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Prevalence and risk factors of atopic diseases in German children and adolescents

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Abstract

Background: Atopic diseases became an important health problem in affluent Western societies.

Methods: To study the prevalence and factors associated with the risk of atopic diseases in Germany, data from the German Health Interview and Examination Survey for Children and Adolescents (KiGGS) were analysed ($n = 17,450$). Standardized, computer-assisted personal interviews with parents and parent-administered questionnaires provided physician diagnoses of allergic rhinoconjunctivitis, atopic dermatitis and asthma as well as data on demographic characteristics, migration background, birth order, age at the beginning of nursery, atopic diseases of parents, parents' smoking status, parents' occupation, breastfeeding and living environment.

Results: The life-time prevalence of atopic dermatitis was 13.2% (95% confidence limit: 12.5–13.9%), 10.7% (10.1–11.3%) for allergic rhinoconjunctivitis and 4.7% (4.3–5.1%) for asthma. At least one atopic disease in parents was the strongest factor associated with atopic diseases in the offspring, with a prevalence ratio of up to 2.6. High and middle socio-economic status (prevalence ratio, 95% confidence limit: 1.28, 1.12–1.46; 1.15, 1.01–1.32) were associated with the risk of atopic dermatitis, whereas a two-sided background of migration reduced the risk (0.76, 0.65–0.88). Factors that reduced the risk of allergic rhinoconjunctivitis were parents working as self-employed farmers (0.48, 0.30–0.76) and older siblings (0.80, 0.71–0.89), whereas the beginning of nursery school at older age was associated with an increased risk in children who were cared for outside the family before school age (1.05, 1.00–1.10). Living in mould-infested rooms (1.64, 1.23–2.19), an urban living environment (1.20, 1.02–1.42) and a smoking mother and/or father (1.20, 1.02–1.40) were associated with the risk of asthma.

Conclusions: Our results are in line with the so-called 'hygiene hypothesis', which emphasizes the role of environmental factors in addition to a genetic predisposition in the development of atopic diseases. Research on factors associated with atopic diseases can facilitate decisions on preventive strategies. Further studies are needed to explore trends in prevalence and risk factors for atopic diseases.

Allergic rhinoconjunctivitis, atopic dermatitis and (allergic) asthma are referred to as atopic diseases, which are defined by an increased production of allergen-specific immunoglobulin E antibodies and an accumulation of this condition in families. Atopic diseases in children and adolescents are widespread in affluent Western societies. Numerous epidemiological studies in different countries confirm the epidemic aspect

to which atopic diseases have developed for the last decades (1–5). Pathogenesis, natural course and involving mechanisms, however, are not fully understood so far. In 1989, Strachan (6) hypothesized that a reduced opportunity for cross infection in young families because of the phenomenon of 'Westernization' may result in a more widespread clinical expression of atopic diseases, which is more prevalent in

wealthier people. This so-called 'hygiene hypothesis' has strengthened the argument that environmental factors may play an important role in the development of atopic diseases. In addition, subjects with a family history of atopic disease are more likely to develop such condition themselves (7).

The largest international study on the prevalence and determinants of allergic diseases in children so far is the International Study on Asthma and Allergies in Childhood (ISAAC), in which school children aged 6–7 and 13–14 yr were enrolled in up to 56 countries all over the world (8). The German Health Interview and Examination Survey for Children and Adolescents (KiGGS), conducted from 2003 to 2006, provides comprehensive and nationwide representative data on health status and health behaviour of children and adolescents for the first time. Our study aimed at investigating the life-time prevalence of allergic rhinoconjunctivitis, atopic dermatitis and asthma as well as factors associated with the risk of each of these atopic diseases in children and adolescents.

Methods

The KiGGS is a population-based cross-sectional study conducted from May 2003 to May 2006 by the Robert Koch Institute in Berlin, Germany. The study aimed at collecting nationally representative health-related data from children and adolescents aged 0–17 yr. The overall response rate was 66.6% (9, 10). In total, 17,641 participants (8656 girls and 8985 boys) were surveyed. The participants and their parents were invited to one of 167 local study centres, in which they filled in self-administered questionnaires followed by a standardized, computer-assisted personal interview (CAPI) by a trained physician with the attending parent or with adolescents (≥ 14 yr of age) themselves. The study teams were thoroughly trained and were led by a physician experienced in paediatrics (11). The German Health Interview and Examination Survey for Children and Adolescents was funded by the German Federal Ministry of Health and the German Federal Ministry of Education and Research. Informed consent was obtained from all parents. The study was approved by the Charité-Universitätsmedizin Berlin ethics committee.

Information on allergic rhinoconjunctivitis, atopic dermatitis and asthma was obtained by CAPI. The participants were asked 'Did a physician ever diagnose X?' If 'yes', 'when did this happen for the first time?' Parent questionnaires provided information on demographic characteristics (age, sex), migration background (at least one of the child's parents was not born in Germany and/or has no German citizenship), birth order, age at the beginning of nursery, at least one atopic disease of mother and/or father (atopic parents), current smoking (mother and/or father), occupation like self-employed farming (mother and/or father), breastfeeding (exclusively, without additional administration of formula milk, infant formula or complementary foods; 6 months or more; breastfeeding at time of examination was not concerned), living environment (rural and urban) and living conditions. An index for socio-economic status (low, middle and high) was constructed using questionnaire information on

household income, education and profession as proposed by Winkler and Stolzenberg (12, 13).

All statistical analyses were performed using SAS, version 9.2 (SAS Institute, Cary, NC, USA). We estimated the life-time prevalences with their 95% confidence limits (95% CI) of physician-diagnosed atopic diseases. For each atopic disease ('ever') separately, we performed log-binomial or log-poisson regression, which is implemented in the SAS procedure PROC GENMOD as a generalized linear model with binomial or poisson-distributed outcome variable and log-link function. This approach provides crude prevalence ratios (PR) with 95% CI from bivariate models as well as adjusted PR with 95% CI from multivariate models (14, 15). At first, we investigated bivariate associations with atopic diseases. Associations that were statistically significant ($p \leq 0.05$) in bivariate models were investigated in subsequent multivariate models. In multivariate models, each association was adjusted for all the other associations in the model. Within modelling, we analysed possible effect modification by investigating interaction between factors selected for multivariate models. Using PROC LIFETEST, hazard functions of risk factors were generated. By definition, hazard functions depict the risk of a factor in relation to age at first disease diagnosis.

The design of the KiGGS study (two-stage clustered sample) was accounted for by using the survey commands in SAS. To assure that the derived estimates are representative at the national level, a sampling weight was applied throughout statistical analyses that correct for age, sex, residence (East/West/Berlin) and nationality.

Results

From the total of 17,641 study participants, 17,450 children and adolescents (51.3% males and 48.7% females) provided CAPI data and were therefore eligible for analyses. General information about the study population is given in Table 1.

According to parental information from KiGGS data, 22.6% (95% CI 21.8–23.4%) of German children and adolescents had at least one physician-diagnosed atopic disease. The life-time prevalence of atopic dermatitis was 13.2% (12.5–13.9%), followed by 10.7% (10.1–11.3%) for allergic rhinoconjunctivitis and 4.7% (4.3–5.1%) for asthma. The prevalence of two or three atopic diseases ranged between 0.6% (0.5–0.7%) (atopic dermatitis + asthma) and 2.0% (1.8–2.2%) (atopic dermatitis + allergic rhinoconjunctivitis). In KiGGS, children and adolescents with asthma most commonly had a diagnosis of at least one another atopic disease (61.7%), whereas this proportion was considerably lower in children and adolescents with atopic dermatitis (27.3%) (Fig. 1).

In Tables 2, 3 and 4, factors associated with allergic rhinoconjunctivitis, atopic dermatitis and asthma, respectively, are shown. In general, gender-stratified analysis showed no gender-specific risk factors for the individual diseases. A genetic predisposition, defined as parents with a history of atopic disease, was the most important associated factor of allergic rhinoconjunctivitis. There was a 2.58-fold probability (95% CI 2.33–2.85; $p < 0.0001$) of being diagnosed in children and

Table 1 Basic characteristics of the study population

Characteristics	n = 17,450
Age (yr) % (n)	
0–2	13.6 (2770)
3–6	21.0 (3832)
7–10	21.8 (4107)
11–13	17.3 (3040)
14–17	26.3 (3701)
Sex % (n)	
Male	51.3 (8880)
Female	48.7 (8570)
Socio-economic status % (n)	
Upper	27.1 (4366)
Middle	45.4 (7901)
Lower	27.5 (4760)
Background of migration % (n)	
Two sided	17.2 (2580)
One sided	8.3 (1283)
None	74.5 (13,507)
Birth order % (n)	
Last or middle born	49.8 (8156)
First born, as part of multiples or w/o siblings	50.2 (8291)
Mean age at the beginning of nursery, in years (SD)	2.8 (1.2)
Parental atopy % (n)	
Yes	37.9 (6255)
No	62.1 (10,804)
Parents are self-employed farmers % (n)	
Yes	2.1 (313)
No	97.9 (16,564)
Smoking mother and/or father	
Yes	49.8 (8716)
No	50.2 (8479)
Breastfeeding (exclusively 6 months or more) % (n)	
Yes	25.3 (3796)
No	74.7 (11,825)
Living environment	
Urban	54.7 (8987)
Rural	45.3 (8463)
Living in mould-infested rooms	
Yes	5.1 (893)
No	94.9 (16,199)

SD, standard deviation.

adolescents whose parents (mother and/or father) reported at least one atopic disease. We also found allergic rhinoconjunctivitis being associated with male sex (PR, 95% CI: 1.77, 1.35–2.34; $p < 0.0001$) and increasing age (1.16, 1.14–1.18, for each additional year of age; $p < 0.0001$). However, sex interacted with age, although statistically significant in the unadjusted model only. The interaction (0.98, 0.96–1.00, male, for each additional year of age; $p = 0.0997$) indicates effect modification by gender meaning that the higher prevalence of allergic rhinoconjunctivitis in boys is not independent from age (Table 2). The hazard function for gender demonstrates that with increasing age, the risk of a diagnosis increases up to school entrance age but then decreases in boys disproportionately compared to girls, so that prevalences

in boys and girls become more and more equal from childhood to adolescence (Fig. 2).

Children and adolescents whose parents (mother and/or father) were self-employed farmers had only half the risk (0.48, 0.30–0.76; $p = 0.0019$) of having allergic rhinoconjunctivitis. The existence of older siblings was also associated with a decreased risk of this atopic disease (0.80, 0.71–0.89; $p < 0.0001$). In addition, children with either a lower SES or exclusive breastfeeding for 6 months or more were less likely to have allergic rhinoconjunctivitis later in life, although these associations failed to achieve statistical significance after adjustment in multivariate models (Table 2).

Children who were cared for outside their families before school age were often reported to be less diagnosed with atopic diseases, especially with allergic rhinoconjunctivitis. Therefore, we investigated the association of age at the beginning of nursery and atopic diseases. We observed a significant association only with allergic rhinoconjunctivitis, that is, allergic rhinoconjunctivitis was more likely in children who had started nursery school at older age (1.05, 1.00–1.10, for each additional year; $p = 0.0345$).

Atopic dermatitis was positively associated with atopic disease in parents (1.68, 1.52–1.86; $p < 0.0001$), followed by high (1.28, 1.12–1.46; $p = 0.0002$) and middle (1.15, 1.01–1.32; $p = 0.0366$) SES and increasing age (1.02, 1.02–1.03, for each additional year of age; $p < 0.0001$). We observed exclusive breastfeeding for 6 month or more as being an effect modifier, because of its interaction with atopic disease in parents (1.22, 1.00–1.49; $p = 0.0451$). Atopic parents try to reduce the risk of atopic dermatitis in their babies by breastfeed them exclusively. We found atopic dermatitis being about one-third less likely in children and adolescents with a two-sided background of migration as compared to those with a one-sided or no background of migration (0.76, 0.65–0.88; $p = 0.0002$) (Table 3).

Similar to the other atopic diseases, we observed a genetic predisposition in children and adolescents being the strongest associated factor also for asthma (1.83, 1.55–2.16; $p < 0.0001$). Living in mould-infested rooms (1.64, 1.23–2.19; $p = 0.0007$), an urban living environment (1.20, 1.02–1.42; $p = 0.0325$), a smoking mother and/or father (1.20, 1.02–1.40; $p = 0.0271$), increasing age (1.14, 1.11–1.17, for each additional year of age; $p < 0.0001$) and male sex (2.31, 1.63–3.28; $p < 0.0001$) were also found to be associated with asthma. Of note, there was an interaction between sex and age, which was statistically significant independently from all other examined factors and which indicated gender as an effect modifier (0.96, 0.93–0.99, male, per additional year; $p = 0.0031$). Indeed, as the hazard function for gender illustrates in Fig. 3, boys do have a higher risk of being diagnosed with asthma as compared to girls. However, from puberty onwards, approximately 13 yr of age, the risk decreases, but decreases disproportionately in boys compared to girls. Therefore, the prevalences change around puberty. Children and adolescents with older siblings and those who were exclusively breastfed for 6 months or more were less likely to be reported with a diagnosis of asthma, although

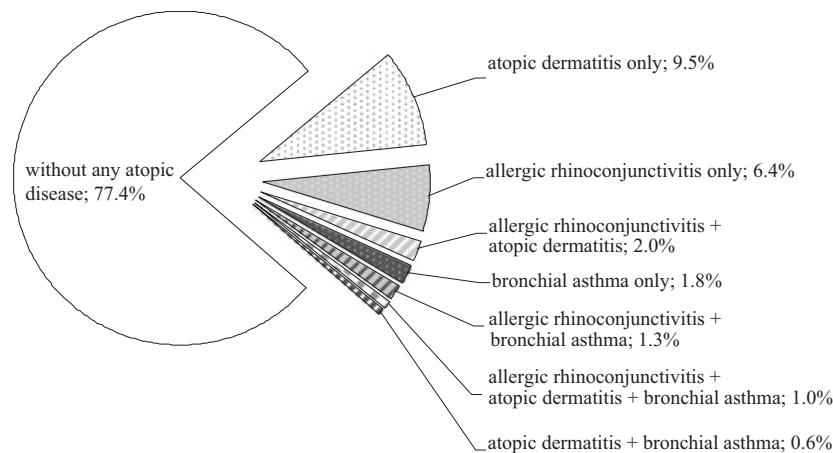


Figure 1 Life-time prevalence of atopic diseases.

these associations did not remain statistically significant after adjustment in multivariate models (Table 4).

Discussion

Based on data from the KiGGS, we report life-time prevalence estimates of allergic rhinoconjunctivitis, atopic dermatitis and asthma as well as factors associated with each of these diseases ('ever') in children and adolescents aged 0–17 yr. First results on prevalence of allergic diseases, stratified by socio-demographic characteristics, were reported previously (16).

The life-time prevalence of physician-diagnosed disease was highest for atopic dermatitis (13.2%), somewhat lower for allergic rhinoconjunctivitis (10.7%) and lowest for asthma (4.7%). Similar percentages of physician diagnoses were found in other European countries among children aged 6–7 yr, for instance in Spain for asthma with 6.1% (17), in Austria for asthma with 5.1% and for atopic dermatitis with 13.8% (5), in Italy for hay fever with 9.0% (1) and in Turkey for allergic rhinitis with 7.9% (children aged 6–12 yr) (18). A relative homogeneity across at least Western Europe could also be observed with respect to 12-months prevalences of atopic disease symptoms as assessed in the ISAAC study (19).

Table 2 Factors associated with allergic rhinoconjunctivitis; prevalence ratio (PR) and 95% confidence interval

Associated factors	Crude PR 95% CI	p-value	Adjusted PR* 95% CI	p-value
Parental atopy				
Yes	2.47 (2.25–2.72)	<0.0001	2.58 (2.33–2.85)	<0.0001
No	(1)		(1)	
Sex				
Male	1.41 (1.28–1.54)	<0.0001	1.77 (1.35–2.34)	<0.0001
Female	(1)		(1)	
Age (per additional year)	1.14 (1.13–1.15)	<0.0001	1.16 (1.14–1.18)	<0.0001
Sex*Age (male, per additional year)	0.97 (0.96–0.99)	0.0064	0.98 (0.96–1.00)	0.0997
Parents are self-employed farmers				
Yes	0.46 (0.29–0.73)	0.0010	0.48 (0.30–0.76)	0.0019
No	(1)		(1)	
Birth order				
Last or middle born	0.70 (0.63–0.77)	<0.0001	0.80 (0.71–0.89)	<0.0001
First born, as part of multiples or w/o siblings	(1)		(1)	
Socio-economic status				
High	1.32 (1.13–1.53)	0.0004	1.08 (0.91–1.28)	0.3730
Middle	1.29 (1.13–1.48)	0.0002	1.12 (0.97–1.29)	0.1140
Low	(1)		(1)	
Exclusive breastfeeding, 6 months or more				
Yes	0.86 (0.75–0.98)	0.0271	1.03 (0.90–1.18)	0.6667
No	(1)		(1)	

*Each association was adjusted by all the other associations in the model.

Table 3 Factors associated with atopic dermatitis; prevalence ratio (PR) and 95% confidence interval

Associated factors	Crude PR 95% CI	p-value	Adjusted PR* 95% CI	p-value
Parental atopy				
Yes	1.89 (1.74–2.06)	<0.0001	1.68 (1.52–1.86)	<0.0001
No	(1)		(1)	
Socio-economic status				
High	1.56 (1.37–1.78)	<0.0001	1.28 (1.12–1.46)	0.0002
Middle	1.32 (1.16–1.50)	<0.0001	1.15 (1.01–1.32)	0.0366
Low	(1)		(1)	
Age (per additional year)	1.02 (1.01–1.02)	0.0011	1.02 (1.01–1.03)	<0.0001
Background of migration				
Two sided	0.56 (0.48–0.64)	<0.0001	0.76 (0.65–0.88)	0.0002
One sided	0.93 (0.80–1.07)	0.3102	0.93 (0.81–1.08)	0.3527
None	(1)		(1)	
Parental atopy*exclusive breastfeeding, 6 month or more (yes, yes)	1.24 (1.02–1.51)	0.0293	1.22 (1.00–1.49)	0.0451
Exclusive breastfeeding, 6 months or more				
Yes	1.15 (1.04–1.26)	0.0046	1.00 (0.85–1.16)	0.9466
No	(1)		(1)	
Smoking mother and/or father				
Yes	0.91 (0.83–0.99)	0.0206	1.02 (0.94–1.11)	0.6591
No	(1)		(1)	
Living environment				
Urban	0.89 (0.81–0.99)	0.0338	0.93 (0.83–1.03)	0.1663
Rural	(1)		(1)	

*Each association was adjusted by all the other associations in the model.

Table 4 Factors associated with bronchial asthma; prevalence ratio (PR) and 95% confidence interval

Associated factors	Crude PR 95% CI	p-value	Adjusted PR* 95% CI	p-value
Parental atopy				
Yes	1.73 (1.47–2.04)	<0.0001	1.83 (1.55–2.16)	<0.0001
No	(1)		(1)	
Living in mould-infested rooms				
Yes	1.65 (1.27–2.15)	0.0002	1.64 (1.23–2.19)	0.0007
No	(1)		(1)	
Sex				
Male	1.41 (1.23–1.61)	<0.0001	2.31 (1.63–3.28)	<0.0001
Female	(1)		(1)	
Living environment				
Urban	1.19 (1.02–1.40)	0.0317	1.20 (1.02–1.42)	0.0325
Rural	(1)		(1)	
Smoking mother and/or father				
Yes	1.20 (1.03–1.39)	0.0203	1.20 (1.02–1.40)	0.0271
No	(1)		(1)	
Age (per additional year)	1.11 (1.09–1.13)	<0.0001	1.14 (1.11–1.17)	<0.0001
Sex*Age (male, per additional year)	0.95 (0.93–0.98)	0.0005	0.96 (0.93–0.99)	0.0031
Birth order				
Last or middle born	0.85 (0.73–0.99)	0.0328	1.00 (0.86–1.17)	0.9939
First born, as part of multiples or w/o siblings	(1)		(1)	
Exclusive breastfeeding, 6 months or more				
Yes	0.81 (0.66–1.00)	0.0522	0.97 (0.78–1.20)	0.7758
No	(1)		(1)	

*Each association was adjusted by all the other associations in the model.

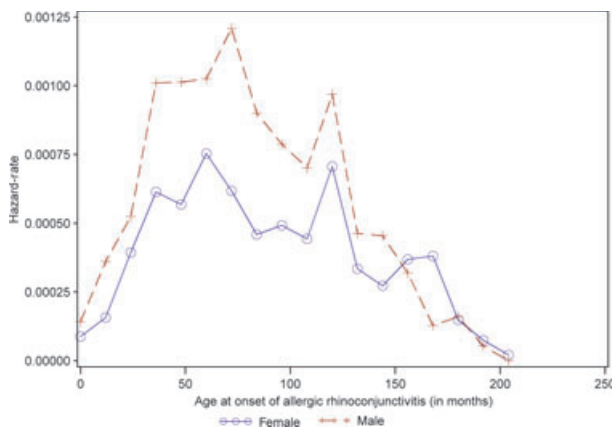


Figure 2 Estimated hazard function of gender in relation to age at onset of allergic rhinoconjunctivitis.

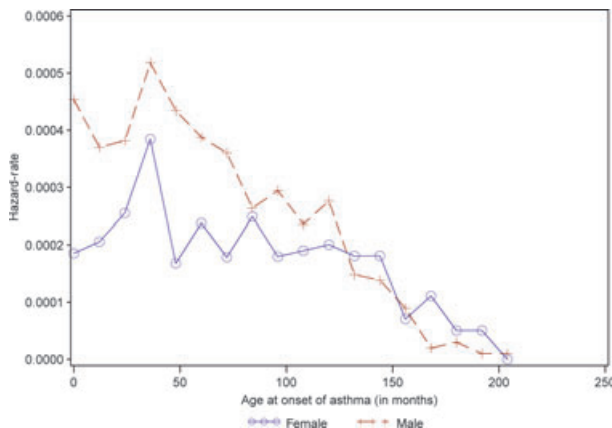


Figure 3 Estimated hazard function of gender in relation to age at onset of asthma.

In general, the prevalence of atopic diseases has increased rapidly during the last century, particularly in affluent Western societies. Genetic factors are supposed to not solely account for this rapid increase. Rather, lifestyle and environmental factors appear to be of particular importance for the occurrence and natural history of atopic diseases (20, 21). There is growing evidence on the interaction between genetic and environmental factors in terms of aetiology (22).

It is well known that a genetic predisposition plays a crucial role for the occurrence of atopic diseases in childhood. In our study, children and adolescents whose parents reported at least one atopic disease had an up to 2.6-fold risk of being diagnosed with an atopic disease compared to children and adolescents with non-atopic parents. As expected, increasing age was also an important factor associated with ever being diagnosed with an atopic disease. We also observed that boys were more likely to have an atopic disease than girls. However, particularly for asthma, the KiGGS data showed an interaction between sex and age. Its

prevalence ratio indicates that disease risk in boys decreased with increasing age and is disproportionately compared to girls. Thus, in adolescence, onset of asthma was more prevalent in girls than boys. Reported changes in prevalence around puberty between boys and girls were subject in a review by Almquist et al. (23). Hormonal changes and gender-specific differences in environmental exposures were considered to be possible explanations for the prevalence switch around puberty. However, in our data, we did not observe different associations for males and females. This may be due to the fact that underlying parameters had not been adequately assessed within the survey.

We observed a lower risk of allergic rhinoconjunctivitis in children whose parents are self-employed farmers. The association between farming environment and atopic disease was extensively studied in recent years. Among others, Bråbäck et al. (24) reported a lower risk of allergic rhinitis in Swedish conscripts whose parents were involved in farming. The PARSIFAL study indicated that growing up on a farm may confer protection from both atopic sensitization and allergic diseases in childhood (25). A very recent study by Ege et al. aimed at evaluating children's exposure to environmental microorganisms associated with living on farms. The authors concluded that exposure to a wide range of microbes explains a substantial fraction of the inverse relation between asthma and growing up on a farm (26).

Another finding consistent with the hygiene hypothesis is a lower probability of allergic rhinoconjunctivitis when starting nursery school at an early age. We also found that allergic rhinoconjunctivitis was less likely in last- or middle-born children. This is in line with the described protective sibling effect in a review by Karmaus et al. (27), in which all of the included 17 studies for allergic rhinoconjunctivitis showed that effect, even though the sibling effect was differently defined, by birth order, number of siblings, family size, number of older siblings, number of younger siblings or even by the number of brothers.

In the KiGGS study, similar to the results found by Apfelbacher et al. (28), a diagnosis of atopic dermatitis was more likely in children and adolescents with a higher socioeconomic status, but less likely in those with a two-sided background of migration. The latter was generally associated with a low SES. However, the associations of SES and migration with atopic dermatitis were independent from each other, as shown by multiple adjustments in our logistic regression model. Nevertheless, these are merely epidemiological associations in view of the hygiene hypothesis, for which the underlying mechanisms are still unknown.

The role of breastfeeding in the development of allergic diseases was thoroughly discussed. Recent reviews concluded that exclusive breastfeeding should be encouraged for at least 4–6 months in infants both at high and low risk of atopy, because of the large benefit in general (29, 30). We observed a strong interaction between atopy in parents and exclusive breastfeeding for 6 months or more for atopic dermatitis. As atopic parents in particular voluntarily apply preventive measures such as prolonging breastfeeding to their vulnerable children, our association can be interpreted as an indicator of

reverse causality. The assessment of breastfeeding for a wide age range from 0 to 17 yr like in the KiGGS study is per se susceptible for memory bias, which has to be commented as a limitation of the study. Nevertheless, because the identification of the mentioned interaction with atopy in parents, we do not assume our data to be systematically biased in this regard.

Exposures to tobacco smoke and mould or dampness as well as an urban living environment are counted among well-established risk factors for asthma (17, 31–33). In KiGGS, we also found these factors to be associated with asthma.

Further potential risk factors for atopic diseases had been investigated in recent years, for instance, factors from pre- and perinatal periods. Such information could not be assessed in KiGGS, which may be considered as a limitation of the study. However, KiGGS is distinguished by the large and nationally representative and unselected sample of chil-

dren and adolescents covering a wide age range and standardized questions. In total, information of 89% of the gross sample was available. We, therefore, assume that our results are not substantially influenced by selection bias. We rather suppose that KiGGS provides robust and valid data, as we could confirm important and well-established factors associated with atopic diseases in German children and adolescents. Ongoing research is now needed to clarify the impact of risk factors at different onset ages.

Overall, our results confirm important aspects of the present understanding of the 'hygiene hypothesis' underlying the development of atopic diseases during the last decades. Knowledge on prevalence as well as on factors associated with the risk of atopic diseases is important to evaluate the proportion of the population that can be reached by prevention measures.

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