

ORIGINAL ARTICLE

Epidemiology of urticaria in infants and young children in Germany – Results from the German LISApplus and GINIplus Birth Cohort Studies

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Keywords

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Abstract

Background: Although urticaria is considered one of the most frequent skin diseases, reliable epidemiologic data are scarce.

Objective: To evaluate the incidence and cumulative prevalence of urticaria in infants and children up to age of 10, to characterize the relationship of specific IgE levels (food and inhalative allergens) with urticaria, and to monitor the joint occurrence of urticaria with other diseases, such as eczema, asthma, and hay fever.

Methods: The study population consisted of two prospective birth cohort studies: the LISApplus and GINIplus studies. Information on physician-diagnosed urticaria, asthma, eczema, or hay fever was collected using self-administered questionnaires completed by the parents. Blood samples were drawn, and specific immunoglobulin E measured at 2 (only LISApplus), 6 and 10 yr of age.

Results: The incidence of urticaria was approximately 1% per year of age. The cumulative prevalence of urticaria in children up to the age of 10 yr was 14.5% for boys and 16.2% for girls. Cumulative prevalence of urticaria at the age of ten was significantly ($p < 0.05$) associated with allergic sensitization to peanut, soy, and wheat flour, but not with inhalant allergens. Both a parental history of atopy/urticaria and the children's diagnosis of asthma, eczema, and hay fever were strongly related ($p < 0.0001$) to the occurrence of urticaria.

Conclusions: Urticaria is a frequent event during childhood, with highest incidence in infants and preschool children. Comorbidity with atopic disease is high.

Urticaria is a heterogeneous group of disorders characterized by the sudden development of pruritic transient dermal wheals and/or angio-edema (1). Urticaria shows a wide spectrum of clinical presentations, and according to the current EAACI/GA2LEN/EDF/WAO guideline (2), urticaria is classified into spontaneous urticaria (acute or chronic), physical urticaria, and other types of urticaria.

Although urticaria is considered one of the most frequent skin diseases, reliable epidemiologic data are scarce, and most

of the published literature deals with adults. The lifetime prevalence of any type of urticaria is estimated up to 22% (3–6). A recent study from Germany on chronic spontaneous urticaria estimated a period prevalence of 0.8% in 1 yr (5). A study of recent time trends in the prevalence and morbidity for allergic disorders in the UK showed that clinical admissions for urticaria have increased by 100% since 1990 (7).

Particularly little is known on the epidemiology of urticaria in infants and children (8). The prevalence for all forms of

urticaria in children (acute, intermittent, and chronic) in Germany has been estimated of $2.1 \pm 6.7\%$ (9), and in general, acute urticaria appears to be more common in children, while chronic urticaria (>6 wk) is more common in adults (10).

To our knowledge, no data are yet available on the incidence of urticaria in infants and children. The present study was undertaken to evaluate the incidence and cumulative prevalence of urticaria in infants and children up to the age of ten from two birth cohorts in Germany. In particular, we were interested in the relationship of specific IgE levels (food and inhalative allergens) with urticaria. We also wanted to evaluate the role of parental history of atopy and urticaria as well as the combination of urticaria with eczema, asthma, and hay fever.

Methods

Study population

The study population consisted of two prospective birth cohort studies: the LISApplus (Life-style Related Factors on the Immune System and the Development of Allergies in Childhood PLUS the influence of traffic emissions and genetics) and GINIplus (German Infant Nutritional Intervention PLUS environmental and genetic influences on allergy development) studies.

LISApplus is a population-based birth cohort study in which a total of 3097 neonates were recruited between 1997 and 1999 from the German cities of Munich, Leipzig, Wesel, and Bad Honnef (11). For GINIplus, a total of 5991 mothers and their newborns were recruited in Munich and Wesel between September 1995 and June 1998. Infants with at least one allergic parent and/or sibling were recruited to the interventional study arm which investigated in a randomized, double-blind manner the effect of different hydrolyzed formulas consumed during the first 4 months of life on the development of allergies (12). All children without a family history of allergic diseases and children whose parents did not give consent for the randomized clinical trial in spite of a family history of allergic diseases were allocated to the non-interventional arm (13). Given that the entire current GINIplus study is composed of both the interventional and non-interventional arm, this cohort is also population based.

Both studies excluded neonates displaying at least one of the following criteria: preterm birth (maturity <37 gestational weeks), low birth weight (<2500 g), congenital malformation, symptomatic neonatal infection, antibiotic medication, hospitalization, or intensive medical care during the neonatal period. In addition, newborns were excluded, if their mothers suffered from immune-related diseases (autoimmune disorders, diabetes, hepatitis B) and were on long-term medication or with known drug and/or alcohol abuse. Only newborns from parents with German nationality were included. Detailed descriptions of the LISApplus and GINIplus studies have been published elsewhere (11–13).

For both studies, approval by the local Ethics Committees (Bavarian Medical Chamber, University of Leipzig, Board of Physicians of North-Rhine-Westphalia) and written consent from participant's families (both parents) were obtained.

Definition of urticaria, asthma, eczema, and hay fever

Information on physician-diagnosed urticaria, asthma, eczema, and hay fever was collected using self-administered questionnaires completed by the parents at ages 6, 12, 18, and 24 months and 4, 5, 6, and 10 years of age in the LISApplus study and 1, 2, 3, 4, 6, and 10 yr in the GINIplus study. For each year, cases were defined by a positive answer to the question 'In the last 6/12 months/at the age of 3/4/5/6/7/8/9/10 yr, has your child been diagnosed with urticaria/asthma/eczema/hay fever?' Controls were defined by a negative answer to the question, or if no answer was given, as long as the questionnaire was returned.

The yearly incidence of urticaria for each year was defined as the number of children with urticaria diagnosis divided by the number of children without urticaria in the previous years.

At each follow-up, the questionnaires asked for information pertaining to the timeframe since the previous follow-up. Therefore, four age groups were defined based on the time of follow-up: up to 2 yr, up to 4 yr, up to 6 yr, and up to 10 yr of age. For each age group, the cumulative prevalence of urticaria, asthma, eczema, and hay fever was calculated and analyzed separately.

Information on hay fever was not available for the first age group (up to 2 yr). The questionnaires were structured so that a parent could tick either a 'yes' or 'no' box in response to the question 'was your child diagnosed with?', which was followed by a list of different diseases. In many questionnaires, a response was only provided if the answer was positive. Therefore, in this analysis, we assume that if no answer was provided but the questionnaire was returned, a child was not diagnosed with the respective disease. This assumption was required to calculate the incidence and cumulative prevalence.

Assessment of allergic sensitization

Blood samples were drawn and specific immunoglobulin E (IgE) analyzed at 2 (only LISApplus), at 3 (only GINI intervention), at 6, and at 10 yr of age. Allergic sensitization was defined by specific serum IgE concentrations, which were assayed by the CAP-RAST FEIA system (Pharmacia Diagnostics, Freiburg, Germany) according to the manufacturer's instructions. Screening tests were used for testing allergic sensitization against food allergens (fx5: egg, cow milk, wheat, peanut, soybean, and codfish) and inhalant allergens (sx1: *Dermatophagoides pteronyssinus*, cat, dog, rye, timothy grass, *Cladosporium herbarum*, birch, mugwort). At 2 yr of age, a positive result in the food screening test was followed by measurements of three single allergens (egg, cow milk and peanut). At 6 and 10 yr of age, all single allergens were followed up after a positive result in the screening test. The limit of detection for specific IgE was 0.35 kU/l. Children were assigned as IgE positive, if their IgE values exceeded the detection limit.

Statistical analysis

The prevalence of urticaria within each age group was analyzed in relation to parental atopy (defined as one or both parents with

Table 1 Description of study population and cumulative prevalence of urticaria according to age groups

	Female	Male	Total
Up to 2 years			
Urticaria [Yes]	3.4% (114/3343)	3.0% (107/3555)	3.2% (221/6898)
Parental atopy			
0	44.9% (1498/3339)	44.4% (1579/3553)	44.6% (3077/6892)
1	39.3% (1312/3339)	40.8% (1448/3553)	40.0% (2760/6892)
2	15.8% (529/3339)	14.8% (526/3553)	15.3% (1055/6892)
Parental urticaria [Yes]	10.5% (342/3247)	9.4% (324/3462)	9.9% (666/6709)
Older siblings			
0	53.5% (1620/3030)	53.6% (1714/3198)	53.5% (3334/6228)
1	34.8% (1053/3030)	35.7% (1142/3198)	35.2% (2195/6228)
>1	11.8% (357/3030)	10.7% (342/3198)	11.2% (699/6228)
Study center			
München	48.1% (1608/3343)	49.5% (1759/3555)	48.8% (3367/6898)
Leipzig	11.5% (384/3343)	10.5% (374/3555)	11.0% (758/6898)
Bad Honnef	3.9% (129/3343)	3.7% (132/3555)	3.8% (261/6898)
Wesel	36.6% (1222/3343)	36.3% (1290/3555)	36.4% (2512/6898)
Up to 4 years			
Urticaria [Yes]	7.1% (220/3077)	6.5% (211/3240)	6.8% (431/6317)
Parental atopy			
0	45.3% (1393/3073)	44.8% (1452/3238)	45.1% (2845/6311)
1	38.9% (1195/3073)	40.6% (1315/3238)	39.8% (2510/6311)
2	15.8% (485/3073)	14.5% (471/3238)	15.1% (956/6311)
Parental urticaria [Yes]	10.5% (315/2991)	9.2% (290/3161)	9.8% (605/6152)
Older siblings			
0	53.6% (1544/2882)	53.2% (1615/3037)	53.4% (3159/5919)
1	34.8% (1002/2882)	36.2% (1098/3037)	35.5% (2100/5919)
>1	11.7% (336/2882)	10.7% (324/3037)	11.2% (660/5919)
Study center			
München	49.2% (1515/3077)	50.6% (1641/3240)	50.0% (3156/6317)
Leipzig	10.7% (330/3077)	9.8% (319/3240)	10.3% (649/6317)
Bad Honnef	4.0% (122/3077)	3.9% (125/3240)	3.9% (247/6317)
Wesel	36.1% (1110/3077)	35.6% (1155/3240)	35.9% (2265/6317)
Up to 6 years			
Urticaria [Yes]	10.2% (290/2852)	9.1% (271/2981)	9.6% (561/5833)
Parental atopy			
0	44.8% (1276/2848)	44.1% (1314/2979)	44.4% (2590/5827)
1	39.3% (1119/2848)	40.9% (1219/2979)	40.1% (2338/5827)
2	15.9% (453/2848)	15.0% (446/2979)	15.4% (899/5827)
Parental urticaria [Yes]	10.5% (290/2773)	9.4% (275/2911)	9.9% (565/5684)
Older siblings			
0	53.2% (1488/2799)	52.7% (1542/2925)	52.9% (3030/5724)
1	35.1% (983/2799)	36.5% (1067/2925)	35.8% (2050/5724)
>1	11.7% (328/2799)	10.8% (316/2925)	11.3% (644/5724)
Study center			
München	50.6% (1442/2852)	52.1% (1552/2981)	51.3% (2994/5833)
Leipzig	9.7% (278/2852)	9.0% (268/2981)	9.4% (546/5833)
Bad Honnef	4.2% (119/2852)	4% (118/2981)	4.1% (237/5833)
Wesel	35.5% (1013/2852)	35% (1043/2981)	35.2% (2056/5833)
Up to 10 years			
Urticaria [Yes]	14.7% (351/2392)	13% (321/2471)	13.8% (672/4863)
Parental atopy			
0	44% (1052/2389)	43.4% (1071/2469)	43.7% (2123/4858)
1	39.8% (952/2389)	41.4% (1022/2469)	40.6% (1974/4858)
2	16.1% (385/2389)	15.2% (376/2469)	15.7% (761/4858)
Parental urticaria [Yes]	10.1% (236/2331)	9.6% (232/2413)	9.9% (468/4744)

Table 1. (Continued).

	Female	Male	Total
Older siblings			
0	53.7% (1259/2346)	52% (1258/2421)	52.8% (2517/4767)
1	35.3% (827/2346)	37.4% (905/2421)	36.3% (1732/4767)
>1	11.1% (260/2346)	10.7% (258/2421)	10.9% (518/4767)
Study center			
München	52.5% (1255/2392)	53.4% (1320/2471)	53.0% (2575/4863)
Leipzig	8.4% (202/2392)	8.2% (203/2471)	8.3% (405/4863)
Bad Honnef	4.3% (102/2392)	3.8% (94/2471)	4.0% (196/4863)
Wesel	34.8% (833/2392)	34.6% (854/2471)	34.7% (1687/4863)

at least one reported atopic disease), parental urticaria (defined as having at least one parent ever reporting a physician's diagnosis of urticaria), presence of older siblings (none, one older sibling, or more than one older sibling), specific IgE against food and inhalant allergens, asthma, eczema, hay fever, and study center. All differences, except study center, were tested using Fisher's exact test. All results are presented as odds ratios (OR) with 95% confidence interval (95% CI). Differences between urticaria prevalence in each age group and study center were tested with Pearson's chi-squared test. Statistical significance was defined as a two-sided alpha level of 5%.

All analyses were performed using the statistical software R, version 2.14.1 (<http://www.R-project.org>) (R Development Core Team 2012). The occurrence of eczema, asthma, urticaria, and hay fever is illustrated by a Venn diagram using 'venneuler' without weights from R package 'venneuler' (<http://CRAN.R-project.org/package=venneuler>) (14).

Results

A total of 9088 newborns were recruited (GINIplus $n = 5991$; LISApplus $n = 3097$) with a sex distribution of about 1:1 in all study centers. During the follow-up of 10 yr, a dropout of 4010 (44%) study subjects occurred (GINI $n = 2674$; LISA $n = 1336$).

In the age group up to 2 yr, information on urticaria was available for 6898 children. Due to loss of follow-up, this number was reduced to 6317 children in the age group up to 4 yr, 5833 children in the age group up to 6 yr, and 4863 children in the age group up to 10 yr (Table 1). The cumulative urticaria prevalence increased from 3.2% in children up to age 2, 6.8% up to age 4, and 9.6% up to age 6–13.8% up to 10 yr. There was a slight preponderance for girls.

Subjects who participated in the 10-yr follow-up examination revealed a higher parental education level and a lower number of elder siblings for the index child and were more likely to live in Munich or Bad Honnef than the families who stopped participating. For cumulative prevalence of urticaria by study center, see supplemental material Table S1.

The incidence of urticaria for each year is presented in Table 2. The incidence was highest during the second year of life (2.3% for girls, 2.2% for boys). Generally, urticaria incidence was higher in preschool children and decreased subsequently in school-aged children.

Table 2 Incidence of urticaria by gender and age

	Female	Male	Total
Age 1	1.1% (38/3574)	0.8% (29/3818)	0.9% (67/7392)
Age 2	2.3% (76/3358)	2.2% (78/3562)	2.2% (154/6920)
Age 3	1.9% (61/3175)	1.7% (58/3340)	1.8% (119/6515)
Age 4	1.5% (45/3001)	1.5% (46/3150)	1.5% (91/6151)
Age 5	1.4% (38/2791)	1.1% (32/2919)	1.2% (70/5710)
Age 6	1.2% (32/2753)	1.0% (28/2887)	1.1% (60/5640)
Age 7	0.5% (12/2277)	0.4% (9/2383)	0.5% (21/4660)
Age 8	0.3% (6/2265)	0.4% (10/2374)	0.3% (16/4639)
Age 9	0.8% (17/2259)	0.5% (12/2364)	0.6% (29/4623)
Age 10	1.2% (26/2242)	0.8% (19/2352)	1.0% (45/4594)

Cumulative prevalence of urticaria in all age groups was strongly associated with parental atopy and parental urticaria (Table 3) in all age groups. Having older siblings was slightly protective against urticaria (Table 3).

Specific IgE (RAST) for food and inhalant antigens was measured, and their association with the cumulative prevalence of urticaria up to the ages of 2, 6, and 10 yr was analyzed (see Tables 4 and S2–S4). There was no significant association of food allergens with the prevalence of urticaria up to age of 2 yr (Table S2). Sensitization to peanuts up to age of six and to 'food mix', peanut, soy, and wheat flour up to age of 10 was significantly associated with cumulative prevalence of urticaria at the age of 10 (see Table 4). Analysis of sIgE levels against aeroallergens revealed a statistically significant positive association with the prevalence of urticaria up to age of 6 only for sIgE against cats and birch and for sIgE against inhalant mix, cat, dog, rye, timothy grass, birch, and mugwort at the age of ten (Table S3). If the analysis was stratified for hay fever diagnosis, no statistically significant associations were left (Table S4).

During the follow-up over 10 yr, the overlap of urticaria with asthma, eczema, and hay fever increased and, except for asthma up to the age of 2, urticaria was strongly associated with each of the three diseases (Fig. 1). For the exact number of children with each diagnosis, see supplemental material Table S5.

Discussion

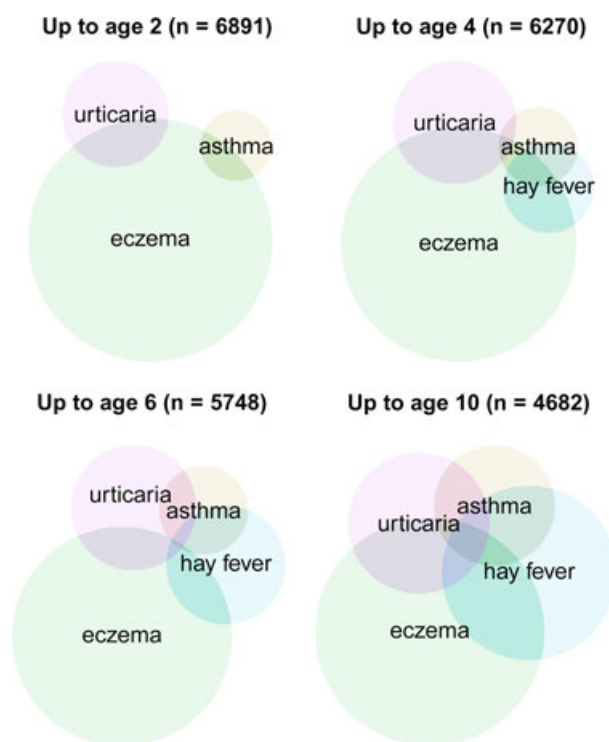
In the present study, we investigated the prevalence and incidence of urticaria in two large prospective birth cohort

Table 3 Cumulative prevalence of urticaria according to age groups and parental atopy, parental urticaria, and having older siblings (crude OR, CI, and p derived from Fisher's exact test)

	n/N	OR (95%-CI)	p value
Up to Age 2			
Parental atopy			
Single vs. No	2760/5837	1.78 (1.30/2.47)	0.0002
Double vs. No	1055/4132	2.02 (1.35/3.00)	0.0004
Parental urticaria			
Yes vs. No	666/6709	2.09 (1.42/3.00)	0.0002
Older siblings			
1 vs. 0	2195/5529	1.05 (0.76/1.44)	0.7536
>1 vs. 0	699/4033	1.14 (0.69/1.99)	0.7155
Up to Age 4			
Parental atopy			
Single vs. No	2510/5355	1.6 (1.28/2.01)	<0.0001
Double vs. No	956/3801	1.86 (1.40/2.48)	<0.0001
Parental urticaria			
Yes vs. No	605/6152	2.21 (1.68/2.89)	<0.0001
Older siblings			
1 vs. 0	2100/5259	0.8 (0.64/1.01)	0.0623
>1 vs. 0	660/3819	1.27 (0.88/1.86)	0.2067
Up to Age 6			
Parental atopy			
Single vs. No	2338/4928	1.53 (1.25/1.88)	<0.0001
Double vs. No	899/3489	2.06 (1.60/2.63)	<0.0001
Parental urticaria			
Yes vs. No	565/5684	2.42 (1.90/3.07)	<0.0001
Older siblings			
1 vs. 0	2050/5080	0.76 (0.62/0.93)	0.0066
>1 vs. 0	644/3674	1.4 (1.02/1.97)	0.0335
Up to Age 10			
Parental atopy			
Single vs. No	1974/4097	1.48 (1.23/1.80)	<0.0001
Double vs. No	761/2884	2.13 (1.69/2.69)	<0.0001
Parental urticaria			
Yes vs. No	468/4744	2.45 (1.94/3.08)	<0.0001
Older siblings			
1 vs. 0	1732/4249	0.82 (0.68/0.99)	0.0387
>1 vs. 0	518/3035	1.29 (0.96/1.76)	0.0927

slight preponderance for girls. The cumulative prevalence of urticaria in children up to the age of 10 yr was 14.5% for boys and 16.2% for girls. The strength of the study lies in its prospective and population-based design.

An important limitation is the lack of information on the course of urticaria (acute or chronic), and the drop-out rate of 44% over the ten-year period. We cannot exclude that our results were partially affected by participation bias. Due to the

**Figure 1** Venn's diagram of occurrence of eczema, asthma, urticaria, and hay fever during the follow-up over ten years. (For the exact number of children with each diagnosis, see supplemental material Table S5)**Table 4** Specific IgE against food allergens (at age 6 and 10) and prevalence of urticaria up to age 6 and 10

	Up to age 6			Up to age 10		
	n/N	OR (95%-CI)	p value	n/N	OR (95%-CI)	p value
Food mix	375/3009	1.32 (0.92/1.87)	0.1098	521/2709	1.41 (1.06/1.87)	0.0167
Egg white	95/3009	1.13 (0.52/2.21)	0.7207	131/2709	0.93 (0.50/1.63)	0.8915
Peanuts	164/3007	1.70 (1.04/2.70)	0.0269	251/2709	1.78 (1.24/2.52)	0.0015
Soy	128/3007	1.39 (0.76/2.40)	0.2175	205/2709	1.61 (1.07/2.37)	0.0189
Milk protein	145/3009	1.29 (0.72/2.18)	0.3117	156/2709	0.94 (0.53/1.57)	0.8998
Codfish	26/3009	2.30 (0.67/6.33)	0.0928	20/2709	1.28 (0.24/4.46)	0.7267
Wheat flour	162/3009	1.13 (0.63/1.91)	0.6782	266/2709	1.69 (1.18/2.39)	0.0029

studies. We observed an incidence of urticaria of approximately 1% for year each age group, being a bit higher in the age group 2–5 and a bit lower in the age group 7–9, with a

structure of the questionnaire, missing values were assigned as controls, as long as the questionnaire was returned. To test the validity of this assumption, we compared the results between

analyses in which the controls were composed of only those who 1) provided a negative answer compared with those who 2) provided a negative answer or no answer but reported the questionnaire. The magnitude of the associations remained similar, although the calculated incidence and cumulative prevalence were higher, as expected.

There was a strong and highly significant association of urticaria with parental atopy and parental urticaria as well as with asthma, eczema, and hay fever. As only 36 infants were not vaccinated within their first 2 yr of life, it was not possible to evaluate the effect of vaccination on the development of urticaria.

In infancy, IgE-mediated food allergy (15) may be a cause of urticaria. More than 90% of IgE-mediated food allergies in childhood are caused by eight foods: cow's milk, eggs, soy, peanuts, nuts, wheat, fish, and shellfish (16). Typically food allergy resolves in early school-age years. In the birth cohorts, we found a nearly statistically significant association of urticaria with specific IgE against egg white in the youngest age group, which disappeared with older age. We also found a strong association with sensitization to peanut, soy, and wheat flour up to the age of 10 years. Both, a parental history of atopy/urticaria as well as the children's diagnosis of asthma, eczema, and hay fever was strongly related to the occurrence of urticaria.

In childhood, acute spontaneous urticaria is thought to be caused by respiratory infections, presumably of viral etiology. A study from Norwich, United Kingdom, and Heraklion, Greece, showed a seasonality of several acute respiratory viral infections that coincided with the observed seasonality of acute spontaneous urticaria, suggesting a potential linkage (17). A study from the Dermatologic University Clinic in Göttingen (18) retrospectively analyzed 43 pediatric patients with presumed drug hypersensitivity using standardized skin testing followed by oral challenges and could exclude drug hypersensitivity in most of them (40 patients). The authors conclude that urticaria developing in temporal relationship to the application of a drug may have originated from other causes than the suspected drug and – as Konstantinou et al. – they assume that this would be in most cases an acute respiratory viral infection.

Causes of chronic spontaneous urticaria comprise infections, intolerance, and auto-reactivity mediated by IgG autoantibodies directed against IgE, against the α -subunit of the high-affinity IgE receptor Fc ϵ RI, and against thyroperoxidase (19–21).

In addition, there are many non-IgE-mediated rashes that occur in association with exercise. The underlying pathophysiologic mechanism is not well understood, but the children are usually older than the children in our study (22).

Conclusions

Spontaneous urticaria is a frequent event during childhood, with the highest incidence in infants and preschool children. Comorbidity with atopic disease is high.

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Conflict of interest statement

None of the authors has a financial relationship with a commercial entity that has an interest in the subject of this manuscript.

Authors contributions

IB was involved in the development of the statistical analysis plan and interpreting the results and wrote the article. MS carried out the statistical analysis and contributed to the article. JH was involved in the development of the statistical analysis plan and interpreting the results. SW, CC, and BH helped to interpret the results by revising the article. SK, CPB, AvB, DB, BS, IL, OH, and JH designed and/or conducted the study and revised the manuscript. All authors had full access to all of the data in the study and can take responsibility for the integrity of the data and the accuracy of the data analysis. All authors read and approved the final article.

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Appendix 1

The **GINIplus** study group (2010) consisted of the following members: Institute of Epidemiology, Helmholtz Zentrum München, German Research Center for Environmental Health, Neuherberg (Heinrich J, Wichmann HE, Sausenthaler S, Zutavern A, Chen, Chih-Mei, Schnappinger M, Rzehak P); Department of Pediatrics, Marien-Hospital, Wesel (Berdel D, von Berg A, Beckmann C, Groß I); Department of Pediatrics, Ludwig Maximilians University, Munich (Koletzko S, Reinhardt D, Krauss-Etschmann S); Department of Pediatrics, Technical University, Munich (Bauer CP, Brockow I, Gröbl A, Hoffmann U); IUF – Leibniz Research Institute for Environmental Medicine, Düsseldorf (Krämer U, Link E, Cramer C); Centre for Allergy and Environment, Technical University, Munich (Behrendt H); The **LISAplus** study group (2010) consisted of the following members: Helmholtz Zentrum München, German Research Center for Environmental

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Supporting Information

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

Table S1. Cumulative urticaria prevalence by study center (p values derived from Pearson’s chi-squared test).

Table S2. Specific IgE against food allergens at age 2 and prevalence of urticaria up to age 2 (only available for the LISAplus study).

Table S3. Specific IgE against inhalant allergens (at age 6 and 10) and prevalence of urticaria up to age 6 and 10.

Table S4. Specific IgE against inhalant allergens at age 10 and urticaria prevalence up to age of 10 years, stratified for hay fever diagnosis up to age of 10 years.

Table S5. Cumulative prevalence of urticaria and prevalence of asthma, eczema and hay fever according to age groups.

Appendix

Table S1

Cumulative urticaria prevalence by study center (p values derived from Pearson's Chi-squared test).

	München	Leipzig	Bad Honnef	Wesel	p value
Up to age 2	104 (3.1%)	29 (3.8%)	9 (3.4%)	79 (3.1%)	0.7607
Up to age 4	214 (6.8%)	44 (6.8%)	15 (6.1%)	158 (7.0%)	0.9577
Up to age 6	289 (9.7%)	52 (9.5%)	20 (8.4%)	200 (9.7%)	0.9367
Up to age 10	350 (13.6%)	59 (14.6%)	22 (11.2%)	241 (14.3%)	0.6329

Table S2

Specific IgE against food allergens at age 2 and prevalence of urticaria up to age 2 (only available for the LISApplus study).

	Up to age 2			
	n/N	OR	95%-CI	p value
Food mix	196/2097	1.80	(0.81/3.65)	0.1239
Eggwhite	113/2095	2.19	(0.82/4.96)	0.0831
Milk protein	106/2095	1.59	(0.49/4.05)	0.3781
Peanuts	37/2093	1.81	(0.21/7.31)	0.3201

Table S3

Specific IgE against inhalant allergens (at age 6 and 10) and prevalence of urticaria up to age 6 and 10.

	Up to age 6				Up to age 10			
	n/N	OR	95%-CI	p value	n/N	OR	95%-CI	p value
Inhalant mixed	873/3009	1.14	(0.87/1.50)	0.3368	1087/2709	1.31	(1.03/1.66)	0.0263
Dermatophagoides	444/3005	1.13	(0.79/1.58)	0.4821	611/2708	1.23	(0.93/1.61)	0.1394
pteronyssinus								
Cat	181/3004	2.1	(1.35/3.18)	0.0009	283/2707	1.47	(1.02/2.07)	0.0338
Dog	149/3004	1.62	(0.95/2.63)	0.0601	294/2708	1.7	(1.21/2.37)	0.0017
Rye	481/3005	1.26	(0.90/1.74)	0.1486	667/2707	1.51	(1.17/1.96)	0.0016
Timothy grass	531/3005	1.28	(0.93/1.74)	0.1200	709/2708	1.56	(1.21/2.01)	0.0005
Cladosporium	44/3004	1.23	(0.38/3.16)	0.6031	44/2708	0.93	(0.28/2.37)	1
herbarum								
Birch	334/3005	1.89	(1.33/2.63)	0.0003	490/2707	1.42	(1.06/1.89)	0.0144
Mugwort	191/3005	1.56	(0.97/2.42)	0.0539	343/2707	1.53	(1.10/2.11)	0.0101

Table S4

Specific IgE against inhalant allergens at age 10 and urticaria prevalence up to age of 10 years, stratified for hay fever diagnosis up to age of 10 years.

	Never hay fever				Ever hay fever			
	n/N	OR	95%-CI	p value	n/N	OR	95%-CI	p value
Inhalant mixed	670/2199	1.05	(0.76/1.43)	0.7579	411/499	0.68	(0.39/1.23)	0.1831
Dermatophagoides pteronyssinus	362/2199	1.22	(0.83/1.76)	0.2914	245/498	0.62	(0.39/1.00)	0.0425
Cat	139/2198	1.46	(0.83/2.45)	0.1437	143/498	0.87	(0.51/1.47)	0.6208
Dog	119/2198	1.66	(0.92/2.82)	0.0601	174/499	0.99	(0.60/1.61)	1
Rye	352/2198	1.15	(0.77/1.67)	0.4973	312/498	1.09	(0.67/1.79)	0.7284
Timothy grass	382/2199	1.25	(0.86/1.79)	0.2222	324/498	1.07	(0.66/1.77)	0.8138
Cladosporium herbarum	17/2198	0	(0.00/2.18)	0.4035	27/499	0.93	(0.27/2.60)	1
Birch	225/2197	1.14	(0.70/1.78)	0.5579	265/499	0.95	(0.59/1.51)	0.8223
Mugwort	156/2198	1.03	(0.56/1.77)	0.8900	186/498	1.20	(0.74/1.93)	0.4846

Table S5

Cumulative prevalence of urticaria and prevalence of asthma, eczema and hay fever according to age groups

		Urticaria				
		No	Yes	OR	95% CI	p value
Up to age 2						
Asthma	No	6586 (98.6%)	210 (98.1%)	1.38	(0.36/3.70)	0.5412
	Yes	91 (1.4%)	4 (1.9%)			
Eczema	No	5614 (84.1%)	159 (74.0%)	1.86	(1.34/2.56)	0.0002
	Yes	1063 (15.9%)	56 (26.0%)			
Up to age 4						
Asthma	No	5745 (97.6%)	366 (95.1%)	2.11	(1.22/3.48)	0.0064
	Yes	141 (2.4%)	19 (4.9%)			
Eczema	No	4620 (78.5%)	253 (63.6%)	2.09	(1.68/2.60)	<0.0001
	Yes	1266 (21.5%)	145 (36.4%)			
Hay fever	No	5703 (96.9%)	365 (93.6%)	2.13	(1.33/3.30)	0.0012
	Yes	183 (3.1%)	25 (6.4%)			
Up to age 6						
Asthma	No	5070 (96.2%)	439 (91.6%)	2.29	(1.56/3.27)	<0.0001
	Yes	202 (3.8%)	40 (8.4%)			
Eczema	No	3999 (75.9%)	286 (57.4%)	2.33	(1.92/2.82)	<0.0001
	Yes	1273 (24.1%)	212 (42.6%)			
Hay fever	No	4910 (93.1%)	414 (85.4%)	2.33	(1.74/3.07)	<0.0001
	Yes	362 (6.9%)	71 (14.6%)			
Up to age 10						
Asthma	No	3899 (93.0%)	424 (85.1%)	2.33	(1.75/3.08)	<0.0001
	Yes	292 (7.0%)	74 (14.9%)			
Eczema	No	3120 (74.4%)	278 (51.1%)	2.79	(2.31/3.36)	<0.0001
	Yes	1071 (25.6%)	266 (48.9%)			
Hay fever	No	3581 (85.4%)	360 (69.8%)	2.54	(2.05/3.14)	<0.0001
	Yes	610 (14.6%)	156 (30.2%)			