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Original Article

Primary and pollen-associated hazelnut allergy in school-aged children in Germany: A birth cohort study

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FA, food allergy; DBPCFC, double-blind placebo-controlled food challenge; KIGGS study, German Health Interview and Examination Survey for Children and Adolescents; ECRHS, European Community Respiratory Health Survey; EuroPrevall, prevalence, cost and basis of food allergy across Europe; iFAAM, integrated approaches to food allergen and allergy risk management; SPT, skin prick testing; sIgE, serum specific immunoglobulin E; Cor a 14, *Corylus avellana* 14

ABSTRACT

Background: Primary hazelnut allergy is a common cause of anaphylaxis in children, as compared to birch-pollen associated hazelnut allergy. Population-based data on hazelnut and concomitant birch-pollen allergy in children are lacking. We aimed to investigate the prevalence of primary and pollen-associated hazelnut allergy and sensitization profiles in school-aged children in Berlin, Germany.
Methods: 1570 newborn children were recruited in Berlin in 2005–2009. The school-age follow-up (2014–2017) was based on a standardized web-based parental questionnaire and clinical evaluation by a physician including skin prick tests, allergen specific immunoglobulin E serum tests and placebo-controlled double-blind oral food challenges, if indicated.
Results: 1004 children (63.9% response) participated in the school-age follow-up assessment (52.1% male). For 1.9% (n = 19, 95%-confidence interval 1.1%–2.9%) of children their parents reported hazelnut-allergic symptoms, for half of these to roasted hazelnut indicating primary hazelnut allergy. Symptoms of birch-pollen allergy were reported for 11.6% (n = 116 95%-CI 9.7%–13.7%) of the children. Both birch-pollen allergy and hazelnut allergy associated symptoms affected 0.6% (n = 6, 95%-CI 0.2%–1.3%) of children. Assessment of allergic sensitization was performed in 261 participants and showed that almost 20% of these children were sensitized to hazelnut, being the most frequent of all assessed food allergens, or birch-pollen, the majority to both.
Conclusions: Based on parental reports hazelnut-allergic symptoms were far less common than sensitization to hazelnut. This needs to be considered by physicians to avoid unnecessary changes in diet due to sensitization profiles only, especially when there is a co-sensitization to hazelnut and birch-pollen.

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Introduction

In children with primary hazelnut allergy severe and potentially fatal reactions are common.[1] Teenagers and adults, on the contrary, are more likely to develop pollen-associated hazelnut allergy with predominantly local symptoms i.e. itching of the mouth.[2]

For the diagnosis of FA, patient history and the allergic sensitization profile are important. The gold standard to diagnose FA is DBPCFC tests.[3] Cor a 14 is a hazelnut seed storage protein (2S albumin) and the best predictor for clinically relevant systemic reactions.[4]

The population-based KIGGS study from 2003 to 2006 showed that 13% of children in Germany between 7 and 10 years were sensitized to birch-pollen.[5] The population based ECRHS showed that almost 15% of 20–44 year old Germans were sensitized to hazelnut.[6] A comprehensive meta-analysis of population-based studies from around the globe reported a prevalence range of parent- or self-perceived allergy against all tree nuts from 0.2 to 2.3% in children aged 6–18 years.[7] The prevalence of tree nut allergy based on food challenge tests had been estimated ranging up to 1.4% in European children.[8] Prospective studies investigating birch-pollen allergy and hazelnut allergy simultaneously are missing.

Prevalence and sensitization profiles differ greatly between regions,[9] still there is no epidemiological data of hazelnut allergy with concomitant birch-pollen allergy in German children. The multi-center EuroPrevall/iFAAM birth cohort is the first population-based study investigating FA Europe-wide and is unique in its size and stringent standardized protocol.[10]

Grabenhenrich *et al.* have recently published the overall prevalence of FA in European school children.[11] Using the same birth cohort dataset, we aimed in the present analysis to describe the relation of birch-pollen allergy and primary and pollen-associated hazelnut allergy in Berlin, Germany, a birch-pollen endemic region.

Methods

Study design and setting

The birth cohort study initiated within the EuroPrevall consortium was a prospectively designed investigation that was conducted in nine European countries including the study center Berlin, Germany. The iFAAM project included the first school-age follow-up assessment of the EuroPrevall birth cohort. All assessments of the birth cohort committed to the Declaration of Helsinki.[12] Detailed descriptions of the study methods were published previously.[10,13]

Study population

In Berlin, 1570 children were recruited from 2005 to 2009. Written informed consent was given by all participating parents. Ethical approval was obtained by the ethical review board (iFAAM: EA2/157/13). The baseline characteristics of the EuroPrevall birth cohort comparing all study centers were published previously.[14]

Web-based questionnaire

For the school-age follow-up we contacted the families via mail, e-mail and/or telephone (June 2014–January 2017). All parents were asked to complete a standardized web-based questionnaire for their child including validated asthma and allergy questions (e.g. from the worldwide ISAAC project[15,16]) being translated and back-translated by a German native speaker. We collected data on sociodemographic characteristics, allergies, environmental factors, lifestyle, symptoms, and diagnosis of previous, current and possible FA ("has your child ever had an illness or trouble caused by eating a food or foods and/or a diagnosis of food allergy?"). The following list included raw and roasted hazelnut separately. A child reacting to a food containing hazelnut in the free text field was categorized like those reporting reactions to hazelnut. The web-based questionnaire was a screening tool and was not used to diagnose hazelnut allergy. If the parents wished so, the online questionnaire was completed through a telephone interview.[13]

Clinical evaluation

At school-age all children were invited to attend a clinical visit. They were examined by a study physician, who completed a standardized questionnaire and performed a physical examination. To children with any allergic signs or symptoms, an assessment of allergic sensitization by SPT and sIgE to core foods and several aeroallergens including birch-pollen was offered. SPTs were carried out using a 1 mm single tine lancet, allergen solution, histamine dihydrochloride as positive and saline solution as negative control (all ALK Abello, Madrid, Spain). The mean wheal diameter after 15 min was considered positive when $\geq$3 mm. A venous blood sample was obtained for measurement of sIgE (Phadia ImmunoCap 250 system, Thermo Fisher, Uppsala, Sweden) in the laboratories at Academic Medical Center, Department of Experimental Immunology (Amsterdam, Netherlands). Specific IgE was considered positive if $\geq$0.35 kU/L. Those with positive sIgE for hazelnut were tested for Cor a 14.[13]

Diagnosis of food allergy

Hazelnut allergy was diagnosed by the diagnostic gold standard, DBPCFC, which was offered to all eligible participants. The challenge protocol for hazelnut included seven cumulative doses (3, 10, 30, 100, 300, 1000, 3000 mg) of commercially available hazelnut flour from raw hazelnuts (ENC Mills, Manchester) which were given at least 20 min apart. Children were diagnosed either allergic, tolerant or tolerant but placebo responder. The DBPCFC was repeated when the placebo and the active challenge were both positive.

Birch-pollen allergy and pollen-associated hazelnut allergy

Our epidemiologic definition of birch-pollen allergy was based on parent-reported symptoms typical for allergic rhinitis, i.e. "in the absence of a cold" as suggested by the ISAAC project[15,16] and widely used in population-based studies.[17,18] They had to be reported at least during the month of April, which is the central month during the birch-pollen season in Germany.[19] To examine the robustness of this definition we performed a sensitivity analysis where we defined birch-pollen allergy by symptoms of allergic rhinitis at least in the 2 months of March and April. We defined children as sensitized if either SPT was positive or sIgE elevated.

Our definition of pollen-associated hazelnut allergy was based on predominantly local symptoms like itching of the mouth, parent-reported tolerance of roasted hazelnut and sensitization to birch-pollen and hazelnut.

Statistical analysis

In the first part of our analysis we included data of the web-based questionnaire. In the second part, data of children with assessed sensitization to birch-pollen and hazelnut were analyzed using information of the web-based questionnaire and the clinical interview. When information conflicted, we reported the data of the clinical interview.

We used IBM®SPSS® Statistics 24 (Armonk, New York, USA) for our analysis. We described the results by absolute and relative frequencies with corresponding 95% confidence interval (Clopper Pearson). We reported the mean age and standard deviation in years. The difference concerning the age of onset was analyzed using an unpaired t-test. Correlation between specific IgE in serum and SPT wheal diameter was calculated for non-normally distributed data (Spearman). Data is available on request due to privacy/ethical restrictions.

Results

Participants

Of the 1570 recruited children, 63.9% (n = 1004) participated in the school-age follow-up. 63.7% (n = 1001) of parents completed the comprehensive web-based questionnaire for their child. 33.2% of participating children (n = 332) and their parents attended a clinical visit and an interview. Three children participated in the clinical visit but did not complete the web-based questionnaire. 26.1% of participating children (n = 261) were tested for sensitization to hazelnut and birch-pollen (Fig. 1). We compared the participants lost to follow-up (about a third) to those who only participated in the online questionnaire and to those who were also tested for allergic sensitization to hazelnut and birch-pollen. The latter showed the highest proportion of parents with allergic rhinitis, allergic asthma, atopic dermatitis, and FA. Those lost to follow up had on average a lower parental educational level and were more often current smokers as compared to the other two groups participating in the school-age follow-up (Table 1).

Web-based questionnaire (parent-reported)

Of the 1001 participants whose parents completed the web-based questionnaire, 96.1% (n = 962) of the parents reported that their children have consumed hazelnut within three months prior to the interview, 67% (n = 671) raw hazelnut and 94.2% (n = 943) roasted hazelnut. For 1.9% of children (n = 19, 95% CI 1.1%–2.9%) symptoms after the consumption of hazelnut were reported, for half of them (n = 10) after the consumption of only raw hazelnut, the other half also after the consumption of roasted hazelnut. Parents of one child reported symptoms only occurring after the consumption of roasted hazelnut, whereas raw hazelnut was tolerated according to the parents. Symptoms of allergic rhinitis in April were much more common in our study population, suggesting a higher rate of birch-pollen allergy. Only a small portion (0.6% n = 6) of study children displayed symptoms of both assessed allergies (Table 2, Fig. 2). For one of these 6 children the typical pollen associated hazelnut allergy symptoms were not reported. For 0.5% of children (n = 5) reactions to only raw hazelnut with exclusively oral symptoms as well as symptoms of allergic rhinitis in April were reported.

When we compared the signs and symptoms of those reacting to roasted hazelnut with those reacting to only raw hazelnut, we saw that the latter showed oral symptoms almost exclusively (Supplementary Table 1).

For 0.8% of children (n = 8) a doctor's diagnosis of hazelnut allergy was reported by their parents in the web-based questionnaire with half of them reporting reactions to roasted hazelnut. Parents of 0.3% (n = 3) of children reported hazelnut allergy supported by a food challenge in the web-based questionnaire.

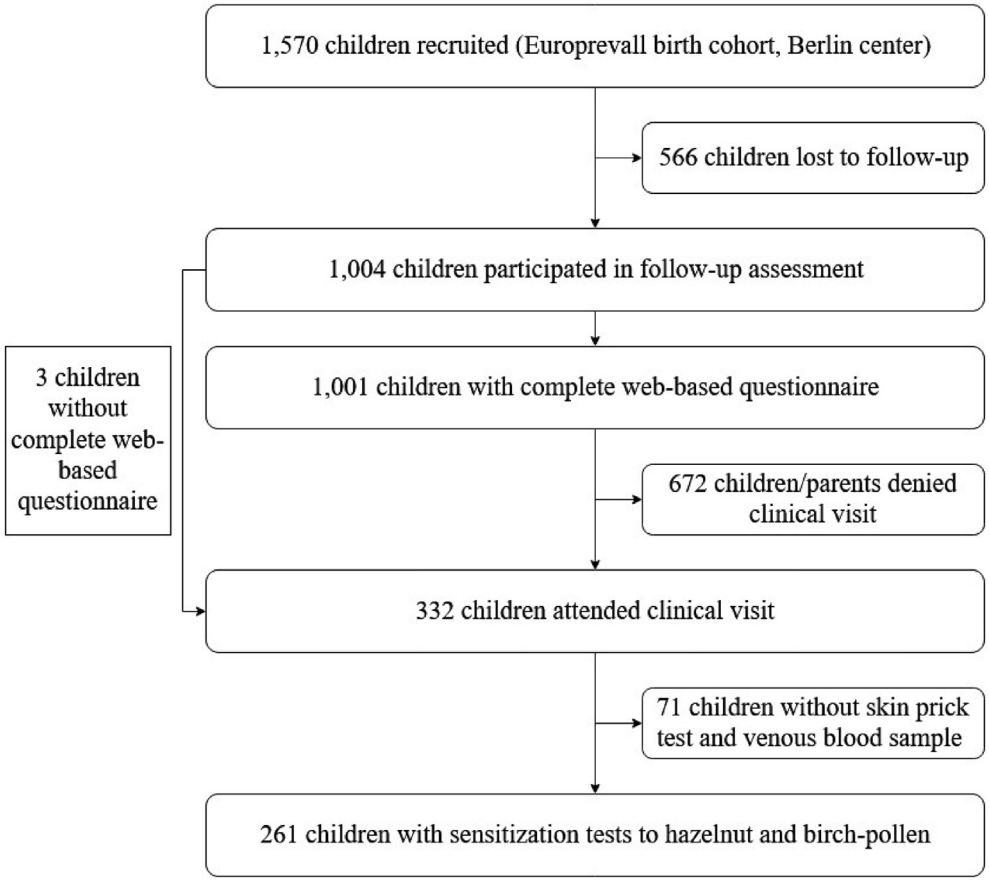

Fig. 1. Participation in Europrevall (The prevalence, cost and basis of food allergy across Europe) birth cohort and iFAAM (Integrated Approaches to Food Allergen and Allergy Risk Management) follow-up assessment from 2004 to 2008.

Table 1
Parent-reported basic characteristics of birth cohort children in Berlin, Germany.

	Children with web-based questionnaire and further diagnostic tests (serum specific immunoglobulin E and/or skin prick test for hazelnut and birch-pollen)	Children with web-based questionnaire and/or clinical visit without further diagnostic tests (serum specific immunoglobulin E and/or skin prick test for hazelnut and birch-pollen)	Children recruited at birth but lost to follow-up in school-age
Total (n)	261	743	566
Sex			
Male (%)	55.2	51.1	50.4
Age at follow-up, questionnaire (mean ± SD, in years)	8.1 (±SD 0.8)	8.3 (±SD 0.9)	–
Mother smoking			
Yes (%)	5.7	6.5	14.5
No, ex-smoker (at least 1 year) (%)	45.6	42.7	43.5
No, never (%)	48.7	50.7	42.0
Mother's age at birth (mean ± SD[$], in years)	32.5 (±SD 5.1)	32 (±SD 5.1)[†]	30 (±SD 5.6)
Father's age at birth (mean ± SD[$], in years)	35.1 (±SD 6.5)[‡]	35.1 (±SD 6.2)[§]	33.7 (±SD 7.1)[¶]
Mother's highest level of education			
Basic education not completed (<10 years) (%)	5.4	6.3	20.3
Basic education completed (10–12 years) (%)	11.9	11.3	9.7
Junior college/vocational training (%)	41.0	35.5	39
University/college (%)	41.8	46.7	30.9
Father's highest level of education			
Basic education not completed (<10 years) (%)	8.0	8.3	15
Basic education completed (10–12 years) (%)	8.0	7.8	9.2
Junior college/vocational training (%)	38.7	30.8	38.5
University/college (%)	44.8	51.8	35.3
Unknown (%)	0.4	1.2	1.9
Mother with allergic rhinitis, atopic dermatitis, and/or asthma			
Yes (%)	41.4	33	35.2
Father with allergic rhinitis, atopic dermatitis, and/or asthma			
Yes (%)	36.4	28.1	25.6
Mother, self-reported food allergy			
Yes (%)	32.2	31.8	27
Father, self-reported food allergy			
Yes (%)	21.8	18.2	16.8
Parent-reported symptoms of birch-pollen allergy			
Yes (%)	21.5	8.2	–
Parent-reported symptoms of hazelnut allergy			
Yes (%)	4.2	1.3	–

[†] Missing for n = 1 mother.
[‡] Missing for n = 1 father.
[§] Missing for n = 4 fathers.
[¶] Missing for n = 7 fathers.
[$] SD = standard deviation.

The mean age for the onset of hazelnut related symptoms was 4.3 years (SD ± 2.9). Children with symptoms only after consumption of raw hazelnut were older at the onset of hazelnut related symptoms than those reacting to both raw and roasted hazelnut: 5.4 (SD ± 2.9) versus 3.1 (SD ± 2.6) years (p = 0.089).

Table 2
Parent-reported symptoms and sensitization rate to hazelnut, birch-pollen and both allergens as well as hazelnut DBPCFC[‡] results as found in the analysis of the web-based questionnaire and further diagnostic assessment.

	1001 children with complete online questionnaire % (n)	261 children with further diagnostic tests % (n)
Parent-reported symptoms of hazelnut allergy	1.9 (19) (95% CI[†] 1.1%–2.9%)	4.2 (11) (95% CI[†] 2.1%–7.4%)
Parent-reported symptoms of hazelnut allergy only after the consumption of raw hazelnut	1 (10)	0.8 (2)
Parent-reported symptoms of allergic rhinitis in April	11.6 (116) (95% CI[†] 9.7–13.7%)	21.5 (56) (95% CI[†] 16.6%–26.9%)
Parent-reported symptoms of hazelnut allergy and allergic rhinitis in April	0.6 (6) (95% CI[†] 0.2–1.3%)	1.5 (4) (95% CI[†] 0.4%–3.9%)
Sensitization to hazelnut	–	17.6 (46)
Sensitization to birch-pollen	–	19.2 (50)
Sensitization to hazelnut and birch-pollen	–	16.1 (42)
Sensitization to hazelnut and parent-reported symptoms of hazelnut allergy	–	2.7 (7)
Sensitization to birch-pollen and parent-reported symptoms of allergic rhinitis in April	–	10 (26)
Eligible for hazelnut DBPCFC[‡]	–	4.2 (11)
Hazelnut DBPCFC[‡] conducted	–	0.8 (2)
Hazelnut DBPCFC[‡] result	–	1 positive, 1 negative

[†] CI = confidence interval.
[‡] DBPCFC = double blind placebo-controlled food challenge.

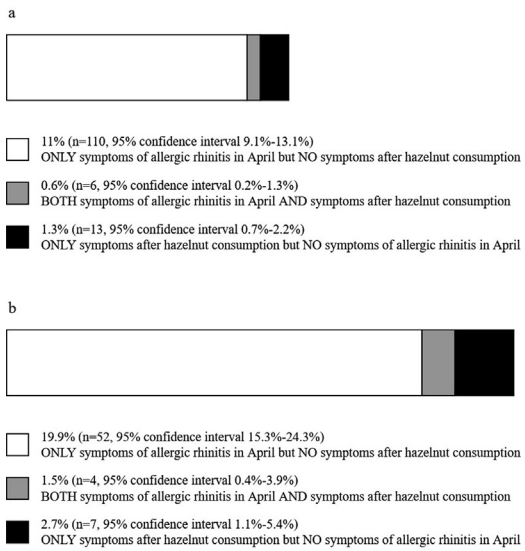

Fig. 2. Overlap of symptoms of hazelnut allergy and symptoms of birch-pollen allergy in study children with complete web-based questionnaire (a, n = 1001) or complete assessment for birch-pollen and hazelnut sensitization (b, n = 261).

Further diagnostic tests (sIgE and/or SPT for hazelnut and birch-pollen)

Clinical symptoms

Approximately half of the children, for whom symptoms of hazelnut or birch-pollen allergy were reported in the online questionnaire, could be further assessed for sensitization.

Of the 261 participants with assessment of sIgE and/or SPT against hazelnut and birch-pollen (n = 261) 96.2% (n = 251) have consumed hazelnut according to parents within three months prior to the interview, 54.4% raw (n = 142) and 95% roasted hazelnut (n = 248). Only 7.7% (n = 20) parents reported that their child has never consumed raw hazelnut and 0.8% reported that roasted hazelnut was never consumed by their children. The proportion of symptomatic children in this group was higher than in the web-based questionnaire (Table 2, Fig. 2). Of these children with parent-reported hazelnut allergic symptoms only a fifth reported reactions to raw hazelnut.

Skin symptoms (eczema, dry skin once, flush/rash/itch/swelling/hives in the face once and on the body five times) and oral symptoms (itching of the mouth) were each reported for 2.3% of children (n = 6), gastrointestinal (vomiting, diarrhea) and respiratory symptoms (asthma, cough, tightness) for 0.8% each (n = 2) in this subgroup.

Sensitization to hazelnut and birch-pollen

The correlation between sIgE concentration in serum and SPT wheal diameter was moderate for both hazelnut (correlation coefficient $r = 0.49$, $p < 0.001$) and birch-pollen ($r = 0.62$, $p < 0.001$).

Sensitization rate to hazelnut and birch-pollen among the tested participants was higher than the proportion of symptomatic children with the majority being sensitized to both allergens (Table 2). Hazelnut sensitization was the most common food allergen sensitization of all that we tested. In children sensitized against hazelnut, the most frequent co-sensitization was against birch-pollen (Table 3).

Clinical symptoms and sensitization

2.7% (n = 7) participants of the subgroup were sensitized to hazelnut and had parent-reported symptoms of hazelnut allergy. In these symptomatic and sensitized children, skin symptoms were mentioned thrice, oral symptoms five times, respiratory and gastrointestinal symptoms twice each. Among study children with hazelnut related symptoms sensitization rates of most tested allergens were higher than in the non-symptomatic children (Table 3). Of the children with symptoms of allergic rhinitis in April approximately half were sensitized to birch-pollen (Table 2).

Among those participants with sensitization to both allergens, the vast majority showed only symptoms of birch-pollen allergy or no symptoms at all, whereas in those participants with sensitization only to hazelnut, symptoms of hazelnut allergy were relatively more frequent (Table 4). No child in the subgroup met our criteria for pollen-associated hazelnut allergy.

Sensitivity analysis

In a sensitivity analysis, we examined if changing our definition of birch pollen allergy from reported typical symptoms in April to typical symptoms in March and April would affect our results. We found no considerable difference with the alternative definition that classified 17.2% (n = 45, 95% CI 12.9%–22.4%) as being birch-pollen allergic with less than half of them (n = 21) being sensitized to birch-pollen.

Component resolved diagnostics

1.9% (n = 4) of 219 children tested for hazelnut specific IgE in serum had a Cor a 14-serum specific IgE value >0.35 kU/L. The characteristics of these children are summarized in Table 5.

Food challenge test

A DBPCFC was offered to eligible children, but in most cases denied by parents. Two hazelnut DBPDFC were conducted within the follow-up assessment (Table 2). One challenge was positive with skin signs/symptoms and oral symptoms. Hence, one child of our Berlin birth cohort was diagnosed with hazelnut allergy. The hazelnut allergic child was sensitized to hazelnut and not to birch-pollen with a Cor a 14 value of 2.71 kU/L (Table 5). The other child (having a negative DBPCFC) was sensitized to hazelnut and birch-pollen and reported oral symptoms with a Cor a 14 value of 0.0 kU/L.

Discussion

Main findings

Our population-based study showed that parent-reported allergic reactions to hazelnut overall affected 2% of school-aged children, half of them to roasted hazelnut. Parent-reported typical allergic rhinitis symptoms in April classified almost 12% of the children as birch-pollen allergic. Less than 1% of children were affected by reactions to both hazelnut and birch-pollen; for those almost exclusively oral hazelnut symptoms were reported as well as for children reacting only to raw hazelnut. For hazelnut, clearly more children were sensitized than symptomatic, whereas for birch pollen more children were symptomatic than sensitized. Most of the children who were sensitized to hazelnut or birch-pollen were sensitized to both allergens. 1.9% of 219 children tested for hazelnut specific IgE in serum had a positive Cor a14 sIgE value, a hazelnut seed storage protein associated with systemic reactions to hazelnut.[4]

Table 3
Sensitization profile of study children with complete assessment of hazelnut and birch-pollen sensitization (n = 261) compared to sensitization profile of study children with sensitization to hazelnut and complete assessment of hazelnut and birch-pollen sensitization (n = 46); sensitization profile of children with complete assessment of hazelnut and birch-pollen sensitization and hazelnut related symptoms (n = 11) vs. those without hazelnut related symptoms (n = 250).

Sensitization to…	Study children with complete sensitization tests to hazelnut and birch-pollen (n = 261), % (n)	Study children with sensitization to hazelnut and complete sensitization tests to hazelnut and birch-pollen (n = 46), % (n)	Study children with complete sensitization tests to hazelnut and birch-pollen and hazelnut related symptoms (n = 11), % (n)	Study children with complete sensitization tests to hazelnut and birch-pollen and without hazelnut related symptoms (n = 250), % (n)
Hazelnut†	17.6 (46)	100 (46)	63.6 (7)	15.6 (39)
Birch-pollen†	19.2 (50)	91.3 (42)	36.4 (4)	18.4 (46)
Grass-pollen†	25.7 (67)	80.4 (37)	54.5 (6)	24.4 (61)
	Missing: 0.4 (1)			Missing: 0.4 (1)
Cat dander‡	14.6 (38)	45.7 (21)	45.5 (5)	13.2 (33)
	Missing: 5.4 (14)	Missing: 2.2 (1)		Missing: 5.6 (14)
Mold‡	6.5 (17)	13 (6)	18.2 (2)	6 (15)
	Missing 6.1 (16)	Missing: 6.5 (3)		Missing 6.4 (16)
House dust mite†	26.8 (70)	56.5 (26)	36.4 (4)	26.4 (66)
	Missing: 0.4 (1)			Missing: 0.4 (1)
Cow's milk‡	0 (0)	0 (0)	0 (0)	0 (0)
	Missing: 5.7 (15)	Missing: 2.2 (1)		Missing: 6 (15)
Hen's egg‡	0.8 (2)	2.2 (1)	0 (0)	0.8 (2)
	Missing: 5.7 (15)	Missing 2.2 (1)		Missing: 6 (15)
Wheat‡	0 (0)	0 (0)	0 (0)	0 (0)
	Missing 5.7 (15)	Missing 2.2 (1)		Missing 6 (15)
Peanut†	11.5 (30)	54.3 (25)	36.4 (4)	10.4 (26)
	Missing 0.4 (1)			Missing 0.4 (1)
Soy‡	0.4 (1)	2.2 (1)	9.1 (1)	0 (0)
	Missing: 5.7 (15)	Missing 2.2 (1)		Missing: 6 (15)
White fish‡	1.5 (4)	6.5 (3)	0 (0)	1.6 (4)
	Missing: 5.7 (15)	Missing 2.2 (1)		Missing: 6 (15)
Oily fish‡	0.4 (1)	2.2 (1)	0 (0)	0.4 (1)
	Missing: 20.3 (53)	Missing 17.4 (8)	Missing: 9.1 (1)	Missing: 20.8 (52)
Crustaceans‡	1.1 (3)	2.2 (1)	0 (0)	1.2 (3)
	Missing: 5.7 (15)	Missing 2.2 (1)		Missing: 5.7 (15)

† Skin prick test and/or serum specific immunoglobulin E positive.
‡ Skin prick test positive (serum specific immunoglobulin E was not measured for this item).

Comparison with other studies

Roehr *et al.* screened a population-based sample of Berlin children. In 0.7% of children aged up to 14 years and 4.2% of children aged 14–17 years they confirmed hazelnut allergy (with oral symptoms only) by DBPCFC.[20] This is slightly higher than the 0.5% of parent-reported pollen-associated hazelnut allergy that we found in our study. This may be comparable considering the older age of the children in the study by Roehr *et al.* although the study was conducted in 2004.

The population based European Community Respiratory Health Survey (ECRHS) showed that 15% of the 20–44 year old German participants were sensitized to hazelnut,[6] which is similar to the 17.6% that we found in our study children, although the study populations differ in terms of age, geographical area, and although the ECRHS took place in 2000.

A retrospective study in Finland, a birch endemic area, analyzed records of mainly adult patients who were tested by SPT for nuts and birch-pollen. 84.1% of individuals with sensitization to birch-pollen were also sensitized to hazelnut.[21] Our results confirm that sensitization between the two are strongly linked. The authors reported that 69% of hazelnut sensitized individuals experienced symptoms.[21] This higher prevalence of symptomatic adults seems to be age related.

Sensitization to birch-pollen was higher in our study cohort than in the German wide KIGGS survey (19.1% vs. 13%, same age group).[5] This might be attributed to a selection bias in our study or to regional differences within Germany including the mixed urban and rural recruitment regions as to our study area focusing on Berlin.

Strengths and limitations

The EuroPrevall/iFAAM birth cohort study is so far unique in stringently investigating FA in children across Europe. Strengths of our analysis are the size of the Berlin sample, the relatively good participation in the follow-up assessment at school-age (63.9% response), the prospective design and its highly standardized protocol including parental questionnaires, clinical examinations, measurement of sIgE in serum and SPT.[10,13]

Table 4
Distribution of symptoms among children with sensitization to hazelnut, to birch-pollen and to both.

	Sensitization to hazelnut with concomitant sensitization to birch-pollen 16.1% (n = 42), % (n)	Sensitization to hazelnut without concomitant sensitization to birch-pollen 1.5% (n = 4), % (n)	Sensitization to birch-pollen without concomitant sensitization to hazelnut 3.1% (n = 8), % (n)
Symptoms after hazelnut consumption and of allergic rhinitis in April, % (n)	4.8 (2)	25 (1)	–
Only symptoms after hazelnut consumption, % (n)	4.8 (2)	50 (2)	–
Only symptoms of allergic rhinitis in April, % (n)	50 (21)	–	37.5 (3)
No symptoms, % (n)	40.5 (17)	25 (1)	62.5 (5)

Table 5
Characteristics of study children with elevated serum specific immunoglobulin E (IgE) to Cora14 (1.8% of 219 tested children, n = 4), a hazelnut seed storage protein related to systemic reactions.

	Child 1	Child 2	Child 3	Child 4
Cor a 14 serum specific IgE[†] (kU/L[‡])	0.46	0.57	1.18	2.71
Hazelnut serum specific IgE[†] (kU/L[‡])	0.45	1.04	29.81	1.47
Sex	Female	Male	Male	Male
Symptoms after hazelnut consumption	No symptoms after hazelnut consumption, consumed hazelnut within three months before the interview	Symptoms after consumption of raw hazelnut only	No symptoms after hazelnut consumption, consumed hazelnut within three months before the interview	Symptoms after consumption of roasted hazelnut
Age at first reaction to hazelnut (years)	No reaction	4	No reaction	2
Parent-reported symptoms after hazelnut consumption	No symptoms	Oral symptoms	No symptoms	Skin symptoms, oral symptoms
DBPCFC[§]	Not conducted	Not conducted	Not conducted	Positive
Sensitization to birch-pollen	No	No	Yes	No
Symptoms of allergic rhinitis in April	No	No	No	Yes

[†] IgE = immunoglobulin E.
[‡] kU/L = kilounit per liter.
[§] DBPCFC = double-blind placebo-controlled food challenge.

Some limitations must be noted. We defined children who had symptoms of allergic rhinitis at least in April as possibly birch-pollen allergic, considering this an epidemiological definition. Our study showed that only approximately half of these children were sensitized to birch-pollen. This could be due to parents not remembering the exact month of the occurrence of allergic rhinitis. It is also possible that parents misinterpreted common colds as allergic symptoms although we specifically excluded this in the corresponding question. Over reporting is very well known and in other fields such as FA even more pronounced.[22] The rate of sensitization in our study on the other hand fits quite well to other reported data as discussed above.[5,6] We included all participants with parent-reported symptoms to hazelnut in our analysis, although some reactions did not seem plausible. Parents with suspected allergy in their children might have been more compelled to take part in the school-age follow-up and to undergo further diagnostics. This was reflected by the higher proportion of symptomatic participants in the subgroup with assessment for allergic sensitization. Also, parents with allergic diseases might have been more interested in taking part in the clinical evaluation of their children. This could be derived from the higher proportion of parents with allergic disease in the subgroup of evaluated children. Those factors might have led to an overestimation of the actual prevalence of hazelnut and birch-pollen allergy. The sensitization test was only conducted in children with suspicion of allergic diseases and was in some cases denied by parents. Only a quarter of eligible children underwent DBPCFC for hazelnut. Therefore, the actual proportion of sensitization and hazelnut allergy might be higher than indicated by our study. In the sensitization subgroup no child met our criteria for pollen-associated hazelnut allergy. This could be due to a problematic clinical definition.

Conclusions

The Europrevall/iFAAM birth cohort study is the first population-based study to investigate hazelnut and birch-pollen allergy simultaneously in school-aged children in Germany using a highly standardized protocol. Allergic sensitization to hazelnut was very common, affected almost 20% of the children and was, in most cases, accompanied by sensitization to birch-pollen. In contrast, parent-reported symptoms of hazelnut allergy occurred in only 2% of the on average 8-year-old children, being relatively frequent but 10-time less common than sensitization. In half of these children the reactions were typical for pollen-associated hazelnut allergy, whereas the other half showed symptoms typical for primary hazelnut allergy which can result in severe reactions.

From our results it can be concluded that sensitization to hazelnut should not be the sole indicator to recommend a hazelnut-free diet as it is often observed in daily clinical praxis. In nine out 10 children it would result in an unnecessary diet and an impairment of their quality of life. In doubt further diagnostics such as measurement of sIgE to individual hazelnut components such as Cor a 14 and/or oral food challenges are necessary to identify the children with primary hazelnut allergy. Our data also suggests, that when testing for sensitization to hazelnut, school-aged children should also be tested for birch-pollen sensitization. Sensitization to both allergens could make primary hazelnut allergy less probable. Future assessments of our birth cohort as well as other population-based settings are needed to describe the course of primary and pollen-associated hazelnut allergy in the transition from childhood to adulthood.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.alit.2021.05.006.

Conflict of interest

RvR has had consultant arrangements with HAL Allergy, Citeq, Angancy and received speaker's fees from HAL Allergy and Thermo Fisher Scientific. KB received personal fees from Aimmune, ALK, Allergopharma, Bausch & Lomb, Bencard Allergie, Danone, Di-Text, Hammer und Rall Media, Hycor, InfectoPharm, Mabylon, Meda Pharma, Med Update, Mabylon, Nestlé and Thermo Fisher and grants to her institution from Aimmune, ALK, Danone, DBV, Good Mills, Hipp, Hycor, InfectoPharm, Thermo Fisher and VDI. MF-R has received personal fees from Aimmune, ALK, Allergy Therapeutics, Bausch & Lomb, DBV, Diater, Fundación SEAIC, GSK, HAL Allergy, Novartis, SPRIM and Thermo Fisher Scientific. The rest of the authors have no conflict of interest.

Authors' contributions

SME: participated in planning the present analyses, contributed to data collection, performed the statistical analysis, interpreted the results, wrote first draft of manuscript. JB, ST, SY, VT: contributed to clinical data collection, participated in reviewing the manuscript and in the interpretation of the results. LG: coordinated the school-age follow-up assessment, participated in the planning of the present analyses and the interpretation of the results, reviewed the manuscript. RvR: participated in planning the cohort study design, responsible for collection and analysis of immunoglobulin E in serum samples, participated in the interpretation of the results, reviewed the manuscript. MF-R: participated in planning the cohort study design, responsible for coordinating (incl materials) and interpreting skin prick tests, participated in the interpretation of the results, reviewed the manuscript. TK: participated in planning the study design and coordinated the birth cohort study, supervised the analyses, participated in the interpretation of the results, participated in writing the manuscript. KB: principal investigator of the birth cohort study, supervised the analyses, participated in the interpretation of the results, participated in writing the manuscript. All the authors read and approved the final manuscript.

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