

Title page

Prenatal and Postnatal Exposure to Antibiotics and Risk of Asthma in Childhood

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Abstract

Background Evidence on the association between postnatal exposure to antibiotics and the development of asthma is extensive, but inconsistent and even less is known about prenatal exposure.

Objective The aim of this study was to examine the associations between prenatal and postnatal exposure to different antibiotics and the risk of childhood asthma in a population- and register-based nested case-control study.

Methods All children who were born in 1996–2004 in Finland and diagnosed with asthma by 2006 were identified from a national health register. For each case, one matched control was selected. Information on asthma diagnoses, purchased anti-asthmatic drugs and antibiotics as well as putative confounders was obtained from national health registries. The associations were analysed using conditional logistic regression for children diagnosed at the age of 3 years or later (n= 6 690 case-control pairs).

Results Maternal use of any antibiotics during pregnancy was associated with an increased risk of asthma in the offspring (adjusted odds ratio [OR] = 1.31 [95% confidence interval [CI]: 1.21–1.42]).

Several maternal specific antibiotics were associated with the risk of asthma and the strongest

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association was observed for cephalosporins (OR = 1.46 [95% CI 1.30–1.64]). Child's use of antibiotics during the first year of life was associated with an increased risk of asthma (OR = 1.60 [95% CI 1.48–1.73]). Child's use of cephalosporins (OR = 1.79 [95% CI 1.59–2.01]), sulphonamides and trimethoprim (OR = 1.65 [95% CI 1.34–2.02]), macrolides (OR = 1.61 [95% CI 1.46–1.78]) and amoxicillin (OR = 1.46 [95% CI 1.35–1.58]) was associated with an increased risk of asthma.

Conclusions and Clinical Relevance Both prenatal and postnatal exposure to antibiotics was associated with an increased risk of asthma. The potential role of adverse effects of antibiotics on the gut microbiota and the development of asthma should be further explored.

Introduction

Asthma is one of the most common chronic conditions in childhood in many countries. In Finland, a prevalence of 13–20% of asthma symptoms has been reported among children [1]. Several environmental factors, such as exposure to smoking, infections or other microbial compounds, have been proposed to influence the asthma epidemic [2]. The knowledge that several antibiotics have adverse effects on gut microbiota and thus antibiotics potentially influence immunological health has encouraged several researchers to explore the potential association between antibiotics and asthma in childhood [3-7]. Recent cohort studies on postnatal exposure have revealed conflicting results [3, 4, 7-12], and the issue of reverse causality and confounding by indication due to respiratory tract infections is still debated [5, 6]. Prenatal exposure to antibiotics has received less attention [11-17], but most studies suggest an increased risk in the offspring [12, 13, 15-17]. Only a few studies have explored both mother's and child's exposure to antibiotics [11, 12, 15] and even less is known about prenatal exposure to different antibiotics [15]. Given the widespread use of antibiotics, the potential association between antibiotics and the risk of asthma is important to examine thoroughly. To assess the association between both prenatal and postnatal exposure to

antibiotics and to explore the role of different classes of antibiotics with the risk of asthma in childhood, we conducted a nationwide population- and register-based nested case-control study.

Methods

Data sources

Data were obtained from four national registers including the Drug Prescription Register [18], the Special Reimbursement Register [18] and the Population Register maintained by the Social Insurance Institution and the Medical Birth Register [19] maintained by the National Institute for Health and Welfare. Data were linked with unique personal identity codes administered to all Finnish citizens shortly after birth or immigration [20].

Information on diagnosed asthma was obtained from the Special Reimbursement Register. Patients with certain severe and chronic diseases, such as asthma, are entitled to special refunds (72% or 100%) for the costs of drugs prescribed by a physician. To be eligible for this special reimbursement, a written certificate is required from the attending physician or pediatrician stating that the patient's condition meets the explicit predefined diagnostic criteria. In addition, a long-lasting antiasthmatic drug therapy, planned to last at least 6 months, is required. Finally, all applications and certificates are reviewed by a physician or pharmacist at the Social Insurance Institution. Non-asthmatic controls were selected from the Population Register.

Information on purchased antiasthmatic drugs and antibiotics was obtained from the Drug Prescription Register maintained since 1994. All drugs prescribed by physicians and reimbursed by the National Sickness Insurance Scheme are registered. In Finland, outpatient antiasthmatic drugs and antibiotics are available by prescription only. The register includes information on drug class [Anatomical Therapeutic Chemical (ATC) Classification System [21]] and the dispensing date.

Information on maternal background and perinatal factors was derived from the Finnish Medical Birth Register.

Study population

From all children who were born between January 1, 1996, and April 30, 2004, those who had received a special reimbursement for the cost of antiasthmatic drugs based on asthma diagnosed with ICD-10 (International Classification of Diseases 10th Revision) code J45 by the end of 2005 were identified ($n = 22\,548$) as cases (Figure 1). For each case, one non-asthmatic control child matched to case by date of birth (± 28 days), sex and hospital district of birth was randomly selected.

The Medical Birth Register data were not available for children who were not born in Finland ($n = 516$ subjects, 183 cases and 333 controls) and they were excluded from the study population. Children who were diagnosed with asthma, but not purchased antiasthmatic drugs at least once after the diagnosis were excluded. Selection of the antiasthmatic drugs was based on the Finnish Current Care guidelines [22] and the recommendations by the Social Insurance Institution. These drugs included inhaled corticosteroids (ATC code R03BA), a fixed combination containing inhaled corticosteroids and salmeterol (code R03AK06), a fixed combination containing inhaled corticosteroids and formoterol (code R03AK07) and montelukast (code R03DC03). Concomitant use of a short-acting beta-agonist (code R03AC) was allowed.

A total of 445 control children had purchased antiasthmatic drugs from birth until the date of asthma diagnosis of the case without special reimbursement. They were excluded from the cohort as we did not have information on whether they were just transient users of antiasthmatic drugs or asthmatic children without a physician-confirmed diagnosis. Controls were allowed to be selected only once and twins from the same family as case-control pairs were not allowed.

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Due to the fact that wheezing is common in young children and therefore the diagnosis of asthma is challenging, children who were diagnosed with asthma before the age of 3 years were excluded. Finally, 6 690 case-control pairs were included in the present study.

Antibiotic exposure

To evaluate prenatal exposure, information on all antibiotics (ATC code J01, antibacterials for systemic use) purchased by the mother during pregnancy was extracted. The pregnancy period was calculated from the child's birth date and the gestational age obtained from the Medical Birth Register. In the absence of information on gestational age ($n = 71$, 0.5%), an assumption of 280 days was made. Prenatal exposure was categorized as maternal overall use (0 vs. ≥ 1 purchases) of any antibiotics and number of any antibiotic purchases (0, 1, 2, ≥ 3 purchases). Antibiotics were further grouped into "specific antibiotics" based on ATC-codes and categorized as overall use (0 vs. ≥ 1 purchases) of most commonly used specific antibiotics i.e. penicillins with extended spectrum (J01CA), cephalosporins (ATC code J01DB-DC), macrolides (J01FA), phenoxymethyl penicillin (J01CE02), tetracyclines (J01AA), trimetoprim and its combinations with sulphonamides (J01EA and EE), and fluoroquinolones (J01MA). Concomitant use of any other specific antibiotics was allowed in each group. Other specific antibiotics were not included due to the low number of purchases.

To evaluate postnatal exposure, information on all antibiotics purchased by the child from birth until the date of asthma diagnosis of the case was extracted. Antibiotics purchased during 6 months before diagnosis were excluded in order to diminish protopathic bias (i.e. the early symptoms of an undiagnosed asthma could have been the reason for the use of antibiotics). Postnatal exposure to antibiotics was categorized as child's overall use (0 vs. ≥ 1 purchases) of any antibiotics and number of any antibiotic purchases (0, 1, 2, 3, 4, ≥ 5 purchases during the first year of life and 0, 1, 2, 3, 4, 5, 6-7, 8-9, ≥ 10 purchases from birth to diagnosis). Antibiotics were further grouped into "specific

antibiotics” and categorized as overall use (0 vs. ≥ 1 purchases) of most commonly used specific antibiotics i.e. amoxicillin (including its combination with enzyme inhibitor, ATC codes J01CA04 and J01CR02), macrolides (J01FA), cephalosporins (J01DB-DC), trimetoprim and its combinations with sulphonamides (J01EA and EE), and phenoxymethyl penicillin (J01CE02). Concomitant use of any other specific antibiotics was allowed in each group.

To further investigate the issue of confounding by indication, we grouped the most commonly used specific antibiotics by the mother and the child into “likely indication” groups based on Almqvist et al [3]. The first group “Only antibiotics for gram-positive bacteria infections” included those mothers/children who had used only antibiotics commonly used to treat respiratory infections i.e. penicillins with extended spectrum (amoxicillin in children), phenoxymethylpenicillin, cephalosporins and macrolides, but not trimethoprim combined with sulfonamides or fluoroquinolones (in mothers). The second group “Only antibiotics for urinary tract infections” included those who had used only antibiotics commonly used to treat urinary tract and other infections i.e. trimethoprim, trimethoprim combined with sulfonamides and fluoroquinolones (in mothers), but not penicillins with extended spectrum (amoxicillin in children), phenoxymethylpenicillin, cephalosporins or macrolides. The third group “Both antibiotics for gram-positive bacteria and urinary tract infections” group included those who had used antibiotics for both indications i.e. penicillins with extended spectrum (amoxicillin in children), phenoxymethylpenicillin, cephalosporins and macrolides as well as trimethoprim, trimethoprim combined with sulfonamides and fluoroquinolones. Each mother/child was allowed to belong to only one “likely indication” group.

Maternal background and perinatal factors

Maternal background and perinatal variables included were maternal age (<25, 25–29, 30–34, ≥35 years), asthma (based on information on received special reimbursement), smoking during pregnancy, socioeconomic status (upper white-collar workers, lower white-collar workers, blue-collar workers and “others” including farmers, entrepreneurs, retired, unemployed, students and housewives [23]), previous deliveries (0, 1, ≥2), previous miscarriages, mode of delivery (vaginal delivery, assisted vaginal delivery, planned and unplanned caesarean section), gestational age and ponderal index of the child (birth weight/birth length³).

Statistical analysis

To examine the associations between maternal background and perinatal factors and the use of antibiotics during pregnancy among control mothers and during the first 3 years of life among control children logistic regression analysis was used. The association between maternal and child use of antibiotics and the risk of asthma was analysed by conditional logistic regression with results displayed as matched odds ratios (OR) and 95% confidence intervals (CI).

Both unadjusted and adjusted models were estimated. Those maternal background and perinatal factors which were associated with both asthma [24] and the use of antibiotics ($P < 0.3$) were included as confounders in the models. The adjusted model for maternal use of antibiotics included maternal asthma and previous deliveries. The main adjusted model for the child's use of antibiotics included maternal asthma, previous deliveries and gestational age. Further adjustment was made with maternal use of antibiotics during pregnancy. The models for the use of specific antibiotics were further adjusted for the total number of antibiotic purchases from which the number of corresponding specific antibiotic purchases was excluded. As these further adjustments

did not substantially change the results, only the results from the unadjusted and the main adjusted models are presented.

The associations between maternal and child's overall use of any antibiotics and the risk of asthma were further analysed separately for children diagnosed between the age of 3 and 5 years (n= 5 271 case-control pairs) and at the age of 6 years or later (n= 1 419 case-control pairs) in order to achieve a group of children where the asthma diagnosis can be considered most reliable.

Altogether 968 cases had purchased their first antiasthmatic drug (any drug with ATC-code R03) before (n= 282 cases) or at the same time (n= 686 cases) as the first antibiotic course was purchased and these children were excluded from the models assessing the child's use of antibiotics leaving 5 722 case-control pairs (n= 4 504 pairs aged 3 to 5 years and n=1 218 pairs aged 6 or more years) to these analysis.

Effect modification by maternal background and perinatal factors on the association between use of antibiotics and the risk of asthma was investigated. In addition, effect modification by maternal or child's use of antibiotics (when applicable) on the association between maternal or child's use of antibiotics and the risk of asthma was investigated. Statistical significance was set at the 5% level and two-sided *P* values were used. All analyses were performed using Stata statistical software, version 9.1.

This study was approved by the national data protection authority, the institutions keeping the registers and the Institutional Review Board of the National Public Health Institute (National Institute for Health and Welfare since 2009).

Results

Maternal use of antibiotics

One-fourth (24%) of the control mothers had used antibiotics during pregnancy. Maternal asthma ($P=0.003$), smoking ($P<0.001$) and previous deliveries ($P<0.001$) were directly associated with maternal overall use of antibiotics during pregnancy.

Maternal overall use of any antibiotic during pregnancy was associated with the risk of asthma in the offspring (adjusted OR = 1.31 [95% CI 1.21–1.42]). The association remained almost similar when further grouping the children according to age at diagnosis (adjusted OR = 1.32 [95% CI 1.21–1.46] for children diagnosed between ages 3 to 5 years of age and adjusted OR = 1.23 [95% CI 1.04–1.48] for children diagnosed at the age of 6 years or later). An increasing trend was observed between the number of antibiotic purchases and the risk of asthma (Figure 2). Of the specific antibiotics, maternal use of cephalosporins, macrolides, penicillins with extended spectrum and phenoxymethylpenicillin was associated with an increased risk of asthma (Table 1). When grouping antibiotics by indication, antibiotics for gram-positive bacteria infections were associated with an increased risk of asthma in the offspring, but the strongest association was observed when antibiotics for both gram-positive bacteria and urinary tract infections were used (Table 1). Population Attributable Risk (PAR) for maternal antibiotics was 7.4%.

Child's use of antibiotics

Half (49%) of the control children had used antibiotics during the first year of life and more than 80% during the first 3 years of life. The prevalence of frequent use (6 or more purchases) of antibiotics during the first 3 years of life was 26%. Maternal age ($P<0.001$), previous miscarriages ($P = 0.02$) and previous deliveries ($P<0.001$) as well as planned caesarean section as the mode of delivery ($P = 0.03$), male sex ($P <0.001$) and maternal use of antibiotics ($P<0.001$) were directly associated with the

child's frequent use of antibiotics. In addition, maternal asthma ($P = 0.02$) and smoking ($P = 0.002$) were directly associated with the child's overall use of antibiotics.

The mean age at diagnosis of asthma was 4.3 years (range 3 to 9 years) and 60% of the cases were boys. Overall use of any antibiotic during the first year of life was associated with an increased risk of asthma (adjusted OR = 1.60 [95% CI 1.48–1.73]). An increased risk of asthma was present also among children who were followed-up at least 6 years (adjusted OR = 1.68 [95% CI 1.54–1.85] for children diagnosed between ages 3 to 5 years of age and adjusted OR = 1.33 [95% CI 1.12–1.58] for children diagnosed at the age of 6 years or later). In addition, the risk of asthma increased with increasing number of antibiotic purchases (Figure 3). The use of all common specific antibiotics during the first year of life, except phenoxymethylpenicillin, was associated with an increased risk of asthma (Table 2). The strength of the effect estimate for the association between antibiotics indicated for gram-positive bacteria infections and urinary tract infections and asthma were similar (OR 1.51 and OR 1.54, respectively), although the latter association did not reach statistical significance (Table 2). Further, the strongest association was observed when the child had used antibiotics belonging to both indication groups (Table 2). Population Attributable Risk (PAR) for child's antibiotics was 69.3%.

Overall use of any antibiotic from birth to 6 months before diagnosis was associated with an increased risk of asthma (adjusted OR = 3.98 [95% CI 3.33–4.77]) and the association did not change substantially in the further analysis according to age at diagnosis (adjusted OR = 4.00 [95% CI 3.31–4.82] for children diagnosed between ages 3 to 5 years of age and adjusted OR = 3.99 [95% CI 2.21–7.22] for children diagnosed at the age of 6 years or later). In addition, the risk of asthma increased with increasing number of antibiotic purchases (Figure 4). All commonly used specific antibiotics were associated with the risk of asthma, with the strongest association observed for macrolides (Table 3). Antibiotics for gram-positive bacteria infection and urinary tract infections were associated

with an increased risk of asthma, but the strongest association was observed when antibiotics for both indications were used (Table 3).

We did not observe significant effect modification by maternal age, asthma, smoking during pregnancy, previous deliveries, previous miscarriages, mode of delivery, gestational age, the child's ponderal index, maternal or child's use of antibiotics on the association between maternal or child use of antibiotics and the risk of asthma.

Discussion

In this large, population and register-based study both prenatal and postnatal exposure to antibiotics was associated with an increased risk of asthma in childhood in a dose-related manner. Further, several commonly used specific antibiotics were associated with the risk of asthma. The increased risk of asthma was observed not only with antibiotics commonly used to treat respiratory infections, but also with antibiotics for urinary tract infections, indicating no clear evidence for confounding by indication.

Evidence on the role of different environmental exposures during the prenatal period in the development of asthma in childhood is accumulating [25], although less studies have focused on prenatal antibiotics [11-17]. An increased risk of asthma or wheeze in the offspring was observed in some studies [12, 13, 15-17], while also null associations have been reported [11, 14]. Evidence on postnatal exposure to antibiotics and the risk of asthma or wheeze is more extensive, although inconclusive [7-12, 26-28]. The largest cohort studies have reported an increased risk of asthma in children exposed to antibiotics in early childhood [3, 9, 12, 26, 29] and our results are in line with these studies. When extending the child's exposure period beyond the first year of life, we observed stronger associations than previously reported.

Evidence on the role of specific antibiotics in the development of asthma is limited and inconsistent [9, 15, 26, 27, 29]. No particular specific antibiotic used by the mother has been reported to be associated with asthma in the offspring [15]. The child's use of macrolides [9, 29], cephalosporins [9, 29], amoxicillin [9, 29], penicillin [9] and broad-spectrum antibiotics [26, 27] has been associated with an increased risk of asthma. In accordance with most previous studies we observed some variation in the strength of the associations between different specific antibiotics and the risk of asthma. In contrast to the study by Almqvist et al [3], we found that the effect estimates for antibiotics against urinary tract infections, although statistically non-significant, were close to the effect estimates for antibiotics against respiratory tract infections. This inconsistency may be due to differences in antibiotic prescription practices between the countries and differences in study methodology, such as asthma definition and follow-up time.

It has been argued that antibiotics could simply serve as a marker for infections and that much if not all of the reported associations between postnatal antibiotics and asthma are accounted for by reverse causality (a form of temporal bias where asthma symptoms are responsible for the prescription of antibiotics) or confounding by indication (the association is confounded by a factor serving as an indication for antibiotics and as a risk factor for asthma, such as respiratory infections) [3, 8, 27]. However, direct associations have been observed also in studies taking infections into account [7, 9, 12, 26, 29]. Further, the associations have been even stronger when those children who had respiratory infections were excluded [7, 9]. We also investigated the issue of confounding by indication by grouping antibiotics according to the study by Almqvist et al [3]. Although, the statistically non-significant associations between antibiotics for urinary tract infection and asthma suggest that confounding by indication may partly explain our findings, the role of low number of observations in the analysis resulting in wide 95% confidence intervals should be taken into account as an explanation for the non-significant findings. Further, we observed an increased risk of asthma also in children who were diagnosed with asthma first time at the age of 6 years or later, indicating that reverse causality is not a major form of bias in our data.

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One mechanism by which prenatal and postnatal antibiotics could influence the development of asthma is their adverse and possible long-term effect [30] on gut microbiota of both the mother and the child and vaginal microbiota of the mother [31]. The delayed colonization of the child's gut microbiota may, in turn, interfere the maturation of the child's immune system and thus affect the development of asthma [32]. Particularly, those antibiotics affecting immunosuppressive bacteria in the gut, such as *Faecalibacterium prausnitzii* [33], may play a role in the development of asthma.

The major strength of this study is that by using the Finnish personal identity code system we were able to link several national registers with nearly complete population coverage, thus providing comprehensive information on both the mother's and child's antibiotic purchases. By using the registers, participation and recall bias related to questionnaire-based data was avoided. Furthermore, our asthma definition was based on a criteria-based diagnosis of asthma made by a physician, mainly by a pediatrician. In addition, it is worth noting that in Finland all citizens, regardless of their socioeconomic status, are entitled to and have equal access to health services [34] and thus the differences in receiving medical care between socioeconomic groups are likely to be small in our cohort.

One of the limitations of the present study is that despite including several putative confounders we missed information on indication of antibiotic prescription, exposure at hospitals and eczema as well as certain factors affecting the composition of the gut's microbiota, such as infant feeding and the use of pre- and probiotics. Thus, residual confounding as an explanation of the observed results cannot be ruled out. Further, despite having a large data some of our sub-group analyses suffered lack of power.

Increased bacterial resistance to antibiotics is a major public health threat worldwide [35], but the adverse effects of antibiotics on child's long-term health needs research attention as well.

Although evidence on the association between antibiotic exposure and the risk of asthma is inconclusive, rational prescription practices are needed. As the use of antibiotics by the mothers

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during pregnancy was not extensive, the observed association between maternal antibiotics and the risk of asthma in the offspring may not have great public health importance (PAR [36], 7.4%). On the contrary, as the use of antibiotics during early childhood is common, the public health importance of the association between child's use of antibiotics and asthma, if confirmed in future studies, may be more significant (PAR [36], 69.3%). Future studies with enough power are needed to clarify the role of specific prenatal and postnatal antibiotics in the development of asthma. Especially, indication for antibiotics, other factors possibly confounding and interacting with the effects of antibiotics and factors related to healthcare-seeking behaviour should be taken into account.

In conclusion, both prenatal and postnatal exposure to antibiotics was associated with an increased risk of asthma among Finnish children. The potential role of adverse effects of antibiotics on the gut microbiota and the development of asthma should be further explored.

Conflict of interest

Minna Kaila has received a fee for speaking (Pfizer, Professio). Other authors declare that they have no conflict of interest.

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Figure legends

Figure 1. A flow chart defining the initial and final study population

Figure 2. The association between number of maternal antibiotics purchased during pregnancy and the risk of asthma in the offspring. Data points are unadjusted (open circles) and adjusted (maternal asthma and previous deliveries) (black circles) odds ratios (OR) with 95% confidence intervals (bars), logarithmic scale, 0 purchases as reference.

Figure 3. The association between number of child's antibiotics purchased from birth to one year of age and the risk of asthma. Data points are unadjusted (open circles) and adjusted (maternal asthma, previous deliveries and gestational age) (black circles) odds ratios (OR) with 95% confidence intervals (bars), logarithmic scale, 0 purchases as reference.

Figure 4. The association between number of child's antibiotics purchased from birth to diagnosis (excluding antibiotics purchased 6 months before diagnosis) and the risk of asthma. Data points are unadjusted (open circles) and adjusted (maternal asthma, previous deliveries and gestational age) (black circles) odds ratios (OR) with 95% confidence intervals (bars), logarithmic scale, 0 purchases as reference.

Table 1. Maternal use of specific antibiotics during pregnancy and the risk of asthma in children diagnosed at the age of 3 years or later.

Group of antibiotic	Discordant case-control pairs n *	Unadjusted model OR [†] (95% CI)	Adjusted model [‡] OR [†] (95% CI)
<u>Specific antibiotics[§]</u>			
Penicillins with extended spectrum	827/664	1.25 (1.12-1.38)	1.23 (1.10-1.37)
Cephalosporins	792/530	1.49 (1.34-1.67)	1.46 (1.30-1.64)
Macrolides	311/228	1.36 (1.15-1.62)	1.28 (1.07-1.53)
Phenoxymethylpenicillin	189/143	1.32 (1.06-1.64)	1.27 (1.01-1.59)
Tetracyclines	77/58	1.32 (0.94-1.87)	1.32 (0.92-1.90)
Sulfonamides and trimethoprim	29/18	1.61 (0.89-2.90)	1.38 (0.74-2.56)
Fluoroquinolones	16/10	1.60 (0.73-3.52)	1.62 (0.72-3.66)
<u>Likely indication</u>			
Only antibiotics against gram positive bacteria infections [¶]	1433/1078	1.33 (1.23-1.44)	1.30 (1.20-1.42)
Only antibiotics against urinary tract infections ^{**}	16/15	1.17 (0.58-2.37)	0.98 (0.47-2.05)
Both antibiotics against gram positive bacteria infections and urinary tract infections	28/13	2.27 (1.17-4.38)	2.17 (1.09-4.33)

* case user, control non-user / case non-user, control user

[†] matched odds ratios

[‡] adjusted for maternal asthma and previous deliveries

[§] grouped based on ATC-codes

^{||} grouping of specific antibiotics based on likely indication

[¶] including penicillins with extended spectrum, macrolides, cephalosporins and phenoxymethylpenicillin, but not trimethoprim, sulphonamides or fluoroquinolones

^{**} including trimethoprim, its combinations with sulphonamides and fluoroquinolones, but not penicillins with extended spectrum, macrolides, cephalosporins or phenoxymethylpenicillin

Table 2. Child's use of specific antibiotics from birth to 1 year of life and the risk of asthma diagnosed at the age of 3 years or later.

Group of antibiotic	Discordant case- control pairs n *	Unadjusted model OR [†] (95% CI)	Adjusted model [‡] OR [†] (95% CI)
<u>Specific antibiotics[§]</u>			
Amoxicillin	1624/1160	1.40 (1.30-1.51)	1.46 (1.35-1.58)
Macrolides	1166/760	1.53 (1.40-1.68)	1.61 (1.46-1.78)
Cephalosporins	801/474	1.69 (1.51-1.89)	1.79 (1.59-2.01)
Sulphonamides and trimetoprim	265/163	1.63 (1.34-1.98)	1.65 (1.34-2.02)

Phenoxymethylpenicillin	203/170	1.19	(0.99-1.46)	1.27	(1.02-1.57)
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Likely indication^{||}

Only antibiotics against gram positive bacteria infections [¶]	1651/1187	1.47	(1.36-1.59)	1.56	(1.44-1.70)
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Only antibiotics against urinary tract infections ^{**}	28/23	1.47	(0.85-2.59)	1.61	(0.90-2.87)
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Both antibiotics against gram positive bacteria infections and urinary tract infections	237/140	2.09	(1.69-2.59)	2.22	(1.77-2.79)
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* case user, control non-user / case non-user, control user

[†] matched odds ratios

[‡] adjusted for maternal asthma, previous deliveries and gestational age

§ grouped based on ATC-codes

^{||} grouping of specific antibiotics based on likely indication

[¶] including amoxicillin, macrolides, cephalosporins and phenoxymethylpenicillin, but not trimethoprim or sulphonamides

^{**} including trimethoprim and its combinations with sulphonamides, but not amoxicillin, macrolides, cephalosporins or phenoxymethylpenicillin

Table 3. Child's use of specific antibiotics from birth to diagnosis* and the risk of asthma diagnosed at the age of 3 years or later.

Group of antibiotic	Discordant case- control pairs n [†]	Unadjusted model OR [‡] (95% CI)	Adjusted model [§] OR [‡] (95% CI)
<u>Specific antibiotics</u>			
Amoxicillin	1100/475	2.32 (2.08-2.58)	2.35 (2.10-2.63)
Macrolides	1910/688	2.78 (2.54-3.03)	2.74 (2.50-2.99)
Cephalosporins	1785/944	1.89 (1.74-2.05)	1.91 (1.76-2.07)
Sulphonamides and trimetoprim	1379/683	2.02 (1.84-2.21)	1.98 (1.80-2.18)
Phenoxymethylpenicillin	1000/762	1.31 (1.19-1.44)	1.33 (1.21-1.47)
 Likely indication [¶]			
Only antibiotics against gram positive bacteria infections**	1113/1340	3.47 (2.91-4.14)	3.53 (2.95-4.24)
Only antibiotics against urinary tract infections ^{††}	10/13	2.44 (1.02-5.83)	2.35 (0.95-5.79)
Both antibiotics against gram positive bacteria infections and urinary tract infections	1374/675	6.44 (5.32-7.80)	6.45 (5.29-7.86)

* antibiotics purchased 6 months prior to diagnosis were excluded

[†] case user, control non-user / case non-user, control user

[‡] matched odds ratios

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^s adjusted for maternal asthma, previous deliveries and gestational age

^{ll} grouped based on ATC-codes

[¶] grouping of specific antibiotics based on likely indication

^{**} including amoxicillin, macrolides, cephalosporins and phenoxymethylpenicillin, but not trimethoprim or sulphonamides

^{††} including trimethoprim and its combinations with sulphonamides, but not amoxicillin, macrolides, cephalosporins or phenoxymethylpenicillin







