

Antibiotics and asthma medication in a large register-based cohort study – confounding, cause and effect

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Summary

Background An association between asthma and antibiotic usage has been demonstrated, and the issue of reverse causation and confounding by indication is much debated.

Objective Our aim was to study the association between different classes of antibiotics and prescription of asthma medication in a register-based cohort of all Swedish children, born between July 2005 and June 2009, ever treated with antibiotics.

Methods Data on dispensed prescriptions of antibiotics (ATC-codes J01) and asthma medication (ATC-codes R03A–D) were requested from the Prescribed Drug Register. The association between dispensed prescriptions of different classes of antibiotics and asthma medication was analysed with Cox regression and a descriptive sequence symmetry analysis.

Results In total, 211 192 children had received prescriptions of antibiotics. There was a strong association between prescription of antibiotics and prescription of asthma medication. The hazard ratios (HRs) for asthma medication associated with prescription of amoxicillin, penicillin, cephalosporin and macrolides (Gram-positive infections) were stronger than HRs associated with prescription of sulphonamides, trimethoprim and quinolones (urinary tract infections) and flucloxacillin (skin and soft tissue infections), e. g. first year HR = 2.27 (95% confidence intervals 2.17–2.37) as compared with HR = 1.04 (0.78–1.40). The HR associated with broad spectrum antibiotics was significantly higher than the narrow spectrum.

Conclusions and Clinical Relevance Our data suggest that the association between antibiotics and asthma is subject to either reverse causation or confounding by indication due to respiratory tract infections. This implies that careful consideration is required as to whether or not symptoms from the respiratory tract in early childhood should be treated with antibiotics or asthma medication.

Keywords antibiotics, asthma, bias, child, confounding factors, epidemiology

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Introduction

Infectious diseases are common in childhood, and antibiotics are commonly prescribed to those who seek medical outpatient care. The association between antibiotic treatment in early life and subsequent development of asthma and allergic disease has been analysed in health data registers or longitudinal birth cohorts, using different epidemiological study designs. Some studies

have shown no correlation between early life exposure to antibiotics and asthma [1, 2] or allergic disease [1, 3]; whereas others have reported clear associations [4–11]. It has been proposed that there is a stronger association between the incidence of asthma and exposure to antibiotics in children who were prescribed antibiotics during the first year of life [4, 11] and that there might be an increased association with the number of antibiotic courses the child has received [6, 11, 12]. There is also

an ongoing discussion regarding whether the association between antibiotic usage and asthma is causal or if methodological issues such as reverse causation (antibiotics prescribed *because* of the respiratory symptoms) or confounding by indication (confounded by a third factor that is *both* an indication for antibiotics and a risk factor for asthma, such as respiratory symptoms) can explain the results [13]. A previous meta-analysis confirmed an association between antibiotic usage in the first year of life and subsequent asthma, although the authors called for a large-scale database-related study to conclude whether the association was causal or due to reverse causation [14]. Wickens et al. concluded that the effect of antibiotics on asthma was strongly confounded by respiratory tract infections [15]. Alm et al. recently showed that treatment with antibiotics in the neonatal period was an independent risk factor for wheezing at 12 months of age [16] and although reverse causation cannot be entirely excluded since antibiotics are given to infants with perinatal respiratory diagnoses, data indicate an early effect on the immune system. This is also supported by interesting data from Jedrowsky et al., whose study suggests that maternal use of antibiotics during pregnancy may prove to be a risk factor for persistent wheezing and development of allergy in early infancy [17]. It has been proposed that asthma is more common in children receiving antibiotics for non-respiratory tract infections compared with those who do not receive antibiotics [11]. However, the impact of antibiotics used for the treatment of urinary tract infections or skin and soft tissue infections, which are less prone to bias due to confounding by indication, has not yet been assessed for asthma.

The overall aim of this study was to estimate the associations between prescribed antibiotics and asthma medication in a large register-based cohort of children in the Swedish population. We also intended to address the issues of reverse causation and confounding by indication, by performing separate analyses for different classes of antibiotics, specifically aiming at separating the effect of antibiotics to treat respiratory tract infections from the effect of antibiotics to treat urinary tract infections or skin and soft tissue infections.

Methods

Study design and register data

The Swedish National Board of Health and Welfare holds several registers covering health information for the entire Swedish population (9.4 million inhabitants) [18]. The Prescribed Drug Register contains all dispensed prescription drugs to Swedish residents since 1 July 2005 [19]. The cohort used in this study included all children born between the inauguration of the

Prescribed Drug Register on 1 July 2005 and 30 June 2009, who had been dispensed antibiotics (ATC-codes J01) at some point between birth and 31 July 2009 ($n = 211\,192$).

Variables

Asthma medication. Dispensed asthma medications were retrieved from the Prescribed Drug Register and divided into the groups oral β_2 -agonists (R03CC), inhaled β_2 -agonists (R03AC), inhaled corticosteroids including those combined with long-acting β_2 -agonists (R03BA, R03AK), and leucotriene receptor antagonists (R03DC). In our analyses we defined asthma outcome (event) as any asthma medication, except oral β_2 -agonists, dispensed at least twice. Date of onset of asthma medication was the date of the first prescription of any of those medications.

Groups of antibiotics. Antibiotics were grouped into amoxicillin, penicillin, cephalosporin, sulphonamide, macrolide and 'other antibiotics', as previously categorized by Marra et al. [11]. To specifically address the effect of antibiotics to treat infections other than those in the respiratory tract, we grouped (1) amoxicillin, penicillin, cephalosporin and macrolides in a group denoted 'Gram-positive' and (2) sulphonamides and other antibiotics to treat urinary tract infections (trimethoprim, nitrofurantoin, quinolones) [20] in a separate group along with flucloxacillin (to treat skin and soft tissue infections), denoted 'Urinary tract or skin and soft tissue infections'. We also categorized the antibiotics into groups of narrow and broad spectrum, modified from Kozyrskyj et al. [12], see Appendix.

Additional variables from the Prescribed Drug Register.

Apart from the ATC-code, the variables birth month (year and month), gender (male or female), the date each prescription was issued (year – month – date) and date of dispensing were retrieved from the Prescribed Drug Register.

Statistical analyses

The children were followed from the last day of their birth month (entry date) until they had the event. Children with only one prescription of asthma medication were treated as no event, and those with date of onset of event before their entry date were excluded from the analyses. For analysis of a possible effect of antibiotics on asthma, we restricted the cohort to the group of children who had a dispensed prescription of antibiotics at least once between birth and end of follow-up. As all children were exposed to antibiotics at some point during follow-up, unexposed person time was the time from

entry date to the date the first antibiotics was dispensed and exposed person time was from the dispensing date till the end of follow-up. If the date was the same for the asthma event and antibiotics prescription, this was treated as an unexposed event, since the antibiotics could not have caused the asthma. Incidence rates were calculated as the number of events per 100 person-years of risk time, with 95% confidence intervals (CI) assuming a Poisson distribution. To estimate the association between exposure to antibiotics and the risk of receiving asthma medication other than oral β_2 -agonists at least twice (event), we used Cox proportional hazards regression, yielding hazard ratios (HR) with 95% CI as a measure of association. The analyses were stratified by birth year and month, to account for birth month as a potential confounder due to seasonality and yearly variations in pollen levels and respiratory tract infections. The timescale in all Cox analyses was time since entry i.e. time since the last day of the birth month. Exposure to antibiotics treatment was analysed as time-varying exposure resulting in the groups/categories 'yes' vs. 'no' (reference category). Likelihood ratio tests were used to formally assess effect of exposure. Since the HRs were significantly non-proportional over follow-up time (age), we included interaction terms between exposure and age in the model using age bands splitting at 1, 2 and 3 years of age. As Cox regression is used, there is an automatic adjustment for the underlying timescale (in this case, age). As gender was considered a potential effect modifier we also included an interaction effect between exposure and gender. Interactions were formally tested using likelihood ratio tests. To disentangle the question of confounding by indication or information bias we performed separate analyses for class-specific antibiotics exposure (antibiotics for Gram-positive bacteria and those to treat Urinary tract or skin and soft tissue infections in separate analyses). In those analyses we excluded children with exposure to more than one class of antibiotics. Further, we analysed the association between asthma and the antibiotic spectrum, where the levels of exposure were before any antibiotics (reference), after first dispensing of narrow spectrum antibiotics and after first dispensing of broad spectrum. A child could only move from before antibiotics exposure, to antibiotics of increased spectrum, not in the reverse direction. We also analysed the impact of the number of prescriptions of antibiotics as 1–2, 3–5 and ≥ 6 , with time before the first prescription as reference.

To further disentangle the association between antibiotics and asthma medication, a descriptive sequence symmetry analysis was performed [21]. The group who had received both types of drugs on different days was selected and the order of the antibiotics and asthma medication was recorded with absolute and relative frequencies.

All statistical analyses were performed using Stata Intercooled (StataCorp. 2009. Stata Statistical Software: Release 11; StataCorp LP, College Station, TX, USA).

Permission for the study was obtained from the regional ethical review board in Stockholm, Sweden.

Results

The study population consisted of 211 192 children born between 1 July 2005 and 31 July 2009, who received at least one prescription of antibiotics between 1 July 2005 and 30 June 2009; 48% of all children born in the country. During the same time period, 95 628 children (45.2%) had received both antibiotics and asthma medication. The most commonly used antibiotics was J01CE02 (phenoxymethylpenicillin), representing 51.6% of all antibiotics prescriptions. This was followed by amoxicillin (26.8%), cephalosporin (5.9%) and macrolides (5.4%).

Table 1 displays characteristics of the cohort, such as person-years, number of events, average age at onset and crude incidence rates for time as unexposed and after first antibiotics exposure.

Table 2 presents characteristics of dispensed antibiotics (J01) and asthma medication (R03) in relation to age and number of prescriptions. For antibiotic usage, average age was 1.17 years with a difference in antibiotics dispensed to treat Gram-positive (mean age 1.18 years) and Urinary tract infections (mean age 1.36) or skin and soft tissue infections (mean age 1.44). In their first year of life, 17.9% of the children received antibiotics, mainly to treat Gram-positive infections. Mean age at first dispensed prescription of any asthma medication or oral β_2 -agonist in the cohort was 1.00 year; any inhaled β_2 -agonist 1.26 years; any inhaled glucocorticoid 1.32 years and oral leucotriene receptor antagonists 1.57 years. The mean and standard deviation age of the first event (asthma medication other than oral β_2 -agonists at least twice) was 1.26 (0.84) years.

Table 2 also displays number of prescriptions. Approximately 27.4% ($n = 57\,781/211\,192$) had at least four prescriptions of antibiotics. There was a difference in prescription rate between antibiotics targeted at Gram-positive and at other infections. For asthma medication, oral β_2 -agonists were most frequently dispensed, often only once or twice, whereas inhaled β_2 -agonists and inhaled corticosteroids were equally dispensed.

Using antibiotics as exposure, there were statistically significant gender differences in the association between antibiotics (any antibiotics and Gram-positive) and asthma medication, $P_{\text{interaction}} < 0.0001$, but not for Urinary tract or skin and soft tissue infections ($P = 0.53$). To facilitate comparisons, separate estimates were produced for boys and girls in all models.

Table 1. Background statistics of the cohort with prescription of asthma medications other than oral β_2 -agonists at least twice as event, for analyses of antibiotics exposure, total and type specific

	Type of antibiotics					
	All		Gram-positive bacteria [‡]		Urinary tract infections or skin and soft tissue infections [‡]	
	Before [†]	After [†]	Before	After	Before	After
No. excluded due to event before entry*	45		37		0	
<i>N</i>	209 972 [§]	199 604	172 897 [§]	163 818	8749 [§]	8651
Gender, % male	53.4	52.8	54.5	53.9	45.4	45.4
Person-years	231 946	289 428	196 121	229 020	11 082	9911
Age at prescription of asthma medication (years), mean (SD)	0.80 (0.51)	1.49 (0.73)	0.81 (0.51)	1.49 (0.72)	0.98 (0.61)	1.44 (0.78)
No. of events	11 543	16 949	9612	13 222	324	211
Incidence rate per 100 person-years	5.0	5.9	4.9	5.8	2.9	2.1

*Time of entry = first day of month after birth month.

[†]Before (not yet exposed) and after (exposed) first dispensed prescription.[‡]Some antibiotics could not be classified into one of those categories (Appendix) and children exposed to more than one type of antibiotics were excluded from the type-specific analyses.[§]Individuals exposed before start of follow-up: all, *n* = 1175; Gram-positive bacteria, *n* = 533; Urinary tract/skin/soft tissue, *n* = 226.**Table 2.** Descriptive statistics of prescribed drugs. Mean age at first prescription and number of prescriptions for antibiotics and asthma medication in total and divided by type

	<i>N</i>	Age at first prescription, mean (SD)	No. of prescriptions*			
			1	2	3	≥4
Antibiotics	211 192	1.17 (0.70)	78 720	46 052	28 639	57 781
Gram-positive bacteria	202 194	1.19 (0.69)	79 228	44 827	27 125	51 014
Amoxicillin	84 607	1.33 (0.70)	47 907	17 990	8114	10 596
Penicillin	170 120	1.28 (0.72)	89 969	42 199	19 851	18 101
Cephalosporin	26 299	1.48 (0.90)	20 798	3768	943	790
Macrolide	23 509	1.47 (0.79)	17 856	3537	1086	5512
Urinary tract or skin and soft tissue infections	37 547	1.44 (0.93)	26 341	6659	2067	2480
Sulphonamides	13 460	1.31 (0.80)	10 445	1903	524	588
Other Gram-negative bacteria [†]	10 288	1.36 (1.04)	6842	1778	588	1080
Flucloxacillin	18 329	1.58 (0.96)	14 995	2536	500	298
Other	283	1.64 (0.81)	237	23	4	19
Any asthma medication	95 628	1.00 (0.66)	43 155	17 818	9076	25 579
β_2 -agonists, oral	82 865	1.00 (0.66)	52 593	18 629	6599	5044
β_2 -agonists, inhaled	31 945	1.26 (0.75)	13 254	7164	4083	7444
Corticosteroids [‡] , inhaled	27 651	1.32 (0.75)	9039	5767	3749	9096
Montelukast	4718	1.57 (0.78)	1949	826	462	1481

*No. of prescriptions during follow-up.

[†]Trimethoprim, nitrofurantoin, quinolones.[‡]Including combination drugs with corticosteroids.

Table 3 shows the association between antibiotics as exposure and asthma event. The incidence of asthma medication other than oral β_2 -agonists at least twice was higher in both boys and girls after exposure to antibiotics, compared with before. HR decreased with

higher age, from HR 2.10 (95% CI 2.01–2.20) in children <1 year to HR 1.05 (95% CI 0.57–1.92) at ≥3 years in boys and from HR 2.37 (95% CI 2.22–2.52) at <1 year of age to HR 1.31 (95% CI 0.65–2.66) at ≥3 years in girls. The results were similar when an

Table 3. Cox regression analysis with time-varying exposure of antibiotics as exposure and prescription of asthma medication other than oral β_2 -agonists at least twice as outcome (event), showing hazard ratios (HR) and 95% confidence intervals (CI). Reference is time before first exposure

	Age at first asthma medication (years)			
	<1 HR (95% CI)	1 HR (95% CI)	2 HR (95% CI)	≥ 3 HR (95% CI)
All	2.20 (2.12–2.28)	1.73 (1.66–1.82)	1.29 (1.15–1.45)	1.15 (0.73–1.83)
Male	2.10 (2.01–2.20)	1.69 (1.60–1.80)	1.21 (1.03–1.42)	1.05 (0.57–1.92)
Female	2.37 (2.22–2.52)	1.81 (1.69–1.94)	1.42 (1.20–1.69)	1.31 (0.65–2.66)

event was restricted to inhaled corticosteroids or leucotriene receptor antagonists at least twice.

Table 4 illustrates the association between different classes of antibiotics as exposure and risk of event. Using prescription for Gram-positive antibiotics as exposure and asthma medication other than oral β_2 -agonists at least twice as event, the results were very similar to those for any antibiotics, HR = 2.19 (95% CI 2.08–2.31). However, for antibiotics to treat Urinary tract or skin and soft tissue infections there was no statistically significant effect on asthma medication, HR = 1.00 (0.70–1.43). In an attempt to take into account the diminishing effect of exposure to antibiotics over time, we also performed analyses where the children were considered as exposed from 2 weeks until 1 year after filling the prescription, with similar results (data not shown).

Table 5 shows the association between different spectra of antibiotics and the number of antibiotics prescription as exposure and risk of event. Regarding the spectrum of the antibiotics there was an increased risk of asthma medication for both narrow and broad spectrum antibiotics. The HR was significantly higher for broad spectrum compared with the HR for narrow spec-

trum after 2 years of life, and no significant modification by gender. There was also an increased risk with an increasing number of prescriptions.

The results of the descriptive sequence symmetry analysis presented in Table 6 show that for children receiving both antibiotics due to treat Gram-positive infections and asthma medication, it was more common that the first prescribed drug was the antibiotics (61.9%). For children treated with antibiotics for Urinary tract or skin and soft tissue infections, it was more common to receive asthma medication before the antibiotics (59.7%).

Discussion

We found an association between antibiotic usage and prescription of asthma medication in this population-based cohort study of more than 210 000 children followed from birth up to 4 years of age. The association was significant for antibiotics to treat Gram-positive infections such as respiratory tract infections, but not for antibiotics to treat Urinary tract or skin and soft tissue infections. It was also stronger for broad spectrum than narrow spectrum antibiotics. Our results, based on the largest register study on antibiotics and asthma to date, thus support the hypothesis that the association between antibiotic usage and asthma may be due to methodological issues such as reverse causation or confounding by indication due to respiratory tract infections.

The data also allowed us to do a descriptive sequence symmetry analysis in children who had received both antibiotics and asthma medication. For children receiving antibiotics to treat Gram-positive infections, it was more common that the first prescribed drug was the antibiotics, whereas for children treated with antibiotics for Urinary tract or skin and soft tissue infections, it was more common to receive asthma medication before the antibiotics. This further confirms that reverse causation or confounding by indication due to respiratory tract infections may explain an association between antibiotic usage and asthma [13, 15]. To our knowledge, the difference in effect of antibiotics used

Table 4. Cox regression analyses with time-varying exposure of different types of antibiotics as exposure and prescription of asthma medication as outcome (event), showing hazard ratios (HR) and 95% confidence intervals (CI). Reference is time before first prescription of antibiotics

	Age at first asthma medication (years)		
	<1 HR (95% CI)	1 HR (95% CI)	≥ 2 HR (95% CI)
Gram-positive bacteria			
All	2.27 (2.17–2.37)	1.72 (1.63–1.81)	1.20 (1.06–1.36)
Male	2.19 (2.08–2.31)	1.68 (1.57–1.79)	1.12 (0.95–1.32)
Female	2.41 (2.24–2.59)	1.80 (1.67–1.95)	1.33 (1.10–1.60)
Urinary tract or skin and soft tissue infection			
All	1.04 (0.78–1.40)	0.79 (0.58–1.06)	0.71 (0.41–1.23)
Male	1.00 (0.70–1.43)	0.64 (0.42–0.96)	0.56 (0.26–1.21)
Female	1.07 (0.68–1.70)	0.98 (0.65–1.46)	0.90 (0.43–1.88)

Table 5. Cox regression analyses with number of doses and spectra as time-varying antibiotics exposure and prescription of asthma medication as outcome (event), showing hazard ratios (HR) and 95% confidence intervals (CI). Reference is time before first prescription of antibiotics

		Age at first asthma medication (years)		
		<1	1	≥2
		HR (95% CI)	HR (95% CI)	HR (95% CI)
Spectrum				
All	Narrow	1.60 (1.35–1.91)	1.28 (1.09–1.50)	0.96 (0.65–1.41)
	Broad	2.04 (1.71–2.42)	1.83 (1.56–2.15)	1.38 (0.94–2.04)
Male	Narrow	1.55 (1.30–1.85)	1.25 (1.06–1.48)	0.92 (0.62–1.38)
	Broad	1.91 (1.60–2.28)	1.78 (1.51–2.10)	1.29 (0.86–1.93)
Female	Narrow	1.69 (1.41–2.03)	1.32 (1.12–1.57)	1.04 (0.69–1.57)
	Broad	2.29 (1.89–2.76)	1.92 (1.62–2.28)	1.56 (1.04–2.35)
No. of prescriptions				
All	1–2	1.72 (1.45–2.05)	1.37 (1.16–1.61)	0.85 (0.53–1.36)
	3–5	2.25 (1.86–2.72)	2.03 (1.72–2.40)	1.26 (0.78–2.02)
	≥6	2.36 (1.76–3.16)	2.50 (2.09–3.01)	1.77 (1.10–2.86)
Male	1–2	1.65 (1.38–1.97)	1.34 (1.13–1.58)	0.79 (0.49–1.28)
	3–5	2.07 (1.70–2.53)	1.98 (1.66–2.35)	1.19 (0.73–1.93)
	≥6	2.21 (1.59–3.07)	2.34 (1.92–2.85)	1.56 (0.95–2.56)
Female	1–2	1.85 (1.54–2.22)	1.42 (1.19–1.68)	0.92 (0.57–1.51)
	3–5	2.61 (2.08–3.27)	2.14 (1.79–2.57)	1.37 (0.83–2.24)
	≥6	2.62 (1.61–4.25)	2.86 (2.31–3.55)	2.13 (1.29–3.51)

Table 6. Sequence symmetry of prescriptions of asthma medication (first of at least two) and antibiotics of any type, as well as first time of specified class (Gram-positive, Urinary tract or skin and soft tissue infections), for children receiving only one type of antibiotics

Type of antibiotics	First drug			
	Antibiotics		Asthma medication	
	<i>n</i>	%	<i>n</i>	%
Any antibiotics	17 056	63.2	9921	36.8
Gram-positive	13 285	61.9	8189	38.1
Urinary tract or skin and soft tissue infections	212	40.3	314	59.7

to treat Gram-positive and other antibiotics has not been previously assessed.

Our study design allowed us to investigate how prescription of asthma medication (event) varies with gender, age, group of antibiotics and number of prescription. In general, the effect of any or Gram-positive antibiotics on prescription of asthma medication was stronger for girls than boys. The effect was also more evident in the younger age groups and already after receiving only one or two prescriptions of antibiotics, which is in line with previous studies [4, 6, 11, 12]. The explanation may be that early wheezing due to respiratory tract infections is difficult to distinguish from asthma and obstructive bronchitis/bronchiolitis in

early age [22]. Consequently, there is a risk of treating the first asthma symptoms with antibiotics, thus inducing an association between antibiotics and asthma medication. It could be argued that the association between prescribed drugs could be confounded by a tendency to seek care and/or ask for prescriptions. We did not, however, observe a significant association between asthma medication and antibiotics to treat Urinary tract or skin and soft tissue infections, indicating this was not an important source of confounding in this study.

We saw a stronger effect of broad spectrum antibiotics on asthma medication, compared with narrow spectrum. This may also be due to confounding by indication, since broad spectrum is mainly given to treat respiratory tract infections [4]. Alternatively, in accordance with the hygiene hypothesis, it has been suggested that broad spectrum antibiotics affect the gut microflora and increase the risk of asthma more than narrow spectrum antibiotics do [23].

The strength of our study is the large dataset with objective measures of antibiotics specified as Gram-positive or antibiotics to treat Urinary tract or skin and soft tissue infections, along with prescriptions of asthma medication. This allows for temporal assessments of the association between antibiotics and asthma medication including aspects of reverse causation and confounding by indication. The findings expand on categorization of antibiotics in a previous meta-analysis [11], with the addition of further subgroups of 'other antibiotics' such as antibiotics to

treat urinary tract infections (trimethoprim, nitrofurantoin, quinolones to the sulphonamides subgroup) and antibiotics to treat skin and soft tissue infections (flucloxacillin). The dataset includes all Swedish children with a prescription of antibiotics or asthma medication, and thus the findings are generalizable.

The study has some limitations. Firstly, we did not have access to diagnoses of infectious diseases or indication for the antibiotics. Based on previous studies and standardized treatment guidelines [20], we have, however, made an effort to carefully categorize the antibiotics into clearly defined groups. Secondly, we did not have access to diagnosis of asthma and although previous studies have shown a good correlation between asthma medication and diagnosis of asthma [24], we were unable to differentiate between phenotypes of preschool wheezing disorders [25, 26]. Also, the children were only followed from birth to between 4 years of age, so the study excludes asthma cases that develop after the follow-up period. Thirdly, previous studies have adjusted for presence of lower respiratory tract infections and other confounding factors [2, 5, 11, 27], which we could not. However, we were able to do separate analyses for the effect of different categories of antibiotics on asthma medications. The lack of association between antibiotics to treat Urinary tract or skin and soft tissue infections and asthma is a novel finding.

In conclusion, our study suggests that the association between antibiotics and asthma may partly be an effect of reverse causation (antibiotics prescribed *because* of the respiratory symptoms) or confounding by indication (confounded by a third factor, such as respiratory symptoms, that is *both* an indication for antibiotics and a risk factor for asthma) due to respiratory tract infections. Thus, the risk of treating the first asthma symptoms with antibiotics induces an association between antibiotics and asthma medication. Considering most respiratory infections in preschool children are caused by viruses and symptoms of asthma are often related to virus-induced wheeze [28], overuse of antibiotics may be a reasonable interpretation of our findings. Additional research is needed, as it may have future implications for health care professionals and policymakers.

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Appendix

Appendix. Classification of antibiotics into (1) groups amoxicillin, penicillin, cephalosporin, sulphonamide, macrolide, and others (including those to treat Urinary tract infections and skin and soft tissue infections) and (2) spectrum

Name	ATC code	Groups	Spectrum
Tetracyclines			
Doxycycline	J01AA02	Other	Broad
Beta-lactam antibacterials, penicillins			
Ampicillin	J01CA01	Other	Broad
Amoxicillin	J01CA04	Amoxicillin	Broad
Pivmecillinam	J01CA08	Other	Broad
Piperacillin	J01CA12	Penicillin	Broad
Phenoximetylpenicillin	J01CE02	Penicillin	Narrow
Dicloxacillin	J01CF01	Other	Broad
Flucloxacillin	J01CF05	Skin and soft tissue infections	Narrow
Amoxicillin/clavulanic acid	J01CR02	Amoxicillin	Broad
Piperacillin + enzyhmåmmare	J01CR05	Penicillin	Broad
Other beta-lactam antibacterials			
Cefalexin	J01DB01	Cephalosporin	Narrow
Cefadroxil	J01DB05	Cephalosporin	Narrow
Cefuroxim	J01DC02	Cephalosporin	Narrow
Loracarbef	J01DC08	Cephalosporin	Narrow
Cefotaxim	J01DD01	Cephalosporin	Narrow
Ceftazidim	J01DD02	Cephalosporin	Narrow
Ceftriaxon	J01DD04	Cephalosporin	Narrow
Ceftibuten	J01DD14	Cephalosporin	Narrow
Meropenem	J01DH02	Other	Broad
Sulphonamides and trimethoprim			
Trimethoprim	J01EA01	Urinary tract infections	Broad
Trimethoprim and sulphonamides combined	J01EE01	Sulphonamide	Broad
Macrolides, lincosamides and streptogramins			
Erythromycin	J01FA01	Macrolide	Narrow
Roxitromycin	J01FA06	Macrolide	Unclassified
Chlaritromycin	J01FA09	Macrolide	Narrow
Azitromycin	J01FA10	Macrolide	Narrow
Clindamycin	J01FF01	Macrolide	Narrow
Aminoglycoside antibacterials			
Tobramycin	J01GB01	Other	Broad
Gentamicin	J01GB03	Other	Broad
Quinolone antibacterials			
Ofloxacin	J01MA01	Other	Broad
Ciprofloxacin	J01MA02	Urinary tract infections	Broad
Norfloxacin	J01MA06	Urinary tract infections	Broad
Other antibacterials			
Vancomycin	J01XA01	Other	Narrow
Teicoplanin	J01XA02	Other	Broad

(continued)

Appendix (continued)

Name	ATC code	Groups	Spectrum
Colistin	J01XB01	Other	Broad
Fusidic acid	J01XC01	Other	Narrow

(continued)

Appendix (continued)

Name	ATC code	Groups	Spectrum
Nitrofurantoin	J01XE01	Urinary tract infections	Narrow
Methenamine	J01XX05	Other	Unclassified

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