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 I). 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 $\geq$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 $\geq$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 $\geq$ 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

	All	Children without asthma		Children with asthma	
	N	N	Percentage	N	Percentage
Variables	492,700	463,446	94.1	29,254	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 intrauterine 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 al[3] 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