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Food allergy in infants assessed in two German birth cohorts 10 years after the EuroPrevall Study

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Abstract

Background: The prevalence of food allergies (FA) in children increased rapidly at the turn of the century. The EuroPrevall study identified Germany as a country with very high prevalence of FA at that time. Using two large German birth cohorts, we provide an update of the status quo 10 years later.

Methods: KUNO Kids and Ulm SPATZ Health studies are two ongoing prospective birth cohorts. Information on FA was obtained by questionnaires at birth and after 6, 12, and 24 months. Univariable and multivariable logistic regression analyses were performed to investigate risk factors during pregnancy, birth, and early childhood.

Results: In 1139 and 1006 children from KUNO Kids and SPATZ, the point prevalence of parent-reported FA symptoms at the ages of 1 and 2 years was 13.2% (95% CI: 11.2–15.2) and 13.9% (95% CI: 11.5–17.2) in KUNO Kids. Doctor's diagnosed FA at 1 and 2 years was 2.4% (95% CI: 1.6–3.4) and 2.7% (95% CI: 1.2–4.3) in KUNO Kids and 2.3% (95% CI: 1.3–3.6) and 3% (95% CI: 2.0–4.5) in SPATZ. Cow's milk and citrus fruits were most frequently suspected by parents to cause FA symptoms. Atopy in the child was associated with a higher frequency of FA at any time, whereas atopy in first-degree relatives was only associated with FA at year 1. Smoke exposure during pregnancy was a risk for FA at age 2.

Abbreviations: BMI, Body mass index; CI, Confidence interval; DBPCFC, Double-blind placebo-controlled food challenge; FA, Food allergy; GDM, Maternal gestational diabetes; OR, Odds ratio; SD, Standard deviation.

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Conclusion: The prevalence of food allergy seems to have plateaued in the last 10 years in Germany. FA is often suspected by parents but only rarely diagnosed by oral food challenge. Risk factor analysis may help to establish personalized health approaches.

KEYWORDS
birth cohort, epidemiology, food hypersensitivity, infant

1 | INTRODUCTION

Within the last five decades of the 20th century, the prevalence of atopic diseases like asthma, atopic dermatitis, and allergic rhinitis increased dramatically in children across the world[1-3] and remained high.[4,5] Food allergy (FA) seems to be the epidemic of the new century with rapidly increasing prevalence rates,[3] becoming a major health burden in many countries, especially in children.[6,7] The EuroPrevall birth cohort is the first and largest study to investigate FA in Europe.[8] When recruitment was done in 2005, Germany was identified as one of the European countries with the highest prevalence of FA.[9,10] However, it remains unclear whether FA further increased since then and whether risk factors for the disease changed over time.

Therefore, we investigated the prevalence of FA in infants and young children approximately 10 years after the EuroPrevall study in two large and currently ongoing German birth cohorts, the KUNO Kids Health study (KUNO Kids)[11] and the Ulm SPATZ Health Study (SPATZ).[12,13] Furthermore, we explored the role of factors potentially associated with FA at ages 1 and 2 years, such as medical features of pregnancy and birth, nutrition of the child, and environmental exposures during pregnancy and infancy[14-16] in KUNO Kids and sought for replication in SPATZ. Finally, we compared results to extractable EuroPrevall data.

Key messages

In two ongoing prospective birth cohorts in Germany, the prevalence of parent-reported FA in Germany was assessed and did not increase further in comparison with the EuroPrevall study 10 years ago. Parents suspect a multitude of different foods to cause FA symptoms, and oral food challenge is seldom used to confirm the diagnosis. Risk factors for FA include atopy and smoke exposure, seem to be age specific, and could provide targets for personalized medicine approach.

Based on data from two current birth cohorts, we suggest that FA prevalence reached a plateau in Germany when compared to EuroPrevall data from 10 years ago. Numerous non-core foods contribute to FA nowadays and risk factors for FA may contribute differently to FA occurring at various time points over the course of infancy.

2 | METHODS

2.1 | Description of populations

2.1.1 | The KUNO Kids Health study

KUNO Kids is an ongoing prospective birth cohort started in 2015 which aims to explore the determinants of child health in a holistic approach. Recruitment is still ongoing. For the purpose of this study, we used data from the first and second phase of the study, which comprises 3100 newborns and their families recruited between June 2015 and March 2019. Data captured by follow-up questionnaires received by March 2020 were included in statistical analysis.

The precise methodology and design of the study have been described elsewhere.[11] Briefly, written informed consent was obtained from all eligible mothers who gave birth at the children's and women's hospital St. Hedwig in Regensburg. Exclusion criteria were unavailability for informed consent (i.e., insufficient German language skills) and mother's age below the legal age of 18. The study design and procedures were approved by the ethics committee of the University of Regensburg (file number: 14-101-0347). An interview was conducted within days after birth, and follow-up questionnaires were sent to the families after 4 weeks, 6 months, and on every birthday of the child to collect additional information on the index child and the family. Socio-demographic information, medical history, feeding practices, lifestyle behaviors (nutrition, physical activity, smoking, alcohol consumption), and psychosocial constructs were collected from parents and siblings. Where available, validated questions and measurement instruments were used to allow for joint analyses of data with pre-existing studies, including SPATZ.

In KUNO Kids, parent-reported FA was defined in concordance with the EuroPrevall (using the same questionnaire) as a positive history of gastrointestinal, dermatological, or respiratory symptoms, which appeared in timed correlation to the food intake without other explanations for the symptoms. Gastrointestinal symptoms were nausea, vomiting, diarrhea, abdominal pain, constipation, and soft stools. Dermatological reactions comprised urticaria, angioedema, itching, and the appearance or worsening of eczema. Respiratory symptoms were defined as wheezing, dyspnea, coughing, stridor, and allergic rhinitis symptoms. Information on signs, symptoms, point of time, and clinical diagnostics of FA was

collected using a validated questionnaire at 6 months and 1 and 2 years postpartum. Additional information on lifestyle-related factors like tobacco exposure during pregnancy, birth mode, infant feeding practices, environmental exposures during infancy, maternal and infant antibiotic intake as well as atopic diseases within the family was obtained from the KUNO Kids database. Parent-reported FA in KUNO Kids was defined as a parent report of FA-related symptoms in the past 12 months, while the doctor-reported FA was defined as a positive report of a doctor's diagnosis of FA at 1 and 2 years.

2.1.2 | The Ulm SPATZ Health Study

The Ulm SPATZ Health Study is an ongoing birth cohort study. A total of 1006 newborns and their 970 mothers were enrolled into the study from the general population soon after delivery at the University Medical Centre Ulm, between April 2012 and May 2013. A detailed description of the study can be found elsewhere.[12,13] Mothers were excluded from the study if (i) their German language skills were insufficient to understand the study procedure and consent forms, (ii) they had outpatient childbirth, (iii) they were <18 years of age, (iv) there was postpartum transfer of mother or child to an intensive care unit, or stillbirth. Participation in the study was entirely voluntary after informed consent was given. The study was approved by the Ethics board of Ulm University (no. 311/11).

Demographic, lifestyle, and birth-related data including child gender, delivery mode, birthweight, maternal age, education, maternal body mass index (BMI), smoking status (within 1 year prior to delivery), maternal, paternal, and child history of allergic disease were collected using self-administered questionnaires, hospital electronic charts, and paper-documented routine screening during pregnancy. Smoking status and alcohol consumption were assessed and defined as previously explained.[12]

A reported doctor's diagnosis of FA in the past 12 months was assessed at 1 year, 2 years, and at each further yearly follow-up by separate self-administered questionnaires from parents and the children's primary care pediatricians. In this case, the reports were distinguished between "parent-reported" FA and "pediatrician-reported" FA; however, both were reports of a doctor's diagnosis. The parent-reported FA in SPATZ equals the doctor's diagnosed FA in the KUNO Kids study. FA symptoms were not assessed in SPATZ.

2.2 | Statistical analysis

The statistical analysis was conducted using Statistical Package for Social Sciences® (SPSS.24) and SAS 9.4 (The SAS® Institute). *p*-values <.05 were considered statistically significant. Descriptive statistics are displayed as median and interquartile range and mean and standard deviation for non-parametric and parametric data, respectively. First, univariable logistic regression analyses were used to explore the association of the different previously suggested risk factors with FA at age 1 and at age 2, in the KUNO Kids and in the Ulm SPATZ cohort, respectively. Then, multivariable regression modeling was performed, for the respective FA outcome at age 1 and at age 2 in both cohorts. Risk factors were included in the multivariable models if they were associated with the outcome ($p < .2$) at age 1 or at age 2 in the respective cohort. Odds ratios (OR) and 95% confidence intervals (CI) are displayed.

3 | RESULTS

Of the 3100 newborns and their families enrolled in the KUNO Kids study until March 2020, 2679 were at least one year old when the dataset for this analysis was closed. FA data at one or more time points (6 months, 1 year, and 2 years) were available from 1139 infants. Compared with the total study population, cesarean section, having older siblings, exposure to household smoking, and a migration background were less frequent in children with completely available FA questionnaires until 1 year of age, while older mothers and a higher educational level were more frequent (Table 1 and Table S1).

Cumulatively, 23.9% of parents in the KUNO Kids study reported that their child had an adverse reaction to food in the first 2 years of life, not distinguishing between IgE- and non-IgE-mediated self-reported food allergy. The point prevalence was slightly higher at age 6 months and gastrointestinal and dermatological symptoms were most frequent (Figure 1). Cow's milk, citrus fruits, and wheat were most frequently described by parents as allegedly causative, while eggs were mentioned less frequently (Figure 2). In infants younger than 4 months, parents mentioned cow's milk most often to be responsible for the symptoms and fruits in 4 to 6 months old infants. (Figure 2). Some parents (143/1137) reported that a broad variety of fruits and vegetables not listed on the questionnaire (non-core foods) caused putative FA symptoms. For more than half (59.7%) of the children with reported FA at 6 months, no symptoms at the age of 1 year were reported. Of those with suspected FA at age 1 year, 58.1% did not report FA at age 2 years. Only 1.9%, 2.4%, and 2.7% of parent-reported FA were diagnosed by a doctor at 6 months, age 1, and age 2 years, respectively. Diagnostic confirmation by oral food challenge was only obtained in 30.8% of the 6 months cases, in 21.1% of the 1-year cases and 10% of the 2-year cases.

In a univariate analysis, we analyzed risk factors for FA suggested by previous studies for their association with FA at age 1 (Table S2A) and age 2 (Table S2B) in our dataset. The risk of parent-reported FA symptoms at 1 and 2 years of age was significantly higher if the child had other atopic diseases at the time. The presence of atopic diseases in first-degree relatives was related to an increased risk for food allergy at age 1 year, but not at age 2 years. Children with low birthweight had a decreased risk for FA at age 2 years while animal contact of the child or the mother during pregnancy (apart from farms) increased the risk for FA at this time point. Of note, passive smoke exposure of the mother was a strong predictor for FA at age 2 years. Only at age 1 year, a non-significant trend toward an increased risk to develop FA symptoms was observed in children of obese mothers compared with children of normal weight mothers

TABLE 1 Characteristics of the study population (KUNO Kids study)

	Total study population, % or mean ± SD		Study sample with data on FA, % or mean ± SD	
		n		*n*
Child				
Male sex	51.2	2653	49.9	1134
Duration of pregnancy (week)	39.5 ± 1.6	2625	39.6 ± 1.6*	1128
Cesarean section	28.6	2679	27.8	1139
Birthweight (g)	3359 ± 509	2638	3371 ± 500	1130
Antibiotic use	2.7	2600	2.2	1113
Older siblings	43.7	2636	38.5*	1130
Migration background[a]	28.0	1824	14.2*	1065
Mother				
Age (years)	32.7 ± 4.5	2651	33.1 ± 4.1*	1132
Pre-pregnancy BMI (kg/m^2)	23.8 ± 5.0	2614	23.7 ± 4.7	1121
Regular animal contact[b]	54.9	2601	53.8	1116
Higher educational level (>10 years)	56.5	2597	62.8*	1116
Smokers in the household	22.4	2601	17.0*	1114

Note: *Comparison with total study population yielded statistically significant difference ($p < .001$).
Abbreviations: BMI, body mass index; FA, food allergy; SD, standard deviation.
[a]Mother or father with non-German nationality or born not in Germany.
[b]Regular contact (more than once per month) to any pet during pregnancy.

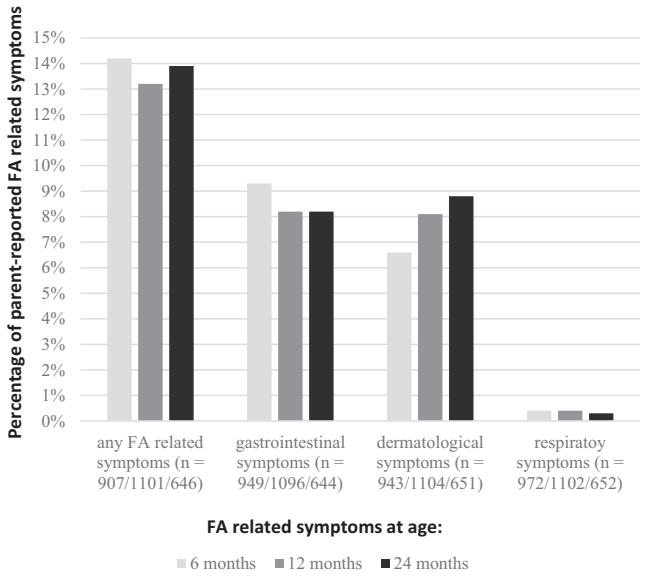

FIGURE 1 Prevalence and characteristics of parent-reported food allergy related symptoms over the first 2 years in the KUNO Kids study

(measured before pregnancy). Of the 1006 infants enrolled into the SPATZ study, 4.1% of the infants had at least one food allergy reported either by the caring pediatrician or by the parent (parental report of the doctor's diagnosis) within the first year of life. Common risk factors for FA were also investigated in the SPATZ study at age 1 and 2 years, whenever available (Table S3A and B). Again, the presence of other allergies in the child was statistically significantly associated with FA (years 1 and 2) and atopic diseases in first-degree relatives were a significant predictor for FA at age 1 year.

Next, we performed multiple regression modeling for the respective FA outcomes at age 1 and at age 2 in both cohorts based on risk factors which $p < .2$ in the univariate analyses. For KUNO Kids, atopic disease in the child was strongly associated with FA at age 1 and 2 years while a positive family history was associated only with FA at age 1 year (Table 2A and B). Gestational diabetes in the mother and exposure to traffic showed suggestive associations ($p < .1$) at age 1 and 2 years, respectively. Multivariate regression in the SPATZ study confirmed the association between another atopic disease in the child and FA at both ages (Table 3A and B). Furthermore, associations between male gender for FA at age 1 and exposure to cigarette smoking with FA at age 1 (suggestive) and age 2 (significant) were identified.

Finally, we compared the data from the KUNO Kids and SPATZ studies with results from EuroPrevall acquired approximately 10 years earlier. (Table 4). On average, mothers in the KUNO Kids study were approximately one to two years older when compared to mothers from the EuroPrevall and SPATZ studies. The frequency of cesarean section birth was lower in the KUNO Kids and SPATZ studies, while antibiotic use during delivery was considerably higher in KUNO Kids compared with EuroPrevall and SPATZ. Also, the prevalence of maternal smoking and passive smoking varied significantly between studies. Data on overall parent-reported and doctor-diagnosed FA frequencies in EuroPrevall were extracted from the manuscript by Schoemaker et al.[17] Frequencies were in a similar range in the two recent birth cohort studies KUNO Kids and

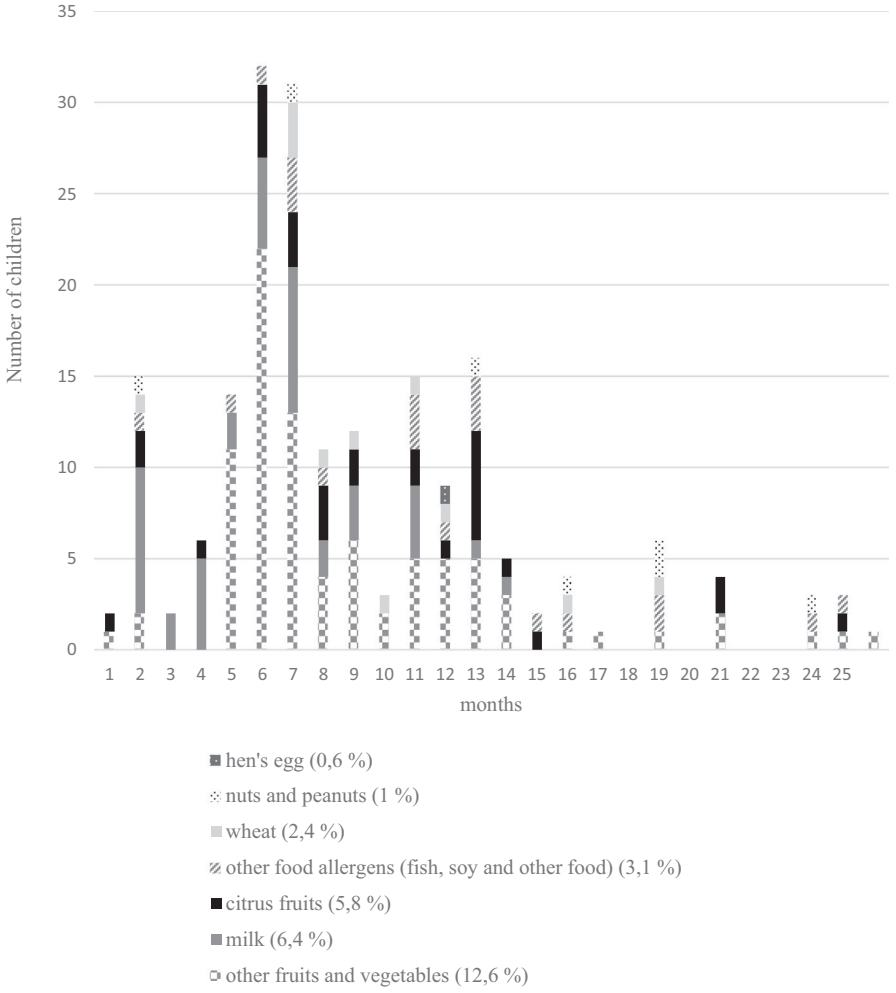

FIGURE 2 First occurrence of parent-reported adverse reactions to food allergens in the first 2 years of life ($n = 189$) and proportion of core foods causing the adverse reactions reported for specific months in the KUNO Kids study

SPATZ as well as the reported German and overall EuroPrevall data for parent-reported FA symptoms and doctor's diagnosis of FA at age 2 years.

4 | DISCUSSION

Data from KUNO Kids and SPATZ show that the prevalence of parent-reported FA and doctor's diagnosis of FA in infants at age 1 and 2 years did not differ substantially from results obtained by the EuroPrevall study 10 years ago. Non-core foods seem to play an important role in FA now. When classic risk factors for FA were investigated in the current studies, family history for atopy was associated with FA at age 1 but less so at age 2, while maternal passive smoke exposure was a risk factor for FA at age 2. Our study demonstrated that FA seems to be a highly dynamic entity with various changes in point prevalence, risk factors, and predictors over the first 2 years of life.

Some differences between study populations were observed, but most of the factors that have been associated with an increased risk of FA in previous studies were more pronounced in KUNO Kids and SPATZ. Due to the population structure of KUNO Kids with older, highly educated mothers, an over-reporting of food allergy symptoms may be expected, and consequently, FA would be overestimated. However, compared with data available in EuroPrevall at age 2 years for Germany and Europe, no clear difference was observed. Even though methodology differed, and the two study regions investigated here are Regensburg (KUNO Kids) and Ulm (SPATZ) and not Berlin (EuroPrevall), results seem comparable enough to assess trends over time. For the prevalence of doctor's diagnosis of food allergy, reports at age 1 and 2 years are very similar for KUNO Kids and SPATZ (Table 3). For EuroPrevall, prevalence data for Europe and Germany were taken from the publication of Schoemaker.[17] Since the focus of that study is on cow's milk allergy, the calculated rate of doctor's diagnosed FA may be underestimated for EuroPrevall Germany. Taking all these factors into account, there is no indication of a significant rise in the prevalence of FA in Germany over the last 10 years. This is of interest, because at the turn of the century a worldwide trend toward an increasing FA prevalence was suggested[6] when hospital admissions for food allergy quintupled[3] and the number of children with FA increased by twelve times between 1995 and 2006.[2] Especially in children below 2 years, an increase in food-induced anaphylaxis was reported.[7] Our data now suggest that the prevalence of food allergies reached a plateau in Germany, similar to what has been observed for many other atopic diseases, such as asthma, years earlier.[18-20]

TABLE 2 Multivariable logistic regression analysis in KUNO Kids of potential risk factors: Outcome parent-reported symptoms of FA

	Odds ratio (95% CI)	*p* Value
A) At age 1		
Child		
Cesarean section	0.828 (0.562–1.219)	.339
Birthweight <2800 g	0.817 (0.466–1.432)	.480
Duration of breastfeeding <6 month	0.920 (0.640–1.322)	.653
Daily animal contact[a]	1.091 (0.725–1.642)	.676
High exposure to traffic, exhaust gases	1.038 (0.739–1.459)	.828
Other atopic diseases[b]	3.681 (2.504–5.412)	<.001
Mother		
Pre-pregnancy BMI		
Underweight	1.894 (0.637–5.633)	.251
Normal weight	reference	
Overweight	1.041 (0.692–1.571)	.841
Obese	1.377 (0.822–2.305)	.224
Gestational diabetes	1.503 (0.960–2.354)	.075
Passive exposure to cigarette smoking	1.049 (0.689–1.598)	.823
Regular animal contact[c]	0.969 (0.641–1.466)	.883
School education		
Low (no degree)	1.463 (0.721–2.969)	.292
Intermediate (<10 years)	reference	
High (>10 years)	1.120 (0.755–1.662)	.572
Atopic disease of first-degree relatives[d]	1.531 (1.042–2.250)	.030
B) At age 2		
Child		
Cesarean section	0.875 (0.482–1.587)	.659
Birthweight <2800 g	0.425 (0.141–1.277)	.127
Duration of breastfeeding <6 month	0.832 (0.478–1.450)	.517
Daily animal contacts[a]	1.685 (0.894–3.177)	.107
High exposure to traffic, exhaust gases	1.608 (0.953–2.712)	.075
Other atopic diseases[b]	2.705 (1.472–4.972)	.001
Mother		
Pre-pregnancy BMI		
Underweight	—/—(no cases with FA)	—/—
Normal weight	reference	
Overweight	1.305 (0.707–2.409)	.395
Obese	1.107 (0.506–2.420)	.799
Gestational diabetes	0.569 (0.240–1.347)	.199
Passive exposure to cigarette smoking	1.569 (0.878–2.804)	.128
Regular animal contact[c]	1.318 (0.697–2.492)	.395
School education		
Low (no degree)	1.999 (0.722–5.535)	.182
Intermediate (<10 years)	reference	
High (>10 years)	1.081 (0.576–2.028)	.808
Atopic disease of first-degree relatives[d]	1.470 (0.809–2.669)	.206

Note: Risk factors were included if they were associated with the 1-year or the 2-year outcome ($p < .2$) in univariable analysis; (A) $N = 909$; R^2: .103; (B) $N = 509$; R^2: .123.

Abbreviations: 95% CI, 95% confidence interval; BMI, body mass index; FA, food allergy.

[a]Daily contact to dog, cat, hamster, guinea pig, mouse, rat, or rabbit.

[b]Atopic eczema, allergic rhinitis, allergic conjunctivitis, or asthma.

[c]Regular contact (more than once per month) to any pet during pregnancy.

[d]Atopic eczema, allergic rhinitis, allergic conjunctivitis, asthma, or food allergy in parents or blood-related siblings.

TABLE 3 Multivariable logistic regression analysis in Ulm SPATZ Health Study of potential risk factors: Outcome parent-reported FA

	Odds ratio (95% CI)	*p* Value
A) At age 1		
Child		
Male sex	1.909 (1.003–13.223)	.049
Other atopic diseases[a]	2.99 (3.037–26.321)	<.001
Mother		
Gestational diabetes	1.677 (0.699–11.303)	.145
Cigarette smoking during pregnancy	1.572 (0.852–7.174)	.096
Antibiotic use during pregnancy	1.513 (0.673–7.777)	.185
Atopic disease of first-degree relatives[b]	1.844 (0.932–12.413)	.064
B) At age 2		
Child		
Male sex	1.443 (0.841–5.16)	.113
Other atopic diseases[a]	2.012 (1.639–10.01)	.002
Mother		
Gestational diabetes	1.279 (0.456–5.876)	.450
Cigarette smoking during pregnancy	1.627 (1.099–6.371)	.030
Antibiotic use during pregnancy	1.235 (0.493–4.716)	.464
Atopic disease of first-degree relatives[b]	1.417 (0.807–4.998)	.134

Note: Risk factors were included if they were associated with the 1-year or the 2-year outcome ($p < .2$) in univariable analysis; (A) $N = 729$; R^2: .044; (B) $N = 788$; R^2: .026.

Abbreviations: 95% CI—95% confidence interval; FA—food allergy.

[a]Atopic eczema, hay fever, asthma.

[b]Atopic eczema, hay fever, asthma in parents and blood-related siblings.

TABLE 4 Comparison of study results from KUNO Kids (recruitment 2015–2019), SPATZ (2012–2013) and EuroPrevall (2005–2010)

	KUNO Kids % or mean ± SD	SPATZ % or mean ± SD	EuroPrevall Germany % or mean ± SD	EuroPrevall total (Europe) % or mean ± SD
Study sample	1139	1006	1570	12,049
Symptom-based FA				
6 months	14.2 (95% CI: 12.3–16.2)	–	–	–
12 months	13.2 (95% CI: 11.2–15.2)	–	–	–
24 months	13.9 (95% CI: 11.5–17.2)	–	14.5[a] (95% CI: 13.1–16.3)	16.0 (95% CI: 15.4–16.6)
Doctor's diagnosed FA				
6 months	1.9 (95% CI: 1.2–2.8)		–	–
12 months	2.4 (95% CI: 1.6–3.4)	2.3 (95% CI: 1.3–3.6)	–	–
24 months	2.7 (95% CI: 1.2–4.3)	3.0 (95% CI: 2.0–4.5)	2.0[b] (95% CI: 1.4–2.8)	3.8[b] (95% CI: 3.5–4.2)
Male sex	49.9	52.1	51.7	51.4
Duration of pregnancy (week)	39.6 ± 1.6	38.8 ± 1.7	–	39.6 ± 1.5
Cesarean section	27.8	27.9	31.1	24.0
Birthweight (g)	3371 ± 500	3157 ± 948.3	–	3404 ± 512
Pets				
Dog	9.9	–	9.0	16.0
Cat	19.4	–	15.0	15.1
Other	9.4	–	15.1	12.2
Maternal age (year)	33.1 ± 4.1	32.7 ± 4.7	31.4 ± 5.4	30.7 ± 5.2
Pre-pregnancy BMI (kg/m^2)	23.7 ± 4.7	24.8 ± 5.1	–	23.3 ± 4.3
Maternal antibiotic intake				
During pregnancy	21.0[c]	11.1[c]	18.6	21.1
During delivery	54.3[c]	–	32.4	15.4
Cigarette smoking during pregnancy				
Active	1.3	–	10.8	10.6
Passive	21.7	–	34.7	17.4
Maternal FA	27.1	–	30.2	14.3
Other maternal atopic disease[d]	31.5	34.1	35.2	26.2
Paternal FA	24.2	–	19.0	8.6
Other paternal atopic disease[d]	32.9	35.4	29.2	20.9
Other atopic diseases of siblings[d]	17.1	15.9	19.9	26.0

Abbreviations: 95% CI, 95% confidence interval; BMI, body mass index; FA, food allergy; SD, standard deviation.

[a]EuroPrevall documented this frequency for self-reported FA in siblings of their study children (Schoemaker et al., 2015, *Allergy*).[17]

[b]Calculated from data from Schoemaker et al., 2015, *Allergy*,[17] as percentage of children eligible for DBPCFC.

[c]Different methods: KUNO kids used a specific question ("Did you take any antibiotics during pregnancy/delivery?"), SPATZ used an open question after delivery about any medication intake during pregnancy.

[d]Atopic eczema, allergic rhinitis, allergic conjunctivitis, or asthma.

In KUNO Kids and SPATZ, assessments of FA were based on questionnaires only, while in EuroPrevall, questionnaires and a double-blind placebo-controlled food challenge (DBPCFC) were applied. Several studies suggest that the prevalence of parent-reported FA overestimates the actual FA prevalence.[10,21,22] In our study, parents suspected a multitude of different foods, especially fruit and vegetables, to be responsible for adverse reactions. While known allergens like cow's milk, wheat, hen's egg, soy, and peanut are responsible for IgE-mediated allergy, these putative causative agents seem to represent a fear of parents rather than actual food allergy. Citrus fruit and histamine-rich foods can cause perioral itching and redness (especially in children with eczema) which is not due to IgE-mediated allergy. Further investigations into that observation are needed.

The results of KUNO Kids showed that FA in infants is often not diagnosed with DBPCFC: two-thirds at the age of 6 months, 79% at the age of 1 year, and 90% at the age of 2 years were diagnosed with other methods than DBPCFC which suggests that better education of doctors and parents along with increasing resources for DBPCFC may be necessary and needed to avoid unnecessary and even harmful dietary restrictions in children based on FA assumptions. However, results can be comparable between studies for questionnaire-derived data, especially as KUNO Kids used the same questions as EuroPrevall (for symptoms of FA) and SPATZ (for doctor-diagnosed FA). Simple, questionnaire-based assessment tools are key for replication and comparisons between populations as previously demonstrated by the worldwide ISAAC project.[23]

Some previously suggested risk factors[24-26] were assessed here by univariate analysis in KUNO Kids and SPATZ and followed up in a multivariate analysis. Interestingly, a family history of atopic diseases in first-degree relatives was associated with an increased risk for FA at age 1 but not age 2 in both studies. This may either indicate that the genetic impact on FA decreases with age or that pathogenesis of food allergy at age 2 years differs from FA at age 1 year. Accordingly, we demonstrated an extensive turnaround in presence and absence of FA symptoms over that time span. A (changeable) risk factor for FA at age 2, but less so at age 1, is passive smoke exposure either through maternal smoking during pregnancy or via postnatal environmental exposure in both birth cohorts. This may present a valuable opportunity for future efforts of intervention and prevention.

In conclusion, our study suggests that the prevalence of FA in Germany has reached a plateau in infants and young children. Numerous allergens other than core foods are associated with FA in infants now. While better diagnosis of FA with DBPCFC in clinical practice is needed, questionnaire data can provide valuable comparisons between different populations and inform about time trend and regional differences. Risk factors for the development of FA seem to be age specific and that needs to be taken into account more carefully for further FA prediction analysis, when personalized medicine may be applied to FA.

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CONFLICT OF INTEREST

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SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

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