Parental antibiotics and childhood asthma : a population-based study.

Örtqvist, A.K.; Lundholma, C.; Fang, F.; Fall, T.; Almqvist, C.

Parental antibiotics and childhood asthma – a population-based study

Anne K. Örtqvist[a]; MD, PhD

Cecilia Lundholm[a]; MSc

Fang Fang[a]; MD, PhD

Tove Fall[b]; VMD, PhD

Catarina Almqvist[a,c]; MD, PhD

Affiliations

[a]Department of Medical Epidemiology and Biostatistics, Karolinska Institutet, Stockholm, Sweden

[b]Department of Medical Sciences, Molecular Epidemiology and Science for Life Laboratory, Uppsala University, Uppsala, Sweden

[c]Unit of Pediatric Allergy and Pulmonology at Astrid Lindgren Children's Hospital, Karolinska University Hospital, Stockholm, Sweden

Corresponding Author:

Anne K. Örtqvist MD, PhD

Department of Medical Epidemiology and Biostatistics

PO Box 281, Karolinska Institutet

SE 171 77 Stockholm, SWEDEN

T. +46 737 355 309

E. anne.ortqvist@ki.se

Funding sources

This work was supported by the Swedish Research Council through the Swedish initiative for Research on Microdata in the Social and Medical Sciences (SIMSAM) framework grant no. 340-2013-5867, the Swedish Heart Lung Foundation, grants provided by the Stockholm County Council (ALF project), the Swedish Asthma and Allergy Association's Research Foundation, FORTE grant no 2015-00289 and the Strategic Research Program in Epidemiology at Karolinska Institutet.

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.

References

1. Rusconi F, Galassi C, Forastiere F, et al. Maternal complications and procedures in pregnancy and at birth and wheezing phenotypes in children. *American journal of respiratory and critical care medicine* 2007; **175**(1): 16-21.

2. Metsala J, Lundqvist A, Virta LJ, Kaila M, Gissler M, Virtanen SM. Prenatal and Postnatal Exposure to Antibiotics and Risk of Asthma in Childhood. *Clinical and experimental allergy : journal of the British Society for Allergy and Clinical Immunology* 2014.

3. Mulder B, Pouwels KB, Schuiling-Veninga CC, et al. Antibiotic use during pregnancy and asthma in preschool children: the influence of confounding. *Clinical and experimental allergy : journal of the British Society for Allergy and Clinical Immunology* 2016; **46**(9): 1214-26.

4. McKeever TM, Lewis SA, Smith C, Hubbard R. The importance of prenatal exposures on the development of allergic disease: a birth cohort study using the West Midlands General Practice Database. *American journal of respiratory and critical care medicine* 2002; **166**(6): 827-32.

5. Arrieta MC, Stiemsma LT, Dimitriu PA, et al. Early infancy microbial and metabolic alterations affect risk of childhood asthma. *Science translational medicine* 2015; **7**(307): 307ra152.

6. Heintze K, Petersen KU. The case of drug causation of childhood asthma: antibiotics and paracetamol. *Eur J Clin Pharmacol* 2013; **69**(6): 1197-209.

7. Örtqvist AK, Lundholm C, Kieler H, et al. Antibiotics in fetal and early life and subsequent childhood asthma: nationwide population based study with sibling analysis. *BMJ (Clinical research ed)* 2014; **349**: g6979.

8. Örtqvist AK, Lundholm C, Wettermark B, Ludvigsson JF, Ye W, Almqvist C. Validation of asthma and eczema in population-based Swedish drug and patient registers. *Pharmacoepidemiol Drug Saf* 2013; **22**(8): 850-60.

9. Greenland S, Pearl J, Robins JM. Causal diagrams for epidemiologic research. *Epidemiology (Cambridge, Mass)* 1999; **10**(1): 37-48.

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.