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Perinatal influences on the development of asthma and atopy in childhood

Sabina Illi, PhD^{*}; Juliane Weber, MD^{*}; Anne Zutavern, MD^{*}; Jon Genuneit, MD[†]; Rudolf Schierl, PhD[‡]; Christine Strunz-Lehner, MPH^{*}; and Erika von Mutius, MD^{*}

^{*} University Children's Hospital, Munich, Germany

[†] Institute of Epidemiology and Medical Biometry, University of Ulm, Ulm, Germany

[‡] Institute and Outpatient Clinic for Occupational, Social and Environmental Medicine, University Hospital of Munich, Munich, Germany

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ABSTRACT

Background: In most children with asthma and atopy, onset of disease occurs early in life, indicating a crucial role of in utero and early childhood environment. However, only a small part of this burden of disease established early in life has been explained.

Objective: To examine the effects of early environmental exposures on the development of asthma and atopy within the setting of an affluent urban population.

Methods: The authors followed 526 German children from birth to 5 years of age. Parental interviews in pregnancy and then yearly assessed the health of the child and environmental characteristics. Endotoxin and allergens in house dust were measured at 3 months. Atopic sensitization was assessed at 1 and 5 years.

Results: In atopic mothers, acute atopic symptoms during pregnancy were associated with increased risk of early atopic dermatitis (adjusted odds ratio [aOR] 1.74, 95% confidence interval [CI] 1.00–3.02) and allergic rhinitis at 5 years (aOR 2.11, 95% CI 1.01–4.41). Further, maternal illnesses during pregnancy (ie, repeated common colds) increased the risk of asthma at 5 years (aOR 2.31, 95% CI 1.12–4.78). Endotoxin in the child's mattress was inversely associated with atopic sensitization (aOR 0.79, 95% CI 0.64–0.97) and asthma (aOR 0.71, 95% CI 0.55–0.93). A contrasting effect of early endotoxin and mite exposure was observed for mite sensitization: mite exposure increased the risk of mite sensitization at 5 years (aOR 1.30, 95% CI 1.11–1.53), whereas endotoxin exposure was inversely associated with mite sensitization (aOR 0.73, 95% CI 0.57–0.95).

Conclusion: Factors affecting the in utero environment, such as maternal atopy and infections, and bacterial exposure in pregnancy or early life may act as immunomodulators enhancing or inhibiting the development of asthma and atopy in childhood.

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Introduction

In most children with asthma and atopy, the onset of disease occurs early in life, indicating a crucial role of the in utero environment and of determinants acting in early childhood.^{1,2} However, only a small part of this burden of disease established early in life has been explained. Among others, the role of maternal illnesses during pregnancy has not been resolved, and the role of bacterial and allergen exposure in early life coherently has not been clarified.

The German PAULA (Perinatal Asthma and Environment Long-term Allergy Study) birth cohort was designed within the framework of the Asthma Multicentre Infants Cohort Study (AMICS), a consortium of 4 separate birth cohorts in England, Spain, and

Germany with common study protocols.^{3–6} The aim of these studies was to determine the relation between environmental factors relating to the early development and severity of atopy and the early indications of the development of an asthmatic phenotype. The specific focus was on environmental influences and infection as etiologic factors in atopy and asthma in young children. The German PAULA study comprises a comprehensive assessment of pregnancy-related and early life factors and early endotoxin and allergen exposures. The objective was to shed light on the association of early environment and the outcome of asthma and atopy up 5 years of age in an urban and affluent population.

Methods

Cohort Recruitment and Follow-up

The aim of the longitudinal PAULA study was to examine the effects of pre- and postnatal environmental and lifestyle-based exposures on the development of asthma and atopy in childhood within the fairly affluent and urban setting of Greater Munich, Germany. Recruitment took place from October 1999 to December

Reprints: Sabina Illi, PhD, Dr von Hauner Children's Hospital, Ludwig-Maximilians-University Munich, Member of the German Center for Lung Research, Lindwurmstrasse 4, 80337 Munich, Germany; ; E-mail: sabina.illi@med.uni-muenchen.de.

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2001. All pregnant women presenting for antenatal care in the obstetric department of 1 inner city hospital were invited to participate in the study. Exclusion criteria were hospital admission during pregnancy, no permanent residence within Greater Munich, not having a telephone, and no proficient German-language capability. Five hundred thirteen eligible women agreed to participate, resulting in 526 live births. The cohort was followed until the fifth birthday of each child. The study was approved by the ethics committee of the Bavarian Medical Association. Written informed consent was obtained from all study participants. The Munich birth cohort is part of the AMICS that previously recruited 3 separate birth cohorts in Ashford (United Kingdom), Barcelona (Spain), and Menorca Island (Spain).^{3–6}

Questionnaires

During pregnancy and when the child was 3 and 12 months old and then yearly up to 5 years of age, parents were interviewed to assess the health status of the child and the environmental and socioeconomic characteristics of the household. Questions concerned asthmatic and atopic symptoms and diagnoses and factors concerning hygiene, environmental factors, and socioeconomic factors. Among others, parental history of atopic diseases, maternal illnesses during pregnancy, level of parental education, parental smoking, pet ownership, household size, living space, and number of siblings were assessed.

Definition of Atopic and Wheezing Outcomes

Study outcomes were defined in analogy to other AMICS populations.^{3–5} Symptoms of atopic dermatitis in the first year of life were defined as an itchy rash that came and went or that lasted at least 3 months. In the second year of life, symptoms of atopic dermatitis were defined as an itchy rash with scratching and rubbing on the inner elbows, back of the knees, ankles, neck, or around the eyes. Early atopic dermatitis was defined as present if at least 1 of the following applied in the first 2 years of life: (1) reported doctor's diagnosis, (2) parental reporting of symptoms of atopic dermatitis, and (3) visible atopic dermatitis at the time of the 1-year follow-up based on a positive Scoring Atopic Dermatitis index. Early wheeze was defined as any wheezing in the first 3 years of life. Current wheeze at 4 to 5 years of age was defined as any wheezing in the previous 12 months at the 4- or 5-year follow-up, and current allergic rhinitis at 4 to 5 years of age was defined as sneezing or a runny, blocked, or itchy nose without a cold in the previous 12 months at the 4- or 5-year follow-up. A doctor's diagnosis of asthma ever was defined as a doctor's diagnosis of asthma at least once or a doctor's diagnosis of recurrent wheezy bronchitis ever with repeated (≥ 2) episodes of wheeze up to 5 years of age. Early food sensitization, early atopic dermatitis, current allergic rhinitis, and current inhalant sensitization were grouped as "atopic nonwheezing outcomes" and early and late wheeze and a doctor's diagnosis of asthma were grouped as "wheezing outcomes."

Atopic Sensitization of the Child

At the 1- and 5-year follow-ups, the children were invited to the clinic for the assessment of atopic sensitization. At 1 year blood samples were taken and serum total IgE levels and specific IgE antibodies to relevant food allergens (cow's milk and egg white) were determined by CAP-RAST FEIA (Pharmacia & Upjohn, Freiburg, Germany). Early food sensitization was defined as specific IgE antibodies of at least 0.35 kU/L against either allergen. At 5 years the children underwent skin prick testing to common inhalant allergens: house dust mites (*Dermatophagoides pteronyssinus* and *Dermatophagoides farinae*), cat, *Alternaria* species, grass mix, birch, and hazelnut. A child was defined as sensitized to the respective

allergen if it provoked a mean wheal diameter at least 2 mm larger than that from a negative (saline) control. Current inhalant sensitization was defined as any positive prick test result at 5 years of age.

Parental Atopy and Illnesses

At recruitment in pregnancy, health information was collected from the parents, including a history of allergic diseases and current maternal symptoms, illnesses, and medication during pregnancy. Parental atopy was defined as a reported doctor's diagnosis of asthma, hay fever, or atopic dermatitis. Current maternal atopic symptoms in pregnancy were defined as symptoms of asthma, hay fever, or atopic dermatitis during pregnancy. The number of maternal colds during pregnancy was assessed by the question: "Since beginning of the pregnancy, how often did you have a common cold, eg, runny or stuffed nose, cough, hoarseness, or tonsillitis?" Furthermore, blood samples were taken from both parents to assess specific IgE to 20 common food and inhalant allergens as determined by CAP-RAST FEIA (Pharmacia & Upjohn). Parental atopic sensitization was defined as a specific IgE level of at least 0.35 kU/L to any of the tested allergens.

Allergens and Endotoxin in Dust

At 3 months of age, each family was visited at home by a trained field worker and dust samples were collected. These samples were assayed for concentrations of endotoxin, house dust mite (Der p 1 and Der f 1), and cat (Fel d 1) allergens using standard techniques as described previously.^{6,7} In brief, separate dust samples were collected by vacuuming the child's and mother's mattresses and the living room floor. The main focus of dust analysis was on the assessment of endotoxin. When limited dust was available for a specific site, endotoxin was analyzed first and then the remaining dust was analyzed for the allergens. All allergens were measured by monoclonal antibody enzyme-linked immunosorbent assays and resulting allergen levels were expressed as micrograms per gram of dust. The concentrations of Der p 1 and Der f 1 were added and are presented as the "mite allergen level." Endotoxin content of the dust samples was determined by a kinetic Limulus assay (kinetic-QCL, Lonza Ltd, Basel, Switzerland) with potency against *Escherichia coli* O55:B5 of 13 endotoxin units per nanogram. Resulting endotoxin levels were expressed as endotoxin units per milligram of dust. To take different sleeping situations into account, the authors asked the mother at the child's age of 3 months where the child mostly slept: in its own or in the mother's bed. Based on this information, the respective endotoxin and allergen levels from the child's and mother's mattresses were combined and a new exposure variable, "where the child sleeps," was defined by taking the respective value from the mother's mattress if the child mostly slept there and from the child's mattress otherwise. Low and high exposures of endotoxin and mite allergen levels were defined as levels below or above the respective median. Based on these dichotomized exposures, 4 distinct exposure groups were defined to assess the combined effect on relevant outcomes: (1) high mite allergen/low endotoxin, (2) high mite allergen/high endotoxin, (3) low mite allergen/low endotoxin, and (4) low mite allergen/high endotoxin exposure. This combined variable was based on endotoxin from the child's mattress and defined separately for mite allergen from the mother's and from the child's mattress.

Statistical Analyses

All children with at least 1 nonmissing outcome were included in the statistical analyses. Owing to missing values for questionnaire-based items and for laboratory measurements, the total sample size for various variables may vary. The association of early life exposures with outcomes was assessed by logistic

Table 1
Characteristics and atopic outcomes of study population

Characteristics	n/N	%
Parental atopy (diagnosis of asthma, hay fever, or atopic dermatitis)	311/508	61.2%
Maternal atopy	194/513	37.8%
Paternal atopy	194/502	38.6%
Parental atopic sensitization	333/431	77.3%
Maternal atopic sensitization	216/473	45.7%
Paternal atopic sensitization	203/386	52.6%
Maternal atopic symptoms in pregnancy	125/513	24.4%
Maternal colds in pregnancy, n		
0	123/509	24.2%
1	213/509	41.8%
2	129/509	25.3%
≥3	44/509	8.6%
High maternal education (college, university)	225/513	43.9%
High paternal education (college, university)	300/504	59.5%
Maternal smoking ever at birth	203/513	39.6%
Cat at home		
During pregnancy	49/503	9.7%
At 1 y of age	30/458	6.5%
Dog at home		
During pregnancy	27/496	5.4%
At 1 y of age	22/456	4.8%
Older siblings, n		
0	279/513	54.4%
1	191/513	37.2%
≥2	43/513	8.4%
Atopic and wheezing outcomes		
Early in life		
Early sensitization to egg or milk (1 y)	32/370	8.6%
Early atopic dermatitis (≤2 y)	167/476	35.1%
Early wheeze (≤3 y)	108/505	21.4%
At end of follow-up		
Doctor's diagnosis of asthma ever	42/501	8.4%
Current wheeze (4–5 y)	48/504	9.5%
Current allergic rhinitis (4–5 y)	68/494	13.8%
Any current inhalant sensitization (5 y)	82/361	22.7%
Current sensitization to indoor allergens (5 y)	50/361	13.8%
Current sensitization to pollen (5 y)	60/361	16.6%

Results

Characteristics and Outcomes

Of the 526 children in the PAULA cohort, 513 (97.5%) had at least 1 nonmissing outcome and thus were included in the analyses. Mean gestational age at the time of study inclusion and pregnancy-related questionnaire was 36.8 ± 1.8 weeks. Mean completed weeks of gestation at birth was 39.7 ± 1.5 , and 20 infants (3.9%) were preterm. Of the 513 study children, 136 (26.5%) were born by cesarean section. Mean birthweight was $3,359.7 \pm 522.4$ g. Table 1 lists the characteristics of the study population. A large proportion of families reported an atopic background: in 61.2% of families, either parent had a doctor's diagnosis of asthma, hay fever, or atopic dermatitis. This large percentage of parental atopy also was observed when validating the data by specific IgE: in 77.3% of 431 families with nonmissing parental IgE data, at least 1 parent showed elevated specific IgE to at least 1 of the tested allergens. The relative affluence of the study population is depicted by the high level of education of both parents. Furthermore, more than half the study children were firstborns. As presented in Table 1, the high prevalence of parental atopy was in contrast to the fairly low prevalence in the children (early sensitization to egg or milk 8.6%, early atopic dermatitis 35.1%, early wheeze 21.4%, doctor's diagnosis of asthma ever 8.4%, current wheeze 9.5%, current allergic rhinitis 13.8%, any current inhalant sensitization 22.7%). To assess potential confounding, the association of parental smoking (in pregnancy and currently), mode of delivery, gestational age at birth, birthweight, parental education, pet keeping, and older siblings with all outcomes was analyzed. Older siblings were associated with a lower risk of atopic outcomes, significantly so for early atopic dermatitis (Table 2). None of the other factors showed a significant association with any of the outcomes (data not shown).

Maternal History of Atopy

Parental atopy was associated with an increased risk for non-wheezing atopic outcomes, especially with those assessed at 5 years of age (ie, allergic rhinitis and atopic sensitization; Table 2). In contrast, no association was observed between parental atopy and wheezing outcomes in the child (Table 3).

For the nonwheezing atopic outcomes, the effect of maternal atopy was strongest not only if the mother reported a doctor's diagnosis of atopy but also if current symptoms during pregnancy were prevalent. These associations remained significant even in the subgroup of mothers with an underlying history of atopy (Table 4). This effect was mediated mainly by the association of current maternal symptoms of hay fever and atopic dermatitis in pregnancy and the respective outcome in the child (aOR 2.42, 95% CI

regression analysis and are presented as odds ratio (OR) or as OR adjusted for the potential confounders maternal atopy and older siblings (aOR) and 95% confidence interval (95% CI). Endotoxin and allergen levels are presented as median and interquartile range and as geometric mean and 95% CI. For inclusion in regression models, endotoxin and allergen levels were logarithmically transformed. Statistical analysis was performed with SAS 9.2 (SAS Institute, Cary, North Carolina); a *P* value of .05 was considered significant. Owing to the exploratory character of the analysis, corrections for multiple testing were not performed.⁸

Table 2
Association of characteristics of study population with atopic outcomes

	Early food sensitization			Early atopic dermatitis			Current allergic rhinitis			Current inhalant sensitization		
	OR	95% CI	<i>P</i> value	OR	95% CI	<i>P</i> value	OR	95% CI	<i>P</i> value	OR	95% CI	<i>P</i> value
Parental atopy	1.73	0.78–3.86	.178	1.36	0.92–2.02	.126	2.36	1.30–4.26	.005	2.81	1.58–5.00	<.001
Maternal atopy	2.43	1.17–5.06	.018	1.30	0.88–1.90	.185	1.73	1.04–2.90	.036	2.28	1.38–3.76	.001
Paternal atopy	2.04	0.97–4.29	.059	1.43	0.97–2.10	.075	2.18	1.30–3.65	.003	2.04	1.23–3.39	.006
Parental atopic sensitization	2.03	0.68–6.02	.204	1.67	0.99–2.82	.053	2.99	1.24–7.18	.014	3.34	1.52–7.32	.003
Maternal atopic sensitization	2.11	0.99–4.49	.053	1.25	0.84–1.86	.266	1.48	0.86–2.55	.155	3.99	2.32–6.85	.000
Paternal atopic sensitization	1.62	0.72–3.66	.246	1.51	0.97–2.34	.067	2.28	1.22–4.27	.010	1.66	0.94–2.91	.079
Maternal atopic symptoms in pregnancy	2.78	1.32–5.84	.007	1.60	1.05–2.45	.029	2.19	1.27–3.75	.005	2.78	1.65–4.69	<.001
Maternal colds in pregnancy, n												
0	1.00	—	—	1.00	—	—	1.00	—	—	1.00	—	—
1	0.91	0.36–2.26	.831	1.01	0.62–1.63	.981	1.20	0.62–2.34	.582	0.89	0.46–1.69	.713
2	0.81	0.29–2.27	.693	1.15	0.68–1.97	.600	0.87	0.40–1.88	.715	1.11	0.56–2.22	.757
≥3	0.34	0.04–2.87	.323	1.11	0.53–2.33	.784	1.32	0.50–3.50	.574	0.74	0.27–2.07	.567
Older siblings	0.47	0.21–1.04	.062	0.61	0.42–0.89	.011	0.60	0.35–1.02	.059	0.70	0.43–1.16	.166

Abbreviations: CI, confidence interval; OR, odds ratio.

Table 3

Association of characteristics of study population with wheezing outcomes

	Early wheeze			Current wheeze			Doctor's diagnosis asthma ever		
	OR	95% CI	P value	OR	95% CI	P value	OR	95% CI	P value
Parental atopy	1.06	0.68–1.64	.803	1.45	0.76–2.74	.256	1.87	0.92–3.81	.086
Maternal atopy	1.21	0.79–1.87	.379	1.75	0.96–3.17	.067	1.39	0.74–2.63	.309
Paternal atopy	1.09	0.70–1.68	.707	1.27	0.70–2.32	.436	2.41	1.26–4.61	.008
Parental atopic sensitization	1.18	0.67–2.07	.572	1.13	0.52–2.45	.755	0.78	0.36–1.68	.530
Maternal atopic sensitization	1.15	0.74–1.79	.528	1.55	0.83–2.88	.165	0.98	0.51–1.88	.948
Paternal atopic sensitization	1.20	0.74–1.95	.470	0.75	0.38–1.49	.413	1.04	0.50–2.15	.916
Maternal atopic symptoms in pregnancy	1.30	0.81–2.09	.284	1.17	0.60–2.29	.650	0.96	0.46–2.01	.907
Maternal colds in pregnancy, n									
0	1.00	—	—	1.00	—	—	1.00	—	—
1	1.27	0.70–2.28	.428	0.93	0.41–2.13	.870	1.02	0.42–2.52	.958
2	1.60	0.85–3.00	.143	1.50	0.65–3.48	.345	1.49	0.59–3.77	.404
≥3	2.31	1.04–5.12	.039	2.18	0.77–6.14	.141	3.23	1.13–9.23	.029
Older siblings	1.12	0.73–1.71	.604	0.91	0.50–1.66	.761	1.32	0.70–2.48	.395

Abbreviations: CI, confidence interval; OR, odds ratio.

1.11–5.25 for maternal atopic dermatitis vs. early atopic dermatitis in the child and aOR 2.52, 95% CI 1.24–5.12 for maternal hay fever vs. allergic rhinitis in the child).

Maternal Infections in Pregnancy

In contrast to current maternal atopic symptoms in pregnancy that were associated with nonwheezing atopic outcomes, the number of maternal colds in pregnancy was associated with the wheezing outcomes: the more colds a mother reported during pregnancy, the greater the risk for early wheeze, for a doctor's diagnosis of asthma and, although nonsignificantly so, for current wheeze. These associations remained significant even after adjustment for maternal atopy and older siblings, which might have led to an increased rate of infections within the family (Table 5). Similarly, adjustment for intake of antibiotics or paracetamol and for smoking in pregnancy did not change these associations (data not shown). Furthermore, this association was independent of whether the mother also reported fever with her infection (data not shown).

Allergen and Endotoxin Exposures

When analyzing the levels of allergen and endotoxin exposure assessed from house dust at 3 months of age (eTable 1), it has to be kept in mind that owing to the very small amounts of dust available from the children's mattresses, only endotoxin was assessed for most of these samples: although 62% of the 447 living room floor samples and 63% of the 480 samples from the mother's mattress contained enough dust to analyze allergen and endotoxin levels, this was the case for only 11% of the 408 samples from the child's mattress.

Unadjusted analysis of the association of early endotoxin levels with the atopic and wheezing outcomes showed significant inverse results for early food sensitization, current inhalant sensitization, current wheeze, and doctor's diagnosis of asthma ever (Fig 1).

These inverse associations, however, were observed only for endotoxin levels in the child's mattress; no such effect was seen for the carpet or the maternal mattress. All results remained essentially unchanged when adjusting for maternal atopy and older siblings (Tables 6 and 7). When assessing the allergens assessed in the prick test separately, only mite sensitization (Table 6) and birch sensitization (data not shown) were decreased with increasing levels of endotoxin in the child's mattress. No association with sensitization to any other tested allergen at 5 years of age was observed (data not shown).

In contrast to endotoxin, early mite and cat allergen exposures were significantly associated with an increased risk of the respective type of sensitization 5 years later, ie, cat allergen levels in the carpet for cat sensitization and mite allergen levels in the carpet and the mother's mattress for mite sensitization (Table 6). Mite allergen levels in the child's mattress also showed an increased risk for mite sensitization, although not significantly so, potentially because of the very small numbers. Within the group of children with parental atopy, the association of mite allergen levels in the child's mattress and mite sensitization reached significance ($N = 24$, OR 2.00, 95% CI 1.01–3.99, $P = .048$).

At 3 months of age, 37 of 505 mothers (7.3%) reported that her child slept in her bed. When defining the exposure variable "where the child sleeps," all results remained basically identical to results for levels from the child's mattress alone (data not shown). Only the association between early mite exposure and early wheeze was strengthened: children with higher levels of mite allergen exposure in the mattress they mostly slept on were at increased risk of early wheeze, although not significantly so. In contrast, the inverse but nonsignificant association of cat allergen levels in the mother's mattress and early wheeze was no longer present when using the allergen levels where the child slept (data not shown).

Early endotoxin and mite levels showed contrasting associations with mite sensitization at 5 years of age. When analyzing endotoxin from the child's mattress and mite allergen from the

Table 4

Adjusted analysis of influence of maternal atopic symptoms on atopic outcomes in mothers with an underlying history of atopy

Current atopic symptoms of the mother in pregnancy ^a	Early food sensitization			Early atopic dermatitis			Current allergic rhinitis			Current inhalant sensitization		
	aOR ^b	95% CI	P value	aOR ^b	95% CI	P value	aOR ^b	95% CI	P value	aOR ^b	95% CI	P value
No	1.00	—	—	1.00	—	—	1.00	—	—	1.00	—	—
Yes	2.06	0.78–5.45	.147	1.74	1.00–3.02	.049	2.11	1.01–4.41	.048	1.78	.92–3.47	.088

Abbreviations: aOR, adjusted odds ratio; CI, confidence interval.

^aNo effect on wheeze and asthma.^bAdjusted for older siblings in subgroup of children with an atopic mother.

Table 5

Adjusted analysis of influence of number of maternal colds in pregnancy on wheezing outcomes

Maternal colds during pregnancy, n ^a	Early wheeze			Current wheeze			Doctor's diagnosis asthma ever		
	aOR ^b	95% CI	P value	aOR ^b	95% CI	P value	aOR ^b	95% CI	P value
0	1.00		—	1.00		—	1.00		—
1	1.26	0.70–2.26	.443	0.93	0.41–2.12	.858	1.00	0.41–2.46	1.000
2	1.58	0.84–2.97	.159	1.49	0.63–3.48	.362	1.42	0.55–3.62	.468
≥3	2.28	1.02–5.10	.044	2.27	0.79–6.50	.126	3.09	1.06–8.94	.038

Abbreviations: aOR, adjusted odds ratio; CI, confidence interval.

^aNo effect on nonwheezing atopic outcomes.^bAdjusted for maternal atopy and older siblings.

mother's mattress in a combined analysis, a significant trend was observed (Fig 2): although children with high mite exposure and low endotoxin exposure showed the highest prevalence of mite sensitization at 5 years, the contrasting group of children with low mite exposure and high endotoxin exposure showed the lowest prevalence ($P = .011$ for trend). When including these 4 exposure groups simultaneously in a logistic regression model adjusted for maternal atopy and older siblings, children with low mite exposure and high endotoxin exposure at 3 months of age showed less than one fifth the risk of being sensitized to mites later in life than the reference group with high mite exposure and low endotoxin exposure (aOR 0.15, 95% CI 0.03–0.74, $P = .020$). The respective risks for children with low mite and endotoxin exposure or high mite and endotoxin exposure were in between (aOR 0.39, 95% CI 0.10–1.45, $P = .158$ and aOR 0.61, 95% CI 0.17–2.14, $P = .436$, respectively). Similarly, when applying the same classification to the very few children with available endotoxin and mite allergen levels from the child's mattress, mite sensitization was observed only in the first group with high mite and low endotoxin exposure (50%, 3 of 6), whereas none (0%) of the children in the other 3

groups (0 of 10, 0 of 8, 0 of 7, respectively) were sensitized to mites at 5 years of age.

Discussion

Many studies have observed protective effects of an early-life rural environment on the development of asthma and atopy in childhood. The aim of the PAULA study was to assess the effect of pre- and postnatal environmental and lifestyle-based exposures on childhood atopic disease within the setting of an urban and affluent population. The authors observed a contrasting effect of acute maternal atopic symptoms and common colds during pregnancy on wheezing and atopic outcomes: maternal atopic symptoms during pregnancy in mothers reporting a history of atopy were associated with an increased risk of nonwheezing atopic outcomes, especially of atopic dermatitis and allergic rhinitis, adding risk to an underlying maternal history of atopy. In contrast, reported repeated common colds during pregnancy were associated with an increased risk of the wheezing outcomes up to 5 years of age. This was independent of medication intake and concomitant fever.

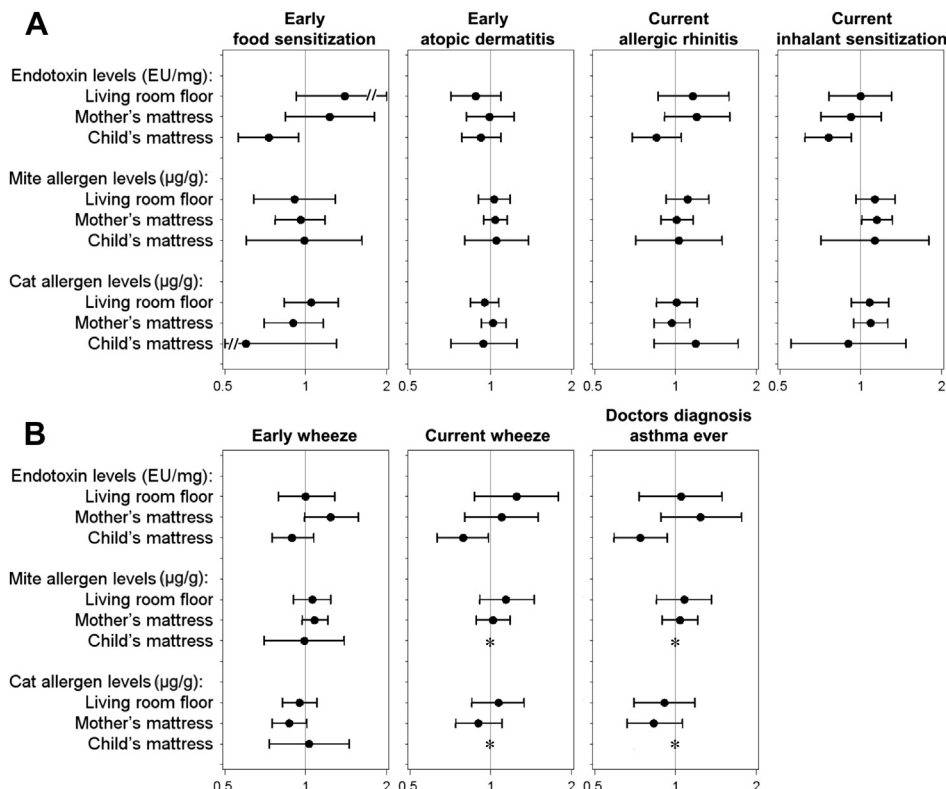


Figure 1. Association of log-transformed early endotoxin and allergen levels with (A) atopic and (B) wheezing outcomes (odds ratio and 95% confidence interval). *Zero cells owing to low numbers for the allergen level in the child's mattress and the respective outcome led to incomputable odds ratios.

Table 6

Association of log-transformed early endotoxin and allergen levels on atopic outcomes, adjusted for maternal atopy and older siblings

	Early food sensitization				Any current inhalant sensitization				Current mite sensitization				Current cat sensitization			
	n	aOR	95% CI	P value	n	aOR	95% CI	P value	n	aOR	95% CI	P value	n	aOR	95% CI	P value
Endotoxin levels (EU/mg)																
Living room floor	312	1.37	0.91–2.05	.127	304	0.96	0.73–1.26	.770	304	0.97	0.66–1.42	.860				
Mother's mattress	346	1.29	0.89–1.89	.181	337	0.93	0.72–1.21	.593	337	1.23	0.85–1.77	.273				
Child's mattress	301	0.75	0.57–0.98	.038	290	0.79	0.64–0.97	.027	290	0.73	0.57–0.95	.018				
Mite allergen levels (μg/g)																
Living room floor		—							187	1.31	1.07–1.61	.009				
Mother's mattress		—							203	1.30	1.11–1.53	.001				
Child's mattress		—							32	1.86 ^a	0.91–3.79	.089				
Cat allergen levels (μg/g)																
Living room floor		—											187	1.57	1.15–2.14	.004
Mother's mattress		—											203	1.09	0.88–1.36	.442
Child's mattress		—											32	1.11	0.64–1.92	.713

Abbreviations: aOR, adjusted odds ratio; CI, confidence interval; EU, endotoxin units.

^aUnadjusted odds ratio owing to too small sample.

When analyzing the association of early exposure to endotoxin in the child's home and atopic and wheezing outcomes at 5 years of age, a consistent inverse association of endotoxin levels in the child's mattress was observed. No such effect was observed for the endotoxin levels in the dust from the mother's mattress or the living room. Furthermore, a contrasting effect of early endotoxin and mite exposure on mite sensitization was observed at 5 years of age: although children with elevated exposure to mite allergen at 3 months of age were at significantly increased risk of being sensitized to mites at 5 years, exposure to higher levels of endotoxin at this young age was inversely associated with sensitization to mites at preschool age.

The study participants of the PAULA cohort were selected randomly. However, the parental level of education, maternal age at study entry (32.0 ± 4.1 years), and the percentage of firstborns among the study children indicate a more affluent population of well-educated mothers.

However, when comparing living space, a potential indicator for the affluence of a society, between the participating PAULA families and other German families, living space per person (including the study child) was similar ($27.6 \text{ m}^2/\text{person}$) compared with other German families ($29.4 \text{ m}^2/\text{person}$).⁹ Furthermore, participating families showed a large percentage of parental allergic illnesses. This reflects the tendency for affected parents to be more willing to participate, as observed in other studies.¹⁰

The role of in utero exposure to various determinants for the development of asthmatic and atopic illnesses has repeatedly been reported. It becomes more and more evident that the evolution of the atopic or asthmatic phenotype has its onset in utero. However, little is known about whether acute maternal symptoms of atopy or asthma during pregnancy can enhance the role of an underlying atopic genetic predisposition. In the present analyses, the occurrence of maternal atopic symptoms during pregnancy increased the risk of atopy up to preschool age. A Japanese study on pregnant women with a history of allergic rhinitis observed similar effects: acute symptoms of allergic rhinitis in pregnancy increased the risk of allergic rhinitis but not of any other atopic illness in the

offspring.¹¹ However, owing to small numbers, the authors could not differentiate between symptoms shortly before and during pregnancy. Thus, the authors were not able to clarify whether the effect of maternal atopic symptoms during pregnancy was actually due to timing or whether this was an issue of severity. Potentially, exposure to acute maternal symptoms of atopy in utero could enhance an inflammatory process affecting the unborn child.

When analyzing maternal factors during pregnancy, repeated common colds were associated with an increased risk of wheezing and asthma up to 5 years of age. Similar to the present results, the KOALA Birth Cohort Study observed an increased risk of wheeze in children with mothers who reported a common cold during pregnancy.¹² However, in contrast to the present results, this effect was restricted to wheeze in the first 7 months of life; no effect was observed thereafter. This difference in effect might be due to an underestimation in the KOALA study, because only the mere occurrence of a common cold was assessed and not the number of episodes. The present results show that the risk of wheezing in childhood increases with the number of maternal common colds during pregnancy. Similar to the KOALA study, the occurrence of any common cold during pregnancy showed no effect on wheeze at 5 years of age (OR 1.25, 95% CI 0.60–2.59, $P = .546$). Maternal illnesses were assessed on a retrospective basis at the time of the first study interview in the third trimester of pregnancy. Thus, recall bias owing to an increased awareness of respiratory infections in mothers with asthma cannot be ruled out. However, the authors observed no association of maternal atopy (neither of an atopic history nor of acute symptoms during pregnancy) with the reported number of colds during pregnancy, thus making a differential recall bias improbable.

As observed in previous studies, exposure to endotoxin in early life was associated with a decreased risk of atopic sensitization in the present birth cohort.^{13–15} This inverse association was not restricted to inhalant sensitization but also was observed for sensitization to egg and milk at as young as 1 year of age. Furthermore, in line with other studies, the authors observed an inverse association of early endotoxin with wheeze and asthma and

Table 7

Association of log-transformed early endotoxin and allergen levels on wheezing outcomes, adjusted for maternal atopy and older siblings

Endotoxin levels (EU/mg)	Current wheeze				Doctor's diagnosis asthma ever			
	n	aOR	95% CI	P value	n	aOR	95% CI	P value
Living room floor	432	1.24	0.87–1.76	.240	429	1.03	0.72–1.48	.859
Mother's mattress	468	1.10	0.80–1.50	.567	466	1.22	0.86–1.73	.256
Child's mattress	397	0.80	0.64–1.00	.047	395	0.74	0.58–0.92	.009

Abbreviations: aOR, adjusted odds ratio; CI, confidence interval; EU, endotoxin units.

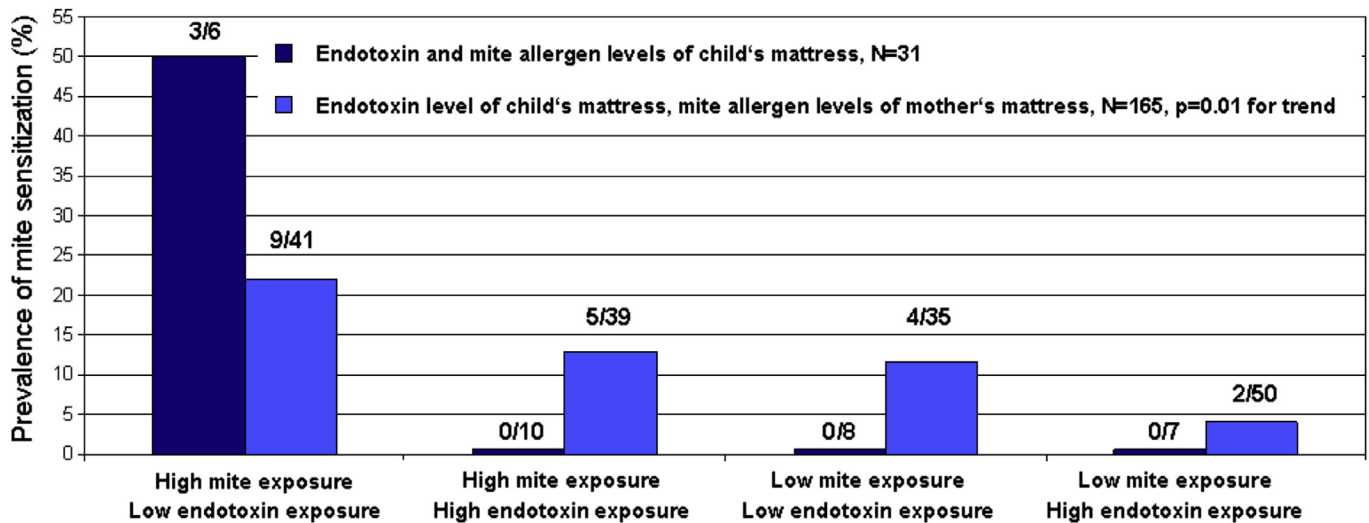


Figure 2. Prevalence of mite sensitization at 5 years of age, stratified for levels of mite and endotoxin exposure. Low exposure was defined as values below the median and high exposure as values above the median. Numbers are presented as sensitized (n) per exposure category (N).

the end of follow-up (ie, at 5 years of age), although no increased risk of early wheeze was observed as recently postulated in a meta-analysis on the association of endotoxin and childhood wheeze and asthma.¹⁶ Interestingly, the authors observed these effects only for endotoxin levels measured in the child's mattress; no significant association was observed for measurements from the mother's mattress or the living room floor. Because none of the environmental variables assessed in the PAULA study were associated with the measured endotoxin levels (data not shown), the effects of the endotoxin from child's bed might be due to reverse causation: endotoxin exposure is not protective against the development of atopic outcomes, but children with atopy might have lower levels of endotoxin released from the gut or skin compared with children without atopy because of a disease-related specific pattern of bacteria. This notion of reverse causation is supported by data from a small study on the source of house dust bacteria in mattresses.¹⁷ According to those data, human-derived bacteria of the occupant account for a large part of the bacterial content of a mattress.

Although cat ownership at birth and 1 year of age showed no effect on any of the outcomes (data not shown), the level of cat allergen measured in the dust from the living room floor was a significant risk factor for cat sensitization at 5 years of age. Similarly, early exposure to elevated levels of mite allergen was associated with an increased risk of mite sensitization 5 years later. This effect contrasted the inverse association of early endotoxin exposure and mite sensitization at preschool age: children with high mite allergen and low endotoxin exposure in early life were at greatest risk of being sensitized to mites. In contrast, children with low mite and high endotoxin exposure showed less than one fifth the risk of being sensitized to mites compared with the high-risk group, indicating the additive effect of favorable home environments. This strengthens the notion that allergen exposure should not be considered in isolation but within the context of microbial exposure. These results also might explain the seemingly counter-intuitive finding from the Manchester Asthma and Allergy Study. In this birth cohort, mite sensitization was increased in the study group with a very stringent environmental control for mite allergen exposure in infancy, possibly because the environmental control also removed endotoxin, ie, a potentially protective factor.¹⁸

In conclusion, this study suggests that illnesses of the mother during pregnancy, such as active hay fever or atopic dermatitis, and repeated viral infections affect the in utero environment and may enhance the outcome of asthmatic and atopic disease in the

offspring. Furthermore, bacterial exposure of the child very early in life might act as an immunomodulator in the development of asthma and atopy in childhood and thus might inhibit the outcome of disease.

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Supplementary Data

Supplementary data related to this article can be found online at <http://dx.doi.org/10.1016/j.anai.2013.11.019>.

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eTable 1

Allergen and endotoxin levels of total study population at 3 months old

Location	Endotoxin (EU/mg)			Mites ($\mu\text{g/g}$)			Cat ($\mu\text{g/g}$)		
	n	Median (IQR)	GM (95% CI)	n	Median (IQR)	GM (95% CI)	n	Median (IQR)	GM (95% CI)
Living room floor	438	32.41 (53.65–18.89)	31.22 (15.81–17.32)	269	0.06 (0.15–0.02)	0.10 (0.09–0.11)	269	0.37 (0.82–0.19)	0.62 (0.54–0.70)
Mother's mattress	474	19.87 (32.26–11.24)	18.73 (0.10–0.10)	296	0.08 (0.80–0.02)	0.19 (0.16–0.22)	296	0.24 (0.55–0.11)	0.43 (0.37–0.49)
Child's mattress	401	18.26 (36.75–9.53)	16.54 (15.50–17.66)	46	0.23 (4.73–0.09)	0.45 (0.33–0.62)	46	0.52 (3.36–0.24)	1.04 (0.76–1.43)

Abbreviations: CI, confidence interval; EU, endotoxin units; GM, geometric mean; IQR, interquartile range.