

Original article

The prevalence of CMA/CMPI in young children: the validity of parentally perceived reactions in a population-based study

Background: The present study aimed to estimate the prevalence of adverse reactions to milk, as population-based prevalence estimates based on objective diagnostic procedures are rare.

Methods: Children with parentally reported reactions to milk were selected for further examination from a population-based cohort of 2721 children. At the age of 2½ years, they underwent a stepwise diagnostic procedure that included diet trials at home, skin prick tests, and open and double-blind, placebo-controlled food challenges. A sample of children with symptoms not attributed to milk was selected for assessment of unrecognized reactions.

Results: The estimated point prevalence of cow's milk allergy and cow's milk protein intolerance (CMA/CMPI) in children with parentally perceived reactions at the age of 2½ years was estimated to be 1.1% (CI 0.8–1.6). However, this was an underestimate, as unrecognized reactions were detected. Most reactions were not IgE-mediated. The positive predictive value of a parentally perceived reaction depended on the number of times it had been reported and was good for reactions reported three times (at 12, 18, and 24 months of age).

Conclusions: The present study confirms previous findings that parents overestimate milk as a cause of symptoms in their children; however, it also indicates that unrecognized reactions may be a problem as well.

**M. Eggesbø¹, G. Botten²,
R. Halvorsen³, P. Magnus¹**

¹National Institute of Public Health, Section of Epidemiology, Department of Population Health Sciences, Oslo; ²Center for Health Administration, National Hospital, University of Oslo; ³Voksentoppen Center for Asthma, Allergy and Chronic Lung Diseases in Children, University Hospital, Oslo, Norway

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Merete Eggesbø
Section of Epidemiology
Department of Population Health Sciences
National Institute of Public Health
Post Box 44 04 Torshov
N-0403 Oslo
Norway

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Food allergy and intolerance is common among small children, and milk is the food item most commonly incriminated (1–3). Prevalence estimates based on parental perception vary between 12% and 15% in children under the age of 3 years (1, 3), declining with age (4, 5). However, objective diagnostic testing has revealed that parents overestimate the role of milk as the cause of symptoms in their children (3, 6). This discrepancy is probably due to the difficult identification of adverse reactions to milk, caused by 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) (7). Prevalence estimates based on objective diagnostic tests are rare, but have been assessed in some population-based studies to range from 1.9% to 7.5% (3, 8–11). DBPCFC has only been used in one population-

based prevalence study, in which the prevalence of cow's milk allergy/cow's milk protein intolerance (CMA/CMPI) was estimated to be 5.2% (3).

The unspecific nature of the symptoms and the long time interval that may pass between ingestion and reaction may also result in failure to identify milk as the offending cause. The potential for unrecognized reactions to milk is an important issue that has not been fully investigated in research to date.

This study estimates the point prevalence of CMA/CMPI in children aged 2½ years, and also calculates a crude estimate of 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 milk. A sample of children without perceived reactions to milk was also examined for the possibility of unrecognized reactions to milk. A stepwise diagnostic procedure including open challenge and DBPCFC was developed to examine these children.

Material and methods

Study population

A population-based cohort of children born in Oslo, Norway, was

Abbreviations. CMA/CMPI: cow's milk allergy/cow's milk protein intolerance; DBPCFC: double-blind, placebo-controlled food challenge; IgE: immunoglobulin E; SPT: skin prick test; CI: 95% confidence interval.

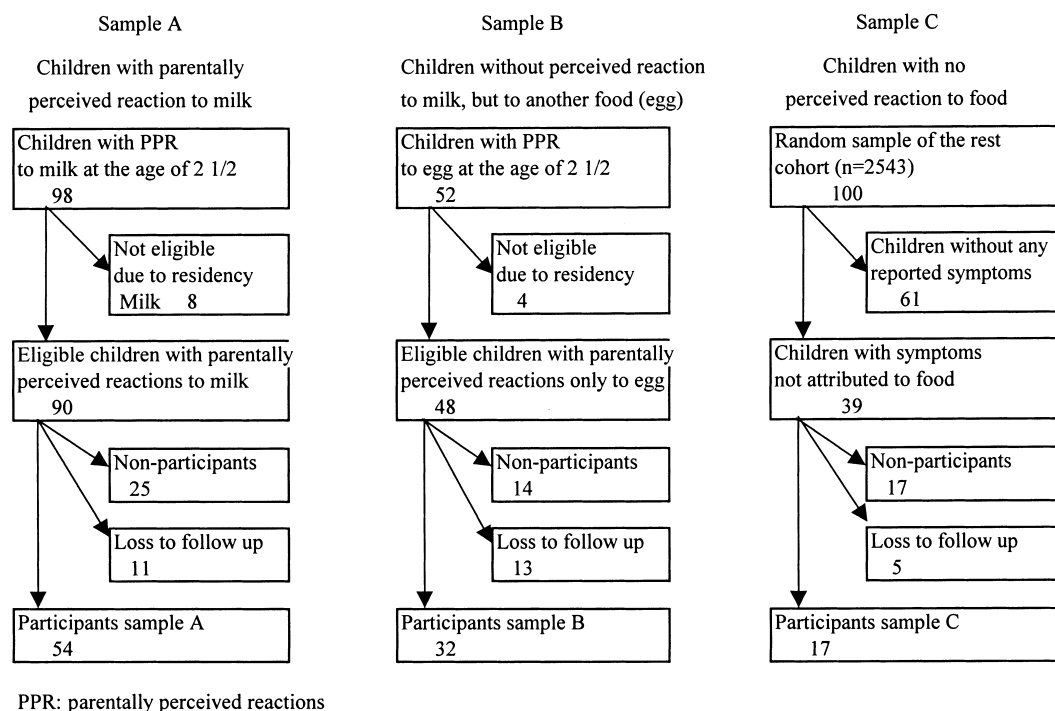


Figure 1. Study samples of children with parentally perceived reaction to milk, those with reactions to foods other than milk, and controls.

followed from birth until the age of 2 years. Details of the study design and collection of data have been described elsewhere (1, 12). The present study is based on families with children born in 1992 ($n=3289$); 2721 families (83%) responded to the questionnaire when the child was 2 years old.

Children with parentally perceived reactions to milk: sample A. The parents completed self-administered questionnaires regarding 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 milk for 98 children at the age of 2½ years, while previously perceived reactions were no longer reported at this age in 217 children. Of the eligible 90 families who were asked to participate, 60% (54/90) completed the study (Fig. 1). Nonparticipation or loss to follow-up was due to the following reasons: 13 families never answered the postal request; five indicated on the reply form that they were not interested; seven indicated that they were willing to be telephoned, but could not be reached despite repeated attempts; two agreed to a telephone interview, but not to further participation; seven agreed to home trials, but did not complete the trials, and two repeatedly cancelled examination dates due to sickness. The mean age at the time of the examination was 2.5 years (CI 2.4–2.6).

Children without parentally perceived reactions to milk: samples B and C. Two samples of children were examined for the possibility of detecting reactions to milk that had not been recognized by the parents. The first, sample B, comprised children with parentally perceived reactions only to egg at the age of 2 years, and the selection of these children has been described in detail previously (13). Among these, 32 of 52 children participated. The second sample, sample C, consisted of 100 families randomly drawn from the cohort at 2 years of age. Among these 100 families, 39 families had reported one of the following conditions in their children: eczema and urticaria during the last 6 months, loose stools, unusual irritability or hyperactivity for periods longer than a

month (13), or asthma. Asthma was defined as two episodes of bronchial obstruction, one verified clinically by a physician (14). Of these 39 families, 22 agreed to participate, but only 17 completed the study.

Variables

The diagnostic procedure has been described in detail elsewhere (13). It included a number of diagnostic steps, as briefly summarized below.

Step 1: interview and dietary trials. The first step consisted of diet trials at home, which all children except those already on a strict elimination diet had to undergo (13). Children for whom the diet trials did not alter their symptoms were classified as tolerant and did not proceed further. The remaining children were seen at the clinic for laboratory tests and food challenges.

Step 2: medical history and specific IgE. The skin prick test (SPT) was performed in duplicate with a lancet with a 1-mm tip (ALK) on the volar surface of the forearm (13). Native skimmed milk 1/10 was employed. As positive and negative references, histamine dihydrochloride 10 mg/ml (ALK) and glycerol diluent were used, respectively. 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+. Pharmacia CAP FEIA was used to determine the concentration of egg- and milk-specific IgE in serum. In children with a SPT of $\geq 3+$ and a history of immediate reaction to small amounts of milk, the reaction was classified as confirmed without further investigation.

Steps 3 and 4: open and double-blind food challenge. For the remaining children, open and double-blind food challenges were performed by a stepwise model (13). Open challenges were performed by means of low-fat milk given as a drink or contained in pancakes while at the clinic. Depending upon the child's level

of sensitivity, one among three challenge procedures was chosen, starting with volumes of either a drop, 1 ml, or 5 ml, the volume doubled every 30 min until a reaction occurred or the predefined volume of either 81, 180, or 380 ml was reached. If no reaction occurred during the 3 days following 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. Children who reacted subjectively to the open challenges, or after they had returned home, proceeded to the double-blind food challenges.

In the DBPCFC, the allergen ingredients were disguised in an equal amount of carrier substance. The carrier substance also served as the placebo. The first choice for a carrier was the milk substitute the child ordinarily used, as this was palatable to the child. PepditeTM was chosen as a carrier/placebo for children not receiving milk substitutes. Two sets of DBPCFC (four challenges) were required for confirmation of untypical and unclear reactions. 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.

Lactase deficiency was excluded by performing additional blind challenges with lactose in all children with gastrointestinal reactions to milk. The lactose challenge consisted of four separate challenges: lactose (40 g dried lactose monohydrate 0.15 mm powder, corresponding roughly to the lactose content in 8 dl milk); milk protein without lactose (AL 110); and placebo (Pepdite) given twice, in a randomly assigned order. The challenge doses were taken home to the child on four successive Fridays. Protein intolerance was diagnosed when a reaction occurred after the protein challenge, a weaker or no reaction occurred after the lactose challenge, and no reaction occurred to the two placebo challenges.

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

Children without parentally perceived reactions to milk: samples B and C

Among the 32 children with parentally perceived reactions only to egg (sample B), those in whom milk-specific IgE was detected and who had residual symptoms while on an egg-free diet were subjected to the same stepwise evaluation as outlined above.

Among the 17 children (sample C) in whom either eczema, urticaria, loose stools, asthma, or irritability/hyperactivity in periods longer than a month was not attributed to any food (13), further information was obtained by telephone interview. Those who had symptoms that did not resolve completely for periods as long as 1 month while on a diet containing milk were also examined further by the stepwise diagnostic procedure outlined above. Children not fulfilling this criterion were not examined further.

Definitions of confirmed and possible milk allergy/intolerance

A reaction to milk was classified as confirmed when:

- 1) There was a history of unequivocal, immediate clinical reaction to small amounts of milk and confirmatory high levels of specific IgE as indicated by SPT of $\geq 3+$.
- 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 distinct reaction to the allergen challenge unequivocally exceeding any reaction to the placebo challenge in the DBPCFC challenges and intolerance to lactose had been ruled out. Two confirmatory DBPCFCs were required in children with a history of dubious nature.

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

Background variables

The results of any allergy test that might have been performed previously were obtained from the questionnaire sent to the parents when the child was 2 years old (13). Information on the sex and the birth weight of the child, birth order, maternal age in years, maternal smoking at the time of the birth, maternal education in years, and family income was obtained from the questionnaire completed by the participating families at the maternity ward (12).

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 for the prevalence estimates of unrecognized reactions and for the positive predictive values were computed by the Wilson method (15), which is appropriate when the prevalence is low, or the study sample is small (16). The validity of parentally reported reactions was assessed by calculating the positive predictive value (17). The CI intervals for the prevalence estimates were calculated by bootstrapping.

Results

Children with parentally reported reactions to milk (sample A)

No significant differences were observed between the examined and unexamined children in the distribution of maternal educational level, maternal age, parental asthma, first-born children, child sex, and family income, or in whether an allergy test had been taken or not. However, the distribution differed, with a higher proportion in the 44 unexamined children than in the 54 examined children with regard to maternal smoking (27% and 13%, respectively; $P=0.08$), children with negative responses to allergy tests (75% and 44%, respectively, $P=0.05$), and children with reactions not reported at all three time points (66% and 48%, respectively; $P=0.08$).

Of the 54 examined children with parentally reported reactions to milk (Fig. 1), CMA/CMPI was either confirmed or held to be possible in 18 children (33.3%) (Table 1). Eleven children were confirmed according to the strictest criteria (Table 2a–c) and seven children were classified as “possible” (Table 3). The symptoms reproduced can be seen in Tables 2 and 3. The majority of the children experienced symptoms from the gastrointestinal tract, with diarrhea as the most predominant symptom.

An adverse reaction to milk was not demonstrated for 36 children. Four of these children were classified as tolerant on the basis of preliminary diets at the children's homes, and 32 children on the basis of either open challenge ($n=21$) or DBPCFC ($n=11$).

Table 1. Number of confirmed and possible reactions to milk in three population-based samples of children with or without parentally perceived reactions to milk, according to diagnostic approach

	Population A <i>n</i> = 54	Population B <i>n</i> = 32	Population C <i>n</i> = 17	All
CMA/CMPI confirmed by				
Specific IgE > 3 and immediate history	2			
Open challenge	2			
DBPCFC	7	1	1	13
CMA/CMPI assessed as possible				
Positive open challenge, no or too few DBPCFC	5	2		
Reintroduction of food into diet caused symptoms	2			9
Total number of children with CMA/CMPI	18	3	1	22

DBPCFC: double-blind, placebo-controlled food challenge; CMA/CMPI: cow's milk allergy and cow's milk protein intolerance.

Population A: children with perceived reactions to milk.

Population B: children without perceived reactions to milk, but perceived reaction to other food (egg).

Population C: no perceived reaction to any food, but reported chronic conditions which could be related to food.

Table 2. In a population-based cohort of 2721 2-year-old children, 13 children were classified as having confirmed reaction to cow's milk, according to one of three criteria

a. Diagnosis based on history of immediate reactions to small amounts of milk and high levels of milk-specific IgE							
S*	History‡			Time†	SPT		RAST
1	Bloody D, Ae in early infancy while still being breast-fed			< 10 min	4		3
2	Ae while breast-fed; small amount of milk-containing porridge caused severe Ae			< 30 min	4		2
b. Diagnosis based on objective reaction to open milk challenge							
S*	History‡	SPT	S-IgE	Open challenge performed at hospital			
				Amount of milk (ml)	Reaction to open challenge		
3	U	2	1	18/32/81	Av, U face; three challenges, due to Av (only ate first mouthful given each day)		
4	U	0	1	180	U face and hands; D next day		
c. Diagnosis based on confirmation by DBPCFC							
S*	History‡	SPT	RAST	Challenges performed at hospital			n§
				Amount (ml)	Reaction to challenges	DBPCFC	
5	D	0	0	250	D	D	4
6	I, C, D, S	0	0	250	D	D	5
7	I, D	0	0	300	D, I	D, I, S	5
8	V, D, Rh, Ab	0	0	380	V	V, I, D	4
9	D, Ab, I	0	2	250	D	D	4
10	Ae, D	0	0	380	D, I	D	4
11	Ae	0	2	250	Ae, A, Ab	Ae, A, D, I	2
12	No PPR, D	0	2	380	D	D	2
13	No PPR, Ae	3	3	100	np	V	2

A: bronchial obstruction; Ab: abdominal pain; Ae: eczematous lesions; An: angioneurotic edema; Av: aversion; C: colic; D: loose stools; I: irritability; np: not performed; PPR: parentally perceived reaction; Rh: rhinitis; S: sleep disturbances; U: urticaria; V: vomiting.

*S: subject number.

†Time from ingestion to appearance of first symptom.

‡History: parentally perceived reactions to milk on earlier occasions.

§Number of blind challenges performed on each child.

||Active challenges performed with high-fat milk; placebo challenges performed with skimmed milk.

Table 3. Measured level of milk-specific IgE and response to elimination diet and open challenges in nine children in whom *possible* CMA/CMPI* was diagnosed (partial fulfillment of diagnostic criteria)

S†	SPTS	Ig	History‡	Comments
14	0	0	D	U face, Ae; Con after OP; no blind challenges
15	0	0	Ae	Worsened Ae after OP; no blind challenges
16	0	0	Av, D, V	Perioral Ex; Con 2 days, then D after OP; no blind challenges
17	0	0	D	D after OP and blind; no lactase challenges
18	0	0	Ae, D	D after OP; blind challenges uncertain; reintroduction, however, caused D to recur
19	0	2	Ae, I, S, D	Con, D, Ae after OP; D after blind; no repeated blind challenges
20	0	2	No PPR§, Ae	D, Ap, Ae after OP; Ae after blind; no repeated blind challenges
21	0	1	No PPR§, D	Chronic D disappeared, Ae improved on elimination, and recurred after OP; no blind challenges
22	0	0	D	D after OP; blind challenges uncertain; reintroduction, however, caused D to recur

Ab: abdominal pain; Ae: eczematous lesions; Av: aversion; Con: constipation; D: loose stools; Ex: exanthema; I: irritability; OP: open challenges; S: sleep disturbance; U: urticaria; V: vomiting.

*CMA/CMPI: cow's milk allergy/cow's milk protein intolerance.

†Subject number.

‡Parentally reported reactions in past.

§No PPR: confirmed egg allergy, but no parentally perceived reaction to milk; however, chronic symptoms on egg-free diet.

However, for 12 of the 36 children, the history strongly suggested that they had previously had CMA/CMPI, which had been outgrown recently (Table 4).

Positive predictive value of a parentally perceived reaction to milk

The positive predictive value of a parentally perceived reaction reported at the age of 2 years, based on the number of children with verified (confirmed and possible) CMA/CMPI at the age of 2½ years, was 33% (CI 20–46). The positive predictive value depended significantly on the number of times the reaction had been reported, and it increased from 8% for a reaction reported once, to 31% and 46% for reactions reported two and three times (at 12, 18, and 24 months of age), respectively.

If the children had been examined at the age of 2 years at the time when the reaction was last reported, the 12 children now classified as previously having CMA/CMPI (Table 4) would presumably have been verified,

too, increasing the positive predictive value of a parentally reported reaction to 55.6% (CI 42–68). Correspondingly, the positive predictive values increased to 8%, 39%, and 86% for reactions reported one, two, and three times, respectively.

Whether or not an allergy test had been administered previously and the results of such testing were not associated with verified CMA/CMPI (data not shown).

Point prevalence at the age of 2½ years

For calculation of a prevalence estimate, assumptions regarding the unexamined children had to be made. The positive predictive value of parentally reported reactions, according to the number of times the reaction had been reported, was assumed to be the same in unexamined children as in the examined children. Of the 44 unexamined children, 14, 15, and 15 children had reported a reaction one, two, and three times,

Table 4. History of previous allergic reactions to milk in 12 children in whom reaction to milk was no longer evident in milk challenges performed at age of 2½ years

S*	First time cow's milk*	Age at onset	Type of milk	Reaction	Time interval	SPT	Tolerance†
1	–	5 weeks	Breast milk	U, Ae, D	<30 min	4+	Yes
2	Yes	6 months	Porridge‡	Generalized An, U	<5 min	3+	–
3	Yes	11 months	Cow's milk	V, D, Ab, I	5–15 min	–	Yes
4	Yes	1 week	Milk substitute	Bloody D, Ae	–	Negative	Yes
5	Yes	8 months	Milk substitute	V, D, Ab, I	6 h	–	No
6	Yes	8 months	Porridge‡	V (±D)	<15 min	Negative	Yes
7	No	9 months	Milk-containing P§	Generalized U	<15 min	3+	Yes
8	Yes	6 months	1 tsp ice cream	Local An, itching	10–15 min	Positive	Yes
9	–	4 weeks	Breast milk	Ex, Ae, D	–	2+	Yes
10	Yes	5 months	Porridge‡	V, D, W/L	5–10 min	–	–
11	Yes	3 months	Milk substitute	D, crying 24 h	<60 min	–	Yes
12	No	7 months	Milk-containing P§	D, I, W/L (±V)	4 h	Positive	No

Ab: abdominal pain; Ae: eczematous lesions; An: angioneurotic edema; D: loose stools; Ex: exanthema; I: irritability; U: urticaria; V: vomiting; W/L: growth retardation.

*Norwegian women traditionally breast-feed for a long time, postponing introduction of cow's milk. Median length of breast-feeding in this cohort in 1992 was 9 months.

†Whether parents prior to examination had given indications that child was growing less hypersensitive.

‡Porridge containing cow's milk.

§Other milk-containing products.

Table 5. Point prevalence of CMA/CMPI* at age of 2½ years in cohort of 2721 children, assuming that positive predictive value of parentally reported reactions to milk was same among examined and unexamined children

	Children with parentally reported reactions to milk at age of 2½ years						Calculated total number of children with CMA/CMPI* <i>n</i>	Estimated point prevalence of CMA/CMPI* at 2½ years % (CI)
	Children examined by objective diagnostics†			Children not examined‡				
	PPR§	Verified	Positive	PPR§	Assumed	Calculated		
	<i>n</i> =54	CMA/CMPI* <i>n</i>	predictive value %	<i>n</i> =44	positive pred. value %	no. with CMA/CMPI* <i>n</i>		
Number of times parents had reported a reaction								
Reported once	13	1	8	14	8	1	2	
Reported two times	13	4	31	15	31	5	9	
Reported three times	28	13	46	15	46	7	20	
Total		18				13	31	1.1% (0.8–1.6)

*CMA/CMPI: cow's milk allergy/cow's milk protein intolerance.

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

‡44 children with parentally perceived reactions at 2½ years of age were not examined, due to either residence outside Oslo, nonparticipation, or loss to follow-up.

§PPR: parentally perceived reactions.

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

CI: 95% confidence interval.

respectively, and it was assumed that one, five, and seven of these children would have been verified had they been examined at the age of 2½ years (Table 5). These 13 estimated children plus the 18 examined children with CMA/CMPI give a total of 31 children, and this figure was then divided by the total number of children in the cohort: 2721. The estimated point prevalence of CMA/CMPI was thus calculated to be 1.1% (CI 0.8–1.6) (Table 5).

Upper estimate of the cumulative incidence of CMA/CMPI

Altogether, 315 children had had a parentally perceived reaction to milk at any time point by the age of 2 years, including the 54 examined children. The distribution of

the number of times these reactions had been reported is shown in Table 6. As already reported above, if the children had been examined at the time of the initial report, the positive predictive value of a parentally reported reaction was calculated to be 8%, 39%, and 86%, for reactions reported one, two, and three times, according to the findings in the examined children. By assuming that the positive predictive values of reported reactions are the same regardless of the age at which they are reported, 14, 17, and 26 of the unexamined children with reactions reported one, two, and three times, respectively, would presumably have been verified. A crude estimate of the cumulative incidence of CMA/CMPI by the age of 2 years may thus be calculated in a similar manner to be 3.2% (CI 2.0–4.7) (Table 6).

Table 6. Cumulative incidence of CMA/CMPI* by the age of 2 years in a cohort of 2721 children was calculated by assuming that positive predictive value of parentally reported reactions to milk is same among examined and unexamined children

	Children with parentally reported reactions to milk at some point by age of 2 years						Calculated total number of children with CMA/CMPI*	Estimated cumulative incidence CMA/CMPI* % (CI)
	Children examined at age of 2½ years†			Children not examined‡				
	PPR§	Previous and current CMA/CMPI	Positive predictive value	PPR§	Assumed positive predictive value	Calculated no. with CMA/CMPI*		
	<i>n</i> = 54	<i>n</i>	%	<i>n</i> = 261	%	<i>n</i>		
Number of times parents had reported reaction**								
Reported once	13	1	8	186	8	14	15	
Reported two times	13	5	39	45	39	17	22	
Reported three times	28	24	86	30	86	26	50	
Total		30				57	87	3.2% (2.0–4.7)

*CMA/CMPI: cow's milk allergy/cow's milk protein intolerance.

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

‡Total of 261 children comprised 44 children who had parentally perceived reactions at age of 2 years but had not been examined for various reasons, and 217 children who were not examined, as reaction to milk was no longer perceived by the parents at age of 2 years.

§PPR: parentally perceived reactions.

||Children in whom CMA/CMPI was verified by objective diagnostics at age of 2½ years (*n*=18) or in whom history was strongly indicative of previous allergic reaction *n*=12.

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

CI: 95% confidence interval.

Table 7. Prevalence of unrecognized CMA/CMPI* in children at age of 2½ years in two samples of children without perceived reactions to cow's milk, assuming that proportion of children with unrecognized reactions was same among examined and unexamined children

	Examined children				Children not examined			Estimated prevalence <i>n</i> /2721	
	No PPR*	Unrecognized CMA/CMPI was diagnosed			No PPR*	Calculated number of unrecognized reactions	Total of unrecognized reactions		
		<i>n</i>	%	CI					
								<i>n</i>	%
Sample B	32	3	9.4	(3.2–24.2)	20	2	5	0.2	(0.1–0.5)
Sample C	17	1	5.9	(1.0–27.0)	805	47	48	1.8	(1.3–2.3)

Sample B: children without perceived reactions to milk, but perceived reaction to other food (egg).

Sample C: no perceived reaction to any food, but reported chronic conditions which could be related to food, although unrecognized.

No PPR: children with symptoms not perceived to be related to cow's milk.

CI: 95% confidence intervals.

Unrecognized reactions to milk (samples B and C)

Children with parentally perceived reactions to food other than milk (sample B). Among the 32 children with parentally perceived reactions to other foods (egg), but not to milk, three were found to have unrecognized reproducible reactions to milk protein (subjects 13, 20, and 21 in Tables 2 and 3). The estimated prevalences of CMA/CMPI among children with perceived reactions only to egg was calculated to be 0.2% (CI 0.1–0.5) by assuming that the proportion of children with unrecognized reactions to milk was the same among examined and unexamined children (Table 7).

Children without perceived reactions to food (sample C). Of the 17 examined children with chronic symptoms, 13 were judged to be tolerant on the basis of the telephone interview, as they no longer had symptoms, or had symptoms that resolved while on a diet containing milk. Two children experienced no effects from a diet trial, and one child had a negative open food challenge. One child was diagnosed as having CMA/CMPI from the occurrence of foul-smelling, watery stools within 2 h of milk ingestion in both open challenge and DBPCFC (subject 12 in Table 2c).

Chronic conditions not attributed to any food were reported for a total of 822 children in the present cohort. If the proportion of children with unrecognized CMA/CMPI is assumed to have been the same among examined and unexamined children, between 1% and 27% of 822 children with chronic conditions not attributed to food may have had CMA/CMPI (Table 7).

Discussion

The point prevalence of CMA/CMPI in children with parentally perceived reactions at the age of 2½ years was estimated to be 1.1%, and the crude estimate of the

cumulative incidence by the age of 2 years was 3.2%. These are underestimates, as the present study indicates that unrecognized reactions to milk are common.

Selection bias

The most important limitation of this study is the large uncertainty tied to the assessment of unrecognized reactions in sample C, primarily due to the small sample size and loss to follow-up. The small sample size was chosen due to the limited capacity of performing DBPCFC. The loss to follow-up is understandable, however, considering the efforts of keeping a child's diet free from milk for 1 week when there was no previous experience of such diets.

In children with parentally reported reactions to other food items (sample B), only those with positive SPT/RAST to milk were examined for the possibility of unrecognized reactions to milk. Non-IgE-mediated reactions may thus have passed unnoticed.

As reported, there was a higher proportion of children with reactions reported more than once among the participants than among the nonparticipants. Furthermore, repeatedly reported reactions were more likely to be confirmed than reactions reported only once. However, this selection bias was handled by taking the actual number of times the reactions had been reported by the nonparticipants into account when calculating the proportion likely to have been verified among them.

Large uncertainty is tied to the cumulative incidence estimate, because children who had outgrown their sensitivity by the age of 2 years were not objectively examined. The assumption that the validity of the parentally perceived reactions is the same regardless of the age at which it was reported is uncertain. This especially concerns the validity of parental reactions reported once. The validity of a reaction reported once at an earlier age is probably better than a reaction reported once, and for the first time at the age of 2 years, as was the case for the examined children. Thus,

the calculation that only 14 of 186 children with a reaction reported once (Table 6) have had CMA/CMPI is probably an underestimate.

Validity of the diagnostic procedure

The diagnostic procedures in this study were initiated for the sole purpose of a research project, with no preceding initiative by the parents, a fact which increased the demands on the safety of the procedures. 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 (19) without compromising validity.

The sensitivity, specificity, and positive and negative predictive value of a SPT of $\geq 3+$ vary widely. If studies on highly selected samples of children with atopic eczema are excluded, the performance of the SPT is generally reported to be good, with the positive predictive value of a SPT of $\geq 3+$ ranging from 86% (20) and 89% (21) to 100% (22), and that of a SPT of ≥ 4 being 100% (20), although none of these studies are directly comparable, as different extracts, wheal ratings, and diagnostics have been applied. In the present study, we also required a history of an immediate reaction to small amounts of the food, a criterion which in itself has high credibility for the causal association between food and reaction, and reduces the risk of misclassification due to asymptomatic sensitization (23).

The DBPCFC represents the best means of controlling for the variability of the disorders, and it eliminates patient and observer bias. The DBPCFC was performed in all children in whom the reaction was subjective in nature or developed after the child had returned home, and the risk of false positive challenges was further minimized by the requirement of two sets of DBPCFC in children with untypical symptoms.

False negative challenge outcomes may be caused by altered allergenicity of processed food (25–27), inadequate amounts of the food (28, 29), random influences causing symptoms in the placebo phase and thus obscuring the effect of the allergen, or the need for additional factors such as exercise after food intake for symptoms to occur (30). A successful reintroduction of the food into the diet was consequently required for all children after a negative challenge outcome.

Synthesis with previous knowledge

The prevalence of CMA/CMPI has been assessed in some studies, the estimates ranging from 1.5% to 7.5% (8–11, 31), when retrospective studies and studies relying on parental reports are excluded (4, 32, 33). It is difficult to interpret this variation in the estimates because there are major differences between the studies

in diagnostic criteria, study samples, and initial selection of cases, and the confidence intervals are wide in small studies.

Studies in which the children have been selected for further examination by the researchers generally report higher prevalence estimates (5.2–7.5%) (3, 8) than studies in which the initial selection of potential cases relied on health workers for referral (1.9–2.2%) (11). One study consisted of two subsamples, and yielded quite different estimates according to how the initial selection of children was made (9). This suggests that there are problems in selecting the children to be further tested for adverse reactions to food, and it emphasizes the need to assess the proportion of children who have been misclassified as false negative by the initial selection procedure.

The initial selection of cases in this study was based on parental perceptions, and depended upon their awareness and attention to the association between food and conditions in their children. Despite the uncertainty of the estimate, our results indicate that unrecognized reactions to food may be frequent. Similar results have been reported in a British study on an adult population, in which 1/13 controls had food allergy confirmed by DBPCFC (34). To our knowledge, this is the first study to assess unrecognized reactions to food in children, and the issue warrants further investigation.

Large differences exist in the diagnostic criteria of adverse reactions to food, which may be based on either one (11), two (8–10), or three (31) open challenges. The only other study partly using the DBPCFC reported the cumulative incidence of confirmed and probable CMA/CMPI to be 5.2% by the age of 3 years (3).

Previous studies indicate that as many as two-thirds of affected children outgrow their milk hypersensitivity by the age of 2½ years (35, 36), and this is in good accordance with the results of the present study.

Intolerance of lactose constitutes a separate entity that should be distinguished from CMA/CMPI, but that has not been properly excluded in previous studies. To distinguish between CMA/CMPI and lactase deficiency on the basis of history is usually not possible, and the two disorders may coexist, as a serious milk-protein-induced enteropathy may result in a secondary lactase deficiency (37), further complicating the condition. To our knowledge, this is the first study which has used double-blind lactose challenges to distinguish between intolerance to milk protein and intolerance to milk lactose. Lactase deficiency was suspected in several children prior to the challenges, but only one child showed a pattern in accordance with lactose intolerance. We speculate that the milk-free diet maintained prior to the challenges may have temporarily increased the lactase level and the threshold for clinical reactions.

As the children in the present study were not studied

at the time of the initial report, allowing for the development of tolerance, we included children with a history strongly suggestive of previous CMA/CMPI when estimating the positive predictive value of parentally reported reactions to milk. However, uncertainty is tied to the classification of previous CMA/CMPI, in which especially children with untypical and slow onset type of reaction may have been missed.

Overall, 33% of the parentally reported reactions in this study were either possibly or certainly confirmed at the time of the examination, and 55% of the reactions would presumably have been verified had they been examined at the time of the last report. Similar results have been reported in other sample-based studies using open challenge and DBPCFC: 35–40% (3) of the perceived reactions to milk have been reproducible.

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 positive predictive value of a parentally perceived reaction depended on the number of times it had been reported and was good for reactions reported three times (at 12, 18, and 24 months of age).

Most reactions were not IgE-mediated and this has important implications for the diagnosis of CMA/CMPI.

Furthermore, this study confirms previous findings that parents tend to overestimate the role of food; however, it highlights the fact that underestimation may be a problem as well. These children will not receive proper diets, and may have unnecessary chronic conditions that could affect growth and general health. However, there is much uncertainty associated with the estimated prevalence of unrecognized CMA/CMPI due to the small sample size, and the finding should be interpreted with caution since it is unsupported in the literature. The prospect of unrecognized reactions to food has received little attention previously, but it is an aspect which deserves to be further investigated.

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