

Mother's and Offspring's Use of Antibiotics and Infant Allergy to Cow's Milk

Johanna Metsälä,^{a,b} Annamari Lundqvist,^c Lauri J. Virta,^d Minna Kaila,^e Mika Gissler,^{f,g}
and Suvi M. Virtanen^{a,b,h}

Background: Evidence on the association between antibiotics and the risk of food allergies is limited. We explored the associations between mother's and offspring's use of antibiotics and the risk of cow's milk allergy in infancy.

Methods: We used a national registry to identify all children who were born in 1996–2004 in Finland and diagnosed with cow's milk allergy after 1 month of age by November 2005 ($n = 15,672$). For each case, we selected one control matched for birth date, sex, and hospital district. Information on antibiotic purchases and putative confounders was obtained from registries. The associations were analyzed using conditional logistic regression.

Results: Maternal use of antibiotics before and during pregnancy was associated with an increased risk of cow's milk allergy in the offspring (odds ratio = 1.26 [95% confidence interval = 1.20–1.33] and 1.21 [1.14–1.28], respectively, adjusting for putative confounders). The risk of cow's milk allergy increased with increasing number of child's antibiotics used from birth to diagnosis (test for trend $P < 0.001$).

Conclusions: Both maternal and child's use of antibiotics were associated with an increased risk of cow's milk allergy. Future studies are needed to confirm these novel findings and to explore the potential biologic mechanisms behind the association.

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Cow's milk allergy is a common food allergy in infancy, with a cumulative incidence of 2%–3% in the first year of life.¹ Food allergies have a major impact on healthcare costs

and quality of life of caregivers of affected children.^{2,3} Information about causes of food allergies, including cow's milk allergy, remains limited, but both genetic and environmental factors are likely to play a role.⁴ As modifiable risk factors for cow's milk allergy or any food allergy are not well-known, effective measures for primary prevention are yet to be discovered.⁵ Accumulating evidence suggests that gut microbiota plays an important role in the maturation and development of the immune system and oral tolerance.⁶ Thus, factors disrupting the gut microbiota, such as antibiotics, may influence the development of food allergies. Owing to the possible long-term adverse effects of antibiotics, even maternal use of antibiotics before and during pregnancy may play a role.⁷ As far as we know, only one study has explored the association between exposure to antibiotics and the risk of food allergy. Eggesbø and colleagues⁸ did not observe associations between maternal or child's use of antibiotics and the risk of egg allergy in the child. Several studies have explored the association between child's use of antibiotics and the risk of asthma and other allergic diseases in childhood (such as eczema, atopic dermatitis, hay fever, and allergic rhinitis), but the evidence is inconsistent.^{9–14} Maternal use of antibiotics has received much less attention.^{15–20} Because antibiotics are commonly and often inappropriately used for upper respiratory tract infections,²¹ the putative association between exposure to antibiotics and the risk of food allergies could have great public health impact. We explore whether a mother's and child's use of antibiotics is associated with cow's milk allergy in infancy in a population-based nested case-control study.

METHODS

Data Sources

Data were obtained from four national registers and linked by the unique personal identity codes that are assigned to all Finnish citizens shortly after birth or immigration.²² We used the Special Reimbursement Register²³ and the Population Register maintained by the Social Insurance Institution to select cases and controls, respectively. Information on purchased antibiotics and special infant formulas (ie, special soy-based formulas, extensively hydrolyzed formulas, or elemental formulas) was obtained from the Drug Prescription Register²³ maintained by the Social Insurance Institution. All drugs and special infant formulas prescribed by physicians

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From the ^aDepartment of Lifestyle and Participation, National Institute for Health and Welfare, Helsinki, Finland; ^bTampere School of Public Health, University of Tampere, Tampere, Finland; ^cDepartment of Health, Functional Capacity and Welfare, National Institute for Health and Welfare, Helsinki, Finland; ^dResearch Department, Social Insurance Institution, Turku, Finland; ^ePediatric Research Centre, Tampere University Hospital and University of Tampere, Finland; ^fDepartment of Information, National Institute for Health and Welfare, Helsinki, Finland; ^gNordic School of Public Health, Gothenburg, Sweden; and ^hResearch Unit, Tampere University Hospital, Tampere, Finland.

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Correspondence: Johanna Metsälä, Department of Lifestyle and Participation/Nutrition Unit, National Institution for Health and Welfare, P.O. Box 30, FI-00271 Helsinki, Finland. E-mail: johanna.metsala@thl.fi.

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and reimbursed by the National Sickness Insurance Scheme are registered in the Drug Prescription Register maintained since 1994. In Finland, both special infant formulas and outpatient antibiotics are available only by prescription and are sold only in pharmacies. The Drug Prescription Register includes information on drug class (Anatomical Therapeutic Chemical [ATC] Classification System)²⁴ and dispensing date of the prescription. We derived information on maternal background and perinatal factors from the Finnish Medical Birth Register,²⁵ currently maintained by the National Institute for Health and Welfare.

Study Population

We identified all infants who were born between 1 January 1996, and 30 April 2004, and we had received a special reimbursement for the cost of special infant formulas, based on diagnosed cow's milk allergy with ICD-10 codes L27.2 or K52.2, by the end of November 2005 ($n = 19,111$). In Finland, infants who need special infant formulas in the management of diagnosed cow's milk allergy are entitled to this special reimbursement up to 2 years of age.²⁶ The Medical Birth Register data were not available for children who were not born in Finland; these children were excluded ($n = 266$ case-control pairs). For strict definition of cow's milk allergy, we excluded from the cohort infants with a special reimbursement of short duration (<6 months, $n = 72$) or with two or fewer purchases of special infant formulas ($n = 2,351$), or both ($n = 185$). For each case, one control infant with no special reimbursement for cow's milk allergy was randomly selected and matched for date of birth (± 28 days), sex, and the hospital district of birth (20 districts). Controls were allowed to be selected only once and twins from the same family as case-control pairs were not allowed. There were 16,237 case-control pairs available for analysis, with a cumulative incidence of 3.4% for cow's milk allergy by the age of 2 years.

Diagnosis of Cow's Milk Allergy

To grant the special reimbursement, the Social Insurance Institution requires a specific pediatrician certificate stating that the diagnosis of cow's milk allergy was made according to specified criteria. The criteria included clinical examination with a careful history, symptoms suggestive of cow's milk allergy, and disappearance of symptoms when cow's milk was eliminated from the diet. Furthermore, a positive skin-prick test, elevated serum-specific IgE, or an open-challenge test performed in the hospital's inpatient or outpatient unit were required. In most cases, final confirmation was based on an open-challenge test.²⁷ Finally, all special reimbursement applications and certificates are reviewed by a clinical specialist, in most cases by a pediatrician, at the Social Insurance Institution.

Antibiotic Exposure

To evaluate maternal use of antibiotics, we extracted information on all antibiotics (ATC code J01, antibacterials for systemic use) purchased by the mother 1 year preceding

pregnancy and during pregnancy. Start of pregnancy was calculated from the date of birth and gestational age of the child as obtained from the Medical Birth Register. In the absence of information on gestational age ($n = 121$, 0.7%), we assumed gestation was 280 days. Maternal use of antibiotics was categorized as any use of any antibiotics (0 vs. ≥ 1 purchases), number of purchases of any antibiotics (0, 1, 2, ≥ 3 purchases), and any use (0 vs. ≥ 1 purchases) of the most common antibiotics, that is, cephalosporins (ATC code J01DB-DC), penicillins with extended spectrum (J01CA), macrolides (J01FA), tetracyclines (J01AA), phenoxymethylpenicillin (J01CE02), combinations of sulphonamides and trimethoprim (J01EA-EE), and fluoroquinolones (J01MA).

To evaluate child's use of antibiotics, we extracted information on all antibiotics (ATC code J01, antibacterials for systemic use) purchased for the child from birth until the date of cow's milk allergy diagnosis of the case. Antibiotics purchased during 1 month before diagnosis were excluded to reduce reverse causation attributable to antibiotics prescribed during the diagnosis process. There were 565 infants excluded on this basis (ie, diagnosed at younger than 1 month of age), leaving 15,672 cases for analysis. As for mothers, the child's use of antibiotics was categorized as overall use (0 vs. ≥ 1 purchases) of any antibiotics, number of purchases (0, 1, 2, 3, 4, ≥ 5 purchases) of any antibiotics, and overall use (0 vs. ≥ 1 purchases) of most commonly used specific antibiotics, that is, amoxicillin (including its combination with enzyme inhibitor, ATC codes J01CA04 and J01CR02), macrolides (J01FA), cephalosporins (J01DB-DC), combinations of sulphonamides and trimethoprim (J01EA-EE), and phenoxymethylpenicillin (J01CE02).

Maternal Background and Perinatal Factors

Maternal background and perinatal variables included maternal age (<25 , 25–29, 30–34, ≥ 35 years), smoking during pregnancy (no/yes), socioeconomic status based on maternal occupation (upper white-collar workers; lower white-collar workers; blue-collar workers; and “others,” including farmers, entrepreneurs, retired, unemployed, students, and housewives), previous deliveries (0, 1, ≥ 2), multiple pregnancies (no/yes), mode of delivery (vaginal, assisted vaginal, planned, and unplanned cesarean section), and child's birth weight (grams, quintiles). More detailed information on these background and perinatal variables and their associations with cow's milk allergy have been published previously.²⁸

Statistical Analysis

Differences in maternal background and perinatal factors between cases and controls were analyzed using Pearson chi-square test for categorical variables and Mann-Whitney U test for continuous variables. We used logistic regression analysis to assess possible associations between maternal background and perinatal factors and the use of antibiotics before and during pregnancy among control mothers, and from birth until

the date of cow's milk allergy diagnosis of the case among control children. The association between maternal and child's use of antibiotics and the risk of cow's milk allergy was analyzed by conditional logistic regression and the results are displayed as odds ratios (ORs) with 95% confidence intervals (95% CIs).

As putative confounding factors in the adjusted models, we included those maternal background and perinatal factors earlier shown to be associated with cow's milk allergy²⁸ and in the present study with the use of antibiotics ($P < 0.3$; Table 2). For maternal use of antibiotics, the main adjusted model included maternal age, socioeconomic status, smoking during pregnancy, previous deliveries, multiple pregnancies, and child's use of antibiotics. Further adjustment was made for maternal use of antibiotics preceding or during pregnancy (when appropriate). For child's use of antibiotics, the main adjusted model included maternal age, smoking during pregnancy, previous deliveries, mode of delivery, and child's birth weight. Further adjustment was made for maternal use of antibiotics preceding and during pregnancy. As these further adjustments only slightly attenuated the results, we presented results only from the unadjusted and the main adjusted models.

To take into account the nonindependency of siblings in the cohort, all main analyses were repeated in a cohort including only one (the first) child per mother. Results did not change substantially.

All analyses were performed using STATA, version 9.1 software (StataCorp LP, College Station, Texas). This study was approved by the National Data Protection Authority, the institutions keeping the registers and the Institutional Review Board of the National Public Health Institute (National Institute for Health and Welfare since 2009).

RESULTS

Our study identified 16,237 cases (9547 boys and 6690 girls, mean age at receiving a special reimbursement = 6 months and standard deviation = 3.7 months) with cow's milk allergy and 16,237 matched controls. Maternal smoking during pregnancy and higher number of previous deliveries were less common and birth by cesarean section was more common among cases than controls (Table 1).

Maternal Use of Antibiotics

One-third (35%) of the control mothers had used antibiotics 1 year preceding pregnancy, 24% during pregnancy, and 12% during both periods. Maternal smoking, previous deliveries, and maternal use of antibiotics before pregnancy were associated with an increased use of antibiotics during pregnancy (Table 2). Similar associations were observed between maternal background factors and use of antibiotics before pregnancy (data not shown).

Overall use of antibiotics before pregnancy was associated with an increased risk of cow's milk allergy in the

TABLE 1. Distribution of Selected Maternal Background and Perinatal Factors Among Cases and Controls Born in 1996–2004 in Finland

Factors	Cases (n = 16,237)	Controls (n = 16,237)
Maternal factors		
Age (years); mean (SD)	29.9 (5.0)	29.3 (5.5)
Smoking during pregnancy; No. (%)		
No	14,287 (90)	13,465 (85)
Yes ^a	1,557 (10)	2,371 (15)
Number of previous deliveries; No. (%)		
0	6,581 (41)	6,741 (42)
1	5,765 (36)	5,333 (33)
≥2	3,870 (24)	4,141 (26)
Child/perinatal factors		
Sex; No. (%)		
Girl	6,690 (41)	6,690 (41)
Boy	9,547 (59)	9,547 (59)
Mode of delivery; No. (%)		
Vaginal delivery ^b	13,213 (82)	13,587 (84)
Cesarean section ^c	2,996 (19)	2,623 (16)
Gestational age (weeks); mean (SD)	39.3 (1.8)	39.3 (1.8)
Birth weight (g); mean (SD)	3,569 (562)	3,538 (566)

^aIncluding those who quit smoking during first trimester (n = 256 for cases, n = 331 for controls).

^bIncluding normal vaginal delivery (n = 12,119 for cases, n = 12,582 for controls) and assisted vaginal delivery (n = 1,094 for cases, n = 1,005 for controls).

^cIncluding planned cesarean section (n = 1,411 for cases, n = 1,210 for controls) and unplanned cesarean section (n = 1,585 for cases, n = 1,413 for controls).

SD indicates standard deviation.

offspring after adjustment for the confounders (OR = 1.26 [95% CI = 1.20–1.33]; Table 3). In addition, the risk of cow's milk allergy increased with increasing number of antibiotic purchases (Fig. 1). Maternal use of cephalosporins (1.29 [1.20–1.39]), macrolides (1.26 [1.15–1.38]), tetracyclines (1.25 [1.14–1.37]), and penicillins with extended spectrum (1.16 [1.06–1.26]) were associated with an increased risk of cow's milk allergy after adjustment for the confounders (Table 3).

Overall use of antibiotics during pregnancy was associated with an increased risk of cow's milk allergy in the offspring (1.21 [1.14–1.28]; Table 3), and the risk increased with increasing number of antibiotic purchases (Fig. 1). Maternal use of cephalosporins (1.27 [1.17–1.38]), macrolides (1.32 [1.15–1.51]), and penicillins with extended spectrum (1.14 [1.06–1.23]) during pregnancy were associated with an increased risk of cow's milk allergy (Table 3).

Child's Use of Antibiotics

One-fifth (21%) of cases and 15% of control children had used antibiotics during the period from birth to 1 month before the diagnosis of the case. Maternal age, previous deliveries, and use of antibiotics, as well as male sex and heavier birth weight of the child were directly associated with the use

TABLE 2. Associations Between Maternal Background and Perinatal Factors and the Use of Antibiotics by the Control Mothers During Pregnancy and the Control Children in Infancy

	Maternal Overall Use ^a OR (95% CI)	Child's Overall Use ^b OR (95% CI)
Maternal age (years)		
≤24 ^c	1.00	1.00
25–29	0.96 (0.86–1.06)	1.07 (0.95–1.19)
30–34	1.04 (0.94–1.15)	1.03 (0.92–1.16)
35+	1.04 (0.92–1.17)	0.89 (0.78–1.01)
Maternal smoking		
No ^c	1.00	1.00
Yes	1.27 (1.15–1.40)	1.09 (0.98–1.22)
Maternal socioeconomic status		
Upper white-collar workers ^c	1.00	1.00
Lower white-collar workers	1.06 (0.95–1.18)	1.11 (0.98–1.25)
Blue-collar workers	1.11 (0.97–1.26)	1.09 (0.94–1.25)
Others ^d	1.12 (0.99–1.27)	1.10 (0.96–1.26)
Maternal previous deliveries		
0 ^c	1.00	1.00
1	1.27 (1.17–1.39)	1.68 (1.52–1.85)
2+	1.49 (1.36–1.62)	2.08 (1.88–2.30)
Multiple pregnancies		
No ^c	1.00	1.00
Yes	1.14 (0.94–1.39)	0.93 (0.75–1.17)
Mode of delivery		
Vaginal delivery ^c	NA ^e	1.00
Assisted vaginal delivery		0.71 (0.59–0.85)
Planned cesarean section		0.90 (0.77–1.05)
Unplanned cesarean section		0.96 (0.83–1.11)
Child's birth weight (g); quintiles		
<3,130 ^c	NA ^e	1.00
3,130–3,439		1.00 (0.92–1.14)
3,440–3,689		1.17 (1.03–1.33)
3,690–3,979		1.20 (1.06–1.37)
≥3,980		1.31 (1.15–1.48)
Child's sex		
Girl ^c	1.00	1.00
Boy	0.92 (0.86–0.99)	1.28 (1.18–1.39)
Maternal use of antibiotics during pregnancy		
No ^c		1.00
Yes		1.45 (1.33–1.58)
Maternal use of antibiotics before pregnancy		
No ^c	1.00	1.00
Yes	2.34 (2.17–2.51)	1.40 (1.29–1.51)

^aDuring pregnancy.^bBefore the date of the diagnosis of the case.^cReference category.^dIncluding farmers, entrepreneurs, retired, unemployed, students, and housewives.^eNot assessed; factor considered as a potential intermediate variable in the causal pathway of the association between maternal use of antibiotics and the risk of cow's milk allergy in the offspring.

of antibiotics among controls (Table 2). In addition, use of antibiotics was associated with mode of delivery (Table 2); compared with children born by normal vaginal delivery, use of antibiotics was less common among children born by assisted vaginal delivery and not associated with cesarean section.

Child's use of antibiotics was associated with an increased risk of cow's milk allergy after adjustment for the confounders (adjOR = 1.71 [95% CI = 1.59–1.84]; Table 3), and increased with number of antibiotic purchases (Fig. 2). All commonly used specific antibiotics were associated with an increased risk of cow's milk allergy, with the strongest association observed for cephalosporins (2.43 [2.14–2.77]; Table 4).

DISCUSSION

In this large, population-based study, both maternal use and child's use of antibiotics were associated with an increased risk of cow's milk allergy in infancy, in a dose-related manner. In addition, several commonly used specific antibiotics were associated with an increased risk of cow's milk allergy.

As far as we know, no previous studies have assessed the exposure to either maternal or child's use of antibiotics and the risk of cow's milk allergy, and only one study has used food allergy as the end point. Eggesbø and colleagues⁸ assessed the association of the mother's use of antibiotics during pregnancy and the child's use of antibiotics during the first 6 months of life with the development of egg allergy in the child by the age of 3 years and found no association. Increased risks of asthma,^{16,18,20} eczema,^{15–17} or hay fever¹⁶ in offspring exposed to maternal use of antibiotics during pregnancy have been observed in some studies, although a null association with asthma has also been reported.¹⁹ Large cohort studies assessing child's own use of antibiotics have also reported both increased risk^{9,13} and no risk^{9,11,12} of various allergic diseases in childhood. This inconsistency may be attributable to methodological differences in assessing the exposure, outcome, and potential confounders.

Research on putative biologic mechanisms for an association of antibiotics and cow's milk allergy is limited. Antibiotics have been suggested to affect the development of allergic diseases via their adverse and possible long-term effect⁷ on gut microbiota of both the mother and the child and vaginal microbiota of the mother. Antibiotic use may delay the early colonization of child's gut microbiota.²⁹ This delay may, in turn, interfere with the maturation of the child's immune system and development of oral tolerance, and thus play a role in the development of cow's milk allergy. In addition, there is accumulating evidence that environmental exposures during the prenatal period can modify gene expression and susceptibility to allergic diseases through epigenetic modification, although the capacity of antibiotics to induce epigenetic changes in gene expression has not been demonstrated.³⁰

Use of antibiotics might also be a proxy for infections. In particular, it has been argued that the reported associations between postnatal antibiotics and asthma may be explained by

TABLE 3. Maternal Use of Antibiotics Before and During Pregnancy and the Risk of Cow's Milk Allergy in Offspring Born in 1996–2004 in Finland and Diagnosed with Cow's Milk Allergy by the End of November 2005

Type of Antibiotic ^a	Cases (n = 15,672) No. (%)	Controls (n = 15,672) No. (%)	Unadjusted Model OR (95% CI)	Adjusted Model ^b OR (95% CI)
Before pregnancy				
Any antibiotic	6,435 (41)	5,553 (35)	1.27 (1.22–1.33)	1.26 (1.20–1.33)
Cephalosporins	2,538 (16)	2,075 (13)	1.27 (1.19–1.35)	1.29 (1.20–1.39)
Penicillins with extended spectrum	1,840 (12)	1,599 (10)	1.17 (1.09–1.26)	1.16 (1.06–1.26)
Macrolides	1,660 (11)	1,306 (8)	1.31 (1.21–1.41)	1.26 (1.15–1.38)
Tetracyclines	1,557 (10)	1,246 (8)	1.28 (1.18–1.38)	1.25 (1.14–1.37)
Phenoxymethylpenicillin	578 (4)	509 (3)	1.14 (1.01–1.29)	1.14 (0.99–1.31)
Sulfonamides and trimethoprim	390 (3)	355 (2)	1.10 (0.95–1.28)	1.00 (0.84–1.18)
Fluoroquinolones	328 (2)	281 (2)	1.17 (1.00–1.37)	1.09 (0.91–1.32)
During pregnancy				
Any antibiotic	4,392 (28)	3,797 (24)	1.22 (1.16–1.28)	1.21 (1.14–1.28)
Cephalosporins	1,955 (13)	1,578 (10)	1.28 (1.19–1.37)	1.27 (1.17–1.38)
Penicillins with extended spectrum	2,203 (14)	1,953 (13)	1.15 (1.07–1.22)	1.14 (1.06–1.23)
Macrolides	685 (4)	509 (3)	1.37 (1.21–1.54)	1.32 (1.15–1.51)
Tetracyclines	111 (1)	121 (1)	0.92 (0.71–1.19)	0.97 (0.72–1.29)
Phenoxymethylpenicillin	292 (2)	262 (2)	1.12 (0.94–1.32)	1.04 (0.86–1.27)
Sulfonamides and trimethoprim	42 (<1)	43 (<1)	0.98 (0.64–1.49)	0.87 (0.51–1.47)
Fluoroquinolones	39 (<1)	24 (<1)	1.63 (0.98–2.70)	1.66 (0.92–3.01)

^aUse defined as at least one purchase during the exposure period.^bAdjusted for maternal age, socioeconomic status, smoking during pregnancy, previous deliveries, multiple pregnancies, and child's use of antibiotics.

confounding respiratory infections (for which the antibiotics were prescribed). However, the relationship between respiratory infections and subsequent development of asthma is controversial,³¹ and there is currently no evidence that infections would play a major role in the development of cow's milk allergy or any food allergy in early childhood. Whether certain infections contribute to the development of asthma and allergic diseases or whether these infections instead reflect susceptibility for these diseases in predisposed children remains to be answered. Moreover, the use of antibiotics is determined not only by the infection but also by complex variations in health-care-seeking behavior, which affect the opportunity to be seen by a physician and to receive an antibiotic prescription.^{32,33}

We observed an increased risk of cow's milk allergy with all specific antibiotics used by the child before the diagnosis, with cephalosporins showing the strongest association. Cephalosporins, macrolides, and penicillins with extended spectrum used by the mother both before and during pregnancy were associated with an increased risk of cow's milk allergy in the offspring. These associations may be explained by the adverse effect of these antibiotics on gut microbiota.³⁴

By using the Finnish unique personal identity codes, we were able to establish a large population-based database and to link comprehensive information from several population-based national registers. Another strength of the present study is the identification of cow's milk allergy cases through the

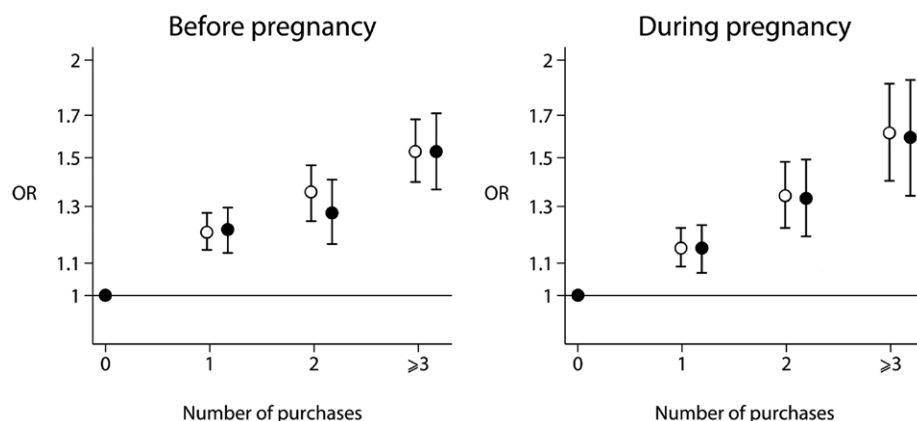


FIGURE 1. The association between number of maternal antibiotic purchases before and during pregnancy and the risk of cow's milk allergy in the offspring born in 1996–2004 in Finland. Data points are unadjusted (open circles) and adjusted (black circles) odds ratios with 95% confidence intervals (bars), on logarithmic scale; 0 purchases are used as the reference. The adjusted model includes maternal age, socioeconomic status, smoking during pregnancy, previous deliveries, multiple pregnancies, and child's use of antibiotics.

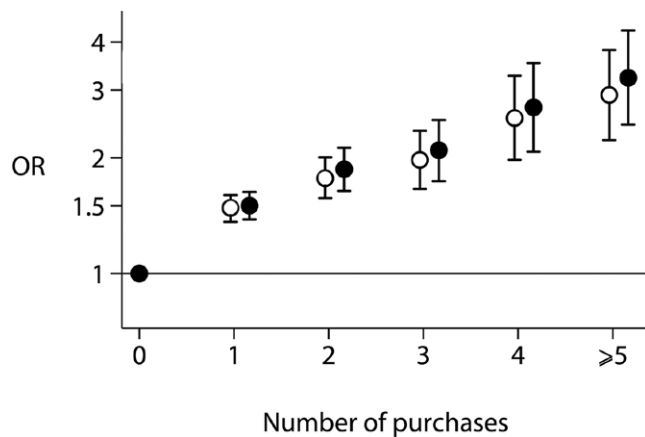


FIGURE 2. The association between number of antibiotic purchases from birth to diagnosis (excluding antibiotics purchased within 1 month before diagnosis) and the risk of cow's milk allergy in infants born in 1996–2004 in Finland. Data points are unadjusted (open circles) and adjusted (black circles) odds ratios with 95% confidence intervals (bars), on logarithmic scale; 0 purchases are used as the reference. The adjusted model includes maternal age, smoking during pregnancy, previous deliveries, mode of delivery, and child's birth weight.

Special Reimbursement Register, as the requirement for the special reimbursement was based on clinical diagnosis made by a pediatrician and further reviewed against diagnostic criteria by another clinician. Eligibility for the special reimbursement does not depend on family's socioeconomic

situation or area of residence in Finland. However, the slightly higher cumulative incidence of cow's milk allergy by the age of 2 years in our cohort (3.4%) compared with Finnish and international figures of cumulative cow's milk allergy incidence in infants by 1 year of age (approximately 2%–3%)^{1,35} suggests possible heterogeneity among the diagnostic procedures in our cohort. For example, some of the cases with severe reactions to cow's milk or of very young age could have received the special reimbursement without undergoing a challenge procedure. The number and impact of these cases are, however, likely to be small because this type of overdiagnosis would dilute the associations and bias the relative risks toward unity. Furthermore, we applied a strict case definition, which included diagnosis of cow's milk allergy, duration of the special reimbursement, and number of purchases of prescribed special infant formulas.

We did not have information on the indication for antibiotic prescription, antibiotics administered in hospitals, and factors presumably influencing the development of cow's milk allergy such as parental allergies and infant feeding (breast-feeding, bottle-feeding, and introduction of solid foods).⁴ Thus, residual confounding as an explanation of the observed results cannot be ruled out. In particular, breastfeeding may be of concern because it has been shown to be associated with both child's use of antibiotics^{36,37} and cow's milk allergy, although inconsistently so.³⁸ In a large Finnish birth cohort, the median durations of exclusive and total breastfeeding were 1.4 months and 7.0 months, respectively, and the proportion of

TABLE 4. Child's Use of Antibiotics from Birth to 1 Month Before Diagnosis and the Risk of Cow's Milk Allergy in Infants Born in 1996–2004 in Finland and Diagnosed with Cow's Milk Allergy by the End of November 2005

Type and Number of Antibiotic Purchases	Cases (n = 15,672) No. (%)	Controls (n = 15,672) No. (%)	Unadjusted Model OR (95% CI)	Adjusted Model ^a OR (95% CI)
Any antibiotic				
0	12,380 (79)	13,266 (85)	1.00	1.00
≥1	3,292 (21)	2,406 (15)	1.67 (1.56–1.78)	1.71 (1.59–1.84)
Amoxicillin				
0	13,483 (86)	13,922 (89)	1.00	1.00
≥1	2,189 (14)	1,750 (11)	1.37 (1.27–1.48)	1.39 (1.29–1.51)
Macrolides				
0	14,394 (92)	14,808 (94)	1.00	1.00
≥1	1,278 (8)	864 (6)	1.62 (1.47–1.79)	1.65 (1.49–1.82)
Cephalosporins				
0	14,753 (94)	15,238 (97)	1.00	1.00
≥1	919 (6)	434 (3)	2.30 (2.04–2.60)	2.43 (2.14–2.77)
Sulfonamides and trimethoprim				
0	15,468 (99)	15,545 (99)	1.00	1.00
≥1	204 (1)	127 (1)	1.62 (1.29–2.02)	1.60 (1.27–2.02)
Phenoxymethylpenicillin				
0	15,506 (99)	15,583 (99)	1.00	1.00
≥1	166 (1)	89 (1)	1.91 (1.47–2.48)	1.97 (1.50–2.58)

^aAdjusted for maternal age, smoking during pregnancy, previous deliveries, mode of delivery, and child's birth weight.

breastfed infants decreased from 95% at the age of 1 month to 58% at the age of 6 months.³⁹ Another limitation is our reliance on pharmacy records, which provides only a rough estimation of drug use. However, misclassification of subjects who failed to take their drugs as users dilutes the associations and biases the relative risks toward unity.

To clarify a possible role of antibiotics in the development of cow's milk allergy or other food allergies, future studies should take into account both maternal and child's use of antibiotics, indication for antibiotics, other factors possibly confounding and interacting with the effects of antibiotics, such as breastfeeding, and the complex variations in parental healthcare-seeking behavior. Further research is also needed on underlying biologic mechanisms, whereby maternal or child's use of antibiotics may influence the development of cow's milk allergy in infancy.

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