



Prenatal and Postnatal Exposure to Antibiotics and the Risk of Type 1 Diabetes in Finnish Children: A Registry-based Study

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Objective To study whether prenatal and postnatal exposure to antibiotics is associated with the risk of type 1 diabetes in childhood.

Study design This case cohort study included 2869 children diagnosed with type 1 diabetes by the end of 2009 who were born between January 1, 1996, and December 31, 2008, in Finland and a reference cohort (n = 74 263) representing 10% of each birth cohort. Exposure to antibiotics was assessed in different time periods. The data were derived from Special Reimbursement Register, Drug Prescription Register, and Population Register and analyzed with weighted Cox proportional hazards regression models.

Results Exposure to any antibiotics before or during pregnancy, in the neonatal ward, during the first year of life, or during the 2 first years of life, was not associated with the risk of type 1 diabetes in the offspring. Exposure to macrolides in the year preceding pregnancy (adjusted hazard ratio [HR], 1.17; 95% CI, 1.02-1.33) and to sulfonamides and trimethoprim during pregnancy (adjusted HR, 1.91; 95% CI, 1.07-3.41) was associated with an increased risk of type 1 diabetes in the offspring. Exposure to sulfonamides and trimethoprim during first 2 years of life was associated with a decreased risk of type 1 diabetes (adjusted HR, 0.84; 95% CI, 0.73-0.97). The number of antibiotic purchases among mothers or children was not associated with type 1 diabetes risk.

Conclusions Prenatal and postnatal exposure to antibiotics in general did not increase the risk of type 1 diabetes in the offspring. However, the type of antibiotic and timing of exposure may play a role in type 1 diabetes risk. (*J Pediatr* 2025;276:114292).

The incidence of type 1 diabetes has been increasing over decades in several countries, including Finland.¹ Although the increase seems to have plateaued, the incidence in Finland is among the highest in the world.² The use of antibiotics has been suggested as a potential risk factor for type 1 diabetes, because antibiotics affect the gut microbiota, and disturbances in the gut microbiota are believed to play a role in the development of type 1 diabetes.³ In contrast, the use of antibiotics may reflect infections, some of which have also been linked to the risk of type 1 diabetes.⁴

Maternal use of antibiotics before or during pregnancy could play a role in child's risk of type 1 diabetes. A Swedish study showed a weak association between maternal antibiotics use during pregnancy and increased risk of childhood type 1 diabetes, although other studies found no association.⁵⁻⁸ The association between child's early exposure to antibiotics and subsequent development of type 1 diabetes has also been studied with inconsistent results.^{5-7,9-12} The associations may depend on the timing of the exposure and the type of antibiotic. A meta-analysis found no association between an overall antibiotic exposure in early childhood and the risk of type 1 diabetes, although antibiotic use increased the risk of several other conditions such as allergic symptoms, asthma and obesity.¹³

In Finland, the association between prenatal and postnatal exposure to antibiotics and the risk of type 1 diabetes has been investigated only in smaller-scale case-control studies including 437 and 102 children with type 1 diabetes.^{14,15} These studies observed no association between an overall exposure to antibiotics in mothers or children and the risk of type 1 diabetes.^{14,15} However, some specific associations were reported, such as maternal exposure to phenoxymethylpenicillins or quinolone antimicrobials before pregnancy and an increased risk of type 1 diabetes in the child.¹⁴ Finally, a recent Finnish study focusing on intrapartum exposure to antibiotics among vaginally delivered infants reported antibiotics

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Data availability: Data protection laws do not permit sharing of the data used in the present study. Access to Finnish register data can be requested from the Finnish Social and Health Data Permit Authority (Findata; www.findata.fi).

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<https://doi.org/10.1016/j.jpeds.2024.114292>

ATC	Anatomical therapeutic chemical (classification system)
CI	Confidence interval
HR	Hazard ratio

to be associated increased risk of any autoimmune diseases in the offspring, but not specifically with type 1 diabetes.¹⁶

Our aim was to study whether prenatal and postnatal exposure to antibiotics is associated with the risk of type 1 diabetes in childhood in a nationwide case-cohort study in Finland. We focused on maternal exposure to antibiotics during the 1 year before pregnancy and during pregnancy, and the child's exposure by the age of 2 years. We also evaluated different types of antibiotics, and interaction analyses, for example, including delivery mode and sex.

Methods

Data for the present case cohort study were obtained from nationwide health registers and linked together using unique personal identity codes assigned to all Finnish residents after birth or when getting permanent residency. The Special Reimbursement Register and the Population Register maintained by the Social Insurance Institution of Finland were used to select case children and the reference cohort, respectively, as described previously.¹⁷ Case children were defined as all those children who were born in Finland between January 1, 1996, and December 31, 2008, and who had received a special reimbursement for the costs of diabetic medicine by the end of 2009 (n = 2920). In Finland, pediatric patients with type 1 diabetes are entitled to a special reimbursement for the cost of the disease-related medication after specialist-verified diagnosis and a Social Insurance Institution review. The administrative process for decision-making takes only a couple of weeks; thus, the date of entitlement decision of the special reimbursement was used as a proxy for the date of diagnosis. Case children who had a type 2 diabetes diagnosis (*International Classification of Diseases*, 10th edition, code E11) (n = 45), who had no insulin purchases after the diagnosis (n = 5), or both (n = 1) were excluded. Finally, 2869 children were included in the study as type 1 diabetes cases. A 10% random sample from each birth year cohort (1996-2008) was selected as a reference cohort (n = 74 646), and after excluding 43 children who died on their birth date, the final reference cohort included 74 603 children. According to the study design, 340 children with type 1 diabetes were also included in the reference cohort.

We used a nationwide prescription database, the Drug Prescription Registry maintained by the Social Insurance Institution to obtain information on dispensed reimbursed antibiotics.¹⁸

All prescribed drugs reimbursed by the National Sickness Insurance Scheme are registered in the Drug Prescription Registry maintained since 1994. In Finland, outpatient antibiotics are available on prescription only and are sold only in pharmacies. The Drug Prescription Registry includes information on drug class (Anatomical Therapeutic Chemical [ATC] Classification System) and dispensing date of the prescription.¹⁹ The register does not include antibiotics administered at hospitals.

Information on all antibiotic (ATC code J01, antibacterials for systemic use) purchases by the mother and for the child between 1995 and 2008 was extracted. For maternal antibiotics, the exposure periods were defined as the 1 year preceding pregnancy and pregnancy (calculated from child's birth date and gestational age or in case of missing gestational age we made an assumption of 280 days for the duration of gestation).

Maternal exposure to antibiotics categorized as overall exposure (0 vs ≥ 1 purchases) of any antibiotics, overall exposure (0 vs ≥ 1 purchases) of most commonly purchased specific antibiotics, namely, cephalosporins (ATC code J01DB-DC), broad-spectrum penicillins (J01CA), macrolides (J01FA), tetracyclines (J01AA), phenoxymethylpenicillin (J01CE02), fluoroquinolones (J01 MA), sulfonamides and trimethoprim (J01E), and number of purchases (0, 1, 2, or ≥ 3 purchases) of any antibiotics.

Child exposure periods examined were the first year of life and the first 2 years of life. Child's exposure to antibiotics was categorized as overall exposure (0 vs ≥ 1 purchases) to any antibiotics, and overall exposure (0 vs ≥ 1 purchases) to the most commonly used specific antibiotics, namely, amoxicillin (including its combination with enzyme inhibitor; ATC codes J01CA04 and J01CR02), macrolides (J01FA), cephalosporins (J01DB-DC), sulfonamides and trimethoprim (J01E), phenoxymethylpenicillin (J01CE02), and number of purchases (0, 1, 2, 3, 4, or ≥ 5 purchases) of any antibiotics. In addition, we obtained information on exposure to antibiotics in the neonatal ward (yes/no) from the Medical Birth Register.

Information on maternal background, pregnancy, and newborn characteristics as derived from the Finnish Medical Birth Register, collected since 1987 and maintained by the Finnish Institute for Health and Welfare. Covariates include maternal age at birth (<25, 25-29, 30-34, or ≥ 35 years), maternal smoking during pregnancy (no, yes), maternal diabetes (type 1 or 2, medication initiated before delivery; no, yes), maternal asthma (medication initiated before delivery; no, yes), maternal previous deliveries (0, 1, or ≥ 2), gestational age (<37, 37-41, or ≥ 42 weeks), child's birth size (small, appropriate, large for gestational age), sex (female, male), season of birth (winter: December-February, spring: March-May, summer: June-August, autumn: September-November), mode of delivery (vaginal delivery, caesarean section), and child's year of birth (continuous).²⁰

Information on maternal asthma, maternal diabetes, and child's asthma before the of 1 and 2 years of age was obtained from the Special Reimbursement Register. In addition to a physician-confirmed diagnosis, a year-round drug treatment, mainly with inhaled corticosteroids and inhaled β_2 -agonists as add-on therapy, is a requirement for special reimbursement for asthma.

The association between exposure to antibiotics and the risk of type 1 diabetes was analyzed using weighted Cox proportional hazards regression that takes into account the case cohort design. Children were followed from birth, age 1 year,

or age 2 years in analyses of maternal exposure, child exposure during first year or during first 2 years of life, respectively, until death, date of type 1 diabetes diagnosis, or the end of follow-up, whichever occurred first. We ran both unadjusted and adjusted models. We considered several maternal and child characteristics that previous research has shown to be associated with type 1 diabetes as confounders in the analyses.¹⁷ Adjusted models on maternal exposure were adjusted for maternal age, maternal smoking during pregnancy, maternal diabetes, maternal asthma, maternal previous deliveries, child's year of birth, and season of birth. Models for child exposure were adjusted for maternal age, maternal smoking during pregnancy, maternal diabetes, maternal asthma, maternal previous deliveries, child's year of birth, season of birth, mode of delivery, sex, gestational age, and birth size.

The proportional hazards assumption for all the models was examined by testing for interaction of Schoenfeld residuals with time and visually from log(-log(survival)) plots, and there were no clear deviations from the assumption (Supplementary Table 1, Supplementary Figure 1, online; available at www.jpeds.com). We investigated interactions between background variables (child's sex, mode of delivery, and child's asthma) and maternal or child's exposure to antibiotics (dichotomous variables) as well as between maternal exposure (before or during pregnancy) and child's exposure to antibiotics by including an interaction term to the regression model. If there was indication of interaction (P for interaction $< .1$), we either stratified the results or created a composite variable and presented results in the categories of this variable, depending on the nature of variables involved. For example, a composite variable combining maternal and child antibiotic exposure was categorized as (1) mother not exposed to antibiotics + child not exposed to antibiotics (reference category), (2) mother exposed, child not exposed, (3) mother not exposed, child exposed, and (4) both mother and child exposed.

Analyses were performed using STATA (StataCorp, College Station, TX, version 17.0)

In Finland, informed consent or ethical review is not required for the use of pseudonymized register data for research purposes. However, this study was approved by the National Data Protection Authority, the institutions keeping the registers and the Institutional Review Board of the Finnish Institute for Health and Welfare.

Results

The mean age of type 1 diabetes diagnosis ($n = 2869$) was 5.2 years \pm 2.9, and 25% and 75% of the children were diagnosed by age of 2.7 and 7.4 years, respectively. The mean age at the end of follow-up in children without diabetes in the reference cohort ($n = 74\,263$) was 7.5 \pm 3.8 years. Characteristics of children with and without type 1 diabetes are presented in Table I.

Table I. Background characteristics of children with type 1 diabetes and the children in the reference cohorts without type 1 diabetes born between 1996 and 2008 in Finland

Characteristics	Children with type 1 diabetes (n = 2869)		Children without type 1 diabetes (n = 74 263)	
	No.	%	No.	%
Maternal age at child's birth, years				
<25	506	17.6	14 390	19.4
25-29	936	32.6	23 624	31.8
30-34	932	32.5	22 904	30.8
≥ 35	495	17.3	13 345	18.0
Maternal smoking during pregnancy				
No	2523	87.9	63 192	85.1
Yes	278	9.7	9083	12.2
Missing	68	2.4	1988	2.7
Maternal diabetes				
No	2761	96.2	73 641	99.2
Yes	108	3.8	622	0.8
Maternal asthma				
No	2658	92.6	70 560	95.0
Yes	211	7.4	3703	5.0
No. of maternal previous pregnancies				
0	1201	41.9	30 859	41.6
1	995	34.7	24 627	33.2
≥ 2	666	23.2	18 636	25.1
Missing	7	0.2	141	0.2
Gestational age, weeks				
<37	198	6.9	4175	5.6
37-41	2562	89.3	66 206	89.2
≥ 42	101	3.5	3562	4.8
Missing	8	0.3	320	0.4
Birth size				
Small for gestational age	40	1.4	1704	2.3
Appropriate for gestational age	2688	93.7	70 123	94.4
Large for gestational age	132	4.6	2 098	2.9
Missing	9	0.3	338	0.5
Sex				
Female	1321	46.0	36 248	48.8
Male	1548	54.0	38 015	51.2
Season of birth				
Winter	667	23.2	17 767	23.9
Spring	787	27.4	19 117	25.7
Summer	736	25.7	19 284	26.0
Autumn	679	23.7	18 095	24.4
Mode of delivery				
Vaginal delivery	2318	80.8	61 765	83.2
Cesarean section	545	19	12 364	16.6
Missing	6	0.2	134	0.2
Year of birth				
1996-1999	1569	54.7	23 063	31.9
2000-2003	947	33.0	22 146	29.8
2004-2008	353	12.3	29 054	39.1
Child's asthma by the age of 1 year				
No	2848	99.3	73 875	99.5
Yes	21	0.7	388	0.5
Child's asthma by the age of 2 years				
No	2791	97.3	73 084	98.4
Yes	78	2.7	1179	1.6

Exposure to any antibiotics in the year preceding pregnancy or during pregnancy was not associated with the risk of type 1 diabetes in the offspring (Table II). Of the specific antibiotics, exposure to macrolides in the year

Table II. Maternal exposure to antibiotics before and during pregnancy and the risk of type 1 diabetes in the offspring born between 1996 and 2008 in Finland

Exposure periods, types of antibiotic	Children with type 1 diabetes (n = 2869)		Children without type 1 diabetes (n = 74 263)		Unadjusted model		Adjusted model*	
	No.	%	No.	%	HR	95% CI	HR	95% CI
One year preceding pregnancy								
Any antibiotic	1037	36.1	25 902	34.9	1.06	0.98-1.14	1.04	0.96-1.12
Cephalosporins	386	13.5	9462	12.7	1.06	0.95-1.18	1.04	0.93-1.16
Broad-spectrum penicillins	266	9.3	7953	10.7	0.92	0.81-1.04	0.93	0.81-1.06
Macrolides	270	9.4	6113	8.2	1.18	1.04-1.35	1.17	1.02-1.33
Tetracyclines	236	8.2	4890	6.6	1.06	0.92-1.22	1.02	0.89-1.17
Phenoxymethylpenicillin	110	3.8	2733	3.7	1.09	0.90-1.33	1.07	0.87-1.30
Fluoroquinolones	65	2.3	1379	1.9	1.30	1.01-1.67	1.27	0.98-1.64
Sulfonamides and trimethoprim	68	2.4	1313	1.8	1.16	0.91-1.49	1.10	0.86-1.42
During pregnancy								
Any antibiotic	698	24.3	18 387	24.8	0.99	0.91-1.08	0.99	0.91-1.08
Cephalosporins	304	10.6	7370	9.9	1.06	0.93-1.19	1.03	0.91-1.17
Broad-spectrum penicillins	344	12.0	9663	13.0	0.95	0.85-1.07	0.97	0.86-1.09
Macrolides	104	3.6	2259	3.0	1.10	0.90-1.34	1.05	0.86-1.29
Tetracyclines	24	0.8	422	0.6	1.21	0.80-1.83	1.18	0.78-1.80
Phenoxymethylpenicillin	44	1.5	1704	2.3	0.77	0.57-1.04	0.76	0.56-1.03
Fluoroquinolones	9	0.3	140	0.2	1.62	0.82-3.19	1.51	0.74-3.10
Sulfonamides and trimethoprim	13	0.5	154	0.2	1.96	1.11-3.47	1.91	1.07-3.41

*Adjusted for maternal age, maternal smoking during pregnancy, maternal diabetes, maternal asthma, maternal previous deliveries, child's year of birth, and season of birth.

preceding pregnancy was associated with an increased risk of type 1 diabetes in the offspring (adjusted hazard ratio [HR], 1.17; 95% CI, 1.02-1.33) (Table II). In addition, exposure to sulfonamides and trimethoprim during pregnancy was associated with an increased risk of type 1 diabetes in the offspring (adjusted HR, 1.91; 95% CI, 1.07-3.41) (Table II).

Exposure to antibiotics in the neonatal ward or during the first year of life was not associated with the risk of type 1 diabetes (Table III). Exposure to sulfonamides and trimethoprim during the first 2 years of life was associated

with a decreased risk of type 1 diabetes in the offspring (adjusted HR, 0.84; 95% CI, 0.73-0.97) (Table III). The number of antibiotic purchases in mothers or children was not associated with risk of type 1 diabetes in the offspring (Table IV).

The studied interactions and *P* values for interactions are shown in Supplementary Table 2, online; available at www.jpeds.com. Sex modified the association between exposure to antibiotics during the first year of life and the risk of type 1 diabetes. Exposure to antibiotics during the

Table III. Early life exposure to antibiotics and the risk of type 1 diabetes in children born between 1996 and 2008 in Finland

Exposure periods, types of antibiotic	Children with type 1 diabetes		Children without type 1 diabetes		Unadjusted model		Adjusted model*	
	No.	%	No.	%	HR	95% CI	HR	95% CI
Neonatal ward								
Any antibiotic	105	3.7	3339	4.5	0.98	0.80-1.20	0.91	0.74-1.12
First year [†]								
Any antibiotic [‡]	1329	47.5	32 066	47.0	0.99	0.92-1.07	0.98	0.90-1.06
Amoxicillin	1026	36.7	25 450	37.3	0.98	0.90-1.05	0.97	0.89-1.05
Macrolides	537	19.2	12 532	18.4	1.00	0.91-1.10	0.99	0.89-1.09
Cephalosporins	251	9.0	5946	8.7	0.95	0.83-1.08	0.93	0.81-1.07
Sulfonamides and trimethoprim	87	3.1	3088	4.5	0.87	0.70-1.08	0.86	0.69-1.07
Phenoxymethylpenicillin	78	2.8	1269	1.9	1.25	0.99-1.57	1.17	0.92-1.50
First 2 years [§]								
Any antibiotic	1838	75.8	50 914	74.7	1.01	0.92-1.11	0.99	0.90-1.09
Amoxicillin	1551	63.9	43 688	64.1	1.00	0.92-1.09	0.98	0.90-1.07
Macrolides	1006	41.5	26 795	39.3	1.01	0.93-1.09	0.98	0.90-1.07
Cephalosporins	544	22.4	14 232	20.9	1.01	0.92-1.12	0.99	0.89-1.09
Sulfonamides and trimethoprim	212	8.7	8436	12.4	0.87	0.75-1.00	0.84	0.73-0.97
Phenoxymethylpenicillin	174	7.2	3747	5.5	1.07	0.91-1.25	1.00	0.85-1.18

*Adjusted for maternal age, maternal smoking during pregnancy, maternal diabetes, maternal asthma, maternal previous deliveries, child's year of birth, season of birth, mode of delivery, sex, gestational age, birth size.

[†]Additionally adjusted for childhood asthma by the age of one year.

[‡]Sex-first-year any antibiotic exposure interaction *P* = .006; female [adjusted HR, 0.86; 95% CI, 0.76-0.97]; male, adjusted HR, 1.09; 95% CI, 0.98-1.11).

[§]Additionally adjusted for childhood asthma by the age of 2 years.

Table IV. Number of antibiotic purchases among mothers before and during pregnancy, and children in first year and 2 first years of life, and the risk of type 1 diabetes in children born between 1996 and 2008 in Finland

Exposure periods, No. of purchases	Children with type 1 diabetes		Children without type 1 diabetes		Unadjusted model		Adjusted model*	
	No.	%	No.	%	HR	95% CI	HR	95% CI
Mother, 1 year preceding pregnancy	2869	100	74 263	100				
0	1832	63.9	48 361	65.1	1.00		1.00	
1	631	22.0	15 988	21.5	1.04	0.95-1.14	1.01	0.92-1.12
2	242	8.4	6 110	8.2	1.05	0.91-1.20	1.04	0.91-1.20
≥3	164	5.7	3 804	5.1	1.16	0.99-1.37	1.12	0.95-1.33
Mother, during pregnancy	2869	100	74 263	100				
0	2,171	75.7	55 876	75.2	1.00		1.00	
1	477	16.6	12 818	17.3	0.97	0.88-1.08	0.98	0.88-1.08
2	149	5.2	3 912	5.3	0.99	0.84-1.18	0.98	0.82-1.17
≥3	72	2.5	1 657	2.2	1.15	0.90-1.46	1.14	0.89-1.45
Child, first year	2 798	100	68 182	100				
0	1 469	52.5	36 116	53.0	1.00		1.00	
1-2	971	34.7	23 043	33.8	1.00	0.92-1.09	0.99	0.91-1.08
3-4	270	9.7	6 519	9.6	1.00	0.88-1.15	0.99	0.86-1.13
5-6	63	2.3	1 831	2.7	0.84	0.65-1.09	0.86	0.66-1.11
≥7	25	0.9	673	1.0	0.98	0.65-1.46	0.90	0.59-1.38
Child, first 2 years	2 426	100	68 154	100				
0	588	24.2	17 240	24.3	1.00		1.00	
1-2	820	33.8	22 728	33.4	1.01	0.90-1.12	1.01	0.90-1.12
3-4	506	20.9	13 406	19.7	1.04	0.92-1.18	1.01	0.90-1.15
5-6	246	10.1	7 409	10.9	0.94	0.81-1.09	0.90	0.77-1.05
≥7	266	11.0	7 371	10.8	1.05	0.91-1.22	1.02	0.87-1.18

Analyses with child's exposure adjusted for maternal age, maternal smoking during pregnancy, maternal diabetes, maternal asthma, maternal previous deliveries, child's year of birth, season of birth, mode of delivery, sex, gestational age, birth size, and childhood asthma.

*Analyses with maternal exposure adjusted for maternal age, maternal smoking during pregnancy, maternal diabetes, maternal asthma, maternal previous deliveries, child's year of birth, and season of birth.

first year of life was associated with a decreased risk of type 1 diabetes in females (HR, 0.86; 95% CI, 0.76-0.97), but not in males (HR, 1.09; 95% CI, 0.98-1.11; *P* for interaction = .006). There was no indication of interaction for mode of delivery and childhood asthma for the studied associations.

Maternal exposure to macrolides modified the association between child's macrolide exposure during the first year (*P* for interaction = .097) and during first 2 years (*P* for interaction = .070) of life and risk of type 1 diabetes (Supplementary Table 2, online; available at www.jpeds.com). Macrolides were not associated with risk of type 1 diabetes when either mother only or child only were exposed, but the risk was increased if both the mother and

the child were exposed (Table V). There was an indication of a mother-child interaction for sulfonamides and trimethoprim exposure (*P* < .01) (Supplementary Table 2, online; available at www.jpeds.com), but stratified analysis was not possible owing to small cell size. No other mother-child exposure interactions were observed.

Discussion

In this large, nationwide, registry-based study, prenatal and postnatal exposure to antibiotics in general did not increase the risk of type 1 diabetes in the offspring. However, exposure to macrolides in the year preceding pregnancy and exposure

Table V. Combined exposure to macrolides in mothers and their offspring and the risk of type 1 diabetes in the offspring born between 1996 and 2008 in Finland

Exposures to macrolides	Children with type 1 diabetes		Children without type 1 diabetes		Unadjusted model		Adjusted model*		
	No.	%	No.	%	OR	95% CI	OR	95% CI	
Mother before or during pregnancy	Child, first year	2 798	100	68 182	100				
No	No	2 019	72.2	50 105	73.5	1			
Yes	No	242	8.7	5 545	8.1	1.10	0.95-1.24	1.04	0.91-1.20
No	Yes	440	15.7	10 760	15.8	0.96	0.86-1.06	0.96	0.86-1.07
Yes	Yes	97	3.5	1 772	2.6	1.30	1.05-1.60	1.29	1.04-1.60
Mother before or during pregnancy	Child, first 2 years	2 426	100	68 154	100				
No	No	1 289	53.1	37 603	55.2	1		1	
Yes	No	131	5.4	3 756	5.5	1.02	0.85-1.23	1.00	0.83-1.21
No	Yes	842	34.7	23 239	34.1	0.97	0.89-1.06	0.96	0.88-1.05
Yes	Yes	164	6.8	3 556	5.2	1.26	1.06-1.48	1.22	1.03-1.45

*Adjusted for maternal age, maternal smoking during pregnancy, maternal diabetes, maternal asthma, maternal previous deliveries, child's year of birth, and season of birth.

to sulfonamides and trimethoprim during pregnancy was associated with an increased risk of type 1 diabetes in the offspring. In addition, sulfonamides and trimethoprim exposure during the first 2 years of life was associated with a decreased risk of type 1 diabetes.

This study does have limitations. As an observational study, no conclusions of causality can be made. Although we were able to include several covariates in our analyses, we missed some key information, such as indication of antibiotic treatment, HLA genotype, use of probiotics, and nutrition. Some uncertainty is associated with antibiotic exposure: First, our exposure variables did not include antibiotics administered at hospital except at neonatal ward; second, we do not know whether purchased antibiotics were actually used, and third, we may have missed some low-cost short-term antibiotic purchases as purchases of <10 Euros were not reimbursed and listed in the Drug Prescription Registry for most of the study period (until 2006). In contrast, in Finland antibiotics are sold in pharmacies and by prescription only, which decreases the chances of potential misclassification. Finally, because we performed multiple tests, but did not adjust for multiple testing, some of the observed associations may be due to type I error.

The large and representative study sample supports generalizability of the results to Finnish pediatric populations. However, generalizability of the findings to children born in the 2010s or later may be limited owing to potential changes in antibiotic prescribing practices and products available in the markets.

Our finding that exposure to any antibiotics during pregnancy is not associated with type 1 diabetes in the offspring is in line with most of the previous studies.^{6-8,14} However, one study found a borderline association between maternal antibiotics exposure during pregnancy and increased risk of childhood diabetes.⁵ Our finding that sulfonamides and trimethoprim exposure during pregnancy increases the risk of type 1 diabetes in the offspring is novel, although a similar, but nonsignificant association was previously observed in the smaller Finnish registry-based study, in which the data partly overlap with the data used in the present study.¹⁴ Some caution is needed in interpretation of this result because the use of sulfonamides and trimethoprim should be avoided during pregnancy; therefore, our observation is based on only a small number of mothers exposed during pregnancy.

Our observation that exposure to antibiotics before pregnancy in general was not associated with offspring risk of type 1 diabetes is in line with the previous smaller Finnish registry-based study.¹⁴ In the present study, exposure to macrolides before pregnancy was associated with increased risk of type 1 diabetes, while other specific antibiotics showed no association with type 1 diabetes. However, when both mother's and child's exposure to macrolides was taken into account, the risk of type 1 diabetes was increased only if both the mother and the child were exposed, which is in line with previous findings.¹⁴ This study did not confirm the previous Finnish observation that exposure to phenoxymethylpenicillin and quinolones before pregnancy increase the risk of type 1 diabetes.¹⁴

Our finding on overall exposure to antibiotics in childhood is not associated with type 1 diabetes is in line with previous studies, and the lack of association between number of purchases and type 1 diabetes further supports the null finding.¹³ However, we observed some novel inverse associations with specific antibiotics: exposure to sulfonamides and trimethoprim during first 2 years of life and exposure to any antibiotics during the first year of life in females was associated with a decreased risk of type 1 diabetes.

The most commonly discussed potential mechanism between the antibiotics and development of type 1 diabetes relates to the antibiotic-induced changes in the gut microbiota, which could affect the immune development and subsequently the risk of type 1 diabetes.^{21,22} Usually, antibiotic-induced changes in the gut microbiota have been considered harmful or disruptive to normal development. Further, maternal antibiotic use may have longstanding effects, and affect the child's microbiota composition and presence of antibiotic resistance genes.^{23,24} Our findings and the literature reporting antibiotic use and risk of type 1 diabetes does not fully support this hypothesis. However, our observation on maternal and child's joint exposure to macrolides and increased risk of type 1 diabetes could be explained potentially by microbiota-related mechanisms or by macrolides' direct effects on islet cells.^{23,25,26} A potential mechanism underpinning our findings on maternal exposure to trimethoprim and sulfonamides and increased risk of type 1 diabetes is trimethoprim's effect on the fetal folate metabolism, which could contribute to impaired beta cell development and risk of type 1 diabetes.^{27,28} Alternatively, this association could be due to confounding by indication, such as maternal urinary tract infection during pregnancy.²⁹

We observed a sex interaction suggesting that female and male children may have different risk of type 1 diabetes related to exposure to antibiotics during the first year of life. We observed no signs of effect modification by mode of delivery on the association of child exposure to antibiotics and the risk of type 1 diabetes, unlike 2 studies that reported higher exposure to antibiotics related risk of type 1 diabetes among children born by caesarean section in comparison with children born vaginally.^{5,6}

Prenatal and postnatal exposure to antibiotics in general did not increase the risk of type 1 diabetes in offspring. However, the role of antibiotics may vary by timing of exposure and type of antibiotic. This study expands understanding of the role of antibiotics and type 1 diabetes risk in humans. ■

CRedit authorship contribution statement

Leena Hakola: Writing – review & editing, Writing – original draft, Funding acquisition. **Annamari Lundqvist:** Writing – review & editing, Conceptualization. **Mika Gissler:** Writing – review & editing, Data curation. **Lauri J. Virta:** Writing – review & editing, Data curation. **Suvi M. Virtanen:** Writing – review & editing, Supervision, Conceptualization. **Johanna Metsälä:** Writing – review & editing,

Writing – original draft, Project administration, Formal analysis.

Declaration of Competing Interest

Supported by The Diabetes Research Foundation, Finland. The study sponsor was not involved in the design of the study; the collection, analysis, and interpretation of data; writing the report; or the decision to submit the report for publication. The authors declare no conflicts of interest.

Submitted for publication Jun 4, 2024; last revision received Sep 3, 2024; accepted Sep 4, 2024.

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References

- Patterson CC, Harjutsalo V, Rosenbauer J, Neu A, Cinek O, Skrivarhaug T, et al. Trends and cyclical variation in the incidence of childhood type 1 diabetes in 26 European centres in the 25 year period 1989–2013: a multicentre prospective registration study. *Diabetologia* 2019;62:408–17. <https://doi.org/10.1007/s00125-018-4763-3>
- Parviainen A, But A, Siljander H, Knip M, Finnish Pediatric Diabetes Register. Decreased incidence of type 1 diabetes in Young Finnish children. *Diabetes Care* 2020;43:2953–8.
- Vatanen T, Franzosa EA, Schwager R, Tripathi S, Arthur TD, Vehik K, et al. The human gut microbiome in early-onset type 1 diabetes from the TEDDY study. *Nature* 2018;562:589–94. <https://doi.org/10.1038/s41586-018-0620-2>
- Lönnrot M, Lynch KF, Elding Larsson H, Lernmark Å, Rewers MJ, Törn C, et al. Respiratory infections are temporally associated with initiation of type 1 diabetes autoimmunity: the TEDDY study. *Diabetologia* 2017;60:1931–40. <https://doi.org/10.1007/s00125-017-4365-5>
- Wernroth M-L, Fall K, Svennblad B, Ludvigsson JF, Sjölander A, Almqvist C, et al. Early childhood antibiotic treatment for otitis media and other respiratory tract infections is associated with risk of type 1 diabetes: a nationwide register-based study with sibling analysis. *Diabetes Care* 2020;43:991–9. <https://doi.org/10.2337/dc19-1162>
- Clausen TD, Bergholt T, Bouaziz O, Arpi M, Eriksson F, Rasmussen S, et al. Broad-spectrum antibiotic treatment and subsequent childhood type 1 diabetes: a Nationwide Danish Cohort Study. *PLoS One* 2016;11:e0161654 <https://doi.org/10.1371/journal.pone.0161654>
- Tapia G, Størdal K, Mårild K, Kahrs CR, Skrivarhaug T, Njølstad PR, et al. Antibiotics, acetaminophen and infections during prenatal and early life in relation to type 1 diabetes. *Int J Epidemiol* 2018;47:1538–48. <https://doi.org/10.1093/ije/dyy092>
- Haupt-Jørgensen M, Morgen CS, Jess T, Buschard K, Josefsen K, Allin KH, et al. Maternal antibiotic Use during pregnancy and type 1 diabetes in children—a national prospective cohort study. *Diabetes Care* 2018;41:e155–7. <https://doi.org/10.2337/dc18-1764>
- Mikkelsen KH, Knop FK, Vilsbøll T, Frost M, Hallas J, Pottegård A. Use of antibiotics in childhood and risk of Type 1 diabetes: a population-based case–control study. *Diabet Med* 2017;34:272–7. <https://doi.org/10.1111/dme.13262>
- Antvorskov JC, Morgen CS, Buschard K, Jess T, Allin KH, Josefsen K. Antibiotic treatment during early childhood and risk of type 1 diabetes in children: a national birth cohort study. *Pediatr Diabetes* 2020;21:1457–64. <https://doi.org/10.1111/peidi.13111>
- Hviid A, Svanström H. Antibiotic use and type 1 diabetes in childhood. *Am J Epidemiol* 2009;169:1079–84. <https://doi.org/10.1093/aje/kwp038>
- Lee D, Choi S, Chang J, Park YJ, Kim JH, Park SM. Association of antibiotics exposure within the first 2 years after birth with subsequent childhood type 1 diabetes. *Endocrine* 2022;77:21–9. <https://doi.org/10.1007/s12020-022-03042-7>
- Duong QA, Pittet LF, Curtis N, Zimmermann P. Antibiotic exposure and adverse long-term health outcomes in children: a systematic review and meta-analysis. *J Infect* 2022;85:213–300. <https://doi.org/10.1016/j.jinf.2022.01.005>
- Kilkinen A, Virtanen SM, Klaukka T, Kenward MG, Salkinoja-Salonen M, Gissler M, et al. Use of antimicrobials and risk of type 1 diabetes in a population-based mother–child cohort. *Diabetologia* 2006;49:66–70. <https://doi.org/10.1007/s00125-005-0078-2>
- Räisänen LK, Kääriäinen SE, Sund R, Engberg E, Viljakainen HT, Kolho K-L. Antibiotic exposures and the development of pediatric autoimmune diseases: a register-based case–control study. *Pediatr Res* 2023;93:1096–104. <https://doi.org/10.1038/s41390-022-02188-4>
- Ainonen S, Ronkainen E, Hakkola M, Pokka T, Honkila M, Paalanne M, et al. Risk of immune-related diseases in childhood after intrapartum antibiotic exposure. *Am J Obstet Gynecol* 2024;231:454.e1–10. <https://doi.org/10.1016/j.ajog.2024.02.020>
- Metsälä J, Hakola L, Lundqvist A, Virta LJ, Gissler M, Virtanen SM. Perinatal factors and the risk of type 1 diabetes in childhood and adolescence—A register-based case-cohort study in Finland, years 1987 to 2009. *Pediatr Diabetes* 2020;21:586–96. <https://doi.org/10.1111/peidi.12994>
- Furu K, Wettermark B, Andersen M, Martikainen JE, Almarsdottir AB, Sørensen HT. The Nordic countries as a cohort for Pharmacoepidemiological research. *Basic Clin Pharmacol Toxicol* 2010;106:86–94. <https://doi.org/10.1111/j.1742-7843.2009.00494.x>
- WHOCC - ATC/DDD Index n.d. Accessed June 30, 2023. https://www.whocc.no/atc_ddd_index/
- Sankilampi U, Hannila M-L, Saari A, Gissler M, Dunkel L. New population-based references for birth weight, length, and head circumference in singletons and twins from 23 to 43 gestation weeks. *Ann Med* 2013;45:446–54. <https://doi.org/10.3109/07853890.2013.803739>
- Fuhri Snethlage CM, Nieuwdorp M, van Raalte DH, Rampanelli E, Verchere BC, Hanssen NMJ. Auto-immunity and the gut microbiome in type 1 diabetes: lessons from rodent and human studies. *Best Pract Res Clin Endocrinol Metab* 2021;35:101544. <https://doi.org/10.1016/j.beem.2021.101544>
- Sosa Alvarado C, Yang K, Qiu H, Mills E, Fouhse JM, Ju T, et al. Transient antibiotic-induced changes in the neonatal swine intestinal microbiota impact islet expression profiles reducing subsequent function. *Am J Physiol Regul Integr Comp Physiol* 2021;321:R303–16. <https://doi.org/10.1152/ajpregu.00090.2021>
- Mueller NT, Bakacs E, Combellick J, Grigoryan Z, Dominguez-Bello MG. The infant microbiome development: mom matters. *Trends Mol Med* 2015;21:109–17. <https://doi.org/10.1016/j.molmed.2014.12.002>
- Leo S, Curtis N, Zimmermann P. The neonatal intestinal resistome and factors that influence it—a systematic review. *Clin Microbiol Infect* 2022;28:1539–46. <https://doi.org/10.1016/j.cmi.2022.07.014>
- Korpela K, Salonen A, Saxen H, Nikkonen A, Peltola V, Jaakkola T, et al. Antibiotics in early life associate with specific gut microbiota signatures in a prospective longitudinal infant cohort. *Pediatr Res* 2020;88:438–43. <https://doi.org/10.1038/s41390-020-0761-5>
- Hettiarachchi KD, Zimmet PZ, Myers MA. Transplacental exposure to bafilomycin disrupts pancreatic islet organogenesis and accelerates diabetes onset in NOD mice. *J Autoimmun* 2004;22:287–96. <https://doi.org/10.1016/j.jaut.2004.02.004>
- Muanda FT, Sheehy O, Bérard A. Use of trimethoprim–sulfamethoxazole during pregnancy and risk of spontaneous abortion: a nested case control study. *Br J Clin Pharmacol* 2018;84:1198–205. <https://doi.org/10.1111/bcp.13542>
- Karampelias C, Rezaejad H, Rosko M, Duan L, Lu J, Pazzagli L, et al. Reinforcing one-carbon metabolism via folic acid/Folr1 promotes β -cell differentiation. *Nat Commun* 2021;12:3362. <https://doi.org/10.1038/s41467-021-23673-0>
- Waernbaum I, Dahlquist G, Lind T. Perinatal risk factors for type 1 diabetes revisited: a population-based register study. *Diabetologia* 2019;62:1173–84. <https://doi.org/10.1007/s00125-019-4874-5>