Early risk factors for cow's milk allergy in children in the first year of life

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ABSTRACT

Background: *Cow's milk allergy (CMA) is a key form of food allergy (FA). It was shown that the frequency of FA seems to have increased during the past 10–20 years, which led to the thought that FA may have different risk factors. Epigenetic regulations and environmental pre- and postnatal factors play a large role in contributing to allergy. Understanding the risk factors that pertain to the development of FA may help to provide reasonable recommendations for prevention of the disease.*

Objective: *To assess the impact of perinatal and environmental risk factors on the incidence of CMA in children in the first year of life.*

Methods: *The study group consisted of 138 infants with CMA and 101 healthy infants without allergy. CMA was confirmed by an elimination test and oral food challenge. To assess infant, parental, and environmental risk factors, we used a validated questionnaire survey.*

Results: *The incidence of CMA was three times higher in infants with a positive family history for allergy ($p < 0.001$). An analysis revealed that mothers of children with CMA were fourfold more frequently university educated than mothers of children without allergy ($p < 0.0001$). The ages of the mothers from the study group were significantly higher than the ages of the mothers from the control group. Children from the study group were breast-fed for a significantly shorter time than children from the control group. The risk of CMA was threefold lower in children who had pets at home ($p = 0.0002$). The risk of IgE-mediated CMA was twofold higher than the risk of non-IgE–mediated CMA if the family had more children ($p = 0.04$) and as many as ninefold higher if multiorgan symptoms were detected ($p = 0.01$).*

Conclusion: *A positive family history of allergy and mother's education increased the risk of CMA in children in the first year of life, whereas having pets at home and a longer period of breast-feeding decreased the risk.*

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Cow's milk allergy (CMA) is an important form of food allergy (FA) whose prevalence in infants has been found to range from 0.3 to 7.5%[1–5] and has been steadily increasing over the past 2 decades.[6] This growth has been attributed to a combination of factors: the Western lifestyle, the hygiene hypothesis, microbial diversity, the delayed introduction of complementary foods, low levels of vitamin D in infancy, skin lesions caused by everyday use of soaps and/or detergents for bathing, and caesarean section delivery. In addition, cofactors, such as antibiotics, administration of proton-pump inhibitors, and dietary factors, including diets poor in omega-3 and omega-6 acids or rich in glycation end products, have also been found to play a role.[7]

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In addition, FA is known to considerably deteriorate the quality of life of patients and their families.[8] It is also an essential factor for pediatric anaphylaxis and contributes to 57% of anaphylactic reactions, 13% of which are fatal.[9] It has been found that ~80% of affected children develop tolerance to cow's milk protein (CMP) by the age of 4–5 years; however, this period is lengthening.[10,11] In addition, CMA is thought to increase the risk of allergy later in life.[12] Moreover, most cases of FA develop in the first few years of life, which suggests that this period is a critical window for its development.

In addition to genetic predisposition and epigenetic regulations, environmental factors that occur in both the pre- and postnatal periods seem to be significant contributors to the development of allergies.[13,14] Environmental prenatal factors include the diet of the pregnant mother (antioxidants, vitamin D, folates, polyunsaturated fatty acids, changes in microbiota, and exposure to external factors (*e.g.*, tobacco smoke, environmental pollution). Postnatal factors associated with the child include the structure of the microbiota of the gastrointestinal tract; exposure to environmental factors, including allergens; and diet. Perinatal factors, such as maternal age, gestation duration, number of

pregnancies, or form of delivery, may also play a role. All these mentioned determinants might affect a development of the juvenile immune system. Hence, Benede *et al.* emphasized the role of the determining factors in the development and prevention of allergic diseases.[6] The aim of our study was to assess the impact of perinatal and environmental risk factors on the incidence of CMA in infants.

METHODS

Subjects

The study was based on a group of 536 infants with suspected CMA. They were recruited from the Departments of Pediatric Allergology, Gastroenterology, the Medical University of Lodz and Collegium Medicum in Bydgoszcz, from 2014 to 2016. The study group consisted of 138 infants with CMA. The inclusion criteria were as follows: age up to 12 months old, confirmation of CMA according to the guidelines,[15,16] and written consent given by the child's parent or guardian. The control group included 101 healthy infants without sensitization, symptoms, or physician diagnosis of FA from an outpatient clinics.

Subjects with immunoglobulin E (IgE) mediated or non-IgE–mediated CMA were identified according to their clinical history, *i.e.,* acute or delayed onset of symptoms after ingestion of CMPs; the result of oral food challenge (OFC), *i.e.,* the occurrence of typical symptoms in ≥2 hours after the administration of the last dose; and the result of serum specific IgE (sIgE). The exclusion criteria were FA to allergens other than CMP, intolerance to lactose, or the presence of any other concomitant disorders that might significantly affect the study result.

Questionnaire Survey

A questionnaire to analyze infant risk factors, parental risk factors, and environmental risk factors was prepared for the purposes of the study.

Elimination Diet

All children with suspected CMA, defined as children with a history of parent-reported adverse reaction to milk, with either a positive or a negative result of sIgE, were further evaluated with an elimination diet. For infants who were breast-fed and suspected of having CMA, the mothers could continue nursing but were asked to follow a diet free of cow's milk for at least 2 weeks. The suspected foods and related symptoms were recorded in diaries by the parents. The subjects whose symptoms improved significantly with the elimination of the CMP were further evaluated by OFC.

OFC

OFC was used to confirm the presence of CMA in the infants, as recommended by European Academy of Allergy and Clinical Immunology[15] and PRACTALL Consensus.[16]

Determination of sIgE Antibodies

Blood was drawn before OFC. Patients' serum was analyzed for sIgE to cow's milk by using the Polycheck method (BioCheck GmbH, Leipzig, Germany); the lower detection limit was <0.35 kU/L.

Statistical Analysis

The Mann-Whitney *U*-test for two independent trials was used to compare quantitative variables in children with and children without CMA. Data were presented as median (Me), mean (M), standard deviation score (SD) and interquartile range (IQR). The χ^2 test and calculated odds ratios (OR) with 95% confidence intervals (CI) were used to compare the distributions of qualitative variables in particular groups. A logistic regression model was applied to identify factors that contributed considerably to CMA. A p value of <0.05 was considered statistically significant for all analyses. All analyses were performed by using STATISTICA 13.1 software (Statsoft, Cracow, Poland). Consent was given by the bioethics committee of the Medical University of Lodz and Collegium Medicum in Bydgoszcz (RNN/101/14/KE and KB 578/201 5) for the study to be conducted.

RESULTS

The disease was confirmed in 138 of the 536 infants with suspected CMA. The course of the study is illustrated in Fig. 1, and the characteristics of the study and control groups are presented in Table 1. The type of allergy and sensitization of children with IgE-mediated and non-IgE–mediated CMA are shown in Table 2.

Infant Risk Factors

The study group and the control group are compared in Table 3. Infants born in the spring season (March–May) were twofold more likely to be affected by CMA than those born in other seasons (OR 2.375 [95% CI, 1.24–4.43]; $p = 0.008$). The mean birth weight was 3500 g for the infants from the study group (IQR, 750) and 3390 g for the controls (IQR, 680) ($p = 0.4$). The two groups did not differ significantly with regard to median Apgar score or median gestation period (Me [IQR] Apgar, 10.00 [1.00] points, $p = 0.058$; and Me [IQR] gestation period, 39.00 [2.0] weeks, $p = 0.36$); however, CMA was twice as common in infants who were prematurely born (OR 2.546 [95% CI, 1.04–6.22]; $p = 0.04$).

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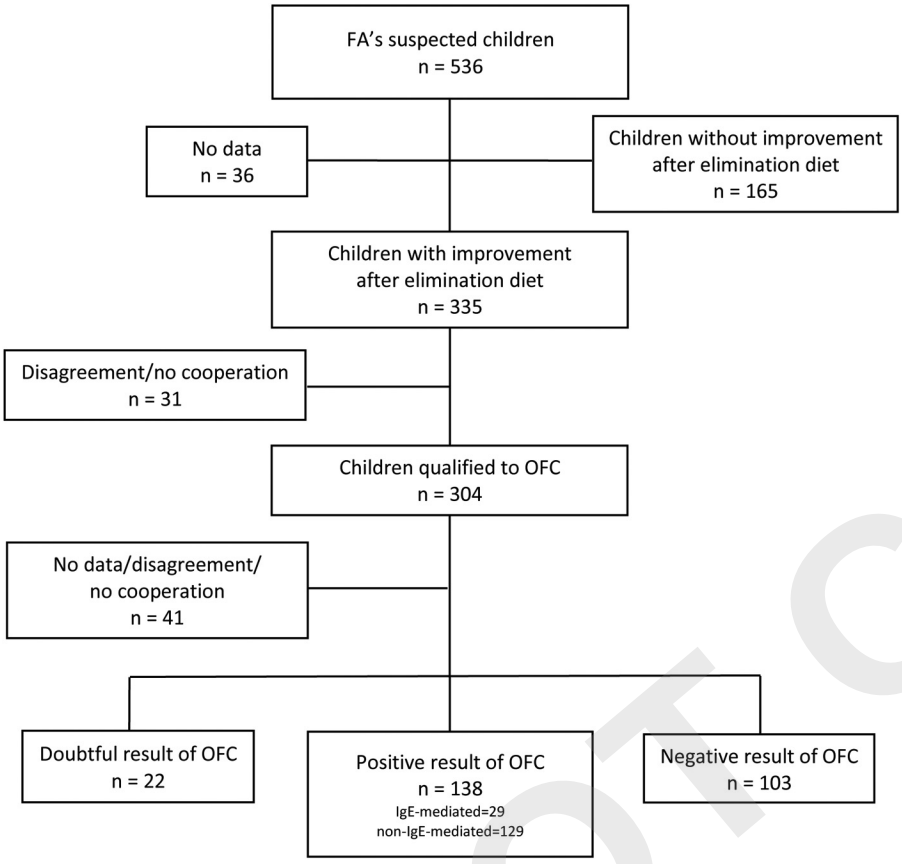


Figure 1. *Study design. Flow chart, depicting steps involved in the patients and tests in this study. OFC = Oral food challenge.*

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Parental Risk Factors

The incidence of CMA was found to be three times higher in infants with a positive family history for allergy and twofold higher if a sibling was also affected (Table 3). In addition, if a family member was affected by atopic dermatitis or asthma, then the risk of CMA in the infant was four- or threefold, respectively higher than for any other diseases. An analysis of a relationship between CMA and the education of parents revealed that the mothers of children with CMA were four times more likely to be university educated than those from the control group. However, the children of fathers who were graduates also seemed to be half as likely to have CMA as those fathers who were not graduates. Moreover, it was also noted that the mothers of children with CMA (Me [IQR], 29.00 [6.00]) were significantly older than those of children from the control group (Me [IQR], 28.00 [8.00]; $p = 0.019$).

Environmental Risk Factors

An analysis of feeding methods showed that children from the study group were breast-fed for a significantly shorter period of time (Me [IQR], 2.00 [4.00]) than the controls (Me [IQR], 2.00 [4.50]; $p = 0.014$). The risk of CMA was four times higher for formula feeding than for breast-feeding; however, the choice of feeding method introduced just after delivery did not influence the development of CMA (Table 3). No relationships were observed between the administration of antibiotics or exposure to tobacco smoke in the first year of life, either in pregnancy or at home as well as living in a nonrural area versus a rural area and the development of CMA. The risk of CMA was threefold lower in children with pets at home (OR 0.296 [95% CI, 0.15–0.56]; $p = 0.0002$). The median (IQR) living area per person was 18 m^2 (11.5 m^2) in the study group and 16.5 m^2 (7.5 m^2) in the control group ($p = 0.381$).

Risk Factors and IgE-Mediated and Non-IgE–Mediated CMA

No significant differences were found between IgE-mediated and non-IgE–mediated CMA with regard to most of the tested characteristics (Table 3). A statistically significant difference was observed regarding the duration of exclusive breast-feeding: half the children with IgE-mediated CMA were breast-fed for a period of 2 months (Me [IQR], 0 [2.00]), whereas the other half, with non-IgE–mediated CMA, were given breast milk for 5 months (Me [IQR], 2.00 [5.00]) ($p = 0.02$) (Fig. 2). The risk of IgE-mediated CMA was 10 times higher in children who were formula fed (OR 21.225 [95% CI, 2.78–161.67]; $p = 0.001$) than in children who were breast-fed (OR 0.059 [95% CI, 0.01–0.45]; $p = 0.004$). The risk of IgE-mediated CMA was twofold higher

Table 1 **Characteristic of the study group and the control group**

Parameter	Study Group, $n = 138$	Control Group, $n = 101$	p
Sex, no. (%)			0.74
Girls	64 (46)	49 (49)	
Boys	74 (54)	52 (51)	
Age, mo			0.052
Median (IQR)	5 (5)	6 (9.5)	
Q_1–Q_3	3–8	3.5–13	
Mean ± SD	7.4 ± 7.2	8.5 ± 6.2	
Place of living, no. (%)			0.63
Nonrural	93 (67)	71 (70)	
Rural	45 (33)	30 (30)	
Weight, no. (%)			0.229
<3 percentile	19 (14)	5 (5)	
3–10 percentile	18 (13)	16 (16)	
10–97 percentile	98 (71)	77 (76)	
>97 percentile	3 (2)	3 (3)	
Height, no. (%)			0.177
<3 percentile	6 (4)	1 (1)	
3–10 percentile	1 (1)	1 (1)	
10–97 percentile	110 (80)	93 (92)	
>97 percentile	21 (15)	6 (6)	
Clinical symptoms, no. (%)			
Rash, atopic dermatitis, urticaria	85 (62)	5 (5)	<0.001
Itching	39 (28)	0	0.002
Angioedema	10 (7)	0	0.018
Diarrhea	40 (29)	0	0.002
Constipation	26 (19)	0	0.007
Colic	39 (28)	11 (11)	0.002
Flatulence and/or reflection	33 (24)	6 (6)	0.001
Massive regurgitation	38 (28)	12 (12)	0.004
Vomiting	28 (20)	0	0.017
Blood and/or mucus in stool	47 (34)	0	0.003
Weight loss or poor weight gain	24 (17)	0	0.009
Runny nose and/or snuffles	16 (12)	2 (2)	0.014
Wheezing, cough, frequent respiratory infections	14 (10)	12 (12)	0.755

IQR = Interquartile range; Q_1 = quartile 1; Q_3= quartile 3; SD = standard deviation.

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than the risk of non-IgE–mediated CMA if the family had more children ($p = 0.04$) and as much as ninefold higher if multiorgan symptoms were detected ($p = 0.01$).

Risk Factors in Multiple Logistic Regression Analyses

To identify the key factors that contribute to CMA, a logistic regression model was applied. A number of potential risk factors for CMA were tested in univariate models. No significant associations were found with sex, place of living, basic and/or secondary education of the mother and father, exposure to tobacco smoke at home and during pregnancy, born outside of the spring season, order of birth order and pregnancy, siblings, type of delivery, antibiotics in the first 6 months, mother's and father's positive history to allergy, allergic rhinitis, FA in the family, or the manner of feeding after birth. Significant associations with CMA were found for the following parameters: maternal and paternal higher education, family history of allergic disease, exposure to pets at home, prematurity, being born in the spring, maternal age, and the period of breast-feeding (Table 3).

Factors with a significant association in the univariate analyses were considered in multivariate analysis. The analysis revealed that maternal higher education increased the risk of CMA by almost threefold (adjusted OR [aOR] 2.887 [95% CI, 1.58–5.25]; $p = .001$), as did a positive family history of allergic disease (aOR

Table 2 **Characteristic of children with IgE-mediated CMA (type of allergic comorbidities and sensitization) and non-IgE–mediated CMA (types of FA)**

IgE-Mediated CMA, n = 29 (100%)		Non-IgE–Mediated CMA, n = 109 (100%)	
Type of allergy	No. (%)	Type of allergy	No. (%)
Rash and/or urticaria	21 (72.4)	Atopic dermatitis	45 (41.3)
Atopic dermatitis	25 (86.2)	FPIP	45 (32.6)
Angioedema	10 (34.5)	Gastroenteropathy	18 (16.5)
Asthma	11 (37.9)	FPIES	5 (4.6)
Rhinitis	14 (48.3)	Eosinophilic esophagitis	2 (1.8)
Gastrointestinal anaphylaxis	19 (65.5)	FGID	34 (31.2)
Sensitization to	No. (%)	Sensitization to	No. (%)
Milk	29 (100)	na	
Egg	7 (24.1)		
Wheat	5 (17.2)		
Soy	3 (10.3)		
Apple	3 (10.3)		
Peanuts	3 (10.3)		
Almonds	3 (10.3)		
Peach	2 (6.9)		
Potato	2 (6.9)		
Hazelnut	1 (3.5)		
Carrot	1 (3.5)		

IgE = Immunoglobulin E; CMA = cow's milk allergy; FA = food allergy; FPIP = food protein–induced proctocolitis; FPIES = food protein–induced enterocolitis syndrome; FGID = functional gastrointestinal disorders; na = not applicable.

3.89 [95% CI, 2.11–7.17]; $p < 0.001$); however, the presence of pets at home reduced the risk (aOR 0.266 [95% CI, 0.13–0.53]; $p < 0.001$). The risk was also slightly decreased with a longer period of breast-feeding (aOR 0.880 [95% CI, 0.80–0.95]; $p = 0.004$) (Fig. 3).

DISCUSSION

There has been a significant increase in the prevalence of allergy over the past decades that cannot be explained by genetic predisposition. Environmental factors, including nutrition, the uterine environment, and lifestyle factors are known to play crucial roles in gene expression through epigenetic modifications. Moreover, environmental factors, especially those that occur in early life, have been linked to disruptions in the development of the microbiome and the immune system.[13] However, few studies have been performed on the risk factors associated with CMA in infants, and epidemiologic studies in this area have led to inconsistent findings. To our knowledge, the present study was the first investigation of suspected risk factors for the development of CMA conducted with the use of OFC in infants from Poland. Due to different prognoses in IgE and non-IgE–mediated CMA,[17,18] it was interesting to compare risk factors in this two types of CMA. To our knowledge, this is also the first clinical study that included such an aim.

Our findings confirmed that the risk of CMA in children in the first year of life was elevated by a positive family history of allergy and higher education level of the mother and was lowered by having pets at home and a longer period of breast-feeding. No significant differences were found between IgE and non-IgE–mediated CMA with regard to most of the tested factors. Many risk factors for FA have been identified, although their mechanisms remain unclear. As in other atopic diseases, a family history of atopy is a strong risk factor for CMA in infants.[19–22] A population-based study of 1-year-old infants found the risk of FA to be 40% higher in patients with one family member with any allergic disease and 80% higher in patients with two family members with any allergic disease.[23] Similarly, in the present study, CMA was observed three times more frequently in children from families with a positive history of allergy.

Epidemiologic evidence on the relationship between allergic disorders and educational level has been inconsistent. Although Dom *et al.* showed a positive association between parental educational level and eczema,[24] other studies found no association or an inverse relationship.[25,26] Our findings confirmed an increased risk of CMA in children whose parents were university educated, particularly mothers. Miyake *et al.*[27] reported that higher maternal educational level is

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Table 3 **Risk factors in children with CMA (IgE-mediated and non-IgE–mediated) and the control group**

Parameter	Study Group, $n = 138$	Control Group, $n = 101$	OR (95% CI)	p	IgE-Mediated CMA, $n = 29$	Non-IgE Mediated CMA, $n = 109$	OR (95% CI)	p
	No. (%)	No. (%)			No. (%)	No. (%)		
Sex								
Girls	64 (46)	49 (49)	1.089 (0.65–1.82)	0.744	15 (52)	49 (45)	1.142 (0.50–2.59)	0.817
Boys	74 (54)	52 (51)	1.089 (0.65–1.82)		14 (48)	60 (55)	1.731 (0.51–1.07)	
Place of living								
Rural	93 (67)	71 (70)	0.873 (0.50–1.52)	0.633	21 (72)	72 (66)	1.349 (0.54–3.33)	0.515
Nonrural	45 (33)	30 (30)	1.145 (0.65–1.82)		8 (28)	37 (34)	0.741 (0.29–1.83)	
Season of birth								
Spring	39 (30)	20 (20)	2.375 (1.24–4.43)	0.008	21 (72)	72 (66)	1.348 (0.54–3.33)	0.516
Summer	19 (15)	18 (18)	0.961 (0.46–1.98)	0.915	3 (10)	16 (15)	0.670 (0.18–2.47)	0.547
Autumn	48 (37)	34 (34)	1.411 (0.78–2.55)	0.253	12 (41)	36 (33)	1.431 (0.61–3.31)	0.401
Winter	32 (24)	29 (29)	1.103 (0.59–2.05)	0.757	3 (10)	29 (27)	0.318 (0.08–1.13)	0.065
Pregnancy order								
First	72 (52)	61 (60)	0.206 (0.42–1.20)	0.207	12 (41)	60 (55)	0.576 (0.25–1.32)	0.190
Second	42 (30)	23 (23)	1.483 (0.82–2.67)	0.190	13 (45)	29 (27)	2.241 (0.96–5.22)	0.058
Third or more	24 (17)	17 (17)	1.040 (0.52–2.05)	0.910	4 (14)	20 (18)	0.712 (0.22–2.27)	0.565
Birth order								
First	83 (60)	63 (62)	0.725 (0.53–1.54)	0.727	13 (45)	70 (64)	0.452 (0.19–1.03)	0.058
Second	41 (30)	27 (27)	1.158 (0.65–2.05)	0.614	13 (45)	28 (26)	2.350 (1.00–5.49)	0.051
Third or more	14 (10)	11 (11)	0.923 (0.40–2.12)	0.852	3 (10)	11 (10)	1.027 (0.26–3.95)	0.968
Siblings	54 (39)	67 (66)	1.266 (0.74–2.16)	0.387	16 (55)	38 (35)	2.299 (1.00–5.27)	0.040
Type of delivery								
Vaginal	88 (64)	28 (28)	0.675 (0.39–1.18)	0.167	21 (72)	67 (61)	0.607 (0.24–1.49)	0.276
Cesarean section	50 (36)	73 (72)	1.481 (0.85–2.56)		8 (28)	42 (39)	1.645 (0.66–4.05)	
Prematurity	22 (16)	7 (7)	2.546 (1.04–6.22)	0.040	5 (17)	17 (16)	1.127 (0.37–3.36)	0.829
Antibiotics in the first six months of life	14 (10)	10 (10)	0.973 (0.41–2.28)	0.951	1 (3)	13 (12)	0.263 (0.03–2.10)	0.178
Positive family history for allergy	76 (55)	26 (26)	3.536 (2.02–6.18)	<0.001	16 (55)	60 (55)	1.005 (0.44–2.28)	0.990
Mother	30 (22)	15 (15)	1.592 (0.80–3.14)	0.181	3 (10)	27 (25)	0.350 (0.09–1.25)	0.094
Father	31 (22)	13 (13)	1.961 (0.96–3.97	0.062	7 (24)	24 (22)	1.126 (0.42–2.95)	0.808
Siblings	24 (17)	8 (8)	2.447 (1.05–5.70)	0.038	0	0	1.721 (0.63–4.65)	0.281
Type of allergy								
Atopic dermatitis	30 (22)	6 (6)	4.398 (1.75–11.02)	0.002	8 (28)	22 (20)	1.506 (0.58–3.85)	0.390
Asthma	28 (20)	7 (7)	3.418 (1.42–8.18)	0.006	5 (17)	23 (21)	0.779 (0.26–2.26)	0.646
Allergic rhinitis	26 (19)	19 (19)	1.002 (0.51–1.93)	0.996	5 (17)	21 (19)	0.873 (0.29–2.55)	0.804
Food allergy	19 (14)	6 (6)	2.528 (0.97–6.58)	0.057	3 (10)	16 (15)	0.670 (0.18–2.47)	0.547

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Table 3 **Continued**

Parameter	Study Group, $n = 138$	Control Group, $n = 101$	OR (95% CI)	p	IgE-Mediated CMA, $n = 29$	Non-IgE Mediated CMA, $n = 109$	OR (95% CI)	p
	No. (%)	No. (%)			No. (%)	No. (%)		
Manner of feeding after birth								
Breast milk	128 (93)	87 (86)	2.059 (0.87–4.84)	0.098	27 (93)	101 (93)	0.935 (0.18–4.66)	0.935
Formula milk	10 (7)	14 (14)	0.485 (0.20–1.14)		2 (7)	8 (7)	1.069 (0.21–5.33)	
Manner of feeding at the time of diagnostics								
Breast milk	42 (30)	31 (31)	0.987 (0.56–1.72)	0.966	1 (3)	41 (38)	0.059 (0.01–0.45)	0.004
Formula milk	90 (65)	31 (31)	4.233 (2.44–7.33)	<0.001	28 (97)	62 (57)	21.22 (2.7–61.67)	0.001
Both breast milk and formula milk	6 (4)	39 (39)	0.072 (0.02–0.17)	<0.001	0	6 (6)	—	0.196
Parents' education								
Mother								
Basic	17 (12)	27 (27)	0.546 (0.27–1.10)	0.090	4 (14)	13 (12)	1.181 (0.35–3.93)	0.785
Secondary	45 (33)	38 (38)	0.878 (0.49–1.56)	0.660	12 (41)	33 (30)	1.625 (0.69–3.78)	0.257
Higher	76 (55)	36 (36)	4.894 (2.58–9.36)	<0.001	13 (45)	63 (58)	0.593 (0.26–1.35)	0.212
Father								
Basic	25 (18)	25 (25)	0.819 (0.43–1.57)	0.550	6 (21)	19 (17)	1.235 (0.44–3.44)	0.685
Secondary	63 (46)	43 (43)	1.127 (0.89–1.42)	0.321	14 (48)	49 (45)	1.142 (0.50–2.59)	0.749
Higher	49 (36)	33 (33)	2.475 (1.29–4.74)	0.006	9 (31)	40 (37)	0.776 (0.32–1.86)	0.571
Pets at home	18 (13)	34 (34)	0.296 (0.15–0.56)	<0.001	5 (17)	13 (12)	1.538 (0.49–4.73)	0.450
Tobacco smoke exposure								
At home	19 (14)	22 (22)	1.744 (0.89–3.43)	0.107	2 (7)	17 (16)	0.636 (0.13–3.01)	0.226
During pregnancy	6 (4)	6 (6)	0.719 (0.23–2.30)	0.579	0	6 (6)	—	0.196

OR = odds ratio; CMA = Cow's milk allergy; IgE = immunoglobulin E.

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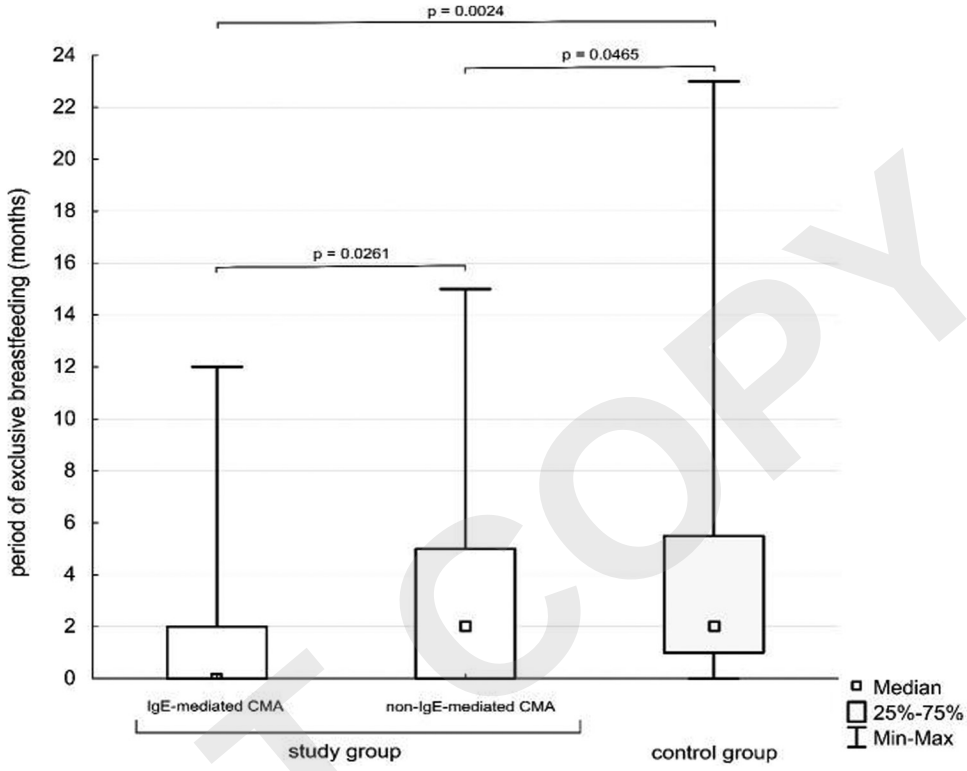


Figure 2. *Breast-feeding period in the study group, including children with IgE and non-IgE mediated cow's milk allergy (CMA) and in the control group.*

associated with an increased risk of wheeze and asthma, whereas a higher paternal educational level increased the risk of eczema. It is possible that parents who completed a university education have a greater awareness of the risks of poor hygiene, and their children are at risk of living in "too hygienic" conditions.

Univariate logistic regression analyses revealed that the mothers of children with CMA were older than those of the control group. However, the multiple regression analysis did not confirm any relationship between CMA in children and the age of their mothers. Peters *et al.*[20] also concluded that maternal age is not associated with any allergy phenotypes. However, other studies found increasing maternal age at delivery to be significantly associated with FA.[28,29] These demographic associations could be associated with disruptions in the acquisition of gut microbiota. Exposure to pets has been found to influence the risk of FA.[30] Unlike Stelmach e*t al.*[19] and Peters *et al.*,[20] our findings indicated that the risk of CMA was threefold lower in children who kept pets at home. These findings were supportive of the hygiene hypothesis.[31]

Breast-feeding is essential for the prevention of allergy, particularly in the earliest stage of life. Cook-Milles[32] indicated that, depending on timing, dose, and the number of antigen challenges, the factors in breast milk can influence the responses of offspring to allergens. Similar to Stelmach *et al.*,[19] our study showed that a shorter duration of breast-feeding increased the risk of CMA (*cf.* Goldsmith *et al.*[33]) and that the risk of CMA was fourfold higher when the infant was formula-fed rather than breast-fed. Many studies found that breast-feeding to have a disease-promoting[34,35] or neutral effect,[36,37] or even a protective effect[38] on the risk of atopy and FA. Other studies showed that prolonged breast-feeding and/or delayed introduction of food allergens may increase the risk of FA,[39] however, this is in contrast to our results.

The observations on the relationship between perinatal factors and FA development are conflicting.[29,40–43] Our findings confirmed an increased risk of CMA in premature babies, as previously noted,[41] which may result from increased intestinal permeability. The type of delivery may also influence FA development. Caesarean section delivery may increase the incidence of CMA by influencing the microbiota, and, hence, the immune system.[44] Similar to Kvenshagen *et al.*,[45] our findings did not indicate any relationship between CMA and the type of delivery, as previously noted.[3,20,28,29,40]

The hygiene hypothesis suggests that the risk of allergy is higher in smaller-sized families but decreases during regular contact with a larger number of family members, subsequent deliveries, and "less hygienic living conditions."[29,46,47] Kvenshagen *et al.*[45] found that a lower risk of CMA is associated with low socioeconomic level, more than five pregnancies in the medical history, and multiple pregnancies. Children with older siblings may be at lower risk of egg allergy at the age of 12 months, which supported the hypothesis that

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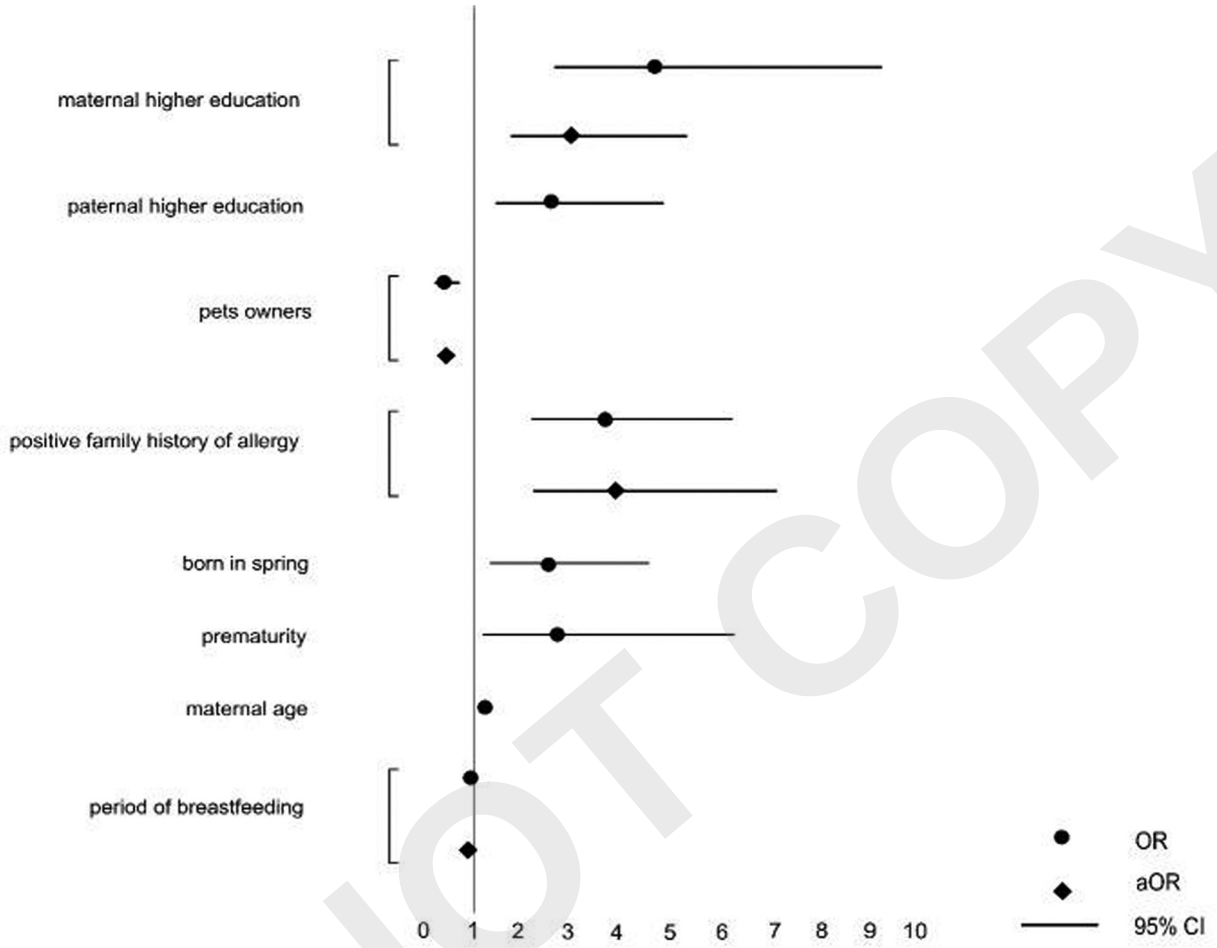


Figure 3. *Significant OR and aOR for the development of CMA in the studied infants. OR = Odds ratio (by univariate logistic regression); aOR = adjusted odds ratio (by multiple logistic regression); CMA = cow's milk allergy; CI = confidence interval.*

increased microbial stimulation in infancy may have a protective effect on allergy.[48] No relationship among CMA development, having siblings, and subsequent pregnancies and deliveries was found in the present study. We showed that children born in the spring were more often affected by CMA than children born in other seasons, whereas other studies indicated the fall or winter.[49,50] This observation indicated that vitamin D, the skin barrier, and exposure to seasonal allergens in an early developmental period may contribute to the development of CMA.

There are studies that indicate that children who, in their pre- and postnatal periods, were exposed to environmental tobacco smoke had a significantly higher risk of food sensitization during the first years of life[29,51]; however, in other studies, maternal smoking was even found to be associated with a decreased risk of CMA in infants.[43,52] Our results, as others,[20,46,52] indicated that exposure to tobacco smoke was not associated with CMA in offspring. In contrast to other findings,[53,54] no association was found between the place of residence or antibiotic use and CMA. Our study had several potential limitations. The study group was not a birth cohort and was relatively small; in addition, a retrospective design and open OFC were used.

CONCLUSION

There is convincing evidence that environmental factors contribute to the incidence of allergic diseases in children.[55] Our findings confirmed that a positive atopic family history, mother's education, the presence of pets at home, and the duration of breast-feeding were independent risk factors for the development of CMA in infants, but further studies are needed to implement new and effective methods of CMA prevention.

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