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Associations between pre- and postnatal antibiotic exposures and early allergic outcomes: A population-based birth cohort study

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Abstract

Background: Early life antibiotic treatment is one likely exposure influencing allergy risk. The objective was to investigate associations between pre- and postnatal antibiotic exposures and the development of allergic manifestations until age 18 months.

Methods: We included 1387 mother–child dyads from the prospective, population-based NorthPop birth cohort study. Data on antibiotic exposures in pregnancy and childhood were collected by web-based questionnaires. Until the child turned 18 months old, parents (n = 1219) reported symptoms of wheeze, eczema, and physician-diagnosed asthma; parents (n = 1025) reported physician-diagnosed food allergy. At age 18 months, serum immunoglobulin E levels to inhalant (Phadiatop) and food (Food mix fx5) allergens were determined. Associations were estimated using bivariable and multivariable logistic regressions.

Results: Prenatal antibiotic exposure was positively associated with food sensitization in the crude (OR 1.82, 95% CI 1.01–3.26) but not in the adjusted analyses (aOR 1.58, 0.82–3.05). A borderline significant association was found between prenatal exposure and wheeze (aOR 1.56, 0.95–2.57). Postnatal antibiotics were positively associated with wheeze (aOR 2.14, 1.47–3.11), asthma (aOR 2.35, 1.32–4.19), and eczema (aOR 1.49, 1.07–2.06). Postnatal antibiotics were negatively associated with food sensitization (aOR 0.46, 95% CI 0.25–0.83) but not with food allergy nor sensitization to inhalants.

Conclusion: Pre- and postnatal antibiotic exposure demonstrated positive associations with allergic manifestations and the former also with food sensitization. In contrast, there was a negative association between postnatal antibiotics and food sensitization. Food sensitization is often transient but may precede respiratory allergies. Future studies should investigate the relationship between antibiotic exposure and food sensitization later in childhood.

KEYWORDS
allergy, antibiotics, asthma, birth cohort, epidemiology, infancy, microbiome, pregnancy, sensitization

1 | INTRODUCTION

The environmental pressures driving the increase in the prevalence of allergic diseases are not fully understood.[1] Microbiota is critical in normal immune ontogeny, and the reduced microbial exposures associated with our modern lifestyle have been implicated in the "allergy epidemic".[2,3] Antibiotics, which alter both the adult and infant microbiota, are prescribed to every fifth pregnant woman[4] and are the most commonly prescribed medication to infants and children in the Western world.[5,6] Even brief treatments may cause dysbiosis[7] and in infants this means disruption of microbiota maturation with possible negative consequences for immune system development.[8,9] In murine models, vancomycin treatment in the pre- and postnatal periods affects gut microbiota composition, increases immunoglobulin E (IgE) levels, reduces regulatory T-cell populations, and increases the risk of developing allergic asthma.[10] Shared microbial strains have been reported in the gut of mothers and their infants due to vertical transmission, with maternal gut strains being more persistent and ecologically better adapted to the infant's gut than those from other sources.[11] Antibiotic treatment in pregnancy may thus influence microbial transmission from mother to infant during delivery.

Prospective studies, meta-analyses, and systematic reviews have shown strong relationships between prenatal antibiotic exposure and asthma in the offspring.[12–15] The association between postnatal antibiotic exposure and allergic manifestations[12] is ambiguous, possibly due to confounding and reverse causation.[16] Prospective studies examining the association between prenatal antibiotic exposure and eczema, food allergy, and IgE-sensitization are still scarce.[17–19]

We hypothesized that pre- and postnatal antibiotic exposures are associated with the development of allergic diseases. The objective was to assess the associations between pre- and postnatal antibiotic exposures and allergic manifestations and IgE-sensitization until 18 months of age in the large population-based NorthPop birth cohort study.

Key Message

Postnatal antibiotic exposure was positively associated with wheeze, asthma, and eczema in early childhood. The association between pre- and postnatal antibiotics and food sensitization was conflicting, and future studies should investigate the relationship between antibiotic exposure and food sensitization later in childhood.

2 | METHODS

2.1 | Study population

This study extracted data from the prospective, population-based NorthPop birth cohort in Sweden.[20] Participants were recruited between May 2016 and August 2018, when all eligible pregnant women in the catchment area of Umeå University Hospital were invited to participate when they were scheduled for their routine ultrasound examination at gestational weeks 17–20. Inclusion criteria were pregnant woman ≥18 years of age, comprehending the Swedish language, viable pregnancy in gestational weeks 14–24, intention to give birth, and residing in the catchment area in the next few years.

We included mother–child dyads providing data on antibiotic exposures and allergic outcomes in the offspring until the child turned 18 months old. Infants that had been admitted to the neonatal ward and received antibiotics were excluded. A flowchart depicting the study sample is presented in Figure 1. The study is reported in accordance with Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines for observational studies.

2.2 | Data collection, blood samplings, and determination of specific IgE

We collected data using web-based questionnaires (Appendix 1). The pregnant woman and her partner completed questionnaires in gestational weeks 18–20, 26, 34, and 35, respectively, with questions on medical history, socioeconomics, household characteristics, and lifestyle factors. The mother answered questionnaires when the child was 4, 9, and 18 months old regarding the indication and number of antibiotic courses prescribed. Information on maternal antibiotic treatment during pregnancy was obtained from questionnaires administered during and after pregnancy. Information on maternal age and infant sex was extracted from medical records and information on delivery mode from The Swedish Pregnancy Register. Allergic manifestations in the child and the time of onset were queried at age 18 months. At that age, venous blood was collected in Vacutainer tubes for determination of allergen-specific IgE levels to inhalant (Phadiatop; birch, timothy, mugwort, cat, dog, horse, *Cladosporium herbarum*, *Dermatophagoides pteronyssinus*, and *farinae)* and food (Food mix fx5; cow's milk, egg white, wheat, codfish, peanut, and soybean) allergens using ImmunoCAP, Thermo Fisher Scientific/Phadia, Uppsala, Sweden, according to the manufacturer's instructions.

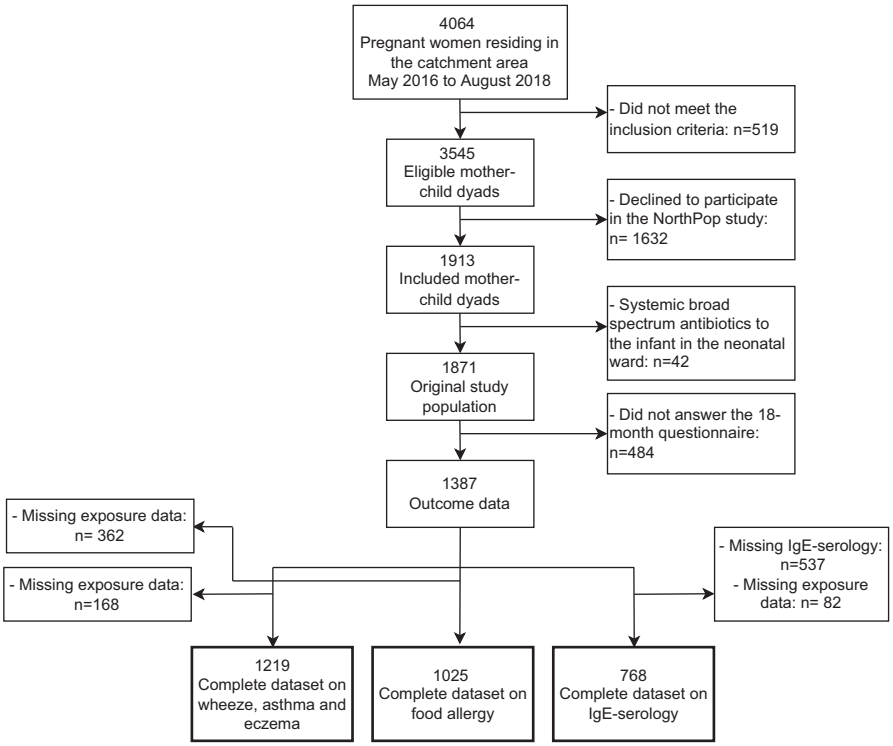

FIGURE 1 A flowchart of the study population.

2.3 | Main exposures

The information from two separate questionnaires administered in gestational week 26 and at 4 months postpartum was used to create the variable prenatal antibiotic exposure (yes/no). Information on antibiotic treatment for the child was collected at 4, 9, and 18 months of age and was used to create the postnatal antibiotic exposure variable (yes/no) and the variables on the number of antibiotic courses during infancy (none, one, two, or more). A combined variable of antibiotic exposure during pregnancy and infancy was constructed (yes/no).

2.4 | Primary outcomes

Wheeze and eczema were defined as the presence of parentally reported symptoms. Asthma and food allergy were defined as physician-diagnosed asthma and food allergy, respectively. Sensitization was defined as positive Phadiatop and/or food mix fx5 (cut-off 0.35 kU/L).

2.5 | Statistical analysis

Differences in the cumulative incidence of allergic outcomes between exposure versus no exposure to antibiotics were analyzed using Pearson's chi-square test. An independent *T*-test was used to compare the mean age in different groups. Associations between pre- and postnatal antibiotic exposure and allergic outcomes and sensitization were estimated using logistic regressions. Results are reported as crude and adjusted odds ratios (OR and aOR) and their 95% confidence intervals (CI). Only covariates that were significantly associated with the outcome were included in the multivariable analyses. Data analysis was conducted using IBM SPSS Statistics version 27 (IBM Corp.). The statistical significance level was defined by a p-value $< .05$.

2.6 | Ethical approval

This research was approved by the Research Ethics Committee in Umeå, Sweden, 2014/224-31. Written informed consent was obtained from both parents.

3 | RESULTS

3.1 | Population characteristics

We included 1387 mother–child dyads. Because of missing exposure and IgE-serology data, the analyses were made in three subpopulations (Figure 1). Overall, 114 (9.2%) of the women received antibiotics during pregnancy and urinary tract infection (UTI) was the most common indication (68.7%). Among the children, 252 (20.2%) received antibiotics in their first 18 months of life; the majority were prescribed a single antibiotic course (65.5%) while fewer received two courses (26.2%) or ≥3 courses (8.3%). The most common indication for antibiotic treatment was ear infection (59.5%) followed by skin infection (10.7%), UTI (9.9%), pneumonia (6.7%), and throat infection (3.6%). Twenty-six (2.3%) children were exposed to antibiotics both prenatally and postnatally.

Maternal history of allergic disease was positively associated with both pre- and postnatal antibiotics (Table 1). Maternal asthma, hay fever, eczema, and food allergy were positively associated with antibiotic treatment during pregnancy. Maternal asthma was positively associated with antibiotic treatment of their child. No differences in maternal education level, cesarean section delivery, or parental smoking, nor in child characteristics according to pre- or postnatal exposure were observed.

Wheeze was reported in 252 (18.2%) of the children and 69 (5%) had physician-diagnosed asthma. The corresponding number for eczema was 424 (30.6%). Parents reported "any adverse reaction to food and drinks" in 255 (22.7%) of the children whereas 44 (3.9%) had a physician-diagnosed food allergy. Data on sensitization were available from 850 children (61.2%) and of these, 148 (17.4%) were sensitized; 139 (16.4%) had a positive Food mix fx5 test and 34 (4%) had a positive Phadiatop test. All but one child was sensitized to ≥2 allergens. Of the food-allergic children, 14.2% had a positive Food mix fx5 test versus 2.5% among those without a food allergy diagnosis ($p = .001$).

Compared with no exposure, children exposed to prenatal antibiotics demonstrated a higher cumulative incidence of wheeze and food sensitization (Table 1). For antibiotic exposure between birth and age 18 months, a higher cumulative incidence of wheeze, asthma, and eczema was observed. Postnatal antibiotics were associated with food sensitization, but in contrast, the cumulative incidence was lower among children exposed to antibiotics (Table 1).

3.2 | Prenatal antibiotics and allergic outcomes

There was an increased risk for food sensitization in relation to prenatal antibiotic exposure but the association did not remain significant after adjusting for confounding factors (Table 2). A borderline significant positive association was found between exposure to antibiotics in utero and wheeze (Table 3). Adjusting for postnatal antibiotic exposure had no major impact on the results (data not shown).

3.3 | Postnatal antibiotics and allergic outcomes

The risk of developing wheeze, asthma, and eczema increased in children exposed to antibiotics in the first 18 months of life. When adjusting for confounders the estimates did not demonstrate any major change in the association with wheeze, asthma, and eczema (Tables 2 and 3). There was a decreased risk of developing food sensitization when exposed to postnatal antibiotics but not with food allergy nor sensitization to inhalant allergens (Tables 2 and 3). Adjusting for prenatal antibiotic exposure did not influence the estimates to any major degree (data not shown). Next, we assessed the associations in a longitudinal analysis within a restricted population of children who did not develop eczema nor wheeze, respectively, until age 9 months, and in which the cumulative incidence of wheeze and eczema between 9 and 18 months was compared according to antibiotic treatment before 9 months. This model showed even stronger associations (Table 4). Further subdivision in those who did or did not receive antibiotics between 9 and 18 months, demonstrated that the positive association for wheeze remained but not for eczema (Table S1).

Since the association between antibiotic exposure and respiratory outcomes could be distorted by respiratory infections we developed a model where we excluded children treated with antibiotics due to respiratory tract infections ($n = 26$) and the estimates remained mostly unchanged; wheeze (aOR 2.03, 95% CI 1.57–3.07) and asthma (aOR 2.00, 95% CI 1.07–3.74). Similarly, the association between antibiotic exposure and eczema could be distorted by skin infections why we excluded children treated with antibiotics due to skin infection ($n = 27$), here the association did not remain (aOR 1.32, 95% CI 0.94–1.86).

We then analyzed the potential additive effect of ≥2 antibiotic courses and although there was a trend of a dose–response relationship for the cumulative incidence of wheeze and asthma, the confidence intervals were overlapping (Figure 2 and Tables S2 and S3).

3.4 | Pre- and postnatal antibiotics and allergic outcomes

Next, we examined the effects of combined pre- and postnatal exposure on allergic outcomes. There was an increased risk of food allergy, but the association did not remain significant in the adjusted analyses (Table 3).

3.5 | Drop-out analysis

In the original cohort, 484 mothers did not complete the questionnaire on allergic outcomes in the child (Figure 1). A drop-out analysis demonstrated that maternal age was lower in the nonresponder group, as was maternal education level (Table S4). In the serology study, 537 IgE-tests were missing. We found that mothers with higher educational level and food allergy were more likely to participate (Table S5) but adjusting for these variables in the analyses on pre- and postnatal antibiotics and IgE-sensitization did not influence the estimates to any major degree (data not shown).

4 | DISCUSSION

To the best of our knowledge, this is the first study investigating the relationship between prenatal antibiotics and food sensitization. We found an increased risk of food sensitization in children exposed to antibiotics in utero in the crude, but not in the adjusted analyses. There was also a borderline positive association between prenatal antibiotic exposure and wheeze, but not with asthma at this young age. Contrary to a study in the PASTURE birth cohort reporting a positive association between prenatal antibiotics and physician-diagnosed food allergy in

TABLE 1 Study population characteristics and allergic manifestations until 18 months of age according to pre- or postnatal antibiotic exposure

	Study population	Prenatal antibiotic use			Postnatal antibiotic use		
		No ($n = 1126$)	Yes ($n = 114$)		No ($n = 993$)	Yes ($n = 252$)	
	N (%)	*N* (%)	*N* (%)	*p*-Value*	*N* (%)	*N* (%)	*p*-Value*
Child characteristics							
Sex							
Female	662 (47.7)	545 (48.4)	48 (42.1)	.200	486 (48.9)	108 (42.9)	.084
Male	725 (52.3)	581 (51.6)	66 (57.9)		507 (51.1)	144 (57.1)	
Feeding method at 4 months							
Breastfeeding	878 (69.5)	772 (69.4)	81 (71.7)	.505	641 (70.0)	159 (68.0)	.186
Breastfeeding and formula	206 (16.3)	183 (16.5)	14 (12.4)		155 (16.9)	34 (14.5)	
Formula	179 (14.2)	157 (14.1)	18 (15.9)		120 (13.1)	41 (17.5)	
Siblings							
Yes	667 (50.0)	543 (50.0)	53 (47.3)	.651	466 (48.8)	133 (53.8)	.157
No	668 (50.0)	543 (50.0)	58 (52.3)		489 (51.2)	114 (46.2)	
Pets (cats and dogs) in the first 18 months of life							
Yes	514 (38.8)	415 (38.2)	48 (42.5)	.376	390 (40.5)	83 (34.3)	.077
No	810 (61.2)	671 (61.8)	65 (57.5)		573 (59.5)	159 (65.7)	
Living on a farm in the first 18 months of life							
Yes	15 (1.1)	12 (1.1)	1 (0.9)	.830	8 (0.8)	5 (2.1)	.096
No	1309 (98.9)	1074 (98.9)	112 (99.1)		955 (99.2)	237 (97.9)	
Parental characteristics							
Mean maternal age (years ± SD)	30.9 ± 4.4	31.1 ± 4.4	30.3 ± 4.6	.059**	**31.1 ± 4.4**	**30.4 ± 4.4**	**.024****
Caesarean section							
Yes	219 (15.8)	172 (15.3)	15 (13.2)	.547	147 (14.8)	47 (18.7)	.133
No	1168 (84.2)	954 (84.7)	99 (86.8)		846 (85.2)	205 (81.3)	
Maternal educational level[a]							
Low	31 (2.3)	25 (2.3)	2 (1.8)	.328	22 (2.3)	4 (1.6)	.445
Middle	341 (25.0)	272 (24.5)	34 (30.9)		237 (24.3)	70 (27.8)	
High	990 (72.7)	814 (73.3)	74 (67.3)		717 (73.5)	178 (70.6)	
Maternal smoking during pregnancy							
Yes	9 (0.7)	8 (0.8)	1 (1.0)	.831	7 (0.7)	2 (0.8)	.882
No	1240 (99.3)	1024 (99.2)	102 (99.0)		986 (99.3)	250 (99.2)	
Maternal smoking after pregnancy							
Yes	16 (1.3)	10 (5.5)	3 (13.6)	.137	14 (8.1)	1 (2.0)	.136
No	1233 (98.7)	173 (94.5)	19 (86.4)		159 (91.9)	48 (98.0)	
Paternal smoking after pregnancy							
Yes	47 (3.8)	33 (3.2)	6 (5.8)	.163	39 (3.9)	8 (3.2)	.574
No	1201 (96.2)	999 (96.8)	97 (94.2)		953 (96.1)	244 (96.8)	
Maternal asthma							
Yes	245 (18.0)	**194 (17.5)**	**28 (25.5)**	**.039**	**164 (16.8)**	**60 (23.8)**	**.011**
No	1115 (82.0)	**916 (82.5)**	**82 (74.5)**		**810 (83.2)**	**192 (76.2)**	
Maternal hay fever							
Yes	363 (26.7)	**284 (25.6)**	**39 (35.5)**	**.025**	252 (25.9)	73 (29.0)	.321
No	997 (73.3)	**826 (74.4)**	**71 (64.5)**		722 (74.1)	179 (71.0)	

(Continues)

TABLE 1 (Continued)

	Study population	Prenatal antibiotic use			Postnatal antibiotic use		
		No (n = 1126)	Yes (n = 114)		No (n = 993)	Yes (n = 252)	
	N (%)	*N* (%)	*N* (%)	*p*-Value*	*N* (%)	*N* (%)	*p*-Value*
Maternal fur allergy							
Yes	288 (21.2)	236 (21.3)	26 (23.6)	.563	202 (20.7)	63 (25.0)	.143
No	1072 (78.8)	874 (78.7)	84 (76.4)		772 (79.3)	189 (75.0)	
Maternal eczema							
Yes	237 (17.4)	**194 (17.5)**	**28 (25.5)**	**.039**	167 (17.1)	47 (18.3)	.575
No	1123 (82.6)	**916 (82.5)**	**82 (74.5)**		807 (82.9)	205 (81.3)	
Maternal food allergy							
Yes	225 (16.5)	**172 (15.5)**	**28 (25.5)**	**.007**	157 (16.1)	47 (18.7)	.336
No	1135 (83.5)	**938 (84.5)**	**82 (74.5)**		817 (83.9)	205 (81.3)	
Paternal asthma							
Yes	193 (16.0)	166 (16.7)	16 (15.8)	.822	131 (15.0)	39 (17.7)	.316
No	1015 (84.0)	827 (83.3)	85 (84.2)		743 (85.0)	181 (82.3)	
Paternal hay fever							
Yes	376 (31.1)	318 (32.0)	30 (29.7)	.633	274 (31.4)	71 (32.3)	.792
No	832 (68.9)	675 (68.0)	71 (70.3)		600 (68.6)	149 (67.7)	
Paternal fur allergy							
Yes	340 (28.1)	291 (29.3)	22 (21.8)	.111	243 (27.8)	62 (28.2)	.911
No	868 (71.9)	702 (70.7)	79 (78.2)		631 (72.2)	158 (71.8)	
Paternal eczema							
Yes	95 (7.9)	82 (8.3)	6 (5.9)	.415	64 (7.3)	22 (10.0)	.187
No	1113 (92.1)	911 (91.7)	95 (94.1)		810 (92.7)	198 (90.0)	
Paternal food allergy							
Yes	135 (11.2)	118 (11.9)	11 (10.9)	.768	99 (11.3)	23 (10.5)	.713
No	1073 (88.8)	875 (88.1)	90 (89.1)		775 (88.7)	197 (89.5)	
Cumulative incidence of allergic outcomes							
Reported wheeze until 18 months							
Yes	252 (18.2)	**193 (17.1)**	**28 (24.6)**	**.049**	**150 (15.1)**	**74 (29.4)**	**<.001**
No	1135 (81.8)	**933 (82.9)**	**86 (75.4)**		**843 (84.9)**	**178 (70.6)**	
Physician-diagnosed asthma until 18 months							
Yes	69 (5.0)	52 (4.6)	10 (8.8)	.052	**35 (3.5)**	**22 (8.7)**	**<.001**
No	1317 (95.0)	1074 (95.4)	104 (91.2)		**958 (96.5)**	**230 (91.3)**	
Any adverse reaction to food and drinks							
Yes	255 (22.7)	211 (22.6)	25 (27.2)	.319	188 (22.9)	54 (25.1)	.488
No	869 (77.3)	723 (77.4)	67 (72.8)		634 (77.1)	161 (74.9)	
Physician-diagnosed food allergy until 18 months							
Yes	44 (3.9)	35 (3.8)	6 (6.5)	.196	29 (3.5)	10 (4.7)	.443
No	1079 (96.1)	898 (96.2)	86 (93.5)		792 (96.5)	205 (95.3)	
Reported eczema							
Yes	424 (30.6)	346 (30.7)	37 (32.5)	.704	**286 (28.8)**	**95 (37.7)**	**.006**
No	962 (69.4)	780 (69.3)	77 (67.5)		**707 (71.2)**	**157 (62.3)**	
Sensitized to food allergens[b] (cut-off: >0.35 kU/L)							
Yes	139 (16.4)	**107 (15.0)**	**17 (24.3)**	**.042**	**112 (18.4)**	**16 (10.3)**	**.015**
No	711 (83.6)	**606 (85.0)**	**53 (75.7)**		**498 (81.6)**	**140 (89.7)**	

TABLE 1 (Continued)

	Study population	Prenatal antibiotic use			Postnatal antibiotic use		
		No ($n = 1126$)	Yes ($n = 114$)		No ($n = 993$)	Yes ($n = 252$)	
	N (%)	*N* (%)	*N* (%)	*p*-Value*	*N* (%)	*N* (%)	*p*-Value*
Sensitized to inhalant allergens[c] (cut-off: >0.35 kU/L)							
Yes	34 (4.0)	28 (3.9)	5 (7.1)	.201	25 (4.1)	5 (3.2)	.608
No	816 (96.0)	685 (96.1)	65 (92.9)		585 (95.9)	151 (96.8)	

*Based on the Pearson chi-square test; **Based on the independent *T*-test. Bold font indicates statistically significant relationship.

[a]Low educational level was defined as elementary school or lower, middle educational level was defined as secondary school and high educational level was defined as University studies.

[b]Cow's milk, egg white, wheat, codfish, peanut, and soybean.

[c]Birch, timothy, mug wort, cat, dog, horse, *Cladosporium herbarum*, *Dermatophagoides pteronyssinus*, and *farinae*.

TABLE 2 Associations between pre- and postnatal antibiotic exposure and eczema, food allergy and food sensitization until 18 months of age

	Eczema			Food allergy diagnosis			Sensitized to food allergens		
		Crude	Adjusted		Crude	Adjusted		Crude	Adjusted
		OR	aOR[a]		OR	aOR[b]		OR	aOR[c]
	n/N	95% CI	95% CI	*n/N*	95% CI	95% CI	*n/N*	95% CI	95% CI
No antibiotics (ref)	346/780	1.00	1.00	86/898	1.00	1.00	107/606	1.00	1.00
Prenatal antibiotic exposure	37/77	1.08	0.92	6/86	1.79	1.24	17/53	**1.82**	1.58
		0.72–1.64	0.58–1.47		0.73–4.38	0.46–3.34		1.01–3.26	0.82–3.05
No antibiotics (ref)	286/707	1.00	1.00	29/792	1.00	1.00	112/498	1.00	1.00
Postnatal antibiotic exposure	95/157	**1.50**	**1.49**	10/205	1.33	1.24	16/112	**0.51**	**0.46**
		1.12–2.00	1.07–2.06		0.64–2.78	0.57–2.73		0.29–0.89	0.25–0.83
No antibiotics (ref)	338/768	1.00	1.00	33/901	1.00	1.00	114/588	1.00	1.00
Both pre- and postnatal antibiotic exposure	11/15	1.67	1.69	3/18	**4.55**	3.32	3/12	1.29	1.28
		0.76–3.67	0.73–3.89		1.28–16.21	0.85–12.95		0.36–4.64	0.34–4.82

Note: Footnotes present covariates included in the multiple logistic regression model. Bold font indicates statistically significant relationship.

[a]Infant sex, maternal and paternal history of allergic disease, exposure to pets (cats and dogs), and exposure to farm animals.

[b]Maternal and paternal history of allergic disease and exposure to pets (cats and dogs).

[c]Infant sex, delivery mode, and paternal history of allergic disease.

the first year of life,[18] this was not observed in our cohort. Our results are consistent with a Norwegian prospective study that found no association between prenatal or postnatal antibiotics and food allergy until age 2 years.[19] When we studied pre- and postnatal antibiotic exposure and its association with physician-diagnosed food allergy, we found an increased risk in the crude analysis although the wide confidence interval introduces uncertainty. Possible explanations for the discrepancy across studies are the lower number of children with food allergy in our cohort compared with the PASTURE cohort and differences in age at diagnosis.[18,19] Differences in diagnostic procedures across studies may also contribute due to variation in the prevalence of food allergy according to the diagnostic criteria used.[21]

The risks for wheeze, asthma, and eczema were increased after postnatal antibiotics, which is in line with previous studies.[22,23] Two-thirds of the children in our study received antibiotics due to ear infection and rarely due to respiratory or skin infection, indicating that the increased risk of wheeze, asthma, and eczema cannot be fully explained by reverse causation. We addressed this in an additional model by excluding antibiotic-treated cases due to respiratory or skin infection. This had no major impact on the association of postnatal antibiotics with wheeze or asthma, but the association with eczema did not remain.

In contrast to our hypothesis, we found a decreased risk of food sensitization in relation to postnatal antibiotics. This association remained when including maternal age and food allergy diagnosis, which differed between the original study population and participants in the IgE serology study, in the model. No previous study has demonstrated postnatal antibiotics to increase the risk of positive skin prick testing, elevated total or specific IgE-levels.[13,24] The majority of the children in our study received penicillin that leave

TABLE 3 Associations between pre- and postnatal antibiotic exposure and wheeze, asthma and sensitization to inhalants until 18 months of age

	Wheeze			Asthma diagnosis			Sensitized to inhalant allergens		
		Crude	Adjusted		Crude	Adjusted		Crude	Adjusted
		OR	aOR[a]		OR	aOR[b]		OR	aOR[c]
	n/N	95% CI	95% CI	*n/N*	95% CI	95% CI	*n/N*	95% CI	95% CI
No antibiotics (ref)	193/933	1.00	1.00	52/1074	1.00	1.00	28/685	1.00	1.00
Prenatal antibiotic exposure	28/86	1.57	1.56	10/104	1.99	1.79	5/65	1.88	2.06
		1.00–2.48	0.95–2.57		0.98–4.02	0.86–3.73		0.70–5.04	0.68–6.26
No antibiotics (ref)	150/843	1.00	1.00	35/958	1.00	1.00	25/585	1.00	1.00
Postnatal antibiotic exposure	74/178	**2.34**	**2.14**	22/230	**2.62**	**2.35**	5/151	0.78	0.92
		1.69–3.22	1.47–3.11		1.51–4.55	1.32–4.19		0.29–2.06	0.34–2.53
No antibiotics (ref)	191/915	1.00	1.00	48/1058	1.00	1.00	29/673	1.00	1.00
Both pre- and postnatal antibiotic exposure	8/18	2.13	1.71	2/24	1.84	1.60	1/14	1.66	1.85
		0.91–4.97	0.70–4.21		0.42–8.00	0.35–7.21		0.21–13.04	0.23–15.10

Note: Footnotes present covariates included in the multiple logistic regression model. Bold font indicates statistically significant relationship.

[a]Infant sex, breastfeeding at 4 months and maternal and paternal history of allergic disease.

[b]Infant sex, maternal history of allergic disease and exposure to pets (cats and dogs).

[c]Paternal history of allergic disease.

TABLE 4 Additional model analyzing the associations between early antibiotic exposure (before age nine months), and eczema and wheeze in two different subpopulations where children did not have the respective allergic outcome before age 9 months

	Eczema between 9 and 18 mo			Wheeze between 9 and 18 mo		
		Crude	Adjusted		Crude	Adjusted
	n/N	OR 95% CI	aOR[a] 95% CI	*n/N*	OR 95% CI	aOR[b] 95% CI
No antibiotics (ref)	152/741	1.00	1.00	119/869	1.00	1.00
Antibiotics before 9 mo	22/58	**1.85**	**1.88**	15/65	1.68	**2.08**
		1.10-3.11	1.07-3.30		0.93-3.05	1.09-3.98

Note: Footnotes present covariates included in the multiple logistic regression model. Bold font indicates statistically significant relationship.

[a]Infant sex, maternal and paternal history of allergic disease, exposure to pets (cats and dogs) and exposure to farm animals.

[b]Infant sex, breastfeeding at four months, and maternal and paternal history of allergic disease.

a lesser mark on the gut microbiota[25] and theoretically also on IgE production.[2] Thus, future studies should stratify analyses according to narrow- versus broad-spectrum antibiotics.

The mechanisms underlying the associations between perinatal antibiotic exposures and allergic diseases still need to be demonstrated. A systematic review reported lower abundance of Bacteroidetes and bifidobacteria with a concomitant increase of Proteobacteria in infants exposed to antibiotics (typically ampicillin and penicillin for Group B *Streptococcus* prophylaxis) in utero[26]. Similar aberrancies were demonstrated in a systematic review on postnatal antibiotics and gut microbiota in children,[27] the effects being most marked following treatment with broad-spectrum macrolides. Reduction of the immunomodulatory gut symbiont *Bacteroides* has been reported in infants before eczema onset[28] and we have previously reported consistent underrepresentation of *Bacteroides* in multi-allergic children from infancy to school age.[9]

Major strengths are the prospective population-based design and inclusion in pregnancy. Both parents contributed detailed information on heredity and environmental exposures, enabling us to explore the effect of multiple potential confounders, making the results independent and reliable. The study design with relatively short intervals between the questionnaires decreases the risk of recall bias. Additionally, prospective cohort studies are less susceptible to confounding by indication than retrospective or register-based studies. There are also possible limitations. Younger age and low educational level were overrepresented in mothers that did not complete the questionnaire on allergic outcomes in the child, and mothers with food allergy and higher education level were more likely to participate in the IgE serology study, making the study population less representative. We included physician diagnosis of asthma and food allergy only, which may lead to an underestimation of the cumulative incidence, but on the other

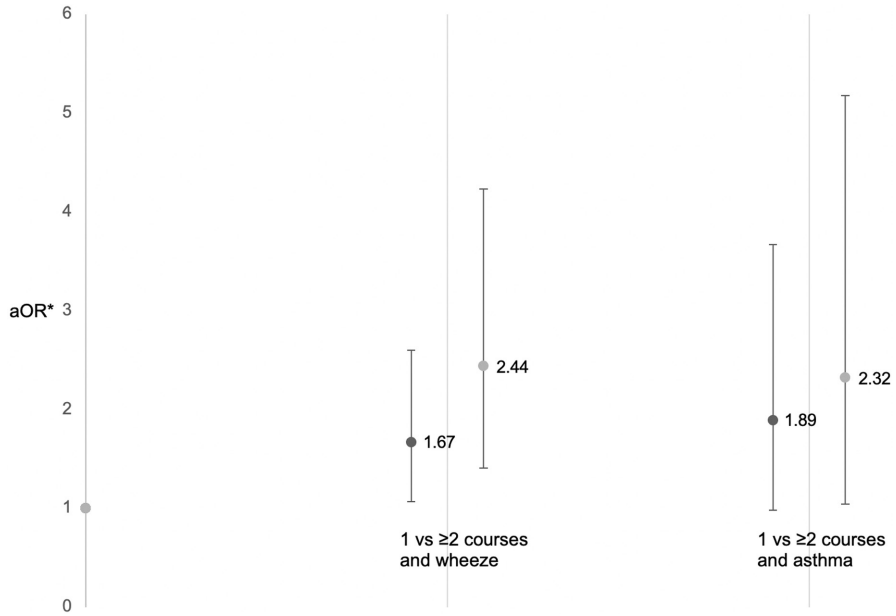

FIGURE 2 Associations between respiratory outcomes and number of antibiotic courses. *Adjusted for infant sex, delivery method, and maternal and paternal history of allergic disease, and exposure to pets.

hand limits detection bias. Although we developed models to address reverse causation for postnatal antibiotics and the outcomes wheeze, asthma, and eczema, we cannot rule out this effect. The study population was mainly selected from urban areas in Sweden, so the results might not be representative for rural areas or other countries. Finally, the follow-up was short.

To summarize, pre- and postnatal antibiotic exposures are associated with the development of allergic diseases in young children. A novel finding is the increased risk of food sensitization after prenatal antibiotic exposure. An unexpected finding is the decreased risk of food sensitization after postnatal antibiotics. Food sensitization is often transient but has been associated with increased risk of developing respiratory allergic diseases[29] and future studies should explore the possible long-term consequences of perinatal antibiotic exposures in the atopic march.

AUTHOR CONTRIBUTIONS

Fanny Kelderer: Conceptualization (equal); data curation (equal); formal analysis (equal); investigation (equal); methodology (equal); software (equal); validation (equal); visualization (lead); writing – original draft (lead); writing – review and editing (equal). **Ingrid Mogren:** Formal analysis (equal); investigation (equal); methodology (equal); software (equal); writing – review and editing (equal). **Catharina Eriksson:** Investigation (equal); writing – review and editing (equal). **Sven-Arne Silfverdal:** Conceptualization (equal); investigation (equal); writing – review and editing (equal). **Magnus Domellöf:** Conceptualization (equal); funding acquisition (equal); investigation (equal); resources (equal); writing – review and editing (equal). **Christina E. West:** Conceptualization (equal); data curation (equal); formal analysis (equal); funding acquisition (equal); investigation (equal); methodology (equal); project administration (equal); resources (equal); software (equal); supervision (lead); validation (lead); writing – review and editing (equal).

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CONFLICT OF INTEREST

Christina West has received speaker honorarium from Thermo Fisher Scientific. The other authors have no conflict of interest to disclose.

PEER REVIEW

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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APPENDIX 1

SURVEY QUESTIONS TRANSLATED FROM SWEDISH TO ENGLISH

Mother, gestational age 18–20 survey (response time: 1 month)

- Do you live with someone? Yes/no
- Who else lives in the household? Biological father/other partner who is not the biological father/relatives, friends, other adults/children
- Number of adults in the household? 1–>8
- Number of children in the household? 1–>8
- What type of home do you live in? House, apartment, farm, other
- Do you (or your biological parents, siblings, or children) have any of the following allergies (asthma, hay fever, allergy to furry pets, food allergy, eczema)? Yes/no
- What is the highest educational level you have reached? Elementary school or lower/secondary school/University

Mother, gestational age 26 survey (response time: 1 month)

- Have you had a urinary tract infection that needed treatment so far during this pregnancy? Yes/no
- Have you had any other infection that needed antibiotic treatment so far during this pregnancy? Yes/no

Child, 4-month survey (response time: 3 weeks)

- Contact with animals—how often? Cat, dog, farm animal (every day–>never)
- What type of milk? Only breastmilk/both/only formula
- Have you had a urinary tract infection that needed treatment during pregnancy since the last time we asked (week 26)? Yes/no
- Have you had any other infection during pregnancy that needed antibiotic treatment since the last time we asked (week 26)? Yes/no
- Did the child receive neonatal care after delivery? Yes/no

Child, 9-month survey (response time: 3 weeks)

- Mother smoking or has smoked ever? Yes/no
- If yes: Mother smoking during pregnancy? Yes/no
- If yes: Smoking after pregnancy? Nothing->20 cigarettes
- Partner smoking or has smoked ever? Yes/no
- If yes: Partner smoking during pregnancy? Yes/no
- If yes: Smoking after pregnancy? Nothing->20 cigarettes
- How often has the child received antibiotic treatment? Never–>2 times or more
- If antibiotic treatment: Why? UTI/ear infection/pneumonia/throat infection/other

Child, 18-month survey (response time: 3 weeks)

- Did the child ever wheeze? Yes/no
- If wheeze: At what age did the child first wheeze? 1–>19 months
- Has the child received an asthma diagnosis from a physician? Yes/no
- Has the child had eczema? Yes/no
- If eczema: At what age did the child first have eczema? 1–>19 months
- Has the child ever had an adverse reaction to food and drinks? Yes/no
- Has the child received a food allergy diagnosis from a physician? Yes/no
- How often has the child received antibiotic treatment between 9 months of age and now? Never–>2 times or more
- If antibiotic treatment: Why? UTI/ear infection/pneumonia/throat infection/other

Partner, pregnancy week 18–20 survey (response time: 1 month)

- Do you (or your biological parents, siblings, or children) have any of the following allergies (asthma, hay fever, allergy to furry pets, food allergy, eczema)? Yes/no
- What is the highest educational level you have reached? Elementary school or lower/secondary school/University