Cow's milk allergy in infancy and later development of juvenile idiopathic arthritis: A register-based case-control study

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Abbreviations: AP, the attributable proportion due to interaction; ATC, Anatomical Therapeutic Chemical; CI, confidence interval; CMA, Cow's milk allergy; FoxP3, forkhead box P3; ICD-10, International Classification of Diseases, Tenth Revision; JIA, juvenile idiopathic arthritis; mRNA, messenger ribonucleic acid; OR, odds ratio; RERI, relative excess risk due to interaction; S, synergy index; SII, Social Insurance Institution of Finland; SND, standardized normal deviate

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Abstract

We have examined the association between cow's milk allergy (CMA) and juvenile idiopathic arthritis (JIA). The material for this case-control-study was collected from national registers of all children born between 2000 and 2010 in Finland and diagnosed with JIA (n=1,298) and age-, gender- and place-matched controls (n=5,179). We identified 235 children with CMA, 66 of these also had JIA. A conditional logistic regression analysis was performed to evaluate the association between CMA and JIA and to test whether exposure to antibiotics would be a covariate for this association. In boys, but not in girls, a diagnosis of CMA and the usage of hypoallergenic formula in infancy associated with the later development of JIA (odds ratio = 2.4, 95% confidence interval: 1.6, 3.6). The association was most evident in those boys diagnosed with JIA before the age of three or with CMA with predominantly gastrointestinal symptoms. There was no statistically significant additive interaction between CMA and antibiotic exposure with later development of JIA. These associations may reflect impaired maturation of intestinal immunity and integrity in those boys with a risk of JIA. Predisposing factors related to JIA pathogenesis seem to display a gender-linked disparity.

Key words: arthritis; child; milk hypersensitivity; juvenile idiopathic arthritis; matched case-control studies

Juvenile idiopathic arthritis (JIA) is a group of heterogeneous diseases characterized by long-standing arthritis of unknown origin (1). While unbalanced interactions between genes and environmental antigens play a role in the pathogenesis of JIA, there is still limited evidence that specific environmental triggers may participate in the pathogenetic process via contact with mucosal peripheral immunity (2). A healthy mucosal immune system does not display immunological reactions against nutritional antigens, but distinguishes nutritional antigens and non-harmful microbes from pathogens (3). This hyporesponsiveness is called “oral tolerance”, and it involves specific suppression of cellular and humoral immune responses to ingested antigens (4). The colonization by intestinal microbiota drives the normal development of mucosal tolerance in infancy (3), but this process can be disrupted by nutritional agents and antibiotics, which may affect mucosal flora and permeability (5). Exposure to antibiotics has been linked both with the risk of cow’s milk allergy (CMA) (6) and JIA (7, 8) and furthermore, increased intestinal permeability (9, 10) has been reported in both of these diseases. Alterations have been found in the fecal microbial flora, such as a high abundance of bacteroides as compared with controls (11, 12).

CMA has been considered to be one of the first indications of an aberrant inflammatory response in early life (13). It has been associated with later autoimmune manifestations, including inflammatory bowel disease (14) or autoimmunity against beta-cells (15). In addition, intestinal intolerance to food proteins has been associated with rheumatic diseases. In rheumatoid arthritis, antibodies against different nutritional proteins, including cow’s milk and soy proteins, have been detected in the jejunum (16). In our earlier work and in a recent British study on children suffering from gastrointestinal symptoms, JIA patients showed evidence of low-grade mucosal inflammatory activation more often than healthy controls (17-20). In our earlier investigations, we detected signs of inflammatory activation such as intestinal lymphonodular hyperplasia, increased expression of intraepithelial γδ+ T cells in the small intestine, cytotoxic lymphocytes in the duodenum and human

leukocyte antigen D-related expression in unexpected locations in the ileal mucosa (17-19). A similar alteration has been previously documented in the delayed-type food allergies (21-24).

In some case reports, elimination of cow's milk from the diet was claimed to improve the course of arthritis in JIA patients (25-27). In a recent British study (20), almost one third of the JIA cases with gastrointestinal symptoms exhibited eosinophilic gastrointestinal infiltrations. Such lesions are typically treated with a restriction diet including elimination of cow's milk (28). Therefore, our aim was to study whether there would be any association between CMA in infancy and the later appearance of JIA. Since antibiotics have been reported to be a risk factor for both JIA and CMA (7, 8), we also determined whether the link between CMA and JIA was associated with exposure to antibiotics.

METHODS

Data sources and study population

Data were obtained from three national registers and linked by the unique personal identity codes (including the date of birth and gender) that are assigned to all Finnish citizens shortly after birth or immigration (http://vrk.fi/en/personal-identity-code1). The cases with JIA and CMA were identified through the Special Reimbursement Register for drug costs maintained by the Social Insurance Institution (SII) of Finland (29, 30). The controls for children with JIA were sampled from the Population Register Center (http://vrk.fi/en/personal-data). Information on purchased hypoallergenic infant formula (soya infant formula included) and antibiotics was obtained from the Drug Purchase Register, which is also maintained by the SII. All hypoallergenic formulas and drugs prescribed by physicians and reimbursed by the National Sickness Insurance Scheme are registered

in the Drug Purchase Register, which has been in operation since 1994 (29). During the time of this study in Finland, hypoallergenic formulas (soya infant formula included) were sold only in pharmacies and antibiotics for outpatients were prescription-only and available exclusively through pharmacies.

Identification of patients with JIA

In brief, we identified all of the children born in Finland between 1st January 2000 and 31st December 2010, and who had received a special reimbursement for the cost of anti-rheumatic drugs, based on a diagnosis of JIA according to the *International Classification of Diseases,* Tenth Revision (ICD-10) code M08 by the end of December 2012. In Finland, patients with chronic diseases including JIA are entitled to a higher refund toward the costs of their medications (30). The International League of Associations for Rheumatology (ILAR) criteria for the diagnosis of JIA were used (31). The administrative process for decision-making by the SII takes a few weeks. In addition to the diagnosis of chronic diseases, register information includes the date of the special refund decision. The drug certificates are checked by a medical examiner, physician or pharmacist at SII before entitlement to a special refund can be granted. This particular date was used as a proxy indicator for the date of JIA diagnosis and is defined here as the index date for both the cases and their respective controls. In this article we have used the term “date of JIA diagnosis”. For each incident case, four eligible control children (with no special reimbursement for JIA) were randomly selected and individually matched according to date of birth (during the same quarter of the year), gender and municipality of residence at birth. In seven cases, fewer than four controls could be found. Thus, we identified 1,298 cases and 5,179 matched controls.

Identification of subjects with CMA

Infants who need hypoallergenic formulas in the management of CMA are entitled to special reimbursement. Before this is granted, the SII requires a pediatrician-signed certificate indicating that the diagnosis of CMA (ICD-10 codes K52.2 or L27.2) has been made according to the approved criteria. During the period of this data registration, the diagnostic criteria of CMA included a clinical examination with details of history, symptoms suggestive of CMA and an open elimination-challenge test for cow's milk (32). Special reimbursement applications and certificates for CMA are reviewed by a clinical specialist, in most cases by a pediatrician working in the local SII office. In our study population, the entitlement to a special refund for CMA was granted to 74 patients with JIA and to 197 control children but not all these subjects made regular purchases of hypoallergenic formula. In order to better ensure the accuracy of the incident cases with CMA, we also extracted information concerning all outpatient purchases of hypoallergenic formula from the Drug Purchase Register. When at least ten packages of hypoallergenic formula had been purchased for a child and she/he was entitled to reimbursement for CMA, then she/he was considered to have definite CMA. With this more stringent evaluation, 66 cases with JIA (5.1%) and 169 controls (3.3%) were judged to have CMA (Table 1). The link between CMA and JIA was re-evaluated separately in three groups according to the age of diagnosis of JIA: very early onset arthritis at <3 years, at 3–6 years and >6 years, because the JIA incidence peak can be found at less than three years of age (33, 34). In addition, an age of >6 years is a part of the criteria for diagnosis of enthesitis-related arthritis category of JIA. Its pathogenesis has been proposed to be triggered by intestinal mucosal factors (35, 36).

Relation between exposure to infant formula and later diagnosis of JIA

Since it has been reported that consumption of hypoallergenic formula could modify intestinal mucosal flora (37), we evaluated whether the risk of JIA increased with an increasing volume of consumed hypoallergenic formula (in liters). Data were obtained from the Drug Purchase Register,

which provides also individual information on the total volume of purchased hypoallergenic formulas. In total, 15,430 liters of formula were purchased for the cases and 38,164 liters for the controls until the age of 23 and 21 months, respectively. The median of the volumes was 185 liters (range 30–1200) for JIA cases and 224 liters (range 30–980) for controls (Table 1). For those with no purchases of hypoallergenic formula, the volume was set to zero.

Covariate analysis of the association between CMA and JIA

Based on previous studies (7, 8), we suspected that early or repeated exposure to antibiotics could be a covariate of the association between CMA and JIA. Therefore, we extracted information on all antibiotics (Anatomical Therapeutic Chemical code J01, antibacterials for systemic use) purchased for the outpatients from birth until the date of JIA diagnosis and the corresponding index date of the controls. The use of antibiotics was classified into two groups: no purchases versus ≥1 purchase of any antibiotic.

Statistics

The data consisted of individually matched sets with one case and four controls. The difference in proportion was tested with the binomial standardized normal deviate test. We evaluated the associations between exposure to formula usage for CMA and diagnosis of JIA using univariate conditional logistic regression analysis. To test the relationship between CMA and exposure to antibiotics, a new four-class variable was created. The reference category was no CMA and no antibiotics purchased until the diagnosis of JIA and the highest rank was CMA and at least one antibiotic purchase prior to the diagnosis of JIA (Web Figure 1). A multivariate conditional regression analysis was performed to investigate the relation of CMA in infancy to the later development of JIA after adjustment for exposure to antibiotics. To evaluate the presence and importance of the main symptoms of CMA in the gastrointestinal tract or in the skin, only those

matched sets in which either a child with JIA or at least one control child had CMA were included in the conditional logistic regression analysis. The strengths of the associations were quantified using matched odds ratios (OR) with 95% confidence intervals (95% CI). The additive interaction between CMA and antibiotics for JIA was evaluated via three measurements: relative excess risk due to interaction (RERI), the attributable proportion due to interaction (AP) and the ratio between the combined effect and individual effects, i.e. synergy index (S) (38, 39). In the absence of additive interactions, RERI=0, AP=0 and S=1. Statistical analyses were performed with IBM SPSS Statistics for Windows, Version 22.0.0 (Armonk, NY: IBM Corp, USA) and Stata/IC 13.1 for Windows (College Station, TX: StataCorp LP, USA).

Ethical considerations

Ethical approval was not necessary, since we used only encrypted register data and did not contact the unidentifiable study subjects.

RESULTS

We analyzed a total of 1,298 children with JIA and 5,179 matched control children. The median age at the diagnosis of JIA was 3.8 years (range 0.7 to 12.9 years) and 37% of the cases were boys (Table 1). In Finland during the years 2010-2012, 332 girls and 213 boys in the age group of <11 years contracted JIA. Thus, during those three years by the age of 11, the mean annual incidence of JIA for girls was 34/100,000 and for boys 21/100,000.

The total frequency of CMA among all study subjects was 235 (66 with JIA and 169 in controls) per 6,477. By the age of one, the cumulative incidence of CMA in our control cohort was 3.0%; by

the age of two, it was 3.3%. All CMA diagnoses were made before the possible diagnosis of JIA and also before the corresponding index date of the controls. The median age at the diagnosis of JIA in those who also had CMA was 4.6 years (range 1.3 to 12.6 years) and slightly more (56%) of the cases with both CMA and JIA were boys. In children with JIA, CMA was more common in boys than in girls (7.8% vs. 3.5%; *P*=0.001) (Table 1). Among those boys with CMA in infancy, there was a statistically significant risk of the development of JIA (OR = 2.4, 95% CI: 1.6, 3.6) (Web Figure 1). This association was not evident in girls (OR = 1.1, 95% CI: 0.7, 1.7). Additionally, every 10-liter purchase of hypoallergenic formula increased the risk of JIA by 2% in boys (OR = 1.02, 95% CI: 1.01, 1.03), but there was no similar increase in the JIA risk in girls.

CMA was a risk factor for the development of JIA, particularly in those boys who were diagnosed with JIA before the age of three (OR = 3.8, 95% CI: 1.9, 7.6) (Table 2.). Adjustment for antibiotic exposure reduced the risk only marginally (OR = 3.5, 95% CI: 1.6, 6.8). At age more than six years, the odds ratio of 2.2 (95% CI: 1.0, 4.8) for JIA was nearly significant only in boys (Table 2). Among boys, those with CMA with mainly a gastrointestinal manifestation displayed a higher risk of developing JIA than those with predominantly a skin manifestation (OR = 4.4, 95% CI: 1.9, 9.9 vs. OR = 1.8, 95% CI: 1.1, 3.0) (Web Figure 1).

Overall, the data comprised 8,559 purchases of antibiotics for cases and 27,374 for controls prior to the diagnosis of JIA. The mean number of purchases of antibiotics was 6.6 (range 0–81) for cases and 5.3 (range 0–52) for controls (Table 1). Among boys, the risk of JIA was highest when both CMA and antibiotic exposure were present (OR = 4.0, 95% CI: 2.3, 6.9) (Web Figure 1). The effect of antibiotic exposure alone increased the odds of subsequently contracting JIA by 1.7 fold in boys (95% CI: 1.2, 2.5) and by 1.5 fold in girls (95% CI: 1.2, 1.9) (Web Figure 1).

Furthermore, in boys, there was a positive but not statistically significant additive interaction between CMA and exposure to antibiotics before the diagnosis of JIA (RERI = 2.2, AP = 0.6, S = 3.8) (Table 3). Almost none of the additive effect could be attributed to the impact of CMA alone (4%), 23% was due to the effect of antibiotics alone and the remaining 73% was estimated as an interaction between CMA and antibiotic use (Table 3).

DISCUSSION

This register-based case-control study provides data on the risk of children suffering from CMA at infancy developing JIA. CMA preceded the diagnosis of JIA more than twice as often in boys than in girls. Boys with CMA had more than a doubling of their risk of developing JIA when compared to boys without CMA. The risk was most evident in those boys with CMA who developed JIA before the age of three. Boys with CMA manifesting with gastrointestinal symptoms showed a higher risk of developing JIA than those with predominantly skin symptoms. In boys, CMA and antibiotic exposure together quadrupled the risk of developing JIA when compared with the absence of both of those exposures. There was no interaction between CMA and antibiotic exposure in the development of JIA on either an additive or multiplicative scale.

Exposure to antibiotics in boys suffering from CMA potentiated the risk of developing JIA. In our previous study in the same study population, we found that both early and overall exposure to any antibiotic was associated with an increased risk of developing JIA (7). In this current study, this association was found to be more evident in boys. Antibiotics have also been reported to be a risk factor for developing CMA in a large Finnish population-based study (6). Previous reports (7, 8) and our current investigation support the proposal that in a subgroup of individuals with JIA and in

CMA, environmental factors may modify the development of mucosal tolerance and trigger the development of these diseases. This hypothesis was supported by the findings that peripheral tolerance was not only needed to outgrow CMA (40), but also to control autoreactive T cells in rheumatic diseases (41). In our earlier study which examined intestinal immune regulation in JIA (17), it was observed that patients in clinical remission displayed higher expressions of mucosal anti-inflammatory mediators in ileal biopsies than patients with an active disease.

Earlier reports support the findings emerging from our current study. The cumulative incidence of CMA in the control group was at about the same level in our study population as that reported previously (3.3% vs. 2.2–2.8%) using the open elimination-challenge test for the diagnosis of CMA (42-44). In our control group, CMA was slightly more frequent among boys (3.5%) than girls (3.1%). The male-female-ratio for the prevalence of CMA has also deviated toward males in European (45), but not in North American, epidemiological studies (46). The annual incidence of JIA in this study and with the current identification method for the cases during the study period 2000–2007 (47) were rather similar to those (21–22/100,000) of an earlier register-based study (33). This study also detected the same sex disparity in the appearance of JIA (63% girls) as in an earlier study (33). Our study results are most likely not biased because there was a similar data collection protocol for both patients and controls. We identified JIA cases through the Special Reimbursement Register for drug purchases, therefore it is possible that some JIA cases with limited symptoms have been missed. However, this should not interfere with the validity of our case-control setting. One could also hypothesize that the current association has been overestimated i.e. a child may be more likely to be referred to a pediatric rheumatologist by a pediatric allergist or vice versa. This is unlikely since all CMA diagnosis were made before the diagnosis of JIA. In addition, children's attendance rates to the cost-free Finnish healthcare system are high. Therefore, we consider that Berkson's bias has not exerted any meaningful effect on the current association.

Because of the limitation of attaining more specific data, the current association could not be compared with the clinical course of JIA or JIA categories (persistent and extended oligoarthritis, seronegative and seropositive polyarthritis, systemic arthritis, enthesitis-related arthritis, psoriatic arthritis and undifferentiated arthritis). Since CMA conferred a higher risk in boys than girls for subsequently contracting JIA, we considered the role of different gender distributions in the JIA categories. It is known that the enthesitis-related arthritis category of JIA is more prevalent in boys; in fact one of the criteria for this category is being a boy and contracting JIA at more than six years of age (31). Here, in boys over six years, CMA in infancy caused only a nearly significant and marginally increased risk of developing JIA, instead the risk was strongest in boys who contracted JIA before age of three (Table 2). Thus, the current gender-dependent association cannot be explained by a link between intestinal immune alterations, CMA and the enthesitis-related arthritis category (14, 35, 36). In Scandinavian countries, low maternal socioeconomic status has been associated with a lower incidence of CMA, but this kind of association has not been documented with JIA (48, 49). Our protocol did not gather data about the socioeconomic status, but cases and controls were matched by place of birth to diminish its potential confounding effect and the effect of local differences in treatment practices. Another limitation is that during the study period, the non-blinded elimination-challenge test was used for diagnosing CMA. In the future, the current epidemiological risk should be studied in a more comprehensive protocol, and it should combine register data with socioeconomic and clinical information from hospital and outpatient registers. It is most likely that this kind of information would support attempts to upgrade the classification system for JIA, which has been criticized since it is still lacking categories for some JIA phenotypes (50, 51).

In the current study, the purchase of a greater volume of hydrolyzed formula was associated with a greater risk of developing JIA. This relationship may be indirect e.g. related to: 1) other environmental factors such as breastfeeding, 2) the effect of the constitution of the hypoallergenic formula on the colonization by intestinal flora, and 3) delay in the challenge with other nutrients (52). 1) Long-term breastfeeding supports the maturation of the intestinal mucosal immune system but its protective effect on the development of JIA is inconsistent (2). Recent Finnish studies have revealed a median duration of exclusive breastfeeding of 1.8 months and total breastfeeding of seven months (53, 54). Unfortunately, the data for breastfeeding rate and duration was not available here. 2) Hydrolyzed formula deprived of lactose has been claimed to reduce the abundance of lactase producing bacteria (37). A trend towards the low representation of lactic acid producing bacteria was found in JIA patients as compared with controls (12). 3) CMA may also affect nutrition after the lactation period. It is known that at least immunoglobulin E-mediated CMA may postpone the challenge to other food proteins beyond the optimal period (55). A delay in the introduction of solid foods may predispose to later food allergies (53) and altered development of peripheral tolerance (3).

This epidemiological case-control study revealed that the appearance of JIA was associated with previous CMA and exposure to antibiotics in boys. Based on these results, it seems that boys and girls exhibit somewhat different risk factors for developing JIA. In the future, studies confirming the gender-dependent associations between CMA with JIA are warranted. In conclusion, earlier studies (14, 15) together with our current findings, link CMA and the risk of developing autoimmunity manifestations. This is evidence supporting the role of mucosal immunity in the pathogenesis of autoimmune diseases.

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Table 1. Characteristics of Children Born Between 2000 and 2010 and Diagnosed Between 2000 and 2012 with Juvenile Idiopathic Arthritis in Finland and their Age-, Gender- and Place of Birth-matched Control Children [a]. Every Case had 1-4 Controls.

Gender and characteristics	JIA			Matched controls		
	No.	%	median (range)	No.	%	median (range)
Boys	476	37		1,903	37	
Age in years at JIA diagnosis			4 (1-13)			4 (1-12)
At least one antibiotic purchase from birth to diagnosis of JIA	441	93	7[b] (0–81)	1,669	88	6[b] (0–42)
At least one antibiotic purchase from birth to the diagnosis of CMA and before the diagnosis of JIA	262	55	1[b] (0–11)	935	49	1[b] (0–11)
Boys with CMA[c]	37	8		66	3	
Age in months at the CMA diagnosis			6 (1–19)			6 (0.6–21)
Time in years from CMA to JIA			3 (0.3–10)			4 (0.7–11)
Volume of hypoallergenic formulas purchased in liters per child			201 (32–1,046)			226 (42–873)
Matched sets in which either a boy with JIA or at least one control boy had CMA						
Number of boys in sets	93			372		
Main symptoms of CMA in the skin	25	27		55	15	
Main symptoms of CMA in the gastrointestinal tract	12	13		11	3	
Girls	822	63		3,276	63	
Age in years at JIA diagnosis			4 (0.7-13)			4 (0.8-13)

At least one antibiotic purchase from birth to diagnosis of JIA	717	87	6[b] (0–50)	2,702	83	5[b] (0–52)
At least one antibiotic purchase from birth to the diagnosis of CMA and before the diagnosis of JIA	382	47	1[b] (0–8)	1,407	43	1[b] (0–18)
Girls with CMA[c]	29	4		103	3	
Age in months at the CMA diagnosis			7 (0.7–15)			6 (0.5–20)
Time in years from CMA to JIA			4 (0.4–12)			4 (0.1–12)
Volume of hypoallergenic formulas purchased in liters per child			168 (30–1,200)			223 (30–980)
Matched sets in which either a girl with JIA or at least one control girl had CMA						
Number of girls in sets	121			479		
Main symptoms of CMA in the skin	17	14		69	14	
Main symptoms of CMA in the gastrointestinal tract	12	10		34	7	
All children	1,298			5,179		
Age in years at JIA diagnosis			4 (0.7-13)			4 (0.8-13)
At least one antibiotic purchase from birth to diagnosis of JIA	1,158	89	7[b] (0–81)	4,371	84	5[b] (0–52)
At least one antibiotic purchase from birth to the diagnosis of CMA and before the diagnosis of JIA	644	50	1[b] (0–11)	2,342	45	1[b] (0–18)
Children with CMA						
Number of children with CMA[c]	66	5		169	3	
Boys	37	56		66	39	
Age in months at the CMA diagnosis			7 (0.7–19)			6 (0.5–21)
Time in years from CMA to JIA			4 (0.3–12)			4 (0.1–12)

Volume of hypoallergenic formulas purchased in liters per child		185 (30–1,200)			224 (30–980)
Matched sets in which either a child with JIA or at least one control child had CMA					
Number of children in sets	214			851	
Main symptoms of CMA in the skin	42	20		124	15
Main symptoms of CMA in the gastrointestinal tract	24	11		45	5

Abbreviations: CMA, cow's milk allergy; ICD-10, International Classification of Diseases, Tenth Revision; JIA, juvenile idiopathic arthritis

[a] Data of ethnic groups distribution is not provided, but the number of people born outside the country is one of the lowest in Europe, no more than 5% of the whole population in 2010 (56)

[b] Number of antibiotic courses purchased is presented in mean (range)

[c] ICD-10 codes K52.2 and L27.2 and at least 10 packages purchased

Table 2. Matched Odds Ratios and Antibiotic Purchase Adjusted Odds Ratios with 95% Confidence Intervals for the Contribution of Cow's Milk Allergy to Juvenile Idiopathic Arthritis. Matched Odds Ratios are Shown Separately for Boys and Girls by Different Age Groups According to the Diagnosis of Juvenile Idiopathic Arthritis.

Gender and study groups	No.	No. of CMA	Matched OR	95% CI	*P*-value[a]	Matched adjusted OR[b]	95% CI	*P*-value[a]
Boys	2,379							
JIA	476	37						
Controls	1,903	66						
Age in years at JIA diagnosis								
< 3 years		16	3.8	1.9, 7.6	< 0.001	3.5	1.6, 6.8	0.001
		18						
3–5.9 years		11	1.6	0.8, 3.4	0.194	1.6	0.8, 3.3	0.218
		29						
≥ 6 years		10	2.2	1.0, 4.8	0.053	2.2	1.0, 4.8	0.052
		19						
Girls	4,098							
JIA	822	29						
Controls	3,276	103						
Age in years at JIA diagnosis								
< 3 years		10	1.1	0.5, 2.3	0.764	1.1	0.5, 2.2	0.871
		36						
3–5.9 years		9	0.8	0.4, 1.6	0.503	0.8	0.4, 1.6	0.452
		45						
≥ 6 years		10	1.7	0.8, 3.7	0.169	1.6	0.8, 3.5	0.201
		22						

Abbreviations: CI, confidence interval; CMA, cow's milk allergy; JIA, juvenile idiopathic arthritis; OR, odds ratio

[a] Conditional logistic regression

[b] Odds ratio of CMA has been adjusted for at least one antibiotic purchase before the diagnosis of JIA/index date

Table 3. Multiplicative and Additive Estimates of Interaction between Cow's Milk Allergy[a] (CMA) and at Least One Antibiotic Purchase on the Prevalence of Juvenile Idiopathic Arthritis (JIA). Only Antibiotic Purchases During the Time Between the Diagnosis of CMA and Before the Diagnosis of JIA and Respectively Before the Corresponding Index Date of the Controls Are Counted.

Gender and Measures of Interaction	Estimate value	95% CI	*P*-value
Boys			
Multiplicative interaction	2.1	0.2, 18.8	0.503
Additive interaction,			
RERI	2.2	-0.7, 5.1	0.138
AP	0.6	-0.1, 1.2	0.084
S	3.8	0.2, 83	0.402
Girls			
Multiplicative interaction	0.6	0.1, 2.2	0.405
Additive interaction			
RERI	-0.8	-3.3, 1.8	0.545
AP	-0.5	-2.2, 1.2	0.559
S	0.4	0.04, 3.7	0.426

Abbreviations: AP, attributable proportion; CI, confidence interval; CMA, cow's milk allergy; ICD-10, International Classification of Diseases; JIA, juvenile idiopathic arthritis; OR, odds ratio; RERI, relative excess risk of interaction; S, synergy index

[a] CMA, ICD-10 codes K52.2 and L27.2 and at least 10 packages purchased

Web Figure 1. Matched odds ratios (OR) for juvenile idiopathic arthritis (JIA) in boys and girls according to cow's milk allergy (CMA), exposure to hypoallergenic formulas and to any antibiotic from birth to the diagnosis of JIA (or to the index date of the controls) and combinations of these parameters. The reference category for conditional logistic regression analysis was no CMA or no purchase of antibiotics. Bars, 95% confidence intervals (CI).