

Title: Maternal and early-life exposure to antibiotics and the risk of autism and attention-deficit hyperactivity disorder in childhood: a Swedish population-based cohort study

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Supplementary Table 1 A: Systemic antibacterials considered in this study according to the Anatomical Therapeutic Chemical (ATC) coding.

Prescription drugs	ATC code
Antibacterials for systemic use	J01
Penicillin beta-lactam antibacterials	J01C
Non-penicillin beta-lactam antibacterials	J01D
Macrolides, lincosamides, streptogramins	J01F
Tetracyclines	J01A
Sulphonamides and trimethoprim	J01E
Quinolone antibacterials	J01M
Nitroimidazoles	P01AB
Combinations of other antibacterials	J01R
Other antibacterials	J01X

Supplementary Table 1 B: Classification of autism and attention-deficit/hyperactivity disorder (ADHD) diagnosis codes considered in this study, based on the Swedish version of the International Classification Diseases (ICD) 10th version

Neurodevelopmental			
disorder	ICD-10 code	Disease	Classification/ specification
Autism	F84.0	Childhood autism	Includes all-pervasive developmental disorder, defined as the presence of abnormal or impaired development that is manifest before the age of three years, and the characteristic type of abnormal functioning in all three areas of psychopathology: reciprocal social interaction, communication, and restricted, stereotyped, repetitive behaviour.
	F84.1	Atypical autism	Includes pervasive developmental disorder that differs from childhood autism in the age of onset. Atypical autism happens when there is abnormal and impaired development which is present only after the age of three

years, and a lack of sufficient demonstrable abnormalities in one or two of the three areas of psychopathology required for the diagnosis of autism (that is, reciprocal social interactions, communication, and restricted, stereotyped, repetitive behaviour) despite other abnormal characteristics in other areas.

			Describe a group of disorders
Attention deficit hyperactivity disorder (ADHD)		Attention-	characterized by early-onset
		deficit	(ordinarily in the first five years
	F90.0	hyperactivity	of life), lack of persistence in
		disorder,	activities that require cognitive
		predominantly	involvement, and a tendency to
		inattentive type	move from one activity to
			another without completing
			anyone, together with
			disorganized, ill-regulated, and
			excessive activity.
		Swedish	Requires
	F90.0B	specific	hyperactivity/impulsivity with or
		subtype	without clinically significant
			attention deficit.

Supplementary Table 2: Maternal and child characteristics according to the outcomes during the study period.

				Child autism			Child ADHD	
				Total	No	Yes	No	Yes
				n	n(%)	n(%)	n(%)	n(%)
				483,459	478,508	4,951	477,848	5,611
Mother Exposed	No	Child Exposed	No	216,839(60.5)	215,145(60.6)	1,694(49.1)	215,281(60.7)	1,558(42.4)
			Yes	141,514(39.5)	139,757(39.4)	1,757(50.9)	139,396(39.3)	2,118(57.6)
	Yes	Child Exposed	No	65,580(52.4)	64,954(52.5)	626(41.7)	64,883(52.7)	697(36.0)
			Yes	59,526(47.6)	58,652(47.5)	874(58.3)	58288(47.3)	1238(64.0)

Supplementary Table 3: Characteristics of the cohort according to the presence of autism and attention-deficit/ hyperactivity disorder (ADHD) among Swedish children between January 1st, 2006, and December 31st, 2016.

	Child Autism		Child ADHD		Total
	No n (%)	Yes n (%)	No (%)	Yes (%)	N (%)
	478,508 (99.0)	4,951 (1.0)	477,848 (98.8)	5,611 (1.2)	483,459 (100.0)
MATERNAL CHARACTERISTICS					
Maternal age at delivery, in years					
< 25	110,408 (23.1)	1,285 (26.0)	109,588 (22.9)	2,105 (37.5)	111,693 (23.1)
25 – 29	172,811 (36.1)	1,602 (32.4)	172,674 (36.1)	1,739 (31.1)	174,413 (36.1)
30 – 34	137,312 (28.7)	1,341 (27.1)	137,438 (28.8)	1,215 (21.7)	138,653 (28.7)
> 34	57,977 (12.1)	723 (14.6)	58,148 (12.2)	552 (9.8)	58,700 (12.1)
Mode of delivery					
Vaginal	389,077 (81.3)	3,723 (75.2)	388,394 (81.3)	4,406 (78.5)	392,800 (81.2)
Cesarean (acute or elective)	89,431 (18.7)	1,228 (24.8)	89,454 (18.7)	1,205 (21.5)	90,659 (18.8)
Smoking/snuff status					
No	446,526 (93.3)	4,495 (90.8)	446,342 (93.4)	4,679 (83.4)	451,021 (93.3)
Yes	31,982 (6.7)	456 (9.2)	31,506 (6.6)	932 (16.6)	32,438 (6.7)
Maternal country of birth					
Non-Nordic	100,868 (21.1)	1,514 (30.6)	101,577 (21.3)	805 (14.3)	102,382 (21.2)
Nordic	377,640 (78.9)	3,437 (69.4)	376,271 (78.7)	4,806 (85.7)	38,1077 (78.8)
Family situation					
Cohabiting	418,473 (87.5)	4,130 (83.4)	418,151 (87.5)	4,452 (79.3)	422,603 (87.4)
Single	10,756 (2.2)	181 (3.7)	10,672 (2.2)	265 (4.7)	10,937 (2.3)
Other	28,046 (5.9)	409 (8.3)	27,856 (5.8)	599 (10.7)	28,455 (5.9)
Missing	21,233 (4.4)	231 (4.7)	21,169 (4.4)	295 (5.3)	21,464 (4.4)
Maternal BMI at gestation					
Underweight	53,690 (11.2)	504 (10.2)	53,694 (11.2)	500 (8.9)	54,194 (11.2)
Normal weight	244,597 (51.1)	2,249 (45.4)	244,408 (51.1)	2,438 (43.5)	246,846 (51.1)
Overweight	101,651 (21.2)	1,124 (22.7)	101,536 (21.2)	1,239 (22.1)	102,775 (21.3)
Obese	46,001 (9.6)	667 (13.5)	45,764 (9.6)	904 (16.1)	46,668 (9.6)
Missing	32,569 (6.8)	407 (8.2)	32,446 (6.8)	530 (9.4)	32,976 (6.8)
CHILD CHARACTERISTICS					
Sex					
Boy	245,193 (51.2)	3,882 (78.4)	244,816 (51.2)	4,259 (75.9)	24,9075 (51.5)
Girl	233,315 (48.8)	1,069 (21.6)	233,032 (48.8)	1,352 (24.1)	234,384 (48.5)
Apgar score at 5 minutes					
< 7	7,457 (1.6)	150 (3.0)	7,500 (1.6)	107 (1.9)	7,607 (1.6)
≥ 7	469,643 (98.1)	4,782 (96.6)	468,961 (98.1)	5,464 (97.4)	474,425 (98.1)
Missing	1,408 (0.3)	19 (0.4)	1,387 (0.3)	40 (0.7)	1,427 (0.3)
Pre-term birth (< 37 weeks)					
No	451,112 (94.3)	4,515 (91.2)	450,458 (94.3)	5,169 (92.1)	455,627 (94.2)

Yes	27,396 (5.7)	436 (8.8)	27,390 (5.7)	442 (7.9)	27,832 (5.8)
Size for gestational age					
Small	15,762 (3.3)	259 (5.2)	15,746 (3.3)	275 (4.9)	16,021 (3.3)
Appropriate (Normal)	453,230 (94.7)	4,577 (92.4)	452,616 (94.7)	5,191 (92.5)	457,807 (94.7)
Large	8,856 (1.9)	101 (2.0)	8,830 (1.8)	127 (2.3)	8,957 (1.9)
Missing	660 (0.1)	14 (0.3)	292 (0.1)	18 (0.3)	674 (0.1)

Abbreviations: BMI: body mass index.

Supplementary Table 4: Maternal and early life antibiotics exposure by class, and by period according to NDDs outcome.

Exposure		Child Autism		Child ADHD		Total
		No <i>n</i> (%) (n=478,508)	Yes <i>n</i> (%) (n=4,951)	No <i>n</i> (%) (n=477,848)	Yes <i>n</i> (%) (n=5,611)	483,459
Maternal Antibiotics Exposure						
Any antibiotic	No	354,902 (74.2)	3,451 (69.7)	354,677 (74.2)	3,676 (65.5)	358,353 (74.1)
	Yes	123,606 (25.8)	1,500 (30.3)	123,171 (25.8)	1,935 (34.5)	125,106 (25.9)
Antibiotics Class						
Beta-Lactam Antibacterials	No	393,158 (82.2)	3,896 (78.7)	392,720 (82.2)	4,334 (77.2)	397,054 (82.1)
	Yes	85,350 (17.8)	1,055 (21.3)	85,128 (17.8)	1,277 (22.8)	86,405 (17.9)
Other Beta-Lactam Antibacterials	No	464,802 (97.1)	4,745 (95.8)	464,227 (97.1)	5,320 (94.8)	469,547 (97.1)
	Yes	13,706 (2.9)	206 (4.2)	13,912 (2.9)	291 (5.2)	13,912 (2.9)
Macrolides	No	472,190 (98.7)	4,858 (98.1)	471,565 (98.7)	5,483 (97.7)	477,048 (98.7)
	Yes	6,318 (1.3)	93 (1.9)	6,283 (1.3)	128 (2.3)	6,411 (1.3)
Tetracyclines	No	469,721 (98.2)	4,838 (97.7)	469,113 (98.2)	5,446 (97.1)	474,559 (98.2)
	Yes	8,787 (1.8)	113 (2.3)	8,735 (1.8)	165 (2.9)	8,900 (1.8)
Sulphonamides and trimethoprim	No	474,547 (99.2)	4,896 (98.9)	473,942 (99.2)	5,501 (98.0)	479,443 (99.2)
	Yes	3,961 (0.8)	55 (1.1)	4,016 (0.8)	110 (2.0)	4,016 (0.8)
Quinolones	No	474,978 (99.3)	4,905 (99.1)	474,336 (99.3)	5,547 (98.9)	479,883 (99.3)
	Yes	3,530 (0.7)	46 (0.9)	512 (0.7)	64 (1.1)	3,576 (0.7)
Nitroimidazole	No	470,222 (98.3)	4,833 (97.6)	469,599 (98.3)	5,456 (97.2)	475,055 (98.3)
	Yes	8,286 (1.7)	118 (2.4)	8,249 (1.7)	155 (2.8)	8,404 (1.7)
Other antibiotics	No	449,337 (93.9)	4,586 (92.6)	448,803 (93.9)	5,120 (91.2)	453,923 (93.9)
	Yes	29,171 (6.1)	365 (7.4)	29,045 (6.1)	491 (8.8)	29,536 (6.1)
Exposure period						
Pre-pregnancy (untill 90 days)	No	438,591 (91.7)	4,478 (90.4)	438,122 (91.7)	4,947 (88.2)	443,069 (91.6)
	Yes	39,917 (8.3)	473 (9.6)	39,726 (8.3)	664 (11.8)	40,390 (8.4)
First trimester	No	438,982 (91.7)	4,421 (89.3)	438,444 (91.8)	4,959 (88.4)	443,403 (91.7)
	Yes	39,526 (8.3)	530 (10.7)	39,404 (8.2)	652 (11.6)	40,056 (8.3)
Second trimester	No	437,977 (91.5)	4,418 (89.2)	437,498 (91.6)	4,897 (87.3)	442,395 (91.5)
	Yes	40,531 (8.5)	533 (10.8)	40,350 (8.4)	714 (12.7)	41,064 (8.5)
Third trimester	No	442,128 (92.4)	4,477 (90.4)	441,594 (92.4)	5,011 (89.3)	446,605 (92.4)
	Yes	36,380 (7.6)	474 (9.6)	36,254 (7.6)	600 (10.7)	36,854 (7.6)
Number of antibiotic courses						
Cumulative antibiotic duration (days)	0	380,812 (79.6)	3,719 (75.1)	380,486 (79.6)	4,045 (72.1)	384,531 (79.5)
	1	67,705 (14.1)	788 (15.9)	67,500 (14.1)	993 (17.7)	68,493 (14.2)
	2	19,542 (4.1)	282 (5.7)	19,471 (4.1)	353 (6.3)	19,824 (4.1)
	≥ 3	10,449 (2.2)	162 (3.3)	10,391 (2.2)	220 (3.9)	10,611 (2.2)
	0	380,818 (79.6)	3,719 (75.1)	380,492 (79.6)	4,045 (72.1)	384,537 (79.5)
	1-7	38,708 (8.1)	434 (8.8)	38,568 (8.1)	574 (10.2)	39,142 (8.1)
	8-14	25,910 (5.4)	337 (6.8)	25,825 (5.4)	422 (7.5)	26,247 (5.4)
	15-21	19,905 (4.2)	279 (5.6)	19,874 (4.2)	310 (5.5)	20,184 (4.2)
	> 21	13,167 (2.8)	182 (3.7)	13,089 (2.7)	260 (4.6)	13,349 (2.8)

Child below two years antibiotics Exposure

Any antibiotic	No	280,099 (58.5)	2,320 (46.9)	28,0164 (58.6)	2,255 (40.2)	282,419 (58.4)
	Yes	198,409 (41.5)	2,631 (53.1)	197,684 (41.4)	3,356 (59.8)	201,040 (41.6)
Antibiotics Class						
Beta-Lactam Antibacterials	No	296,124 (61.9)	2,499 (50.5)	296,203 (62.0)	2,420 (43.1)	298,623 (61.8)
	Yes	182,384 (38.1)	2,452 (49.5)	181,645 (38.0)	3,191 (56.9)	184,836 (38.2)
Other Beta-Lactam Antibacterials	No	458,404 (95.8)	4,681 (94.5)	457,798 (95.8)	5,287 (94.2)	463,085 (95.8)
	Yes	20,104 (4.2)	270 (5.5)	20,050 (4.2)	324 (5.8)	20,374 (4.2)
Macrolides	No	463,812 (96.9)	4,711 (95.2)	463,231 (96.9)	5,292 (94.3)	468,523 (96.9)
	Yes	14,696 (3.1)	240 (4.8)	14,617 (3.1)	319 (5.7)	14,936 (3.1)
Nitroimidazole	No	477,663 (99.8)	4,926 (99.5)	476,995 (99.8)	5,594 (99.7)	482,589 (99.8)
	Yes	845 (0.2)	25 (0.5)	853 (0.2)	17 (0.3)	870 (0.2)
Other antibiotics	No	463,808 (96.9)	4,733 (95.6)	463,194 (96.9)	5,347 (95.3)	468,541 (96.9)
	Yes	14,700 (3.1)	218 (4.4)	14,654 (3.1)	264 (4.7)	14,918 (3.1)
Number of antibiotic courses						
	0	280,101 (58.5)	2,320 (46.9)	280,166 (58.6)	2,255 (40.2)	282,421 (58.4)
	1	100,538 (21.0)	1,136 (22.9)	100,355 (21.0)	1,319 (23.5)	101,674 (21.0)
	2	47,591 (9.9)	619 (12.5)	47,396 (9.9)	814 (14.5)	48,210 (10.0)
	≥ 3	50,278 (10.5)	876 (17.7)	49,931 (10.4)	1,223 (21.8)	51,154 (10.6)
Cumulative antibiotic duration (days)						
	0	280,111 (58.5)	2,320 (46.9)	280,175 (58.6)	2,256 (40.2)	282,431 (58.4)
	1-7	117,417 (24.5)	1,355 (27.4)	117,133 (24.5)	1,639 (29.2)	118,772 (24.6)
	8-14	50,234 (10.5)	686 (13.9)	49,985 (10.5)	935 (16.7)	50,920 (10.5)
	15-21	18,087 (3.8)	317 (6.4)	17,960 (3.8)	444 (7.9)	18,404 (3.8)
	> 21	12,659 (2.6)	273 (5.5)	12,595 (2.6)	337 (6.0)	12,932 (2.7)

Supplementary Table 5: Parameter estimates for exposed children stratified by maternal antibiotic use, expressed as Odds Ratios (OR) and 95% confidence intervals

		Child Autism	Child ADHD
		OR (CI)	OR (CI)
Mother	No	1.47 (1.38-1.57)	1.94 (1.81-2.07)
Exposed	Yes	1.43 (1.29-1.59)	1.82 (1.66-2.00)

All analyses were adjusted for a mode of delivery, maternal age, maternal country of birth, maternal family situation, smoke/snuff consumption, maternal body mass index, sex of the child, preterm birth (<37weeks), Apgar in 5 min (<7), and size for gestational age.

Supplementary Table 6: Adjusted odds ratios (ORs) with 95% confidence intervals (CIs) for Generalized Estimating Equations (GEE) models evaluating the association of maternal and child (i.e., early-life) antibiotic use and parity on the risk of autism and attention-deficit/ hyperactivity disorder (ADHD) in childhood.

		Child Autism		Child ADHD	
		OR	95% CI	OR	95% CI
Antibiotics Exposure (reference: unexposed)					
Any antibiotics	Consumed by mothers	1.19	(1.14-1.24)	1.33	(1.27-1.38)
	Consumed by child	1.52	(1.46-1.58)	1.92	(1.85-2.01)
Parity					
	1 (reference)				
	2	0.63	(0.60-0.66)	0.88	(0.84-0.92)
	3	0.64	(0.59-0.69)	1.02	(0.96-1.09)
	≥ 4	0.71	(0.65-0.78)	1.26	(1.16-1.37)

All analyses were adjusted for a mode of delivery, maternal age, maternal country of birth, maternal family situation, smoke/snuff consumption, maternal body mass index, sex of the child, preterm birth (<37weeks), Apgar in 5 min (<7), and size for gestational age.