

Original article

The prevalence of allergy to egg: a population-based study in young children

Background: The aim of the present study was to estimate the prevalence of adverse reactions to egg, as population-based prevalence estimates based on objective diagnostic procedures are lacking.

Methods: The parents of 2721 children in a population-based birth cohort completed questionnaires on the occurrence of any reaction to food at 12, 18, and 24 months of age. Children with parentally reported reactions to eggs at the age of 2 years were selected for further examination. A stepwise diagnostic procedure was developed that included diet trials at home, skin prick tests, and open and double-blind, placebo-controlled food challenges. The mean age of the children at the time of the examination was 2.5 years (CI 2.5–2.6). A sample of children without perceived reactions to egg was also selected for assessment of unrecognized reactions.

Results: The estimated point prevalence of allergy to egg in children aged 2½ years was 1.6% (CI 1.3–2.0%), with an upper estimate of the cumulative incidence by this age calculated roughly at 2.6% (CI 1.6–3.6). Almost all reactions were IgE mediated. In general, two-thirds of the parentally perceived reactions were verified. However, the positive predictive value of a parentally perceived reaction depended on the number of times it had been reported, and increased from 50% to 100%, for reactions reported one and three times, respectively. Unrecognized reactions were infrequent.

Conclusions: This study confirms that allergy to egg is frequent in a child population.

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Food allergy and intolerance are common among small children, and eggs are, along with milk, one of the two food items most commonly incriminated (1–3). Prevalence estimates based on parental perception vary between 3% and 7% at the age of 2 years (1, 4). On the basis of the positive skin prick tests the prevalence was estimated to be 3.2% in Australia, and similar figures have been reported from several countries of the Far East. However, these estimates are associated with a large degree of uncertainty. Objective diagnostic testing has revealed that parents overestimate the role of food as the cause of symptoms in their children (5), and that only one-third to two-thirds of the perceived reactions are confirmed (3, 4). This discrepancy is probably due to the difficult identification of adverse reactions to food, as a result of the diversity, subjectivity, and unspecific nature of the symptoms. Furthermore, simple objective means of assessment are lacking. The most reliable technique for confirming the diagnosis is the time-consuming and burdensome procedure of the double-blind, placebo-controlled food challenge (DBPCFC) (6). Prevalence estimates based on objective diagnostic tests are lacking.

This study estimates the point prevalence of allergy to

egg among children aged 2½ years, and also calculates a crude upper estimate on the cumulative incidence by this age. The children were identified from a population-based sample and were selected on the basis of parental reports of reactions to egg. A sample of children without perceived reactions to eggs was also examined for the possibility of unrecognized reactions to eggs. A stepwise diagnostic procedure including open food challenges and DBPCFCs was developed to examine these children.

Material and methods

Study population

The study population included children consecutively born at the two main maternity clinics in Oslo, Norway, in which approximately 90% of all births in the capital take place. The families of the children were recruited by the midwives at the maternity wards, during 1992 and part of 1993, and were followed until the age of 2 years. Of the 4973 eligible families, 75% participated in the study. The study population and collection of data are described in more detail elsewhere (1, 7). The present study is based on the children born in 1992 ($n = 3289$); 2721 families (83%) responded to the questionnaires when the child was 2 years old.

Children with parentally perceived reactions to egg

The parents completed questionnaires on the occurrence of any reaction to food at 12, 18 and 24 months of age, and these results have been reported previously (1). The parents reported adverse reactions to egg for 64 children at the age of 2½ years, while previously perceived reactions were no longer reported at this age in 53 children (Fig. 1) (1). Of the eligible 58 families who were asked to participate, 71% (41/58) completed the study. The mean age at the time of the examination was 2.50 years (CI 2.5–2.6).

No significant differences were observed in the distribution of maternal educational level, maternal age, maternal smoking habits, parental asthma, first-born children, child's sex, or family income between the 41 participants and the 23 unexamined children (Table 1). However, whether an allergy test had been taken or not, the distribution of positive responses to allergy tests, and the number of times a reaction had been reported, differed significantly between participants and nonparticipants (Table 1).

Children without parentally perceived reactions to eggs

A sample of children was examined for the possibility of detecting reactions to eggs that had not been recognized by the parents. This sample consisted of two subgroups of children.

One group consisted of 100 families randomly drawn from the cohort at 2 years. Among these, 39 had reported one of the following chronic symptoms not perceived to be related to food: eczema and urticaria during the last 6 months, loose stools, unusual irritability or hyperactivity in periods longer than a month, or asthma. Of these 39 families, 22 agreed to participate, but only 17 completed the study.

The second group comprised children with parentally perceived reactions only to milk (45/86 participated). The sampling of these children has been described in detail elsewhere (8).

Variables

The diagnostic procedure was modified from methods used by other authors (9, 10) and included a number of diagnostic steps (Fig. 2).

Step 1. Interview and dietary trials. All the families were interviewed by telephone in order to determine whether diet trials should be conducted at the children's home before further investigation. Three groups of children were identified. One group was already on a strict elimination diet. They proceeded directly to step 2 (Fig. 2). The diets of the second group contained eggs in reduced amounts, and the children had no current symptoms on this diet. Their parents were asked to increase the amount of egg in the child's diet to customary portions in a 1-week diet trial period at home and to record whether there was any reappearance of symptoms. The third group consisted of children who had current symptoms yet had incomplete or no dietary restrictions. Their parents were asked to restrict the amount of egg in the diet in 1 week and record whether the symptoms subsided. Children for whom the diet trials did not alter the symptoms in either direction were classified as tolerant, and they did not proceed further. The remaining children were seen at the clinic for further examination (Fig. 2).

Step 2. Medical history and specific IgE. The children were examined at Voksentoppen, the Center for Asthma, Allergy and Chronic Lung Diseases in Children, situated in the hills above Oslo, which provided an allergen-restricted environment (perfume, smoking, and furred pets strictly prohibited on the premises; food items containing fish or egg confined to restricted areas). Information on the type of reaction, time between intake and onset of the reaction, and the amount of food necessary to elicit a reaction was obtained from the parents in order to provide a basis for an appropriate challenge of each child.

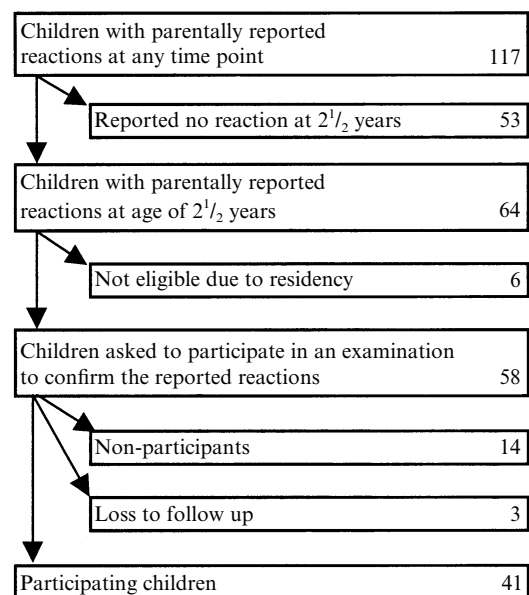


Figure 1. Study sample of children with parentally perceived reaction to egg, according to participation.

Skin prick test (SPT) was performed in duplicate with a lancet with a 1-mm tip (ALK) on the volar surface of the forearm. Standardized allergen extracts from egg in glycerol diluent with a potency of 10 HEP (Soluprick, ALK, Denmark) were employed. As a positive and negative reference, histamine dihydrochloride 10 mg/ml (ALK) and glycerol diluent were used, respectively. The skin wheal diameter was measured at 15 min and compared with the size of the wheal elicited by the histamine control (11). A wheal diameter half the size of the histamine wheal was registered as 2+, an equal size as 3+, and one twice as large as 4+. Blood samples were obtained by venipuncture. Clotted blood was centrifuged at room temperature, and the serum was separated and stored at -20°C . The concentration of egg-specific IgE in serum was determined by the Pharmacia Cap FEIA method according to the specifications of the manufacturer and rated as classes 0–4.

In children with a SPT of ≥ 3 , or a RAST class of 3 or more, and a history of immediate reaction to small amounts of eggs, the reaction was classified as confirmed without further investigation. For the remaining children, open food-challenges were performed (Fig. 2).

Step 3. Open food challenge. The parents had been instructed to discontinue all antihistamines and exclude egg from the diet at home 7 days prior to the challenges. Prior to oral challenge, the presence and degree of any skin lesions or signs of obstructive disease were ascertained during a general physical examination.

The challenges were primarily done by means of pancakes. Eggnog was used when the reactions were attributed to raw egg only. Children who refused to eat pancakes were served muffins. Depending upon the child's level of sensitivity, one among two challenge procedures was chosen, starting with either 1 or 7.5 g, the amount being doubled every 30 min until a reaction occurred or the predefined amount of either 16 or 60 g was reached. All children were observed in the clinic for a minimum of 3 h after the first challenge and 2 h after the last. During the challenge, the amount of food was increased every 30 min. The challenges were terminated when symptoms occurred or when the predefined maximum dosage was reached. If no reaction occurred during days 1–3 after the challenge, the parents repeated the challenge on days 4 and 5 at home while keeping a precoded record describing symptoms displayed by the child for 6 days.

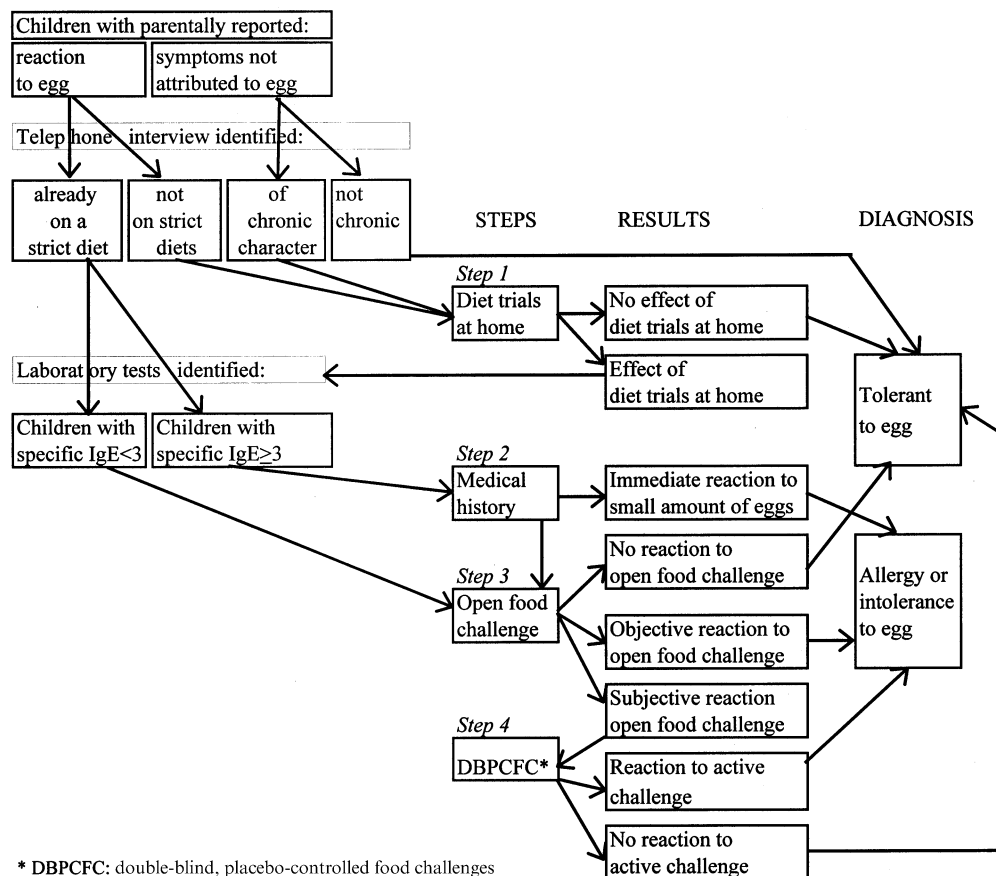


Figure 2. Stepwise diagnostic procedure used to verify parentally perceived reactions to egg in children at age of 2½ years.

Children who reacted with an objective reaction during the challenges were classified as confirmed. Children for whom the open challenges did not elicit any symptoms were classified as nonallergic/tolerant. All other children proceeded to DBPCFC (Fig. 2).

Step 4. DBPCFC. A minimum of a 1-week rest period was required before the DBPCFC. The placebo and the active substances were given on two separate days at least 1 week apart. The children were randomly assigned to the order in which active and placebo substances were administered, and the order was blinded to the researchers (nurse and doctor).

The allergen ingredients were disguised in pancakes or muffins. Corn flour was used to obtain a yellow color in the placebo food. The procedure for the DBPCFC was the same as that described for the open challenges. To control for symptoms not related to food, the parents reported any occurrence of episodic illnesses in the family; if the child had similar symptoms, these symptoms were disregarded. Prior to opening the blinded code, ratings were completed to indicate whether there was a substantial difference in reactions between the active and placebo challenges.

Step 5. Reintroduction of the food into the child's regular diet. When the challenges failed to confirm the reaction, either because no symptoms occurred or because symptoms appeared after both placebo and active challenge, egg was reintroduced into the child's diet openly to determine whether symptoms occurred under normal ingestion conditions and upon repeated intake.

Children without parentally perceived reactions to egg. Among the children with parentally perceived reactions only to milk ($n=45$), those in whom egg-specific IgE was detected, and who had residual symptoms while on a milk-free diet, were subject to the same stepwise evaluation as outlined above (Fig. 2).

Among the children whose symptoms were not attributed to food ($n=17$), those who had symptoms that did not resolve completely for periods as long as a month while on a diet containing egg were also examined further by the stepwise diagnostic procedure outlined above. Children not fulfilling these criteria were not examined further.

Definitions of confirmed and possible allergy to egg

An allergy to egg was confirmed when:

- 1) There was a history of unequivocal, immediate clinical reaction to small amounts of egg and confirmatory high levels of specific IgE as measured by SPT of $\geq 3+$ or RAST class of ≥ 3 .
- 2) There was an objective reaction to an open challenge during the stay at the clinic. Eczematous or morbilliform rashes, urticarial skin eruptions, and vomiting were considered objective symptoms.
- 3) There was a reaction to the allergen challenge unequivocally exceeding any reaction to the placebo challenge in the DBPCFC.

When the above criteria were only partly fulfilled, the food reaction was considered possible.

Table 1. Distribution of sociodemographic variables, maternal smoking, parental asthma, child sex, allergy tests results, and number of times reaction had been reported, among 64 children with parentally perceived reactions to egg, according to participation in study

	Participants (n=41)				Noneligible and nonparticipants (n=23)			
	No n	Yes			No n	Yes		
		n	%	CI		n	%	CI
Low maternal education*	26	15	37	(24–52)	10	13	57	(37–74)
Maternal smoking†	32	9	22	(12–37)	17	6	26	(13–46)
Low maternal age‡	19	22	54	(39–68)	12	11	48	(29–67)
Low family income§	35	6	15	(7–28)	18	5	22	(10–42)
Male sex	21	20	49	(34–64)	12	11	48	(29–67)
Older siblings	23	18	44	(30–59)	9	14	61	(41–78)
Maternal or paternal asthma	32	9	22	(12–37)	17	6	26	(13–46)
Allergy test taken	15	26	63	(48–76)	14	9	39	(22–59)
Positive allergy test	2	24	92	(76–98)	3	6	67	(35–88)
Reported reactions >1 × **	8	13	32	(20–47)	20	3	13	(5–32)

* Maternal education categorized into 12 years or fewer or more than 12 years of education. † Maternal smoking during pregnancy. ‡ Maternal age categorized as 30 years or younger, or older than 30 years. § Low family income defined as under 200 000 Norwegian kroner joint yearly income. || Results of allergy test taken before start of this study. ** Information concerning parentally perceived reactions was obtained at 12, 18, and 24 months of age, and children were classified according to number of times reaction had been reported. CI: 95% confidence intervals.

Background variables

Information on the sex, birth order, maternal age in years, maternal smoking during pregnancy, mother's education in years, family income, and the presence of maternal or paternal asthma was obtained from the questionnaire completed by the participating families at the maternity ward (7). The results of any previous allergy test that might have been performed were obtained from the questionnaire sent to the parents when the child was 2 years old (Appendix 1).

The study was approved by the Norwegian Data Inspectorate and the Regional Ethics Committee for Medical Research, and fully informed, written parental consent was obtained.

Statistical analysis

All data were entered and analyzed by means of SPSS (Release 6.1). Categorical data were presented in contingency tables. The CI intervals in Table 1 were computed by the Wilson method (12), which is appropriate when the prevalence is low, or the study sample is small (13). The validity of parentally reported reactions was assessed by calculating the sensitivity, specificity, and positive and negative predictive values (14). The CI for the positive predictive value of the parentally reported reactions and for the prevalence estimates was calculated by bootstrapping (15).

Results

Verified reactions

Among the 41 examined children with parentally reported reactions to egg (Fig. 1), 22 were confirmed according to the strictest criteria (Table 2). The majority of the reactions were diagnosed on the basis of egg-specific IgE values of 3 or greater and a corresponding history of an immediate reaction (Table 2). Six children were classified as possibly allergic (Table 3).

The symptoms reproduced can be seen in Tables 2 and 3. The majority of the children experienced symptoms of the skin, with urticaria as the most

predominant symptom, often followed by flares in atopic eczema. Less frequent symptoms included vomiting, diarrhea, and bronchial obstruction.

An adverse reaction to egg was not demonstrated in 13 children. For five children, this conclusion was based on responses to diet trials at the children's homes, while the remaining children had negative results in the open challenges or DBPCFC. The children in whom allergy to egg was rejected differed from those in whom a reaction was verified, with regard to the time relationship between ingestion and symptom, which was longer or inconsistently stated, except in two children. Furthermore, for the children in whom an allergy to egg was rejected, several other food items were usually suspected of giving the same reaction, larger amounts of food were needed, and specific IgE was seldom detectable. None of the 13 children had a convincing history of a previous allergic reaction.

Unrecognized reactions to egg

No unrecognized reaction to egg was found among the 17 children with chronic symptoms not attributed to food.

Among the children with perceived reactions to foods other than egg (milk), one child with a possible unrecognized reaction to egg was found. The diagnosis of a possible allergy to egg in this child was based on diarrhea and abdominal cramps occurring after an open egg challenge.

Validity of a parentally perceived reaction to egg

A parentally reported reaction had a sensitivity of 96% (CI 87–100), a specificity of 99% (CI 99–100), and a negative predictive value of 100% (CI 99–100). The positive predictive value of a parentally perceived

Table 2. Of 41 children with parentally perceived reactions to egg, 22 children in whom allergy to egg was confirmed are shown, according to diagnostic criteria

a) Diagnosis based on history of immediate reactions to small amounts of egg and high levels of egg-specific IgE							
S*	History of previous allergic reactions to egg			Time†	SPT	RAST	
1	E and O in face and neck after licking cake			<5 min	3	2	
2	U when ingesting egg contained in products; subsequent AE			<5 min	4	3	
3	U when ingesting egg contained in products; subsequent AE			<5 min	5	3	
4	OAS and generalized Ex when accidentally exposed to food containing egg			<5 min	4	3	
5	Generalized Ex and irritability after ingestion of one teaspoon egg			<5 min	1	3	
6	U when ingesting egg contained in products; subsequent AE			<30 min	4	2	
7	V after egg-containing cake, followed by generalized U, apathy, and stomach pain			<5 min	3	4	
8	Circumoral Ex and O; generalized E when exposed to food containing egg; subsequent AE			<10 min	3	np‡	
9	U when ingesting egg contained in products; subsequent AE			<5 min	3	2	
10	O and U upon skin contact with egg in very small amounts; Av, AE, and A			<5 min	4	4	
11	Perioral E; itching, acne-like generalized Ex; and irritability after one teaspoon boiled egg			<30 min	3	3	
12	Egg cooking in household causes acute A			<10 min	4	2	
13	Generalized U, acute A, and facial O when licking egg peel or egg-contaminated food			<5 min	4	3	
b) Diagnosis based on objective reaction to open egg challenge							
S*	History§	SPT	S-IgE	Open challenge performed at hospital			
				Amount of egg (g)	Symptoms		
14	Rh, U	3	2	1.5	U on abdomen		
15	U	3	2	16	U and E in face within 60 min; V several hours later		
16	U	0	0	1	U within 2 min; itching lips; flare in current AE lesions (30 min)		
17	E, Ex, AE	2	1	11	Erythema in face within 30 min; subsequent new AE lesions		
c) Diagnosis based on confirmation by DBPCFC							
S*	History§	SPT	RAST	Challenges performed at hospital			
				Amount (g)	Open	DBPCFC	Comments
18	E	3	0	1	AE	AE	Moderate to severe increase in AE within 24 h
19	V, An, D, AE	3	3	3	V, D, AE	Av	V (30 min), D (2 h), AE (24 h), Av
20	—	3	2	3	U, D	D	Listless, U chin (1 h), D (24 h)
21	AE	0	0	16	AE	AE	New AE lesions (12 h)
22	E, U	2	1	16	A, Rh	U, A	A (<90 min), Rh (3 h), U face/hands

A: bronchial obstruction; AE: eczematous lesions; An: angioneurotic edema; Av: aversion; D: loose stools; E: erythema; Ex: exanthema; gen.: generalized; O: edema; Rh: rhinitis; U: urticaria; V: vomiting.

DBPCFC: double-blind, placebo-controlled food challenge.

* S: subject number.

† Time from ingestion to appearance of first symptom.

‡ np: not performed.

§ History: parentally perceived reactions to egg on earlier occasions.

|| Aversion when different types of egg containing food were offered. No aversion to placebo food.

Table 3. Measured level of egg-specific IgE and response to elimination diet and open challenges in six children in whom *possible* egg allergy was diagnosed (partly fulfillment of diagnostic criteria)

S*	SPT	S-IgE	History§	Comments
23	0	0	AE	Effect of elimination diet trial and severe gen. AE 24 h after open challenge with 60 g egg
24	1	2	V, Ex	Abdominal cramps and D developed 12 h after open challenge with 16 g egg
25	2	2	AE, Av, U†	Av to all offered egg-containing challenge food
26	2	2	Gen, U, An	Convincing history‡; listlessness (1 h) and AE (12 h) after 16 g eggs openly administered
27	2	2	AE	Convincing history ; no egg challenges performed
28	2	2	A	Listlessness after open challenges performed with 1 g egg

For abbreviations, see Table 2 notes.

* Subject number.

† Urticaria on skin when in contact with eggs.

‡ Convincing history of gen. U and An after ingesting piece of pancake size of postage stamp.

§ History: parentally perceived reactions to egg at earlier occasions.

|| Convincing history of V within 20 min of ingesting small bite of pancake. Subsequent worsened AE. Child had challenge-confirmed allergy to cow's milk.

Table 4. Point prevalence of allergy at age of 2½ years in cohort of 2721 children, assuming that positive predictive value of parentally reported reactions to egg was same among examined and unexamined children

	Children with parentally reported reactions to egg by age of 2 years						Calculated total <i>n</i> of children with egg allergy	Estimated point prevalence of egg allergy at 2 ½ years % (CI)
	Children examined by objective diagnostics†			Children not examined‡				
	PPR§	Verified egg allergy	Positive predictive value	PPR§	Assumed positive predicted value	Calculated <i>n</i> with egg allergy		
	<i>n</i> =41	<i>n</i>	%	<i>n</i> =23	%	<i>n</i>		
Number of PPR*								
Reported once	8	4	50	14	50	7		
Reported two times	20	11	55	6	55	3		
Reported three times	13	13	100	3	100	3		
Total		28				13	41	1.5 (1.0–2.0)

† 41 children with parentally perceived reactions to egg at 2½ years of age were examined by objective diagnostics.

‡ 23 children with parentally perceived reactions at 2½ years were not examined, due to residency outside Oslo, nonparticipation, or loss to follow-up.

§ PPR: parentally perceived reactions.

* Parentally perceived reactions were reported at 12, 18, and 24 months.

reaction, based on all verified reactions, was 68% (CI 53–80), and 54% (CI 39–68) based on only those with strictly confirmed reactions.

The positive predictive value depended on the number of times the reaction had been reported. The overall positive predictive value of a reported reaction increased from 50% for a reaction reported once, to 100% for a reaction reported three times (at 12, 18, and 24 months of age) (Table 4).

Point prevalence at the age of 2½ years

Among the participants, there was a higher proportion of children with positive allergy tests to egg, and with reactions reported more than once (Table 1). Allergy test results and the number of times a reaction was reported were significantly associated with each other). Furthermore, positive allergy test responses and repeatedly reported reactions were significantly associated with the probability of the reaction to be confirmed (Table 4). To assume that the actual prevalence of allergy to egg is the same among participants and nonparticipants would thus result in an overestimation of the prevalence. However, by assuming that the positive predictive value of a parentally reported reaction, depending on the number of times a reaction has been reported, is the same among participants and unexamined children, a prevalence estimate adjusted for the differential distribution among participants and the unexamined may be calculated.

The total number of children with egg allergy in the cohort at the age of 2½ years was calculated by applying the positive predictive values of a reported reaction in the participating children (Table 4) to all children with parentally perceived reactions to egg at the age of 2½ years. The estimated prevalence, based on all children with verified reactions (confirmed and possible), was thus calculated to be 1.5% (CI 1.0–2.0).

A minimum estimate, based on children with strictly confirmed reactions only, was calculated in a similar manner to be 1.2% (CI 0.9–1.5) ((22 + 10)/2721).

When an assessment of unrecognized reactions was included, the prevalence estimate increased to 1.6% (CI 1.3–2.0).

Upper estimate of the cumulative incidence of allergy to egg

By assuming that the positive predictive value of a reaction reported once, twice, or three times is the same regardless of the age at which it was reported, a crude estimate of the cumulative incidence of allergy to egg may be calculated. Altogether, 117 children (Fig. 1) had had a parentally perceived reaction to egg at any time point, and the distribution of the number of times the reactions had been reported is shown in Table 5. A crude upper estimate of the cumulative incidence of allergy to egg by the age of 2 years was calculated to be 2.6% (CI 1.6–3.6).

Discussion

This study estimates the point prevalence of allergy to egg in children at the age of 2½ years to be 1.6%, and provides a crude upper estimate of the cumulative incidence by this age of 2.6%.

Methodological considerations

There was a higher proportion of children with positive allergy tests to egg and with reactions reported more than once among the participants (Table 1); however, this selection bias was to a large degree adjusted for in the point prevalence estimate by taking the number of times a reaction has been reported among the nonparticipants into account in the calculations.

There is a high degree of uncertainty linked to the assessment of reactions that go unrecognized by the parents, primarily due to the small sample size.

Table 5. Cumulative incidence of allergy to egg by age of 2 years in cohort of 2721 children was calculated by assuming that positive predictive value of parentally reported reactions to egg was same among examined and unexamined children

	Children with parentally reported reactions to egg at some point by age of 2 years						Calculated total <i>n</i> of children with allergy to egg <i>n</i>	Estimated cumulative incidence of allergy to egg %CI
	Children examined at age of 2½ years†			Children not examined‡				
	PPR§ <i>n</i> =41	Verified allergy to egg <i>n</i>	Positive predictive value %	PPR§ <i>n</i> =76	Assumed positive predicted value %	Calculated <i>n</i> with allergy to egg <i>n</i>		
Number of PPR**								
Reported once	8	4	50	53	50	27		
Reported two times	20	11	55	16	55	9		
Reported three times	13	13	100	7	100	7		
Total		28				42	70	2.6 (1.6–3.6)

† 41 children with parentally perceived reactions to egg at 2½ years of age were examined by objective diagnostics.

‡ Group comprised 23 children who had parentally perceived reactions at age of 2 years, but had not been examined due to various reasons and 53 children who were not examined as reaction to egg was no longer perceived by parents at age of 2.

§ PPR: parentally perceived reactions.

* Parentally perceived reactions were reported at 12, 18, and 24 months.

Because the children were not examined at the time of the initial complaint, a previous allergy cannot be certainly excluded in the 13 participating children in whom an allergy to egg was rejected; however, the large differences in the histories between children with confirmed and unconfirmed reactions makes this very unlikely.

Great uncertainty is linked to the upper cumulative incidence estimate, because children who had outgrown their sensitivity by the age of 2½ years were not objectively examined, and the assumption that the validity of the parentally perceived reactions is the same regardless of the age at which it was reported is uncertain. However, information regarding the natural history of allergy to egg is lacking, and the provided upper estimate on the cumulative incidence is interesting, as it indicates that a substantial number of children may develop tolerance before the age of 2 years.

Validity of the diagnostic procedure

We developed a stepwise diagnostic procedure, modified from methods used by other authors, in which the requirements for a confirmed reaction increased progressively with the prior level of uncertainty of the reaction. This procedure was intended to reduce the risk of severe reactions without compromising validity. Reduction of the risk of anaphylactic reactions was considered especially important in this study, in which the diagnostic procedures were initiated for the purpose of a research project, as opposed to studies in which the procedures are performed as part of a diagnostic evaluation initiated by the patient. A highly significant association between high levels of specific IgE to egg (CAP class 3) in combination with patient history of a reaction and the need for subsequent parenteral medication due to the strength of the clinical reaction has been reported (16).

The potential misclassification based on specific IgE

values decreases with increasing IgE level and is small at the chosen level. A positive predictive value of 60–80% has been reported for RAST class 3 or more and SPT values of $\geq 3+$ (17–19). These results are, however, not directly comparable, as the wheal size is rated differently, the age group is different, and the positive predictive value depends on the actual prevalence of the disease in the population studied. Most importantly, these studies have been performed on selected children with atopic eczema, in whom the number of false positive results may be more frequent than in others due to altered skin reactivity or the high total IgE levels reported in these children. We postulate that the risk of misclassifications in the present study is small for the following reasons. The actual level of specific IgE was even higher (SPT values of ≥ 4 or CAP-RAST of ≥ 4) in eight of the 13 children diagnosed by this criterion, and we also required a history of an immediate reaction to small amounts of the food, a criterion which in itself has high credibility as to the causal association between food and reaction (16), and which reduces the risk of misclassification due to asymptomatic sensitization (20).

The ratio criterion, which relates the size of the allergen wheal to the size of the histamine wheal, was used in this study. It has been recommended for epidemiologic studies, as it is less influenced by the variation due to growth of wheal size by age (21, 22) and observer bias (11, 23), and has been used in several studies on food hypersensitivity (24–26). A criterion based solely on allergen wheal size may underestimate the sensitization, especially in small children (23).

The risk of false positive food challenges due to natural variation of disease or random symptoms was minimized by the stepwise diagnostic design and the allergen-free surroundings in which the challenges were performed, and by performing DBPCFC in all children in whom the reaction was subjective in nature or developed after the child had returned home (27).

False negative challenge outcomes may occur for various reasons including inadequate amounts (28, 29), lack of exercise (30), and, perhaps most importantly, altered allergenicity of processed food (31–33). Children with hypersensitivity only to raw egg may have a false negative outcome if challenged with pancakes. In the present study the challenge food was chosen on the basis of the history of previous reactions, and if this was in doubt, challenges were repeated with raw eggs. Furthermore, a successful reintroduction of the food into the diet was required for all children after a negative challenge outcome in order to reduce the possibility of false negative challenges.

Synthesis with previous knowledge

Although egg is among the food items most commonly incriminated (1) and confirmed to cause adverse reactions (34), there are few studies on the prevalence of adverse reaction to egg in children. On the basis of three open challenges, 13 of 1752 children (0.7%) were diagnosed as allergic to egg in an older study; however, this was not a population-based study (35). In a population-based study, three of 480 children (0.6%) had reactions to egg before the age of 3 years, confirmed by objective methods; however, a reliable estimate could not be reached due to the small numbers (3). Furthermore, in a cross-sectional study from Finland of children aged 2 and 3 years, 7% and 9%, respectively, had parentally reported reactions to egg. Among these, about 25–50% of the reactions were reproducible when challenged at home by the parents (4).

Overall, reported reactions to egg were verified in 68% of the children in this study. Others have reported similar results. In a study on a selected sample of children, adverse reactions to egg were confirmed in 63% (36), a result which is very similar to our findings. It is noteworthy that the positive predictive value of a parentally perceived reaction increases with the number of times it has been reported. This confirms that reactions incorrectly associated with food have a shorter duration than reactions correctly associated with food (3) and provides a tool in evaluating children with parentally reported food reactions.

In conclusion, the present study is the first population-based study to assess the prevalence of allergy to egg in children based on objective criteria. Furthermore, it has the advantage that parentally unrecognized reactions are assessed. The estimated point prevalence of 1.6% at the age of 2½ years is thus the best current estimate on the prevalence of allergy to egg in young children. Moreover, our results indicate that the cumulative incidence of allergy to egg by this age may be somewhat higher. Almost all the reactions were IgE-mediated reactions.

The most striking finding was that, although in general only two-thirds of the parentally perceived

reactions were verified, reactions that had been parentally reported three times, when the children were 12, 18, and 24 months of age, were all verified.

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Appendix 1

- Does the child react to any food items?
- ☐ Yes (if yes, describe the reaction by marking off for each symptom)
- ☐ No
- | Type of reaction | Caused by |
|--|-----------|
| ☐ Respiratory problems | _____ |
| ☐ Diarrhea | _____ |
| ☐ Stomach pain | _____ |
| ☐ Exacerbated eczema | _____ |
| ☐ Restlessness/irritability | _____ |
| ☐ Vomiting | _____ |
| ☐ Other reactions. Specify: | _____ |
- Has the child suffered from any of the conditions listed below during the first two years of life?
- ☐ Unusually loose stools for long periods of time (more than a month).
- ☐ Unusually active or irritable for long periods of time (more than a month).
- Has the child had hives in the last 6 months?
- ☐ Yes
- ☐ No
- Has the child had any episodes/occurrences of eczema in the last 6 months?
- ☐ Yes (if yes, how old was the child the first time it occurred?)
- ☐ No
- Has a physician been consulted due to the adverse reaction to food?
- ☐ Yes (if yes, were any allergy tests performed?) ☐ Yes
- ☐ No
- ☐ No
- If allergy tests were performed, what were the results of these tests?

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