

SUPPLEMENTARY DATA

Classification of antibiotics

Narrow-spectrum antibiotics: beta-lactamase sensitive penicillin (J01CE), beta-lactamase resistant penicillin (J01CF), trimethoprim and derivatives (J01EA), short-acting sulfonamides (J01EB), macrolides (J01FA), glycopeptides (J01XA), steroid antibacterials (fusidic acid) (J01XC), nitrofurantoin derivatives (nitrofurantoin) (J01XE) and metronidazole (J01XD01 or P01AB01), clindamycin (J01FF).

Broad-spectrum antibiotics: tetracyclines (J01AA), penicillin with extended spectrum (J01CA), combinations of penicillin incl. beta-lactamase inhibitors (J01CR) and fluoroquinolones (J01M), cephalosporins and related substances (J01DB, J01DC and J01DD), carbapenems (J01DH), combinations of sulfonamides and trimethoprim, incl. derivatives (J01EE), linezolid (J01XX08), methenamine (J01XX05) and chloramphenicol (J01BA).

Prenatal life, groups according to the 4:th level of ATC: penicillin with extended spectrum (J01CA), beta-lactamase sensitive penicillin (J01CE), beta-lactamase resistant penicillin (J01CF), first-generation cephalosporins (J01DB), nitrofurantoin derivatives (nitrofurantoin) (J01XE). Less than 1% of the mothers had dispensed antibiotics from other groups.

First year of life, groups according to the 4:th level of ATC: penicillin with extended spectrum (J01CA), beta-lactamase sensitive penicillin (J01CE), beta-lactamase resistant penicillin (J01CF), penicillin incl. beta-lactamase inhibitors (J01CR), first-generation cephalosporins (J01DB), trimethoprim and derivatives (J01EA), combinations of sulfonamides and trimethoprim, incl. derivatives (J01EE), macrolides (J01FA). Less than 1% of the children had dispensed antibiotics from other groups.

Potential confounders

We collected information on the following potential confounding variables from the MBR: parity, maternal body mass index and smoking at first visit to the antenatal care clinic, mode of delivery, maternal age at delivery, child's sex, gestational age, small or large for gestational age and birth year and month. If maternal BMI was missing, but recorded for an earlier pregnancy, it was imputed using last observation "carry forward" (n=12 619 (1.8%)). We retrieved the following variables from the Longitudinal Integration Database for Health Insurance and Labor Market Studies: residence at the year of birth (municipality), parental level of education and disposable income (based on household income and adjusted for the number of adults and children, and their consumption weight). If education level was only known in one parent, the education level in the other parent was imputed to that level. We categorized disposable income into fifths, using quintiles for each year as cut-offs. Statistics Sweden provided population density (inhabitants per km²) for each municipality.

Parents were defined as having type 1 diabetes if they, before the child's first birthday, had 1) type 1 diabetes diagnosis (ICD-10: E10, O240) in the NPR and a prescription of insulin before end of follow-up 2) diabetes diagnosis before the age of 30 (ICD-9: 250, ICD-8:250, ICD-7:260) in the NPR and a prescription of insulin before end of follow-up, or 3) at least two prescriptions of insulin (ATC: A10A) according to the Swedish Prescribed Drug Register, not due to gestational diabetes, before the age of 30. Mothers were classed as having gestational diabetes if they had a gestational diabetes diagnosis (ICD-10:O244) in the NPR or the MBR.

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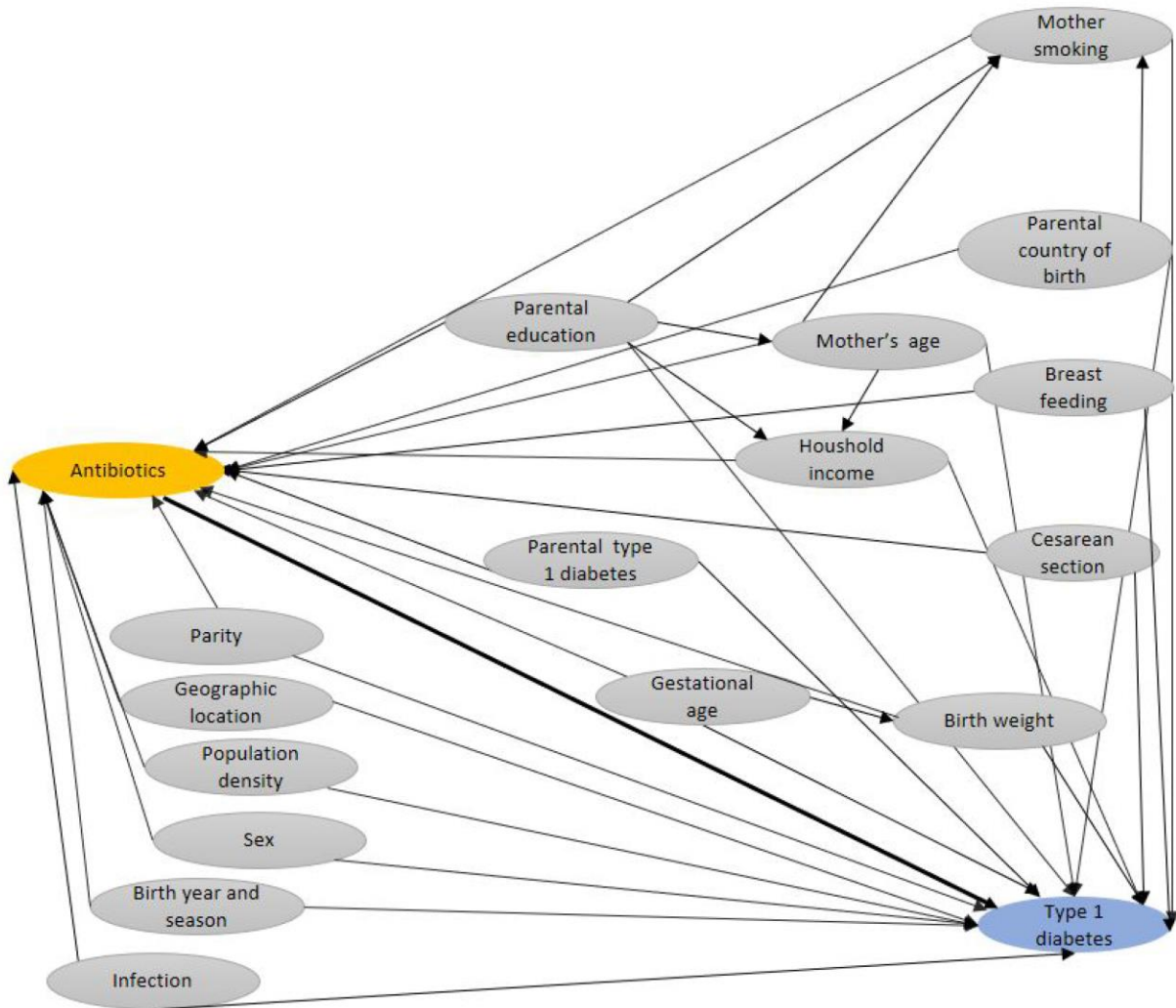
Supplementary Table 1. Swedish national registers used in the study and the personal identity number.¹

Register	Description
The Swedish Register of the Total Population (TPR)	Held by the government agency of Statistics Sweden and updates are transmitted daily from the Tax Agency to the TPR. It contains the personal identity number for all Swedish residents and information on for example country of birth, date of death and migration.
The Multi-Generation register	A special register based on the TPR. It contains data on all residents born after 1932 and any relationship to biological and adoptive parents
The Migration register	A special register based on the TPR which contains dates of immigration and migration.
The Longitudinal Integration Database for Health Insurance and Labour Market Studies	Held by the government agency of Statistics Sweden and integrates existing data from the labour market, educational and social sectors registers. It is updated annually and includes an extensive set of socio-economic factors for all Swedish residents 16 years of age.
The Medical Birth Register	Held by the Swedish National Board of Health and Welfare. It is compulsory for every health care provider in Sweden to report to the register and it includes data on practically all deliveries in Sweden. Only 0.5-3.0 per cent of the deliveries are not reported to the register. The information is collected from medical records from the prenatal, delivery and neonatal care.
Swedish Prescribed Drug Register	Held by the Swedish National Board of Health and Welfare. It contains information on all dispensed prescribed drugs at pharmacies in Sweden since July 2005 using the Anatomical Therapeutic Chemical (ATC) classification system.
National Patient Register	Held by the Swedish National Board of Health and Welfare. It contains information on all inpatient diagnoses since 1987 and specialist outpatient diagnoses since 2001.
The personal identity number (PIN) is a unique identifier and consist of a six-digit birth date and a four-digit identification number. The PIN is used in all public administration in Sweden and enables unambiguous linkage between the Swedish registers. At birth, the midwife or the hospital are obliged to report the birth to the National Tax Board and the child will be given a PIN. It is estimated that <0.1 % of newborns are not reported to the Population Registers within 30 days.	

¹Ludvigsson JF, Almqvist C, Bonamy AK, et al. Registers of the Swedish total population and their use in medical research. *Eur J Epidemiol.* 2016;31(2):125-136.

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Supplementary Figure 1. Directed acyclic graph for antibiotic exposure in early childhood and type 1 diabetes



Directed acyclic graph for antibiotic exposure in early childhood (orange) and the outcome type 1 diabetes (blue), and the other variables shown in this graph are identified as confounders (grey) using the d-separation criteria. The arrows represent causal effects.

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Supplementary Table 2. Reported indication in a random sample of 800 antibiotic prescriptions dispensed in the first year of life.

Site	Any antibiotic n = 800		Penicillin V (J01CE) n = 408		Otitis media and other respiratory tract antibiotics n = 689		Urinary tract or skin and soft tissue antibiotics n = 111	
	n	Percent	n	Percent	n	Percent	n	Percent
Ear	259	69.6	186	89.9	257	79.6	2	4.0
Urinary tract	43	11.6	0	0.0	14	4.3	29	58.0
Lower airways	8	2.2	4	1.9	8	2.5	0	0.0
Upper airways	20	5.4	15	7.2	20	6.2	0	0.0
Unspecified airways	8	2.2	1	0.5	8	2.5	0	0.0
Skin	33	8.9	1	0.5	14	4.3	19	38.0
Gastrointestinal	2	0.5	0	0.0	2	0.6	0	0.0
No information	428		201		366		62	

*Percent among the 372 prescriptions with information. Note that one of the prescriptions had 2 indications reported.

† Percent among the 207 prescriptions with information

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Supplemental Table 3. Distribution of the variable “dosage form” for the prescribed antibiotics during prenatal life and first year of life. Only dosage forms that was used for >0.01% of the prescriptions are shown

Dosage form	Prenatal life (mothers) Percent	First year of life Percent
Granules for oral suspension		66.5
Powder for oral suspension		18.7
Granules for oral drops, solution	<0.1	4.9
Oral suspension		4.4
Oral solution		2.8
Tablet	23.5	1.7
Granules for oral solution	0.1	0.4
Granules for oral suspension in sachet		0.2
Granules and liquid for oral suspension		0.2
Film-coated tablet	66.8	0.1
Soluble tablet	0.1	<0.1
Powder for oral suspension, sachet	<0.1	<0.1
Unspecified		<0.1
Capsule, hard	7.3	
Powder for solution for infusion	<0.1	
Entero-capsule	1.6	
Dispersible tablet	0.3	

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Supplemental Table 4. Child and family characteristics, for children born in Sweden between July 1, 2005 and September 30, 2013 by antibiotic exposure.

	Antibiotic exposure			
	Prenatal life*		First year of life†	
	No	Yes	No	Yes
No of children	566 141	164 098	607 636	189 682
Smoking during pregnancy‡, No (%)				
Non-smoker	511 849 (90.4)	143 927 (87.7)	545 680 (89.8)	167 250 (88.2)
1 - 9 cigarettes/day	24 982 (4.4)	10 072 (6.1)	28 250 (4.6)	10 460 (5.5)
> 9 cigarettes/day	6878 (1.2)	3273 (2.0)	8105 (1.3)	3283 (1.7)
Missing	22 432 (4.0)	6826 (4.2)	25 601 (4.2)	8689 (4.6)
Gestational diabetes, No (%)	6139 (1.1)	2318 (1.4)	6509 (1.1)	2455 (1.3)
Region of residence, No (%)				
Götaland	270 327 (47.7)	76 291 (46.5)	284 601 (46.8)	93 464 (49.3)
Svealand	232 064 (41.0)	71 334 (43.5)	251 649 (41.4)	79 920 (42.1)
S Norrland	34 973 (6.2)	9215 (5.6)	38 925 (6.4)	9509 (5.0)
N Norrland	28 618 (5.1)	7209 (4.4)	32 449 (5.3)	6783 (3.6)
Population density§, median (IQR)	90.8 (35.7:1016.7)	98.1 (39.4:1094.9)	89.8 (34.9: 963.2)	101.1 (43.2:1086.6)
Missing, No (%)	159 (<0.1)	49 (<0.1)	12 (<0.1)	6 (<0.1)
Birth year, No (%)				
2005 - 2008	196 542 (34.7)	61 801 (37.7)	237 670 (39.1)	88 734 (46.8)
2009 - 2012	369 599 (65.3)	102 297 (62.3)	369 966 (60.9)	100 948 (53.2)
Birth season, No (%)				
Mars - May	151 197 (26.7)	45 981 (28.0)	153 643 (25.3)	53 340 (28.1)
June - Aug	159 559 (28.2)	47 538 (29.0)	167 631 (27.6)	55 097 (29.0)
Sept - Nov	130 631 (23.1)	36 288 (22.1)	146 772 (24.2)	40 840 (21.5)
Dec - Feb	124 754 (22.0)	34 291 (20.9)	139 590 (23.0)	40 405 (21.3)
Mother's highest education, No (%)				
Compulsory school	54 667 (9.7)	21 136 (12.9)	59 105 (9.7)	23 777 (12.5)
Upper secondary school	216 057 (38.2)	65 754 (40.1)	233 612 (38.4)	77 321 (40.8)
University	294 436 (52.0)	76 914 (46.9)	314 069 (51.7)	88 251 (46.5)
Missing	981 (0.2)	294 (0.2)	850 (0.1)	333 (0.2)
Father's highest education, No (%)				
Compulsory school	64 093 (11.3)	22 399 (13.6)	68 326 (11.2)	25 992 (13.7)
Upper secondary school	268 456 (47.4)	79 233 (48.3)	289 821 (47.7)	91 900 (48.4)

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	Antibiotic exposure			
	Prenatal life [*]		First year of life [†]	
	No	Yes	No	Yes
University	232 611 (41.1)	62 172 (37.9)	248 639 (40.9)	71 457 (37.7)
Missing	981 (0.2)	294 (0.2)	850 (0.1)	333 (0.2)
Household income fifths, No (%)				
1 (Lowest)	94 396 (16.7)	31 413 (19.1)	99 655 (16.4)	37 307 (19.7)
2	114 439 (20.2)	35 059 (21.4)	121 575 (20.0)	41 568 (21.9)
3	118 067 (20.9)	33 888 (20.7)	126 272 (20.8)	39 802 (21.0)
4	119 767 (21.2)	32 177 (19.6)	129 536 (21.3)	36 513 (19.2)
5 (Highest)	119 426 (21.1)	31 544 (19.2)	130 550 (21.5)	34 469 (18.2)
Missing	46 (<0.1)	17 (<0.1)	48 (<0.1)	23 (<0.1)

Abbreviations: IQR, interquartile range.

^{*}Children from pregnancies with an estimated start date on or after July 1, 2005. At least one antibiotic prescription during estimated duration of pregnancy.

[†]At least one dispensed antibiotic prescription in the child's first year of life.

[‡]At the first visit at the antenatal clinic.

[§]Inhabitants/km²

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Supplementary Table 5. Subgroup analysis of the association between exposure to antibiotics in early life and childhood-onset type 1 diabetes.

Subgroup	Prenatal life*				First year of life†			
	Total N	Events N	Adjusted HR (95% CI)	P _{int}	Total N	Events N	Adjusted HR (95% CI)	P _{int}
Vaginal delivery	571 829	856	1.10 (0.94 - 1.28)	0.37	634 863	997	1.10 (0.96 - 1.28)	0.016
Cesarean section	113 173	216	1.27 (0.95 - 1.71)		126 044	241	1.60 (1.22 - 2.08)	
Boy	352 128	555	1.13 (0.93 - 1.37)	0.90	391 068	631	1.24 (1.04 - 1.47)	0.54
Girl	332 874	517	1.15 (0.94 - 1.40)		369 839	607	1.14 (0.95 - 1.38)	
No parental type 1 diabetes‡	675 003	943	1.11 (0.95 - 1.28)	0.29	749 936	1092	1.20 (1.05 - 1.38)	0.56
Parental type 1 diabetes§	9999	129	1.37 (0.95 - 1.98)		10 971	146	1.07 (0.74 - 1.55)	
Birth year < 2009	237 762	625	1.00 (0.83-1.20)	0.031	306 753	823	1.19 (1.02 - 1.38)	0.91
Birth year ≥ 2009	447 240	447	1.35 (1.10 - 1.66)		454 154	415	1.21 (0.97 - 1.51)	

Abbreviations: HR hazard ratio; CI confidence interval; Pint p-value for interaction

*Children from pregnancies with an estimated start date on or after July 1, 2005. At least one dispensed antibiotic prescription during estimated duration of pregnancy.

†At least one dispensed antibiotic prescription in the child’s first year of life.

‡Neither of the parents had type 1 diabetes.

§At least 1 of the parents had type 1 diabetes

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Supplementary Table 6. The fifteen most common complications of labor and delivery in cesarean deliveries

<i>ICD 10</i>		<i>n</i>	<i>Percent</i>
O34	Maternal care for known or suspected abnormality of pelvic organs	30 192	22.7
O62	Abnormalities of forces of labor	24 938	18.7
O68	Labor and delivery complicated by fetal stress [distress]	23 290	17.5
O99	Other maternal diseases classifiable elsewhere but complicating pregnancy, childbirth and the puerperium	22 110	16.6
O32	Maternal care for known or suspected malpresentation of fetus	20 828	15.7
O61	Failed induction of labor	19 752	14.8
O67	Labor and delivery complicated by intrapartum haemorrhage, not elsewhere classified	12 959	9.7
O60	Preterm delivery	12 634	9.5
O36	Maternal care for other known or suspected fetal problems	11 612	8.7
O75	Other complications of labor and delivery, not elsewhere classified	10 199	7.7
O26	Maternal care for other conditions predominantly related to pregnancy	9408	7.1
O14	Gestational [pregnancy-induced] hypertension with significant proteinuria	8736	6.6
O48	Prolonged pregnancy	8691	6.5
O64	Obstructed labor due to malposition and malpresentation of fetus	8101	6.1
O41	Other disorders of amniotic fluid and membranes	4779	3.6

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Supplementary Table 7. The association between exposure to specific antibiotics and childhood-onset type 1 diabetes.

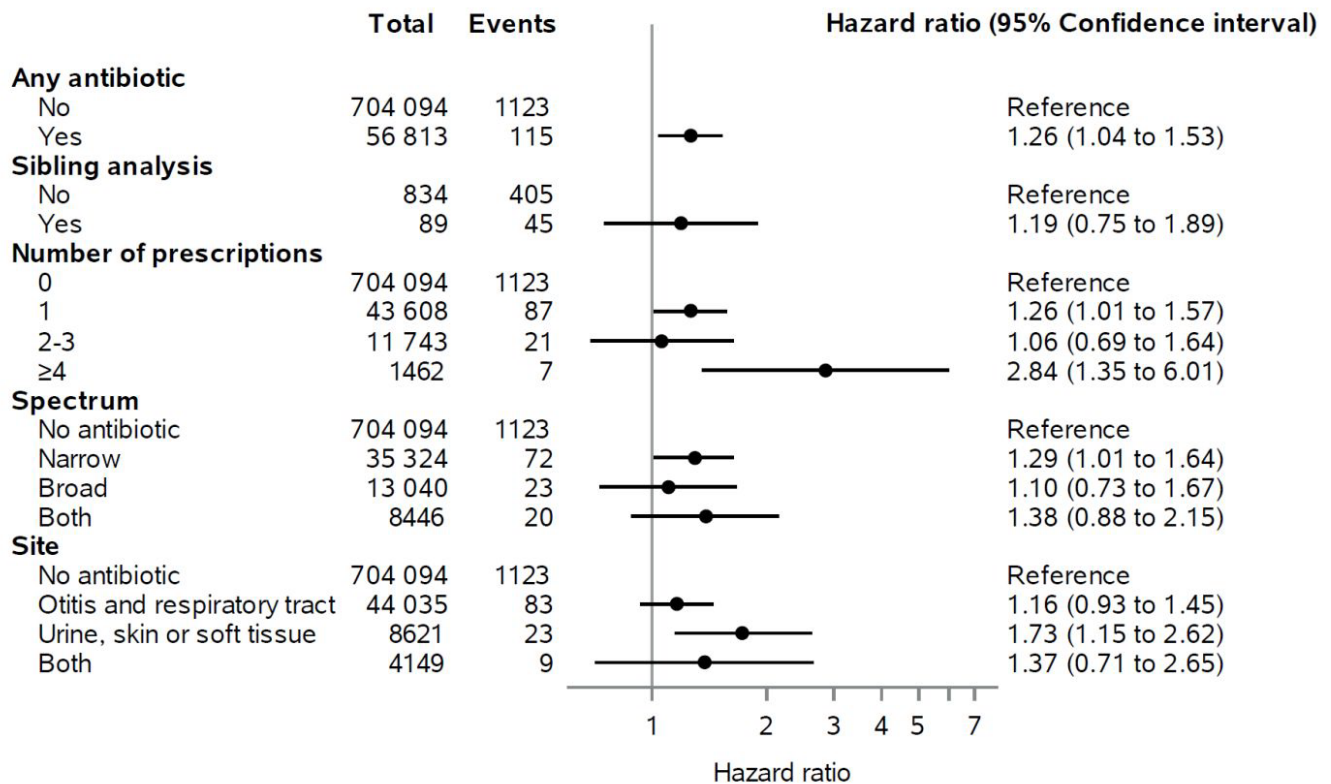
Exposure	Events/Total		Adjusted Hazard Ratio (95% CI)
	Yes	No	
Prenatal life*			
Penicillin with extended spectrum (J01CA)	80/ 49 347	992/ 635 655	1.08 (0.86 - 1.36)
Penicillin V (J01CE)	127/ 70 954	945/ 614 048	1.10 (0.91 - 1.33)
First generation cephalosporins (J01DB)	21/ 13 909	1051/ 671 093	0.74 (0.47 - 1.15)
Nitrofurantoin derivatives (nitrofurantoin) (J01XE)	68/ 33 259	1004/ 651 743	1.23 (0.95 - 1.60)
First year of life[†]			
Penicillin with extended spectrum (J01CA)	69/37 621	1169/723 286	0.98 (0.76 - 1.26)
Penicillin V (J01CE)	258/130 143	980/630 764	1.23 (1.06 - 1.42)
B-lactam resistant (J01CF)	24/11 534	1214/749 373	1.31 (0.87 - 1.97)
Combination of penicillins (J01CR)	35/15 108	1203/745 799	0.99 (0.70 - 1.40)
First generation cephalosporins (J01DB)	23/11 334	1215/749 573	1.12 (0.74 - 1.70)
Combination of sulfonamides and trimethoprim (J01EE)	21/8751	1217/752 156	1.23 (0.80 - 1.90)
Macrolides (J01FA)	21/10 082	1217/750 825	0.99 (0.64 - 1.54)

*At least one dispensed antibiotic prescription during estimated duration of pregnancy.

[†]At least one dispensed antibiotic prescription in the child's first year of life.

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Supplementary Figure 2. The association between exposure to antibiotics in the first 6 month of life and childhood-onset type 1 diabetes



Only families with at least 1 type 1 diabetes event and at least 1 type 1 diabetes-free individual at the age of event in the type 1 diabetes case are included in the sibling analysis