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

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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).

References

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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.