items on psychological attributes divided into five subscales: emotional symptoms, conduct problems, hyperactivity/inattention, peer relationship problems, and prosocial behavior. Each item is reported as 0 = 'not true', 1 = 'somewhat true', and 2 = 'certainly true'. For present analysis, the subscale emotional symptoms was used, and scores were categorized according to the norms of the German SDQ version (11) into three groups indicating a 'normal', 'borderline', or 'abnormal' amount of symptoms. The 'abnormal emotional symptoms' category reflects a substantial risk of clinically significant depression and anxiety (12).

Assessment of atopic and non-atopic asthma

Doctor-diagnosed asthma was defined as parent report of having a physician's diagnosis of asthma at the 10-year follow-up of the GINI-plus and LISA-plus study. Parents were asked the following: 'Has your child ever had a diagnosis of asthma according to a physician?' If the parents selected yes, the child was defined to have physician-diagnosed asthma ever. Specific IgE levels including the most common inhalant allergens locally (SX1 that includes ambrosia, mugwort, birch, *cladosporium herbarum*, *dermatophagoides pteronyssinus*, grass, cat, dog, and rye), and food allergens (FX5 that includes fish, peanut, hen's egg, cow's milk, soy, and wheat) were measured at age 10 years using the CAP-RAST FEIA allergy screening test (Pharmacia Diagnostics, Freiburg, Germany).

Inhalant sensitization and food sensitization were defined positive as any specific IgE antibody value of 0.35 kU/l or greater. Children with a positive RAST test to an inhalant or food allergen were labeled atopic. Atopic asthma was defined as the presence of both physician-diagnosed asthma and a positive specific IgE test, whereas non-atopic asthma was defined as the presence of physician-diagnosed asthma but with no IgE sensitization to the tested inhalant or food allergens.

Statistical analysis

Student's *t*-tests and chi-squared tests were used to compare several variables between genders; mean and standard

deviations (SD) were used to describe continuous variables. A 0.05 level of significance was considered. Data were analyzed by logistic regressions to determine the association between abnormal emotional symptoms and asthma, controlled for potential confounders gender, study center, parental educational level, household income, body mass index (BMI), other allergic diseases, and pubertal status. To account for the onset of the gender gap in depression associated with puberty (13), pubertal status was included as a confounding factor in the model. Because throughout puberty, there is evidence for both greater incidence of asthma in females (14) and also depressive symptoms (13), we considered a possible interaction with gender by conducting gender-stratified analyses. The effect of atopic asthma and non-atopic asthma was evaluated separately on the dichotomous coded SDQ subscale emotional symptoms (0 = 'normal or borderline emotional symptoms', 1 = 'abnormal emotional symptoms'). Results are presented as odds ratios (OR) with corresponding 95% confidence intervals.

Parental education was determined by the highest grade completed by either the mother or the father and was grouped into low (less than tenth grade), medium (tenth grade), or high (more than tenth grade) parental education. Net household income per month was reported in the 10-year questionnaire using a 9-point scale ranging from <€500 to >€3500. The calculation of equivalent income was carried out according to the Organization for Economic Cooperation and Development (OECD) guidelines (15) and grouped into low, medium, and high household income. The body mass index [BMI: weight (kg)/height (m)²] was calculated from weight and height measured by a physician during the clinical examination. Atopic eczema and allergic rhinitis were defined as the presence of parent-reported physician diagnosis of these diseases. Pubertal status was calculated using a German version of the pubertal development scale (16). All computations were performed using the statistical software package sas for Windows, version 9.2 (SAS Institute, Cary, NC, USA).

Results

Of a total of 2814 children, 182 (6.5%) were identified with atopic asthma, and 63 (2.2%) with non-atopic asthma. 294 children (10.4%) were identified with abnormal emotional symptoms. Children with abnormal emotional symptoms were different from children with normal/borderline emotional symptoms in relation to lower parental income ($p = 0.0001$), more atopic asthma and non-atopic asthma ($p < 0.0001$), and more atopic eczema ($p < 0.03$; Table 1). There was no significant difference by the presence of abnormal emotional symptoms in gender, parental education, BMI, positive RAST IgE test, allergic rhinitis, and puberty development.

With regard to differences in asthma phenotype, the prevalence of atopic asthma is higher in boys than in girls ($p < 0.01$; Table 2). Children with non-atopic asthma had a higher BMI ($p < 0.04$) and were less frequently physician-diagnosed with allergic rhinitis ($p < 0.0001$), but not in any of the other characteristics.

The association of emotional symptoms from atopic asthma or non-atopic asthma was investigated by logistic regression

models (Table 3). Our results showed that the risk of emotional symptoms was increased for non-atopic asthma when the confounders study center, gender, parental education, household income, BMI, atopic eczema, and allergic rhinitis were included in a multivariate model ($OR_{adj} = 3.39$, $CI_{95\%} = 1.82-6.31$), whereas no significant association showed for atopic asthma ($OR_{adj} = 1.56$, $CI_{95\%} = 0.98-2.50$). Adding pubertal developmental score to the multivariate model, the association between non-atopic asthma and emotional symptoms remained significant ($OR_{adj} = 2.90$, $CI_{95\%} = 1.46-5.73$).

Gender-stratified logistic regression results showed that non-atopic asthma was associated with about 3-fold higher likelihood of emotional symptoms in girls ($OR_{adj} = 3.18$, $CI_{95\%} = 1.23-8.23$), whereas no significant association showed for boys ($OR_{adj} = 2.37$, $CI_{95\%} = 0.86-6.55$).

Discussion

Summary of main findings

Considering common inhalant and food allergens, we found an association between non-atopic asthma and abnormal emotional symptoms (clinically relevant depressive or anxiety symptoms), but not with atopic asthma. Thus, we suggest that the relationship between asthma and depression might depend on the non-atopic phenotype in school-aged children. Gender-stratified results showed that the non-atopic asthma/emotional symptoms relationship remained statistically significant in girls.

Possible explanations for the observed difference between non-atopic asthma and emotional symptoms in children with advancing puberty

Our results do not support atopy as an explanation for the mechanisms behind both allergic and depressive symptoms. Our results are in line with a recent study that has also reported non-atopic asthma increases risk for depression (7). They found that the association between non-atopic asthma and depression was more frequent in girls at age 11–14, and we also found that the association was restricted to girls.

The association between non-atopic asthma and emotional symptoms in our study was only minimally confounded by socioeconomic background, BMI, and other allergic diseases. This is against previous suggestions, as socioeconomic factors (17) and childhood adversities (18) are associated with depression.

One explanation for the depression/non-atopic asthma relationship is that children at age 10 experience specific developmental challenges during advanced pubertal development. Children at this age must not only comply with their chronic condition but also with the general developmental challenges associated with maturation: transitioning to more advanced cognitive abilities, becoming a separate and independent person, and fitting with peers and the social environment (19). There may have been a serious risk for the coexistence of non-atopic asthma and depression in our study sample from the cumulative effects of these specific developmental challenges.

Table 1 Characteristics of the GINI-plus and LISA-plus Study sample (N = 2814) stratified by the presence of abnormal emotional symptoms at 10-year follow-up

	Normal/borderline emotional symptoms N = 2520 (89.6%)		Abnormal emotional symptoms N = 294 (10.4%)		p-Value
	n/N mean	% SD	n/N mean	% SD	
Age	10.05	0.18	10.05	0.17	0.9232
Study group					
GINI-plus	1568/2520	62.2	194/294	66.0	0.2068
LISA-plus	952/2520	37.8	100/294	34.0	
Study center					
Munich	1385/2520	55.0	171/294	58.2	0.3735
Leipzig	239/2520	9.5	219/294	6.5	
Bad Honnef	132/2520	5.2	15/294	5.1	
Wesel	764/2520	30.3	87/294	30.3	
Gender					
Boys	1295/2520	51.4	145/294	49.3	0.5080
Girls	1225/2520	48.6	149/294	50.7	
Parental education					
High	1667/2413	69.1	180/285	63.2	0.0937
Medium	618/2413	25.6	84/285	29.5	
Low	128/2413	5.3	21/285	7.4	
Income					
High	1841/2520	73.1	181/294	61.6	0.0001
Medium	514/2520	20.4	82/294	27.9	
Low	165/2520	6.6	31/294	10.5	
BMI	17.35	2.45	17.62	2.73	0.0796
Positive RAST IgE test					
No	1393/2520	55.3	159/294	54.1	0.6964
Yes	1127/2520	44.7	135/294	45.9	
Physician diagnosis of asthma ever and positive RAST IgE at age 10					
0 No asthma	2318/2520	92.0	251/294	85.4	<0.0001
1 Atopic asthma	155/2520	6.2	27/294	9.2	
2 Non-atopic asthma	47/2520	1.9	16/294	5.4	
Physician diagnosis of atopic eczema at 10 years					
No	2319/2433	95.3	266/288	92.4	0.0296
Yes	114/2433	4.7	22/288	7.6	
Physician diagnoses of allergic rhinitis at 10 years					
No	2217/2426	91.4	252/286	88.1	0.0668
Yes	209/2426	8.6	34/286	11.9	
Puberty development scale (PDS): markers of pubertal development					
0 None	1771/2237	79.2	186/253	73.5	0.1005
1 Marker	274/2237	12.3	34/253	13.4	
2 Markers	133/2237	6.0	22/253	8.7	
3 Markers	54/2237	2.4	11/253	4.4	
4 Markers	5/2237	0.2	0	0	

*Educational status of parents defined as 1 = high, 2 = medium, 3 = low.

†Income status of parents defined as 1 = high, 2 = medium, 3 = low.

**p-Value (< 0.01) significant.

Another explanation for our findings is the diathesis-stress model (20) implying stress-related hormonal effects on neurotransmitter systems exerted via the HPA as a complex interaction of biological predisposition and environmental triggers. The latter hypothesis suggests that the stress and psychosocial impairment induced by asthma underlies our observed association. According to this theory, we may

hypothesize that asthma might have affected stress-related hormonal effects, which might have led to more depressive symptoms in our children, but the cross-sectional nature of our data does not allow causal conclusions. How atopic status in asthma may influence stress and deregulation of HPA remains to be elucidated in future studies.

Table 2 Characteristics of children with atopic vs. non-atopic asthma

	Atopic asthma (n = 182)		Non-atopic asthma (n = 63)		p-Value
	n/N mean	% SD	n/N mean	% SD	
Age	10.04	0.23	10.04	0.15	0.9808
Gender					
Boys	123/182	67.6	31/63	49.2	0.0093
Girls	59/182	32.4	32/63	50.8	
Parental education					
High	120/175	68.6	33/60	55.0	0.0968
Medium	49/175	28.0	22/60	36.7	
Low	6/175	3.4	5/60	8.3	
Income					
High	133/182	73.1	38/63	60.3	0.0965
Medium	40/182	22.0	18/63	28.6	
Low	9/182	5.0	7/63	11.1	
BMI	17.39	2.67	18.22	3.15	0.0441
Physician diagnosis of atopic eczema at 10 years					
No	159/178	89.3	53/59	89.8	0.9129
Yes	19/178	10.7	6/59	10.2	
Physician diagnoses of allergic rhinitis at 10 years					
No	110/175	62.9	57/60	95.0	<0.0001
Yes	65/175	37.1	3/60	5.0	
Abnormal Emotional problems					
No	155/182	85.2	47/63	74.6	0.0575
Yes	27/182	14.8	16/63	25.4	
Puberty development scale (PDS): markers of pubertal development					
0 None	132/164	80.5	37/54	68.5	0.1215
1 Marker	20/164	12.2	8/54	14.8	
2 Markers	7/164	4.3	7/54	13.0	
3 Markers	5/164	3.1	2/54	3.7	

Table 3 Unadjusted and adjusted regression estimates for the association between asthma and SDQ abnormal emotional problems at 10 years of age

	SDQ Abnormal emotional problems												
Predictors	Unadjusted OR	95% CI			p	Adjusted* OR	95% CI		p	Adjusted† OR	95% CI		p
No asthma	1	—			—	1	—		—	1			
Atopic asthma‡	1.61	1.05	2.47	0.0298	1.56	0.98	2.50	0.0622	1.35		0.81	2.26	0.2551
Non-atopic asthma§	3.15	1.76	5.63	0.0001	3.39	1.82	6.31	0.0001	2.90		1.46	5.73	0.0023
Girls													
Atopic asthma	1.81	0.90	3.66	0.0985	1.63	0.76	3.47	0.2075	1.08		0.43	2.74	0.8702
Non-atopic asthma	3.47	1.57	7.66	0.0021	4.30	1.83	10.12	0.0008	3.18		1.23	8.23	0.0172
Boys													
Atopic asthma	1.54	0.90	2.66	0.1183	1.54	0.84	2.82	0.1590	1.56		0.83	2.93	0.1638
Non-atopic asthma	2.81	1.19	6.66	0.0189	2.51	0.98	6.39	0.0545	2.37		0.86	6.55	0.0951

OR for atopic/non-atopic asthma at age 10 years for prediction of SDQ abnormal emotional problems.

*Adjusted for study center, gender, parental education, household income, BMI, atopic eczema, allergic rhinitis.

†Adjusted for model1 plus pubertal status.

‡Asthma ever and SX1 or FX5 allergens.

§Asthma ever and no SX1 and no FX5 allergens.

Discussion of the observed gender difference

Why does the relationship between asthma and emotional symptoms only show in the non-atopic asthma phenotype in girls? Gender-related effects might be important factors in the relationship of depression with non-atopic and atopic asthma. Studies throughout puberty support a greater incidence of asthma in females (14), and also in depression with a female/male risk ratio of about 2:1. (13). Thus, possible explanations for the gender difference are hormonal changes and gender-specific differences in environmental exposures with advancing puberty (21).

It might have been the case that some females matured physically earlier than normally expected at age 10. This earlier maturation might have led to an increased risk for emotional symptoms. This hypothesis is supported by evidence that earlier maturation in girls is linked to higher likelihood of depression (22), and also raises their risk of asthma (23).

Strengths and limitations

The strength of our study was its population based, wide generalizability, and comparison of children with atopic vs. non-atopic asthma and a non-asthma reference group. It offered the possibility to investigate asthma phenotypes, behavior problems, and a wide range of potential confounders. Our results are based on data of two independent population-based birth cohorts. Stratified analysis for both studies showed similar results.

Our study has also limitations; first, due to the small sample size of children with non-atopic asthma and atopic asthma, we may not have had enough power to detect differences between asthma phenotypes in several characteristics. However, we could demonstrate a significant relationship with emotional symptoms. Second, because the present analyses were cross-sectional, the direction of the relationship of both disorders cannot be determined, but there is evidence for the relationships to be bidirectional: Early development of respiratory symptoms and asthma is associated with a greater risk of depressive and anxiety disorders (24), and early development of psychiatric disorders is associated with a greater subsequent risk of asthma (18). Third, the use of questionnaires that indicates no exact physician diagnoses. However, we used the standardized and well-validated, brief SDQ behavioral screening that has been especially developed for use in epidemiological studies. Due to

our study design, we had to rely solely on parental report of physician diagnoses and behavioral problems, and reporting biases limit generalization of our results to parent-rated data. Fourth, aspects of childhood adversities (18), such as physical abuse, sexual abuse, divorce, family violence that are likely to have an impact on both asthma and mental health in childhood were not included as confounders, effect on our results is unknown. Finally, one of the possible important confounding variables considered by previous studies (25) but not by us was the influence of mothers' psychopathology. However, there are discrepant findings that mothers' mental health may increase the risk of asthma (26).

Conclusions

The observed relationship between the non-atopic asthma phenotype and emotional symptoms might be dependent on gender. The differential association of asthma phenotypes with depression and gender requires further investigation. Independently of the presence of an atopy, primary care physicians should be aware of the increased psychopathology of children with asthma around puberty, because psychiatric symptoms are known to be associated with higher asthma symptom burden (27), and additive functional impairment in youth (28).

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Conflict of interest

No conflict of interest declared.

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Supporting Information

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

Appendix S1. GINI-plus Study Group and LISA-plus Study Group.

Appendix S1 GINI-plus Study Group and LISA-plus Study Group:

§The GINI-plus Study Group comprises the Helmholtz Zentrum München, German Research Center for Environmental Health, Institute of Epidemiology, Munich (Heinrich J, Wichmann HE, Sausenthaler S, Zutavern A, Chen, Chih-Mei, Schnappinger M, Rzehak P); Department of Pediatrics, Marien-Hospital, Wesel (Berdel D, von Berg A, Beckmann C, Groß I); Department of Pediatrics, Ludwig Maximilians University, Munich (Koletzko S, Reinhardt D, Krauss-Etschmann S); Department of Pediatrics, Technical University, Munich (Bauer CP, Brockow I, Grübl A, Hoffmann U); IUF - Institut für Umweltmedizinische Forschung at the Heinrich-Heine-University, Düsseldorf (Krämer U, Link E, Cramer C); Centre for Allergy and Environment, Technical University, Munich (Behrendt H).

§§ The LISA-plus Study Group consists of the following: Helmholtz Zentrum München, German Research Center for Environmental Health, Institute of Epidemiology, Munich (Heinrich J, Wichmann HE, Sausenthaler S, Chen CM, Schnappinger M); Department of Pediatrics, Municipal Hospital “St.Georg”, Leipzig (Borte M, Diez U), Marien-Hospital Wesel, Department of Pediatrics, Wesel (von Berg A, Beckmann C, Groß I); Pediatric Practice, Bad Honnef (Schaaf B); Helmholtz Centre for Environmental Research – UFZ, Department of Environmental Immunology/Core Facility Studies, Leipzig (Lehmann I, Bauer M, Gräbsch C, Röder S, Schilde M); University of Leipzig, Institute of Hygiene and Environmental Medicine, Leipzig (Herbarth O, Dick C, Magnus J); IUF - Institut für Umweltmedizinische Forschung, Düsseldorf (Krämer U, Link E, Cramer C); Technical University Munich, Department of Pediatrics, Munich (Bauer CP, Hoffmann U); ZAUM - Center for Allergy and Environment, Technical University, Munich (Behrendt H, Grosch J, Martin F).