Exposure to antibiotic use was categorized into the following 3 groups: any antibiotics; antibiotics for respiratory infections; and antibiotics for urinary tract or skin and soft tissue infections. Asthma diagnosis was defined as having both an asthma diagnosis and receipt of asthma medications. The association between antibiotic exposure and asthma was investigated with multivariate Cox proportional hazards model conditional on sibling group was used to adjust for shared factors within families.

RESULTS. Overall, 6% of the children in the study were defined as having asthma. In total, 20% of the children in the full cohort had been exposed to antibiotics in fetal life, and at least 1 prescription of any antibiotic during childhood was filled for 62% of children. Antibiotic exposure in fetal life was associated with an increased risk of asthma in multivariate cohort analyses (hazard ratio 1.28, 95% confidence interval 1.25–1.32), but not in sibling analyses (0.99, 0.92–1.07). In multivariate cohort analyses, antibiotics used to treat respiratory infections in childhood were associated with a more pronounced increased risk of asthma (4.12, 3.78–4.50) than antibiotics used for urinary tract and skin infections (1.54, 1.24–1.92). In sibling analyses, the excess risks after exposures to antibiotics for respiratory infections decreased (2.36, 1.78–3.13) and disappeared for antibiotics for urinary tract and skin infections (0.85, 0.47–1.55).

CONCLUSIONS. Previous positive associations between exposure to antibiotics in fetal and early life and subsequent childhood asthma could have been caused by shared familial factors, in addition to confounding by respiratory infections.

REVIEWER COMMENTS. This study uses the breadth of administrative data available in Sweden to investigate the association between antibiotics and childhood asthma, taking familial factors into account. Earlier studies are conflicting with systematic reviews highlighting that the association between antibiotic exposure and asthma could be caused by bias. This study corroborates the potential for reverse causation and confounding by indication; the latter implies that the association is confounded by a third factor (such as respiratory infection) that could both explain the indication for antibiotic use and act as a risk factor for asthma.

STUDY POPULATION. All children born in Finland between 1996 and 2004 and diagnosed with asthma and 1 matched control per case were identified from 4 national health registries (Drug Prescription Register, Special Reimbursement Register, Population Register, and Medical Birth Register), resulting in 6690 case-control pairs.

METHODS. Prenatal exposure to antibiotics was identified by extracting purchasing history of all antibiotics (ATC Code J01—antibiotics for systemic use) by the mother during pregnancy from the Drug Prescription Registry. Postnatal exposure to antibiotics was identified by extracting purchasing history of all antibiotics for the child from birth until the date of asthma diagnosis from the same Drug Prescription Registry. Maternal background and perinatal variables were also measured and include maternal age, maternal asthma, smoking during pregnancy, socioeconomic status, previous deliveries, previous miscarriages, mode of delivery, and gestational age and birth weight/birth length. Logistic regression was used to identify associations between maternal background and perinatal factors and the use of antibiotics in pregnancy and during the first 3 years of life in the control group. Conditional logistic regression was used to analyze associations between maternal and child use of antibiotics and the risk of asthma diagnoses in the case group.

RESULTS. Maternal use of antibiotics during pregnancy, particularly cephalosporins, macrolides, extended spectrum penicillins, and phenoxymethylpenicillin, was associated with an increased risk of asthma in the child [adjusted odds ratio = 1.31 (95% confidence interval, 1.21–1.42)]. Antibiotics administered during the first year of life also increased the risk of asthma [adjusted odds ratio = 1.60 (95% confidence interval, 1.48–1.73)].

CONCLUSIONS. Both prenatal and postnatal exposure to antibiotics was associated with an increased risk of developing childhood asthma. A dose-related response was observed in this analysis of large population and registry based data sets.

REVIEWER COMMENTS. This study used data from the Finnish national health registry. Because of that country’s socialized medical system, this mitigates bias in patient selection, access to health care, cost of treatment, and social determinants. Although wheezing is common in children, this cohort used strict diagnostic criteria to identify asthmatic patients and accurately documented the administration of asthma medications. All prenatal and postnatal antibiotics were captured, eliminating the recall bias often seen in other studies that examine the role of antibiotics on the development of asthma. Prenatal antibiotic use changes the vaginal flora, thus altering the initial colonizing bacteria for the infant. It is

Prenatal and Post-natal Exposure to Antibiotics and Risk of Asthma in Childhood


PURPOSE OF THE STUDY. The purpose of this study was to explore associations between prenatal and postnatal exposure to antibiotics and the risk of childhood asthma.

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also postulated that antibiotics profoundly affect the symbiotic relationship between gut flora and the immune system, ultimately modifying the nature and intensity of the human immune response. The combination of these 2 factors may lead to the immunologic changes that lead to asthma.

Antibiotics in the First Week of Life Is a Risk Factor for Allergic Rhinitis at School Age


**PURPOSE OF THE STUDY.** To analyze risk factors and protective factors for allergic rhinitis in school age children in a Swedish birth cohort.

**STUDY POPULATION.** Birth cohort of 8341 children born in western Sweden in 2003. Questionnaires were distributed at age 8, and 4051 (49%) were returned.

**METHODS.** Data were collected by questionnaires at ages 6 months and 1, 4.5, and 8 years and from the Swedish Medical Birth Registrar. The 8-year questionnaire addressed health, family, environment, feeding habits, and specifically allergic rhinitis. To be considered positive for allergic rhinitis, children had to have both symptoms and medication use. Information regarding antibiotic use in the first week of life, farm living, eczema, and food allergy were collected on earlier questionnaires.

**RESULTS.** Allergic rhinitis symptoms were reported in 14% of the children at age 8, with 10.9% reporting both symptoms and medication use. Mean age of onset of symptoms was 5.7 years. Multivariate analysis showed positive associations between allergic rhinitis and antibiotic use during the first week of life (odds ratio 1.75; 95% confidence interval 1.03–2.97), paternal allergic rhinitis (2.73; 2.12–3.52), doctor-diagnosed food allergy in the first year (2.45; 1.61–3.73), eczema in the first year (1.97; 1.50–2.59), and male gender (1.35; 1.05–1.74). Living on a farm with animals at preschool age was associated with a decreased risk of allergic rhinitis (0.31; 0.13–0.78). Tree and grass pollen were reported as the most common triggers.

**CONCLUSIONS.** The major findings of this study are that antibiotic exposure in the first week of life is associated with an increased risk of allergic rhinitis at age 8 and that living on a farm with animals while in preschool is associated with a decreased risk of allergic rhinitis at age 8. Both of these findings are in accordance with the hygiene hypothesis.

Effect of Antibiotic Use and Mold Exposure in Infancy on Allergic Rhinitis in Susceptible Adolescents


**PURPOSE OF THE STUDY.** To explore the risk of allergic rhinitis (AR) in adolescents with the independent and combined effect of antibiotic use and mold exposure in infancy.

**STUDY POPULATION.** The study population consisted of 7389 students recruited from 8 middle schools in Seoul, Korea.

**METHODS.** The International Study of Asthma and Allergies in Childhood written questionnaire was obtained from 7389 adolescents. Interleukin 13 (IL-13) (rs20541) and toll-like receptor 4 (rs1927911) polymorphisms were performed on TaqMan genotyping in 1395 randomly selected adolescents.

**RESULTS.** Of the total 7286 completed surveys, almost one-third used antibiotics, and 10.3% were exposed to mold in infancy. The data showed age, parental history of AR, antibiotic use in infancy, and pet ownership during pregnancy or infancy were linked with an increased risk of current AR. The presence of an older sibling was noted to have a protective effect. Increased odds ratio for current AR was seen with combined antibiotic use and mold exposure in infancy. Antibiotic use had an adjusted odds ratio of 1.25, whereas mold exposure had an adjusted odds ratio of 0.99 when considered independently. Patients also had increased risk of current AR with IL-13 (rs20541) GA or AA genotype and CT + TT genotype of toll-like receptor 4 (rs1927911).
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Rebecca Deal Poston and Angela Duff Hogan
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