

Antibiotic use in the first year of life and risk of atopic disease in early childhood

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Summary

Background Reduced post-natal microbial stimulation resulting from improvements in public health measures, smaller family size, and through increased antibiotic use has been postulated to account for the increasing prevalence of atopic diseases seen predominantly in developed countries.

Objective To investigate use of antibiotics in the first year of life and subsequent development of atopic disease in early childhood.

Methods A prospective birth cohort of 198 children at high atopic risk was recruited prenatally and followed for 5 years. Illnesses and antibiotic use were ascertained through daily diaries, and diagnoses of asthma and hayfever were collected by questionnaire interviews. The children were examined regularly for eczema, and atopic status was defined by skin prick tests and serum total IgE. The effect of antibiotic use on subsequent atopic disease was examined using logistic regression with propensity score adjustment.

Results 54.0% (107/198) of children received at least one course of antibiotics, mainly for acute respiratory illnesses (ARI). Thirty-three percent (329/984) of the ARI involved the lower respiratory tract (LRI). Twenty-three percent (222/984) of ARI were treated with antibiotics, with LRI significantly more likely to receive antibiotics. Antibiotic use was associated with asthma (unadjusted odds ratio 2.3; 95% confidence interval 1.2–4.5; $P=0.01$) but this association was reduced after propensity score adjustment. No associations were found between antibiotic use and eczema, current wheeze, current asthma, atopic asthma, allergic rhinoconjunctivitis or atopy.

Conclusion Although this was a small study, systematic and careful monitoring of ARI, antibiotic use, and asthma and atopic diseases did not indicate that receipt of antibiotics early in life led to subsequent asthma or atopy at 5 years.

Keywords antibiotic use, asthma, atopy, early childhood, eczema

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Introduction

Decreased post-natal microbial stimulation resulting from improvements in public health measures, smaller family size and increased use of antibiotics has been suggested as a major contributor to the huge increase in the prevalence of atopic disease in industrialized countries over the last three decades [1–3].

The time around pregnancy and early infancy is associated with a skewed T-helper type 2 (Th2) cytokine pattern and maturation of the immune system is thus

characterized by development of a balanced Th1/Th2 immunity [4]. Post-natally, microbial, allergen and adjuvant stimulations appear to be the principal triggers for Th1 maturation, and in non-atopic individuals, this process is established by the age of 5 years [5–7]. Studies within our centre [4, 8] and others [9, 10] have demonstrated impaired Th1 development in atopic individuals.

Studies investigating associations between antibiotic use and subsequent atopy have reported conflicting findings. Wickens and Alms postulated that decreased antibiotic use, associated with an anthroposophic lifestyle,

may be a contributory factor to the reduction in the prevalence of asthma and wheeze at age 5–10 years [11] and less atopy [12].

Several studies have reported associations between early antibiotic use and subsequent asthma, hayfever and eczema [11–20]. These studies were cross-sectional [12], performed retrospectively [11, 15–17, 19], or a meta-analysis of prospective as well as retrospective studies [18]. Disease outcome measurements were performed over wide age ranges and the diagnosis of atopic disease was based only on history [11, 13, 14, 16, 17, 19, 20].

More recently, several studies have found no association between early antibiotic use and subsequent atopic disease [21, 22]. A prospective study of children at a genetic risk of atopy found no significant associations between receipt of antibiotics in the first year of life and asthma or atopy at 5 years [21]. The children were followed up closely and total IgE measurements were performed as an objective measure of atopy. Indications for antibiotic use were also determined.

A large longitudinal study of more than 4000 children from birth to 5 years found no associations between early antibiotic use and asthma at 5 years, but concluded that antibiotic use in early life was more common in asthmatic children [22]. A large nested case-control study of children identified from two large general practice databases in the United Kingdom found no associations between use of antibiotics in infancy and subsequent development of hayfever [23]. General practitioner (GP) attendance was found to be a strong confounder, with antibiotics being prescribed more frequently to atopic asthmatic children with chest illnesses, who develop hayfever later in childhood.

Alteration of the immune response to common childhood infections as well as to the gut flora through the increased use of antibiotics have been postulated as mechanisms for delayed maturation of the immune system, thus predisposing these individuals to the development of atopic disease in later life [24].

An association between early antibiotic use and objective measures of atopy would be evident if antibiotics increased the risk of asthma through alterations in the intestinal flora, thus leading to Th1/Th2 imbalance and atopy. Of several prospective and retrospective studies utilizing objective measures of atopy such as positive skin prick tests (SPT) or elevated serum IgE, only one found an association between early antibiotic exposure and atopy using such measures [25]. This association was, however, only seen in a subgroup, concentrating among those children who had been breastfed for at least 4 months, or those who had less than two pets in the home.

This birth cohort study of children at high risk of atopy aimed to investigate the association between antibiotic use in the first year of life and the development of atopic disease at 5 years.

Methods

One hundred and ninety-eight children from a prospective birth cohort described previously [26] were recruited between July 1996 and June 1998 and followed for 5 years. The children were all at high genetic risk of atopy, with the criteria for inclusion in the study having at least one parent with a doctor diagnosis of asthma, hayfever or eczema. Parents kept a daily diary of their child's health for 5 years from the time of birth of their child. The diaries were completed on a daily basis, usually by the mother, and involved ticking the relevant boxes if their child had a fever, runny/blocked nose, cough or wheeze, as well as the use of prescribed and over-the-counter medication. Whenever their child exhibited any symptoms of a respiratory illness, such as fever, runny/blocked nose or cough, the parent would notify the study centre and a home visit was arranged within 72 h. Detailed information about each respiratory illness episode was collected during the home visit and fortnightly follow-up telephone calls were made until resolution of the child's symptoms. The information sought included duration of symptoms, doctor diagnosis, if the child was seen by a doctor and oral antibiotic use. A single course of antibiotics was considered to be use of an antibiotic for up to 10 days as well as repeat prescription of the same antibiotic within 7 days of each other. We used prospective, frequent and standardized surveillance of all subjects through home visits in the event of a reported respiratory illness and fortnightly follow-up telephone calls until resolution of all respiratory symptoms.

Diagnosis of eczema

The children, all born at full term, underwent medical examination by the study doctor (M. K.) at 6 weeks, 6 months, 12 months of age, and then annually, with specific attention to the presence of eczema. The diagnosis was based on the criteria set out by Hanifin and Rajka [27], with a positive diagnosis made if three or more of the primary features were present.

Diagnosis of asthma and wheeze

History of doctor-diagnosed asthma and current wheeze were obtained annually by a face-to-face interview with the mother.

Skin prick tests and immunoglobulin E measurements

The children underwent SPT at 5 years of age to a panel of seven allergens (fresh cow's milk, egg white, rye grass, alternaria, aspergillus, house dust mite and cat dander). Histamine 10 mg/mL was used as the positive control and

normal saline as the negative control. The weal size was measured after 15 min, with a weal size ≥ 3 mm considered a positive reaction at 5 years. Antihistamines, if taken, were withheld for at least 96 h. SPT were also performed on all the parents with the same panel of allergens, and a weal size of ≥ 3 mm was considered positive. Parental history of doctor-diagnosed eczema, hayfever and asthma was obtained by a face-to-face questionnaire interview.

Blood samples to measure serum total IgE were obtained when the children were 5 years old. The measurements were made using Pharmacia Unicap 100 (Fluoro enzyme immunoassay, Pharmacia Unicap, Uppsala, Sweden). In accordance with the manufacturer's recommendations, serum total IgE > 48 kU/L was considered to be elevated.

Definitions

Upper respiratory illness (URI) – any episode of illness with runny/blocked nose or cough, with or without fever.

Lower respiratory illness (LRI) – episodes of fever or runny/blocked nose associated with a rattly chest or wheeze. A rattly chest was described as moist, wet, noisy breath sounds from the child's chest. Wheeze was defined as a high-pitched whistling sound heard on expiration. LRI were further classified into non-wheezy LRI and wheezy LRI based on the presence of any wheeze reported by the parent or the family doctor.

Current asthma – doctor-diagnosed asthma and current wheeze between 4 and 5 years of age.

Atopic asthma – current asthma and either positive SPT at 5 years or elevated serum total IgE (at 5 years).

Allergic rhinoconjunctivitis (ARC) – having ever had recurrent episodes of itchy, watery eyes or runny/blocked nose with or without sneezing, which were not associated with symptoms of an infection.

Statistical analysis

Early infections may be more likely in children who develop asthma and atopy in childhood. The use of antibiotics is also dependent on the occurrence of infection so that, in the absence of randomizing children to antibiotics or not after infection occurs, one way to estimate the effect of administration of antibiotics on subsequent atopic disease is by use of propensity score adjustment. Although it does not completely make up for the fact that exposures were not randomized, this is one way of allowing for the non-random allocation of covariate values to subjects in observational studies, developed by Donald Rubin and colleagues over the last 30 or so years [28], so that the effect of a treatment (in this case, antibiotic use) is only compared between subjects who are equally likely to have received it, as in a randomized trial.

Estimation of a propensity score for receiving a 'treatment' using known prior covariates, followed by stratification on this score in an analysis including the 'treatment', produces less bias and is more efficient for estimating the likely causal effect of the 'treatment' than merely including all the covariates in a large multifactorial model [28].

The approach in this study used the propensity score paradigm, but was necessarily slightly different. Antibiotic data were collected for each infection occurrence so that we estimated the probability for receiving antibiotic treatment for each infection in the first year of life using all covariates relating to the characteristics of the infection as well as characteristics of the child and their parents. Characteristics of the infection were presence and duration of fever, runny/blocked nose, cough, rattly chest and wheeze as well as colour of any mucous produced and paracetamol use. Characteristics of the child that were included in the analysis were gender, duration of breastfeeding, daycare attendance, environmental tobacco smoke exposure, number of sibs, pet ownership and parental histories of asthma and atopy.

Whether there was an associated physician visit was not included as a predictor, because in Australia it is a necessary condition of antibiotic use, and is therefore a part of the 'treatment' being predicted. Thus, in the imaginary clinical trial that this analysis is trying to mimic, subjects would be randomized at the onset of symptoms, to either a doctor visit and antibiotics or not (which could still include a doctor visit with no antibiotics). The scores were then summed for each child over all illnesses in the first and the second 6 months of life, as well as over the whole year, as were the number of antibiotic treatments in the same periods, to give an overall antibiotic predictor (AP) score. The 12 children with no infections had a zero AP score. AP scores were then grouped by quintiles for stratification in the analyses, and analyses for each of the nine binary responses (listed in Table 3) were performed in the same way: logistic regression with just any antibiotic use (1–6 and 7–12 months, or 1–12 months), then adjusting for the AP score group, then adjusting for other confounders, namely, number of doctor visits (both continuous and categorical), sex, childcare and pets. Analyses were also repeated using the actual number of antibiotic treatments instead of any use. Some exploration of possible differences in effects of antibiotic use within subgroups was carried out using interaction terms in these models. Analyses were performed using SPSS11 and STATA9, including the STATA routine *pscore*.

Fully informed written consent was obtained from the parents before recruitment into the study, and approval for the study was obtained from the ethics committee of King Edward Memorial and Princess Margaret Hospitals.

Results

Characteristics of the cohort

One hundred and ninety-eight of the 263 (75.3%) children remained in the study for the full 5 years. 41.5% of the withdrawals occurred in the first 6 months of the study with interstate moves, prematurity and lack of time being the most commonly cited reasons for withdrawal. Withdrawals after the second year were due to transfers away from the study centre in Perth, Western Australia. No significant differences were found in the number of ARI experienced, or antibiotic prescriptions between the children who had withdrawn from the study compared with the remaining cohort. No significant differences were found in the number of sibs, pet ownership, duration of breastfeeding or prevalence of parental atopy between the study participants and those children who had withdrawn from the study. Ninety-seven percent of the children had their daily diaries completed for the first year of life.

There were more boys than girls, and the majority of the children were 'only' children (52.5%) (Table 1). Most of the

children lived in a household with a pet, most often a dog. Three quarters of the cohort (77.3%) were breastfed for more than 6 months, and were unlikely to attend day-care in the first year of life (Table 1). 79.3% of the mothers and 80.3% of the fathers had a positive SPT test (Table 1).

Only eight (4.0%) of the mothers smoked during the antenatal period and 16 (8.0%) mothers smoked during their child's first year of life. Forty-three (21.7%) mothers took oral antibiotics during pregnancy, with respiratory infections and cystitis being the most common conditions for which antibiotics were prescribed.

A total of 984 episodes of ARI were reported in the first year of life. 48.6% (478/984) of these episodes presented to the child's primary care physician, and 45.2% (216/478) of these episodes were treated with antibiotics.

Atopic disease

As reported previously [26], two-thirds (66.2%) of the cohort had eczema at some time during the 5 years, and 31.3% (62/198) had current eczema (i.e. eczema between 4 and 5 years) (Table 3). 28.8% (57/198) had been diagnosed with asthma by a doctor; the majority (57.9%) were diagnosed between 1 and 3 years of age. Only 18.7% (37/198) had current asthma, and 75.7% (28/37) of the current asthmatics were atopic. 39.9% (79/198) had symptoms of ARC (Table 3). 31.8% had a positive SPT reaction and 55.8% of the cohort had elevated serum total IgE (> 48 kU/L) at 5 years (Table 3).

Antibiotic use in the first year of life

Fifty-four percent (107/198) of the cohort had antibiotics in the first year, the majority (94/198) between 7 and 12 months of age (Table 2). 56.1% (60/107) had only one course of antibiotics, 29.9% (32/107) had two courses and 14% (15/107) had three or more courses of antibiotics in the first year (Table 2). The most common antibiotics used were those from the penicillin group (57.6%), followed by cephalosporins (21.0%) and macrolides (6.6%). The majority of the antibiotics were prescribed for acute respiratory illnesses (ARI) (99.1%), followed by skin infections such as impetigo. Antibiotics were prescribed more frequently for wheezy LRI (34.7%) compared with non-wheezy LRI (30.8%) and URI (17.9%) (Table 2). Children with any LRI were significantly more likely to be prescribed antibiotics [odds ratio (OR) 2.2; 95% confidence interval (CI) 1.6–2.9; $P < 0.001$] than children with URI.

Relationship between the use of antibiotics and atopic disease

Children who were prescribed antibiotics in the first year of life were more likely to have a doctor diagnosis of asthma in the first 5 years in univariate analysis (OR 2.3

Table 1. Characteristics of the cohort

Characteristic	Prevalence number (%)
Males	111 (56.1)
Number of siblings	
0	104 (52.5)
1	55 (27.8)
2	32 (16.2)
3 or more	7 (3.5)
Pet ownership	
Yes	113 (57.1)
Cat	50 (25.3)
Dog	58 (29.4)
Duration of breastfeeding (weeks)	
≤ 6	11 (5.6)
7–12	16 (8.0)
13–25	18 (9.1)
≥ 26	153 (77.3)
Day care attendance	
Never attended day care	141 (71.2)
Before 6 months of age	12 (6.1)
7–12 months of age	45 (22.7)
Parental atopy	
Mother	
Asthma	97 (49.0)
Hayfever	131 (66.2)
Eczema	61 (30.8)
SPT positive	157 (79.3)
Father	
Asthma	62 (31.3)
Hayfever	93 (47.0)
Eczema	22 (11.1)
SPT positive	159 (80.3)

SPT, skin prick test.

95% CI 1.2–4.5; $P=0.01$), mainly because of the strong association with antibiotic use in the first 6 months (OR 2.4 95% CI 1.2–4.5; $P=0.01$) (Table 3). Children with wheezing LRI between 7 and 12 months of age were

significantly more likely to be prescribed antibiotics (OR 2.3; 95% CI 1.3–3.8; $P<0.05$), compared with those with URI or non-wheezy LRI at this age. These children were also significantly more likely to be diagnosed with asthma (OR 3.1; 95% CI 1.2–7.3; $P<0.05$) than those who did not have any wheezy LRI at this age. No large or significant univariate associations were found between antibiotic use and ARC, eczema or atopy (SPT or high IgE).

While the chief predictors of antibiotic use were fever, unclear mucus production and wheezy or rattly chest, all the covariates listed in the 'Methods', and their two-way interactions, were used in the propensity score predictions. AP scores ranged from 0 to 3.2 and after grouping by quintiles, the proportions of children receiving any antibiotics ranged from 17.5% in the lowest fifth to 95% in the highest fifth, with approximately equal mean scores whether receiving antibiotics or not in each fifth.

After adjusting by the strata of the AP score only, all the ORs from unadjusted analyses for wheezy outcomes were reduced, for example for doctor-diagnosed asthma, the adjusted OR changed from 2.3 to 1.4 (95% CI 0.7–3.0) and for current wheeze the OR was reduced from 1.5 to 1.0 (95% CI 0.5–2.1) for any use in the first 12 months. Additional adjustment for other covariates (GP visits – total number), sex, childcare (any in first year) and pets (any or none) did not appreciably alter these estimates (Table 3). Adjustment by the AP score alone or the AP score and other confounders made little difference to the effect estimates for the atopic outcomes, which were all close to unity.

Analyses were repeated using numbers of antibiotic courses (0, 1, 2, 3+) as a categorical predictor, and no increasing (or decreasing) trends were observed (Fig. 1). Because the strongest suggested effects of antibiotic use were 0–6 months and on wheezing phenotypes, possible differences in the effects of such use within different subgroups were examined for atopic asthma and current wheeze and antibiotic use, by looking at interaction

Table 2. Frequency of acute respiratory illnesses (ARI) and antibiotic use in first year of life

Number of episodes of ARI in first year	Number of children (% of cohort)
Upper respiratory illness	
0	25 (12.6)
1–3	110 (55.6)
4–6	53 (26.8)
≥7	10 (5.0)
Non wheezy lower respiratory illness	
0	97 (49.0)
1–2	79 (39.9)
≥3	22 (11.1)
Wheezy lower respiratory illness	
0	144 (72.7)
1–2	49 (24.8)
3	5 (2.5)
Antibiotics ever (age) (months)	
0–6	29 (14.6)
7–12	94 (47.5)
0–12	107 (54)
Number of antibiotic courses in first year	
0	91 (46.0)
1	60 (30.3)
2	32 (16.2)
3 or more	15 (7.5)
Antibiotic use by type of ARI	
Type of ARI	Number of episodes (% of episodes)
Upper respiratory illness	117 (17.9)
Non-wheezy lower respiratory illness	72 (30.8)
Lower respiratory illness with wheeze	33 (34.7)

Table 3. Relationship between any use of antibiotics in the first year and atopic disease

Characteristic	Antibiotic use OR (95% CI)	0–6 months Adjusted* OR (95% CI)	Antibiotic use OR (95% CI)	0–12 months Adjusted* OR (95% CI)
Current eczema ($n=62$)	1.2 (0.6–3.2)	1.2 (0.6–2.5)	1.4 (0.8–2.6)	1.5 (0.7–3.3)
Asthma				
Doctor diagnosis of asthma ($n=57$)	2.4 (1.2–4.5)	1.7 (0.8–3.6)	2.3 (1.2–4.5)	1.5 (0.7–3.2)
Current wheeze ($n=56$)	1.5 (0.8–2.7)	1.3 (0.6–2.7)	1.5 (0.8–2.7)	1.0 (0.5–2.2)
Current asthma ($n=37$)	1.7 (0.8–3.6)	1.4 (0.6–3.2)	1.7 (0.8–3.6)	0.9 (0.4–2.3)
Current atopic asthma ($n=28$)	1.9 (0.8–4.6)	1.4 (0.5–3.4)	1.9 (0.8–4.5)	1.1 (0.4–3.1)
ARC ($n=79$)	0.9 (0.5–1.7)	0.8 (0.4–1.6)	0.9 (0.5–1.7)	0.6 (0.3–1.2)
Atopy				
Skin prick test positive (SPT) ($n=67$)	0.9 (0.5–1.7)	0.8 (0.4–1.7)	0.8 (0.5–1.5)	0.6 (0.3–1.4)
Elevated total IgE ($n=98$)	0.8 (0.4–1.5)	1.1 (0.5–2.2)	0.8 (0.4–1.5)	1.0 (0.5–2.1)
SPT positive or elevated IgE ($n=141$)	0.8 (0.4–1.5)	0.8 (0.4–1.8)	0.9 (0.5–1.6)	1.0 (0.5–2.1)

*Adjusted for antibiotic predictor score, sex, any first year pets, childcare, GP visits.

OR, odds ratio; CI, confidence interval; ARC, allergic rhinoconjunctivitis.

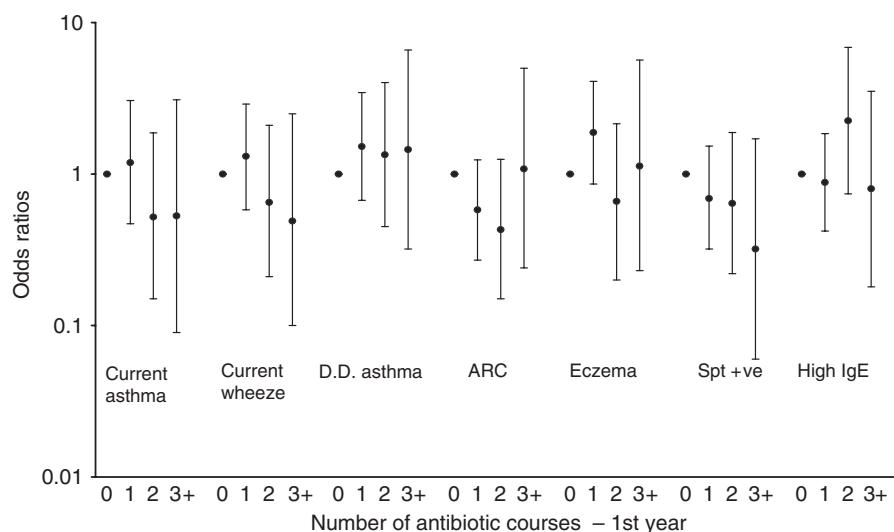


Fig. 1. Change in odds of 5-year outcomes for number of antibiotic courses taken: adjusted for antibiotic predictor score, sex, any first year pets, childcare, GP visits. GP, general practitioner; ARC, allergic rhinoconjunctivitis; SPT, skin prick test.

effects between 0- and 6- month use and gender, pets, childcare and GP visits (two or more compared with one or none). No major differences were indicated with gender, childcare or GP visits, on either outcome, although there was a significant ($P=0.03$) interaction between antibiotic use and the presence of pets, which showed an increased odds of atopic asthma at 5 (but not current wheeze) with pets and no antibiotics or with no pets and antibiotics, but not with both. This effect was most likely due to chance, given the number of analyses.

Discussion

In this high-risk birth cohort, we have found no significant relationship between antibiotic use in the first year and paediatric atopic disease. Although we found that children who had antibiotics in the first year of life had more than twice the odds of a doctor diagnosis of asthma, this relationship was reduced after adjustment.

Although the small sample size has been a limitation to this study, the major findings were that there was no evidence for increased risk when we used more specific diagnoses such as atopic asthma and current asthma at 5 years. Furthermore, no dose-response effect was observed between numbers of antibiotic courses and any asthma/atopy outcome. The size of the study precluded a convincing investigation of the major effects of antibiotic use within subgroups and no striking differences were found between boys and girls, children attending childcare or not or children with more than one visit to their doctor, although we did find an unusual difference in the association of early antibiotic use between children with or without pets that was probably due to chance.

Diagnosis of asthma in pre-schoolchildren is difficult and Martinez *et al.* [29], in their prospective birth cohort,

found that 48.5% of children under the age of 6 years reported at least one episode of wheezing, and almost 60% of these had stopped wheezing by 6 years.

In the present study, antibiotic use was accurately recorded and verified by study personnel. More than half the cohort (54.0%) had at least one course of antibiotics in the first year, with ARI, especially LRI, being the most common reason for antibiotic use. Children with wheezing LRI between 7 and 12 months of age were more likely to be prescribed antibiotics compared with those with URI. These children were also more likely to be diagnosed with asthma.

Early infections have been shown to be associated in some way with subsequent development of asthma and atopic disease. The use of antibiotics is also dependent on occurrence of infection. In this study, we used a form of propensity score adjustment so that the effect of antibiotic use was only compared between children who were equally likely to have received it. As discussed earlier, this method of analysis produces less bias and is more efficient for estimating the likely association of the 'treatment' than merely including all the covariates in a large multifactorial model. Much of the relationship between antibiotic use in the first year of life and doctor diagnosis of asthma can thus be accounted for by confounding, in that both antibiotic use and a doctor diagnosis of asthma are related to early infection, or that early symptoms of infection are part of the early natural history of asthma.

The children were examined closely for eczema at regular intervals over the full 5 years of the study. Atopic status was measured objectively by SPT and serum total IgE. No associations were found between use of antibiotics in the first year and eczema or atopy.

This study involved 198 children genetically predisposed to atopy. The small sample size has limited the

ability of the study to detect small associations between antibiotic use and atopic disease and this is made clear in the wide CIs for our main effects, where for example, although our best estimate of the effect of antibiotic use on current wheeze is an OR of 1.0, we are unable to rule out a causal effect as high as an OR of 2.2, or a protective effect as low as 0.5.

We also determined effects on many outcomes but these were all asthma/atopy related and we have described them all, and so there was no benefit to be gained by any adjustment for multiple testing [30, 31]. McKeever et al. [13] found that antibiotic exposure *in utero* was associated with an increased risk of eczema, asthma as well as hayfever in a dose-related manner. Care has to be taken in the interpretation of these results, as the data were collected from a General Practice database, with no verification of the percentage of antibiotic prescriptions actually being used. Droste and Farooqi found positive associations between asthma, hayfever and eczema and antibiotic use in the first year of life in children with a family history of hayfever [15, 16]. They did not find any association between antibiotic use and current asthma or eczema. Although Bohme et al. [14] found associations between antibiotic use and atopic dermatitis, they also found significant associations between atopic dermatitis and respiratory infections such as pneumonia and otitis media for which antibiotics were used. Objective measures such as SPT or IgE measurements were not used in these studies [14–16].

Families who follow an anthroposophic lifestyle have fewer vaccinations and tend to use less antibiotics. Alm et al [12, 32] investigated the prevalence of atopy through SPT and allergen-specific IgE in anthroposophic families in Sweden. In this cross-sectional study, they recruited children from two anthroposophic (Rudolf Steiner) schools and compared them with age-matched controls from two other schools. They found a lower prevalence of atopy in the children from the Steiner schools. Wickens also investigated 5–10 year old children with an anthroposophic lifestyle in New Zealand and found that children who had antibiotics in the first year of life had an increased risk of asthma [11]. No associations were, however, found for hayfever. Although these two studies found positive associations between antibiotic use early in life and atopy, it is not known which aspects of the anthroposophic lifestyle are associated with lower atopy prevalence. Besides being more restrictive in their use of antibiotics, dietary differences are also seen in these families, who include foods containing live lactobacilli in their diet, thus altering the intestinal microflora.

Although associations were reported between antibiotics in the first year and asthma between 1 and 2 years, as well as hayfever in adulthood, no association was found with atopy, defined by SPT in Cullinan's retrospective study [33]. The relationships found between antibiotic use

and asthma in that cohort were largely confined to antibiotic prescriptions for LRI, which may have been manifestations of pre-existing asthma. Also, as asthma diagnosis was made when the children were aged between 1 and 2 years, it is likely that a large percentage of these children represent the transient wheezers described by Martinez et al. [29].

Wheezing was reported to be associated with increasing doses of antibiotics in a population-based study of children aged 5–14 years [20]. There was a likelihood the wheezing attacks, induced by viral respiratory infections and treated with antibiotics may have been the first indication of asthma. A case-control study reported that children who had more antibiotics in the first 5 years of life were more likely to wheeze; however, asthma was not an outcome measure [28]. Febrile respiratory infections and antibiotic prescriptions were reported to be associated with asthma and wheezing in school-aged children [29]. This study, however, also reported that for the asthmatics, the number of courses of antibiotics and febrile infections were inversely related to the risk of atopy and current wheeze, suggesting a protective effect. A prospective study of children at high risk of atopy (at least one parent with a history of atopic disease) did not find any relationship between atopic disease at 5 years and antibiotic use in the first year of life after adjusting for confounding by lower respiratory infections [21]. The prevalence of asthma, hayfever and eczema was determined through a telephone questionnaire of physician diagnoses of these conditions. Less than half the cohort (46.2%) underwent total serum IgE measurements. A systematic review and meta-analysis of eight prospective and retrospective studies by Marra et al. [18] found associations between receipt of antibiotics in the first year of life and development of asthma only in the pooled data from retrospective studies. The number of participants in these studies was small and results could be affected by recall bias as asthma and antibiotic use was ascertained by parental reporting whereas in our study, close follow-up of the cohort with daily diary recordings of antibiotic use as well as fortnightly telephone surveillance of all ARI episodes reduced the likelihood of recall bias for antibiotic use.

Observational studies demonstrating causal links between asthma and early antibiotic use are confounded by the effect of antibiotic prescription for wheezing illnesses in early childhood, a practice that has been strongly discouraged. Care must therefore be taken in the interpretation of these studies because of issues of confounding, as it is plausible that children with asthma are more likely to present with wheezing illnesses early in life and are thus more likely to be prescribed antibiotics. Causal links could, however, be strengthened if an association is found between antibiotic use for non-asthma-related conditions and atopic disease.

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