ASTHMA

Early prescriptions of antibiotics and the risk of allergic disease in adults: a cohort study

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Background: It is frequently asserted that antibiotic prescriptions in childhood are associated with the development of allergic disease, especially asthma. A study was undertaken to establish the direction of this relationship.
Methods: A retrospective cohort study of 746 adults was performed in three general practices. Antibiotic prescriptions in the first 5years of life, collected from contemporary medical records, were related to self-reports of asthma and hay fever and the results of skin prick testing with common aeroallergens.
Results: There was no relationship between early antibiotic prescription and atopy, either for all antibiotic use (OR 1.01) or for antibiotics prescribed at different ages. The significant associations between prescriptions at ages 4 and 5 and hay fever (OR 1.23 and 1.16, respectively) were explained by coexisting asthma. Relationships between antibiotic use and asthma (allergic or otherwise) were statistically significant and strengthened with increasing age of prescription, but were largely confined to antibiotics prescribed for lower respiratory symptoms.
Conclusions: The reported associations between childhood antibiotic use and asthma are most plausibly explained by ''reverse causation''—the tendency for prescriptions to be written for the early manifestations of pre-existing asthma.

If, as is commonly believed, early contact with microbes protects against the development of allergic diseases, then early treatment with antibiotics might plausibly have the opposite effect.[1] Given the high rates of antibiotic prescription to children in most countries, this is an issue of considerable importance. Several studies have set out to examine it. Their findings and their interpretations have been conflicting, particularly with respect to the development of asthma where the question of ''reverse causation'' has remained unresolved.[2] Where associations between antibiotic use and asthma have been reported, are they causal or do the early manifestations of asthma so closely resemble respiratory tract infection that they invite antibiotic prescribing?

We describe the findings of a further study undertaken in a cohort of UK adults and incorporating an objective measure of atopy as well as self-reported diagnoses of asthma and hay fever. Details of antibiotic prescriptions in early childhood were collected from contemporary general practice records. By careful analysis of their indications we aimed to unravel the direction of the associations between prescription and allergic disease.

METHODS

The parents of a representative birth cohort recruited in Ashford, Kent, UK over 18 months from November 1993 were studied; 93% of eligible families agreed to participate. At recruitment all but three of the mothers and 552 (87%) of the fathers underwent skin prick tests with Allergopharma (Hamburg, Germany) allergens. Five years later a questionnaire was administered in person to 583 (97%) of the mothers and 480 (90%) of the fathers who had continued to participate. Information was collected on self-reported diagnoses of asthma and hay fever, self-reported asthma, hay fever or eczema in either of the parents, and current occupation from which an index of socioeconomic class was derived for all but 54 participants. Permission was requested to examine each participant's general practice records collected up to and including the age of 5 years.

The relevant records were obtained for 746 (70%) individuals. They were less often available for men (68%) than for women (72%), and for those aged 35 years or more (57%) than those who were younger (77%). There were no important differences in rates of atopy or reports of allergic diseases between those whose records were or were not examined. Two research nurses (JF and AM) who were unaware of the atopic status or allergic history of the participants transcribed each antibiotic prescription by antibiotic class onto a standard form. The indication for each prescription was determined by examining the clinical record at the time of prescription, again using pre-established and standardised criteria. In this way it was possible to categorise antibiotic prescriptions into those prescribed for respiratory (upper and lower) and non-respiratory (ear, skin, eye, urinary and other) infections. Lower respiratory indications included ''bronchitis'', ''chest infection'', ''bronchiolitis'', and ''pneumonia'', and other respiratory infections where abnormal chest sounds were recorded. We were able to identify an indication for over 99% of prescriptions.

The study was approved by the local ethics committee and each participant provided informed consent.

Statistical methods

Participants were considered to be atopic if they had one or more positive (mean weal diameter ⩾3 mm) skin tests to extracts of *Dermatophagoides pteronyssinus*, cat fur, or grass pollen. They were also categorised by their self-reported asthma or hay fever and by whether these were accompanied by atopy or, in the case of ''hay fever'', a positive prick test to grass pollens.

Simple descriptive analyses were conducted using Student's *t* test and χ^2 statistics as appropriate. Associations between antibiotic prescriptions (expressed continuously) and atopic and allergic disease were estimated using logistic

regression analyses. Analyses with categorical expressions of antibiotic prescription were also carried out and produced the same patterns but with lower precision (data available on request). The analyses were stratified according to the age at which the prescriptions were written; this is not necessarily the age of the first prescription. The results are expressed as odds ratios (OR) with 95% confidence intervals. Analyses were carried out using SAS (SAS Institute Inc, Cary, NC, USA) and Stata (Stata Corporation, TX, USA) software.

A post hoc estimation showed that the study had 80% power to detect an OR of 1.9 or more for the association between antibiotic use and asthma.

RESULTS

Thirty six percent of the 746 adults were atopic; this proportion increased with age and was higher in men (table 1). Most of those who reported asthma were atopic (88% of men, 68% of women). Twice as many reported hay fever although only a little more than half of these had positive skin tests to mixed pollens. There were no important differences by age in the prevalences of either asthma or hay fever. Each outcome was markedly and significantly more common among those who reported parental allergies and, with the exception of asthma, among those from small families. They were also more frequent among those from higher social classes although the differences here were small.

Among the 564 (76%) adults who received at least one antibiotic by the age of 5 years, the median number of prescriptions was 3 (range 1–31) and the median age at first prescription was 1.5 years (range 0–5). Variations by current age suggested a secular increase in prescription patterns (table 2). There was no clear pattern between family size and receiving at least one prescription, but adults with fewer siblings were significantly more likely to have received at least five prescriptions by the age of 5 years ($p<0.001$). Of the seven classes of antibiotics which we categorised, the most commonly prescribed was penicillins with 374 (50%) of adults receiving at least one prescription before the age of 5. Broad spectrum penicillins and tetracyclines were also prescribed relatively frequently (26% of adults for each class). Most "other" antibiotic prescriptions were for chloramphenicol in eye drops or ointments.

Prescription of antibiotics was significantly related to both asthma and atopic asthma with risk estimates of 1.08 and 1.09 per prescription respectively (table 3). The relationships with tetracycline and sulfonamide prescriptions were significant for each asthma subgroup. The risks rose consistently with age of prescription and were thus highest for antibiotics prescribed between the age of 4 and 5 years. Similar patterns were not evident for the other outcomes although there were associations between prescriptions at the age of 3–4 and 4–5 years and pollen sensitive hay fever. Each of these was reduced (to OR 1.17 (0.99 to 1.38) $p = 0.07$ and 1.08 (0.93 to 1.26) $p = 0.32$, respectively) and lost its statistical significance after adjustment for the co-presence of asthma.

One fifth of antibiotic prescriptions were for lower respiratory tract infections, a further 36% were for upper respiratory infections, and the remainder were for non-respiratory infections (table 4). These proportions did not change significantly by age at which the prescription was issued. Analyses by indication of prescription (table 4) suggested that the significant associations with asthma found above were stronger and essentially confined to antibiotics issued for lower respiratory infections.

The median age at first antibiotic prescription was a little higher for all adults with atopic or allergic disease, although none of the differences reached conventional levels of statistical significance. The median age at first antibiotic

Table 1 Prevalence of atopy, asthma and hay fever by age, sex, parental allergy, social class, and sibship

	N	Atopy n (%)	Asthma OR (95% CI); p†	Asthma n (%)	Asthma OR (95% CI); p†	Atopic asthma n (%)	Atopic asthma OR (95% CI); p†	Hay fever n (%)	Hay fever OR (95% CI); p†	Grass-positive hay fever n (%)	Grass-positive hay fever OR (95% CI); p†
Age (years)											
⩽30	292	96 (33%)	1.03 (1.00 to 1.06)	44 (15%)	0.97 (0.92 to 1.02)	31 (11%)	1.02 (0.97 to 1.08)	80 (27%)	1.03 (0.99 to 1.07)	45 (16%)	1.03 (0.98 to 1.08)
31–34	250	94 (38%)	*Per year*	34 (14%)	*Per year*	27 (11%)	*Per year*	70 (28%)	*Per year*	41 (16%)	*Per year*
⩾35	199	79 (40%)	p=0.17	28 (14%)	p=0.26	24 (12%)	p=0.44	63 (32%)	p=0.20	35 (18%)	p=0.23
Sex											
Female	419	138 (33%)	1.48 (1.05 to 2.09)	56 (13%)	1.57 (0.98 to 2.51)	38 (9%)	2.02 (1.19 to 3.44)	127 (30%)	0.94 (0.65 to 1.36)	69 (17%)	1.15 (0.73 to 1.80)
Male	322	131 (41%)	p=0.02	50 (16%)	p=0.06	44 (14%)	p=0.01	86 (27%)	p=0.74	52 (16%)	p=0.55
Parental allergic disease											
–	469	148 (32%)	1.75 (1.25 to 2.47)	50 (11%)	2.26 (1.44 to 3.54)	35 (8%)	2.78 (1.66 to 4.64)	107 (23%)	2.18 (1.52 to 3.11)	53 (11%)	2.56 (1.66 to 3.95)
+	340	102 (43%)	p=0.001	50 (21%)	p<0.001	41 (17%)	p<0.001	93 (39%)	p<0.001	59 (25%)	p<0.001
Social class*											
I/II	106	44 (40%)	1.00	19 (18%)	1.00	16 (15%)	1.00	39 (37%)	1.00	23 (22%)	1.00
III	415	155 (38%)	0.93 (0.60 to 1.45)	57 (14%)	0.75 (0.42 to 1.35)	45 (11%)	0.74 (0.39 to 1.40)	114 (27%)	0.65 (0.41 to 1.03)	67 (16%)	0.68 (0.39 to 1.19)
IV/V	166	53 (33%)	0.77 (0.46 to 1.31)	20 (12%)	0.67 (0.33 to 1.37)	13 (8%)	0.56 (0.25 to 1.26)	43 (26%)	0.73 (0.42 to 1.27)	24 (15%)	0.77 (0.39 to 1.49)
			p=0.57		p=0.53		p=0.37		p=0.19		p=0.41
No. of siblings											
0/1	306	131 (43%)	0.85 (0.74 to 0.97)	54 (18%)	0.90 (0.74 to 1.08)	46 (15%)	0.79 (0.63 to 1.00)	108 (35%)	0.81 (0.69 to 0.94)	78 (26%)	0.64 (0.51 to 0.80)
2	223	75 (34%)	*Per unit increase*	26 (12%)	*Per unit increase*	21 (10%)	*Per unit increase*	57 (26%)	*Per unit increase*	25 (11%)	*Per unit increase*
3	118	38 (32%)	p=0.02	15 (13%)	p=0.25	8 (7%)	p=0.04	29 (25%)	p=0.004	8 (7%)	p<0.001
4+	94	25 (27%)		11 (12%)		7 (8%)		19 (20%)		10 (11%)	

*54 participants could not be classified by their occupation (unemployed, Armed Forces etc).
†Odds ratios (95% confidence intervals) and p values adjusted for the other factors in the table.

Table 2 Antibiotic prescriptions by age, sex, parental allergy, social class, and sibship

	N	⩾1 prescriptions by age 5		⩾5 prescriptions by age 5	
		n (%)	p value*	n (%)	p value*
Age					
⩽30	294	246 (84%)	<0.001	101 (34%)	<0.001
31–34	251	180 (72%)		54 (22%)	
⩾35	201	138 (69%)		25 (12%)	
Sex					
Female	421	322 (76%)	0.49	105 (25%)	0.014
Male	325	242 (74%)		75 (23%)	
Parental allergic disease					
−	472	360 (76%)	0.48	104 (22%)	0.22
+	238	177 (74%)		67 (28%)	
Social class					
I/II	110	86 (78%)	0.23	24 (22%)	0.94
III	416	305 (73%)		103 (25%)	
IV/V	166	128 (77%)		40 (24%)	
No. of siblings					
0/1	309	232 (75%)	0.24	86 (28%)	0.01
2	224	179 (80%)		53 (24%)	
3	119	86 (72%)		24 (20%)	
4+	94	67 (71%)		17 (18%)	

*Adjusted for the other factors in the table.

prescription for atopic adults was 1.70 compared with 1.44 years for non-atopic subjects (p = 0.09); for asthma the ages were 1.59 and 1.49 years, respectively (p = 0.38), and for hay fever 1.64 and 1.47 years, respectively (p = 0.20). We searched for further evidence of a dose effect by summing prescriptions through each year to the age of 5 years. There was no evidence that the risks of any outcome were related to accumulated prescriptions (data not shown).

DISCUSSION

Principal findings

We have been unable to detect any independent association between early antibiotic prescriptions and adult atopy as measured by skin prick testing to three common UK aeroallergens. The findings for self-reported hay fever were similar although a weak effect was evident among those with reported hay fever who were sensitised to grass pollens; this

Table 3 Relationships between atopy, asthma, and hay fever and antibiotic use in the first 5 years of life

	No of prescriptions	Atopy		Asthma		Atopic asthma		Hay fever		Grass-positive hay fever	
		Adjusted OR* (95% CI) per prescription	p value	Adjusted OR* (95% CI) per prescription	p value	Adjusted OR* (95% CI) per prescription	p value	Adjusted OR* (95% CI) per prescription	p value	Adjusted OR† (95% CI) per prescription	p value
Total antibiotics	2372	1.01 (0.97 to 1.05)	0.68	1.08 (1.03 to 1.13)	0.002	1.09 (1.03 to 1.14)	0.003	1.04 (0.99 to 1.08)	0.10	1.03 (0.98 to 1.08)	0.23
Total penicillins	888	1.02 (0.93 to 1.10)	0.73	1.09 (0.98 to 1.20)	0.12	1.13 (1.02 to 1.26)	0.03	1.06 (0.97 to 1.15)	0.19	1.08 (0.98 to 1.20)	0.12
Total broad spectrum penicillins	463	0.96 (0.85 to 1.08)	0.48	1.14 (1.01 to 1.29)	0.05	1.08 (0.92 to 1.27)	0.35	1.01 (0.89 to 1.14)	0.90	1.03 (0.89 to 1.20)	0.65
Total cephalosporins	35	1.52 (0.81 to 2.88)	0.19	1.72 (0.87 to 3.42)	0.14	2.25 (1.05 to 4.80)	0.05	0.73 (0.34 to 1.56)	0.40	1.07 (0.49 to 2.33)	0.87
Total tetracyclines	365	1.16 (0.99 to 1.36)	0.06	1.29 (1.09 to 1.53)	0.01	1.34 (1.11 to 1.62)	0.004	1.16 (0.99 to 1.35)	0.07	1.06 (0.87 to 1.28)	0.57
Total aminoglycosides	114	0.97 (0.72 to 1.31)	0.86	1.19 (0.84 to 1.69)	0.34	1.19 (0.80 to 1.75)	0.41	1.14 (0.84 to 1.54)	0.42	1.02 (0.69 to 1.51)	0.92
Total macrolides	148	0.84 (0.66 to 1.06)	0.12	0.98 (0.76 to 1.26)	0.87	1.00 (0.76 to 1.31)	0.99	0.99 (0.80 to 1.23)	0.93	0.94 (0.72 to 1.22)	0.62
Total sulfonamides	106	1.06 (0.78 to 1.45)	0.72	1.84 (1.29 to 2.62)	0.001	1.60 (1.08 to 2.36)	0.02	1.18 (0.86 to 1.62)	0.32	1.24 (0.86 to 1.79)	0.26
Total other	253	1.11 (0.90 to 1.37)	0.35	1.28 (0.99 to 1.64)	0.07	1.24 (0.92 to 1.66)	0.17	1.19 (0.95 to 1.49)	0.13	1.04 (0.79 to 1.38)	0.78
Total antibiotics age 0–1	396	0.86 (0.73 to 1.02)	0.07	1.02 (0.83 to 1.25)	0.87	0.90 (0.68 to 1.19)	0.44	0.95 (0.80 to 1.13)	0.56	0.77 (0.59 to 1.01)	0.04
Total antibiotics age 1–2	499	0.99 (0.87 to 1.12)	0.83	1.18 (1.03 to 1.35)	0.02	1.18 (1.01 to 1.38)	0.05	1.06 (0.93 to 1.20)	0.37	1.05 (0.89 to 1.22)	0.58
Total antibiotics age 2–3	460	1.06 (0.93 to 1.21)	0.40	1.14 (0.97 to 1.34)	0.13	1.20 (1.00 to 1.43)	0.06	1.12 (0.97 to 1.29)	0.13	1.03 (0.87 to 1.22)	0.76
Total antibiotics age 3–4	525	1.06 (0.93 to 1.22)	0.38	1.23 (1.05 to 1.44)	0.01	1.30 (1.09 to 1.56)	0.01	1.13 (0.99 to 1.30)	0.08	1.23 (1.05 to 1.45)	0.01
Total antibiotics age 4–5	492	1.09 (0.96 to 1.24)	0.17	1.32 (1.15 to 1.53)	<0.001	1.32 (1.13 to 1.54)	0.001	1.11 (0.97 to 1.27)	0.12	1.16 (1.00 to 1.35)	0.05

*Odds ratios and 95% confidence intervals adjusted for age, sex, social class, parental allergic disease, and number of siblings.

Table 4 Relationship between asthma and antibiotic use in the first 5 years of life according to indication

	Lower respiratory infections					Non-respiratory infections				
		Asthma		Atopic asthma			Asthma		Atopic asthma	
	No of prescriptions	Adjusted OR* (95% CI)	p value*	Adjusted OR* (95% CI)	p value*	No of prescriptions	Adjusted OR* (95% CI)	p value*	Adjusted OR* (95% CI)	p value*
Total antibiotics	513	1.30 (1.15 to 1.47)	<0.001	1.29 (1.13 to 1.46)	<0.001	1016	1.09 (0.98 to 1.20)	0.11	1.11 (0.99 to 1.24)	0.08
Total penicillins	166	1.37 (1.05 to 1.79)	0.01	1.37 (1.05 to 1.79)	0.01	329	1.12 (0.90 to 1.39)	0.33	1.21 (0.96 to 1.53)	0.11
Total broad spectrum penicillins	130	1.39 (1.08 to 1.79)	0.01	1.38 (1.04 to 1.83)	0.04	149	1.03 (0.72 to 1.47)	0.87	0.91 (0.57 to 1.45)	0.68
Total cephalosporins	10	3.21 (0.86 to 11.97)	0.10	5.19 (1.33 to 20.23)	0.03	12	1.17 (0.27 to 5.16)	0.84	0.81 (0.10 to 6.31)	0.84
Total tetracyclines	128	1.79 (1.32 to 2.44)	0.001	1.85 (1.34 to 2.56)	<0.001	138	1.01 (0.67 to 1.50)	0.98	1.05 (0.65 to 1.70)	0.85
Total aminoglycosides	3	–	–	–	–	101	1.22 (0.83 to 1.79)	0.34	1.23 (0.81 to 1.87)	0.36
Total macrolides	35	0.98 (0.49 to 1.96)	0.96	0.93 (0.41 to 2.10)	0.86	46	1.13 (0.59 to 2.18)	0.72	1.24 (0.59 to 2.62)	0.58
Total sulfonamides	27	5.13 (2.30 to 11.45)	0.001	5.19 (2.21 to 12.15)	0.001	43	1.62 (0.92 to 2.85)	0.11	1.32 (0.68 to 2.55)	0.44
Total other	14	2.63 (0.75 to 9.27)	0.17	–	–	198	1.29 (0.94 to 1.77)	0.12	1.42 (1.01 to 2.02)	0.06
Total antibiotics age 0–1	87	1.23 (0.81 to 1.88)	0.36	0.95 (0.51 to 1.77)	0.86	186	0.95 (0.65 to 1.40)	0.81	0.82 (0.49 to 1.35)	0.40
Total antibiotics age 1–2	115	1.59 (1.11 to 2.27)	0.01	1.71 (1.16 to 2.51)	0.01	197	1.24 (0.94 to 1.64)	0.14	1.28 (0.93 to 1.74)	0.15
Total antibiotics age 2–3	107	1.68 (1.22 to 2.32)	0.002	1.86 (1.31 to 2.65)	0.001	207	1.07 (0.81 to 1.41)	0.64	1.14 (0.86 to 1.52)	0.39
Total antibiotics age 3–4	107	1.86 (1.33 to 2.62)	<0.001	1.96 (1.36 to 2.81)	0.001	214	1.22 (0.91 to 1.64)	0.20	1.28 (0.92 to 1.79)	0.16
Total antibiotics age 4–5	97	2.06 (1.45 to 2.93)	<0.001	1.95 (1.33 to 2.85)	0.001	212	1.23 (0.93 to 1.62)	0.15	1.32 (0.97 to 1.78)	0.09

*OR (95% confidence interval) and p value per prescription adjusted for age, sex, social class, parental allergic disease, and number of siblings.

appeared to be confined to those who had coexisting asthma. Among those with self-reported asthma, however, and particularly those who were sensitised to common aeroallergens, there was a clear and statistically significant age related relationship between risk and the issue of antibiotics. This was largely accounted for by antibiotics prescribed for lower respiratory infections. We found no systematic differences between antibiotic classes or between broad and narrow spectrum drugs; the associations with asthma were evident for all antibiotic types.

Strengths and weaknesses of the study

Ours is a relatively small, albeit representative, cohort and it might be argued that it had insufficient power to detect weak associations between antibiotic use and atopy. We also used self-reports of allergic disease which may lack some sensitivity but which are probably fairly specific in this age group; we attempted to improve specificity by examining sensitised asthmatics and hay fever sufferers separately. We were, however, able to reproduce standard associations with parental allergy, sex, and family size which are seen in much larger studies. We did not collect information on the age of onset of asthma or hay fever, in part to avoid bias but also because it is difficult to do so with a questionnaire which depends on recall in adulthood. In the majority of cases—particularly of asthma[3]—onset was probably early in life. Because the records of antibiotic prescriptions were made contemporaneously and transcribed ''blind'', we think there is very little likelihood of systematic information bias. Antibiotics are not accessible to children in the UK without a doctor's prescription; in most cases this is likely to have been written by their general practitioner and so will have been recorded. Prescription, of course, does not necessarily imply ingestion.

Other studies

There have been at least seven other studies of this subject, mostly in children; these are summarised in table 5.[4–10] In all instances, with the exception of von Mutius and colleagues,[6] the authors have interpreted the findings as evidence for a causal relationship between antibiotic use and subsequent allergic disease, especially asthma. Only two,[4 10] as in our study, used contemporary medical records to measure the frequency of antibiotic prescriptions, a practice which is made considerably more simple by the centralised medical system in the UK. The remainder relied on parental recall. Three of the studies[5 6 8] included, as we did, an objective measure of ''atopy''; in each case the risk estimates were lower than for other outcomes. A dose-response was reported for five studies,[4 6 7 9 10] in one case by its absence.[9] In all but one the risk estimate associated with asthma was higher than that for hay fever or eczema.

Explanations and implications

There are at least three possible explanations for the consistently reported associations between antibiotic use and allergic disease. The first might be termed a reporting bias whereby recall of prescriptions is systematically linked to the reporting of allergic symptoms or associated atopy, or whereby the probabilities of both antibiotic prescription and allergic diagnosis are dependent on health seeking behaviour. In both the UK studies[4 10] an attempt to correct for this effect

Table 5 Summary of other studies of early antibiotic prescription and allergic disease

Author (ref)	Country	Age (years)	N	Age of prescription (years)	No of prescriptions	Adjusted risk estimate			
						Atopy	Asthma	Hay fever	Eczema
Farooqi[4]	UK	14–23	1934	<2	1+ *v* 0	NR	3.19	2.04	2.04
Alm[5]	Sweden	5–13	675	Ever	1+ *v* 0	1.24	NR	NR	NR
Von Mutius[6]	Germany	5–11	6174	<1	1–2 *v* 0	0.96	1.64	1.12	1.26
Wickens[7]	New Zealand	5–10	456	Ever	1+ *v* 0	NR	2.74	1.99	1.23
Droste[8]	Belgium	7–8	1206 (675)	<1	1+ *v* 0	1.1	1.7	2.3	1.3
Illi[9]	Germany	7	1314	Ever	2+ *v* 0/1	"No effect"	1.08	NR	NR
McKeever[10]	UK	0–11	29238	<1	5+ *v* 0	NR	1.99	1.14	1.01
This study	UK	19–46	746	<5	1+ *v* 0	1.16	1.84	1.24	*NR*

NR = not reported.

was made by controlling for the total number of visits made to the family doctor; in each case this resulted in reduced, albeit not abolished, risk estimates. The second more popular explanation is that antibiotic prescription is indeed causally related to the development of allergic disease, perhaps through inhibition of the immunomodulatory effects of early (bacterial) infection or through disruption of normal gut flora. If this was the case, then estimates of similar strength might be expected for the spectrum of Th2 characterised outcomes including atopy. The collective evidence suggests that the effects are strongest for asthma and weakest for atopy. Furthermore, the risks should be apparent for all indications for prescription. Farooqi and Hopkin[4] found positive associations between "atopy" and prescriptions for urinary and skin infections. Our study suggests, however, that the positive relationships (with asthma) were essentially confined to antibiotics used in the treatment of lower respiratory infections. The features of respiratory infection in early childhood are very similar to those of asthma, especially where viral infections induce an increase in bronchial responsiveness with more severe and prolonged obstructive airway symptoms. Our findings are, we suggest, best explained by the third explanation—namely, a protopathic bias ("reverse causation") in which asthma, manifest by "respiratory infection", rather than being caused by antibiotic use predates and gives rise to antibiotic use.

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