**Conflict of interest statement**

D. Rothenbacher received research grants from Danone Nutritia Research and J. Genuneit is the project manager of research grants from Danone to both Ulm University and Leipzig University in relation to studies of the composition of breast milk including data of the Ulm SPATZ Health Study. All authors declare that they have no competing financial or personal interests.

**Funding**

The KUNO Kids study is funded by research grants of the EU (HEALS: 603946) and the German Federal Ministry for Education and Research (SYSINFLAME: 01ZX1306E and NAMIBIO: 01EA2108B). Further financial support was provided by the University Children’s Hospital of the University of Regensburg and the Order of St. John. The funding bodies had neither influence on the design of the study, on the collection, analysis and interpretation of data, nor in the writing of the manuscript. The Ulm SPATZ Health Study was funded through an unrestricted grant by the Medical Faculty of Ulm University and by the German Federal Ministry for Education and Research (NAMIBIO: 01EA2108B).

**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 ten 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. Univariate 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% and 13.9 % in KUNO Kids. Doctor’s diagnosed FA at 1 and 2 years was 2.4% and 2.7% in KUNO Kids and 2.3% and 3% 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.

**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:** Food hypersensitivity, infant, birth cohort, epidemiology

**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 to the EuroPrevall study ten 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.

**Abbreviations used**

FA Food allergy

OR Odds ratio

BMI Body mass index

CI Confidence interval

DBPCFC Double-blind placebo-controlled food challenge

GDM Maternal gestational diabetes

SD Standard Deviation

**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 world1-3 and remained high4,5. Food allergy (FA) seems to be the epidemic of the new century with rapidly increasing prevalence rates3, becoming a major health burden in many countries, especially in children6,7. The EuroPrevall birth cohort is the first and largest study to investigate FA in Europe8. When recruitment was done in 2005, Germany was identified as one of the European countries with the highest prevalence of FA9,10. However, it remains unclear whether FA further increased since then and if 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 infancy14-16 in KUNO Kids and sought for replication in SPATZ. Finally, we compared results to extractable EuroPrevall data.

**Methods**

**Populations descriptions**

***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 2020. 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 elsewhere11. 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 local ethics committee (file number: 14-101-0347). An interview was conducted within days after birth and follow-up questionnaires were sent to the families after four weeks, six 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 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, obstipation and soft stools. Dermatological reactions comprised urticaria, angioedema, itching and the appearance or worsening of eczema. Respiratory symptoms were defined as wheezing, dyspnoea, coughing, stridor and hay fever. Information on signs, symptoms, point of time and clinical diagnostics of FA was collected using a validated questionnaire at 6 months, 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 FA related symptoms, while the doctor reported FA was defined as a positive report of a doctor’s diagnosis of FA at 1 and 2 years.

***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 elsewhere12,13. 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 child birth, (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, birth weight, maternal age, education, maternal body mass index (BMI), smoking status (within one year prior to delivery), maternal, paternal and child history of allergic disease was 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 explained12.

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.

**Statistical analysis**

The statistical analysis was conducted using Statistical Package for Social Sciences® (SPSS.24) and SAS 9.4 (The SAS® Institute, Cary, NC, USA). P-values <0.05 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.Univariate logistic regression analyses were used to explore the association of the different previously suggested risk factors with FA. Odds ratios (OR) and 95% confidence intervals (CI) are displayed.

**Results**

Of the 3.100 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, 2 years) were available from 1139 infants. Compared to the total study population, caesarean 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).

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. 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 3). 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 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 2a) and age 2 (Table 2b) 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 birth weight 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 timepoint. 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 towards an increased risk to develop FA symptoms was observed in children of obese mothers compared to children of normal-weight mothers (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 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 whenever available (supplementary Tables 2a and 2b). Again, the presence of other allergies in the child was statistically significantly associated with FA (year 1 and 2) and atopic diseases in first degree relatives was a significant predictor for FA at age 1 year.

Finally, we compared the data from the KUNO Kids and SPATZ studies with results from EuroPrevall acquired approximately 10 years earlier. (Table 3). On average, mothers in the KUNO Kids study were approximately 4 years older when compared to mothers from the EuroPrevall and SPATZ studies. The frequency of caesarean section birth was lower in the KUNO Kids and SPATZ studies, while antibiotic use during delivery was considerably higher in KUNO Kids compared to 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 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.

**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 across over the first two years of live.

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 to data available in EuroPrevall at age 2 years for Germany and Europe, no difference was observed. Even though methodology differed, 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 Schoemaker17. 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 towards an increasing FA prevalence was suggested6 when hospital admissions for food allergy quintupled3 and the number of children with FA increased by twelve times between 1995 and 20062. Especially in children below 2 years, an increase in food-induced anaphylaxis was reported7. Our data now suggests 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 earlier18-20.

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 prevalence21,22,10. 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. 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 project23.

A number of previously suggested risk factors were assessed here by univariate analysis in KUNO Kids and SPATZ. 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 two years differs from FA at age one year. Accordingly, we demonstrated an extensive turnaround in presence and absence of FA symptoms over that time span. A strong (and changeable) predictor 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 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.

**Impact statement:**

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 timepoints over the course of infancy.

**Acknowledgment:**

We are grateful to all participants in the KUNO Kids and the Ulm SPATZ Health Studies and to their parents for filling out questionnaires over years. We thank all the students who contributed time and effort in the collection of data and all the partners in the study for their input and support.

**Authors’ contributions:**

Study design: MK, JG

Data collection: MK, DVR, JCP, MM, CA, AP, CT, VP, JR, LN, JP, JG, DR

Statistical analysis and data interpretation: SB, VDG, DVR, LS, SH, CA, JG, MK

Manuscript writing: DVR, VDG, DR, SB, SH, MK