

Early exposure to infections and antibiotics and the incidence of allergic disease: A birth cohort study with the West Midlands General Practice Research Database

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Background: It has been suggested that the rise in prevalence of allergic disease in westernized countries is due in part to a decrease in exposure to infections and an increase in the use of antibiotics early in life.

Objective: The purpose of this investigation was to quantify the relationships between (1) exposure to personal infections, infections in siblings, and use of antibiotics in early life and (2) the incidence of allergic disease.

Methods: Using the West Midlands section of the UK General Practice Research Database, we established a historical birth cohort of children (N = 29,238). For each child, we identified all personal infections and infections in siblings and determined the use of antibiotics in early life; we also noted incident diagnoses of asthma, eczema, and hay fever. The data were analyzed through use of Cox regression.

Results: There was no clear protective effect of exposure to either personal infections or infections in siblings with respect to the incidence of allergic disease. Antibiotic exposure was associated with an increased risk of developing allergic disease in a dose-related manner: having 4 or more courses of antibiotics in the first year of life was associated with an increased incidence of asthma (hazard ratio [HR], 3.13; 95% CI, 2.75-3.57), eczema (HR, 1.48; 95% CI, 1.31-1.68), and hay fever (HR, 2.12; 95% CI, 1.68-2.66). However, adjusting for consulting behavior reduced these effects (adjusted HR [95% CI]: asthma, 1.99 [1.72-2.31]; eczema, 1.01 [0.88-1.17]; hay fever, 1.14 [0.88-1.47]).

Conclusions: We found no evidence that exposure to infections reduced the incidence of allergic disease, and infections did not explain the previous findings of a strong birth order effect in this cohort. The use of antibiotics might be associated with early diagnoses of allergic disease. (*J Allergy Clin Immunol* 2002;109:43-50.)

Key words: Asthma, eczema, hay fever, infections, siblings, antibiotics, cohort

The "hygiene hypothesis" proposes that the protection against the development of allergic disease provided by the presence of older siblings is mediated by infection.¹ The findings of studies specifically designed to test this hypothesis, however, have been inconclusive.² There are data suggesting that infections with measles,³⁻⁵ hepatitis A,^{6,7} and mycobacteria,^{8,9} as well as repeated episodes of a runny nose,¹⁰ might reduce the risk of having allergic disease, but other studies have found either no protective effect of early infection¹¹⁻¹³ or even a positive association.^{14,15}

In animal models, the presence of intestinal bacteria appears to be important for normal immune development.¹⁶ In human beings, epidemiologic evidence suggests that children in Sweden and children in Estonia, who have very different levels of atopy, have significant differences in their intestinal flora.¹⁷ Furthermore, a recent study has shown that children might have differences in their gut microflora before they develop atopy.¹⁸ It seems likely, therefore, that the composition of the gut microflora early in life is an important determinant of atopic status.

Because exposure to antibiotics causes major disruptions to the gut bacterial flora, the use of antibiotics early in life might be a risk factor for the development of allergic disease. Certainly the use of antibiotics has increased in western societies at the same time that the incidence of allergic disease has increased.

Four cross-sectional studies have found a positive association between the use of antibiotics and the development of asthma, atopy, or allergic disease.^{12,15,19,20} However, these studies have all relied on retrospective parental recall of antibiotics exposure and could therefore be subject to bias.

Data are also available from 2 longitudinal studies, and here the findings are conflicting. The first study found an increased risk of allergic disease after the use of antibiotics in the first year of life; this was independent of the type of infection.¹⁴ The second study found no relationship between the development of asthma, wheeze, or bronchial hyperactivity and the use of antibiotics (excluding those given for lower respiratory infections).¹⁰

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Abbreviation used
HR: Hazard ratio

We have previously identified a historical cohort of children within the West Midlands General Practice Research Database (GPRD) and have demonstrated strong birth order effects within this cohort for hay fever, eczema, and asthma diagnosed after the age of 2 years.²¹ In the present study, we examined whether exposure to infections—either personal infections or siblings' infections—protects against the risk of developing allergic disease and whether early exposure to antibiotics increases the subsequent risk of allergic disease. In addition, we sought to determine whether exposure to infections and/or antibiotics explains the strong birth order effects present in this data set.

METHODS

Cohort

This study makes use of data from a birth cohort of children identified historically within the GPRD, which is the largest longitudinal primary care data set available and involves information collected as part of routine clinical care.^{22,23} The methods that we used to establish our cohort of children and to establish their family structures have been described in detail elsewhere.²¹ Briefly, we identified children for whom the following were true: each had been registered with his or her primary care doctor (GP) within 3 months of birth, and the medical history of each contained at least 1 consultation as an indicator that the child was using this GP for their medical needs. We established the family structure for each child, recording the numbers of older and younger siblings and identifying the mother and father whenever possible. We then extracted incident diagnoses of asthma and wheeze, eczema, and hay fever using (1) Oxford Medical Information System (OXMIS) codes, which were derived from the International Classification of Disease (version 8), and (2) Read codes, which are hierarchic codes commonly used in GP practices in England. Our results showed a strong dose-related protective effect of older siblings on the incidence of eczema, hay fever, and asthma diagnosed after the age of 2 years.²¹

For this study, we identified all infections recorded by the GP during 6-month intervals beginning at birth. The GPRD uses both OXMIS and Read codes, and we used both of these systems to categorize infections as follows: gastrointestinal infections, respiratory tract infections, conjunctivitis, otitis media, and *Candida*. The prevalence of other infections was low, so for the purposes of analysis they were combined into the following groups: bacterial (impetigo, tuberculosis, and urinary tract infections) and viral (measles, mumps, rubella, hepatitis, chicken pox, herpes, and mononucleosis). We also identified infections recorded in the siblings' records during the index child's early life, again using 6-month time intervals from the birth of the index child. We then extracted data for all prescribed antibiotics in 6-month intervals from birth and grouped them into the following categories; penicillin, amoxycillin, co-amoxiclav, macrolides, cephalosporin, and other. To attain an estimate of the frequency of visits to the doctor, we extracted the number of medical visits recorded in 6-month intervals from birth, excluding visits for vaccinations and allergic disease outcomes. As a proxy measure of disease severity for children with asthma or wheeze, we also extracted the number of prescriptions for asthma medications in the year following diagnosis.

Statistical analysis

Our primary hypothesis was that exposure to infections and antibiotics during the first year of life would affect the subsequent incidence of allergic disease. Therefore, the data were initially examined with recorded infections or antibiotic prescriptions in the first year of life as the primary exposures and incidence of disease after the age of 1 year as the primary outcome. However, we also repeated the analyses with exposures in the first 6 months and the first 2 years. Rates of disease were calculated from the end of the exposure period, so any subject diagnosed with an allergic disease or lost to follow-up before this time was excluded from the analyses. Cox regression models were used to analyze the impact of exposures on disease incidence and to estimate the hazard ratios (HRs) and 95% CIs. Each exposure was initially examined in a series of univariate analyses as a binary "ever or never" indicator variable and then as an ordered categorical variable in a search for evidence of a dose-response relationship. We then used multivariate analyses to examine the effect of possible confounders, including sex, parental allergic disease, parental smoking, and consulting behavior (modeled as an ordered categorical variable divided into 5 categories), and the impact of our asthma severity variable. To examine whether exposure to infections or antibiotics influenced the birth order effect, total antibiotics and total number of infections were modeled as ordered categorical variables. In all analyses, the proportional hazards assumption was examined by means of the STATA diagnostic command *phtest1*; when the proportional hazard assumption was not met, the HRs were examined on either side of the midpoint of person-year time. All analyses were performed with STATA 7.0 through use of robust standard errors (Stata Corporation, College Station, Tex).

RESULTS

The full cohort contains 29,238 children with a median follow-up time of 2.9 years (range, 0-11 years) and includes marginally more boys ($n = 14,957$; 51%) than girls. Information on the presence of siblings was available for 95% of the cohort; of these, 20,172 children (69%) had siblings. More than 99% of those in the cohort had at least 1 consultation with their doctors in the first year of life for a nonallergic disease, and there was a clear dose-response relationship between number of consultations in the first year of life and subsequent incidence of all 3 allergic disease: having 14 or more consultations (the highest quintile), in comparison with having 0 to 4 consultations (the lowest quintile), was associated with a HR for asthma of 3.75 (95% CI, 3.28-4.30), a HR for eczema of 3.75 (95% CI, 3.28-4.30), and a HR for hay fever of 3.87 (95% CI, 2.98-5.03). The characteristic of the timing of onset disease in children diagnosed after the age of 1 year is shown in Table I.

The results for exposure to infections, infections occurring in siblings, and antibiotics and incidence of allergic disease are shown in Tables II through IV. The univariate HRs suggest that personal infections were associated with an increased risk of developing all 3 allergic diseases. After adjustment for consulting behavior, however, all of these relationships were attenuated and most disappeared altogether. There was a small increased risk in the incidence of asthma after respiratory tract infections, and this effect was dose-dependent: having 4 or more respiratory tract infections, in compar-

TABLE I. Characteristics of children diagnosed with disease after the age of 1 year*

	N (%)	Boys (%)	Girls (%)	Age of onset (y)	
				Mean	Range
Asthma	2948 (14)	1635 (55)	1313 (45)	2.50	1-9.43
Eczema	3580 (19)	1781 (50)	1799 (50)	2.22	1-10.29
Hay fever	915 (4)	533 (58)	382 (42)	3.48	1-9.35

*In examining the effect of siblings' infections, the number of children with sibling data reduces the number of diagnoses by approximately 5%.

ison with having no infections, was associated with an adjusted HR for asthma of 1.63 (95% CI, 1.41-1.88). A similar dose-response relationship was seen for hay fever: having 4 or more respiratory infections, in comparison with having no infections, was associated with an adjusted HR of 1.44 (95% CI, 1.13-1.85). After adjustment for consulting behavior, a small protective effect emerged between viral infections and the development of asthma (adjusted HR, 0.81; 95% CI, 0.70-0.94), but there was no such effect for hay fever or eczema. Adjusting for other potential confounders, such as sex, parental atopy, parental smoking exposure, general practice, and older siblings, had virtually no impact on the HRs. There were no notable differences in exposure to infections among children with different numbers of older siblings.

There was also no clear relationship between exposure to siblings' infections and development of allergic disease. After adjustment for consulting, a small protective association was apparent between the incidence of asthma and conjunctivitis (adjusted HR, 0.87; 95% CI, 0.76-0.99), and there was also a weak but protective effect for eczema (adjusted HR, 0.88; 95% CI, 0.77-0.99); however, there was no relationship with hay fever (adjusted HR, 0.95 95%; CI, 0.76-1.20). Viral infections in the siblings were associated with a possible protective effect for the development of asthma (adjusted HR, 0.84; 95% CI, 0.71-1.00), but there was no relationship with eczema or hay fever. Bacterial infections were associated with a decreased incidence of eczema (adjusted HR, 0.79; 95% CI, 0.66-0.94), but there was no relationship with the development of asthma or eczema. Again, adjusting for potential confounders did not change these HRs.

Approximately 65% of those in the cohort were exposed to at least 1 antibiotic in the first year of life, and approximately 8% had more than 4 courses during that time. There was no evidence for a time-period effect with the prescription of antibiotics. In univariate analysis, exposure to antibiotics was associated with an increased risk of developing all 3 allergic diseases in a dose-related manner. In addition, broader-spectrum antibiotics such as co-amoxiclav tended to have a larger effect than narrow-spectrum antibiotics such as penicillin. After adjustment for consulting behavior, however, these dose-response relationships persisted only for asthma. At the highest exposure level, having 4 or more courses of antibiotics in the first year of life, in comparison with having no courses, had a HR of 1.99 (95% CI, 1.72-2.31). In the majority of the models fitted for the association of antibiotics and the development of allergic disease, the proportional assumption was not met; in the

first half of the person-year time antibiotics had a strong effect, whereas in the second half the effect was diminished or absent. In other words, the apparent effect of antibiotics was on the diagnosis of allergic disease earlier rather than later in childhood. In the first half of the follow-up time, having 3 or more antibiotics in the first year of life increased the risk of developing asthma (HR, 2.68; 95% CI, 2.38-3.01), eczema (HR, 1.54; 95% CI, 1.39-1.70), and hay fever (HR, 2.39; 95% CI, 1.86-3.05). Consultation remained a strong confounder in the analyses, and after adjusting for consulting behavior the effect of 3 or more antibiotics reduced to the following: for asthma, the HR was 1.99 (95% CI, 1.74-3.12); for eczema, the HR was 1.25 (95% CI, 1.12-1.40); and for hay fever, the HR was 1.28 (95% CI, 0.97-1.69). Again, adjusting for other potential confounders did not impact the HRs (data not shown).

We repeated all analyses for exposure in the first 6 months or the first 2 years, and the results were similar. We also examined these relationships in children who were in the top quarter of asthma medication usage; this group showed no significant differences from the group of all children with asthma.

In our previous study we found a strong protective effect with the number of older siblings for the development of eczema, hay fever, and asthma after the age of 2 years.²¹ Adjusting for exposure to infections, siblings' infection, and consulting behavior did not impact the strong birth order effects (Table V).

DISCUSSION

In this study, we used a large, prospective primary care data set to examine 2 hypotheses relating to the etiology of allergic disease. Our results provide no consistent evidence for a protective effect of personal or siblings' infections with respect to the incidence of allergic disease, and the exposures did not explain the strong birth order effects that are apparent in our data. Exposure to antibiotics was associated with an increased risk of developing allergic disease, but these effects were small and could be explained to a large extent by consulting behavior; again, they did not explain the birth order effects.

There are limitations in using routine general practice data for research. For each child, the data are dependent on the parent's bringing him or her to the GP for a consultation, so it is likely that there will be an underreporting of the number of infections that the child has experienced in early life. The ascertainment might be more

TABLE II. Asthma, infections, siblings' infections, and antibiotic exposure

		n	Percent	HR: Crude	95% CI	HR: Adj	95% CI
Infections (n = 21,129)							
Gastrointestinal	Never	13,714	64.9	1.34	1.25-1.45	1.00	0.92-1.08
	Ever	7,415	35.1				
Respiratory	Never	9,725	46.0	1.66	1.54-1.79	1.26	1.16-1.36
	Ever	11,404	54.0				
Conjunctivitis	Never	13,951	66.0	1.23	1.13-1.32	0.97	0.90-1.05
	Ever	7,178	34.0				
Otitis media	Never	16,709	79.1	1.45	1.33-1.57	1.13	1.04-1.23
	Ever	4,420	20.9				
Candida	Never	17,306	81.9	1.24	1.13-1.36	0.99	0.90-1.08
	Ever	3,823	18.1				
Bacterial	Never	20,339	96.3	1.49	1.27-1.76	1.18	1.00-1.40
	Ever	790	3.7				
Viral	Never	20,133	95.3	0.98	0.83-1.16	0.82	0.69-0.97
	Ever	996	4.7				
Siblings' infections (n =15,122)							
Gastrointestinal	Never	12,982	865.8	1.08	0.95-1.21	0.98	0.87-1.11
	Ever	2,140	14.2				
Respiratory	Never	9,520	63.0	1.16	1.06-1.26	1.02	0.93-1.11
	Ever	5,602	37.0				
Conjunctivitis	Never	13,379	88.5	0.94	0.83-1.08	0.87	0.76-0.99
	Ever	1,743	11.5				
Otitis media	Never	12,234	81.0	1.08	0.97-1.20	1.00	0.90-1.11
	Ever	2,888	19.1				
Bacterial	Never	14,185	93.8	1.04	0.87-1.24	0.95	0.80-1.13
	Ever	937	6.2				
Viral	Never	14,019	93.0	0.93	0.78-1.10	0.84	0.71-1.00
	Ever	1,013	7.0				
Antibiotics (n = 21,129)							
Penicillin	Never	18,701	88.5	1.22	1.09-1.35	0.99	0.89-1.10
	Ever	2,428	11.5				
Amoxycillin	Never	10,144	48.0	1.64	1.52-1.76	1.25	1.16-1.36
	Ever	10,985	52.0				
Macrolides	Never	16,656	78.8	1.76	1.63-1.90	1.41	1.30-1.53
	Ever	4,473	21.2				
Cephalosporins	Never	19,795	93.7	1.88	1.67-2.12	1.44	1.28-1.63
	Ever	1,334	6.3				
Augmentin	Never	20,603	97.5	1.76	1.47-2.11	1.43	1.19-1.72
	Ever	526	2.5				
Total no. of prescriptions of antibiotics							
0		7,632	36.1	—	—	—	—
1		5,539	26.2	1.45	1.31-1.61	1.26	1.13-1.40
2		3,446	16.3	1.86	1.66-2.08	1.46	1.30-1.65
3		2,043	9.7	2.41	2.13-2.72	1.76	1.56-2.01
4		1,179	5.6	2.66	2.31-3.07	1.82	1.56-2.13
>4		1,290	6.1	3.13	2.75-3.57	1.99	1.72-2.31

HR, Hazard ratio; Adj, adjusted for consultation rates in the first year of life.

complete for serious infections, but for milder diseases, social and behavioral factors will be an important determinant for the decision to consult. It seems likely that parents who have a tendency to consult for infection will also have a lower threshold for consulting for symptoms compatible with an allergic disease, and this bias would lead to an erroneous positive association between exposure and disease. To try to correct for this effect, we examined the impact of consulting in general; we found it to be strongly associated with the incidence of allergic

disease and to explain much of the apparent association with infections. Because a child is required to present to his or her GP to receive a diagnosis of an infection or a course of antibiotics, there will be a strong correlation between these exposures, so it is possible that by adjusting for consulting behavior we have "overadjusted" our analyses and obscured a true association with these exposures.

One other research project has considered consulting behavior as a potential confounder. The authors showed

TABLE III. Eczema, infections, siblings' infections, and antibiotic exposure

		n	Percent	HR: Crude	95% CI	HR: Adj	95% CI
Infections (n = 19,133)							
Gastrointestinal	Never	12,373	64.7				
	Ever	6,760	35.3	1.23	1.15-1.32	1.03	0.95-1.10
Respiratory	Never	8,677	45.4				
	Ever	10,456	54.7	1.27	1.19-1.36	1.05	0.98-1.13
Conjunctivitis	Never	12,582	65.8				
	Ever	6,551	34.2	1.20	1.12-1.28	1.03	0.96-1.11
Otitis media	Never	15,098	78.9				
	Ever	4,035	21.9	1.24	1.15-1.34	1.05	0.97-1.14
<i>Candida</i>	Never	15,564	81.4				
	Ever	3,569	18.7	1.11	1.03-1.21	0.95	0.88-1.03
Bacterial	Never	18,482	96.6				
	Ever	651	3.4	1.53	1.31-1.79	1.33	1.14-1.56
Viral	Never	18,241	95.3				
	Ever	892	4.7	1.10	0.95-1.27	0.98	0.85-1.14
Siblings' infections (n = 13,690)							
Gastrointestinal	Never	11,896	85.6				
	Ever	1,996	14.4	1.01	0.90-1.12	0.95	0.85-1.06
Respiratory	Never	8,586	61.8				
	Ever	5,306	38.2	1.02	0.94-1.10	0.94	0.87-1.02
Conjunctivitis	Never	12,252	88.2				
	Ever	1,640	11.8	0.92	0.81-1.02	0.88	0.77-0.99
Otitis media	Never	11,166	80.4				
	Ever	2,726	19.6	1.00	0.91-1.10	0.96	0.87-1.05
Bacterial	Never	13,016	93.7				
	Ever	876	6.3	0.83	0.70-0.99	0.79	0.66-0.94
Viral	Never	12,695	93.3				
	Ever	927	6.7	1.00	0.87-1.17	0.96	0.83-1.11
Antibiotics (n = 19,133)							
Penicillin	Never	17,017	88.9				
	Ever	2,116	11.1	1.23	1.11-1.35	1.07	0.97-1.18
Amoxycillin	Never	8,800	46.0				
	Ever	10,333	54.0	1.31	1.22-1.40	1.09	1.01-1.17
Macrolides	Never	14,877	77.8				
	Ever	4,256	22.4	1.13	1.05-1.22	0.96	0.89-1.04
Cephalosporins	Never	17,744	92.7				
	Ever	1,389	7.3	1.10	0.98-1.24	0.90	0.80-1.02
Augmentin	Never	18,564	97.0				
	Ever	569	3.0	1.36	1.15-1.60	1.16	0.98-1.38
Total no. of prescriptions of antibiotics							
0		6,636	34.7	—	—	—	—
1		4,852	25.4	1.38	1.26-1.51	1.22	1.12-1.34
2		3,139	16.4	1.48	1.34-1.64	1.21	1.09-1.35
3		1,895	9.9	1.57	1.40-1.76	1.22	1.08-1.38
4		1,164	6.1	1.51	1.32-1.74	1.11	0.95-1.28
>4		1,447	7.6	1.48	1.31-1.68	1.01	0.88-1.17

HR, Hazard ratio; Adj, adjusted for consultation rates in the first year of life.

that with increasing numbers of visits, children were more likely to be diagnosed with an allergic disease; however, when the results were stratified by the number of consultations, an effect of antibiotics was still present.¹⁴

Our study has sufficient statistical power to examine the effect of 14 different types of infections. However, none of the personal infections appeared to consistently

protect against the development of allergic disease, even after adjustment for consulting behavior. We did find evidence that children with asthma were more likely to have early respiratory tract infections, and these findings are similar to previous research showing that respiratory tract infections—particularly respiratory syncytial virus infections—increase the risk of subsequently being diag-

TABLE IV. Hay fever, infections, sibling infections, and antibiotic exposure

		n	Percent	HR: Crude	95% CI	HR: Adj	95% CI
Infections (n = 23,604)							
Gastrointestinal	Never	15,077	63.9				
	Ever	8,527	36.1	1.57	1.38-1.79	1.20	1.05-1.37
Respiratory	Never	10,438	44.2				
	Ever	13,166	55.8	1.63	1.42-1.86	1.22	1.05-1.41
Conjunctivitis	Never	15,294	64.8				
	Ever	8,310	35.2	1.16	1.02-1.33	0.91	0.79-1.04
Otitis media	Never	18,431	78.1				
	Ever	5,173	21.9	1.34	1.16-1.55	1.03	0.89-1.20
<i>Candida</i>	Never	19,162	81.2				
	Ever	4,442	18.8	1.25	1.07-1.46	0.99	0.84-1.16
Bacterial	Never	22,671	96.1				
	Ever	933	4.0	1.55	1.17-2.06	1.24	0.94-1.65
Viral	Never	22,466	95.2				
	Ever	1,138	4.8	1.07	0.81-1.42	0.90	0.68-1.19
Sibling's infections (n = 17,409)							
Gastrointestinal	Never	14,609	85.7				
	Ever	2,440	14.3	0.97	0.77-1.21	0.88	0.70-1.11
Respiratory	Never	10,486	61.5				
	Ever	6,563	38.5	1.12	0.96-1.31	0.99	0.84-1.15
Conjunctivitis	Never	15,005	88.0				
	Ever	2,044	12.0	1.03	0.82-1.30	0.95	0.76-1.20
Otitis media	Never	13,659	80.1				
	Ever	3,390	19.9	1.06	0.88-1.28	0.97	0.80-1.18
Bacterial	Never	15,949	93.6				
	Ever	1,100	6.5	0.88	0.63-1.23	0.81	0.58-1.12
Viral	Never	15,878	93.1				
	Ever	1,171	6.9	1.37	1.06-1.78	1.27	0.98-1.66
Antibiotics (n = 23,604)							
Penicillin	Never	20,801	88.1				
	Ever	2,803	11.9	1.29	1.07-1.54	1.05	0.87-1.26
Amoxycillin	Never	10,579	44.8				
	Ever	13,025	55.2	1.42	1.25-1.63	1.05	0.91-1.21
Macrolides	Never	18,072	76.6				
	Ever	5,532	23.4	1.39	1.21-1.60	1.09	0.94-1.27
Cephalosporins	Never	21,812	92.6				
	Ever	1,792	7.6	1.37	1.10-1.69	1.01	0.81-1.26
Augmentin	Never	22,880	96.9				
	Ever	724	3.1	1.19	0.85-1.67	0.94	0.67-1.32
Total no. of prescriptions of antibiotics							
0		7,829	33.2	—	—	—	—
1		5,992	25.4	1.39	1.15-1.67	1.14	0.94-1.38
2		3,918	16.6	1.58	1.29-1.93	1.13	0.92-1.40
3		2,444	10.4	1.45	1.14-1.84	0.95	0.74-1.22
4		1,519	6.4	2.17	1.69-2.78	1.29	0.99-1.69
>4		1,902	8.1	2.12	1.68-2.66	1.14	0.88-1.47

HR, Hazard ratio; Adj, adjusted for consultation rates in the first year of life.

nosed with asthma.^{24,25} Whether early respiratory tract infection is truly a risk factor for disease or is merely an early manifestation of disease is unclear.

This is one of the first studies to test the assumptions of the "hygiene hypothesis" by examining the specific impact of exposure to infection in a child's siblings. We found some evidence that some of the infections in the siblings, such as conjunctivitis, viral infections, and bacterial infections, appeared to play a protective role;

importantly, however, none of these was consistent throughout the 3 different allergic diseases. Furthermore, the protective effects were quite small, ranging from a 10% to a 20% reduction in the incidence of allergic disease, and the protective effects had no impact on the relationship between the number of older siblings and the development of allergic disease.

Collectively, the available data on early exposure to antibiotics and the development of allergic disease sug-

TABLE V. Effect of antibiotics, infection on the birth order effect

	No. of older siblings	Asthma		Eczema		Hay fever	
		HR	95% CI	HR	95% CI	HR	95% CI
Unadjusted	0						
	1	0.88	0.80-0.95	0.88	0.81-0.95	0.74	0.63-0.86
	2	0.87	0.78-0.97	0.82	0.74-0.90	0.69	0.56-0.85
	>2	0.82	0.71-0.94	0.62	0.54-0.71	0.67	0.52-0.88
Adjusted for antibiotics	0						
	1	0.81	0.74-0.88	0.84	0.78-0.91	0.69	0.59-0.81
	2	0.78	0.69-0.87	0.78	0.70-0.86	0.63	0.51-0.77
	>2	0.70	0.61-0.81	0.58	0.51-0.67	0.60	0.46-0.78
Adjusted for personal infections	0						
	1	0.86	0.79-0.94	0.87	0.80-0.94	0.73	0.63-0.85
	2	0.84	0.75-0.94	0.80	0.72-0.88	0.67	0.54-0.82
	>2	0.80	0.70-0.93	0.61	0.53-0.70	0.66	
Adjusted for siblings' infections	0						
	1	0.77	0.69-0.86	0.82	0.74-0.90	0.62	0.50-0.77
	2	0.74	0.64-0.85	0.74	0.65-0.84	0.55	0.42-0.71
	>2	0.67	0.57-0.80	0.55	0.47-0.65	0.50	0.37-0.69

HR, Hazard ratio.

gest the presence of a positive association.^{12,14,15,19,20} The size of our database means that we are able to subdivide antibiotic exposure into 5 groups and compare broad- and narrow-spectrum antibiotics. Using the GP records, we will have an accurate account of the numbers of prescriptions for antibiotics, which should accurately reflect exposure to antibiotics, though antibiotics not taken would lead to nondifferential misclassification bias and an underestimation of the effect of antibiotics. In the unadjusted model, the broader-spectrum antibiotics appear to produce stronger increases in risk than the narrow-spectrum antibiotics, and we also saw a dose-response relationship for each antibiotic. However adjusting for consulting behavior appeared to reduce the effect of antibiotics by 20% to 30%, explaining nearly all of these effects. Again, inasmuch as children are required to consult to be prescribed antibiotics, we might have "overadjusted" our analysis. The positive association that remained for asthma and the use of antibiotics could be present because asthmatic individuals are more likely to have early respiratory tract infections and are often given antibiotics for these. We found that the effect of antibiotics was time-dependent, showing stronger HRs in the first half of follow-up time than in the second half for all 3 allergic diseases. This finding is perhaps in keeping more with a bias due to reverse causation than with a true casual association. However, the dose-response effects, both in terms of number of courses and broadness of spectrum, means that we cannot completely dismiss the possibility that early use of antibiotics is related to the incidence of allergic disease.

In summary, we have found no consistent evidence for a protective influence of infections, either in the child or in his or her siblings, on the incidence of allergic disease. Furthermore, exposure to infections does not explain the strong birth order effect in this cohort. In addition, we

have found no consistent evidence that antibiotics increase the risk of developing disease, though there might be an increased risk of early diagnoses of allergic disease with use of antibiotics; further research is needed to understand this relationship. Our findings are not consistent with the "hygiene hypothesis" explanation of the birth order effects, and they suggest that further hypotheses might be required to explain the strong birth order effects evident in this and other data sets.

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