Association of Prenatal Antibiotics and Mode of Birth With Otolaryngology Surgery in Offspring

A National Data Linkage Study

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Background: Pediatric otolaryngology surgery is commonly performed after recurrent infections and allergy/atopy. Prenatal antibiotic exposure and cesarean section deliveries increase the risk of severe infection and allergy/atopy in the offspring, but the relationship with common, related surgical outcomes is unknown. This study measures the associations between prenatal antibiotic use and mode of birth with common pediatric otolaryngology surgery.

Methods: Data linkage analysis of all live-born, singleton children, born between 2008 and 2018 was done using Norwegian national health registry data. Exposures of interest were prenatal antibiotics and mode of birth. The primary outcome was common otolaryngology surgery before 10 years of age. Exposure–outcome associations were estimated through multivariable Cox proportional hazards models adjusting for predefined covariates. Interaction between exposures was explored.

Results: Of 539,390 children, 146,832 (27.2%) had mothers who were prescribed antibiotics during pregnancy, 83,473 (15.5%) were delivered via cesarean section, and 48,565 (9.0%) underwent an otolaryngology surgery during the study period. Prenatal antibiotic exposure [adjusted hazard ratio (aHR), 1.22; 95% CI: 1.20–1.24] and cesarean section (aHR, 1.14; 95% CI: 1.11–1.16) were each associated with otolaryngology surgery after mutual adjustment. There was some evidence of an interaction between the 2 exposures ($P = 0.03$).

Conclusions: Antibiotic exposure in pregnancy and cesarean section may adversely affect early immune development and increase the risk of recurrent upper airway infections and allergy/atopy that may require otolaryngology surgery. Mechanistic studies are warranted to explore genetic and/or molecular pathways that explain these findings. This may identify potential therapeutic targets to reduce the burden of otolaryngology surgery.

Key Words: pregnancy, antibiotics, cesarean section, infection, pediatric otolaryngology surgery

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Otolaryngology surgery is one of the most frequent surgical interventions in childhood.[1,2] The incidence rate in children of 0–14 years of age for ventilation tubes placement varies from 2 to 35/1000[3] and tonsillectomy between 0.2 and 11.8/1000,[4] with considerable variation between countries.[4,5] Rates for some common procedures, such as ventilation tube placement, are increasing in the United States.[6] Recurrent infections of the respiratory tract and allergic/atopic diseases contribute to pathologies, such as adenotonsillar hypertrophy and chronic middle ear effusions that may necessitate surgical management.[7–10] The causative pathogens and allergens are extremely widely distributed, but only a minority of children require otolaryngology surgery. Shared heritable and postnatal environmental factors, such as cigarette smoke, contribute modestly to differential risk.[11–13] Pre- and perinatal exposures, such as maternal medication use and mode of birth, have been associated with other immune-related outcomes in the offspring.[14–22] It is largely unexplored whether they may influence the likelihood of otolaryngology surgery.

Between 25% and 40% of women in high-income countries are prescribed antibiotics in pregnancy, predominantly for urinary, skin, ear and respiratory infections,[23] or intrapartum to prevent mother to child transmission of group B streptococcus.[24] Prenatal exposure to antibiotics has been linked to immune-related outcomes in offspring, including asthma[14,17,18] and allergy,[19] as well as increased susceptibility to severe infections.[16] Mode of birth has been associated with similar outcomes; children born by cesarean section have increased risk of asthma,[20] some types of allergy,[21] and infection-related hospitalization.[15,22]

Robust data on milder nonhospitalized infections and allergic/atopic outcomes, which are extremely prevalent, are not available from large population-based registries. This study aimed to examine the independent and joint associations between antibiotic exposure in pregnancy and delivery by cesarean section with risk of otolaryngology surgery, using total population-linked data from Norway.

MATERIALS AND METHODS

Setting and Study Population

We analyzed data available from the Norwegian national health registries. Each person is assigned a unique personal identification number at birth, allowing registry data linkage. The Medical Birth Registry of Norway includes all children born in Norway

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from 1967 onward and contains information about the child's birth parameters and the mother's health before and during pregnancy.[25] The Norwegian Prescription Database started in 2004 and holds information on dispensed medications.[26] The Norwegian Patient Register contains hospital records for each individual, procedural codes and date of hospital admission from 2008 onward.[27]

We identified all live-born, singleton births between January 1, 2008 and December 31, 2017 (n = 591,376). Children with missing information on gestational age or mother's identification number, gestational age <24 or >43 weeks, with birth weight <500 or >5500 g, with any recorded congenital malformation, and children who emigrated were excluded (n = 539,390). The end of the follow-up information available in the registries was December 31, 2017.

Exposures

Prescribed antibiotics recorded in the national prescription registry were defined by Anatomical Therapeutic Chemical codes "J01" (any systemic antibacterial).[28] The start of pregnancy was calculated as the child's date of birth minus the estimated gestational age. We defined prenatal antibiotic exposure as any antibiotic prescription filled during this pregnancy window. Trimesters were defined as 0–12 weeks, 13–26 weeks and 27+ weeks from the calculated start of pregnancy. Prenatal antibiotic exposure was examined in 4 different ways: (1) any prescribed antibiotics during pregnancy; (2) the total number of antibiotic prescriptions during pregnancy (categorized as 0, 1, 2 or ≥3); (3) the timing of antibiotic prescription (first, second, third or multiple trimesters) and (4) the timing of last antibiotic prescription (first, second or third trimester). Mode of birth was considered in 2 categorizations: (1) any cesarean section and (2) cesarean section type (elective or emergency) with vaginal birth as a reference.

Outcome: Otolaryngology Surgery

Surgical procedures were recorded in the Norwegian Patient Register using the NOMESCO Classification of Surgical Procedures. Otolaryngology surgeries included ventilation tubes (DCA 10 and DCA 20), myringoplasty (DCD 00), tympanoplasty (DCD 10), incision of tonsils (EMA 00), incision of adenoid (EMA 20), suture of tonsil or adenoids (EMC 00) and tonsillectomy and/or adenectomy (EMB 10–30). Children were classified as having a surgical procedure if they had a recorded procedural code between birth and the end of the study period. Surgical outcomes were limited to the first otolaryngology operation.

Covariates

From the Norwegian birth registry, additional data were obtained on maternal smoking during pregnancy, maternal preexisting disease (hypertension, kidney disease, diabetes and asthma), maternal age at delivery, pregnancy complications (including preeclampsia and gestational diabetes), calculated gestational age and birth weight. Data on maternal body mass index (BMI) was introduced in the birth registry from 2007 but was missing for approximately 40% of mothers. Thirteen percent of mothers declined to provide information regarding smoking habits at the start of pregnancy across the study period.

Statistical Analysis

Multivariable Cox proportional hazard models were used to model the associations (hazard ratios) between each exposure and time to first otolaryngology surgery in the child, with age as the timescale. Children were followed from birth to first otolaryngology surgery, 10 years of age, death or December 31, 2017, whichever occurred first. The main exposures were antibiotics prescribed during pregnancy and mode of birth. Additionally, we explored potential interaction between the 2 exposures by including a product term in the multivariable model and conducted stratified analyses of each of the exposures by the other exposure of interest. Additive interaction was assessed through the relative excess risk due to interaction measure.[29] Directed acyclic graphs were used to identify possible confounders and mediators (see Figure, Supplemental Digital Content 1, http://links.lww.com/INF/E677). Multivariable analyses adjusted for the following: preexisting maternal hypertension (yes/no), maternal kidney disease (yes/no), diabetes [no, pregestational diabetes (type 1 or 2), gestational diabetes, unknown (antidiabetic medication during pregnancy registered)], maternal asthma (yes/no), maternal smoking at start of pregnancy (no, sometimes, daily, declined answer), mother's age at birth (<20, 20–24, 25–29, 30–34, ≥35), hypertension during pregnancy (yes/no), parity (0, 1, 2, ≥3), preeclampsia (yes/no), child sex, gestational age (<28, 28–31, 32–33, 34–35, 36–37, 38–40, >40), and gestational age- and sex-specific birth weight Z score percentiles (≤10, >10–25, >25–75, >75–90, >90). We used robust standard errors to account for the presence of siblings in the population.

Secondary Analyses

In a secondary analysis, we categorized otolaryngology surgery of the ears and throat separately, then estimated the association between any antibiotic exposure during pregnancy and the risk of each procedure category.

Sensitivity Analyses

To minimize the risk of including craniofacial anatomical variants, we performed a sensitivity analysis that only included otolaryngology surgery occurring after 1 year of age, excluding those who were not observed until 1 year of age and those who had an otolaryngology surgery before 1 year of age.

To explore potential confounding by whether the child had siblings, we conducted a sensitivity analysis restricted to first-born children and a sensitivity analysis including a binary variable for siblings in the overall model derived from parity information or the presence of siblings in the data. The latter was restricted to the first 5 years of births (2008–2012) to allow for more complete capture of subsequent siblings.

Data on maternal BMI was missing for 40% of the study population and was therefore not included in the primary analyses. We performed a sensitivity analysis that included additional adjustment for maternal BMI (<18.5, 18.5–24.9, 25–29.9, ≥30 kg/m^2) in those with available data (n = 321,248). We also performed a sensitivity analysis in a subpopulation considered at "low risk" for adverse outcomes defined as maternal age 20–34 years without any preexisting risk factors (ie, no diabetes, no asthma, no kidney disease, no preexisting hypertension, nonsmokers and BMI between 18.5 and 24.9 kg/m^2), nor pregnancy complications (preeclampsia, hypertension or gestational diabetes), birth weight between 10th and 90th percentile for sex and gestational age, and gestational age of 37–43 weeks (n = 98,525). This low-risk population was to assess whether findings may be further confounded by unmeasured differences between the exposed and unexposed groups. All analyses were performed using R statistical software, version 3.6.2.[30]

RESULTS

A total of 539,390 children were followed from birth up to a maximum of 10 years of age (mean duration of follow-up was 4.77 years, SD 2.84). Of the 539,390 children, 146,832 (27.2%) had mothers who were prescribed antibiotics during pregnancy and 83,473 (15.5%) were delivered via cesarean section. In total, 48,565 children (9.0% of the study population) underwent first-time otolaryngology surgeries yielding a rate of 19 events per 1000 person-years of observation. Baseline characteristics, shown in Table 1,

TABLE 1. Maternal and Child Characteristics Comparing Maternal Antibiotic Exposure During Pregnancy With No Maternal Antibiotic Exposure During Pregnancy and Comparing Vaginal Births With Cesarean Section Births

Characteristic	No antibiotics prescribed; n = 392,558 (72.8%)	Antibiotics prescribed; n = 146,832 (27.2%)	*P* value*	Vaginal birth; n = 455,917 (84.5%)	Cesarean section birth; n = 83,473 (15.5%)	*P* value*
Maternal characteristics						
Mother's age at birth, n (%)			<0.001			<0.001
<20	5297 (1.3)	3852 (2.6)		8253 (1.8)	896 (1.1)	
20–24	48,112 (12.3)	24,669 (16.8)		64,433 (14.1)	8348 (10.0)	
25–29	125,973 (32.1)	46,842 (31.9)		149,797 (32.9)	23,018 (27.6)	
30–34	134,676 (34.3)	44,776 (30.5)		151,253 (33.2)	28,199 (33.8)	
35 and over	78,500 (20.0)	26,693 (18.2)		82,181 (18.0)	23,012 (27.6)	
Parity, n (%)			<0.001			<0.001
0	168,501 (42.9)	58,461 (39.8)		187,796 (41.2)	39,166 (46.9)	
1	141,769 (36.1)	55,839 (38.0)		170,381 (37.4)	27,227 (32.6)	
2	59,581 (15.2)	22,900 (15.6)		70,347 (15.4)	12,134 (14.5)	
≥3	22,707 (5.8)	9632 (6.6)		27,393 (6.0)	4946 (5.9)	
Asthma, n (%)	16,854 (4.3)	9001 (6.1)	<0.001	21,022 (4.6)	4833 (5.8)	<0.001
Diabetes, n (%)			<0.001			<0.001
No	378,450 (96.4)	140,539 (95.7)		441,407 (96.8)	77,582 (92.9)	
Pregestational diabetes (type 1 or type 2)	2359 (0.6)	1242 (0.9)		2051 (0.4)	1550 (1.9)	
Gestational diabetes	11,322 (2.9)	4856 (3.3)		11,963 (2.6)	4215 (5.0)	
Unknown	427 (0.1)	195 (0.1)		496 (0.1)	126 (0.2)	
Prepregnancy hypertension, n (%)	2072 (0.5)	905 (0.6)	<0.001	1973 (0.4)	1004 (1.2)	<0.001
Prepregnancy kidney disease, n (%)	2111 (0.5)	1496 (1.0)	<0.001	2876 (0.6)	731 (0.9)	<0.001
Hypertension during pregnancy, n (%)	6723 (1.7)	2676 (1.8)	0.006	7382 (1.6)	2017 (2.4)	<0.001
Preeclampsia, n (%)	10,536 (2.7)	4344 (3.0)	<0.001	9395 (2.1)	5485 (6.6)	<0.001
BMI before pregnancy, n (%)			<0.001			<0.001
<18.5	9488 (2.4)	3710 (2.5)		11,757 (2.6)	1441 (1.7)	
18.5–24.9	148,200 (37.8)	50,075 (34.1)		172,107 (37.7)	26,168 (31.3)	
25–29.9	51,206 (13.0)	19,982 (13.6)		58,604 (12.9)	12,584 (15.1)	
30 and over	26,112 (6.7)	12,475 (8.5)		29,777 (6.5)	8810 (10.6)	
Missing	157,552 (40.1)	60,590 (41.3)		183,672 (40.3)	34,470 (41.3)	
Smoking at start of pregnancy, n (%)			<0.001			<0.001
No	316,825 (80.7)	113,378 (77.2)		365,190 (80.1)	65,013 (77.9)	
Sometimes	4088 (1.0)	2118 (1.4)		5172 (1.1)	1034 (1.2)	
Daily	21,761 (5.5)	13,117 (8.9)		28,961 (6.4)	5917 (7.1)	
Declined to answer	49,884 (12.7)	18,219 (12.4)		56,594 (12.4)	11,509 (13.8)	
Mode of birth, n (%)			<0.001			
Vaginal	333,033 (84.8)	122,884 (83.7)				
Planned cesarean section	21,791 (5.6)	9206 (6.3)				
Emergency cesarean section	37,708 (9.6)	14,724 (10.0)				
Unspecified cesarean section	26 (0.0)	18 (0.0)				
Antibiotics during pregnancy, n (%)				122,884 (27.0)	23,948 (28.7)	<0.001
Child characteristics						
Female, n (%)	191,949 (48.9)	71,763 (48.9)	0.884	22,4701 (49.3)	39,011 (46.7)	<0.001
Birth weight Z score, n (%)			<0.001			<0.001
≤10	40,041 (10.2)	14,771 (10.1)		45,300 (9.9)	9512 (11.4)	
>10–25	59,554 (15.2)	21,886 (14.9)		70,321 (15.4)	11,119 (13.3)	
>25–75	196,929 (50.2)	73,089 (49.8)		232,433 (51.0)	37,585 (45.0)	
>75–90	57,891 (14.7)	22,012 (15.0)		66,662 (14.6)	13,241 (15.9)	
>90	38,143 (9.7)	15,074 (10.3)		41,201 (9.0)	12,016 (14.4)	
Gestational age in weeks, n (%)			<0.001			<0.001
<28	389 (0.1)	180 (0.1)		221 (0.0)	348 (0.4)	
28–31	1495 (0.4)	592 (0.4)		653 (0.1)	1434 (1.7)	
32–33	2125 (0.5)	837 (0.6)		1347 (0.3)	1615 (1.9)	
34–35	5827 (1.5)	2391 (1.6)		5408 (1.2)	2810 (3.4)	
36–37	25,118 (6.4)	10,517 (7.2)		27,189 (6.0)	8446 (10.1)	
38–40	255,326 (65.0)	95,934 (65.3)		300,471 (65.9)	50,789 (60.8)	
>40	102,278 (26.1)	36,381 (24.8)		120,628 (26.5)	18,031 (21.6)	
Otolaryngology procedure, n (%)	32,566 (8.3)	15,999 (10.9)	<0.001	40,057 (8.8)	8508 (10.2)	<0.001
Follow-up time in years, mean (SD)	4.74 (2.85)	4.86 (2.80)		4.77 (2.84)	4.74 (2.83)	
Age at procedure, mean (SD)	3.60 (1.65)	3.52 (1.67)		3.58 (1.66)	3.52 (1.63)	
Total person-years	1,858,905	713,671		2,176,694	395,881	

*P value calculated using chi-square test for categorical variables and one-way analysis of variance for numerical variables.

indicated that mothers who were prescribed antibiotics during pregnancy and mothers who delivered via cesarean section both had, on average, a higher prevalence of health conditions, higher smoking levels and higher BMI. The most prescribed antibiotics were beta-lactam penicillins (80%) (Table 2).

Prenatal Antibiotic Exposure and Risk of Otolaryngology Procedure

Prenatal antibiotic exposure was associated with an increased risk of otolaryngology surgery [adjusted hazard ratio (aHR), 1.22; 95% CI: 1.20–1.24]. The association was seen in all

TABLE 2. Number of Antibiotic Prescriptions During Pregnancy by Antibiotic Class in Study Population

Antibiotic class	Number prescribed
J01A, tetracyclines	2066 (0.9%)
J01C, beta-lactam antibacterials and penicillins	181,035 (80%)
J01D, other beta-lactam antibacterials	1895 (0.8%)
J01E, sulfonamides and trimethoprim	8846 (4%)
J01F, macrolides, lincosamides and streptogramins	13,145 (6%)
J01G, aminoglycoside antibacterials	12 (0.005%)
J01M, quinoline antibacterials	582 (0.3%)
J01X, other antibacterials	19,212 (8%)
Total	226,793

trimesters. A dose–response pattern was observed; aHR, 1.16, 95% CI: 1.13–1.18; 1.29, 95% CI: 1.24–1.33; 1.44, 95% CI: 1.38–1.50 for 1, 2 and 3 or more antibiotic courses, respectively (Table 3). The association between antibiotics and otolaryngology surgery remained the same (aHR, 1.22; 95% CI: 1.19–1.24) after additional adjustment for maternal BMI. A similar risk was observed for throat procedures (aHR, 1.24; 95% CI: 1.21–1.27) and ear procedures (aHR, 1.21; 95% CI: 1.18–1.24) categorized separately, and both associations were comparable with the overall hazard ratio.

Mode of Birth and Risk of Otolaryngology Surgery

Birth by cesarean section was also a risk factor for otolaryngology surgery, after adjusting for prenatal antibiotic exposure during pregnancy (aHR, 1.14; 95% CI: 1.11–1.16) (Table 4). This association was similar after additional adjustment for maternal BMI (aHR, 1.13; 95% CI: 1.11–1.16). In the model examining the interaction between prenatal antibiotic exposure and mode of birth, there was evidence of a weak antagonistic interaction on the multiplicative scale (interaction term, 0.95; 95% CI: 0.90–1.00; $P = 0.03$); the risk associated with prenatal antibiotic exposure may be lower among cesarean section births compared to vaginal births (aHR, 1.16; 95% CI: 1.11–1.22 and aHR, 1.23; 95% CI: 1.21–1.26, respectively) and the risk associated with cesarean birth may be lower among those exposed to prenatal antibiotics compared to no prenatal antibiotics (aHR, 1.10; 95% CI: 1.05–1.14 and aHR, 1.16; 95% CI: 1.12–1.19, respectively) (Table 5). The relative excess risk due to interaction was estimated as −0.04 (95% CI: −0.10 to 0.02; $P = 0.9$), indicating no evidence of additive interaction between the 2 exposures.

Sensitivity Analyses

In a sensitivity analysis only including surgery after 1 year of age, we observed the same estimated hazard ratio as the overall model for prenatal antibiotic exposure. In the analysis restricted to first-born children, we observed slightly lower estimated hazard ratios to our overall model but with overlapping confidence intervals, whereas the analysis adjusting for siblings found comparable hazard ratios for both exposures. In the low-risk subpopulation analysis, we observed a slightly lower hazard ratio than in the overall model for prenatal antibiotic exposure (aHR, 1.19; 95% CI: 1.13–1.26) but a much lower hazard ratio for cesarean section mode of birth (aHR, 1.06; 95% CI: 0.98–1.14). Results of sensitivity analyses are shown in Supplementary Table 1, Supplemental Digital Content 2, http://links.lww.com/INF/E678.

DISCUSSION

In this national registry-based study, both prenatal antibiotic exposure and cesarean section delivery were independent risk factors for otolaryngology surgery in children less than 10 years of age. Furthermore, the association between prenatal antibiotic exposure and risk of otolaryngology surgery showed a dose–response pattern with increasing number of prescribed antibiotics. Using otolaryngology surgery as a marker of recurrent infection and/or allergy/atopy, our findings are in keeping with previous research showing increased risk of severe infections and allergic/atopic diseases for children prenatally exposed to antibiotics, and those born by cesarean section.[14–22] These findings are also consistent with a modestly sized cohort study which suggested that prenatal

TABLE 3. Cox Proportional Hazards Models Analyzing Association Between Prenatal Antibiotic Exposure and Time to First Otolaryngology Surgery

Exposure	No. of surgical procedures/no. of subjects	No. of person-years	Crude hazard ratio (95% CI)	Adjusted* hazard ratio (95% CI)
No prenatal antibiotics	32,566/392,558	1,858,905	1 [Reference]	1 [Reference]
Model 1: Any exposure to antibiotic				
Any prenatal antibiotics	15,999/146,832	713,671	1.27 (1.25–1.30)	1.22 (1.20–1.24)
Model 2: Number of antibiotic courses prescribed in pregnancy				
1 antibiotic course	9989/98,323	475,202	1.19 (1.17–1.22)	1.16 (1.13–1.18)
2 antibiotics courses	3628/30,776	151,646	1.36 (1.31–1.40)	1.29 (1.24–1.33)
3+ antibiotics courses	2382/17,733	86,823	1.55 (1.49–1.62)	1.44 (1.38–1.50)
Model 3: Timing of antibiotic exposure in pregnancy				
First trimester only	3676/34,327	166,801	1.25 (1.21–1.29)	1.20 (1.16–1.24)
Second trimester only	4120/40,567	194,667	1.20 (1.17–1.24)	1.16 (1.12–1.20)
Third trimester only	4246/41,078	201,219	1.20 (1.16–1.23)	1.17 (1.13–1.21)
Multiple trimesters	3957/30,860	150,983	1.49 (1.44–1.54)	1.39 (1.34–1.43)
Model 4: Timing of last antibiotic exposure in pregnancy				
Last antibiotic in first trimester	3676/34,327	166,801	1.25 (1.21–1.29)	1.20 (1.16–1.24)
Last antibiotic in second trimester	5196/48,786	234,732	1.26 (1.22–1.30)	1.20 (1.17–1.24)
Last antibiotic in third trimester	7127/63,719	312,138	1.29 (1.26–1.33)	1.24 (1.21–1.28)

The reference group for models 1–4 is no prenatal antibiotics.

CI, confidence interval.

*Adjusted for preexisting maternal hypertension, maternal kidney disease, maternal diabetes, maternal smoking, maternal asthma, mother's age at birth, hypertension during pregnancy, parity, preeclampsia, gestational age, child's gestational age- and sex-specific birth weight Z score, child sex, and cesarean section.

TABLE 4. Cox Proportional Hazard Models Analyzing Association Between Mode of Birth and Time to First Otolaryngology Surgery

Exposure	No. of surgical procedures/no. of subjects	No. of person-years	Crude hazard ratio (95% CI)	Adjusted* hazard ratio (95% CI)
Vaginal	40,057/455,917	2,176,694	1 [Reference]	1 [Reference]
Model 5: Any cesarean section				
Cesarean section	8508/83,473	395,881	1.17 (1.14–1.20)	1.14 (1.11–1.16)
Model 6: Cesarean section type				
Planned cesarean section	3114/30,997	151,381	1.12 (1.08–1.16)	1.14 (1.10–1.18)
Emergency cesarean section	5390/52,432	244,276	1.20 (1.17–1.23)	1.13 (1.10–1.17)

The reference group for models 5 and 6 is vaginal birth.

CI, confidence interval.

*Adjusted for preexisting maternal hypertension, maternal kidney disease, maternal diabetes, maternal smoking, maternal asthma, mother's age at birth, hypertension during pregnancy, parity, preeclampsia, gestational age, child's gestational age- and sex-specific birth weight Z score, child sex, and prenatal antibiotic exposure.

antibiotic exposure was associated with increased risk of otitis media and ventilation tube insertion in offspring.[31]

A major strength of this study is the use of total population data from Norway over a 10-year period. Registrations in the health registries used in this study are mandatory and of high quality.[27] Population-based data reduces the risk of selection and retention bias, which are limitations of single-center or cohort studies. The large sample size (n = 539,390) allows for adjustment of confounders, subgroup and sensitivity analyses, although we are unable to exclude residual confounding. The population-based design means that the findings are generalizable to other high-income settings. The long follow-up period allowed us to capture the peak incidence of otolaryngology surgeries between 3 and 7 years of age.[32–34] Pneumococcal vaccine (PCV-7) was introduced into the Norwegian Childhood Immunization Program in July 2006, with 80% coverage of the complete 3 immunizations in children >13 months by January 2008,[35] and is therefore unlikely to have impacted the findings.

There are some limitations to our study. First, the prescription database does not include in-hospital antibiotic prescriptions, such as those for prevention of group B streptococcus (GBS) or surgical prophylaxis at the time of cesarean section, and only captures filled prescriptions regardless of whether the medication was used. Prophylactic antibiotics for GBS may affect the neonatal microbiome up to 12 weeks of age,[36] but are not linked to subsequent risk of allergy or asthma in the offspring.[37] In addition, guidelines for GBS antibiotic prophylaxis in Norway are more restrictive than those in the United States,[38] and antibiotics are only prescribed for defined subgroups of GBS-colonized women.[39] Indications for prophylactic antibiotics for cesarean section varied between obstetric units in Norway during the study period. Most centers gave them selectively and the majority administered antibiotics to the mother after cord clamping, so the fetus was unexposed.[40]

Second, we were unable to adjust for socioeconomic status (SES), as these data were not available. However, Norway has relatively low social inequality[41] and a free public healthcare system, so the influence of SES and healthcare access may be relatively limited. Adjusting for certain maternal health characteristics may partially account for SES, particularly adjustment for smoking which is strongly associated with the education level.[42] The lower hazard ratios in the low-risk population, especially for the association of cesarean section with otolaryngology surgery, may indicate further residual confounding not captured by the adjusted covariates, or alternatively, that maternal health factors modify the risk associated with prenatal antibiotic exposure and mode of birth on infection and allergy susceptibility in the child. We were also unable to account for exposures after birth which may be important including

TABLE 5. Cox Proportional Hazards Model With Interaction Term Between Prenatal Antibiotic Exposure and Mode of Birth Analyzing Association With Time to First Otolaryngology Surgery

Exposure	No. of surgical procedures/no. of subjects	No. of person-years	Crude hazard ratio (95% CI)	Adjusted* hazard ratio (95% CI)
Model 7: Interaction model				
Vaginal birth, no prenatal antibiotics	26,916/333,033	1,579,022	1 [Reference]	1 [Reference]
Vaginal birth, prenatal antibiotics	13,141/122,884	597,673	1.28 (1.26–1.31)	1.23 (1.21–1.26)
Cesarean section, no prenatal antibiotics	5650/59,525	279,883	1.18 (1.15–1.22)	1.16 (1.12–1.19)
Cesarean section, prenatal antibiotics	2858/23,948	115,998	1.44 (1.38–1.49)	1.35 (1.30–1.40)
Model 8: Stratified analysis – prenatal antibiotic exposure among cesarean births				
No prenatal antibiotics	5650/59,525	279,883	1 [Reference]	1 [Reference]
Prenatal antibiotics	2858/23,948	115,998	1.21 (1.16–1.27)	1.16 (1.11–1.22)
Model 9: Stratified analysis – mode of birth among those who had prenatal antibiotics				
Vaginal birth	13,141/122,884	597,673	1 [Reference]	1 [Reference]
Cesarean section	2858/23,948	115,998	1.12 (1.08–1.17)	1.10 (1.05–1.14)

CI, confidence interval.

*Adjusted for preexisting maternal hypertension, maternal kidney disease, maternal diabetes, maternal smoking, maternal asthma, mother's age at birth, hypertension during pregnancy, parity, preeclampsia, gestational age, child's gestational age- and sex-specific birth weight Z score, and child sex.

breastfeeding, household environment, animal exposure and childcare attendance.[43,44] Further adjustment for siblings did not change our findings. Data on ethnicity were unavailable in our study. In 2017, 16.8% of the Norwegian population were either immigrants or Norwegian-born to immigrant parents.[45] Data from other populations suggest that ventilation tubes insertion is less frequent in ethnic minority groups, suggested to arise from clinician bias in management or different healthcare-seeking behaviors.[46] However, in Norway, the universal healthcare system should theoretically reduce differences in access to otolaryngology surgery.

Finally, antibiotic prescriptions are a marker for clinical infection episodes in pregnancy, but it is not possible to further differentiate the extent of confounding by indication; antibiotics are usually prescribed for clinical infection and mild infections in pregnancy, not treated by antibiotics, are not captured by population-level databases. Our findings are in keeping with previous research that found prenatal antibiotic exposure and cesarean section to be associated with immune-mediated outcomes, including asthma and hospitalized infection.[14–22] Although the study design precluded investigation of underlying mechanisms, it is possible that the associations reflect suboptimal colonization of the postnatal offspring microbiome because of either antibiotic-induced maternal dysbiosis shared with the infant during vaginal birth, or lack of vaginal microbiome transfer due to birth by cesarean section.[47] In addition, antibiotics may alter the maternal gut microbiome, which in turn may affect specific products of bacterial metabolism, such as short-chain fatty acids, which impact fetal immune development.[48] Epigenetic modification has also been hypothesized as a molecular mechanism through which prenatal antibiotic exposure or cesarean section may affect disease risk.[49,50] While changes to epigenetic marks is a plausible contributory mechanism, data are limited. There was some evidence of a weak antagonistic interaction between prenatal antibiotic exposure and mode of birth on the multiplicative scale but no evidence of interaction on the additive scale. Interaction on at least 1 scale was expected as both exposures had an effect on the outcome.[51] On the multiplicative scale, the association of prenatal antibiotic exposure was lower among cesarean section deliveries compared to vaginal deliveries. This is consistent with the hypothesis of exposure to the maternal microbiome during vaginal delivery seeding the initial infant microbiome. However, the increased risk associated with prenatal antibiotics was observed even for planned cesarean section births and was similar for exposure across the 3 trimesters, suggesting there may be multiple mechanisms. These hypotheses cannot be directly tested in observational data and warrant further mechanistic studies.

The early life microbiome influences postnatal immune function,[52,53] which in turn may impact the incidence and severity of immune-mediated outcomes, particularly infection and allergy/atopy. Recurrent infection and allergic stimulation of the respiratory tract, which does not usually result in hospitalization (so is not captured by population registries) may increase the risk of otolaryngology surgery. Alternative mechanisms, which are not mutually exclusive, may also explain the observed associations. Maternal antibiotic prescriptions may be surrogate for maternal infection during pregnancy, which may increase the risk of infection in the offspring and subsequent otolaryngology surgery.[54,55] In addition, antibiotic exposure may be a proxy for shared genetic or environmental factors between the mother and child that predispose them to infection and are not captured by measures included in this study.[14] Previous research showing the heritability of certain pathologies that may necessitate otolaryngology surgery indicates that this may be a source of unmeasured confounding.[56,57] Future studies with multigenerational health data should explore adjustment for maternal history of otolaryngology surgery.

In summary, prenatal antibiotic exposure and cesarean section are each associated with increased risk of otolaryngology surgery in childhood, which may be indicative of heightened susceptibility to recurrent early life infections and/or allergy/atopy. Potential biological mechanisms underlying these epidemiological associations warrant further investigation. This may inform management decisions during pregnancy and early interventions to optimize the pregnancy and child's immune development.

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