

Clinical Communications

Parental antibiotics and childhood asthma—a population-based study

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Clinical Implications

- In this population-based study on antibiotic treatment before, during, and after pregnancy, using paternal exposure as negative control, we confirm that associations between maternal antibiotic exposure and childhood asthma are partly explained by familial confounding such as genes and environment.

TO THE EDITOR:

Previous studies have found positive associations between maternal antibiotic exposure in fetal life and childhood asthma.^{1–4} It has been hypothesized that maternal antibiotic treatment may trigger the development of the immune system of young children, and thus be an important factor in asthma development.⁵ Yet, systematic reviews have highlighted that the associations between antibiotic exposure and asthma could be due to bias such as confounding by indication, reverse causation, or factors shared within families.⁶ We recently provided evidence that the association between maternal antibiotics during pregnancy and childhood asthma is due to familial confounding such as genes and environmental factors, for example, socioeconomic status, parental smoking, and health seeking behavior.⁷ Assessment of paternal antibiotic treatment during pregnancy, as a negative control, could help to disentangle the relationships further, as the intrauterine environment cannot be directly influenced by the father.³ If similar estimates are seen for paternal antibiotics as for maternal antibiotics, as well as for exposure to antibiotics before, during, and after pregnancy, then this supports our previous findings that the association is at least partly explained by familial factors.

We aimed to address the association between parental (father's and mother's) exposure to antibiotics from 6 months before, during, and up to 6 months after pregnancy, and subsequent childhood asthma by prospectively investigating a nationwide cohort of children.

The Swedish Medical Birth Registry (MBR) and the Multi-Generation Registry were linked through the personal identity number to identify a nationwide population-based cohort of children ($N = 492,700$) born in Sweden to women who were pregnant between July 2005 and December 2010, along with their biological fathers. Details regarding the Swedish registers and the methodology are provided in this article's Online Repository at www.jaci-inpractice.org.

We collected information on dispensed systemic parental antibiotics from the Swedish Prescribed Drug Register (SPDR). Exposure windows were defined as follows: *during pregnancy*—between estimated date of conception (from gestational age in days) to date of birth; *before pregnancy*—up to 6 months before

estimated date of conception; and *after pregnancy*—up to 6 months after date of birth. Childhood asthma was defined as having both a diagnosis of asthma registered in the National Patient Register (NPR) and fulfilling criteria for asthma medication from the SPDR. This proxy for asthma at 0 to 17 years of age has previously been validated against criteria of asthma, set by the Swedish Paediatric Association's section for Allergy.⁸

Potential confounders were identified based on previous knowledge and through directed acyclic graphs.⁹ Information on parents' highest education, country of birth and history of asthma (asthma diagnosis or asthma medication), parental cohabitation during pregnancy, parity, and maternal smoking during pregnancy was obtained from the Longitudinal integration database for health insurance and labor market studies (LISA), MBR, NPR, and SPDR.

The association between maternal and paternal antibiotic exposure and childhood asthma was analyzed using Cox proportional hazard regression with attained age as analysis time scale and sandwich estimator of standard errors to account for clustering within sibling groups. End of follow-up was defined as the first of positive outcome, emigration, death, or end of study period (December 31, 2011). Nonproportional hazards were found for exposure to antibiotics at all exposure periods. Consequently, we allowed for time-varying effects by splitting data at the age of 2.5 years. The study was approved by the regional ethical review board in Stockholm, Sweden.

In total, 14% of the children had mothers who were exposed to antibiotics before pregnancy, 19% during pregnancy, and 16% after pregnancy (Table 1). The proportion of fathers with exposure before pregnancy was 8%, during pregnancy 11%, and after pregnancy 8%. The overall proportion of asthma in children was 6% and approximately 7% to 8% in children who had been exposed to antibiotics.

Children whose mothers had been exposed to antibiotics were at increased risk of asthma at all ages. The estimates for exposure among children up to 2.5 years were as follows: before pregnancy: adjusted hazard ratio (HR_{adj}) 1.31, 95% confidence interval (CI) 1.27–1.35; during pregnancy: HR_{adj} 1.27, 95% CI 1.23–1.30; after pregnancy: HR_{adj} 1.34, 95% CI 1.30–1.38. Point estimates for children ≥ 2.5 years were somewhat lower, but still significant (Figure 1 and Table E1, available in this article's Online Repository at www.jaci-inpractice.org).

Children whose fathers had been exposed to antibiotics were also at increased risk for asthma up to 2.5 years: before pregnancy: HR_{adj} 1.17, 95% CI 1.12–1.21; during pregnancy: HR_{adj} 1.13, 95% CI 1.09–1.17; after pregnancy: HR_{adj} 1.19, 95% CI 1.14–1.25; however, the association disappeared in children ≥ 2.5 years (Figure 1 and Table E1, available in this article's Online Repository at www.jaci-inpractice.org).

To further understand if the differences in results between children < 2.5 years or ≥ 2.5 years could be explained by the fact that young children with older siblings may be more prone to both infections and thus antibiotics, an interaction term between having older siblings and antibiotic exposure was included, where estimates were similar to the main findings (Table E2, available in this article's Online Repository at www.jaci-inpractice.org).

TABLE I. Descriptive table of study population and variables included in analyses

Variables	All	Children without asthma		Children with asthma	
	N 492,700	N 463,446	Percentage 94.1	N 29,254	Percentage 5.9
Maternal antibiotics					
Before pregnancy	66,882	61,888	13.3	5,071	17.3
During pregnancy	95,558	88,429	19.1	7,129	24.4
After pregnancy	76,665	70,787	15.3	5,878	20.1
Paternal antibiotics					
Before pregnancy	39,196	36,445	7.9	2,751	9.4
During pregnancy	56,243	52,424	11.3	3,819	13.1
After pregnancy	37,139	34,472	7.44	2,667	9.1
Highest paternal education					
≤9 y	23,038	21,574	4.7	1,464	5.0
10-12 y	179,358	167,312	36.1	12,046	41.2
>12 y	287,852	272,143	58.7	15,709	53.7
Missing	2,452	2,417	0.5	35	0.1
Parity					
No siblings	217,449	205,816	44.4	11,633	39.8
≥1 sibling	275,251	257,630	55.6	17,621	60.2
Parental cohabitation during pregnancy					
Yes	446,034	419,869	90.6	26,165	89.4
No	24,172	22,596	4.9	1,576	5.4
Missing	22,494	20,981	4.5	1,513	5.2
Mother's country of birth					
Sweden	389,180	364,472	78.6	24,708	84.5
Other	103,520	98,974	21.4	4,546	15.5
Father's country of birth					
Sweden	387,926	363,557	78.5	24,369	83.3
Other	104,774	99,889	21.6	4,885	16.70
Mother with asthma					
No	452,685	428,369	92.4	24,316	83.1
Yes	40,015	35,077	7.6	4,938	16.9
Father with asthma					
No	457,841	432,227	93.3	25,614	87.6
Yes	34,859	31,219	6.7	3,640	12.4
Maternal smoking during pregnancy					
No	439,418	414,309	89.4	25,109	85.8
Yes	32,255	29,560	6.4	2,695	9.2
Missing	21,027	19,577	5.0	1,450	4.2

Test of independence between asthma status and background characteristics by Fisher's exact test provided *P* values <.005 for all variables.

In this nationwide population-based register study of parental antibiotics treatment, we found an association between both maternal and paternal exposure to antibiotics before, during, and after pregnancy and childhood asthma in children <2.5 years of age. The associations between exposure to maternal, but not paternal, antibiotics and asthma remained in children ≥2.5 years. Although this could not be explained by having older siblings, the fact that there is an association between the father's antibiotic exposure and the child's asthma suggests that the association may be due to confounding from shared environmental factors (U1 in Figure E1, available in this article's Online Repository at www.jaci-inpractice.org) or paternal environmental factors (U3 in Figure E1), such as sharing of infections, caring of children, or health-seeking

behavior that differs between mothers and fathers. Although the effect of maternal antibiotics seems to be stronger, the similar pattern of estimates, independent of exposure period, indicates that the association is, although not causal, explained by additional maternal confounders (U2 in Figure E1), such as genes or environmental factors that are related to the intra-uterine environment and the mother's risk of antibiotic treatment. This is in line with and confirms the findings from our previous sibling design study,⁷ and illustrates the beauty of using paternal exposure as negative control. In contrast, Mulder et al³ did not find a significant association between exposure to paternal antibiotics in the third trimester and childhood asthma that may be explained by the limited exposure period or power issues. However, we cannot exclude that the antibiotic

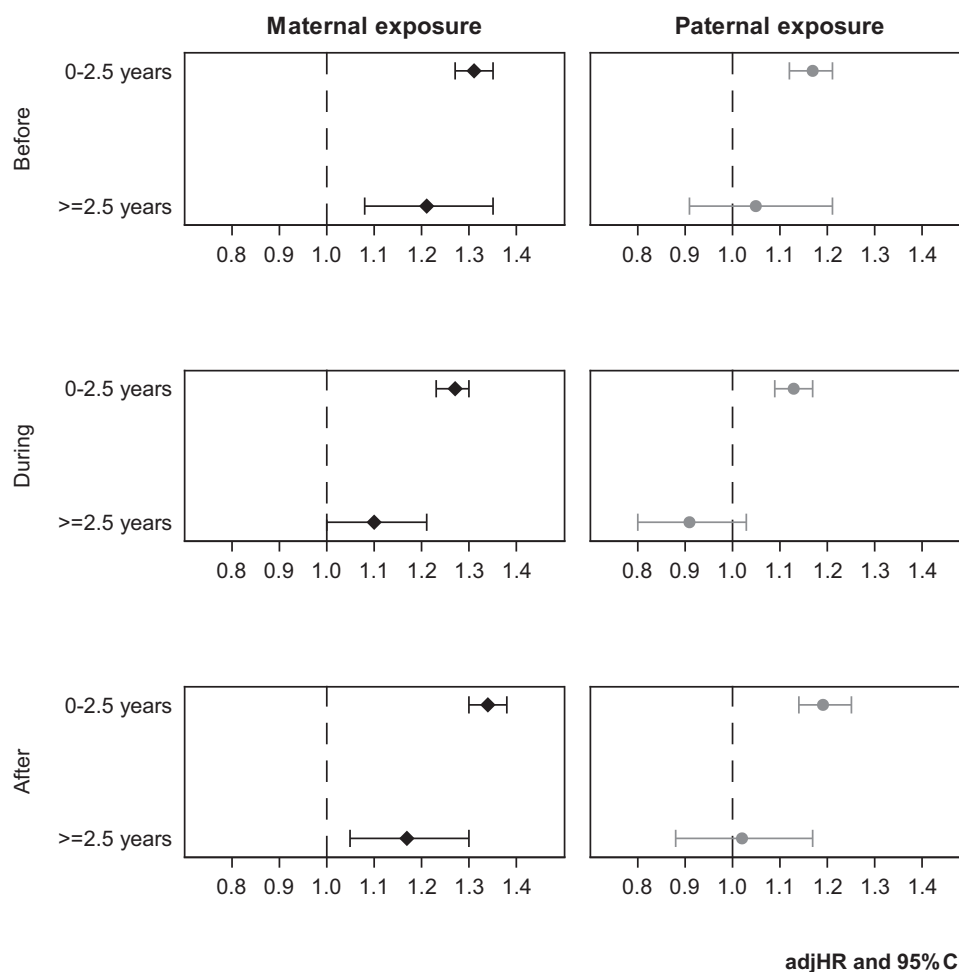


FIGURE 1. Adjusted* hazard ratio (HR) and 95% confidence intervals (CI) for childhood asthma in relation to age, after exposure to antibiotics before, during, and after pregnancy in mothers and fathers, respectively. **Maternal exposure*: Adjusted for parents' highest education, mother's country of birth and history of asthma, parental cohabitation during pregnancy, parity, age as analysis time scale (before pregnancy, pregnancy, after pregnancy), and maternal smoking (pregnancy). *Paternal exposure*: Adjusted for parents' highest education, father's country of birth and history of asthma, age as analysis time scale (before pregnancy, pregnancy, after pregnancy), and parental cohabitation during pregnancy (pregnancy).

exposure to any of the parents alters the child's neonatal exposure to a healthy microbiome, and that this could in turn lead to an increased risk of asthma.

The population-based registers allowed us to estimate the association between parental antibiotics and childhood asthma prospectively with objective measures of exposure and validated outcomes,⁸ precluding recall bias. Although we were able to adjust for maternal smoking during pregnancy and parental country of birth, information on paternal smoking, which may be a potential confounder, was not available in the registers. We were also unable to control for antibiotics prescribed abroad; however, sensitivity analyses restricted to children of Swedish-born parents produced similar estimates.

In conclusion, we have shown an association between parental exposure to antibiotics and subsequent childhood asthma in children (<2.5 years for maternal and paternal exposure and

≥2.5 years for maternal exposure), with a pattern that confirms shared familial (genetic and environmental) factors.

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ONLINE REPOSITORY**METHODS****Study population**

The personal identity number (PIN) enables unambiguous linkage between population-based registers held by the Swedish National Board of Health and Welfare and Statistics Sweden.^{E1} The Swedish Medical Birth Register (MBR) and the Multi-Generation Registry were linked through the PIN to identify a nationwide population-based cohort of children born in Sweden to women who were pregnant between July 2005 and December 2010 along with their biological fathers. After linkage of the registers, performed by the Swedish National Board of Health and Welfare, the PINs were replaced with anonymous study numbers. In total, 492,700 children were identified after excluding individuals with missing study numbers ($n = 14,681$) and children who had their first migration record registered as immigration ($n = 14$).

Exposure and outcome

The Swedish Prescribed Drug Register (SPDR) contains complete data on all dispensed drugs from outpatient care and in the primary health care since July 1, 2005.^{E2} All drugs are classified according to the Anatomical Therapeutic Chemical (ATC) classification system. From the register we collected information on parents' dispensed systemic antibiotics, which are coded under ATC J01A-J01X and parents' and children's asthma medication, coded under ATC R03, as well as the date of dispensed prescription.

The National Patient Register (NPR) was established in 1964, with a complete national coverage as of 1987, and is based on hospital discharge records.^{E3} The cause of hospitalization is coded at the time of discharge according to the current version of the Swedish translation of the International Classification of Disease (ICD) as determined by the WHO. From the register, the following variables were collected: child and parents' asthma diagnoses (ICD: J45) and date of diagnosis.

Childhood asthma was defined as having both a diagnosis of asthma registered in the NPR and fulfilling one or both criteria of asthma medication from the SPDR: (1) ≥ 2 dispensed inhaled corticosteroids, leukotriene receptor antagonists, or fixed combinations of β_2 -agonists and corticosteroids, with ≥ 2 weeks' gap between distributions; or (2) ≥ 3 dispensed asthma medications as above, or short-acting β_2 -agonists, within a year. Date of onset was set as the date of prescription of any of the medications or date of diagnosis, whichever came first. This proxy for asthma has previously been validated in children 0 to 17 years of age, where positive predictive value (PPV) was estimated based on the gold standard for asthma suggested by the Swedish Paediatric Association's section for Allergy.^{E4} The criteria of asthma include ≥ 3 obstructive periods before 2 years of age and/or ≥ 1 obstructive period after 2 years of age and/or ≥ 1 obstructive period independent of age when the child has 1 or more of the following: eczema, allergy, parents and/or siblings with asthma, or no improvement between periods of respiratory tract infections. Children under 2 years of age with ≤ 2 asthma-like symptoms during respiratory tract infections and without symptoms between infections are defined as having obstructive bronchitis.

The PPV of these 2 separate outcomes of asthma (asthma diagnosis in the NPR and asthma medication in SPDR) varied between 75% and 99%, with the lower being in children 0 to 4.5

years of age. Thus, to increase the specificity of the outcome of asthma based on register information, children in the present study had to have both an asthma diagnosis registered in the NPR and fulfilling asthma medication criteria in the SPDR. For a more detailed description of the validation study, refer to the paper by Örtqvist et al.^{E4}

Other variables

The MBR has information on 98% of all pregnancies resulting in a delivery since 1973. Starting at the first prenatal visit at the antenatal care clinic, information is prospectively collected on standardized records. The MBR has been validated, and the quality of the variables included in the present study is considered high.^{E5} From the register, these variables were collected: child's date of birth and gestational age in days, which were used to estimate the date of conception and the different exposure periods, parity (child's birth order), parental cohabitation (mother cohabits with child's father, or other, during pregnancy), parents' country of birth (Sweden or other), and maternal smoking during pregnancy (yes or no).

The Longitudinal integration database for health insurance and labour market studies (LISA) includes information on education for all individuals aged 16 years or older and registered in Sweden. From the register, the highest level of education for either parent was identified (≤ 9 , 10-12, >12 years).

Maternal and paternal asthma was defined as either having a diagnosis of asthma in the NPR or fulfilling asthma medication criteria from the SPDR. Sensitivity analyses were performed to further study potential differences between those with and without parents with a history of asthma, by including an interaction term between exposure to antibiotics and parental asthma.

Directed acyclic graphs

To assess causality in an epidemiological study and to identify potential confounders, a directed acyclic graph (DAG) may be used.^{E6,E7} The DAG can be applied to various analyses, for example, a study of the association between a maternal antibiotic exposure and childhood asthma. A directed arrow between these 2 variables indicates that the exposure is associated with the outcome, but the arrow does not say anything about whether the association is positive or negative, or about the strength of the association. DAGs can be used to identify all potential confounders that may exist, to know which variables should be adjusted for in the analyses. A factor that lies in the causal pathway between the exposure and the outcome is defined as a mediator. There are almost always mediators on the causal pathway, but this does not indicate that the exposure is not causal. When the exposure and the outcome are common causes for a third factor (a common effect), this factor is called a collider. Pathways through colliders are closed, unless the collider is adjusted for (included in the multivariate analyses), which will then open the path between the exposure and the outcome and potentially cause spurious associations.

Unmeasured and unknown confounders may also bias the association between an exposure and an outcome, and can also be displayed in a DAG. The use of negative controls is one way to detect unmeasured confounding.^{E7} The negative control is closely related to the exposure or the outcome and thus likely to be affected by the same confounders, but it is not on the direct pathway between the exposure and the outcome being investigated (Figure E1).

RESULTS

Table E1 presents the crude and adjusted hazard ratios (HR) and 95% confidence intervals (CI) for asthma in relation to maternal and paternal exposure to antibiotics before, during, and after pregnancy, corresponding to Figure 1 in the main text. The inclusion of the 3 exposures (before, during, and after pregnancy) within the same statistical model for mothers and fathers, respectively, provided very similar estimates; for maternal antibiotics in children <2.5 years, the HR_{adj} was 1.31 (95% CI 1.27-1.35) and in children ≥2.5 years, the HR_{adj} was 1.16 (95% CI 1.05-1.28). The corresponding HR_{adj} for paternal antibiotics in children <2.5 years was 1.20 (95% CI 1.15-1.25) and 1.03 (95% CI 0.89-1.18) for children ≥2.5 years.

Table E2 shows the adjusted HR and 95% CI after including an interaction term between exposure and older siblings (≥2.5 years older), where estimates were similar to the main findings.

Table E3 displays the adjusted HR and 95% CI for the association between paternal antibiotics and childhood asthma, with the adjustment of maternal antibiotics during the same exposure period, where estimates were found to be very similar to the main findings.

Sensitivity analyses of parental asthma provided similar estimates as the main findings (data not shown).

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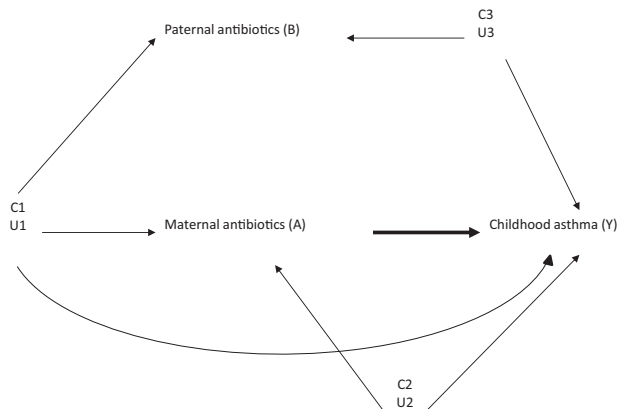


FIGURE E1. A directed acyclic graph (DAG) showing the potential pathways for paternal antibiotic exposure as a negative control to the association between maternal antibiotic exposure and childhood asthma, modified from Brew et al.^{E7} “A” represents maternal exposure to antibiotics before, during, and after pregnancy. “Y” is the outcome of childhood asthma. “B” represents paternal antibiotic exposure. “C” denotes measured and “U” unmeasured confounders that are shared (C1, U1) or unshared (C2, C3, U2, U3) between parents.

TABLE E1. Crude and adjusted hazard ratios (HR) and 95% confidence intervals (CI) for asthma in relation to maternal and paternal exposure to antibiotics before, during, and after pregnancy

		Crude				Adjusted*			
	Age (y)	Events	Person-years	HR	95% CI	Events	Person-years	HR	95% CI
Maternal exposure									
Before pregnancy	0-2.5	26,469	1,032,281	1.33	1.29-1.37	25,125	983,389	1.31	1.27-1.35
	≥2.5	2,450	472,835	1.23	1.10-1.37	2,294	442,414	1.21	1.08-1.35
During pregnancy	0-2.5	26,755	1,051,287	1.34	1.30-1.38	25,315	998,713	1.27	1.23-1.30
	≥2.5	2,491	480,323	1.16	1.06-1.28	2,325	448,740	1.10	1.00-1.21
After pregnancy	0-2.5	26,753	1,070,218	1.38	1.33-1.42	25,400	1,019,663	1.34	1.30-1.38
	≥2.5	2,491	489,249	1.21	1.10-1.34	2,331	457,834	1.17	1.05-1.30
Paternal exposure									
Before pregnancy	0-2.5	26,170	1,037,764	1.20	1.15-1.25	26,170	1,037,764	1.17	1.12-1.21
	≥2.5	2,442	474,413	1.08	0.94-1.25	2,442	474,413	1.05	0.91-1.21
During pregnancy	0-2.5	26,375	1,047,960	1.17	1.13-1.21	25,040	998,603	1.13	1.09-1.17
	≥2.5	2,461	478,697	0.92	0.81-1.04	2,304	448,096	0.91	0.80-1.03
After pregnancy	0-2.5	26,543	1,061,021	1.23	1.18-1.28	26,543	1,061,020	1.19	1.14-1.25
	≥2.5	2,478	484,911	1.05	0.91-1.21	2,478	484,911	1.02	0.88-1.17

**Maternal exposure:* Adjusted for parents' highest education, mother's country of birth and history of asthma, parental cohabitation during pregnancy, parity, age as analysis time scale (before pregnancy, pregnancy, after pregnancy), and maternal smoking (pregnancy). *Paternal exposure:* Adjusted for parents' highest education, father's country of birth and history of asthma, age as analysis time scale (before pregnancy, pregnancy, after pregnancy), and parental cohabitation during pregnancy (pregnancy).

TABLE E2. Adjusted* hazard ratios (HR) and 95% confidence intervals (CI) after including an interaction term between exposure and older siblings (≥ 2.5 years older)

	Before pregnancy, HR (95% CI)		During pregnancy, HR (95% CI)		After pregnancy, HR (95% CI)	
	No older siblings	Older siblings	No older siblings	Older siblings	No older siblings	Older siblings
Maternal exposure						
Age (y)						
0-2.5	1.31 (1.24-1.40)	1.34 (1.27-1.42)	1.25 (1.19-1.31)	1.34 (1.27-1.41)	1.38 (1.30-1.45)	1.54 (1.46-1.63)
≥ 2.5	1.29 (1.07-1.55)	1.17 (0.93-1.47)	1.06 (0.90-1.23)	1.15 (0.94-1.41)	1.19 (1.01-1.40)	1.25 (1.00-1.55)
Paternal exposure						
Age (y)						
0-2.5	1.18 (1.10-1.27)	1.14 (1.06-1.22)	1.14 (1.07-1.21)	1.13 (1.06-1.21)	1.20 (1.11-1.29)	1.20 (1.11-1.29)
≥ 2.5	0.92 (0.72-1.17)	1.12 (0.85-1.46)	1.00 (0.82-1.21)	0.84 (0.64-1.09)	0.94 (0.75-1.19)	1.19 (0.92-1.54)

**Maternal exposure:* Adjusted for parents' highest education, mother's country of birth and history of asthma, parental cohabitation during pregnancy, parity, age as analysis time scale (before pregnancy, pregnancy, after pregnancy), and maternal smoking (pregnancy). *Paternal exposure:* Adjusted for parents' highest education, father's country of birth and history of asthma, age as analysis time scale (before pregnancy, pregnancy, after pregnancy), and parental cohabitation during pregnancy (pregnancy).

TABLE E3. Hazard ratios (HR) and 95% confidence intervals (CI) for asthma in relation to paternal exposure to antibiotics before, during, and after pregnancy, with adjustment for maternal antibiotics

	Age (y)	Paternal exposure			
		Adjusted*		Adjusted*,†	
		HR	95% CI	HR	95% CI
Before pregnancy	0-2.5	1.17	1.12-1.21	1.13	1.08-1.17
	≥ 2.5	1.05	0.91-1.21	1.01	0.88-1.17
During pregnancy	0-2.5	1.13	1.09-1.17	1.10	1.06-1.14
	≥ 2.5	0.91	0.80-1.03	0.80	0.77-1.00
After pregnancy	0-2.5	1.19	1.14-1.25	1.15	1.11-1.20
	≥ 2.5	1.02	0.88-1.17	0.98	0.85-1.13

**Paternal exposure:* Adjusted for parents' highest education, father's country of birth and history of asthma, age as analysis time scale (before pregnancy, pregnancy, after pregnancy), and parental cohabitation during pregnancy (pregnancy).

†Analyses adjusted for maternal antibiotics during the same exposure period.