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Parental antibiotics and childhood asthma – a population-based study

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Clinical Implications box

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 is partly explained by familial confounding such as genes and environment.

Key words: antibiotics, asthma, maternal, paternal, public health, register

Word count: 1175

To the editor:

Previous studies have found positive associations between maternal antibiotic exposure in fetal life and childhood asthma.[1-4] It has been hypothesised 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 e.g. socio-economic status, parental smoking and health seeking behaviour.[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 the Online Repository.

We collected information on dispensed systemic parental antibiotics from the Swedish Prescribed Drug Register (SPDR). Exposure windows were defined as *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 0-17 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, were obtained from the Longitudinal integration database for health insurance and labour market studies, MBR, NPR and SPDR.

The association between maternal and paternal antibiotic exposure and childhood asthma was analysed 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 31st, 2011). Non-proportional 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 pre-pregnancy, 19% during pregnancy and 16% post-pregnancy (*Table 1*). The proportion of fathers with pre-pregnancy exposure was 8%, during pregnancy 11%, and post-pregnancy 8%. The overall proportion of asthma in children was 6% and approximately 7-8% 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 pre-pregnancy exposure was (adjusted Hazard Ratio (HR_{adj}) 1.31, 95% CI 1.27-1.35); during pregnancy (HR_{adj} 1.27, 95% CI 1.23-1.30) and post-pregnancy (HR_{adj} 1.34, 95% CI 1.30-1.38) among children up to 2.5 years. Point estimates for children ≥2.5 years were somewhat lower, but still significant, *Figure 1 and Table E1*.

Children whose fathers had been exposed to antibiotics were also at increased risk for asthma up to 2.5 years; pre-pregnancy (HR_{adj} 1.17, 95% CI 1.12-1.21); during pregnancy (HR_{adj} 1.13, 95% CI 1.09-1.17) and post-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*.

To further understand if the differences in results between children <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).

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. While this could not be explained by having older siblings, the fact that there is an association between 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) or paternal environmental factors (U3 in Figure E1), such as sharing of infections, caring of children or health-seeking behaviour that differs between mothers and fathers. While the effect of maternal antibiotics seem to be stronger, the similar pattern of estimates, independent of exposure period, indicate 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 intrauterine environment and the mother's risk of antibiotic treatment. This is in line with, and confirms findings from our previous sibling design study,[7] and illustrates the beauty of using paternal exposure as negative control. On the contrary, Mulder et al did not find a significant association between exposure to paternal antibiotics in the third trimester and childhood asthma[3] which may be explained by the limited exposure period or power issues. However, we cannot exclude that the antibiotic exposure to any of the parents alters the child's neonatal exposure to a healthy microbiome, and that this could in turn lead to 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. While 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.

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.

We would like to acknowledge Åsa Eck for excellent data management.

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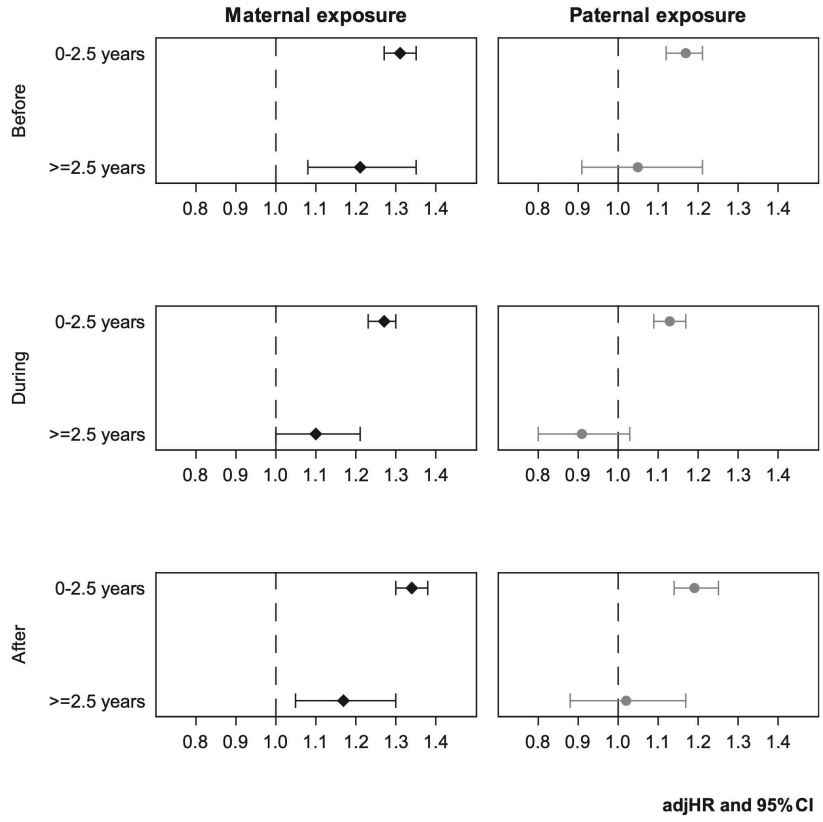
Figure legends

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 (pre-pregnancy, pregnancy, post-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 (pre-pregnancy, pregnancy, post-pregnancy) and parental cohabitation during pregnancy (pregnancy).



Tables

Table 1. Descriptive table of study population and variables included in analyses.

	All	Children without asthma		Children with asthma	
	N	**n**	**%**	**n**	**%**
Total	492 700	463 446	94.1	29 254	5.9
Variables					
Maternal antibiotics					
Pre-pregnancy	66 882	61 888	13.3	5 071	17.3
During pregnancy	95 558	88 429	19.1	7 129	24.4
Post-pregnancy	76 665	70 787	15.3	5 878	20.1
Paternal antibiotics					
Pre-pregnancy	39 196	36 445	7.9	2 751	9.4
During pregnancy	56 243	52 424	11.3	3 819	13.1
Post-pregnancy	37 139	34 472	7.44	2 667	9.1
Highest paternal education					
≤9 yrs	23 038	21 574	4.7	1 464	5.0
10-12 yrs	179 358	167 312	36.1	12 046	41.2
>12 yrs	287 852	272 143	58.7	15 709	53.7
Missing	2 452	2417	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 <0.005 for all variables.

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. [1] The Swedish Medical Birth Register (MBR) and the Multi-Generation Registry was linked through the personal identity number 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 contains complete data on all dispensed drugs from outpatient care and in the primary health care since July 1, 2005.[2] 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. [3] 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/both of two criteria of asthma medication from the SPDR; a) ≥ 2 dispensed inhaled corticosteroids, leukotriene receptor antagonists, or fixed combinations of β2-agonists and corticosteroids, with ≥ 2 weeks' gap between distributions; or b) ≥ 3 dispensed asthma medications as above, or short acting β2-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 0-17 years of age, where Positive predictive value (PPV) was estimated based on gold standard for asthma suggested by the Swedish Paediatric Association's section for Allergy.[4] The criteria of asthma includes ≥ 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 of the following: eczema, allergy, parents and/or siblings with asthma or no improvement between periods of respiratory tract infections. Children under two years of age with ≤ 2 asthma-like symptoms during respiratory tract infections and without symptoms between infections are defined as suffering from obstructive bronchitis.

The PPV of these two separate outcomes of asthma (asthma diagnosis in the NPR and asthma medication in SPDR) varied between 75% - 99%, with the lower being in children of 0-4.5 years of age. Thus in order 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 please see Örtqvist AK et al. [4]

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. [5] 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 Labor 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 was 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.[6,7] 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 two variables indicate 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 strength of the association. DAGs can be used to identify all

potential confounders that may exist, in order to know which variables that 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 which will then open the path 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.[7] 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 manuscript. Inclusion of the three 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 was 1.31 (95% CI 1.27-1.35) and in children ≥2.5 years the HR was 1.16 (95% CI 1.05-1.28). Corresponding HR 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 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 legends

Figure E1. A directed acyclic graph (DAG)* to show the relationship between parental antibiotics and childhood asthma, modified from Brew et al.[7]

*A DAG showing the potential pathways for paternal antibiotic exposure as a negative control to the association between maternal antibiotic exposure and childhood asthma. 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.

Figure E1.

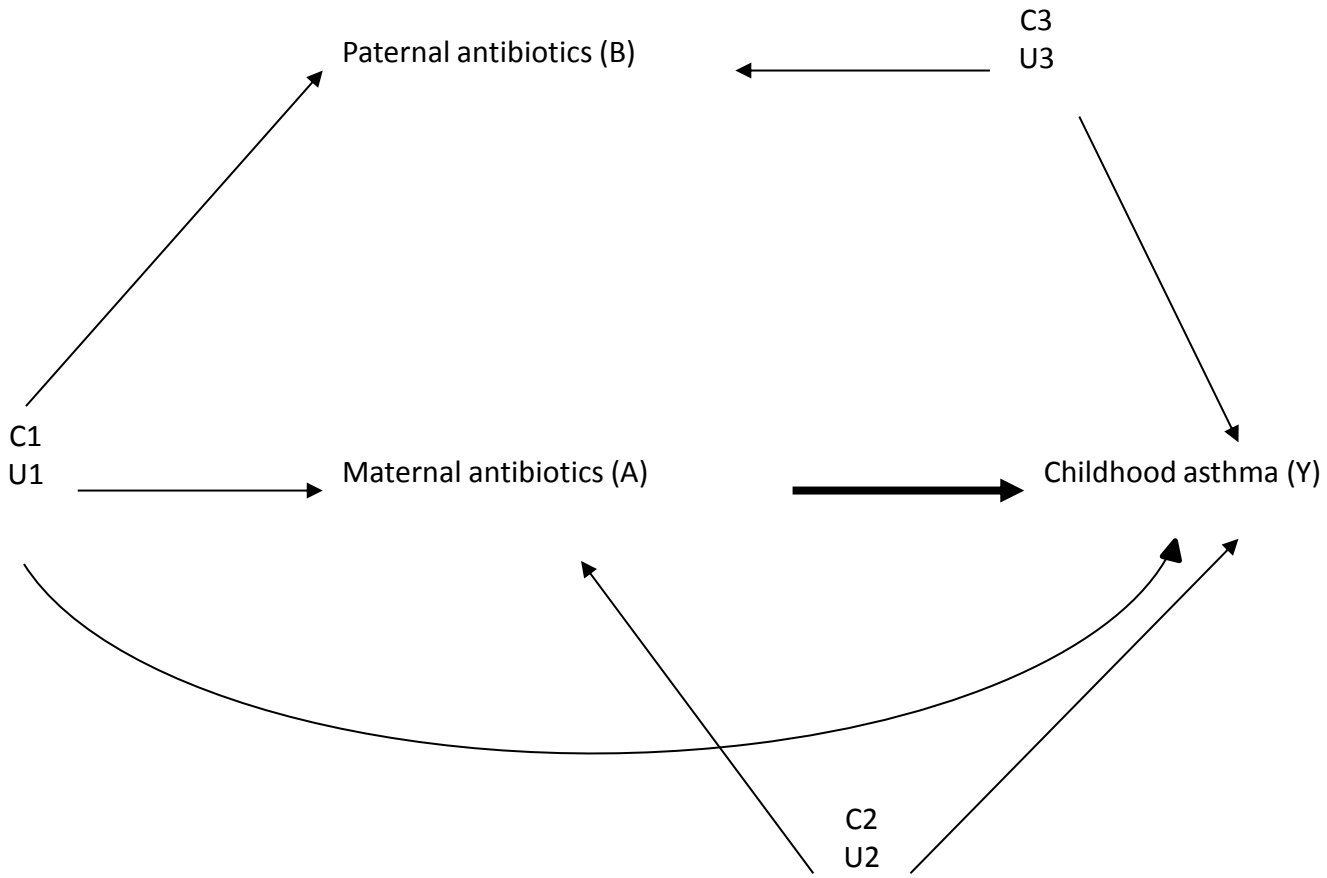
C3
U3
Paternal antibiotics (B)
C1
U1
Maternal antibiotics (A)
Childhood asthma (Y)
C2
U2

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*			
Maternal exposure	**Age (yrs)**	**Events**	**Person-years**	**HR**	**95% CI**	**Events**	**Person-years**	**HR**	**95% CI**
Pre-pregnancy	*0-2.5*	26469	1032281	1.33	1.29-1.37	25125	983389	1.31	1.27-1.35
	>2.5	2450	472835	1.23	1.10-1.37	2294	442414	1.21	1.08-1.35
During pregnancy	*0-2.5*	26755	1051287	1.34	1.30-1.38	25315	998713	1.27	1.23-1.30
	>2.5	2491	480323	1.16	1.06-1.28	2325	448740	1.10	1.00-1.21
Post-pregnancy	*0-2.5*	26753	1070218	1.38	1.33-1.42	25400	1019663	1.34	1.30-1.38
	>2.5	2491	489249	1.21	1.10-1.34	2331	457834	1.17	1.05-1.30
Paternal exposure	**Age (yrs)**	**Events**	**Person-years**	**HR**	**95% CI**	**Events**	**Person-years**	**HR**	**95% CI**
Pre-pregnancy	*0-2.5*	26170	1037764	1.20	1.15-1.25	26170	1037764	1.17	1.12-1.21
	>2.5	2442	474413	1.08	0.94-1.25	2442	474413	1.05	0.91-1.21
During pregnancy	*0-2.5*	26375	1047960	1.17	1.13-1.21	25040	998603	1.13	1.09-1.17
	>2.5	2461	478697	0.92	0.81-1.04	2304	448096	0.91	0.80-1.03

Post-pregnancy	*0-2.5*	26543	1061021	1.23	1.18-1.28	26543	1061020	1.19	1.14-1.25
	>2.5	2478	484911	1.05	0.91-1.21	2478	484911	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 (pre-pregnancy, pregnancy, post-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 (pre-pregnancy, pregnancy, post-pregnancy) and parental cohabitation during pregnancy (pregnancy).

Table E2. Adjusted* Hazard Ratio (HR) and 95% Confidence Intervals (CI) after including an interaction term between exposure and older siblings (≥2.5 years older)

Maternal exposure	**Pre-pregnancy, HR (95% CI)**		**During pregnancy, HR (95% CI)**		**Post-pregnancy, HR (95% CI)**	
Age (yrs)	*No older siblings*	*Older siblings*	*No older siblings*	*Older siblings*	*No older siblings*	*Older siblings*
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 (yrs)	*No older siblings*	*Older siblings*	*No older siblings*	*Older siblings*	*No older siblings*	*Older siblings*
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 (pre-pregnancy, pregnancy, post-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 (pre-pregnancy, pregnancy, post-pregnancy) and parental cohabitation during pregnancy (pregnancy).

Table E3. HR and 95% CI for asthma in relation to paternal exposure to antibiotics before, during, and after pregnancy, with adjustment for maternal antibiotics.

		Paternal exposure			
		Adjusted*		Adjusted*¶	
	Age	**HR**	**95% CI**	**HR**	**95% CI**
Pre-pregnancy exposure	*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
Pregnancy exposure	*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
Post-pregnancy exposure	*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 (pre-pregnancy, pregnancy, post-pregnancy) and parental cohabitation during pregnancy (pregnancy).

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