

Early-life exposure to antibacterials and the subsequent development of hayfever in childhood in the UK: case–control studies using the General Practice Research Database and the Doctors' Independent Network

S. A. Bremner*, I. M. Carey*, S. DeWilde*, N. Richards†, W. C. Maier‡, S. R. Hilton*, D. P. Strachan* and D. G. Cook*

*Department of Community Health Sciences, St George's Hospital Medical School, London, †CompuFile Limited, Send, Surrey and ‡Worldwide Epidemiology Group, GlaxoSmithKline, Greenford, Middlesex, UK

Summary

Background Theoretically, antibacterial agents in early life might influence allergic sensitization in two ways: (i) as an indicator of infectious illness, they might be expected to protect against allergy; (ii) alternatively they might increase the risk through effects on the commensal bowel flora. Epidemiological evidence linking the prescription of antibacterial agents in early life to the subsequent development of hayfever is conflicting.

Objective To establish definitively whether an association exists between early-life antibacterial exposure and childhood hayfever diagnosis.

Methods Nested case–control studies were based on birth cohorts of children identified within two large UK general practice databases of electronic patient records. One hundred and sixteen thousand and four hundred and ninety-three children from 605 general practices were identified as being continuously registered from birth to at least age 5 years. Seven thousand and ninety-eight cases were diagnosed with hayfever after the age of 2 years. One control per case was matched for practice, birth month, sex and still being registered on case diagnosis date. Odds ratios were derived from conditional logistic regressions within each database followed by pooling using a fixed-effect model.

Results The pooled odds ratio for hayfever was 1.11, 95% CI (1.03–1.20) if exposed to antibacterials in the first year of life, 1.35 (1.25–1.46) in year 2 and 1.47 (1.37–1.59) in year 3. Adjusting for consultation frequency reduced these odds ratios to 0.92, 1.05 and 1.10, respectively. There was no evidence that broader spectrum antibacterials, exposure in any specific month of year 1 or in the grass pollen season influenced the risk of hayfever.

Conclusion These data exclude any important effect of antibacterial exposure in infancy on subsequent hayfever risk. Associations reported in earlier studies have likely been exaggerated through publication bias and by lack of control for the tendency of some families to consult frequently for a range of conditions.

Keywords general practice databases, hayfever, oral antibacterials

Submitted 16 April 2003; revised 16 June 2003; accepted 5 August 2003

Introduction

In the past decade, there has been renewed interest in the proposition that atopy and infections are inversely related [1]. Associations of allergic diseases with small family size and high birth order are consistent with this 'hygiene hypothesis', although studies of specific infectious diseases have generally not found a protective effect [2]. Treatment with antibacterial agents might influence allergic sensitization in two ways. Firstly, as an indicator of infectious illness, it might be expected to protect against allergy. Alternatively, through its

effect on the commensal bowel flora, particularly in early infancy, antibiotic therapy might shift immune expression in favour of Th2 rather than Th1 responses, increasing the likelihood of allergic sensitization and allergic disease [3, 4].

Epidemiological evidence for a link between early antibacterial exposure and subsequent hayfever came from a study in a single general practice in 1934 patients, which found a doubling in the odds of hayfever with antibacterials prescribed before the age of 2 years and raised the possibility of a stronger association with broader spectrum antibacterials [5].

A population-based study of 1206 7- and 8-year-old children in Belgium found in excess of a doubling of the odds of hayfever, given antibacterial exposure in the first year of life, which was stronger in children with a parental history of the disease [6]. A questionnaire-based study of 456 parents of children attending Rudolf Steiner schools in New Zealand

Correspondence: Derek G Cook, PhD, Professor of Epidemiology, Department of Community Health Sciences, St. George's Hospital Medical School, Cranmer Terrace, London SW17 0RE, UK.

E-mail: d.cook@sghms.ac.uk

recorded antibacterial use in early childhood and the development of asthma. It may have been under-powered for investigating hayfever, but nevertheless found a doubling in the odds of disease [7].

In contrast, no association was found between antibacterial use and hayfever in 863 Tasmanian children, as ascertained by home parental interview conducted in 1995 [8]. A lack of any association was also reported between asthma and atopic diseases, including allergic rhinitis at age 5 and antibacterials in the first year of life in a study of 448 children with a parental history of atopy in the US city of Boston [9].

Finally, a recent study of 29 238 children registered with the West Midlands section of the General Practice Research Database (GPRD) found that, after adjustment for consultation behaviour, the observed association between antibacterials and hayfever disappeared [10]. However, this study was based on a median follow-up time of 2.9 years and the mean age of diagnosis for the 915 cases was 3.5 years. Case ascertainment included a number of less-specific labels, including 'chronic rhinitis', which may have diluted true associations with seasonal-allergic rhinitis.

In order to resolve the epidemiological picture, we carried out nested case-control studies in two large UK general practice databases: the GPRD and the Doctors' Independent

Network (DIN). The studies were executed to the same specification in each database to test the following hypotheses: (1) that exposure to antibacterials in the first year of life is associated with an increased risk of hayfever later in childhood; (2) more specifically, that broad-spectrum antibacterials are implicated in this increased risk and (3) that exposure during the grass pollen seasons, indicating infectious illness at the time of early allergen exposure, reduces the risk of subsequent hayfever.

Materials and methods

Study design

We conducted two separate nested case-control studies, one within a DIN cohort of 40 183 children born between 1989 and 1997 from 141 general practices and the other within a GPRD cohort of 76 310 children born between 1989 and 1993 from 464 practices. All children had at least 5 years of follow-up from birth and were deemed born-in i.e. registered with the practice within 3 months of birth. Practices were primarily in England and Wales, but Scotland and Northern Ireland were also represented.

Table 1. Case definitions: diagnoses and therapies; classification of antibacterial exposures

	GPRD	DIN
<i>Hayfever diagnoses</i>		
OXMIS	Read Codes (5-byte)	Read Codes (4-byte)*
		14B1 H/O hayfever
507 HF hayfever	14B1.00 H/O hayfever	H28. hayfever
5070S hayfever symptoms	H170.11 hayfever – pollens	
	H171.14 hayfever – other allergens	
	H172.11 hayfever – unspecified allergen	
	H330.13 hayfever with asthma	
<i>Hayfever therapies</i>		
BNF chapters		Read Codes (4-byte)*
3.3.1. cromoglicate and related therapy		I8.. nasal allergy drugs
3.4.1. antihistamines		c8.. antihistamines
11.4.2. other anti-inflammatory preparations		k61. antazoline salts
12.2.1. drugs used in nasal allergy		k69. sodium cromoglicate (eye)
		k6e. nedocromil sodium (eye)
		k6h. azelastine hydrochloride (eye)
		I95. compound nasal decongestants
<i>Antibacterial exposure</i>		
BNF chapter		Read Codes (4-byte)*
5.1. antibacterial drugs		e1.. penicillinase sens. penicillins
except:		e2.. penicillinase res. penicillins
5.19. antituberculous drugs		e3.. broad-spectrum penicillins
5.1.10. antileprotic drugs		e4.. antipseudomonal penicillins
		e5.. other penicillins
		e6.. cephalosporins and cephamycins
		e9.. macrolides
		ec1. co-trimoxazole† (generic)
		ec2. co-trimoxazole† (proprietary)
		ecc. trimethoprim

H/O stands for 'history of'. BNF = British National Formulary.

*In a 4-byte Read Code, trailing dots '.' imply the inclusion of that level and all lower levels in the hierarchy. †co-trimoxazole = trimethoprim/sulphamethoxazole

While our GPRD data set was last updated in 1998, our DIN data set runs to 2002. DIN has an enumeration district level socio-economic marker called A Classification of Residential Neighbourhoods (ACORN) available [11], constructed from a subset of 1991 census variables and linked to each individual through their postcode. The advantages of using the two separate databases are: (i) we can assess the consistency of results across databases; (ii) pooling data from both databases increases power; and (iii) where necessary, adjustments for confounders only available in one or other database can be assessed.

For much of the study period, practices in GPRD used the Oxford Medical Information System (OXMIS) coding system, but since 1997 some practices have used Read Codes (Unified 5-Byte Version 2 Set) for diagnoses. Prescription Pricing Authority (PPA) codes were used for recording drugs, which we mapped to British National Formulary (BNF) chapters. DIN practices used Read Codes (GP 4-byte set) for recording both drugs and diagnoses.

We aimed to be consistent across the two databases in our case definition of hayfever and selection of relevant drugs, despite the various coding systems used. We produced monthly counts of all the consultations coded as hayfever or allergic rhinitis to ascertain which diagnoses exhibited

marked seasonality. Those that did were used by us to identify cases and are listed in Table 1 along with the codes for hayfever therapies and antibacterials. Subjects who only ever had a hayfever diagnosis before age 2, or non-specific allergic rhinitis diagnoses, which did not exhibit a seasonal pattern were excluded from being cases or controls (Fig. 1).

Given that hayfever is often diagnosed after 5 years of age, and there were different lengths of follow-up for each child beyond age 5, we allowed two levels of 'caseness' in our analyses. We refer to these as 'certain' and 'less certain'. Figure 1 shows how we arrived at our case definitions in both the cohorts.

For each case of hayfever, we selected one control child, matched for general practice, sex, birth month and follow-up of control to at least the date of diagnosis of the case (the date of first diagnosis if a 'less certain' case; the date of confirmatory diagnosis or therapy if a certain case) i.e. the index date. Priority was given to the selection of controls for the most certain cases with the longest follow-up. Where more than one control was eligible to be matched to a case, a random selection was made. Cases remaining unmatched were entered into two further selection sweeps, where the age criterion was relaxed by 1 month on either side of the actual birth month. Thereafter, unmatched cases were excluded from further consideration.

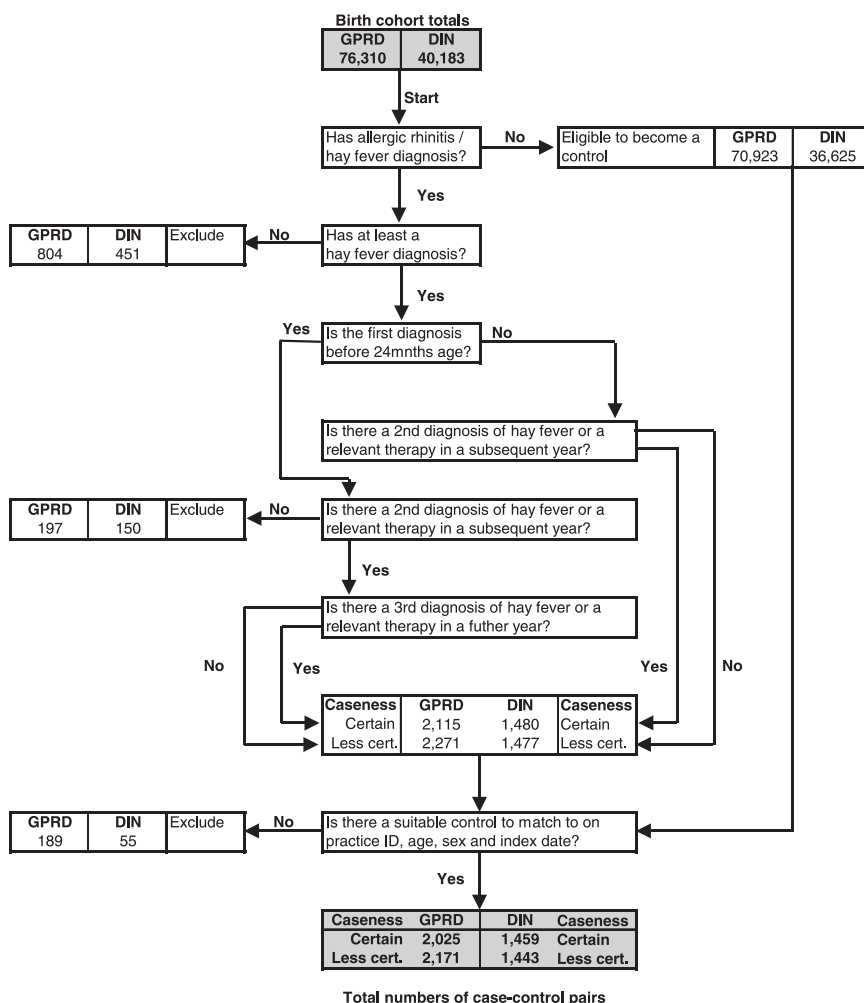


Fig. 1. Flow diagram to illustrate the selection of cases and controls from the birth cohorts.

Exposure to oral antibacterials (Table 1) was established for the cases and controls from each cohort by identifying the relevant drug issues from the patient records. Variables were defined as follows: any courses of antibacterials in the first, second or third years of life; any in each of the first 12 months of life and the number of courses in the first year of life (categorized as none, 1, 2, 3 or more). Issues for antibacterials were classified into penicillins, cephalosporins, macrolides and trimethoprim/co-trimoxazole (trimethoprim/sulphamethoxazole). The timing of exposure was captured by variables defined as: any issue only in or only outside the grass pollen season (defined as May, June and July), or both in and out with the grass pollen season.

The consultation counts in the first 5 years of life were grouped into 10 categories (0–10, 11–20, ..., >90). For this, we were interested in patient contacts (restricted to one per day) i.e. any day on which a drug issue was recorded or any other Read/OXMIS code, which was not administrative or relating to secondary-care procedures. Further, as our exposure variables centred on antibacterials, we excluded

contact days on which antibacterials were prescribed. This gave us a marker of consultation frequency.

We reanalysed the data after excluding case-control pairs where either member had had a diagnosis of wheeze or asthma ever. We supposed that antibacterials could have been prescribed for early respiratory infections with wheeze, a possible sign of later asthma. Further, we excluded pairs where the control had had no GP contact within the period of 6 months before the case attained his/her case status or at any time afterwards. This was to identify and exclude matched pairs where the control demonstrated the possibility of being a ghost i.e. no longer attending the practice, but still registered on the system. Such controls may have an understated exposure history.

Statistical analysis

We analysed the pairs from each cohort in two sets: all cases and then only the 'certain' cases. We present the numbers of discordant and concordant pairs by exposure groups in Table

Table 2. Case-control study of hayfever and exposure to antibacterials: 2×2 tables for GPRD and DIN

	GPRD					DIN				
	Case – Control –	Case + Control –	Control + Case –	Control + Case +	Total %(+)	Case – Control –	Case + Control –	Control + Case –	Control + Case +	Total %(+)
<i>Any antibacterials</i>										
0–11 months	734	905	752	1805	62.8	584	712	564	1042	57.9
12–23 months	373	931	592	2300	73.0	365	701	494	1342	66.8
24–35 months	436	1091	639	2030	69.0	476	761	535	1130	61.3
<i>Any antibacterials</i>										
0–30 days	4052	81	62	1	1.7	2843	27	31	1	1.0
31–60 days	3824	193	161	18	4.6	2701	96	98	7	3.6
61–90 days	3709	256	207	24	6.1	2627	137	129	9	4.9
91–120 days	3537	351	275	33	8.4	2533	204	142	23	6.8
121–150 days	3377	408	343	68	10.6	2417	241	214	30	8.9
151–180 days	3229	455	414	98	12.7	2309	289	267	37	10.9
181–210 days	3119	518	453	106	14.1	2234	355	258	55	12.5
211–240 days	3040	537	467	152	15.6	2187	345	285	85	13.8
241–270 days	3024	564	477	131	15.5	2158	338	339	67	14.0
271–300 days	3046	535	475	140	15.4	2159	369	315	59	13.8
301–330 days	2933	598	510	155	16.9	2112	394	315	81	20.4
331–360 days	3031	578	452	135	15.5	2121	386	320	75	14.7
<i>Class of antibacterial in first year</i>										
Penicillins	989	967	787	1453	55.5	692	735	585	890	53.4
Cephalosporins	3655	261	219	61	7.2	2555	174	147	26	6.4
Macrolides	2798	609	504	285	20.1	2164	351	291	96	14.4
Trimethoprim/co-trimox.	3667	234	222	73	7.2	2636	121	110	35	5.2
<i>Number of courses in first year</i>										
0	1829	754	896	717	36.7	1061	564	711	566	41.5
1	2387	761	814	234	24.3	1667	537	525	173	24.3
2	2974	549	530	143	16.3	2118	392	316	76	14.8
3 or more courses	2589	745	569	293	22.6	1916	451	392	143	19.5
<i>Exposure group</i>										
No Ab in Y1	1829	754	896	717	36.7	1061	564	711	566	41.5
Ab in Y1 non-gp only	1573	911	956	756	40.3	1137	679	612	474	38.6
Ab in Y1 gp only	3787	196	196	17	5.1	2598	161	133	10	5.4
Ab in Y1 in both	2892	646	459	199	17.9	2150	356	304	92	14.5

The ratio of counts of discordant pairs gives the unadjusted odds ratio of hayfever given exposure.

gp = grass pollen season; Ab = antibacterial; co-trimox. = co-trimoxazole (trimethoprim/sulfamethoxazole); Y1 = first year of life.

Table 3. Results of case-control studies of hayfever and antibacterials in early life.

	GPRD			DIN		
	OR	95% CI	P-value	OR	95% CI	P-value
<i>Any antibacterials</i>						
0–11 months	1.08	0.98–1.20	0.13	1.15	1.03–1.29	0.02
12–23 months	1.40	1.26–1.56	<0.0001	1.29	1.15–1.46	<0.0001
24–35 months	1.59	1.44–1.75	<0.0001	1.32	1.17–1.48	<0.0001
<i>Any antibacterials</i>						
0–30 days	1.25	0.90–1.75	0.18	0.83	0.49–1.39	0.48
31–60 days	1.10	0.89–1.36	0.39	0.88	0.66–1.18	0.40
61–90 days	1.17	0.97–1.41	0.10	0.95	0.74–1.22	0.69
91–120 days	1.20	1.02–1.42	0.02	1.38	1.11–1.72	0.004
121–150 days	1.09	0.94–1.26	0.28	1.04	0.86–1.25	0.72
151–180 days	1.02	0.89–1.17	0.75	0.99	0.84–1.18	0.94
181–210 days	1.06	0.93–1.20	0.40	1.31	1.11–1.55	0.001
211–240 days	1.06	0.93–1.20	0.40	1.13	0.96–1.33	0.14
241–270 days	1.10	0.97–1.25	0.12	0.91	0.78–1.06	0.22
271–300 days	1.06	0.93–1.20	0.40	1.10	0.95–1.29	0.21
301–330 days	1.11	0.98–1.25	0.10	1.19	1.02–1.39	0.02
331–360 days	1.22	1.08–1.39	0.002	1.14	0.98–1.33	0.09
<i>Class of antibacterial in first year</i>						
Penicillins	1.20	1.09–1.32	0.0002	1.23	1.10–1.37	0.0003
Cephalosporins	1.13	0.94–1.36	0.19	1.09	0.87–1.36	0.45
Macrolides	1.16	1.03–1.31	0.02	1.15	0.98–1.34	0.09
Trimethoprim/co-trimox.	0.97	0.81–1.17	0.76	1.04	0.80–1.35	0.77
<i>Number of courses in first year</i>						
0	REF	REF	REF	REF	REF	REF
1	1.07	0.96–1.20	0.24	1.17	1.02–1.34	0.02
2	1.18	1.03–1.36	0.02	1.39	1.18–1.64	<0.0001
3 or more courses	1.40	1.23–1.58	<0.0001	1.30	1.12–1.52	0.0006
<i>Exposure group</i>						
No Ab. in Y1	REF	REF	REF	REF	REF	REF
Ab. in Y1 non-gp only	1.10	0.99–1.22	0.07	1.22	1.09–1.38	0.001
Ab. in Y1 gp only	1.15	0.94–1.42	0.18	1.37	1.08–1.74	0.009
Ab. in Y1 in both	1.50	1.31–1.72	<0.0001	1.32	1.12–1.56	0.001

Each estimate in a block (each block appears under an italic heading) is adjusted for all the other variables in that block.

OR stands for odds ratio and 95% CI for 95% confidence interval.

REF = baseline category; gp = grass pollen season; Ab = antibacterial; co-trimox. = co-trimoxazole (trimethoprim/sulphamethoxazole); Y1 = first year of life.

2 for all cases, from which crude odds ratios may be derived as the ratio of the discordant pairs: (case +, control –) ÷ (case –, control +). However, such odds ratios are difficult to interpret as the baseline group differs line by line. A more informative analysis is based on conditional multifactorial logistic regression (Table 3), with the matched pairs forming separate strata, using *proc phreg* in SAS (version 8.1 for SunOS) [12]. Finally, to simplify the presentation of the results, the estimates from the two case-control studies were pooled using a fixed-effect model by way of the *meta* command in Stata (version 5.0 for Windows) [13, 14].

Results

Among 76 310 children, followed for 5 or more years, who are members of the GPRD birth cohort, 4196 cases of hayfever were identified. Two thousand and twenty-five of these cases

(48.3%) were deemed 'certain'. A further 1001 subjects were excluded because they had a diagnosis of: (i) hayfever before the age of 2 years with no subsequent confirmation or; (ii) at least one allergic rhinitis code other than those interpreted as indicative of hayfever, but no hayfever code after age 2. A further 189 cases (48% 'certain') could not be allocated a suitable control (Fig. 1).

The DIN cohort comprised 40 183 children followed up for at least 5 years from birth. Two thousand nine hundred and two hayfever cases were identified. There were 150 exclusions and 55 unmatched cases (38% 'certain'). One thousand four hundred and fifty-nine (50.3%) of all cases were classed as 'certain' (Fig. 1). The cumulative incidence of hayfever over the entire follow-up in DIN was 7.3%.

In GPRD, the cases were followed up for a mean of 7.4 years with a median of 39 consultations (excluding those in which antibacterials were prescribed) in the first 5 years of life. The mean age of first diagnosis of hayfever was 4.6 years. The corresponding figures in DIN were 8.2 years and 42

Table 4. Results of case-control studies of hayfever and antibacterials in early life.

	Adjusted*			Adjusted†		
	OR	95% CI	P-value	OR	95% CI	P-value
<i>Any antibacterials</i>						
0–11 months	1.11	1.03–1.20	0.006	0.92	0.85–1.00	0.05
12–23 months	1.35	1.25–1.46	<0.001	1.05	0.96–1.15	0.29
24–35 months	1.47	1.37–1.59	<0.001	1.10	1.01–1.20	0.02
<i>Any antibacterials</i>						
0–30 days	1.11	0.84–1.47	0.46	0.99	0.73–1.34	0.94
31–60 days	1.02	0.86–1.21	0.84	0.94	0.78–1.14	0.54
61–90 days	1.09	0.94–1.26	0.28	0.99	0.84–1.16	0.86
91–120 days	1.26	1.11–1.44	0.001	1.10	0.95–1.27	0.20
121–150 days	1.07	0.95–1.20	0.25	0.94	0.82–1.06	0.30
151–180 days	1.01	0.91–1.12	0.88	0.89	0.79–1.00	0.05
181–210 days	1.15	1.04–1.27	0.008	1.03	0.92–1.15	0.67
211–240 days	1.09	0.98–1.20	0.11	0.95	0.85–1.06	0.38
241–270 days	1.02	0.92–1.12	0.71	0.91	0.82–1.01	0.09
271–300 days	1.08	0.98–1.19	0.14	0.89	0.80–0.99	0.03
301–330 days	1.14	1.04–1.25	0.007	0.97	0.87–1.08	0.54
331–360 days	1.19	1.08–1.31	0.001	1.01	0.91–1.13	0.85
<i>Class of antibacterial in first year</i>						
Penicillins	1.21	1.13–1.30	<0.001	0.97	0.92–1.03	0.35
Cephalosporins	1.11	0.97–1.28	0.14	0.95	0.86–1.06	0.34
Macrolides	1.16	1.05–1.27	0.003	0.97	0.91–1.04	0.46
Trimethoprim/co-trimox.	0.99	0.85–1.15	0.92	0.92	0.82–1.02	0.12
<i>Number of courses in first year</i>						
0	REF	REF	REF	REF	REF	REF
1	1.11	1.02–1.22	0.02	0.98	0.89–1.08	0.75
2	1.26	1.14–1.41	<0.001	0.92	0.82–1.03	0.15
3 or more courses	1.36	1.23–1.50	<0.001	0.82	0.74–0.92	<0.001
<i>Exposure group</i>						
No Ab. in Y1	REF	REF	REF	REF	REF	REF
Ab. in Y1 non-gp only	1.15	1.07–1.25	<0.001	0.93	0.85–1.01	0.09
Ab. in Y1 gp only	1.24	1.06–1.45	0.007	1.06	0.89–1.26	0.52
Ab. in Y1 in both	1.43	1.28–1.58	<0.001	0.86	0.76–0.97	0.01

*Each estimate in a block (each block appears under an italic heading) is adjusted for all the other variables in that block and then pooled across DIN and GPRD in a fixed-effect model. †Estimates further adjusted for contacts days when antibacterials were not prescribed and then pooled across DIN and GPRD in a fixed-effect model.

OR stands for odds ratio and 95% CI for 95% confidence interval.

REF = reference category; gp = grass pollen season; Ab = antibacterial; co-trimox. = co-trimoxazole (trimethoprim/sulphamethoxazole); Y1 = first year of life.

consultations. The first diagnosis occurred at a mean age of 5.1 years. The cumulative incidence of hayfever in GPRD over the entire follow-up was 5.6%.

Overall, 6.9% (GPRD: 7.2%; DIN: 6.6%) of all cases had a first diagnosis of hayfever before the age of 2 years, subsequently confirmed in a later year by a further diagnosis or treatment. A first diagnosis after the age of 5 years occurred in 43.6% (GPRD: 40%; DIN: 48.8%) of all cases.

Counts of matched case-control pairs, as well as the percentages of (cases+controls) in each exposure category, are shown in Table 2. The latter are very similar to percentages from the whole cohort. Only the pairs discordant in terms of exposure status contribute any information, and the ratio of counts of pairs (case +, control –) to (case –, control +) gives an estimate of the crude odds ratio (not shown) of hayfever given that exposure.

Table 3 presents the adjusted results of both nested case-control studies separately. Generally, the findings from the

two databases were very similar and so pooled fixed-effect results are presented in Table 4, which forms the basis of the discussion here. The extra power afforded by combining the estimates from the two studies allows us to detect substantially smaller odds ratios. Table 4 illustrates several highly significant associations and small effect sizes (left-hand column). We emphasize the magnitude of the pooled odds ratios and the effect of adjustment for the number of consultations where antibacterials were not prescribed, as shown in the right-hand column.

Exposure to any antibacterial in the first year of life was related to an 11% increase in the odds of hayfever, rising to 35% in the second year and 47% in the third year. However, adjustment for consultation frequency substantially reduced these associations.

On partitioning the first year of life into 30-day intervals and mutually adjusting antibacterials in 1 month for all the others, small positive associations were noted in each

month, some of which were statistically significant. However, after adjusting for consultation frequency, none of the effects were significant and most odds ratios were below 1 (Table 4).

There was a strong association, although small in magnitude, between penicillins (the most commonly prescribed class of antibacterials in these children), macrolides and increased risk of hayfever in the first year. These associations were completely removed by adjusting for consultation frequency. There was no relationship between cephalosporins, which have a broad spectrum, and later hayfever.

There was some evidence that the more courses of antibacterials issued in the first year of life, the higher the risk of later hayfever. Relative to non-exposure, odds were elevated by 11%, 26% and 33% for 1, 2, 3+ courses, respectively (Table 4). However, adjustment for consultation frequency resulted in the risk being greatest in the non-exposed group (Table 4).

Relative to those children with no courses of antibacterials in year 1, those prescribed any either in or outside the hayfever season had very similar and non-statistically significant odds of hayfever. A greater risk was attached to having been prescribed antibacterials in both periods, analogous with having been prescribed multiple courses. This was reversed on adjustment for consultation frequency.

Very similar results were found when analyses (data not shown) were restricted to: (i) the 'certain' cases; (ii) pairs where the control had had some GP contact in the period 6 months before case definition or at any time afterwards (92% of cases in GPRD and 90% of cases in DIN). When analyses were restricted to exclude case-control pairs having had any recorded diagnoses of asthma or wheeze (52.3% of pairs in GPRD and 56.7% of pairs in DIN), the odds ratios tended to be closer to 1.

Discussion

The two large case-control studies that we have reported show definitively the lack of any strong associations between oral antibacterials in infancy and later hayfever. Specifically, we found no support for the hypothesis that antibacterials in the first year of life were an independent risk factor for later hayfever, nor for the suggestion that antibacterials taken in the grass pollen season, i.e. at the time of early aeroallergen exposure, were particularly influential in the subsequent development of pollen sensitization.

Despite differences in coding conventions and data structure, the two databases revealed very similar results, which instills greater confidence in the generalizability of our conclusions. There is only a limited overlap between our data and those reported by McKeever et al. [10], which was based on a regional subset of approximately 10% of the GPRD. Their study in the West Midlands region included 915 cases of chronic or allergic rhinitis diagnosed at a mean age of 3.5 years, whereas we ascertained 2025 'certain hayfever cases' from the full 100% GPRD. This suggests that our more specific case definition excludes many of the cases analysed by McKeever et al., so the findings of the two GPRD studies are statistically independent to a large extent.

The outcome in each study is hayfever with the exception of:

- * Allergic rhinitis
- ** Atopy

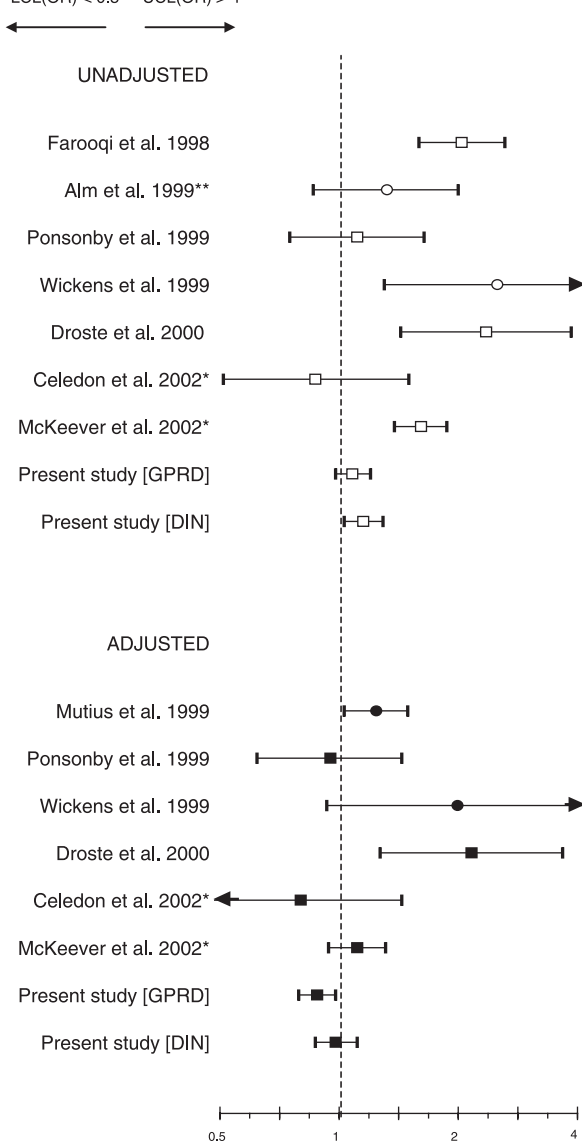
The plot shows estimated odds ratios and 95% confidence intervals on the log-scale.

The estimates are denoted by the following symbols:

- Longitudinal (Unadjusted)
- Longitudinal (Adjusted)
- Cross-sectional (Unadjusted)
- Cross-sectional (Adjusted)

Where the confidence limit exceeds the scale, the following symbols are used:

LCL(OR) < 0.5 UCL(OR) > 4



Odds ratios: associations between hay fever and antibacterials

Fig. 2. Forest plot of studies of the association between atopy and antibacterials.

We considered hayfever to be a suitable atopic disease to investigate, as it is not uncommon, is confined to the spring and early summer months and has a tight clinical definition compared with asthma, which is not necessarily atopic, and also has rather specific therapies. Further, the crucial development period of the immune system investigated here and the diagnosis of hayfever have substantial temporal separation.

There were a large number of exclusions from the GPRD study, relative to those in DIN. Two likely reasons for this are: (1) the greater variety of allergic rhinitis codes available from the OXMIS and Read Codes (5-byte) coding systems compared with those in Read Codes (4-byte), allowing the practitioner greater variability in diagnosis and (2) the greater mean follow-up beyond the age of 5 years in DIN (an excess of 2.6 years in DIN and 2.0 years in GPRD), increasing the likelihood of confirmatory diagnoses of hayfever in DIN.

Approximately 10% of cases from each study were potentially matched to 'ghosts', among whom recent antibacterial exposure may have been underestimated. However, this is less likely to affect analyses of medication in infancy and our sensitivity analyses showed little difference when these pairs were excluded. Restriction of analyses to pairs with no record of asthma or wheeze at any point in follow-up reduces the association between antibacterials and hayfever. This supports a possible explanation for partial reverse causation, i.e. antibacterials being prescribed for chest illnesses in atopic asthmatic children who subsequently develop hayfever. However, a more influential and general phenomenon appears to be that of consultation frequency, which was shown to be a strong confounder. Frequent attenders were more likely to be prescribed antibacterials, possibly because they were presenting with the early symptoms of atopic disease.

These two very large nested case-control studies exclude any important effect of antibacterial exposure in infancy on the subsequent risk of developing hayfever. All effects reported are small before allowing for consultation frequency and disappear on adjustment. The greater effect seen in year 3 accords with consultation frequency strongly confounding the relationship between antibacterials and hayfever and strengthens evidence against the early-exposure hypothesis.

The associations reported in previous studies have likely been exaggerated through publication bias and a lack of control for the confounding tendency of some families to consult more frequently than others. Figure 2 places our results and those of McKeever et al. [10] in context against earlier reports, in the form of a 'Forest plot'. The findings from two large primary-care databases in the United Kingdom provide reassurance to clinicians that the prescription of antibacterial therapy to young infants is unlikely to impact adversely on their subsequent risk of developing allergic disease. Our results, particularly in relation to the timing of early antibiotic exposure, challenge the hypothesis that patterns of bacterial colonization of the intestine during the first few months of life strongly influence the process of allergic sensitization to common aeroallergens.

Acknowledgements

We thank Mr Steve Caine of CompuFile Ltd for support with DIN and Dr Philip Sedgwick of St George's Hospital Medical School for support with GPRD. This work was supported by a grant from The Wellcome Trust (065177/Z/01/Z).

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