

Atopic disease and its determinants – a focus on the potential role of childhood infection

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Summary

Background Atopic diseases develop on a genetic background and are modulated by environmental factors among which some infectious diseases are thought to have a protective influence.

Objective The aim of this study was to determine the influence of infectious diseases in younger ages, bacterial and viral, on atopic diseases and sensitization to aero- and foodallergens in adults.

Methods A population-based sample of 4262 subjects aged 25–74 years were interviewed concerning their history of infectious disease within the first 18 years of life. Information about allergic disease, including atopic eczema, allergic rhinitis (AR), and asthma was obtained. A blood sample was drawn and analysed for allergen-specific IgE antibodies against food- and aeroallergens.

Results Multiple logistic regression analyses identified viral infection to be associated with AR (adjusted odds ratio (OR) = 1.39; 95% confidence interval (95% CI): 1.13–1.72) and sensitization to aeroallergens (OR = 1.21; 95% CI: 1.05–1.41). Bacterial disease was a negative predictor for atopy development in the subgroup of patients sensitized to nutritional allergens with concomitant atopic eczema (OR = 0.34; 95% CI: 0.11–0.99), AR (OR = 0.67; 95% CI: 0.42–1.07), or asthma (OR = 0.41; 95% CI: 0.19–0.87). Influences of viral and bacterial infection on AR differed with regard to family history of atopic disease.

Conclusion In our study population, history of viral infection was consistently positively associated with AR. Our data suggests that bacterial infections might be preventive for specific subgroups of atopy.

Keywords adults, allergic rhinitis, allergy, asthma, atopic eczema, atopy, bacterial, hayfever, infection, sensitization, viral

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Introduction

Atopic diseases are an increasing health problem in western countries [1, 2]. Changing patterns of infection have been associated with this development. With the hygiene hypothesis, Strachan [3] postulated a potential hazard for atopy by increased hygiene standards associated with changing life styles in affluent countries [4].

Several studies suggest an association of declining incidence of infections with the rising prevalence of atopic disease [5, 6]. It has been postulated that the total burden of microbial stimuli rather than single infections is critical for the maturation of the immune system [7]. The number of siblings, the attendance of a day-care centre and living on a farm were used

as corresponding surrogate parameters in epidemiological studies [8–12].

For tuberculosis and hepatitis A in particular a protective effect was described, whereas other infections such as pertussis or respiratory syncytial virus (RSV) were associated with an increased risk of atopy [13–15]. So far, a stable association of a distinct infectious disease with a consecutive change in atopic disease manifestation has not been demonstrated. Other environmental modulators, like air pollution, socio-economic status, family size, and passive smoking, as well as genetic parameters, play a role in a complex interaction of allergy promotion [16–21].

Influences during early childhood seem to be important for the development of an allergy-prone immune response including a shift in the T-helper type 1 (Th1)–Th2 balance and distortion of the anti-inflammatory regulatory network (IL-10, TGF- β) [22–25].

The influence of childhood infections on atopic diseases has mostly been studied in children so far. We followed the hypothesis that viral or bacterial infections in childhood

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would exhibit preventive effects on both allergic sensitization and clinical atopy in adulthood in a dose-dependent manner. This large cross-sectional study in adults analysed the lifetime prevalence of various outcomes of atopy with regard to childhood viral or bacterial infections, taking relevant confounders into consideration.

Subjects and methods

Study design

The study was based on data from the KORA-Survey 2000 (KOoperative Gesundheitsforschung in der Region Augsburg). It was a cross-sectional study performed subsequent to previous epidemiological studies in this region including the earlier WHO MONICA project (MONItoring of trends and determinants of Cardiovascular disease) [26].

Study population

A total of 6640 participants, representative of the population in the study area according to age and gender, were selected from a community population register. Inhabitants with their main place of residence in the study area were included. The study population comprised 4262 volunteering participants, aged 25–74 years.

The study area is located in Bavaria, in the south of Germany. In 2000, the study area was inhabited by 614 667 people, 41.5% of these living in the City of Augsburg. The remainder lived in the adjacent counties of Augsburg (38.5%) and the county of Aichach–Friedberg (20.1%). In accordance with previous studies, the study population was classified as rural (living in a community of less than 8000 inhabitants), suburban (8000–30 000), or urban (more than 30 000) [27].

Data collection

The data-collection phase ran from October 1999 to April 2001. The sampled subjects were requested to come for a computer-assisted personal interview (CAPI) in the study centre in the city of Augsburg or to one of the 12 temporarily opened study centres, distributed over the study area. Furthermore, a venous blood sample was drawn.

Atopy status

The atopy status was assessed by a positive response to the question 'Have you ever suffered from atopic eczema/allergic rhinitis (AR) (hayfever)/asthma?' and a positive response to the question whether the respective disease had been diagnosed by a doctor. Only a history of the atopic entity diagnosed by a doctor was evaluated as positive.

History of infectious disease

Participants were asked whether they had suffered from 'classical' infectious diseases before the age of 18 years. A list of 11 specific infectious diseases was queried (diphtheria, pertussis, measles, mumps, rubella, varicella, scarlet fever, tuberculosis, shigellosis, thyphoid/parathyphoid fever, poliomyelitis).

According to the concept of total microbial burden of infectious disease as critical for the maturation of the immune

system, scores for bacterial and viral infections were established. The scores were defined as the sum of childhood bacterial and viral infectious diseases, reported by each subject. Bacterial and viral infections were included in the analysis as dichotomized variables (median split; Fig. 1).

Confounders and control variables

To adjust for potential confounding, information on age, gender, ethnicity, marital status, educational level, smoking, alcohol consumption, family history of atopic disease, and body mass index (BMI) were taken into account. Educational level was included as a dichotomized variable, differentiating participants with ≤ 10 years of schooling from those with more than 10 years of schooling. The analysis controlled for the participants' origin (native German vs. immigrant) and social environment (living as a single vs. not living as a single). BMI was dichotomized into normal vs. non-normal BMI. Age was included as a continuous variable. Detailed information about history of atopic eczema, AR/hayfever, and asthma for all first-degree relatives (mother, father, siblings, children) was recorded. The family burden was defined as a sum of the first-degree relatives with history of atopic disease.

Serological tests

Serum was separated by centrifugation, frozen, and stored at -80°C until further analysis. Specific IgE antibodies were measured against allergen mixtures using the fluorescence enzyme immunoassay technique (CAP-RAST, Pharmacia, Uppsala, Sweden).

The Sx-1 test measures specific IgE antibodies to important aeroallergens (house dust mite, cat/dog dander, mixed grass, mugwort and birch pollen, and *Cladosporium herbarum*). Similarly, the Fx-5 test is a multi-allergen test for common foodallergens (egg white, cow's milk, cod fish, wheat flour, peanut, and soybean). The test results are regarded positive when at least for one allergen the detection level of 0.35 kU/L was reached. All analyses were performed in one central laboratory of the Department of Dermatology and Allergology of the Technical University, Munich.

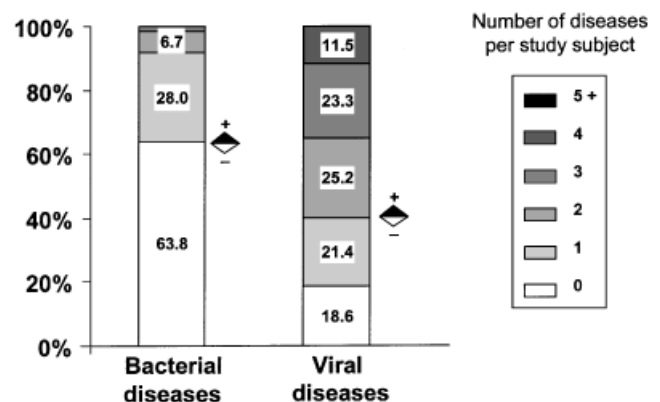


Fig. 1. Sum of viral disease and bacterial disease per study subject – frequency distribution in study population (%). Dichotomization of disease scores as indicated with +/– aside each bar.

Subgroup analyses

For the stratified analysis, the sample was divided into subjects with and without a positive family history of atopic disease. All study subjects with at least one family member (first-degree relative) with atopic disease were considered to have a positive family history of atopic disease.

Subgroups exhibiting atopic disease (atopic eczema/AR/asthma) and allergic sensitization were analysed further and depicted graphically in Fig. 2.

Statistical methods

Lifetime prevalence of atopic disease and atopic sensitization were adjusted for age and gender by direct standardization using 5 years age groups. Calculations were based on the weights of the age distribution of the population of the Federal Republic of Germany in May 1987 (Source: Statistisches Bundesamt).

Multiple logistic regression models were used to adjust for potential confounders and to model the potential associations of infections with atopic disease. Variables with known impact on atopic disease and a P -value ≤ 0.2 in the bivariate analysis were included in the regression analysis. Forward selection was used to identify relevant factors of influence.

Statistical analysis was performed using SAS for Windows, Release 8.01 (SAS Institute, Cary, NC, USA).

Ethical aspects

The research protocol was approved by the chamber of physicians ethics committee (Landesärztekammer Bayern). All participants had given their informed consent prior to inclusion into the study.

Results

Overall analysis

In Table 1, baseline characteristics of the study population are listed. There was an almost equal gender distribution. More than 83% of the study population was of German origin. Of the 17% of participants immigrated from other countries, more than 50% had been living in Germany for 40 years or longer. Approximately one-half (52.4%) of the population had an educational level of more than 10 years of school. About half of the subjects (45.4%) lived in the urban environment of the city of Augsburg and the remainder in the suburban (31.7%) or rural (22.9%) communities in the region. The sex and age standardized lifetime prevalence was higher for AR (15.9%) as compared with asthma (6.2%) and atopic eczema (5.3%) (Table 2).

The infections reported most frequently were measles (63.2%), varicella (52.3%), and mumps (44.1%). The distributions of the sum scores of viral and bacterial infections are shown in Fig. 1. Accordingly, viral diseases were more frequent than bacterial diseases.

In Table 3, multiple logistic regression models for infectious disease controlling for the potential confounding variables are shown. Increasing age was associated with a decreased risk of

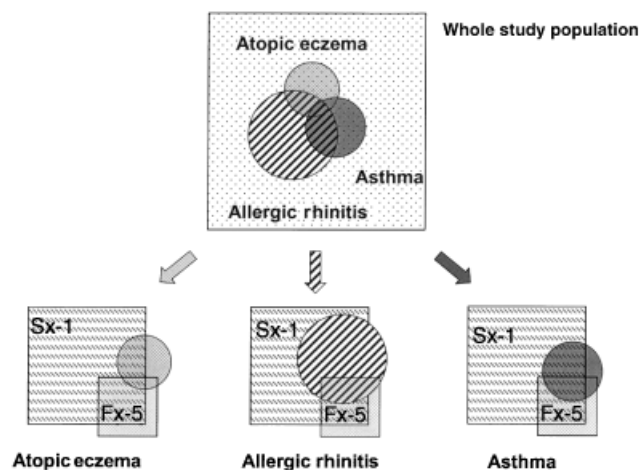


Fig. 2. Schematic diagram: atopic diseases in the study population. Sensitization to aeroallergens (Sx-1) and foodallergens (Fx-5) and their relation to atopic disease (size of squares and circles according to number of affected subjects).

atopic eczema, AR, and asthma, as well as sensitization to aeroallergens.

Family history was found to be an important predictor for atopic disease. The more family members were affected by atopic eczema, AR, or asthma as measured by the overall family burden, the higher was the risk for suffering from atopic disease. Accordingly, a family burden score was defined as the sum of family members (first-degree relatives) affected by atopic disease and included in the model. Family burden (score) was consistently associated with a positive relative risk estimate for any manifestation of atopy.

There was a significant hazard for suffering from AR attributable to viral disease under the age of 18 years (adjusted odds ratio (OR) = 1.39; 95% confidence interval (95% CI): 1.13–1.72). This effect was also seen for sensitization to aeroallergens (OR = 1.21; 95% CI: 1.05–1.41). In contrast, bacterial disease was found to be a significant negative predictor for sensitization to foodallergens (OR = 0.76; 95% CI: 0.59–0.98) (Table 3).

Rural vs. urban environment conferred significant protection for atopic eczema (OR = 0.62; 95% CI: 0.41–0.95), AR (OR = 0.71; 95% CI: 0.55–0.91), and sensitization to aeroallergens (OR = 0.75; 95% CI: 0.62–0.90) in all infection models (data not shown).

Subgroup analyses by family history of atopic disease

There was a consistently higher prevalence of atopic disease and sensitization to aeroallergens and nutritional allergens in the subgroup of participants with a positive family history of atopic disease compared with those with no family history of atopic disease (Table 2). To test for a differential prediction pattern of atopic disease with regard to positive or negative family history, we performed subgroup analyses for the two subgroups. The baseline characteristics of the two subgroups are listed in Table 1.

Bacterial disease showed a positive, albeit statistically not significant, association with AR in the stratum of subjects without family history of atopic disease (OR = 1.38; 95% CI: 0.99–1.93) (Fig. 3).

Table 1. Baseline characteristics of the sample population

	Total sample (<i>n</i> = 4261)	Positive family history of atopic disease (<i>n</i> = 2081)	No family history of atopic disease (<i>n</i> = 2180)
Baseline variables			
Female (%)	50.95	55.26	46.83
Age (years)	49.18	48.28	50.05
German origin (%)	83.11	85.39	80.93
Single (%)	16.64	14.90	18.30
Low educational status (%)*	47.64	43.78	51.33
Normal BMI (%)†	32.93	35.47	30.49
Community character			
Urban environment (%)	45.36	45.12	45.60
Suburban environment (%)	31.73	32.29	31.19
Rural environment (%)	22.91	22.59	23.21
Total infectious burden (95% CI)			
Bacterial disease (%)	36.19 (34.74–37.65)	38.35 (36.25–40.48)	34.13 (32.14–36.16)
Viral disease burden (%)	60.08 (58.59–61.55)	64.10 (62.00–66.17)	56.24 (54.13–58.33)

*Dichotomized: participants with ≤ 10 years of schooling vs. those with more than 10 years of schooling. †Dichotomized: normal BMI vs. non-normal BMI according to WHO classification.

BMI, body mass index; 95% CI, 95% confidence interval.

Table 2. Age and sex standardized lifetime prevalence of atopic disease and sensitization to food- and aeroallergens (%)

Diagnosis of atopic disease (self-reported)	Total sample (<i>n</i> = 4261)	Positive family history of atopic disease (<i>n</i> = 2081)	No family history of atopic disease (<i>n</i> = 2180)
Atopic eczema (%)	5.32	7.56	2.81
Allergic rhinitis (%)	15.89	21.48	9.89
Asthma (%)	6.22	8.18	4.18
Allergic sensitization			
Sensitization to aeroallergens (%)*	31.72	36.24	27.02
Sensitization to nutritional allergens (%)†	7.85	8.35	7.31

*Measured by Sx-1 (CAP-RAST, Pharmacia). †Measured by Fx-5 (CAP-RAST, Pharmacia).

In the group of participants with positive family history, bacterial disease was associated with a trend to reduced lifetime prevalence of atopic eczema (OR = 0.73; 95% CI: 0.50–1.06), AR (OR = 0.83; 95% CI: 0.65–1.07), and reduced sensitization to nutritional allergens (OR = 0.59; 95% CI: 0.41–0.84). In contrast, viral disease in the first 18 years of life was found to be a positive predictor for AR (OR = 1.45; 95% CI: 1.11–1.90), asthma (OR = 1.46; 1.01–2.09), and sensitization to aeroallergens (OR: 1.34; 95% CI: 1.08–1.66) (Fig. 3).

Subgroup analyses by atopic sensitization

Figure 2 illustrates the distribution of atopic disease and sensitization status relative to each other in the sample. The intersection of specific sensitization and atopic disease was analysed in the subgroups of atopic eczema/AR/asthma with sensitization status to aeroallergens or nutritional allergens.

Here, a subgroup of diseased subjects, who also had a positive test result for sensitization to nutritional allergens was identified. The risk of testing positive for nutritional allergen sensitization and concomitant allergic disease was modified by the history of bacterial disease in the first 18 years of life (Table 4). The bacterial disease was associated with reduced lifetime prevalence for Fx-5-positive eczema (atopic eczema $\cap$ Fx-5: OR = 0.34; 95% CI 0.11–0.99), Fx-5-positive

AR (AR $\cap$ Fx-5: OR = 0.67; 95% CI 0.42–1.07), and Fx-5-positive asthma (asthma $\cap$ Fx-5: OR = 0.41; 95% CI 0.19–0.87). For the subgroup of atopics with concomitant sensitization to aeroallergens bacterial disease was not a significant predictor (Table 4).

Discussion

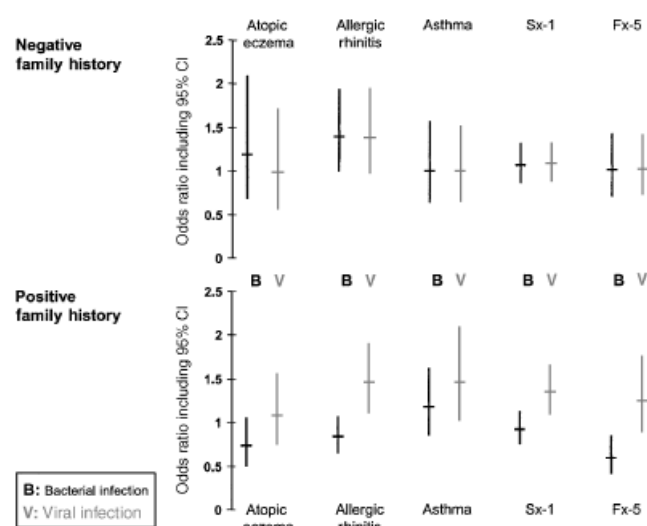
Viral infection and atopic disease

Considering the whole study population there is considerable evidence that viral disease during childhood and adolescence contributes to the development of AR. Viral disease is further associated with increased rates of sensitization to aeroallergens (Table 3). Viral infection is known to at least temporarily elevate serum IgE levels [28]. Viral diseases have also been associated with atopic disease development. Wheezing and lower respiratory tract illnesses due to RSV or other viruses are thought to alter normal lung development and predispose to development of asthma later in life [13, 29]. Importantly, viral but not bacterial infection has been related to asthma exacerbation [30].

In a cross-sectional study examining family size and atopic disease, it was shown that measles may have some protective

Table 3. Adjusted effect estimates of potential predictors for atopic eczema, allergic rhinitis, asthma and sensitisation to aeroallergens and nutritional allergens [multiple logistic regression models adjusted for age, gender, BMI, family history of atopic disease, ethnic origin, community character and level of education; forward selection applied]

Variables	Atopic eczema (n: 209 out of 4102)			Allergic rhinitis (n: 565 out of 3877)			Asthma (n: 254 out of 4113)			Sensitisation to aeroallergens (n: 1244 out of 4105)			Sensitisation to food allergens (n: 317 out of 4106)		
	OR	95%CI	P-value	OR	95%CI	P-value	OR	95%CI	P-value	OR	95%CI	P-value	OR	95%CI	P-value
Bacterial disease	0.840	0.615–1.147	0.2724	0.995	0.813–1.219	0.9845	1.114	0.855–1.452	0.4242	0.992	0.855–1.151	0.9181	0.760	0.591–0.977	0.0325
Viral disease	1.046	0.767–1.425	0.7782	1.394	1.128–1.723	0.0021	1.227	0.931–1.615	0.1459	1.213	1.045–1.409	0.0113	1.130	0.888–1.437	0.3210

**Fig. 3.** Adjusted effect estimates of potential predictors for atopic disease and sensitization to aero- and food allergens including 95% confidence intervals (bars). Stratified analysis according to family history of atopic disease (multiple logistic regression models adjusted for age, gender, body mass index, family history of atopic disease, ethnic origin, community character and level of education; forward selection applied).

effect against asthma. For rubella, pertussis, and varicella a slightly increased risk of eczema was found [5]. Studies from anthroposophic children reported less atopic disease [24]. Other studies claim to have shown that after measles infection, individuals are protected from atopic disease [31].

Illi et al. [32] provided more detailed insights into the epidemiological impact of viral infectious disease on asthma. Lower respiratory tract infections were positively associated with asthma, while upper respiratory tract infections demonstrated a strong protective effect. The hazard of viral disease on atopy, however, cannot be uniformly attributed to single infections. Moreover, for some viral diseases like hepatitis A, there seems to be a protective effect for atopic disease as shown in a study of Italian military students [33]. On the other hand, infection with hepatitis A is considered to be a marker for poor hygiene. Here, the association of hepatitis A infection and reduced atopic disease could well be explained by confrontation with an overall high microbial load due to low hygiene standards.

Bacterial infection and atopic disease

Bacterial disease was a negative predictor for atopy development in the subgroup of patients sensitized to nutritional allergens with concomitant atopic eczema (OR = 0.34; 95% CI: 0.11–0.99), AR (OR = 0.67; 95% CI: 0.42–1.07), or asthma (OR = 0.41; 95% CI: 0.19–0.87) (Table 4).

Several patient-based studies have shown a clinically relevant association of nutritional sensitization and other atopic diseases like hayfever and asthma [34–36]. This clustering of atopic diseases and allergic sensitization is also found to be a prognostic parameter for severity and higher need for medical intervention [37]. In our analysis, we took a closer look at these subgroups exhibiting factors, which could predispose for atopic disease in conjunction with sensitization to food-allergens. For the subpopulation of participants with atopic disease and positive test for Fx-5, a reduced number of

Table 4. Adjusted effect estimates of potential predictors for atopic eczema, allergic rhinitis, and asthma combined with sensitization according to fx-5 and sx-1 [multiple logistic regression models adjusted for age, gender, BMI, family history of atopic disease, ethnic origin, community character and level of education; forward selection applied]

Variables	Atopic eczema $\cap$ fx-5 (n: 24 out of 4225)			Allergic rhinitis $\cap$ fx-5 (n: 104 out of 4209)			Asthma $\cap$ fx-5 (n: 42 out of 4225)		
	OR	95%CI	P-value	OR	95%CI	P-value	OR	95%CI	P-value
Bacterial disease	0.338	0.114–0.998	0.0496	0.670	0.422–1.066	0.0907	0.410	0.193–0.874	0.0209
Viral disease	1.286	0.527–3.142	0.5808	1.222	0.787–1.897	0.3721	0.795	0.420–1.505	0.4801
Variables	Atopic eczema $\cap$ sx-1 (n: 109 out of 4225)			Allergic rhinitis $\cap$ sx-1 (n: 460 out of 4209)			Asthma $\cap$ sx-1 (n: 157 out of 4225)		
Bacterial disease	0.697	0.443–1.099	0.1201	1.038	0.832–1.294	0.7431	1.028	0.733–1.443	0.8713
Viral disease	1.251	0.803–1.951	0.3226	1.366	1.082–1.724	0.0087	1.311	0.914–1.879	0.1412

bacterial diseases during infancy may have been an important factor for manifestation of atopic disease. Interestingly, here bacterial infection was consistently associated with a reduced prevalence of all atopic diseases analysed in this study – atopic eczema, AR and asthma.

Rural lifestyle, farming and atopic disease

We found that living in a community with a rural/suburban character was significantly negatively associated with atopic eczema, AR, and sensitization to aeroallergens compared with urban environment [38, 39]. Farming and rural environments are seen, in context of bacterial infection, as a protective determinant against the development of atopic disease. Due to the low number of farmers ($n = 41$) in the population, there was no statistically significant impact of farming on atopic disease development (data not shown).

Family history and atopic disease

Interestingly, the protective effect of bacterial infections and the hazard of viral infection on atopic disease was more pronounced in the stratum of study subjects with positive family history of atopic disease. These results can be viewed in the light of studies analysing the effect of cat ownership with atopic disease and sensitization. Here, the protective effect of pet ownership was confined to a subgroup of study subjects whose parents were atopic [40–42]. This finding was interpreted as an allergen-specific development of IgG4 as part of a modified Th2 response [43]. The fact that family history of atopic disease changed the prediction patterns of viral and bacterial infection for atopic disease suggests a complex interaction of genetic and external stimuli in atopic disease development.

Study limitations

A strength of our study was the detailed information concerning childhood infection and family history of atopic disease for each subject. Rather than testing for single infections as determinants for the atopic disease development, we have focused our study on differentiating the effect of overall burden of bacterial or viral disease on the development of atopy. Including history of infectious disease in the analysis does not rule out that the individual immunologic predisposition for acquiring infection, rather than the microbial agent *per se*, may be the measured influencing factor in atopic disease development. However, the differential effect of viral disease and bacterial disease argues against a general susceptibility to infectious disease, as an underlying factor associated with atopic disease.

Unfortunately, no information about the number of (older) siblings as important confounder was recorded [5]. There was no information concerning the immunization of study individuals for the same period of life. Therefore, it was not possible to contrast the potential influence of infections with the influence of vaccinations in the development of atopic disease.

It is certainly a major limitation of this study that, due to the cross-sectional design, the temporal sequence of exposure and outcome cannot be disentangled. It is also plausible that persons with atopic diseases especially asthma are prone to

acquire infectious diseases. Yet, a certain sequence in events could be assumed for childhood infections in relation to lifetime manifestations of atopic disease. The most impressive results of this study, however, arise from associations of infections and allergic sensitization. Since it seems not likely that allergic sensitization itself increases the risk of infections the opposite pathway is postulated.

Although we were able to give detailed information about distinct childhood infections, we did not include in our analysis the vast majority of the most common non-characterized childhood respiratory infections, i.e. rhinovirus, RSV, influenza, and parainfluenza viruses, which may contribute in both directions to the development of an 'allergy-prone Th2' biased vs. an 'allergy-protective Th1' biased immune response [44].

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